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Computer-Based Techniques for Cardiac Mapping and Electrogram Analysis

by

Edward B. Caref

A dissertation submitted to the Graduate Faculty in Computer Science in
partial fulfillment of the requirements for the degree of Doctor of Philosophy,
The City University of New York

1996

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This manuscript has been read and accepted for the Graduate Faculty in Computer Science in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

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Abstract

Computer-Based Techniques for Cardiac Mapping and Electrogram Analysis

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The integration of computer science and technology into biomedical science is required to investigate nearly all major aspects of basic and clinical research, including the area of cardiac electrophysiology. The isochronal activation mapping technique is most commonly used to understand the basic mechanisms of arrhythmias. There are, however, significant shortcomings toward utilizing this technique, including an adequate design and implementation of computer-based mapping systems to simultaneously record from multiple electrode sites, and objective, accurate analysis techniques applied to electrogram data. The latter is exacerbated when applied to data acquired from diseased cardiac tissue. Recent reports support the use of analytic statistical approaches to selected electrogram features, based on biophysical theory, which can provide more accurate and objective analysis of electrograms. The goals of this dissertation were to:

1. develop a computer-based mapping system that could perform state-of-the art mapping experiments in terms of data acquisition, accurate and reproducible analysis of waveforms, real-time interpretation of electrograms, ease of use, upgradability, and cost effectiveness;
2. develop a set of more strict guidelines for assigning activation time to both the unipolar and bipolar modes of electrogram recordings from normal cardiac epicardial sites;
3. develop a model that created a measurable technique for assessing the error rate of several electrogram features, and combine them into a discriminant function model to optimize the selection of electrogram features which minimize the error when compared to a standard of activation in an in vivo ischemic model of myocardial infarction;
4. determine the accuracy and usefulness of activation-recovery intervals obtained transmurally by extracellular unipolar electrograms in an in vivo model of polymorphic ventricular tachycardia.

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Chapter I . Introduction

The understanding of how the body functions and our ability to apply corrective therapy to disease states and other abnormalities has been greatly facilitated by modern technology. Indeed, modern medicine has been revolutionized by the application of computers and computer science techniques. Computers and computer science techniques are now employed at virtually every level of biomedical practice; from the benches of basic science laboratories to the offices of health practitioners. Its entrenchment is complete and completely welcome, for it has been, perhaps, the primary technological reason that health care in the latter part of this century has been revolutionized, in terms of our ability to deliver reasonable care at a modest social cost.

Computers and computer science techniques are now essential for researching the basic questions posed today at the frontiers of biomedical scientific investigation. From the mapping of the human genome, to the computer imaging techniques currently employed to discern tissue structures in three dimensions with fine detail, they have proven indispensable. Cardiac research is no less dependent on computer technology; we are currently witnessing an explosive growth in cardiac pacing and anti-defibrillatory devices, paved mainly by technological advances in computer, electrical, materials, and micro-machining technologies. Other areas

enjoying the benefits of advanced computer and computer science techniques are the design and application of artificial heart-assist devices, the design and development of safer and more effective pharmaceutical agents, molecular modeling to understand structure/function relationships of diverse fundamental living structures, and statistical analysis of large mega-trials currently underway to address problems in epidemiology and therapy.

Understanding cardiac electrophysiology, which concerns itself primarily with the electrical activity of the heart which precedes and mediates cardiac contraction, is also enjoying revolutionary growth with the aid of computer and computer science technology. The understanding of electrical disorders, which are currently responsible for hundreds of thousands of deaths per year in the US alone, and the administration of therapy designed to counteract these derangements, are greatly dependent upon the use of techniques and applications developed from the mathematical and physical sciences. This dissertation is but one example of an application of computer science and technology to enlarge our understanding of some basic scientific issues in this area.

The heart contains unique properties which readily allow it to be excited by a variety of stimuli, such as electrical, chemical, or mechanical. Nearly all cells in the heart are said to be excitable cells, which promptly respond to stimuli, causing other events to occur, especially a change in the electrical properties of the cell's membrane. Cardiac electrophysiology is the study of

the excitation of the heart, from the genesis of the heart beat to the propagation of electrical activity to all the heart's cells, and subsequent changes made returning to the resting state, readied for the next excitatory sequence. The heart contains a special conduction pathway consisting of cells with remarkable electrically conductive properties, allowing them to become electrogenic in a spatially and temporally unique manner which aids in the contraction process. These cells propagate their electrical current loads to neighboring cells throughout the main muscle mass of the heart, and once excited, they undergo rapid changes which lead to cell contraction. The contraction process occurs in a syncytium, due to the manner in which the electrical wave is delivered to the muscle mass by the specialized conduction system throughout the entire heart. This rhythmic electrophysiologic process occurs more than three billion times in an average human lifetime.

Abnormalities of the heart rhythm, known as arrhythmias, have been studied by cardiac mapping experiments, in which multiple, simultaneous recordings on, in, or under the surface of the heart are made. With this technique, it is possible to follow the electrical wave of propagation spatially and temporally throughout the heart, allowing for more scientific understanding and classification of arrhythmias.

The investigation of the electrical conduction properties of the heart and the study of arrhythmias has a long and productive history. Beginning with the initial cardiac mapping experiments by Mines ¹, mapping of arrhythmias

has grown tremendously in recent years. With the ability to apply sophisticated computer-based techniques to acquire and analyze large amounts of data, cardiac electrophysiologists have made significant inroads into understanding the mechanisms of arrhythmias and provide guidance in the design of treatment modalities. There are, however, many questions still unresolved, and computer science and technology promises to play an increasingly important role in future discoveries.

Chapter II . Statement of the problem

Cardiac arrhythmias

Cardiac arrhythmias have long been considered to be the cause of many serious illnesses, including cardiac sudden death.² When areas of the heart do not activate either appropriately or at the proper time, the contractile strength of the heart suffers in terms of its effectiveness and efficiency. Since the body's organs are vitally dependent on a continuous supply of blood to support metabolic activity, any loss in the blood supply becomes immediately important, and incurs serious and/or lethal consequences unless an ample blood supply can be restored. While other factors may contribute to a decrease in the blood flow rate, such as congestive heart failure, myocardial infarction, valvular heart disease, electrolyte imbalance, or aortic stenosis, cardiac arrhythmias are considered a major factor leading to reduced cardiac output and the leading cause of sudden death. Furthermore, a long-lasting, continued decrease in cardiac output leads to morbidity and a lower quality of life. To address this issue, the biomedical community has established several areas of study. Within the Internal Medicine Departments of medical schools across the US, the medical specialty of Cardiology created the Cardiac Electrophysiology subspecialty. Many departments of Physiology, Biophysics, Molecular Biology, Biomedical Engineering, and Mathematics have also turned their attention to address problems of cardiac

electrophysiology. The commercial rewards from understanding and treating cardiac arrhythmias have produced a multi-billion dollar industry in the US alone.

Mapping techniques to investigate cardiac arrhythmias

Arrhythmias are based on an electrical occurrence, and electrophysiologists have developed specialized tools to investigate this class of problems. With the demonstration by Einthoven ³ in 1909 that the heart's electrical activity could be recorded and analyzed by placement of electrodes on the body's surface, creating the electrocardiogram, medical scientists could begin to understand the electrical properties of the heart. With this technique, many of the heart's electrical abnormalities were documented, defined, and classified.

An understanding of the mechanism of these rhythm disturbances was subsequently pursued. The placement of electrodes on the surface of animal hearts to record electrical activity gave birth to the first mapping experiments. These studies, by Mines, ¹ Garrey, ⁴ Lewis ⁵ and others, showed that several mechanisms could be responsible for the genesis and perpetuation of arrhythmias. For example, Mines discussed circus movement tachycardia, a mechanism of both ventricular tachycardia and atrial flutter, and performed unreported mapping experiments to confirm the existence of this mechanism. ¹ Several years later, Lewis conducted the first published

mapping experiments, confirming the existence of circus movement atrial flutter.^{5,6} These studies showed that the mapping technique was a powerful tool which could be applied to study arrhythmology.

Isochronal activation mapping

The preferred method of analyzing data obtained from the experiments described above, as well as others during this century, has been to create activation maps. To create these maps, recording sites are spatially distributed in grid-like manner to cover the area of interest, and an activation time is determined for each waveform, usually by visual inspection. The time of activation of each recorded electrogram is considered the temporal moment when the electrical wavefront is directly below the recording site. The individual activation times may be grouped into 10 or 20 msec intervals, according to their relation to a reference time. These times are written on a map showing the relative location of each site on the heart surface. Closed contours inscribing the sites grouped within each time interval are created; the result is an isochronal activation map which can describe the propagating wavefront spatially from beat to beat.

Figure 1 shows isochronal activation maps of reentrant activation induced by programmed premature stimulation (S_1 - S_2). The isochronal maps are presented as polar projections of the epicardial ventricular surface. The center of each map corresponds to the apex of the heart and the outer

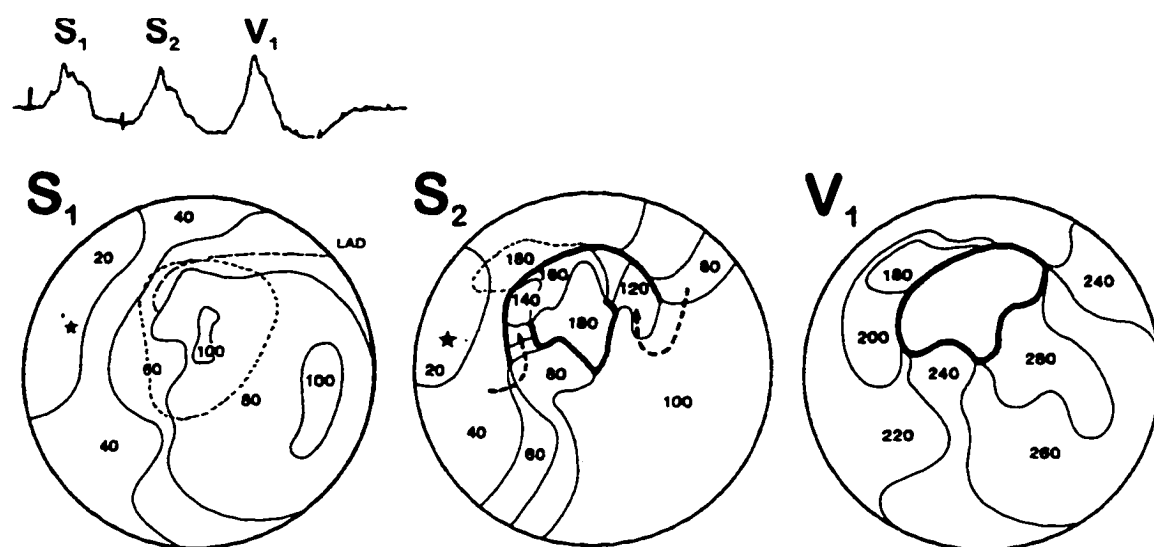


Figure 1. Isochronal activation maps.

perimeter represents the atrioventricular annulus. As shown in the S_1 map, the left anterior descending artery (LAD) is depicted by the dashed line, which originates at the two o'clock position on the map, and the apical left ventricular surface originates below the line. The surviving epicardial layer overlying the infarct is contained within the dotted line, shown in the S_1 map. Stars denote the stimulation sites. A Lead II electrocardiogram (ECG) is shown at the top of the figure.

During regular pacing (S_1) at a rate of 380 msec, there is no evidence of conduction block and the heart activates within 100 msec. As shown in the middle map, a premature stimulated beat (S_2), at a coupling interval of 180 msec, gave rise to an unstimulated beat, V_1 . Within 40 msec, the S_2 activation wavefront encountered an arc of functional unidirectional conduction block. The arc is demarcated by the heavy line in the S_2 map. Two circulating wavefronts traveled clockwise and counterclockwise around the arc of conduction block, joined distal to the arc and conducted slowly through the ischemic region. The common reentrant wavefront reexcited a region on the proximal border of the arc 180 msec later. The difference in activation time across the arc, in the region of reactivation, was 120 msec and the impulse could reenter, creating the V_1 beat. A single reentrant response was elicited and terminated after one beat.

Isochronal activation maps allow investigators to study the mechanisms of a number of important arrhythmias. For example, it was possible to differentiate various types of ventricular tachycardia, a potentially lethal

arrhythmia in which the ventricles activate more than 200 times per minute, much higher than the normal rate of 72 beats/minute. Mapping showed that in some instances, an irritable foci was responsible for the arrhythmia, abnormally initiating the activity at each beat.⁷ On other occasions, a circus movement reentry could be shown to be responsible, with activation continuously circulating around an arc of tissue blocked from activating.⁸

As the understanding of the mechanisms of arrhythmias developed, mapping experimentation grew in complexity to answer questions or to clarify issues. For example, the number of electrodes required for adequate whole heart mapping was significantly beyond the scope of pre-computer-based recording systems. The need for simultaneous recording sites was evident, as studies showed that beat-to-beat variations in heart beats could vary greatly. The quality of recordings also became an issue, since certain electrical events occurred more quickly than recordings systems could capture. Before the aid of computers and digital technology, researchers pushed the limits of analog recording methodology to 14 simultaneous recording channels.⁹

Develop a computer-based mapping system

Even as computer-based mapping systems appeared in the 1970s, the requirement of the number of simultaneous recording sites continued to outstrip the reaches of technology. In order for data to be recorded

simultaneously from hundreds of sites, multiplexed systems are a necessity. Each of these sites must have correct amplification and low noise characteristics. The digitized data obtained can be massive, and special requirements to transfer and store data are required. For example, if 500 recordings sites sampled at 2,000 samples/sec at 16 bit resolution are made for 10 sec, the file size would be 20 megabytes. In the course of an experiment, dozens of such recordings may be obtained, and 1 gigabyte of data must be obtained, stored, and retrieved.

Analysis of large amounts of electrographic data also presents a formidable challenge. There are currently several methods employed to analyze mapping data, though none of them is considered ideal. They may be divided into two classes, real-time and off-line analysis. With real-time analysis, the collected data is analyzed by algorithms designed to assign accurately the moment of activation time to individual electrograms, and plot the results in a graphic display in a manner which allows for rapid discernment of the temporal and spatial distribution of the analyzed electrograms. This type of analysis is particularly important in the clinical setting when rapid interpretation of map-guided therapy of serious arrhythmias is performed. There are two main problems with this technique: there is no standard application that allows practical comparison between electrophysiology laboratories, and the algorithms used to assign activation times have not proven accurate.

Manual analysis of mapping data, though more tedious, allows greater time to understand and appreciate the complexities of electrogram waveforms. While algorithms may be employed to assign activation time on a first-pass basis, each electrogram assignment is checked visually and in relation to its neighbors or other features to improve accuracy of the activation time assignments. This method is employed most often in basic science electrophysiology laboratories, where accuracy and understanding of the nature of arrhythmias is preferred over speed. There are, however several problems with this approach: 1) the analysis can be very slow, especially as the number of recording sites increases; 2) the assignment of activation time may be biased by individual users, making accurate reproducibility of results by other laboratories difficult, if not impossible; and 3) the algorithms used to assign activation time remain inadequate, whether performed by computer or by man.

Other problems to address in developing a computer-based mapping system deal with data sets, flexibility issues, and cost/performance analysis. Data can come from human hearts or animal models and an ideal system must be quickly able to adapt to the different sets. For example, electrograms recorded from rat hearts have several significant differences in their feature set, based on size and ion channel composition. Also, mapping of different pathologies creates differences in the feature sets of electrograms, as in the case of mapping hearts with ischemic heart disease showing many

low-amplitude fractionated waveforms, hearts with no structural heart disease, or hypertrophic hearts, which have much larger amplitude electrogram sets.

Flexibility issues arise on several levels. One problem occurs when one wishes to allow a mapping system to be used by several laboratories for basic or clinical use. Laboratories have differing technical support facilities, with varying degrees of support, ranging from computer science or electrical engineering departments at university-based labs, to those with little or no technical support at smaller hospitals without academic affiliation. Therefore, the ideal system should be user-friendly, allowing for changes to be made by researchers, life scientists and clinicians who are not computer scientists. To address this issue, a question of primary concern is whether to build a system based solely on programming and custom-built hardware, or integrate a liberal use of off-the-shelf software and hardware to construct the system. Another flexibility based issue deals with the upgradability of the ideal system. As improved hardware becomes available, design considerations should allow them to be easily implemented. As improvements in software become available, particularly algorithms for determining activation time, these too, should be implemented rapidly and easily in the ideal mapping system. It is of concern for investigators to be able to implement different algorithms because they may improve the analysis of electrograms.

The ideal mapping system must address a cost/benefit/performance analysis. Some current commercial mapping systems cost more than \$200,000. These systems are closed-architecture systems, with less than optimal upgradability characteristics (for example, they are severely limited by the number of channels available for recording), and there is no allowance for upgrading activation time algorithms as these are discovered in the scientific community. In other cases, some hardware may have poor “mean time between failure” specifications, which results in significant down-time and repair costs. In the current clinical setting, hospitals charge between \$1,500 and \$5,000 for services employing mapping systems. These amounts may decrease if innovative and improved mapping systems are utilized which have significantly lower cost.

Given the issues discussed above, one of the primary goals of this dissertation is to develop a computer-based mapping system that could:

- a) perform state-of-the art mapping experiments, in terms of simultaneous data acquisition of hundreds of recording sites,
- b) provide accurate and reproducible analysis of waveforms,
- c) allow for rapid interpretation of electrograms utilizing algorithms based on sound biophysical theory and empirical analysis,
- d) be easy to use so that nontechnical investigators could use the system,

- e) be upgradable to incorporate and test new findings,
- f) be cost effective, to reduce the financial burden on society.

Activation time analysis of epicardial electrograms

The delineation of activation time of individual electrograms is of crucial importance to perform accurate isochronal activation mapping. Electrograms recorded from each electrode site can often show bizarre, long-lasting waveforms, making it very difficult to determine time of activation, which can occur only once for each beat for each electrogram.

The assignment of activation time is further complicated by the recording methodology. The two principal modes of recording are unipolar and bipolar configurations. With unipolar electrodes, one electrode is situated close to the area of interest, and the other is placed far from the area, usually on the right leg, or on the right side of the chest.¹⁰ With this arrangement, the difference in voltage between the two recordings produces a waveform in which the common electrical noise influence is subtracted by the differential amplifier. The unipolar electrode on the heart is said to have a large electrical “view”, and the recorded potential may be as high as 50 mV. On the other hand, bipolar recordings have two electrodes placed in close proximity to each other, perhaps only 0.5-5 mm apart, and when the differential between the two sites is taken, a local, smaller waveform is produced, usually only a few millivolts in amplitude.¹¹ Both recordings

modes have strengths and weaknesses in their analysis, and explanations on the comparisons of each recording are not well understood. While there has been considerable work in biophysical theory to explain the genesis of the unipolar electrogram,¹²⁻¹⁴ fewer research studies have been performed to explain bipolar recordings.¹⁵ In both cases, little or no work has been completed which investigates both modes in pathological settings.

Most efforts at assigning activation time of electrograms are based on two methods: visual inspection, and computer-based assignment based on algorithms deduced by partial theoretical explanations or empirical findings. Visually inspected assignment of activation time is considered an inferior approach to this problem because of the inherent bias and large error that is possible. In addition, the issue of reproducibility raises much concern. Computer-based assignment of activation time significantly reduces the issue of reproducibility, but questions arise as to how closely the algorithms employed represent sound scientific findings. In the unipolar mode, the maximum negative temporal derivative has been shown to correlate closely in time to the maximum upstroke of an action potential elicited by a cell in close proximity to the recording site.¹⁶ This is true mostly for unipolar waveforms which are categorized as uniphasic and come from normal tissue. Besides this determinant, algorithms for activation time are based on features which are only loosely based on scientific grounds.¹⁷⁻²¹ A second goal of this study was to develop a set of more strict guidelines for assigning

activation time to both the unipolar and bipolar modes of electrogram recordings from normal cardiac epicardial sites.

Statistical analysis to assign activation time in ischemic unipolar electrograms.

Clinical electrophysiologists routinely perform mapping procedures on patients to understand the cause of arrhythmias and prescribe corrective therapy. As the complexity of mapping systems has grown, there is currently a need to perform real-time analysis of the recorded electrograms so that arrhythmias can be understood as quickly as possible. To highlight this issue, consider the simulated case of a patient with recurrent ventricular tachycardia. The patient is taken to an operating room, where a sternotomy is performed to expose the heart. The electrophysiologist then places a sock with 128 bipolar electrodes over the epicardial surface of the ventricles, and performs programmed electrical stimulation to induce the ventricular tachycardia. Once the arrhythmia is induced, recordings are obtained for analysis. The arrhythmia must be quickly terminated, because in many cases, the blood pressure falls dangerously low due the reduced cardiac output caused by the inefficiency of the activation sequence. The electrophysiologist wants to analyze quickly the electrograms in an attempt to localize the “site of origin” of the arrhythmia. This site can then either be surgically resected or be ablated by radiofrequency energy. This situation

points to the need for rapid analysis of the waveforms, a situation ideally suited for a computer-based algorithm based on sound electrophysiologic principles.

There are numerous electrogram features which may be extracted to assign activation time and be combined into an algorithmic form. Examples include the maximum negative temporal derivative of a unipolar electrogram,²² or the absolute voltage maximum of a bipolar electrogram.¹⁷ The current approach has been to apply only one or two features based mainly on trial and error, and is clearly in need of refinement. Few studies have been able to employ an appropriate standard of activation time from which the accuracy of different features in various settings could be statistically assessed. The third goal of this study was to develop a model that created a measurable technique for assessing the error rate of several electrogram features, and combine them into a discriminant function model to optimize the selection of electrogram features that minimized the error when compared to a reliable standard of activation time.

Activation-recovery time analysis of transmural electrograms

Polymorphic ventricular tachycardia is an extremely serious arrhythmia, and if not treated quickly, is usually lethal. This arrhythmia may be

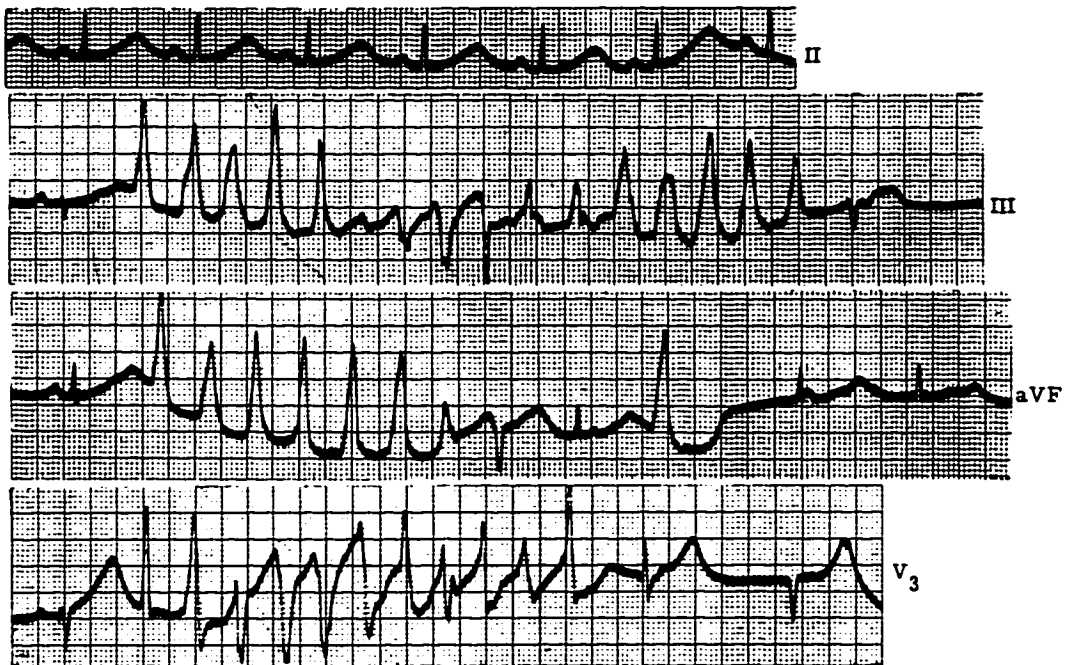


Figure 2. Torsades de Pointes arrhythmia. (From: Goldman, M.J. Principles of Clinical Electrocardiography. California: LANGE Medical Publications, 1982.)

congenital, idiopathic, or acquired, and is marked on the surface electrocardiogram by nonuniform wide-complex QRS complexes with a rate greater 200 beats/minute. Sometimes the surface QRS pattern is of a curious, twisting form, and is termed Torsade de Pointes (TdP). An electrocardiographic example of TdP from a patient taking excessive doses of quinidine is shown in Figure 2. The QT interval during sinus rhythm in the top panel is prolonged (corrected QT >0.6 sec), and lower panels show the spontaneous onset of short runs of polymorphic ventricular tachycardia. Note the polarity changes of the tachycardia in lead III, which is consistent with the TdP arrhythmia. Reports recently published by molecular biologists describe several human gene disorders in families with either dominant or recessive Long QT Syndrome, ^{23,24} a high risk marker of TdP. One reported human gene mutation of the sodium channel has kinetic effects, ²⁵ which bear strong resemblance to sodium channels exposed to sea anemone toxin Anthopleurin-A, used in our laboratory in a canine model to induce bradycardia dependent TdP and study its mechanisms in vivo. ²⁶

Polymorphic ventricular tachycardia may also be caused by antiarrhythmic drugs (e.g., quinidine, d-sotalol) exhibiting a dangerous proarrhythmic effect in a certain number of individuals. ²⁷ The mechanism(s) of this acquired arrhythmia is under intense investigation, and one hypothesis is that the initiation of TdP is dependent upon a steep regional difference in the recovery time of myocardial cells from an activated state. ²⁸ On the surface electrocardiogram, the recovery from activation is seen as the T wave, a low

frequency waveform observed following the QRS complex. It is also clearly seen on electrogram recordings from the surface or within the heart muscle, and is termed a local T wave.²⁹ The activation-recovery interval electrogram approximates the electrocardiographic QT interval, defined as the time interval between the onset of the QRS complex and end of the T wave.

There are several techniques that have been utilized to investigate the activation-recovery properties of hearts in which models of polymorphic ventricular tachycardia were created. These include monophasic action potential (MAP) recordings,³⁰ optical recordings of cardiac slices,³¹ and transmural electrogram recordings.³² Of these, only the latter technique has the tridimensional spatial resolution to analyze accurately the genesis, perpetuation, and termination of this arrhythmia in vivo.

There are, however, many issues that need to be addressed before activation-recovery analysis of transmurally recorded electrograms matures as a respected technique. Analysis of local T waves has only been performed in the unipolar mode on epicardial surfaces, and while studies have shown that in many instances, the maximum positive temporal derivative of the T wave coincides closely with the duration of an action potential recording in close proximity to the unipolar site,^{29,32,33} it is not known whether this accuracy of measurement holds for transmural recordings. Theoretical work by Steinhaus on computer modeled recovery potentials showed that analysis of unipolar recordings of activation-recovery intervals can be affected by

nonuniform coupling resistance and nonuniform membrane properties.³⁴ Furthermore, little work has been performed to study the relation of bipolar versus unipolar recordings obtained transmurally. The effect of electrotonic interaction³⁵ on recordings have also not been addressed. Therefore, the fourth goal of this study was to investigate the accuracy and usefulness of activation-recovery intervals obtained transmurally by extracellular unipolar electrograms in an in vivo model of polymorphic ventricular tachycardia.

Summary of goals

To summarize, the goals of this dissertation was to:

- 1) develop a computer-based mapping system that could perform state-of-the art mapping experiments in terms of data acquisition, accurate and reproducible analysis of waveforms, real-time interpretation of electrograms, ease of use, upgradability, and cost effectiveness;
- 2) develop a set of more strict guidelines for assigning activation time to both the unipolar and bipolar modes of electrogram recordings from normal cardiac epicardial sites;
- 3) develop a model that created a measurable technique for assessing the error rate of several electrogram features, and combine them into a discriminant function model to optimize the selection of electrogram features that minimized the

- error when compared to an appropriate standard of activation time in an ischemic model;
- 4) determine the accuracy and usefulness of activation-recovery intervals obtained transmurally by extracellular unipolar electrograms in an in vivo model of polymorphic ventricular tachycardia.

Chapter III . Current status of work in the area

Introduction to cardiac electrophysiology

The cardiac action potential

Myocardial cells belong to a class of cells known as excitable cells. ³⁶

These cells consist of a bilipid membrane layer which surrounds the nucleus and cytoplasm. The bilipid layer consists of 2 layers of phospholipids arranged with the hydrophobic ends facing toward each other, and the hydrophilic ends facing away from the membrane, either toward the cytoplasm on the inside of the cell, or toward the interstitial fluid on the outside of the cell. Figure 3 provides a drawing of the bilipid layer. The electrical characterization of the bilipid layer is that of a capacitor, storing charges on either side of the membrane. Interspersed throughout the bilipid layer are thousands of membrane-spanning pores or channels, each one with selective gating permeabilities allowing different ions to pass through the membrane. Channels are classified as voltage-gated or ligand-gated, which describes the action that activates or opens the channel. The channels consist of proteins, and have special properties and kinetics which uniquely characterize their behavior. ³⁷ Ions such as sodium, potassium, calcium, and chloride each have associated channels that selectively allow them passage at

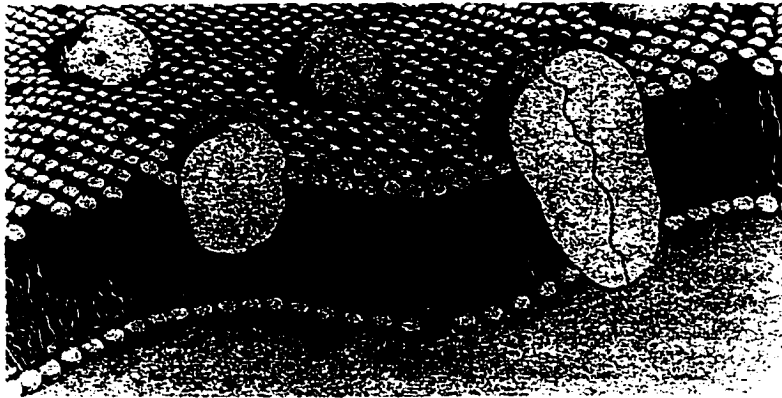


Figure 3. Cell membrane model showing proteins embedded in the phospholipid bilayer. (From Singer SJ: Architecture and topography of biologic membranes. In: Weissman, G, Clairborne R (eds): Cell Membranes, Biochemistry, Cell Biology, and Pathology. New York, HP Publishing Co., 1975, pp. 35-44.)

different rates, different times, and with different kinetics. The concentration differences of ions on the inside with respect to the outside of cells, combined with the ability of the membrane to store and release charge, establish the fundamental conditions required for cell excitability, signaling, and electrical propagation of potential. A brief and general description of cardiac cellular electrophysiology is given below.

The resting potential

The action potential is a recording of a cell's electrical activity as it passes from its resting state to its active state, and cycles back to the resting state. Electrophysiologists have classified the cardiac action potential into 5 phases, from *phase 0* to *phase 4*. Three drawings of action potentials from different cardiac regions are shown in Figure 4. Panel A shows a ventricular muscle action potential, while Panel B shows an action potential of a sinus node, and Panel C shows a Purkinje fiber action potential. To record an action potential, a thin ($\sim 0.5 \mu\text{m}$), hollow, glass microelectrode filled with 3 M KCl is pressed against the cell membrane until it just pierces through the membrane. A chlorided silver wire in the KCl solution is connected to a high impedance amplifier which measures the intracellular potential and referenced to a wire in the solution containing the cell. During the resting state, the recording of a typical ventricular myocyte shows a transmembrane potential of about -90 mV, meaning that the inside of the cell is negative by 90 mV with respect to the outside of the cell. Many experiments have shown

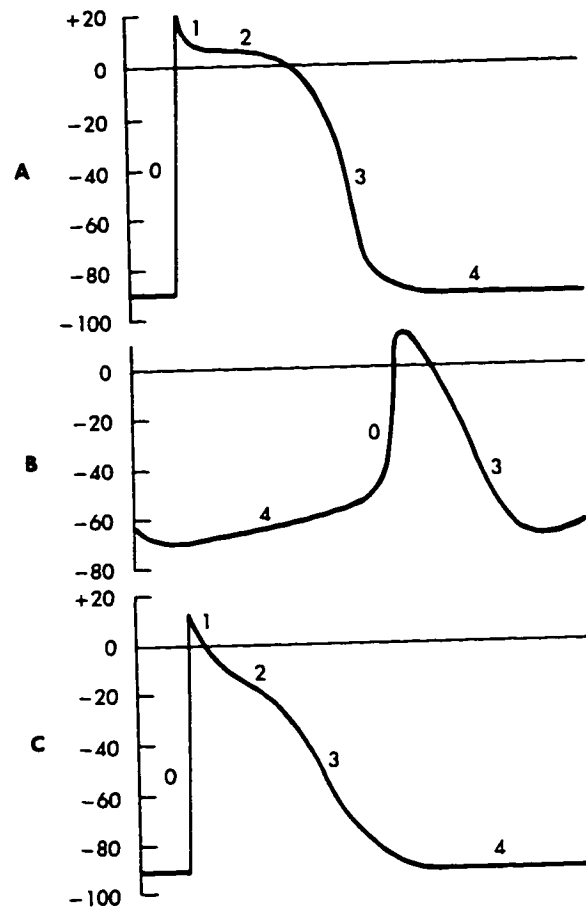


Figure 4. A, typical ventricular muscle action potential; B, sinus node action potential; C, Purkinje fiber action potential. The ordinate is in millivolts. (From Berne R, Levy MN: Physiology. St. Louis, C. V. Mosby Co., 1983.)

that the resting membrane voltage is due primarily to the concentration difference of potassium, which is well described mathematically by the Nernst equation.³⁶

In the human heart, typical normal values for the electrolytes sodium and potassium are:

Table 1 Electrolyte concentrations for human heart

Electrolyte	Outside mM/liter	Inside mM/liter
Sodium (Na)	140	25
Potassium (K)	3.8	150

The Nernst equation states that transmembrane voltage potential is related to the ion concentration differences between the inside and outside of the cell by:

$$V_{ion} = \frac{RT}{F} \ln \frac{[Ion]_o}{[Ion]_i} \quad \text{where } V_{ion} \text{ is the transmembrane voltage, } R \text{ is the}$$

universal gas constant, T is the absolute temperature, F is the Faraday constant, $[Ion]_o$ and $[Ion]_i$ are the concentrations of an ion on the outside and inside, respectively. The Nernst equation, applied to sodium and potassium concentrations, yields voltages of +46 mV and -98 mV, respectively. If the conductance, g , of the membrane of these two ions is known and taken into

account, a ratio can be determined and calculation for the combination of ionic concentrations can be found by:

$$V_{\text{membrane}} = \frac{RT}{F} \ln \frac{[K]_o + g_{Na} / g_K [Na]_o}{[K]_i + g_{Na} / g_K [Na]_i} = -90mV$$

which is known as the equilibrium, or resting potential. The conductance ratio of g_{Na}/g_K at highly negative voltages has been shown to be between 0.01 and 0.05. Other experiments in which both sodium and potassium ions have been replaced were performed to show that this relation is also valid experimentally. These experiments show that the resting potential is close to the potential of potassium, and in fact, experiments have shown that potassium is primarily responsible for maintaining the resting potential.³⁶ The differences between the predicted potential due solely to potassium and the resting potential are due mainly to the activities of the Na/K pump, an active process which pumps out 3 Na ions in exchange for 2 K ions, and other ions such as chloride, which are mildly active during the resting state.

Depolarization of the membrane-Phase 0

When the cell membrane is stimulated so that the membrane potential rises to about -50 mV, the stimulus threshold is said to have been reached, and the conductance of sodium rises dramatically, causing a change in the transmembrane voltage to jump to about +20 mV in only a few milliseconds. The depolarized membrane discharges its stored voltage, facilitating an increase in sodium conductance by way of a positive-feedback mechanism.

This event is termed phase 0, when the membrane is depolarized by the rapid influx of sodium, and the action potential recording displays a sharp upstroke. Phase 0 is crucial to both the initiation of the mechanical contraction process required to pump blood, and the conduction process of activating neighboring cells, thus creating an energy-efficient process which allows all the cells in the heart to contract as a syncytium.

An interesting kinetic property of sodium channels is the rapid opening of the channel, called the open state, followed by an equally rapid closing of the channel, termed the closed state. Once the sodium channel closes, it becomes inactivated (inactivation state), and cannot be reopened for about 100 ms, when the channel returns to the resting state. Experiments on the kinetics of channels have been made possible by the patch clamp technique, which makes possible the investigation of either whole cell or single channel currents on an individual basis.³⁷

Transient and early repolarization-Phase 1

Just after depolarization, when the recorded action potential is at the peak of the upstroke, the transmembrane recording quickly and transiently shows a negative-sloped deflection settling at a range of 0 to +20 millivolts. This activity is primarily due to the closing of sodium channels, and also to the transient opening of an outward potassium channel, termed I_{to} , for transient outward current. A discrete notch marks the end of this phase and the beginning of the next.

The plateau-Phase 2

One of the striking differences between action potentials recorded from myocytes and other excitable cells is the consistently prolonged phase 2 plateau seen in recordings. The plateau is suspended between 0 and -20 mV for about 100 msec, and is due to a variety of ionic mechanisms that activate during this period. A balance between inward “slow” sodium channels, which do not close quickly like the predominant “fast” sodium channels, and outward flow of calcium ions, due to conductance increase in calcium channels which rise at membrane voltages > -40 mV, with the outward flow of potassium ions, which flow through several different channels, such as I_K , I_{K1} , I_{K-Ca} , and I_{K-Pl} , maintains the plateau. ⁷

Late rapid repolarization-Phase 3

The phase 2 plateau phase lasts for about 100 msec, and as the inward calcium current, I_{Ca} , begins to decrease, the action potential recording displays a rapid repolarizing, negative-slope deflection. Outward potassium currents contribute to the return of membrane potential back to the resting state.

In addition to the inward and outward currents described above which predominate in the voltage and time course of the action potential, there are several other currents which play a role. There are 2 pump currents, I_{Na-K} and I_{Na-Ca} , which also contribute to the action potential. The I_{Na-K} pump

extrudes 3 sodium ions in exchange for 2 potassium ions, creating a net outward current. On the other hand, the I_{Na-Ca} pump extrudes 1 calcium ion for 3 sodium ions, creating a net inward current, since a calcium ion contains 2 free electrons to sodium's 1 free electron. These pumps help to maintain the resting potential and the correct concentration relationships for proper function of the cell.

Resting membrane potential-Phase 4

The membrane potential remains constant during the diastolic interval for most cardiac cells, due to reasons discussed earlier. There are certain cells dispersed throughout regions of the heart, however, in which the resting potential does not remain constant during diastole. These include cells in the sinus node, His-Purkinje system, the muscle of the mitral and tricuspid valves, and the distal portion of the AV node. For these groups of cells, slow depolarization occurs during diastole, and if an impulse does not arrive within a normal time interval, they may fire action potentials spontaneously.⁷ The depolarization process is termed *phase 4 diastolic depolarization*, and if spontaneous action potentials are elicited, a condition known as *automaticity* develops. Abnormal automaticity will be discussed later in this chapter.

The role of ion conductance through the cell membrane in generating action potentials is extremely important in terms of understanding how pathology effects the excitability and functions of cardiac cells. Different

diseases effect the action potential in different ways, and electrophysiologists and pharmacologists can use this information to develop precise strategies to counteract abnormal properties. The electrophysiologist's approach has been to understand how diseases change what is occurring at the cellular level, the tissue level, and finally, at the organ level. With such a comprehensive approach, it will be possible to design accurate "magic bullet" strategies to target abnormalities which correct only what is required.

Effect of pathology on action potential shape and duration

In the pathologic state, various electrophysiologic properties of myocytes are altered, and are dependent upon the type, organization, and extent of the disease. One method electrophysiologists use to investigate how disease alters cellular electrophysiology is to conduct experiments to measure the changes of action potential shape and duration. These changes are classified according to the manner in which the action potential is effected, and are considered to be possible mechanisms underlying arrhythmias. These changes are briefly presented here to help to explain the cellular origin of arrhythmias.

Automaticity is the property of spontaneous impulse formation, and may be divided into four subsets: normal, enhanced, abnormal, and triggered. In normal automaticity, depolarization occurs in sinus node fibers during phase 4 due to a slow inward Na current, I_f , which initiates rapid depolarization (phase 0), after the membrane reaches threshold potential. In enhanced

automaticity, a number of changes can change the rate and site of firing, including the maximum diastolic potential, the rate of phase 4 depolarization, the threshold amplitude, and the action potential duration. A significant increase in outward K currents hyperpolarizes the cell, increasing the maximum diastolic potential. This may lead to a slower automatic rate, as it now takes longer for the cell to reach threshold, except that with increased K currents, the action potential duration shortens, giving I_f more time to depolarize the membrane. Both of these effects act to shorten the automatic rate.

Abnormal automaticity results when cells remain partially depolarized and is generally attributed to disease. Both atrial and ventricular cells can become automatic and begin firing action potentials spontaneously, which disrupts the normal propagation process. Hypoxia or low pH, both of which occur during ischemic attacks, can provide the substrate for a change in decreased membrane potential, making it easier for cells to reach threshold and spontaneously fire action potentials.

Triggered activity is an abnormality which describes abnormal activity occurring during the plateau or repolarizing phases, termed early afterdepolarizations³⁸ (EAD, Figure 5), or just after repolarization, termed delayed afterdepolarizations (DAD).⁷ The EAD abnormality is due to a net increase in inward current which disrupts the repolarization process, as shown in Figure 5, and may force the cell to prematurely fire action

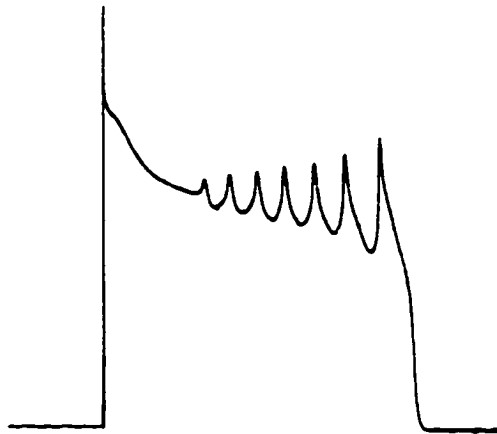


Figure 5. Early afterdepolarization (Adapted from reference 26.)

potentials.³⁸ This could be caused by a reduction in outward K currents, an increase in inward Na or Ca currents, or a combination of both. An EAD is seen as a series of one or more humps during phase 2 or phase 3 in action potential recordings. DADs are generally believed to be caused by an intracellular overload of Ca, and in turn lead to repetitive release of Ca stores in the sarcoplasmic reticulum organelle located inside each myocyte. The result is an inward depolarizing current which is recorded as a series of one or more humps during phase 4.⁷

Finally, diseases can cause a disruption in the upstroke of an action potential, by blocking the conductance of sodium channels, which leads to a block of action potential formation or a reduced upstroke when an action potential does occur in this setting. In other cases, the Na channels may fail to inactivate completely as they normally do within several milliseconds, leading to a prolongation of the action potential and an extended refractory period, the interval when a cell can not elicit an action potential. In fact, all channel, receptor and pump abnormalities can play an important role in the formation of arrhythmias, and remain the subject of intense scientific investigation.

Propagation of the cardiac action potential

Passive electrical properties

The ability of cells, which undergo changes in membrane voltage, to transmit current to neighboring cells, thus forming an activation wavefront, is due to the passive electrical properties of the cell membrane. The simplest model of conduction is known as the *core-conductor theory*,³⁶ which describes the activation process of a single fiber as a poorly insulated cable in mathematical terms. Consider a current elicited through a part of the membrane of a single fiber. This creates a voltage (V_o) at that point, and the voltage across the membrane at some distant point x (V_x), will vary with time t , since the membrane behaves as a capacitor. The core-conductor theory predicts how the voltage varies with x and t , assuming that the system is stable and is infinitely long. Figure 6 is a diagram of this circuit model.

The transverse current, i_m flowing through the membrane is equal to the sum of currents flowing through the resistances of the membrane, r_m , and the membrane capacitance, c_m :

$$i_m = \frac{V}{r_m} + c_m \frac{dV}{dt} .$$

The current flowing in the longitudinal direction faces

resistance from the external medium, r_o , on the outside of the membrane, as well as resistance from the cytoplasm on the inside of the membrane, r_i . This current can be described as:

$i = \frac{dV}{dx} \left(\frac{1}{r_o + r_i} \right)$, and since the current gets smaller as the distance gets

larger, $i_m = -\frac{d_i}{dx}$. Therefore, with substitution of i , one finds:

$i_m = \left(\frac{1}{r_o + r_i} \right) \frac{d^2V}{dx^2}$. Equating the first equation of i_m with the last, one gets:

$\frac{V}{r_m} + c_m \frac{\partial V}{\partial t} = \left(\frac{1}{r_o + r_i} \right) \frac{\partial^2 V}{\partial x^2}$, which can be rewritten as:

$V = \left(\frac{r_m}{r_o + r_i} \right) \frac{\partial^2 V}{\partial x^2} - r_m c_m \frac{\partial V}{\partial t}$. Two substitutions are made, namely:

$\lambda^2 = \frac{r_m}{r_o + r_i}$, and $\tau = r_m c_m$, where λ is called the space constant, and τ is

termed the time constant. The equation above can be rewritten above in a

usable form: $V = \lambda^2 \frac{\partial^2 V}{\partial x^2} - \tau \frac{\partial V}{\partial t}$. The complete solution to the equation above

requires the use of several transform methods that are not addressed here,

however, some simple important solutions can be understood. For example,

for the case where a constant current source has been applied for a long time

(approaching infinity), the equation reduces to $V = \lambda^2 \frac{\partial^2 V}{\partial x^2}$, and the relevant

solution is $V_x = V_0 e^{-\frac{x}{\lambda}}$. This means that the voltage across the membrane falls

off exponentially with distance from the current source. If one makes $x = \lambda$,

the solution simplifies further to $V_x = V_0 e^{-1}$; λ can now be defined as the

length over which the voltage drops to 1/e of its initial value.

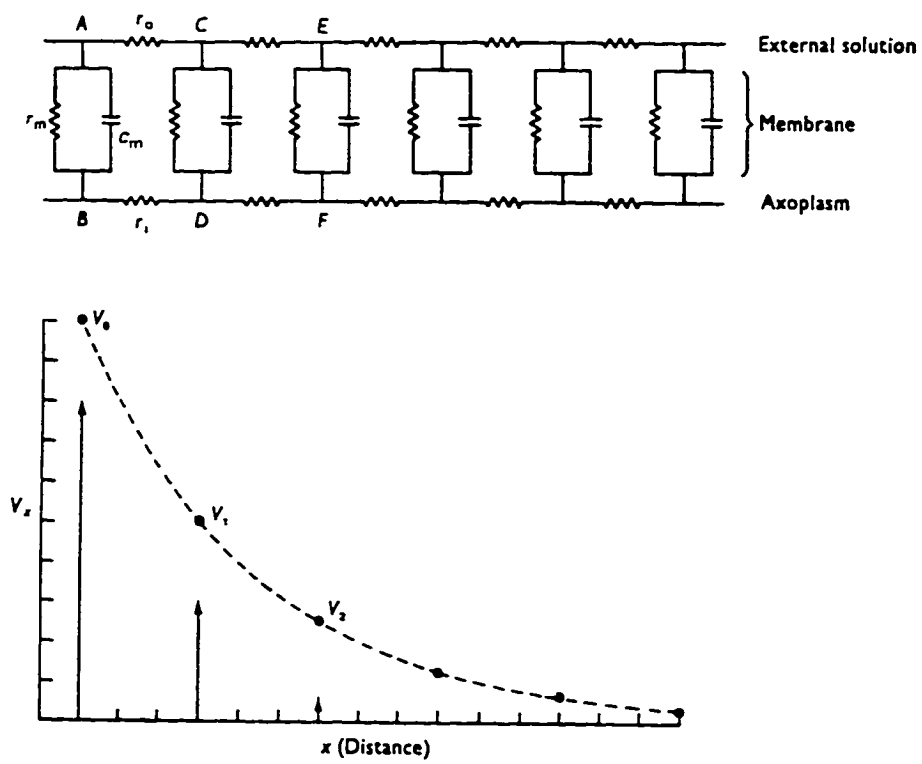


Figure 6. Equivalent circuit for core-conductor model

The core-conductor model, shown in Figure 6, has been shown to be fairly accurate in the experimental setting for both nerve fibers and cardiac muscle fibers. It has also proven useful in that it allows electrophysiologists to view the tissue as an electrical circuit consisting of an infinite number of cells in a parallel arrangement, each with an r_m and c_m in parallel (see Figure 6). The inclusion of the resting potential simply requires the placement of a battery in series with r_m .

Local circuit theory

Using the information based on the core-conductor model, it is possible to understand how an action potential propagates to neighboring cells. This model is diagrammed in Figure 6. If a small section of a cardiac muscle fiber is stimulated with current which is above the stimulus threshold, an action potential develops in that section. If an assumption is made that V_0 is about 4 times greater than the membrane voltage, the potential across CD will now rise towards the point V_1 . But before reaching V_1 , this section reaches the stimulus threshold and then fires an action potential at this section too. The next section at EF, initially moving toward the potential V_2 in response to the initial potential V_0 , now moves higher toward V_1 , and it too, reaches action potential threshold. In this manner, action potentials propagate from section to section, and continue to do so at constant velocity so long as there are no other changes in this simple system. This local circuit theory, first proposed by Hermann ³⁹ in the beginning of this century, was so named because

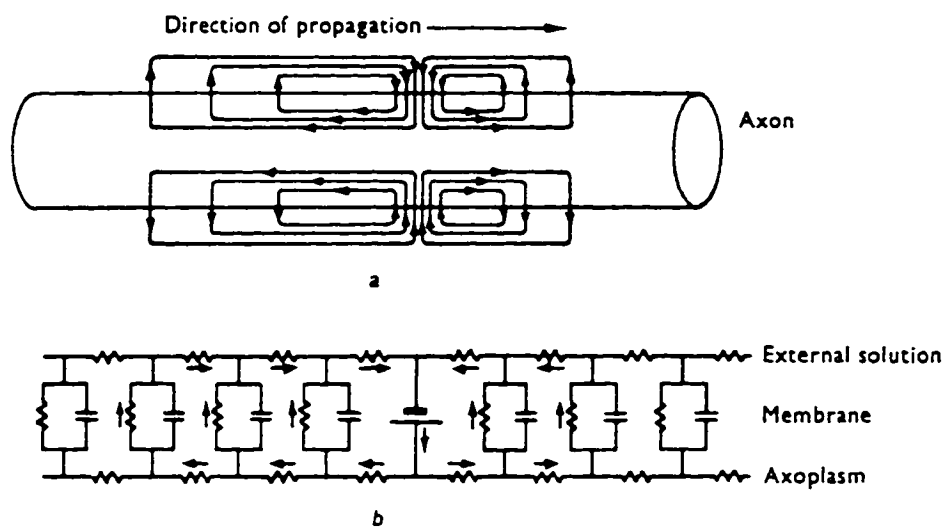


Figure 7. Description of propagation of current based on local circuit model

propagation relies solely on the electrotonic currents flowing across the membrane occurring just in front of the action potential.

Figure 7 depicts in more detail how the propagation process unfolds. Firstly, propagation of an impulse requires an inward current, i.e. sodium influx, to establish the passive electrotonic current flow during the upstroke of the action potential. The current flow is from negative to positive, and thus represents the flow inside a battery. The electrotonic current flows from positive to negative. While this one dimension core-conductor model is a useful representation of propagation and has been validated by a number of isolated fiber experimental studies, a number of assumptions have been made which render this analysis inappropriate for 2-dimensional or 3-dimensional structures. For example, resistances r_o , r_i and r_m are all assumed to be constant, and clearly this is not the case for most cardiac tissue structures. The model also assumes there are no discontinuities, and radial resistances in the interstitial fluid and in the cytoplasm are ignored. However, it offers a basic description of propagation based on the passive, electrotonic properties of cellular electrophysiology, and has served as a guide toward understanding how electrographic recordings obtained some distance from the action potential sites can be analyzed. A more useful manner to view current flow is shown in Figure 8. The basis for this drawing is the fact that conduction occurs through membrane-spanning channels,

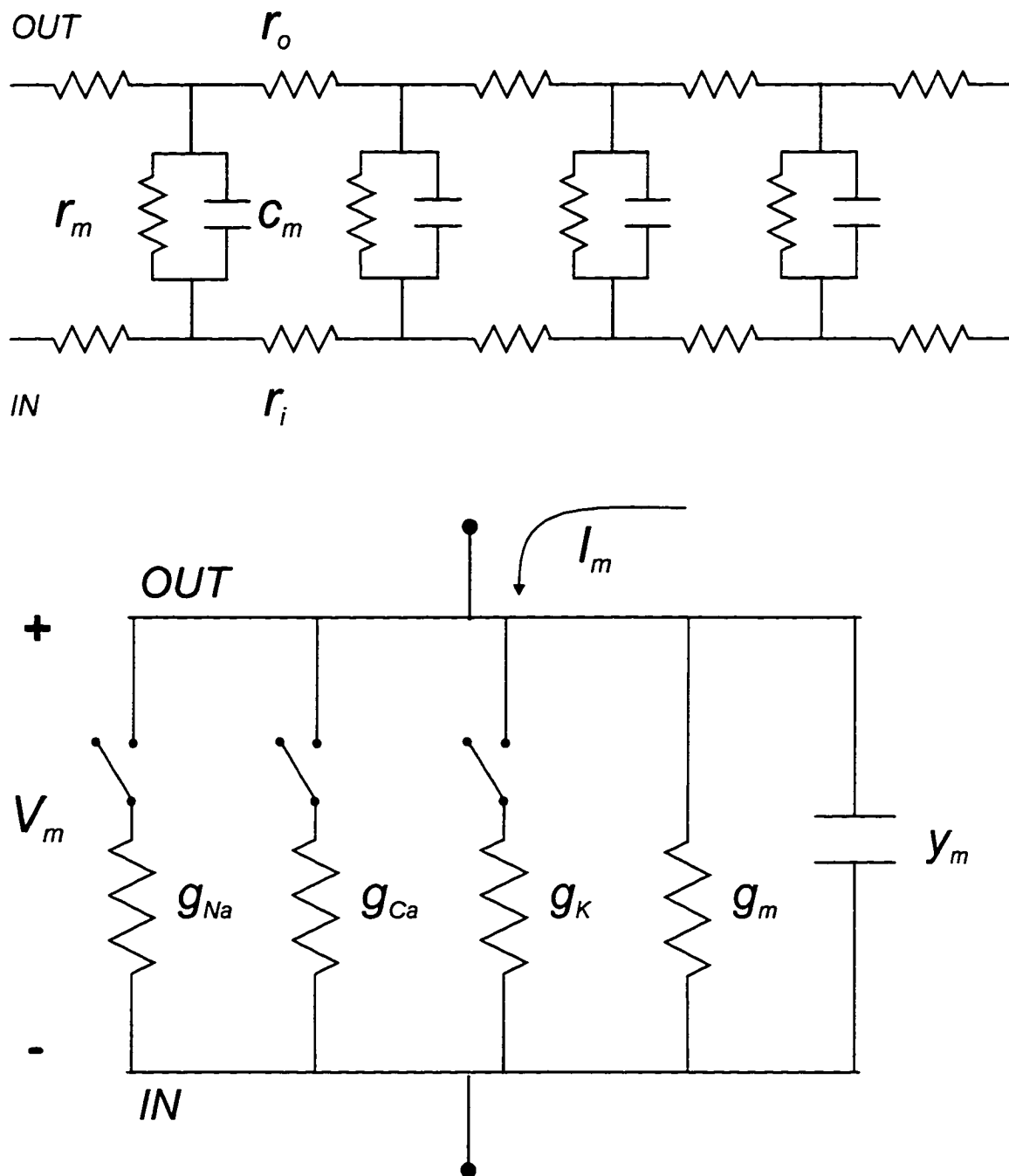


Figure 8. Active membrane circuit diagram

each having unique conductance properties and dynamics. In this graphic, the conductances of Na, Ca, K, and leakage (g_m) are indicated.

Conduction in the normal heart

Figure 9 provides a drawing of the specialized conduction pathways and their relative anatomic locations in the heart. In the normal beating human heart, excitation begins at a cluster of cells in the upper right atrium, termed the sinoatrial or sinus node. The sinus node has special electrophysiological characteristics that allow it to be the most the most easily excitable, and is largely invaginated by nerve endings from the autonomic nervous system. It can therefore control the heart's rhythm, acting as the heart's pacemaker. Propagation flows through specialized conduction fiber bundles to the atrio-ventricular node (A-V node), a superficial structure which is situated anterior to the ostium of the coronary sinus, and directly above the insertion of the septal leaflet of the tricuspid valve. The propagating impulse then passes into the ventricles. The first structure to activate is the Bundle of His, situated at the base of the right ventricle near the interventricular septum. Propagation then proceeds through the ventricles by way of the Purkinje fiber network, skirting down the left and right branches of the septum toward the apex, and then traveling upwards to the lateral walls. The Purkinje-muscle junction transfers the activation wavefront to the muscle cells, which comprise most of the mass of the heart. Action potentials from

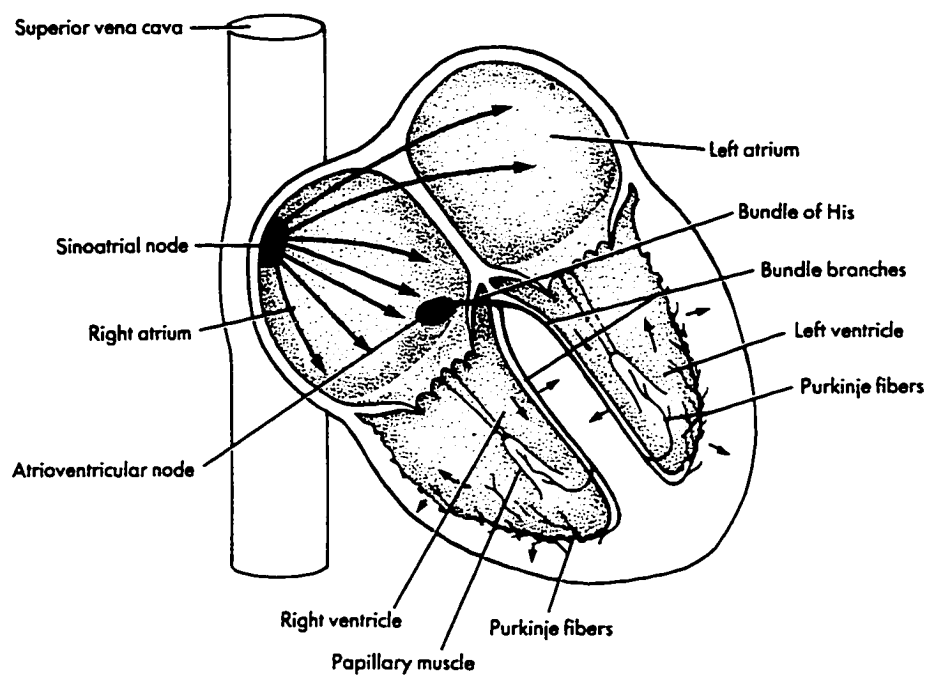


Figure 9. Heart with conduction anatomy. (From Berne R, Levy MN: Physiology. St. Louis, C. V. Mosby Co., 1983.)

muscle cells generally have slower upstroke, indicating slower activation properties, and longer plateaus, which indicates longer duration recovery from activation. Since the propagating wavefront starts from the Purkinje fiber network on the endocardial surface, the wavefront moves from the endocardial surface, through the midmyocardium, and finally activates the epicardial surface of the ventricles. Durrer et al.⁹ were the first to describe normal activation in humans by mapping with up to 72 intramural multi-electrode needles carrying 10 or 20 platinum terminals. Recordings were obtained by means of a 14 channel FM tape recorder connected to a switchbox which could connect up to 660 electrodes. This was the first study to identify propagation with whole heart mapping techniques. Heart beats which originate from the sinus node and follow a temporal and spatial spread of activation as described above is termed *normal sinus rhythm* (Figure 10, top panel).

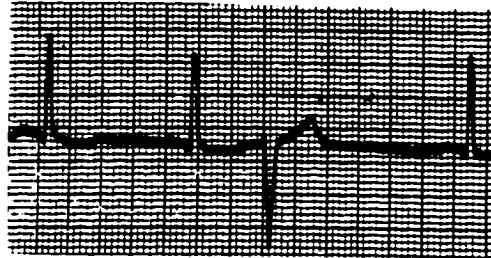
Cardiac conduction disturbances

Arrhythmias, the alteration of normal sinus rhythm, are classified into 3 general groups based on their anatomic origin: atrial or supraventricular, ventricular, and nodal. While atrial and nodal arrhythmias are generally non-lethal, they can cause reduced pumping of blood, and in the case of atrial fibrillation, can cause thrombus formation, leading to stroke. On the other hand, many ventricular arrhythmias can often be fatal if not treated

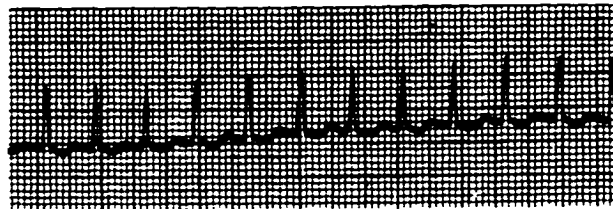
Normal
Sinus Rhythm



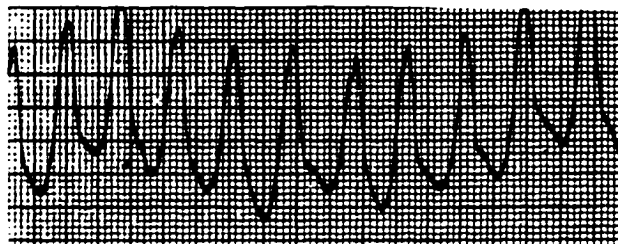
Premature
Ventricular
Contraction



Sinus
Tachycardia



Ventricular
Tachycardia



Ventricular
Fibrillation

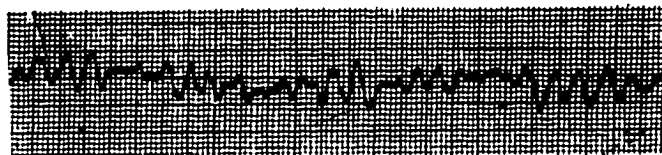


Figure 10. Normal rhythm and common conduction disorders recorded electrocardiographically. From top to bottom, sinus rhythm, premature ventricular contraction, atrial tachycardia, ventricular tachycardia, ventricular fibrillation. (Adapted from Berne R, Levy MN: Physiology. St. Louis, C. V. Mosby Co., 1983.)

promptly or correctly. Diagnosis and management of arrhythmias is an important subset of the practice of cardiology, and its complexities have lead to the creation of a subspecialty in cardiology termed cardiac electrophysiology. Many patients with arrhythmias experience symptoms such as palpitations or the feeling of “skipped beats”, shortness of breath, dizziness, or loss of consciousness. The cardiac electrophysiologist conducts a physical examination of the patient, and records the 12-lead ECG. If arrhythmias are suspected, a 24 hour ambulatory monitor may be ordered to obtain a long-term recording of the patients’ heart rhythms. Accurate diagnosis and selection of proper therapy of an arrhythmia can be confirmed by invasive electrophysiologic evaluation. Arrhythmias can be caused by anatomic changes produced by a progression of cardiac disease, functional disturbances in which the cellular electrophysiological properties are disrupted, drugs which detrimentally effect the heart, or by a combination of these problems.

Types of conduction disturbances

Supraventricular arrhythmias

Supraventricular arrhythmias include atrial tachycardia (Figure 10, middle panel), atrial flutter, atrial fibrillation, sinus tachycardia, paroxysmal supraventricular tachycardia, multifocal atrial tachycardia, and sinoatrial block. Diagnosis of each type of atrial arrhythmia can usually be made based on information from 12-lead ECG or ambulatory monitoring devices. The

electrical activity arising from the heart can be easily detected on the body surface as a vector summation producing unique waveforms. These waveforms are compared with the waveforms recorded at particular locations on the body surface, with particular attention to polarity, temporal relationship of neighboring waveforms, and amplitude. Years of empirical study combined with investigation of these arrhythmias by invasive and experimental procedures have resulted in a body of knowledge that provides good indicators for correct identification of these arrhythmias.

Therapeutic choices vary with the type arrhythmia treated, and are routinely classified as pharmacological, surgical or ablative, or use of electrical devices. In some cases such as atrial flutter, pre-excitation syndromes, or A-V nodal reentry, precise localization of the origin of arrhythmia is required to deliver targeted therapy.

Mapping techniques remain the foremost method of localizing the origin of arrhythmias. In the clinical setting, catheters with as many as 8 bipolar electrodes at and near the tip are inserted into the venous or arterial system, typically via cutdown incisions at the femoral or antecubital veins (for right heart mapping) or arteries (for left heart mapping). As many as 4 catheters are guided into the heart, with the proximal tips of the catheters situated on the endocardial surface, close to the area of interest. The distal catheter ends are connected to an electrocardiographic recording device. The catheter electrodes may also be used for programmed stimulation of the heart, which

is employed to induce the arrhythmia, or evaluate electrophysiologic characteristics such as refractoriness. The electrogram recordings obtained are then analyzed to reveal the origin or type of arrhythmia, and the clinical electrophysiologist can make proper management choices. ⁴⁰⁻⁴²

Nodal arrhythmias

Nodal arrhythmias include AV junctional escape beats, premature AV junctional complexes, AV junctional rhythm, nonparoxysmal AV junctional tachycardia, and AV nodal reentrant tachycardia. These rhythm disturbances may be diagnosed by 12 lead ECG or invasive electrophysiologic studies. Treatment of those arrhythmias which are considered detrimental can be performed by a variety of vagal maneuvers to terminate the arrhythmia on a short-term basis. Drugs, such as verapamil, digitalis, or propranolol can also be effectively employed to terminate these arrhythmias and prevent their occurrence. For arrhythmias resistant to these attempts, ablation of the AV node, followed by implantation of electrical pacing devices is a common, acceptable therapeutic choice. ⁷

Ventricular arrhythmias

Management of ventricular arrhythmias is particularly important because many types are potentially lethal. Arrhythmias with rates above 160 beats/minute may compromise the mechanical-contraction process, even in young normal adults, leading to reduced pumping action and ejection of

blood. In patients with cardiac disease, fast heart rates can be deadly. The faster heart rate produces a degradation of pumping action, precisely when the energy and oxygen needs of the heart muscle are substantially increased. As the heart muscle becomes starved for oxygen (hypoxia), leading to a condition known as *ischemia*, a positive feedback mechanism engages, in which the autonomic nervous system sends stimulating impulses to the heart in an attempt to reduce ischemia and increase blood flow. The result is *sudden cardiac death* unless emergency medical intervention occurs, usually performed by delivering a large direct current (DC) shock of 300 to 400 joules across the chest of the patient.

Premature ventricular complexes (PVCs, Figure 10, 2nd panel from top) are diagnosed when one or more wide QRS complexes are recorded electrocardiographically. They may originate from any location in the ventricles, and the wide complex waveform is registered due to propagation which does not follow along the specialized conduction pathways, making the total activation time of the ventricles longer. In addition, because the vector summation of dipoles points to a different direction when activation patterns are abnormal, the configuration and polarity changes of the QRS complex is also common (see Figure 10, 2nd panel from top). PVCs can be recorded in many if not most normal people, and is not considered serious in these instances. However, in patients with heart diseases such as ischemic heart

disease, recording of frequent and clustered PVCs may be a marker for the development of more serious arrhythmias.

Ventricular tachycardia (VT, Figure 10, 4th panel from top) occurs when 3 or more PVCs are recorded in a row. VT may be nonsustained, lasting ≤ 30 sec, or sustained (≥ 30 sec), and has a rate between 100 and 200 beats/minute. Sustained VT rarely converts back to sinus rhythm, but instead degenerates into *ventricular fibrillation* (Figure 10, bottom panel), a condition where multiple areas of the ventricle activate chaotically, and is lethal unless terminated by DC shock. *Ventricular flutter* is another disorder marked by large, rapid (> 200 beats/minute), and uniform sinusoidal waveforms, and also generally degenerates into deadly *ventricular fibrillation*.

Patients exhibiting frequent PVCs or nonsustained and sustained VT usually undergo invasive electrophysiologic evaluation to assess the origin and mechanism of arrhythmias and guide therapy. Computer-assisted mapping studies are frequently employed to assist in these important tasks. If the site can be localized, then ablation can be performed by delivering substantial radio frequency energy (25-400 joules) through a catheter to the site, creating a lesion which prevents future occurrences of the arrhythmia.

Mechanisms of conduction disturbances

Different mechanisms have been reported responsible for the various arrhythmias described above. The understanding of these mechanisms is important because proper treatment is dependent upon its precise understanding, and is briefly presented below. Many of these mechanisms have been studied in isolated tissue preparations or from animal models which may markedly differ from the human heart. However, they nevertheless may have important contributions to the genesis of cardiac arrhythmias.

Reentry

Reentrant excitation is an important mechanism of ventricular and atrial arrhythmias which has been demonstrated in a variety of models, and has also been described in human hearts. It has been well characterized in models of myocardial ischemia and infarction. Reentry was initially defined by Mines as consisting of a wavefront which proceeds in one direction with slow enough conduction to allow areas previously excited to become reexcited when the wavefront reapproaches.¹ Two physiologic requirements of reentry, therefore, are slow conduction, and unidirectional block of the propagating wavefront. The former allows reexcitability to occur, while the latter forces the wavefront into one direction in the circuit and creates a return path to complete the circuit. Mines first demonstrated reentry in 1913 in an isolated frog heart preparation in which only a hollowed strip of tissue

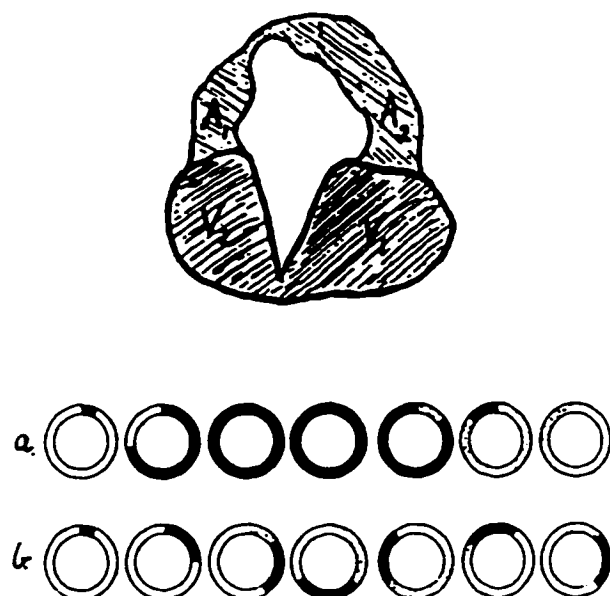


Figure 11. Mines figure of reentry. (From reference 1)

remained functionally viable.¹ The preparation he used is shown in the top panel of Figure 11, and the two graphics in the bottom panel depict normal activation (a) and circus movement reentry (b). In (a), activation begins at the top of the ring and completely activates the entire ring. In (b) the activation wavefront moves clockwise continuously around the ring, always able to conduct from site to site in a stable fashion. Since then, many studies have been performed to further characterize this phenomenon. Reentry is classified as anatomic or functional, each form having distinct mechanisms underlying the tachyarrhythmia.

Anatomic reentry

Anatomic reentry depends on differences in anatomic structures to define the conduction pathways, as well as conditions of unidirectional block and slowed conduction, the prerequisites for reentry. Forms of anatomic reentry include bundle branch reentry, atrioventricular nodal reentry (preexcitation syndrome), Wolff-Parkinson-White syndrome, and reentry around the tricuspid valve.^{43,44} These forms of reentry can be mapped by invasive electrophysiologic procedures, and in a vast majority of cases, are corrected by radio frequency ablative lesions of a critical site in the circuit.

Functional reentry

On the other hand, functional reentry depends on difference in electrophysiologic properties of cells to create a reentrant circuit. Functional reentrant circuits were first described by Allessie et al.,⁴³ Mehra et al.,¹⁴⁹

and El-Sherif et al.⁸ In a post-infarction canine model of stable ventricular tachycardia, the circuit is topographically described with a figure-8 shape. The mapped circuits have been shown to comprise two separate wavefronts, traveling in both clockwise and counterclockwise directions, coalescing into a common reentrant zone of slow conduction. Zones, or arcs of block, are defined as differences in activation of > 40 msec between neighboring recording sites (see Figure 1). During normal programmed stimulation, these same sites did not exhibit any differences in activation time that were abnormal. It was only upon challenging the heart with a faster rhythm, which simulates a premature ventricular contraction, that disparate functional properties arose, leading to conduction block and development of figure-8 ventricular tachycardia. Functional reentry may be subdivided into two categories: differences in refractoriness, and differences due to anisotropy, and are described below.

Recall that conduction block and slowed impulse conduction around an obstacle are the two prerequisites for circus movement reentry. The substrate for reentry can be classified as anatomical and/or functional. The former requires an anatomically predetermined pathway while the latter type depends on regional differences in the functional properties of cardiac tissue. Schmitt and Erlanger first demonstrated segmentally depressed conduction in anatomically determined pathways by elevated extracellular KCl.⁴⁵ Numerous investigators have postulated that regional differences in

refractoriness in the heart may have a causal role in the initiation of reentrant tachycardias and fibrillation. Allesie et al. showed that differences in refractory periods of atrial fibers at adjacent sites can result in functional block if premature stimulation is applied to the site of shorter refractoriness and can thus set the stage for circus movement reentry.⁴³ Boineau et al. showed that conduction block and slow conduction during reentrant activation are dependent on the distribution of refractoriness in the atrium.¹⁷⁶ Gough et al. later showed that circus movement in the surviving epicardial layer overlying an infarcted left ventricle in the canine, developed around arcs of functional conduction block, due to a spatial inhomogeneity (i.e., gradient) of refractoriness.⁴⁶ Measurements using sites spaced 5-10 mm apart showed that gradients of 200 ms/mm were needed for block to occur.⁴⁶ Restivo et al., using bipolar electrograms and unipolar stimulation test sites, established that functional block necessary for the induction and sustenance of reentry was due to abrupt changes in refractoriness occurring over distances <1 mm and proposed that gradients of only 10 ms/mm were needed for block to occur.⁴⁷ The abrupt changes in refractoriness were unrelated to specific geometrical characteristics or anisotropic conduction properties of the ischemic myocardium.⁴⁷ On the other hand, Spach and colleagues have proposed the anisotropic properties of the heart alone can account for all the conduction disturbances necessary for circus movement reentry.⁴⁸ Brugada et al. demonstrated reentrant activation using the frozen rabbit heart model.⁴⁹ Because there are no spatial differences in electrophysiological

properties in these otherwise normal cardiac fibers, anisotropy has been invoked as the basis of circus movement in this functional model.⁴⁹ Although the studies of Dillon et al.,⁵⁰ in the canine post-infarction model of reentry, have suggested that anisotropic conduction properties of the ischemic epicardial layer may result in “pseudo-conduction block” that can sustain circus movement tachycardia, recent high resolution recordings tend to refute this mechanism.⁴⁷ Later, Spach suggested that both spatial inhomogeneity of refractoriness and anisotropic conduction properties may contribute to the induction of reentrant excitation in the atrium.⁵¹

Reentry based on refractoriness

Conduction delay and conduction block can develop due to a differential of electrophysiological properties between neighboring cells. Restivo et al. showed a close correlation between conduction block and abrupt differences in measurements of refractoriness.⁴⁷ This is shown in Figure 12. Using a lower resolution electrode array which covered the epicardial surface of the left ventricle, the location of an arc of block was determined by the isochronal mapping technique. Electrograms *a* through *f* were recorded in four patches, I through IV, across an arc of block, shown in the lower right panel. The resolution of the electrode array was 1 mm interelectrode distance. Clear double potentials are apparent in electrogram *d* of patches I-III, indicating conduction block across the arc. Measurements were also obtained to

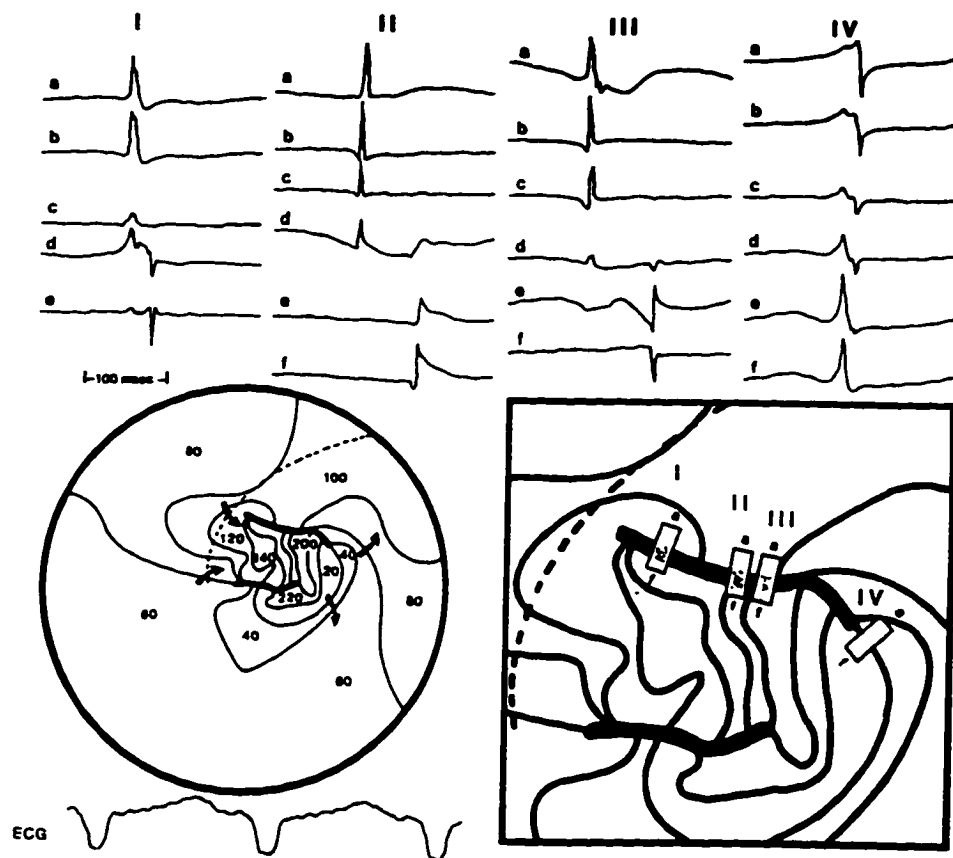


Figure 12. Demonstration of conduction block across an arc of block, which correlated with abrupt changes in effective refractory period measurements. (From reference 47.)

determine the *effective refractory period* (ERP) of sites located on either side of the arc of block. This was performed by stimulating each site with a train of 8 pulses (basic cycle length of 300 msec, S_1) at twice diastolic threshold, followed by a closely coupled stimulus (S_2) of varying intervals less than the basic cycle length. The ERP of that site was defined as the longest interstimulus interval (S_1 - S_2) that failed to produce a propagated response. Restivo et al. showed that, at the site of an arc of block, there was a corresponding abrupt jump of the ERP. The hypothesis proposed was that the wavefront of a premature stimulation would be able to excite areas with shorter ERPs, and would block at sites with longer ERPs, thus creating unidirectional block, one prerequisite for reentrant excitation. The wavefront would continue to excite areas around the heart, finally breaking through the arc, which would then recover from their refractory state, and reexcite the proximal side, establishing the complete reentrant circuit. Thus, the mechanism for reentrant ventricular arrhythmias could be attributed largely to differences in ERP.

Reentry based on anisotropy

On the other hand, other laboratories using a similar canine model to investigate the mechanism of reentrant ventricular arrhythmias have offered competing explanations. In a study by Dillon et al., the primary role of anisotropy was invoked to explain the creation of an arc of block.⁵⁰ In their study, Dillon et al. assumed that electrophysiologic properties of myocardial

cells have returned to normal 5 days after initial changes caused by previous myocardial infarction. However, edema and fibrosis between fiber bundles is extensive in the borders of the infarct site, and causes disruption in the normal propagation properties. Myocardial muscle fibers are arranged in bundles, which are grouped mainly in a parallel orientation to each other. The edema and subsequent formation of connective tissue is more apparent between bundles, and causes increased resistance to current flow. Therefore, conduction abnormalities would be more apparent in the transverse direction (across the bundles), than for the longitudinal direction (along the bundles). To create conduction block, activation in normal areas would proceed normally, and upon encroaching the border zone of an infarct region, would change from uniform propagation to nonuniform propagation, due to the increased resistance in the transverse direction. "Apparent" conduction block and slow conduction would be seen mainly between bundles in the transverse direction, with transverse conduction traveling in a very slowly, circuitous manner, until activation in normal areas would be encountered. Dillon et al. used mapping techniques to explore this hypothesis, which is demonstrated in Figure 13. The arrows in the upper panel show the wavefront direction around the line of apparent block. Below each electrogram site designated with a letter are numbers representing activation times, which were selected where the small arrows point. Electrograms A-I are shown in the lower left panel along with their activation time points. Some sites appear to be

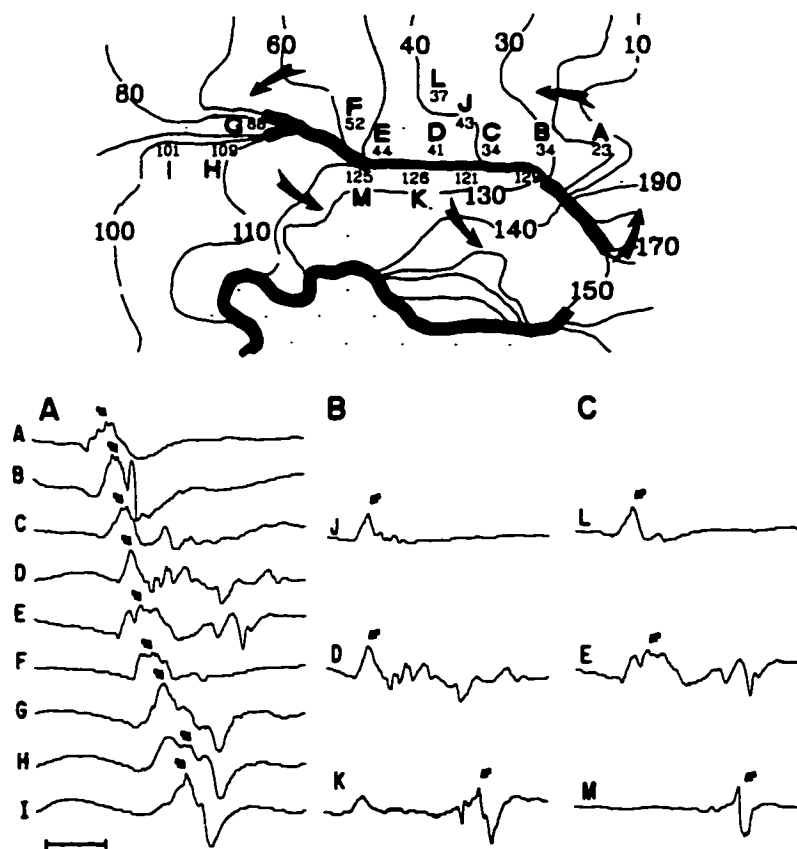


Figure 13. Demonstration of apparent conduction block. (From reference 50.)

activated earlier than predicted if conduction followed the route as shown by the large arrows in the upper panel, and was used to argue that activation must have bridged the arc, albeit slowly.

The debate on the mechanism of reentrant ventricular tachycardia between those due to differences in refractory properties and those due to anisotropic behavior remains largely unresolved. Differences in recording methodology may be primarily responsible for differences in electrogram analysis, including the selection of filter settings, interpolar distance, and electrode size. Others have attributed differences to the number of days following infarction that recordings were obtained ⁵¹ (3-4 days in the Restivo model versus 5 days in the Dillon report). However, these time differences are minimized due to the overlap between groups that occurred during mapping experiments. One of the goals of this dissertation was to examine the role that electrogram analysis may play in the analysis of experiments.

Microreentry

Microreentry is a form of reentry, but on a smaller scale. The entire reentrant circuit occurs in an area of 1-2 cm. Microreentry has been mapped only with 2-4 endocardial recordings by using electrode tipped catheters. ⁵² The evidence for microreentry is based on the recording of continuous electrical activity which spans the cardiac interval from closely spaced bipolar electrodes. A small area is thought to be “protected” from the surrounding tissue which is refractory to excitation. The continuous

electrical activity recording contains multicomponent waveforms that are temporally aligned from cardiac cycle to cycle, and is coterminal with the tachycardia, that is, it begins and ends with the initiation and termination of the tachycardia. An extensive mapping of a microreentrant circuit has not been performed, so conclusiveness of this theory remains to be firmly established. If whole heart mapping of microreentry were performed, the small circuit size of the tachyarrhythmia would appear almost focal in origin, except for the recording of continuous fractionated waveforms at one area of the heart.

Saltatory conduction

This form of conduction refers to the process of activation “jumping” from one site to the next. First seen in nerve fibers, where action potentials jump from one Node of Ranvier to the next, saltatory conduction was proposed as a possible cardiac conduction abnormality.⁵³ Electrotonic conduction in zones of inexcitable or poorly excitable tissue between zones of normally conducting tissue is the primary mechanism for this occurrence. Saltatory conduction may be responsible for a subclass of reentry known as *reflection*,⁵³ in which a circuit is bridged by an area of impaired conduction via electronic interaction in a back and forth pattern of wave propagation. This mechanism has not yet been established in mapping studies.

Decremental conduction

In some situations, the amplitude of the propagating wavefront progressively diminishes, and if it becomes small enough, it is not able to excite tissue proximal to the wavefront and propagation blocks. This concept of decremental conduction has been invoked to explain how reentrant arrhythmias may develop in the early infarction period. Differences in electrophysiological properties of cardiac tissue are assumed in this model; a decrease in transmembrane potential due to increased potassium concentration will lead to smaller sodium conductance, and hence, smaller depolarization potentials. As the action potential amplitude decreases, conduction slows and the developing capacitance, due to local circuit current, increases, causing further slowing of conduction. This process was first demonstrated by Schmidt and Erlanger in a long strip of ventricular muscle, in which high concentrations of potassium were applied to the midzone.⁴⁵ While evidence of this mechanism in the clinical setting has not been reported, it is conceivable that such conditions exist after acute myocardial infarction.

Parasystole

This abnormality is based on a focus which fires action potentials at a fixed rate, but asynchronously from the dominant rhythm surrounding it. In complete entrance block, the focus is insulated from surrounding electrical events, while for exit block, the focus fails to propagate its activity to the

surrounding myocardium. While some examples of parasystole have lent credence to the occurrence of this mechanism in humans, ⁵⁴ firm evidence remains to be reported.

Triggered activity

Abnormalities which occur in cardiac cells can often lead to conduction problems, and the nature of the abnormality defines the disturbance type. In a previous section, the effect of cellular dysfunction was described on action potential shape and duration. Cells that abnormally depolarize earlier than normal can displace the normal pacemaker cells of the heart located in the sinus node, and by firing earlier, can establish an arrhythmic disturbance which is lethal. Electrophysiologists refer to this process as triggered activity, and have classified these arrhythmias as due to early afterdepolarizations and delayed afterdepolarizations.

Early afterdepolarizations (EAD)

Spontaneous arrhythmic activity can occur due to the occurrence of early afterdepolarizations. They have been reported in Purkinje fibers, ²⁶ and are hypothesized to occur in the deep subendocardial layers where midmyocardial cells behave with functionally different characteristics from either epicardial or endocardial cells. ⁵⁵ EADs are secondary depolarizations which occur before full repolarization transpires. A decrease in the resting potential, which can occur in damaged or ischemic Purkinje fibers (PF),

combined with a decrease in I_K conductance can cause the phase 2 repolarization to markedly prolong, or oscillate at a potential that can lead to the triggering of an EAD.³⁸ Other pharmacologic agents which slow the inactivation of Na channels have also produced EADs.⁵⁶⁻⁵⁸ It must be emphasized that for conduction to occur, cells surrounding those from which EADs arise must be receptive to conduction, i.e., they must not be in the absolute refractory state. If these two conditions are met, that is, a spontaneously arising EAD combined with a pathway for conducting to the myocardium, then the possibility for establishing an abnormal rhythm exists. Evidence of this type of arrhythmia has been difficult to describe because of the high resolution, three dimensional mapping required to examine this phenomenon. Our laboratory has recently performed a set of experiments designed to establish this phenomena,⁵⁹ which is described in *Chapter VII*.

EADs are thought to provide a primary mechanism for a ventricular tachyarrhythmia in humans who have an abnormally long QT interval. The long QT Syndrome (LQTS) is a clinical electrophysiologic anomaly characterized by prolongation of cardiac repolarization, reflected as a long QT interval in the surface ECG and the frequent occurrence of polymorphic ventricular tachyarrhythmias, sometimes with a twisting QRS morphology, better known as Torsades de Pointes (TdP).^{27,38,60} The LQTS can be either congenital, idiopathic or acquired. Literally any pharmacologic agent whose action can result in prolongation of the QT interval can cause the acquired

LQTS in a certain number of individuals. The onset of TdP in the congenital and idiopathic LQTS is not necessarily bradycardia (slow heart rate) dependent, as is frequently the case in the acquired type, and the arrhythmia frequently occurs in the setting of increased adrenergic activity. These differences in clinical presentation have been cited by some investigators to suggest different electrophysiologic mechanisms.³⁸ However, the similarities between the congenital and acquired LQTS are compelling since both are associated with a prolonged QT interval. Furthermore, indirect in vivo and in vitro evidence implicate EADs and dispersion of repolarization, sometimes as competing but often as synergistic hypotheses, as mechanisms for TdP in both situations.^{55,61} The EAD hypothesis comes primarily from in vitro studies that show the development of EAD and EAD-induced triggered activity, preferentially in Purkinje fibers (PF), under the influence of agents that prolong cardiac repolarization.^{26,62}

Delayed afterdepolarizations (DAD)

DADs are action potentials which occur abruptly after repolarization to the resting potential has been achieved.⁶³ The precursor of a DAD is a membrane oscillation which can reach the threshold for slow Ca current or fast Na current activation, initiating the firing of an action potential. Once the process has begun, where an initial DAD occurs, it can repeat itself in a spontaneous train of action potentials and lead to global arrhythmia. Studies have shown that increased cellular Ca is an essential requirement for DADs,

and their amplitude may be enhanced by pacing or catecholamines. The increase in intracellular Ca is mainly from the sarcoplasmic reticulum, and may be caused by a variety of complex interactions, either by abnormal Na/Ca exchange current, or enhanced nonselective Ca-activated cation conductances which induces the oscillations.

Several hours after coronary artery occlusion, spontaneous ventricular rhythms often occur; this window lasts 1 to 2 days. These rhythms arise from PF overlying the infarction area, and are attributed to DADs. The initiating impulse may be a critically timed PVC which induces the initial DAD. Few mapping studies have been performed to examine DAD-induced ventricular tachycardia. Hariman and colleagues ⁶⁴ obtained filtered epicardial, unipolar electrogram recordings from a canine heart 1-day post ligation of several branches of the left anterior and circumflex arteries. After pacing the heart at a cycle length of 400 ms, 3 spontaneous ventricular beats were recorded. The electrogram with the earliest time of activation of the first ventricular beat was on the border zone overlying the infarct, and showed negative diastolic waveforms preceding the activation complex. Furthermore, upon termination of a nonsustained tachycardia, multiple, slow rhythmic negative waveforms in diastole were apparent, consistent with subthreshold DADs. ⁶³ Malfatto and Rosen ⁶⁵ developed a model of triggered activity in dogs 24 to 72 hours postinfarction, showing induced triggered rhythms in 2 of 7 hearts by

applying overdrive pacing of the sinus rhythm to produce an accelerated ventricular tachycardia.

Dispersion of repolarization

Dispersion of repolarization has been hypothesized to play a significant role in polymorphic tachyarrhythmias, based on deductive analysis of the QT interval on body surface recordings and limited intracardiac recordings.⁶⁶⁻⁶⁸ This hypothesis has received strong support from recent studies that showed a marked heterogeneity of cell types found in the heart, believed to be based on putative differences in the expression of ion channels that control cardiac repolarization.²⁸ However, it is not known whether differences of regional action potential durations (APD) observed in vitro approximate differences in the intact heart where extensive cell to cell coupling would allow a higher degree of electrotonic interaction which would minimize the differences in APD. The actual spatial dispersion of repolarization in in vivo normal hearts or in the long QT syndrome is not known in man or in animal models.

Techniques employed to understand mechanisms of ventricular arrhythmias

To investigate the mechanism of arrhythmias, electrophysiologists have resorted to many animal models which imitate, in some manner, the conditions connected to the human pathologic state. There are both similarities and differences in the hearts of many mammal hearts. For

example, some hearts, such as canine and porcine hearts, have sizes of similar scale as the human heart, and whole heart mapping studies can be more directly correlated to humans. Other hearts, while smaller, have a preponderance of particular ionic channels or receptors, which make favorable conditions for study of their behavior. An example is the use of rat hearts, which have a large potassium transient outward (I_{to}) current, to study drug effects on I_{to} in this model. In summary, it is necessary to have a variety of animal models available to study the nature of human electrophysiologic abnormalities.

In some areas of research, however, the information gleaned from animal studies can be used to formulate computer models which can closely characterize an electrophysiologic parameter or feature. For example, consider the cardiac action potential. Numerous *in vivo* and *in vitro* experiments have delineated many of the primary currents responsible for the shape of the action potential described earlier in this chapter. Cellular studies employing modern current and voltage clamping techniques have described the kinetics of each of these primary currents, including their temporal contribution to the action potential, to such an extent that mathematical equations can be used to describe their action, either individually or in combination.⁶⁹⁻⁷² These models have been implemented in computer programs to characterize various cardiac action potentials, for example, from the rat or guinea pig, or from Purkinje fibers or ventricular

muscle. In these computer models, the currents can be modulated, as they might be by drugs, and their changes on the whole action potential can be investigated. From these changes, an inference can be utilized to suggest how these drug-based changes would effect arrhythmias. However, generally these models only include primary currents, and these are normal currents as well. Characterizing these currents during ischemic or remodeled pathologies is less well understood, so that currently, mathematically-based computer modeling is still considered a technique requiring greater robustness.

Computer modeling has also been employed to simulate mapping studies.^{48,73-80} Features such as conduction velocity, refractoriness, and anatomic obstacles are taken into account when constructing these models. They are generally restricted to two-dimensional surfaces because of the computational difficulties inherent in extending the model to three dimensions. However, they have been successfully implemented to show that the site and cycle length of stimulation can cause significant changes in a reentrant circuit.

In vivo vs. In vitro models

Experimental mapping data is classically obtained by two methods: in vivo and in vitro preparations. In vivo methods are generally preferred because they most closely simulate actual physiologic conditions. In this setting, the heart is studied while it is still performing its vital bodily

function of pumping blood throughout the body; the interactions with the autonomic system and other humoral systems remains intact. If one is concerned with particular areas of the heart, then in vivo experiments may not be possible. For example, if one wants to study the interaction between Purkinje fibers and the subendocardial ventricular muscle, then excision of this area is required for close investigation. In this case, an in vitro preparation is preferred, and the excised tissue is perfused in a bath of physiologic, oxygenated solution that keeps the tissue electrophysiologically viable. Transmembrane or extracellular recordings may now be obtained with this model that closely resemble physiologic conditions.

For the purpose of understanding the mechanism of arrhythmias, and in particular reentrant-type arrhythmias, whole heart in vivo mapping is the preferred technique used to investigate this phenomena. This is required because it has been shown that parameters such as conduction velocity and refractoriness can vary from region to region, and even on a millimeter by millimeter scale, making whole heart in vivo mapping a requirement to discern both the whole as well as subunits of activation circuits.

Isochronal activation time mapping

Circus movement reentry, as a hypothesis of a mechanism of ventricular tachycardia, was first postulated by Mines.¹ Mines cited three criteria to prove that reentry was the cause of an arrhythmia:

1. For the initiation of reentry, an area of unidirectional block must be present. (This area of block may be functional or anatomic.)
2. The movement of the excitatory pathway should be observed to pass through a pathway, return to its point of origin, and then continue its excitation through the same pathway.
3. Since it is still possible to achieve this same excitatory movement by spontaneous focal impulse formation, "the best test for circulating excitation is to cut through the ring at one point. If the impulse continues to arise in the cut ring, circus movement as a cause can be ruled out."

In order to ascertain if an arrhythmia meets the criteria for reentry, it is necessary to obtain simultaneous recordings from many sites in the circuit. Many sites are required to establish that an area of unidirectional block exists, because it is generally not known a priori where the site of block occurs, although it may be localized to a region (e.g., the border zone of an infarct). Multiple sites are required to establish the second point of Mines' criteria, i.e., the establishment of a circuit. The recordings at each site must show a temporal progression in the activation wavefront by the registration of activation times embedded in each activation waveform. Multiple recording sites are also necessary to demonstrate Mines' third point.

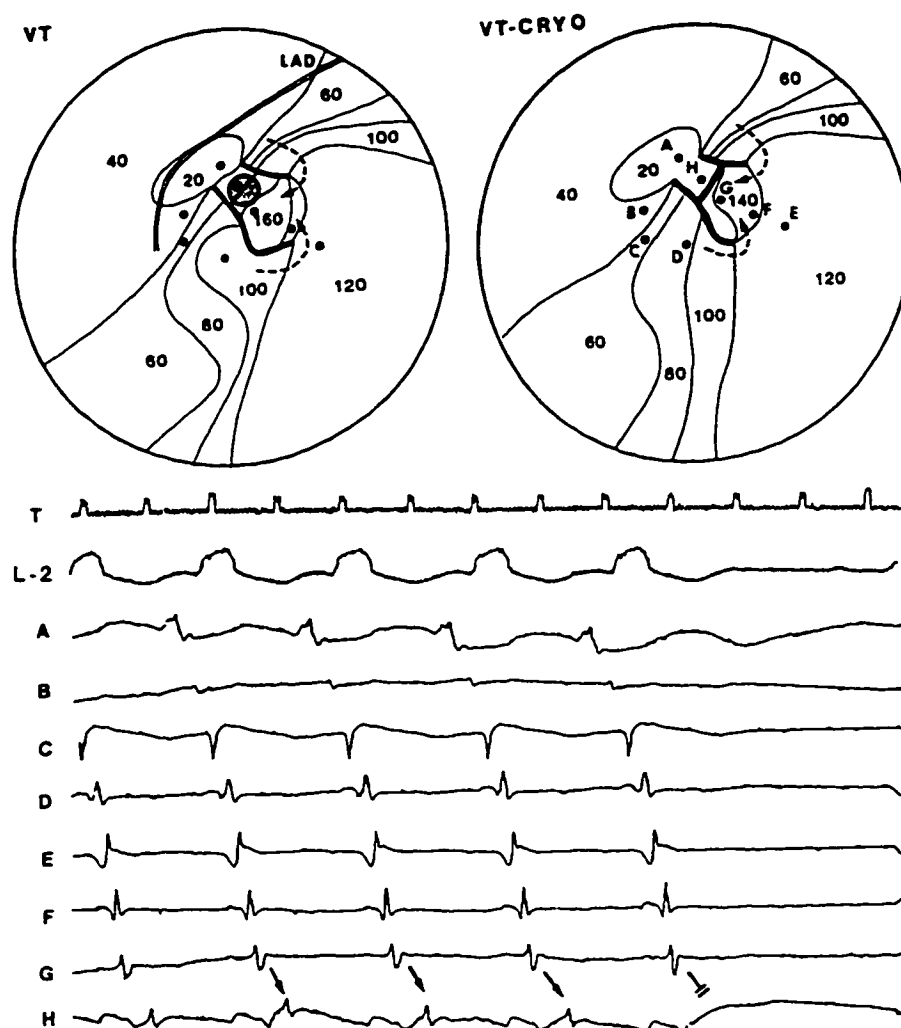


Figure 14. Cryothermal lesion terminating reentrant ventricular tachycardia. From Assadi M, Restivo M, Gough WB, El-Sherif N: Reentrant ventricular arrhythmias in the late myocardial infarction period: 17. Correlation of activation patterns of sinus and reentrant ventricular tachycardia. *Am Heart J* 1990;119:1014-1024.

Once an arrhythmia has been ascribed to a pathway, the blocking of the pathway can be performed by several techniques; i.e., resection, cryothermal lesion, or radiofrequency ablation, and the circuit must be monitored subsequently to confirm that the arrhythmia has terminated. An example of termination of a reentrant rhythm is shown in Figure 14. The map on the left shows the reentrant circuit from a canine heart 4 days post myocardial infarction, formed by two arcs of block. During ventricular tachycardia with a cycle length of 200 msec, the wavefront traveled in both clockwise and counterclockwise directions and coalesced into a central common pathway. Electrograms A-H, shown in the bottom panel, were located at corresponding sites shown in both maps, and lettered in the VT-CRYO map on the right. A cryo probe was placed between sites H and G, which terminated the arrhythmia at that site. The arrows at the bottom highlight the progressive delay in activation from site G to site H, until its eventual block.

To ease the burden of analyzing the massive amounts of data collected by the activation mapping technique, electrophysiologists bin the collected activation times into isochrones of 5-20 msec. A map of the recording sites in relation to anatomical landmarks is made and closed contours of the activation times are inscribed over the map of sites. With this technique, a reentrant arrhythmia can be fully

demonstrated, and represents a powerful method of analyzing the mechanisms of arrhythmias.

There are, however, a number limitations and weaknesses in utilizing this technique. They include the number of recording sites (how many recording sites are necessary to accurately map the circuit or define block?), the location of the sites (epicardial versus endocardial versus tridimensional), the representation of isochrones, and a reliable definition of activation time. The latter limitation is the subject of much of the work described in this paper.

The research described in this paper is based on improving methods used in isochronal activation mapping. The 4-day post-infarction model of ventricular tachycardia used in this laboratory lends itself well to this type of mapping because the infarction creates essentially a two-dimensional thin layer of abnormally surviving epicardium, which gives rise to both spontaneous and induced reentrant arrhythmias. Figure 15 shows sectioned slices of a canine heart 4 days post ligation of the left anterior descending artery. The left panel is the fourth section from the top. The dark color represents tissue which was stained with nitroblue tetrazolium. The necrotic areas are unstained. A thin rim of stain is seen overlying the infarcted area, which was localized to the anteroseptal region and extends to the endocardium. This thin surviving layer can then be mapped with a high resolution array of epicardial electrodes to study basic electrophysiological

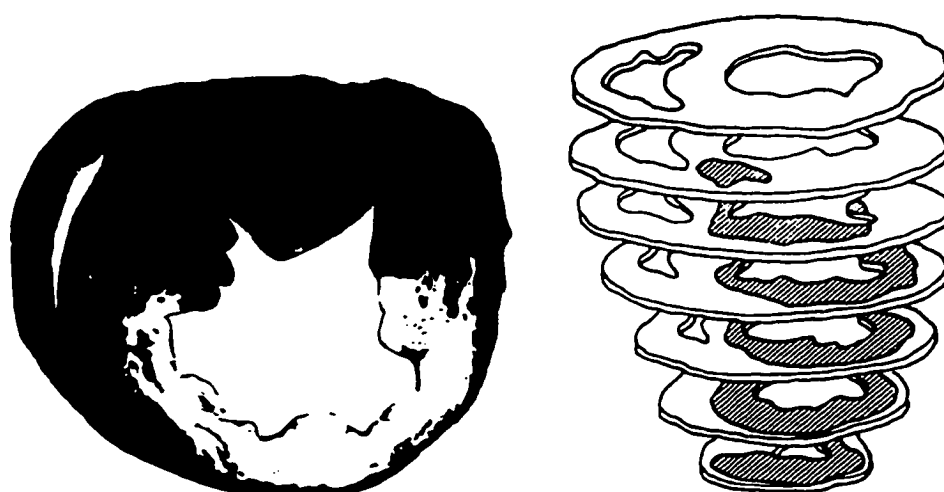


Figure 15. Sectioned canine heart 4 days post left anterior descending artery ligation. From reference 149.

parameters such as conduction velocity, refractoriness, the area of block, etc. The understanding of multiphasic, long duration electrograms recorded from these areas during reentrant rhythms have proven difficult to interpret accurately.

Potential distribution mapping

Potential distribution mapping is based on the concept that a varying potential distribution exists in relation to the propagating wavefront, and this distribution can be successfully analyzed to map the circuit of an arrhythmia. Taccardi et al. have shown that with an endocardial to epicardial (i.e., radial) spread of activation, the negative field tends to be distributed eccentrically along the radial axis and perpendicular to the fiber orientation.⁸¹ The eccentricity of the distribution is most likely related to the orientation of the myocardial fiber bundles, which predominately coarse perpendicularly to the radial axis of the ventricles. Taccardi et al. also noted that areas of the largest negative potential in the early temporal phase of activation were closely correlated with the breakthrough of propagation from the endocardial surface, containing the Purkinje network, into the subendocardial myocardium. With these findings, it was possible to demonstrate an isopotential distribution map of the electric field at one instant of time during the depolarization or repolarization process, with the site displaying the most negative potential correlating with the site of earliest activation.⁸¹ This is illustrated in Figure 16, which shows potential

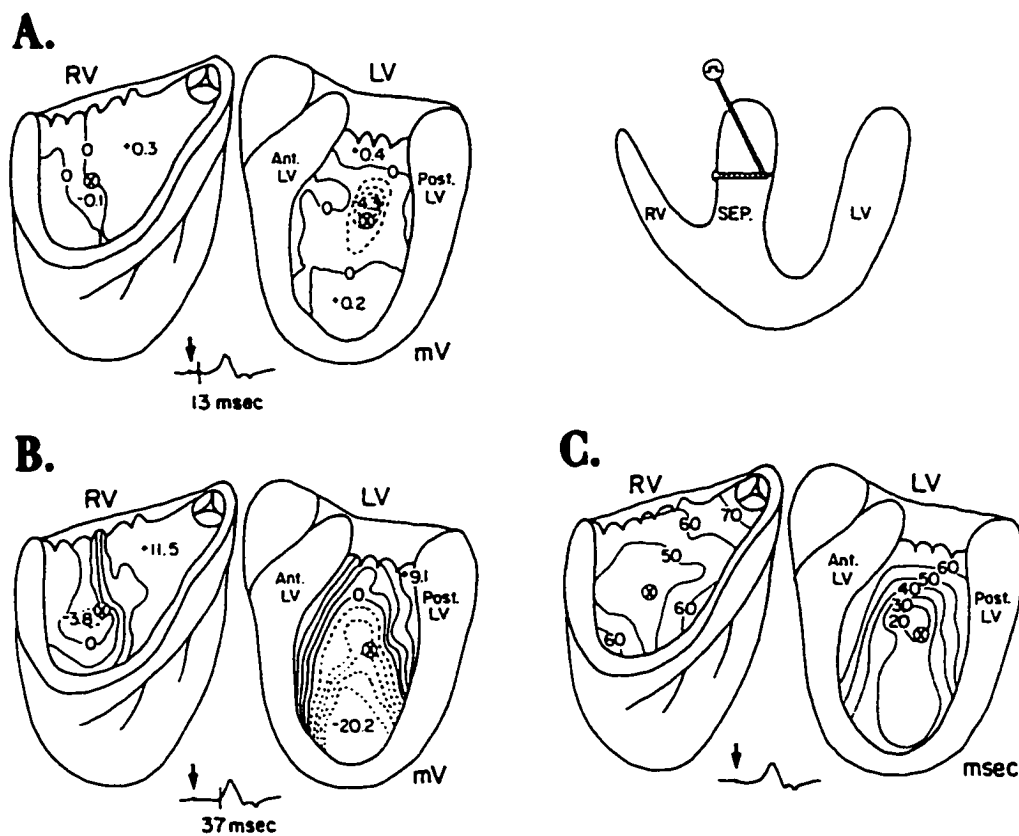


Figure 16. Correlation between potential distribution mapping and activation mapping.
(Boineau JP, Schuessler RB, Eisenberg SB, Tweddell JS, Harada A, Rokkas CK, Cox JL:
Potential distribution mapping of ventricular tachycardia. In: Cardiac Pacing and
Electrophysiology (El-Sherif N, Samet P (eds), W. B. Saunders Co., 1991; pp85-107.)

distribution maps in panel A and B, and an activation map in panel C, taken during left sided septal pacing (upper right panel). A minimum in panel A (marked by the circled x) correlates well with the site of earliest activation in Panel C. Eisenberg et al., by substituting pacing at an endocardial site for a focal-based ventricular tachycardia, were able to localize the intramural activation origin by determining the site which first reached -3 mV in a series of potential distribution maps.⁸²

One of the primary reasons for the development of potential distribution mapping was to overcome one of the limitations of isochronal activation time mapping, the difficulty in quickly editing and interpreting maps for clinical use. Another consideration was an attempt to localize the site of origin of a focal or microreentrant circuit which was intramural. Harada et al. were able to localize intramurally stimulated sites in cases where distance from the stimulated site to the endocardium was < 6.5 mm.⁸³ While these results are promising, others questions arise regarding the usefulness of this technique for detection of reentrant arrhythmias. These have larger circuits, and display diastolic potentials, leading to simultaneous overlapping depolarizing and repolarizing currents.⁸⁴

Body surface mapping

An interesting and useful approach to identifying the site of origin of certain arrhythmias is the body surface potential mapping technique. With technological advances, mostly coming from computer technology, body

surface potential mapping has become an easier tool for use in the electrophysiology laboratory. An important feature of this technique is its noninvasive approach to mapping, which offers the main advantage of this technique. The technique is particularly useful in identifying the site of preexcitation to the ventricles, called the Wolff-Parkinson-White syndrome,⁸⁵ in which the heart has an otherwise normal electrophysiologic profile. In this case, the anomaly is considered focal, and can be reliably represented as a single dipole. Savard et al. employed 63 electrodes applied to the body surface, 43 on the front and 20 on the back, to construct the map.⁸⁶ Isopotential distributions were obtained during the delta wave, drawn at 0.5 mV isochrones based on the positivity or negativity of sites in relation to a 0 mV potential. Epicardial activation maps were also constructed during surgery, and the two types of maps were correlated. Figure 17 shows body surface potential maps recorded during the delta wave in six different Wolff-Parkinson-White syndrome patients, with their preexcitation site determined during surgery. The negative potentials depicted in the figure relate to anatomic locations within the heart, and assist in identifying the site of earliest activation. For example, negative potentials covering the right side of the thorax are associated with right ventricular preexcitation, while negative potentials over the back correspond with left ventricular preexcitation. Others have used body surface potential maps to ST segment shifts in patients undergoing percutaneous transluminal coronary angioplasty,⁸⁷ and to localizing focal ventricular tachycardia.⁸⁸

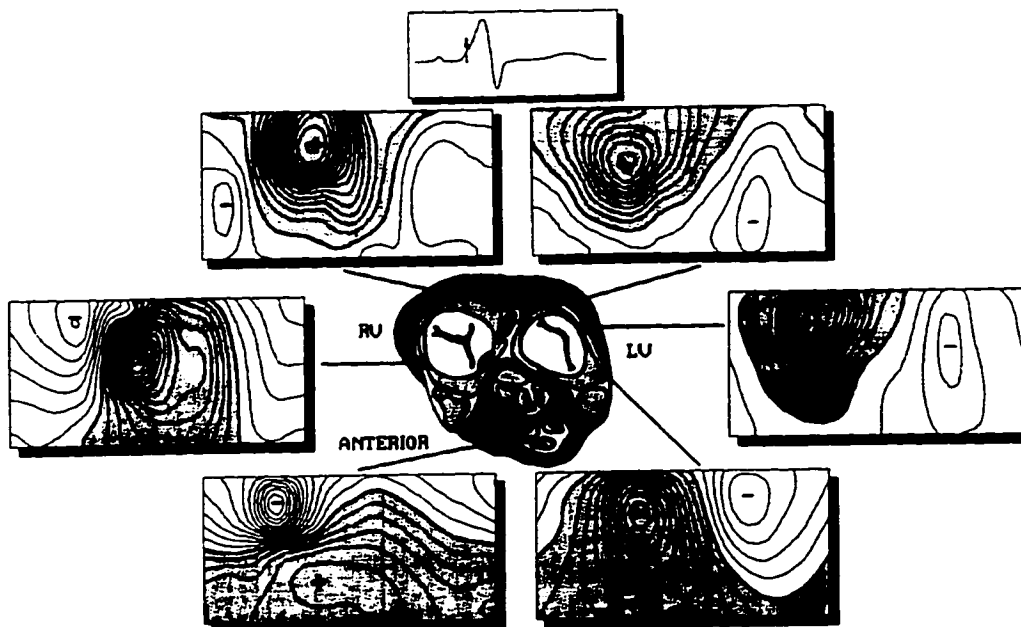


Figure 17. Body surface potential maps of six patients with Wolff-Parkinson-White syndrome.

Optical techniques using potentiometric fluorescent dyes

Optical mapping techniques are based on the ability of voltage-sensitive dyes to be absorbed by cardiac cells, and fluoresce in the process, in proportion to the changes in transmembrane voltage. First introduced for use in the heart by Salama and Morad ⁸⁹, this technique is applied to study cardiac development, propagation of impulses, action potential changes from different regions of the heart, dispersion of repolarization, cardiac arrhythmias, and defibrillation. Many dyes have recently been developed which offer improved sensitivity, linearity, less toxicity, and larger signals, all of which aid in the utilization of the technique. In addition, hardware is now capable of multiplexing many more photodetectors, so that greater accuracy and scope of the heart can be investigated.

Because the optical signal is based on changes in cellular transmembrane voltage, the transduced electrical signal is a reflection of the cardiac action potential. Thus, optical mapping permits good interrogation of action potential changes under various manipulations. The main drawbacks to the technique are the motion artifacts caused by contraction, and the toxicity of the dyes. Photodetectors can be focused to view areas ranging as small as 10 μm^2 to 1 cm^2 , and come in a variety of types, such as photodiodes, charged coupled devices, laser scanning beams, and focal plane detectors.

Other mapping techniques

A number of other mapping techniques, both invasive and noninvasive, have been utilized to identify the site of origin of arrhythmias or investigate the mechanisms of conduction disturbances. Of these, three promising techniques include: 1) endocardial catheter mapping,^{90,91} which is most often used in the clinical setting to identify sites of earliest activation for surgical resection or radiofrequency catheter ablation; 2) magnetocardiographic mapping,⁹² which has been employed to noninvasively identify preexcitation sites; and 3) vector mapping of ventricular tachycardia after myocardial infarction. Kadish et al. showed that four electrode recordings arranged orthogonally in two dimensions (two electrodes in the x plane and two electrodes in the y plane, all equidistant from a center point) could be summed into a vector loop.⁹³ These vector loops, which describe the direction of activation, could depict when activation spreads from the site of earliest epicardial activation, and could direct mapping of the region of earliest ventricular activation. This technique employs only four electrodes, but many sites have to be recorded and analyzed to get a reasonable target for the origin of tachyarrhythmias. Furthermore, Kadish et al. had difficulties in recording suitable vector loops in infarcted areas, where many critical zones of arrhythmias often exist.

Magnetocardiographic mapping is a recent technique that has developed out of the technological advances in magnetic field sensors utilizing

superconducting quantum interference devices (SQUID), multiplexed data acquisition, and adequate computer technology to control and analyze the data. Magnetocardiography measures the dynamic magnetic field distribution generated by the electrical activation of the heart, and is much less sensitive to tissue inhomogeneities than electrical activation.⁹²

Isomagnetic lines of the field distribution were obtained from 36 SQUID magnets applied to the precordial surface of twenty-one patients with Wolf-Parkinson-White syndrome, and used successfully to localize the accessory pathway.⁹⁴ These lines represent the position and direction of the generated current source, forming an equivalent current dipole. These “magnetic” dipoles can then be analyzed for their depth and three-dimensional position by producing maps which bear strong resemblance to those obtained by potential distribution mapping. The technique has only been reported in a few studies, and further validation needs to be performed on its usefulness in the clinical setting.

Computer-assisted isochronal mapping techniques

While computer-assisted mapping procedures have proven invaluable in helping clinical electrophysiologists to diagnose arrhythmias and localize their site of origin, the exact mechanisms underlying arrhythmias are also required to optimize therapy development and design newer treatment modalities. Computer-assisted mapping has also proven to be an extremely useful tool toward understanding the various mechanisms responsible for

arrhythmias. With the aid of experimental animal models that closely represent the human counterpart, combined with technologically advanced computer-assisted mapping systems, electrophysiologists have made many significant contributions into our understanding of the mechanisms underlying arrhythmias.

The use of computers and computer technology is mandatory for all but the simplest mapping requirements. Without these technologies, the number of simultaneous recordings is limited to about a dozen, and manual analysis would prove exceedingly difficult, subjective, and nonreproducible. In a paper on the ideal mapping system, Ideker et al. claimed that 30,000 electrodes would be required to map satisfactorily the entire human heart with excellent resolution.⁹⁵ It is impossible to imagine achieving this capability without the aid of a computer-based system. The first multichannel system was first described by Moe et al. in 1941, who developed a 3 channel string galvanometer mapping system.⁹⁶ In the 1970s, the first computer-based mapping systems appeared, and by the end of the decade, 32 channel computer-based systems had evolved. In the 1980s, the number of recording sites increased another order of magnitude, with some investigators employing computer-based mapping systems having almost 300 channels. Some current mapping systems now have recording capability of more than 500 channels.

Data acquisition

Computer requirements can be divided into two categories: data acquisition, and data analysis. Several parameters must be addressed to achieve adequate data acquisition useful for isochronal activation mapping, including electrodes (size, number, and type), simultaneous recording of multiple channels, proper sampling rates, adequate resolution, amplification, noise reduction, length of recordings, and adequate storage of large amounts of data. Each one of these parameters is described in some detail below.

Electrode type, size, and number

Electrode materials which reduce the bias voltage are preferred; ⁹⁷ silver-silver chloride electrodes are most commonly used, although other metals, such as tungsten, platinum, stainless steel, or gold may be used in circumstances when special requirements, such as size or strength are required. ⁹⁷ The number and size of electrodes are important to maintain adequate spatial resolution. If the number of recording sites are too thinly interspersed, it is often impossible to map correctly the activation sequence. If the electrode size is too large, a number of possible difficulties may arise. If the electrode diameter is very large, then the distance between neighboring sites must necessarily be large to avoid electrical shorting problems. Since some investigators have discovered discrete electrophysiological differences between cells in close proximity to each other, on a millimeter scale, electrode sizes too large, encompassing a much larger electrical "view," would

completely miss recording of these differences. Recall that Restivo et al., using a high-resolution electrode array consisting of 64 bipolar sites separated by 1 mm, of ischemic ventricular myocardium, found large, abrupt, and statistically significant differences of ERPs between sites separated by 1 millimeter or less (see Figure 12).⁴⁷ For this study, Restivo et al. used Teflon-coated silver electrodes of 125 μm diameter.

Performing isochronal activation mapping to investigate the mechanisms of various arrhythmias requires different types, sizes, and number of electrodes. To map atrial flutter circuits which are typically confined to the right atrium and especially the lower right atrium, a reasonable amount of required electrodes could be calculated by determining the area of the right atrium ($\sim 20 \text{ cm}^2$ for adult canine) divided by the resolution required by empirical mapping studies. If 0.01 cm^2 were used as the “resolution criterion”, 200 electrodes would be required to map the right atrium. Fortunately, not all areas are created equal, in other words, some areas of the right atrium (e.g. the lower right atrium) could be weighted with a greater density of electrodes than other areas (e.g. the higher right atrium) because they are more critical to arrhythmia generation. In our laboratory, we have been able consistently to map with adequate resolution the activation sequence of atrium flutter utilizing 128 electrodes on the epicardial surface.⁹⁸

Determining the activation sequence of a ventricular tachycardia requires far more electrode sites because: 1) the surface area of the ventricles is an order of magnitude larger (approximately 200 cm²); and 2) in many cases it is impossible to localize the site of origin of the arrhythmia to a particular location. If the same 0.1 cm² coverage were applied to this setting, then 2,000 electrodes would be required, an order of magnitude more than what is currently available. In order to make due with current technical abilities, a tachycardia is first mapped with an electrode grid consisting of 200-300 equidistant electrodes, and after localizing the site of interest, a high resolution grid of 100-200 electrodes confined to that site is applied. In future systems having greater technological capability to record, to store, and to analyze data orders of magnitude larger, mapping studies with excellent spatial resolution will be possible.

Multiplexed data acquisition

To determine accurately conduction patterns in the heart, the spatial locations of recording sites are registered. For example, if a patch containing 128 unipolar electrodes is fabricated with an interpolar distance of 1 mm, then the spatial resolution is accurately known. Continuing with this example, let us consider recordings from each of the sites simultaneously. The patch is placed on the left ventricle of the heart, and after proper connections are made and proper contact with the heart surface achieved, recordings for one heart beat are obtained for each of the 128 sites

simultaneously. Upon analysis of each electrogram, an “activation time” for each electrographic waveform is assigned, that is, each waveform has only one instant in time associated with it when electrical propagation has passed directly below to the electrode site. We may now correlate the spatial locations with the temporal activation times for each site. If one chooses to view the activation process in discrete steps of 5 msec, then closed contours are drawn on a map which has the combined spatial and temporal distributions, enclosing all activation times of 0-4 msec, 5-9 msec, etc., and an isochronal activation map is drawn, elucidating the sequence of propagation in the process.

Generally, dozens to hundreds of channels are recorded to make an adequate isochronal activation map. These data need to be recorded simultaneously in order to make the precise correlations, because the only other alternative would be to make recordings sequentially from different heart beats, and it has long been known that subtle and not-so-subtle variations in the conduction pattern of the heart frequently occur. Therefore, electrophysiologists have employed multiplexors in mapping systems to record multiple channels simultaneously. Few multiplexors are commercially available which can multiplex more than 128 channels into a PC-based system, although the technology is changing rapidly.

Sampling rate

The sampling rate is important to achieve accurate data reproduction in digital form.⁹⁹ While some cellular events occur on a microsecond time scale, for mapping purposes, events of interest are in the range of hundreds of microseconds, or even milliseconds. Barr and Spach, in a study of digital sampling rates required for isochronal mapping, found that a sampling rate of 1000 samples per second was sufficient for reasonable data analysis.¹⁰⁰ However, Cabo et al., in a study in which the frequency content at selected frequencies were investigated for their ability to be used as discriminators of local vs. distant activation time, found 750 Hz to be of significance in analyzing electrograms.¹⁰¹ Others have shown similar frequency content for unipolar and bipolar extracellular recordings from normal cardiac tissue.¹⁰³ Taking the Sampling Theorem¹⁰² into account, which briefly, states that the sampled data rate should be at least twice the frequency of the highest frequency the data contains to represent precisely that data, the sampling rate should be at least 1500 samples per second. Practically, the sampling rate should be several times higher than the highest frequency of interest to allow for a degree of error in frequency calculation. Currently, most electrophysiology laboratories sample between 1000 and 2000 samples per second.

Resolution of digital data

The multiplexed data stream is sampled and converted to a digitized signal, and the resolution of the data should be optimized for use. Typically, bit resolution is between 8 bits, offering 256 voltage levels, 12 bits, with 4,096 discrete voltage levels, and 16 bits, with 65,536 discrete levels. Because the data values are both positive and negative, the middle level is generally selected to be 0 mV. In the current usage, 12 or 16 bit resolution is deemed acceptable resolution. For unipolar mode recordings, electrogram voltages are usually within the ± 50 mV range, and bit sampling errors of 12.2 μ V and 0.8 μ V for 12 and 16 bit sampling, respectively, are well within acceptable levels for accurate electrogram analysis, and similar to levels of amplifier noise. Bipolar mode recorded voltages are almost an order of magnitude smaller, which makes 12 and 16 bit sampling rates well suited for electrogram analysis.

Amplifiers

The electrographic signals recorded from the heart have high impedance due to the tissue-electrode interface, and therefore the impedance of the first stage of amplifiers should be isolated and large, on the order of $10^{11}\Omega$. Fortunately, almost all modern operational amplifiers have impedances greater than this requirement. For example, a typical operational amplifier has an impedance of $10^{14}\Omega$.¹⁰⁴ CMOS or MOSFET semiconductors are routinely used, and are well suited for mapping purposes. While there may

be several amplifier stages, for optimum noise reduction, the first stage should have the highest allowable gain requirement. If bipolar signals are desired, then they can readily be obtained by the use of a differential amplifier with 2 unipolar signals as inputs. If the unipolar mode is used, the signal can go to the positive input with the ground used as reference attached to the negative input.

Amplification

The amplification of signals is extremely important to optimize the resolution of the electrogram signals. For example, if the operational amplifiers are constructed at ± 1 Volt, and the bit resolution is 8 bits, then each level represents 7.8125 mV, and the resolution is 3.9 mV, which is quite unacceptable for electrogram signals, which are in the millivolt range. Furthermore, signal sizes vary with the mode of recording and with tissue type. A signal recorded from the epicardial left ventricle in unipolar mode can be as large as 50 mV, while the same signal recorded in bipolar mode may be only 1 mV. To deal with these large differences, the amplifiers should have variable gain that can be quickly changed to match the mode of recording and the tissue type of interest.

Noise reduction

Noise sources can be divided into 2 categories, extracardiac and intracardiac. Extracardiac noise sources include noise emanating from other

muscle sources such as muscle groups assisting in the respiration process, neural electrical generators, electromagnetic interference (commonly referred to as 60 Hz noise) from the room's environment, and electronic or "shot noise" (a form of white noise) from the amplifiers.¹⁰⁵ Safeguards can be taken to adequately reduce the effects of these noise sources. Electromagnetic interference can be reduced by proper grounding procedures,¹⁰⁶ or by applying notch filters which specifically remove the 60 Hz frequency or its harmonics. In an experimental setting, noise effects due to respiration or motion artifact can be limited by proper anesthesia technique by maintaining O₂ and CO₂ levels, and inspiratory and expiratory rates, in the physiologic range. Shot noise from the amplifiers is negligible with modern amplifiers when compared to the signal of interest, and may be ignored.

Intracardiac noise sources are more difficult to cancel. If one is investigating ventricular arrhythmias, the atrial signal generally does not overlap temporally, and can be often ignored. The main problem is to separate local from distant activity, with distant activity considered to be a noise source. For example, a unipolar recording obtained from the free wall of the left ventricle may include "electrotonic" potentials arising several centimeters from the site, and could seriously effect the interpretation of the electrogram recording. Bipolar recordings have a much smaller electrical "view", and cancel distal noise sources substantially. However, bipolar recordings are often difficult to analyze because there is little biophysical

theory to support their interpretation. This problem is extensively detailed in later chapters.

Length of recordings

Arrhythmias may be short lived, lasting only one beat, or they may continue for thousands of beats, lasting many tens of minutes or hours before converting either back to normal sinus rhythm or degenerating to a fibrillation. In some cases, it is desired to capture the events leading to a conversion, termination, or degeneration, including events just previous to the change. For this purpose, recordings may have to capture many minutes or even hours of electrographic data. Holter monitors are designed to obtain up to 48 hours of continuous ECG data from two channels in patients with suspected cardiac arrhythmias.¹⁰⁷ However, for multichannel recording from hundreds of sites, this task becomes more formidable. Several methods have been developed to allow long-term recording or to record events happening many minutes from the initial recording time. One mapping system, designed in Europe, employs video recording technology to record analog multiplexed data onto VHS video tapes.⁷⁴ In this manner, up to 2 hours of 128 channels can be continuously recorded. Once an event has occurred, the computer can encode into digital format the event of interest and perform the required data analysis. One serious shortcoming of this technique is the upper data rate allowed by the VHS format of 16.7 ms. For many events, this rate may be too slow to see details of importance. Another method,

commonly used to record events at some time far from the initial recording time, is the circular buffer or double buffer technique. This technique keeps the digitized data flowing through a portion of main memory, with the oldest data being written over with the newest data until the event of interest has occurred. The data in the circular buffer is then transferred to the hard disk or other storage medium for off-line analysis. The circular buffer is often used in conjunction with a pretrigger which, after an event has occurred, captures data preceding the triggering event by an adjustable time window. This system works well, minimizing hardware requirements, and allows faster data sampling, to the limit of either the A/D boards, or memory constraints. The length of the circular buffer is memory limited. Most modern PC-based systems can have up to 128 Mb of DRAM, and a large portion of this can be retained for the buffer.

The use of a circular buffer may or may not require human intervention to act as the trigger for capture and storage of the data. Some Holter monitors contain sophisticated program modules which analyze each ECG waveform and the heart rate for abnormal behavior, and once sensed, the program triggers an offload of the buffer into a storage area for future interrogation.

Storage of large amounts of data

The multiplexed data obtained from the duration of a single experiment can be quite large and requires a thoughtful storage strategy. The amount of

data acquired depends on the type of arrhythmia to be recorded and the experimental design, but often data in the hundreds of megabytes are captured in the course of a single experiment. Older systems stored data on 9-track tapes, capable of 80-100 Mbytes storage.⁴⁶ This technique became disadvantageous for two reasons: 1) the data is stored sequentially, and for example, obtaining the 15th data run meant that the operator had to read through the initial 14 runs before arriving at the 15th; and 2) the amount of data has increased as the number of multiplexed signals and the data rate increased, making the use of multiple tapes a requirement, all properly logged and stored.

Newer formats include the use of DC2120 data tapes, capable of storing 240 Mbytes of data, digital audio tapes, and optical or recordable CD-ROM disks, which hold up to 680 Mbytes. Other data storage hardware systems have been introduced, and several other high density media will soon be available. One point worthy of mention is that the cost associated with each technology varies, although generally, the ratio of data storage per unit cost has increased significantly. This issue can become increasingly important if there are a number of investigators who wish to perform and share data analysis simultaneously. One way to deal with this situation is to purchase multiple storage units, so that each investigator has his or her own unit for data retrieval. Another method is to put the whole system on a network so

that each investigator (client) has the ability to download data from the server application to his/her workstation.

Analysis of mapping data

The analysis of mapping data also has a great need for computer technology. For mapping of ventricular arrhythmias, hundreds of channels acquire data at 1-2 kHz sampling rates are used for the analysis of the temporo-spatial distribution of complex activation patterns. This large amount of data then undergoes several conditioning stages before features can be extracted.¹⁰⁸ Digital filtering algorithms are commonly used for this purpose. The multiplexed data may need to be sorted before it can be analyzed, and a variety of sorting algorithms are currently employed. Once the data has been sorted and filtered, the process of feature recognition and extraction is employed to determine the activation time of each waveform from each channel. Finally, isochrones based on mathematical formulations such as triangulation, gridding, or krigging may be used to create closed contours around sites having similar activation times.^{109,110} From this description, it is readily seen that the use of computer science and technology is an indispensable tool for both the clinical and basic cardiac electrophysiologist. The following is a description of the process collectively termed "analysis of mapping data."

Sorting routine

Sorting routines used for relational databases, such as the Bubble Sort or QuickSort, ¹¹¹ are not necessarily appropriate for this type of sorting, because the main requirement is to place the data in a usable format, without initial consideration of ascendancy, location, etc. Sorting of the data is a necessary step to begin analysis because the multiplexor outputs the data in a raw form that is not quickly retrievable. This varies from system to system, however, the important point is to sort the raw data into a usable format with the greatest efficiency.

Signal conditioning

Most signal conditioning of electrograms for activation mapping is based on bandpass filtering techniques, and can be accomplished by impulse response or finite response filtering schemes. ^{108,112} Butterworth filters having 4- or 8-poles are most commonly used because of their flat frequency response in the bandpass and sharp rolloff at 3 dB. ¹¹³ Nearly all laboratories set the high pass filter setting to at least 0.05 Hz to remove baseline wander. The low pass setting varies from 250 to 500Hz, and usually depends on the sampling rate, with the high pass set to one half the sampling rate. ¹¹² For repolarization measurements, the low pass setting is much lower to reduce the effects of high frequency noise which seriously effects the feature extraction . The T wave mostly contains frequencies under 25 Hz. ²⁹ High

pass filtering at 50 Hz or smoothing techniques have been used to condition these signals before feature extraction.³³

Graphing routines

Several graphic methods are important to display and interpret the data. One of the first requirements is the ability to view the data near real-time, for verification that the system is recording properly and the experimental setup is correct. This requires a quick display of the data on a monitor.¹¹⁴ Other requirements are rapid display of the data in a “waterfall plot”, so that temporal and spatial relationships between electrogram complexes may be viewed. The results of an entire array is normally plotted to find the areas of block, double potentials, slow conduction, etc., in order to locate the circuit of an arrhythmia. Still other graphic displays require the placement of plotted electrograms in the locations where they were recorded. Because preliminary and final analysis of mapping data relies mainly on visual interpretation, graphic routines play a primary role in the design of a mapping system.

Feature extraction routines

Once electrograms have been recorded and displayed, it is important to rapidly determine the activation time in each electrogram. The activation time is the moment when the depolarizing propagation wave passes directly below the recording site. The recording electrode may be a unipolar, bipolar, or quadripolar electrode arrangement. Activation time determination may be

easy or difficult, depending on the waveform and the pathology at the site. For example, bipolar electrograms recorded from normal tissue during local stimulation are generally uniphasic signals,¹¹⁵ while recordings from ischemic sites can often have bizarre, long-duration, multiphasic signals.¹¹⁶ Accurate determination of activation time in these cases requires the use of several feature extraction algorithms to calculate the location of various electrogram landmarks, and combine them into a statistical approach that, when compared to a “standard of activation time”, achieves a low error rate.

There are many features that have been used to determine activation time of both unipolar and bipolar electrograms. A summary is presented below.

Several algorithms use the first or second derivatives of electrogram signals to establish features used in analysis, and inquiry of the most appropriate difference equations for this purpose was undertaken by several investigators. Marble et al. found that the five point Lagrange difference equation was best suited for 12-bit data, with negligible error rates.¹²⁷ Blanchard et al. tested four digital algorithms (1, 3, 5, and 17 point difference equations) for reproducibility on unipolar electrograms and found that although the 17-point second order data fit algorithm performed slightly better than the five-point algorithm, it did not increase its accuracy enough to justify its use because of its high calculation time.¹²⁸

Table 2. Summary of electrogram features used for activation time analysis

Electrogram Feature	Description	Unipolar	Bipolar	Used by
Peak positive voltage	Maximum positive voltage		✓	Durrer, ¹¹⁷ Gallagher, ¹¹⁸ Kramer, ¹¹⁹ Witkowski, ¹²⁰ Pieper, Ndrepepa ¹¹⁵
Secondary peak voltage	Maximum positive voltage of secondary deflection		✓	Ndrepepa ¹¹⁵
Peak negative voltage			✓	Ndrepepa ¹¹⁵
Maximum positive derivative	Positive slope		✓	deBakker, ¹²¹ Ndrepepa ¹¹⁵
Maximum negative derivative	Negative slope	✓	✓	Paul, ¹⁷ Ndrepepa, ¹¹⁵ Spach, ²² Anderson ^{122,123}
Peak-to-nadir second derivative	Absolute value of d^2V/dt^2		✓	Anderson ¹²³
Absolute potential	Absolute voltage value		✓	Paul ¹⁷
Potential onset	Onset of electrogram		✓	Paul ¹⁷
Morphological	Assignment varied based on # of peaks		✓	Pieper ¹⁸
> 45° angle shift from baseline	Upstroke from baseline reaches 45°		✓	Scherlag, ¹²⁴ Paul ¹⁷
Zero crossings	Signal crosses baseline		✓	Wyndham ¹²⁵
Ratio of dV^2/dt^2 to absolute potential		✓		Spach, ¹²⁶ Anderson ¹²³

Statistical analysis

Although a number of reports employing the electrogram features described above have examined those features to discover which best identify activation time with the lowest error, none has yet to provide a foolproof marker or set of markers.^{11,129} It is clear that a statistical analysis of these features is required for optimal analysis. Anderson et al. suggested that optimal criteria for detecting local activation depends on the characteristics of grouped electrogram signals of an experimental protocol, and that a statistical approach is required to identify criteria for a given protocol.¹²³ In addition, the selected features must be compared to a “standard of activation”, which accurately and objectively represents the true activation time. In most reports, electrogram features have been compared to the visual detection of activation time by investigators.¹¹⁸ This approach is limited by the subjective bias of investigators, and clearly requires a better standard against which more accurate comparisons can be made. Furthermore, an appropriate standard of activation time should strongly reflect biophysical theory, be reproducible, and have the ability to allow examination by many investigators. Anderson and colleagues developed a “standard of activation” based on electrode location, evidence of propagation, and a computed bipolar electrogram which was used to compare with several electrogram features.¹²³ Additionally, they applied receiver operator characteristics¹³⁰ (ROC) curves to the features as a statistical test of accuracy in an attempt to separate local

from distant activity. They then applied statistical tests on those features and proposed a linear combination of features as the best discriminator of local from distant activation. If a standard of activation can be described for a population of signals, then by use of statistical tests, it is possible to characterize each activation feature as a probabilistic measure that the feature correctly identifies local activation time. In this manner, the features with the highest probability are selected as the markers for activation time, and theoretically should provide the lowest error rates compared to other nonstatistically or nonbiophysically based techniques.

Toward an ideal automated electrogram analysis algorithm

If local activation times can be correctly identified by use of a standard of activation time combined with statistical techniques, then it is possible to incorporate these findings into an algorithm which could be applied automatically. This would represent a significant achievement in electrophysiology because of the number of serious problems it would solve.

Firstly, clinicians who perform invasive electrophysiologic evaluation of patients with arrhythmias require a method of quickly determining parameters that describe the arrhythmias they are diagnosing. Currently, there are no universal features or algorithms that can be applied to accurately aid the electrophysiologist in this concern.

Secondly, mapping data contains massive amounts of data, much of which has to be analyzed both automatically by computer algorithm as a first pass, and then manually in a second pass, to find the best location or feature that describes activation time, and is, therefore, a considerable time sink.

Thirdly, because there are no universal rules governing the assignment of activation time, it is performed by sets of individualized guidelines, perhaps subjectively biased, and this makes comparison of findings between different laboratories more difficult to reconcile.

There are several problems to overcome in attaining the goal of an automatic activation time detector. First, is the need to utilize different types of data analysis from the same type of data sets. This will occur because, for example, patients' hearts will have different amplitudes of voltage potential due to heart size, pathology, percentage of fatty tissue below the derma, etc. Second, mapping is performed in many different animal models, and this will require that the parameters used in a detector to be variable. Third, is the fact that different arrhythmias from different pathologies are studied, and will require major changes accordingly. For example, the electrogram characteristics of atrial electrograms obtained from atrial fibrillation are very different from ventricular electrograms obtained from failing hearts.

Furthermore, the ideal automated activation time detector should be flexible enough to be used by a life scientist or clinician whose computer

skills are not those of a computer professional. This allows the features of the program to grow in an “open architecture” environment, giving users, who have considerable professional skills other than “computerese”, the ability to contribute to scientific understanding. This formulation is in sharp contrast to many commercial ventures which seek to monopolize information for their personal profit. A number of recent events have shown how an open architecture can create significantly improved working environments. The most popular example was IBM’s decision in 1982 to provide full details of its first personal computer, a decision which catapulted its use into a common household and academic item within a few years.

With this approach in mind, programs should be written in the most universally accepted environment. Currently, this translates into using the Windows or Windows ’95 (Microsoft Corp., Redmond, OR) operating system environment, which is common in electrophysiology labs today. To eliminate redundancy, cost overhead, and decrease development time, programs should take advantage of commercial packages that already exist, which can be tailored to carry out the specific tasks required. This may include spreadsheets, databases, graphics, data visualization, signal processing, statistical analysis, all combined with Object Linking and Embedding (OLE) and Dynamic Data Exchange (DDE) capabilities. There are a number of customized packages, already commercially available, that take advantage of this approach. SYSTAT for Windows, ver. 5.2, ¹³¹ recommends that the data

be input or obtained through Microsoft Excel 5.0, ¹³² then input into their package to perform high level statistical analysis. Many data acquisition software packages already provide a direct conduit from acquired data into an Excel spreadsheet. It is not advocated to use all of these commercially available packages, because to do so would pose an integration problem with unnecessary burdens. The package should include the fewest number of software packages that gives “user friendliness”, high flexibility, accuracy of data interpretation, and allows for future discoveries to be implemented easily.

Computer-assisted mapping techniques in the clinical setting

The clinical electrophysiology laboratory began about 25 years ago as knowledge of electrophysiology and techniques became available to diagnose successfully and manage arrhythmias. ⁴¹ Even now, electrophysiological data obtained by invasive procedures are considered the standard for the diagnosis of most tachyarrhythmias. ⁴¹ Electrophysiologic procedures are indicated whenever ECG diagnosis of arrhythmias are uncertain. These studies are often used to guide therapy and to test its efficacy. They are required before implantation of implantable cardioverter-defibrillator devices. The indications for these studies has grown tremendously over the past 25 years, and promises to grow still further as therapies become more and more tailored to newly discovered specific mechanisms of arrhythmias.

Electrophysiologic evaluation consists of obtaining waveforms under a variety of conditions, and analyzing those waveforms for abnormalcy. Recordings are obtained by the placement of catheters through the femoral or jugular arteries or veins, and positioning them on the endocardial surface of the heart, locating precise positions with the aid of fluoroscopy. The catheters come in a wide variety of types, but generally contain between 2 and 16 electrode recording or stimulating sites. It is common for more than one catheter to be inserted at a time. Once proper placement has been achieved, two electrode sites are selected for stimulation, and the remaining electrodes are used for recording. Early clinical mapping systems consisted of catheters with electrodes inscribed at or near the proximal tip which were positioned in the endocardial surface of the heart, connected to a series of analog amplifiers. The outputs were fed to a monitor and to a photographic device, allowing several recordings to be viewed simultaneously. As computer technology became available, the bipolar signals were fed into operational amplifiers, digitized utilizing analog-to-digital circuitry, filtered with real-time digital filters, and moved to a storage device (typically a hard disk or optical disk).¹³³ Post-processing of the signals was greatly enhanced, as notch filters to reduce 60 Hz electromagnetic interference became possible, and selection of only useful waveforms, scaling, and other techniques utilizing digital technology became available. Analysis algorithms were introduced which improved upon the accuracy and objectivity of the recorded signals. The number of recordings channels increased dramatically as

multiplexors became available. Endocardial catheter recordings are commonly obtained from most invasive electrophysiologic procedures, with up to 16 bipolar electrodes used for stimulation and recording.^{52,90,91,133}

Currently in clinical trials is a “basket electrode”, which consists of 84 electrodes which open up in an umbrella-like fashion after the catheter is properly positioned in the heart.¹³⁴

Therapy for arrhythmias

After an arrhythmia has been diagnosed, and an understanding of its origin or mechanism understood, a variety of therapies are available for matched treatment, and include the use of drugs, surgery, ablation, or implantation of electronic devices. The choice of therapy depends on many factors, including severity and type of disease, age, type of arrhythmia, and mechanism of the arrhythmia. The following is a brief explanation of therapeutic modalities currently available to electrophysiologists to manage arrhythmias.

Antiarrhythmic Drugs

Agents which modify myocardial cell electrophysiologic behavior have a storied past. The first drug used for the treatment of ventricular and supraventricular arrhythmias was quinidine, widely used since 1918.¹³⁵ Another drug of historical and clinical importance is digitalis, a product obtained from the dried leaf of the foxglove plant.¹³⁵ These and others have

been used to prevent death due to ventricular tachycardia/fibrillation or to improve the quality of life by preventing or suppressing arrhythmias or the symptoms of arrhythmias. The mechanism of action of drugs on myocardial cells is complex and many aspects remain unknown, however, they continue to play a large role in the management of arrhythmias. Foremost in our approach must be an intimate understanding of the alterations of channels and their properties during and after pathologic occurrences, and how these changes effect the whole organ properties. The Vaughn-Williams classification scheme for antiarrhythmic drugs was devised to characterize drug effects on cellular electrophysiology.¹³⁶ A recent paper criticized this scheme, and proposed modifications based on the concept of “vulnerable parameters”, which might be most accessible to drug effect.¹³⁷ As electrophysiologists investigate drug effects on protein synthesis and regulation and cell properties, in order to understand these effects at the whole heart level, mapping techniques must be utilized.

A watershed in drug treatment of ventricular arrhythmias after myocardial infarction was the Cardiac Arrhythmia Suppression Trial (CAST).¹³⁸ This study was designed to assess the efficacy of Class Ic antiarrhythmic agents compared to a placebo in the largest multicenter study ever conducted by the National Institutes of Health (NIH) for cardiac treatment. Approximately 5-10% of patients who develop myocardial infarction die suddenly from ventricular tachycardia/ventricular fibrillation

in the US currently. CAST was designed to test whether the Class Ic drugs, flecainide, encainide, and moricizine, all acting primarily by blocking sodium channels, and thus slowing conduction, could reduce the incidence of sudden death in this population. These drugs had been shown to markedly suppress ventricular ectopy.¹³⁵ Analysis of the CAST study found that nearly twice as many patients taking these drugs had died suddenly compared to those on placebo, and the study was abruptly halted.¹³⁸ While many electrophysiologists thought that the slowing of conduction would reduce the incidence of ventricular tachyarrhythmias, unforeseen was the reality that significant lethal proarrhythmic consequences were also at work. A recent report from our laboratory described a basic proarrhythmic mechanism of action of flecainide in this setting.¹³⁹ In that report, Restivo et al. described no significant change in refractory measurements between normal and ischemic tissue, but instead, found significant rate-dependent slowing of conduction in ischemic tissue. This slowing, combined with no change in the activation pathway, allowed additional time for a wavefront to reexcite an area proximal to the initial site of block and develop a reentrant rhythm.¹³⁹

Interest has recently shifted from Class I agents to Class III agents, those that prolong refractoriness. However, these agents typically have their greatest effect at slow heart rates,¹⁴⁰ while it is preferred to have most effect at high heart rates, the so-called reverse-use-dependent effect. Experimental

work to design and discover a “magic bullet” treatment remains the foremost challenge to antiarrhythmic therapy.

Ablation

Since arrhythmias often have a critical localized site which is necessary for its perpetuation, it has long been sought to locate this site and destroy it, with the ultimate intent of negating the arrhythmia. Accurate location by mapping techniques of a site causing a conduction disturbance is often used to deliver radio frequency energy of sufficient power that the site can be selectively and permanently destroyed.^{41,141-143} Radio frequency energy causes cell death by evaporation of intracellular water and desiccation, and has several advantages over the formerly used direct-current method: 1) it does not cause arcing or barotrauma; 2) there is no risk of bubble formation or gas embolization; 3) the procedure is painless, so anesthesia is not required; and 4) it causes less damage to electrode catheters, causing less problems with misdirected energy.¹⁴⁴ Ablation has been most successful in treating supraventricular tachyarrhythmias because the critical site is easily mapped and the ablation catheters can be guided to deliver their energy precisely. Other arrhythmias readily treatable by this technique are the Wolff-Parkinson-White syndrome, atrio-ventricular nodal arrhythmias, and His bundle disturbances.¹⁴⁴ Ventricular tachycardias remain difficult to ablate successfully because locating the critical site is much more difficult.¹⁴³ There are a number of reasons: 1) the ventricles are

much thicker, and the critical site may be located deep in the subendocardial muscle layers, making endocardial recordings difficult to analyze and ablation catheters difficult or impossible to position; 2) electrogram recordings of long duration, fractionated, multiphasic waveforms remain difficult to analyze; and 3) the area of the ventricles are much larger, requiring acquisition and analysis of massive amounts of data, which is still beyond the technological reach of most clinical electrophysiology laboratories.

Surgical resection

Incessant ventricular tachycardia is often managed by surgical resection,¹¹⁸ which initially requires mapping of the ventricle to localize the critical site, which may either a focal site giving rise to the arrhythmia, or a zone of slow conduction of a reentrant tachycardia. Anti-tachycardia/defibrillator electrical devices are not indicated in these cases because the arrhythmia occurs spontaneously and frequently, and the use of electrical devices would quickly discharge the battery or over-challenge their capability. Surgeons normally perform a midsternal thoracotomy to expose the heart, place the heart on cardio-pulmonary bypass, and after localizing the site based on a combination of epicardial and endocardial recordings, surgically remove the site. This technique is very costly, time consuming, and has highly variable success rates.

Electro-therapy

Electrical devices which can sense, pace, and shock the heart out of a lethal arrhythmia have become increasingly popular due to their sophistication, compactness, lowered cost, extended lifetimes, ease of installation, and sophisticated programming abilities. Pacemakers have been employed to prevent the deleterious effects of sick sinus syndrome, atrio-ventricular disorders, and other supraventricular or nodal disturbances. The basic features of the modern pacemaker include both sensing and dual chamber pacing abilities, obtained from lead wires affixed to the endocardial surface on one end, and to a small stainless steel encased unit embedded subcutaneously on the precordial body surface on the other end.

Antitachycardia/defibrillation devices are designed to sense a lethal arrhythmia, make attempts to pace the heart out of the arrhythmia and back to sinus rhythm, and when all else fails, deliver direct current shocks to terminate the arrhythmia. The size of these devices is greater than those of pacing-only devices, but they can still be implanted in a pouch subcutaneously in the precordial body surface. The commercial introduction of these devices has significantly affected the management of arrhythmias, particularly after the results of CAST.⁴¹

Combinational therapy

Antiarrhythmic therapy which uses two or more approaches to management is termed combinational therapy. It may include the use of

several different pharmacologic agents, or include treatment from different modalities. For example, a common treatment for spontaneous monomorphic ventricular tachycardia is to insert an Automatic Implantable Cardioverter/Defibrillator (AICD), and give amiodarone, a drug which has Class I, II, III, and IV properties.

Electrogram analysis

The cardiac activation sequence and potential distribution are routinely determined through the analysis of multiple local electrograms recorded from the heart. The interpretation of extracellular waveforms in the intact heart is based on theoretical studies of normal tissue using idealized recording electrodes and experimental data from isolated tissue preparations from normal hearts. The most common modalities for measuring extracellular electrical activity are the unipolar and bipolar recordings.

One of the primary benefits of unipolar electrograms in normal myocardium is that they provide much information for which the interpretation is supported by biophysical theory. As early as 1879, Hermann provided mathematical insight into the understanding of extracellular potentials. In a seminal work, Spach et al. found that the maximum negative derivative, or intrinsic deflection, of unipolar extracellular electrograms obtained from isolated Purkinje strands coincided with the upstroke of intracellular action potential recordings obtained in

close proximity.¹⁶ Biophysical theory of the core conductor model in a one dimensional model¹³ or multidimensional tissue structure¹⁴⁵ have been used to depict accurately extracellular waveforms from intracellular parameters.¹⁴⁶

For multichannel recording systems, unipolar recordings have the additional benefit that either fewer wires need be brought out from the heart or more sites can be recorded. Unipolar electrograms are more commonly used for isopotential mapping. Because of the large electrical “view” of a unipolar electrode, much of the waveform reflects distant electrical events (Figure 18A, top). The inherently long electrogram duration and contamination by distant effects are less desirable for activation mapping, where the main goal is to determine the moment of activation. Though new analysis tools have been applied to the analysis of unipolar electrograms,¹²³ the usefulness, to date, of unipolar electrograms recorded from diseased hearts for activation mapping has not been firmly established.

The bipolar electrogram is the most common recording modality used in clinical electrophysiology and in experimental activation mapping studies. Because the output of the differential amplifiers used to record bipolar electrograms is the potential difference between the two inputs, common mode distant potentials are significantly attenuated, with the resulting bipolar signal generally having a shorter duration and a more distinct activation potential (Figure 18A, bottom). However, there are problems with

bipolar recordings, such as sensitivity of bipole orientation to the direction of propagation, and electrode contact, which may result in drastic and inaccurate changes in the morphology of the electrogram. As an example of this problem, consider the diagram of Figure 18B, showing two idealized electrodes separated by some distance x lying on the horizontal plane. When the direction of activation is also horizontal, or parallel to the sites, a sharp deflection is recorded and the moment of activation is the intrinsic deflection, which occurs when the signal passes midway between the sites. However, if the activation wavefront is vertical, or perpendicular to the recording sites, then the bipolar result is always zero, since each site records exactly the same potential at all times. Since it is seldom possible to know a priori the direction of the activation wavefront, this problem remains a persistent possibility during mapping experiments.

Generally, the analysis of bipolar electrograms is based on subjective visual interpretation. The criteria for activation time determination varies amongst investigators and is based loosely on theoretical models which have not been experimentally validated in the intact heart. There are very few theoretical studies on activation time determination in bipolar signals.¹⁵ The analysis of bipolar electrograms from diseased states of the heart, such as myocardial ischemia, for which there is little or no theoretical foundation, is further confounded.

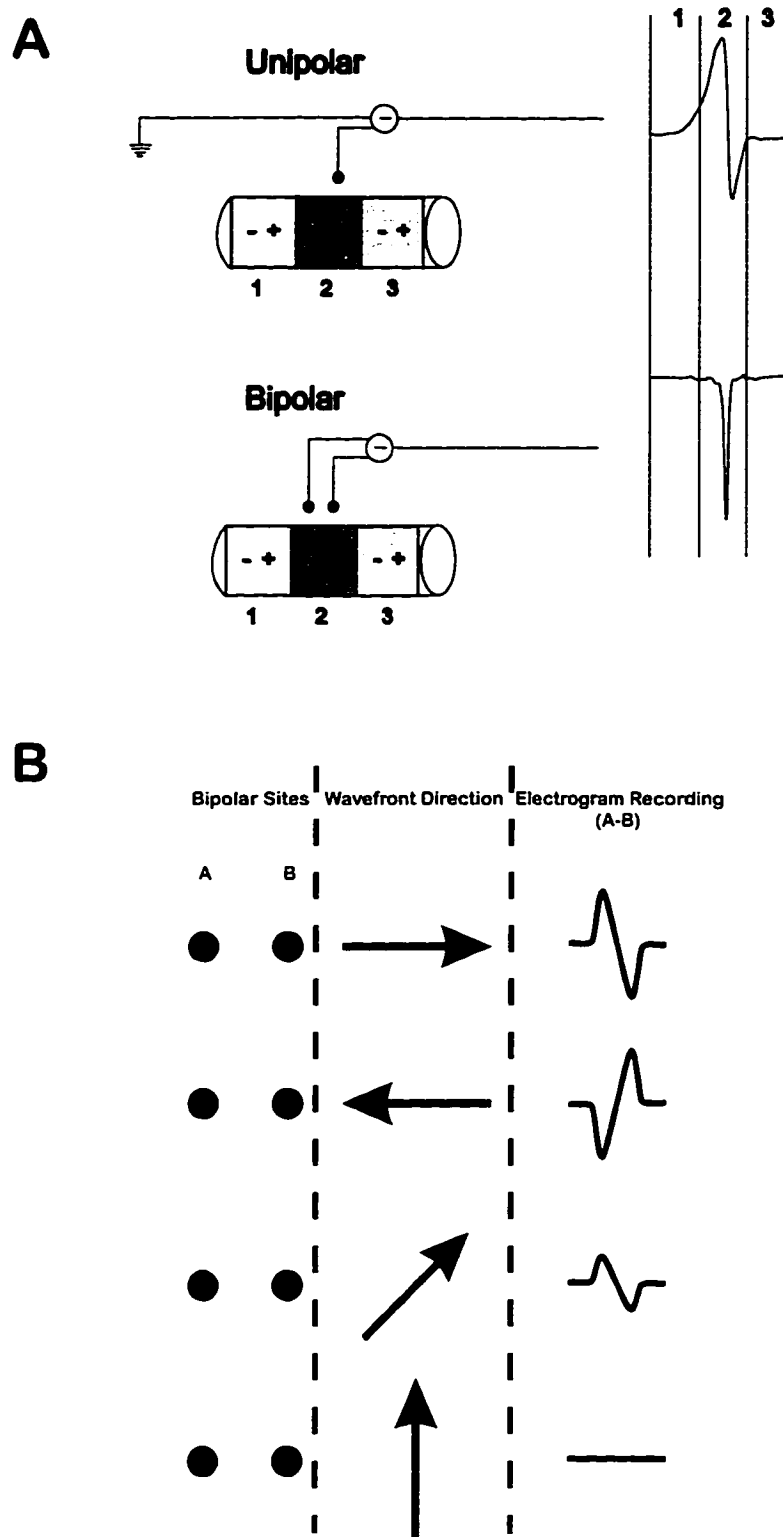


Figure 18. Idealized bipolar electrograms based on orientation of bipoles to wavefront direction.

Therapeutic techniques such as radio frequency catheter ablation depend on a sound understanding of the signals recorded from the heart and have the potential for the treatment of lethal ventricular tachyarrhythmias in humans. New catheters have been developed which allow recording from dozens of endocardial sites. Advances in electrographic identification of target sites for ablation or surgical resection are lagging. Much of the confusion revolves around recordings of fractionated multicomponent electrograms, that have been ascribed to slow conduction, circuitous conduction and/or conduction block by using deductive analyses based on limited or misapplied biophysical theory.^{50,147-149} The distinction between slow conduction and conduction block in both functional and anatomical models remains a source of controversy.^{47,51,147,148,150} Further complicating the issue is the fact that fractionated electrical activity can be recorded from sites which are unrelated to the reentrant arrhythmia.¹⁴² Thus distinctions must be made: 1) between local activation directly below the recording bipoles and distant electrotonic potentials; and 2) the difference between slow conduction and conduction block. Even though bipolar signals significantly attenuate distant potential recordings, Blanchard and coworkers have shown that extracellular bipolar electrograms remain heavily influenced by distant activation potentials unrelated to activation in the tissue immediately beneath the electrode.¹⁵¹

Restivo et al. have shown that discrete activation events may occur on a millimeter scale and cautioned that electrical activity from electrodes with wide bipolar spacing or high highpass filter settings may produce misleading results.⁴⁷ They used closely spaced bipolar recordings, with pairs separated by 1 mm to show that large, discrete differences in activation time exist across an arc of functional conduction block.⁴⁷ Based on the work of Spach and coworkers relating fractionated atrial signals to inhomogeneities in tissue orientation, Dillon and coworkers have analyzed long duration, multicomponent electrograms from the border zone of abnormal myocardium overlying infarcts, and hypothesized that very slow circuitous conduction occurs across the longitudinal fiber axis rather than long arcs of block as previously believed.⁵⁰ Because both groups^{47,50} use the same animal model, it seems reasonable that the differences are mainly due to the recording methodology. This controversy has been addressed recently in an editorial comment by Spach.⁵¹ Because there is almost no theoretical basis for the analysis of electrograms recorded from diseased myocardium, the criteria by which electrograms are analyzed vary widely amongst investigators. These problems associated with the interpretation of extracellular electrograms have been recognized by many investigators and point to the need for detailed analysis of electrical activity recorded from normal and ischemic myocardium.^{11,74}

Background of work accomplished by the candidate relating to the dissertation project

The following mapping studies were performed at the Brooklyn Veterans Administration Medical Center during the candidate's training. This work provides a background of the problems associated with activation mapping and analysis of extracellular electrograms. The candidate was involved in all phases of these studies and is a co-investigator on all reports summarized here.

One of the recent objectives in our laboratory was to study the effects of antiarrhythmic compounds on conduction properties of normal and ischemic myocardium.¹³⁹ We have studied the effects of flecainide, a Class Ic antiarrhythmic, which has recently been shown to provoke lethal proarrhythmia in humans. Using whole heart activation mapping, it was found that flecainide was arrhythmogenic, especially at more rapid basic cycle lengths. Applying high resolution mapping techniques, flecainide had no effect on effective refractory periods of normal and ischemic tissue but, in a selective and rate dependent manner, depressed conduction in ischemic versus normal tissue. It was concluded that in this model, the arrhythmogenic effect of flecainide is due to preferential slowing of conduction in the ischemic central pathway of unmodified lines of conduction block.

We have recently published results that indicate that lidocaine, a Class Ib local anesthetic most often used in the acute phase of myocardial infarction, can be both proarrhythmic and antiarrhythmic.¹⁵² Figure 19 shows isochronal maps in control and following lidocaine infusion. The right panels show that after a basic drive of 29 S₁ beats at 500 msec, a premature stimulation, S₂, elicited only a single reentrant response, V₁, which blocked at the entrance to the slowly conducting reentrant pathway. When the basic drive cycle length was shortened to 300 msec, conduction during S₂ was even slower in the central pathway and a sustained monomorphic ventricular tachycardia was induced. Results (not shown) also showed that lidocaine can prevent reentry at both fast and slow rates, by blocking at the entrance to the slow zone, due to markedly prolonged refractoriness at these sites.

Utilizing high resolution techniques, the selective effects of lidocaine on conduction in normal and ischemic tissue were also studied. Figure 20 illustrates the rate dependent and tissue dependent effect of lidocaine; conduction velocities are normalized to the 600 msec cycle length. The right panels show that the rate dependent depression of conduction was more pronounced in the central reentrant path located in the ischemic zone when compared to the normal zone (left panels). This result was independent of propagation with respect to fiber orientation (top vs. bottom panels). The rate dependent slowing of conduction by lidocaine can be used to explain its proarrhythmic effect at faster rates. However, unlike flecainide, analysis

showed that lidocaine prolongs refractoriness in the ischemic zone. This can result in a slightly longer arc of block (proarrhythmic, by increasing the pathway) or an arc which is long enough to prevent the activation impulse from entering into the central pathway (antiarrhythmic, by blocking entrance to the central pathway).

In another study, the electrophysiologic mechanisms of the spontaneous termination of sustained ventricular tachycardia were investigated.¹⁵³ Epicardial activation maps were obtained from 8 dogs, 4-5 days after ligation of the left anterior descending artery. During the subacute phase of myocardial infarction, programmed premature stimulation of the ventricles often induces a sustained, monomorphic ventricular tachycardia, due to circus movement reentry with a characteristic figure-8 pattern (see Figure 14), which sometimes terminates spontaneously. Isochronal maps of 20 of these terminations, 30 seconds to 10 minutes after induction of the tachycardia, were analyzed utilizing a sock electrode array comprising 254 bipolar recordings, with a high density of sites, 2.5-2.8 mm apart, over the infarct. Two basic mechanisms of termination were observed: 1) an acceleration of conduction occurred in some parts of the reentrant circuit while conduction slowing occurred in the central common pathway, leading to conduction block in this zone; and 2) a breakthrough across a stable arc of block occurred, leading to premature activation in the central common pathway and conduction block.

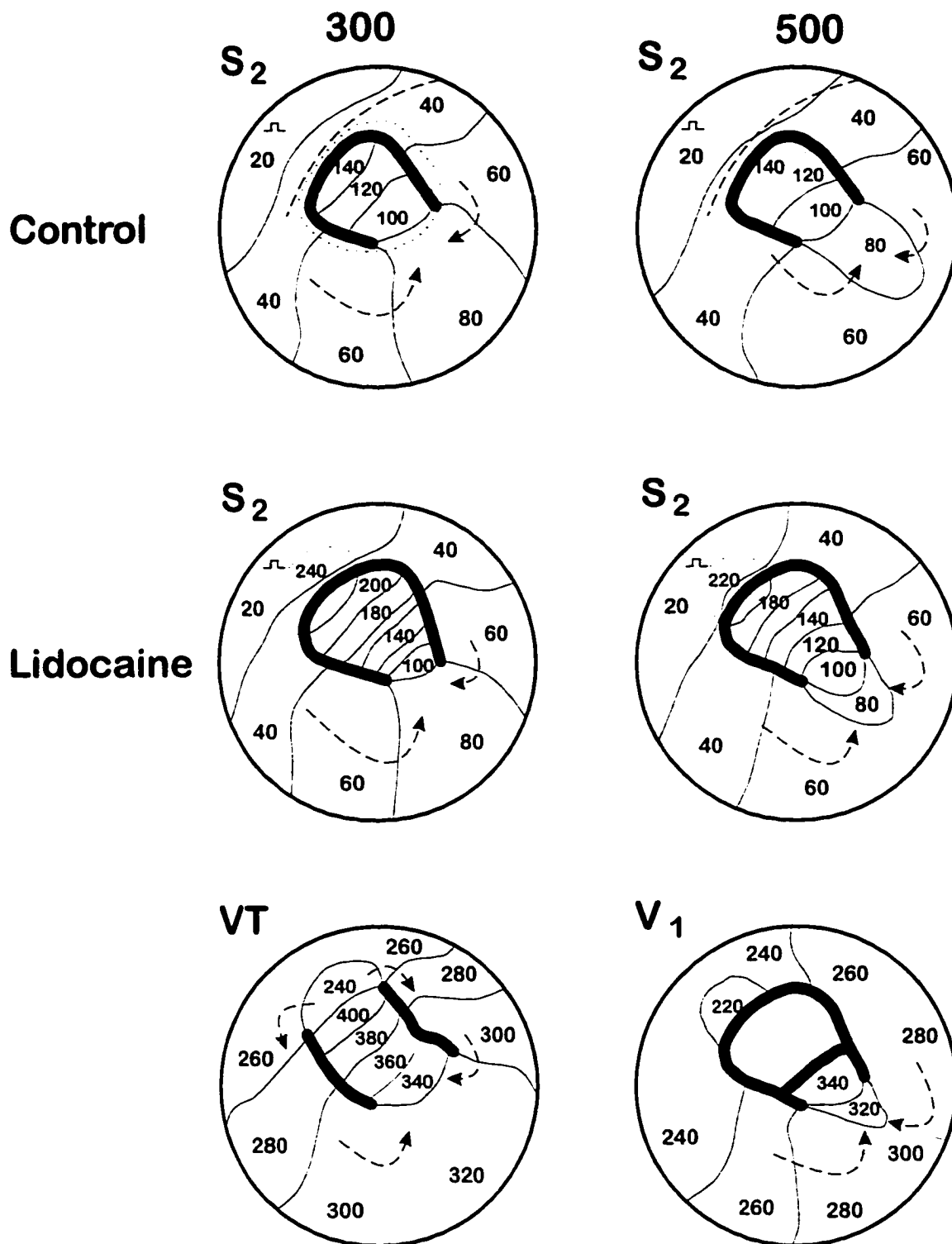


Figure 19. Isochronal activation maps during control and after lidocaine infusion.

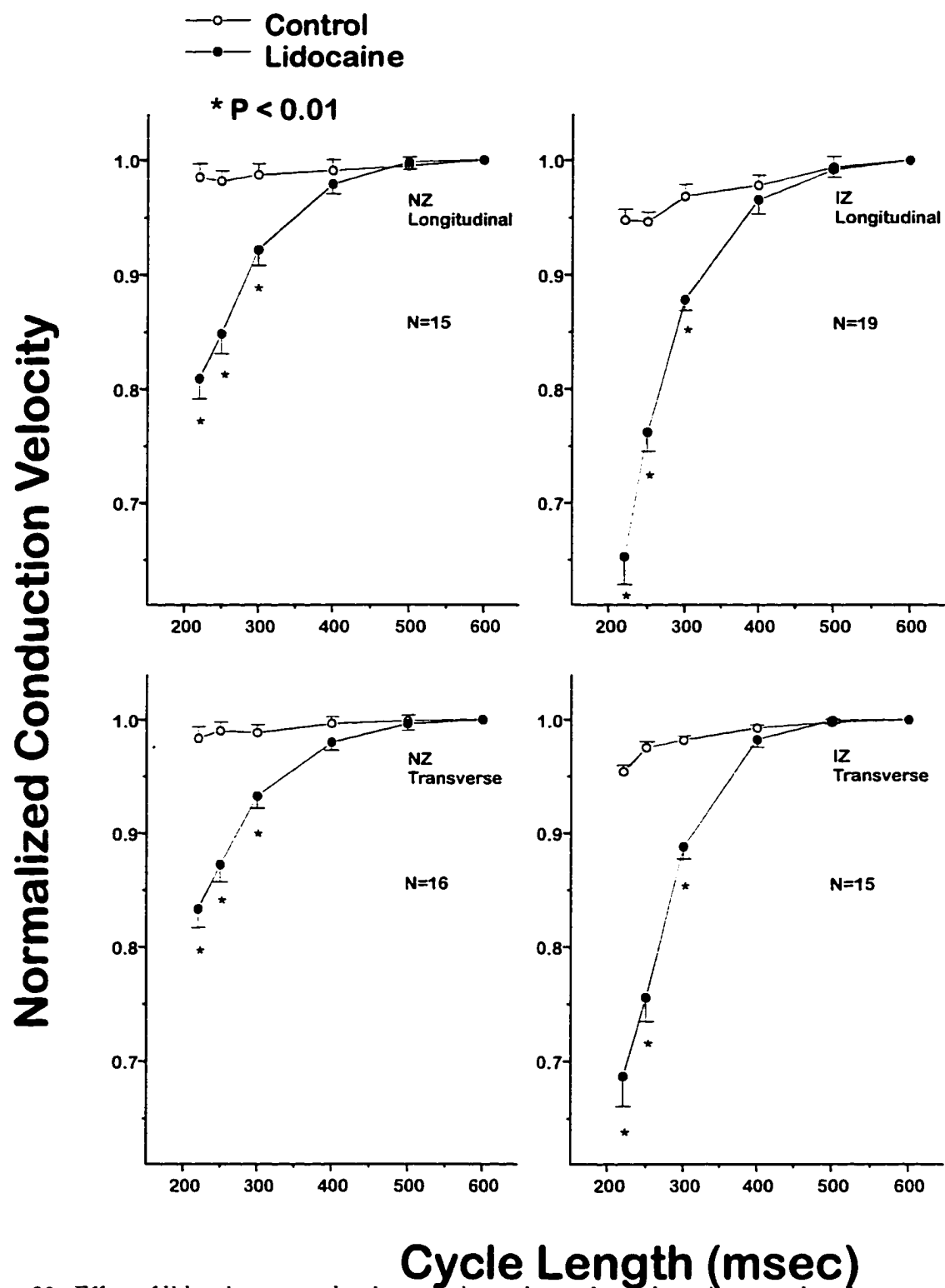


Figure 20. Effect of lidocaine on conduction velocity and rate dependence in normal and ischemic zones

The electrophysiologic effects of azimilide dihydrochloride, a Class III antiarrhythmic agent, were investigated in the canine sterile pericarditis model of atrial flutter.¹⁵⁴ This model is produced by dusting talcum powder on the right and left atria, and after allowing the resulting irritation to the atrial surface continue for 3-5 days, a stable, uniform, sustained circus movement atrial flutter can usually be induced by burst stimulation. Isochronal activation mapping of the right atrium was performed in 8 dogs with a nylon mesh sock containing 138-222 bipolar electrodes sutured to the epicardial surface. Only the right atrium was mapped because it was previously found that the reentrant circuit predominately occurs there. Conduction and effective refractory period properties were measured in control and after administration of 3, 10, and 30 mg/kg iv. infusion of azimilide. The drug terminated the arrhythmia in all 8 dogs, 3 at the 3 mg/kg dose, and all at the 10mg/kg dose. Atrial flutter could not be reinduced in 2 dogs at 3 mg/kg, 4 dogs at 10 mg/kg, and all 8 dogs at 30 mg/kg infusion of azimilide. The cycle length of the flutter always increased prior to termination, and mapping showed that the increase was due to conduction slowing in a slow zone of the reentrant circuit. In addition, termination of flutter always occurred in the slow zone, situated in the lower right atrium between the line of functional conduction block and the atrio-ventricular ring. Effective refractory period measurements at selected sites showed that azimilide preferentially prolonged refractoriness in the slow conduction zone compared to the normal conduction zone (42 ± 20 msec

vs. 23 ± 15 msec, $p < 0.0001$). Furthermore, the increase in cycle length observed just prior to termination of the flutter corresponded to the increase in refractory period in the slow zone.¹⁵⁴

The electrophysiologic effects of azimilide were also investigated in the canine subacute model of myocardial infarction, by employing high resolution activation mapping techniques. Ligation of the left anterior descending artery was performed in 14 mongrel dogs, and were studied 4-5 days later. Local conduction velocities were measured by a linear regression of activation time of closely spaced bipolar electrodes (0.5 mm interpolar distance) versus distance with a high resolution cross electrode array, and refractory measurements were performed at selected sites in normal and ischemic zones. At 3 mg/kg dose of azimilide, no significant electrophysiologic effects were observed. At 10 mg/kg and 30 mg/kg doses of azimilide, ventricular tachycardia was successfully terminated in 4 of 5 dogs, and suppressed the induction of reentrant ventricular arrhythmias in 5 of 8 dogs. There was no significant effect of azimilide on conduction velocity or stimulus threshold in either the ischemic or normal zones. There was also no change in the rate dependence (500 msec and 300 msec pacing) on effective refractory periods in either zone, however, the drug caused a significant preferential increase in effective refractory periods of the ischemic zone compared to the normal zone. This produced statistically significant lengthening of arcs of block in the activation maps, and the development of new arcs of block which led to

conduction block in the ischemic zone. It was concluded that the selective electrophysiologic effect of azimilide which prolonged refractoriness in the ischemic zone resulted in conduction block and termination of ventricular tachycardia and suppresses reentrant ventricular arrhythmias.

In another related area of electrophysiology, new optical mapping techniques were applied to study the contribution and location of EADs and dispersion of action potential duration (APD) in the genesis of polymorphic ventricular tachycardia (Figure 21).¹⁵⁵ The optical mapping technique was applied to 8 Langendorff-perfused guinea pig hearts infused with 100 µg/L toxin AP-A, which slows sodium inactivation kinetics and causes EADs and bradycardia-dependent polymorphic ventricular tachycardia and Torsades de Pointes. Infusion of the potentiometric fluorescent dye RH421 (150-300 nMoles) was also performed, and the fluorescent signals were captured with a 128 channel photodiode array focused on a 13 mm by 13 mm section of the epicardial left ventricular free wall. The accumulated current collected from each diode was transduced into a voltage signal via current-to-voltage amplifiers, sampled at 1394 Hz, multiplexed to an analog-to-digital converter, and moved to storage for off-line analysis.

The top panel of Figure 21 illustrates not only spatial dispersion of repolarization but also beat to beat alternans in APD and a 2:1 conduction pattern in part of the heart of a guinea pig in the presence of 25 µM AP-A. The data shown here represent selected sites for 4 successive beats at a drive

of 500 msec. While the antero-septal sites have a 1:1 pattern of APD, lateral sites exhibit increasing prolongation of APD with appearance of alternans of APD. At the most lateral aspect, the APD exceeded the basic CL and a 2:1 conduction pattern can be seen.

The activation maps for the first 2 beats and repolarization map of the first beat for the same experiment are shown in the lower panel of Figure 21. Stimulation was applied at the right ventricular outflow tract. The imaged region was the epicardial surface of the anterior left ventricle. The isochronal activation map (panel A) shows some conduction slowing between the 3 and 9 msec isochrones. In the following beat (panel A), the impulse wavefront encountered a continuous line of functional conduction block at the lateral aspect of the left ventricle, as indicated by the heavy solid line. Sites distal to the block corresponded to the short APD shown above. The isochronal repolarization map shows that conduction block was due to spatial discontinuities in APD. Interestingly, repolarization in this experiment seems unrelated to the activation sequence as was seen in normal anisotropic conduction. APDs proximal to the site of block range from 260 msec to 360 msec. In this experiment, there was a marked spatial gradient of APD at the lateral aspect (indicated by the heavy solid line), with APD ranging from 460 ms to greater than 500 ms (greater than the pacing interval). The border of spatially nonuniform APD corresponded to the location of the line of functional conduction block in map B.

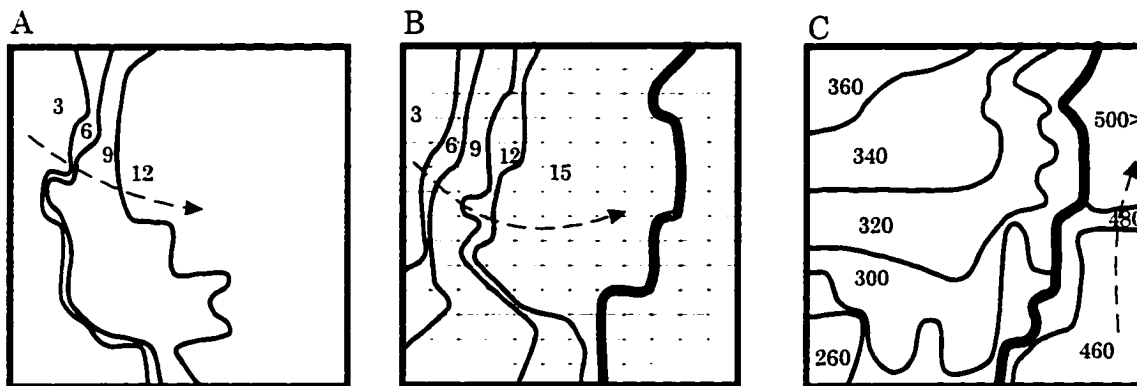
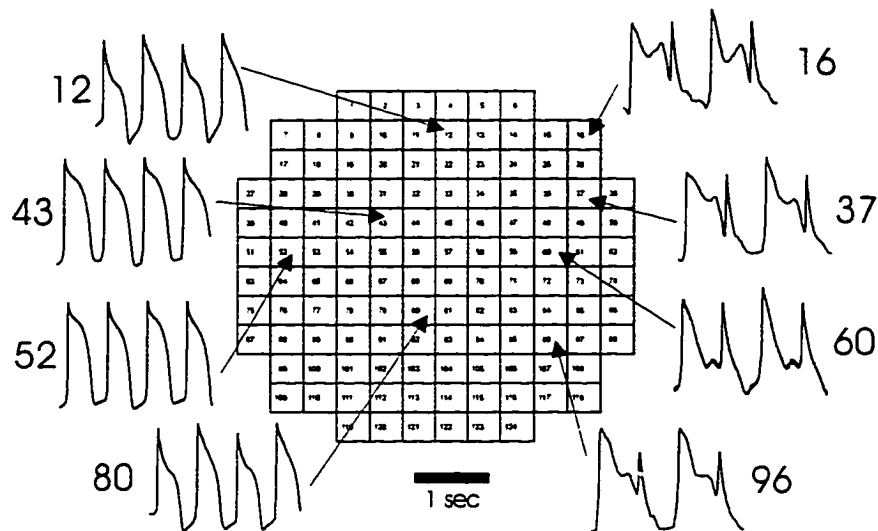


Figure 21 Optical mapping techniques were employed to investigate early afterdepolarizations and dispersion of action potential durations in the guinea pig heart.

Chapter IV . Design and Implementation of Computer Mapping System

Recording electrodes

Several types of recording electrodes were used for mapping, tailored to the specific requirements of different phases of the project. The most common material for recording is silver, which has a low offset potential and impedance.⁹⁷ The silver wires used as electrodes had diameters of 125 μm and 250 μm . They were insulated either by a Teflon coating or a polyurethane coating. For electrodes with very small diameters, tungsten wire of 50 μm diameter and polyurethane insulation was used.⁹⁷

Whole ventricle electrode array

A sock electrode array was fabricated for simultaneous recording at 254 epicardial sites (Figure 22A).¹⁵⁶ After a pair of tan nylon stockings was obtained, the stocking was cut approximately 20 cm from the toe, and the top portion discarded. The foot portion was slipped over a plaster mold of an adult canine heart. Anatomic locations such as the left anterior descending artery, interventricular septum, and atrioventricular groove were marked on the sock with a black permanent marker. The number and location of electrodes and each region of the ventricles was then marked with a dot, according to a design previously determined. To make the high resolution

recording area seen in the gray zone of panel B, a grid of dots was created by CorelDraw, ¹⁵⁷ and printed on 12 weight “onion skin” paper. The dots were 0.5 mm diameter, and were accurately patterned using the “Grid Layout” feature of the program. The high resolution recording area consisted of 16 rows, with alternating rows offset to the spaces bisecting the interelectrode distance. All rows were 2.8 mm apart, and the total number of recording sites in this area was 184. Approximately 1 cm of the Teflon coating of 125 μ m diameter silver wires was removed at the tip, leaving the remaining 49 cm insulated, and the tips were then inserted into the marked dots of the sock, using a magnifying glass for improved vision, and a double suture knot tied on the inside of the sock, aided with use of a forceps. Each pair of electrodes was formed in this manner until all wires were inserted. The distance between the poles was 0.8-1.2 mm.

The opposite ends of the wires were then exposed at the tips and were soldered into 36 pin Centronics connectors, each column containing one pole of the electrode, with 16 bipolar electrodes soldered to each connector. Each electrode was given a unique number and marked on a dotted diagram of the heart to register its location for later use. When it was time to place the sock array on the heart, the alignment was performed by placing the markings for the left anterior descending artery over the in situ vessel. After correct positioning was visually verified and the sock was manipulated to guarantee

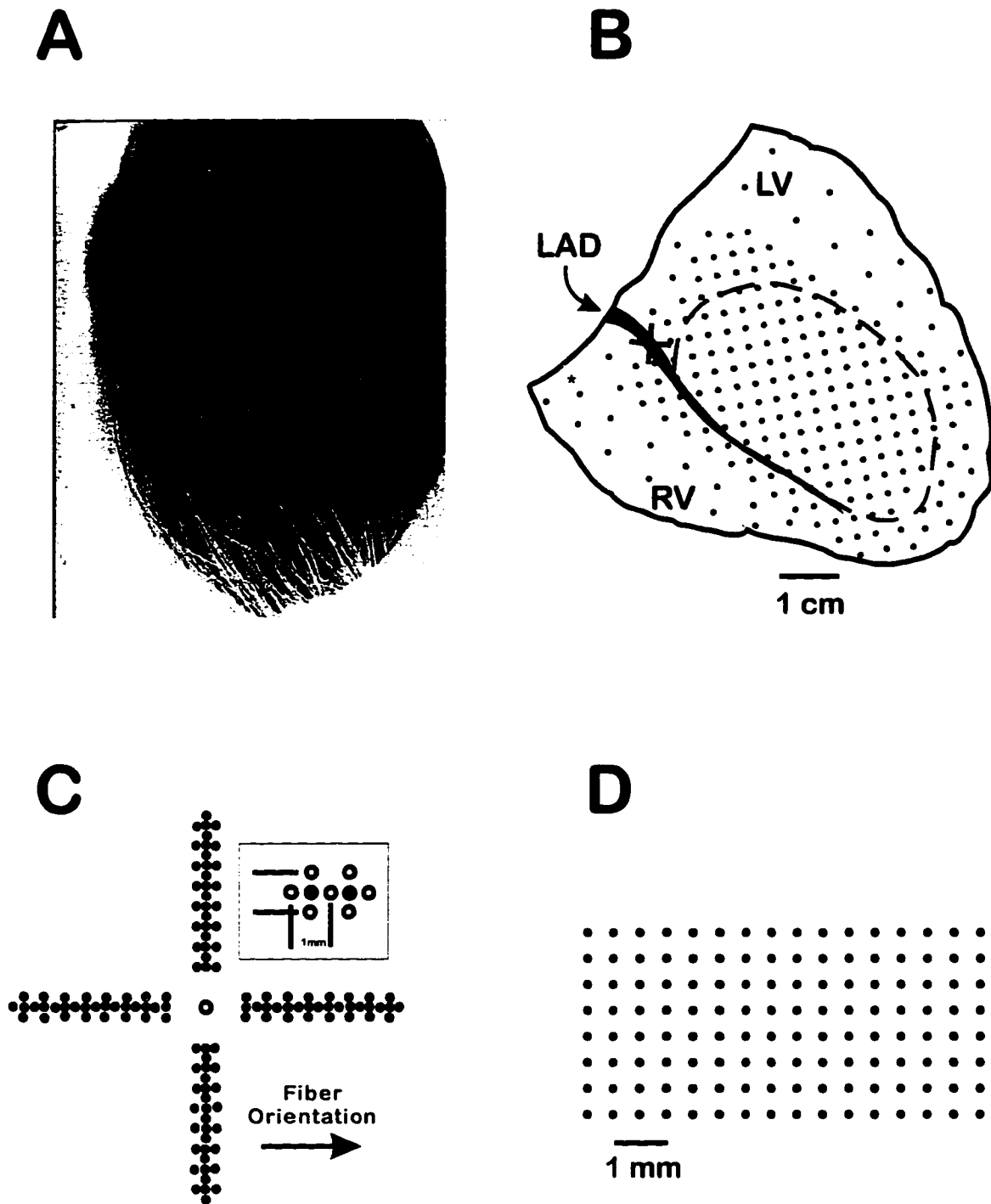


Figure 22. Picture of sock used for whole heart activation mapping (A), high resolution portion of sock (B), high resolution cross electrode array (C), and high resolution rectangular electrode array (D).

a snug fit so that all electrodes were in contact with the epicardial surface, calibration and testing recordings were obtained. After each use, the sock was removed and cleaned with an enzymatic detergent, and after drying was maintained to make sure that all connections remained intact and operable.

High resolution cross electrode array (HRCEA)

A schematic diagram of the HRCEA is shown in Figure 22C. The HRCEA consisted of 128 unipolar recording electrodes arranged in a cross configuration. Each limb of the HRCEA is comprised of 3 parallel columns separated by 500 μm . The center column of each limb consists of 16 electrodes with an interelectrode spacing of 500 μm , and the 2 lateral columns consist of 8 electrodes with a 1 mm interelectrode spacing in the radial direction. To minimize virtual cathode effects, the first recording electrode pole in each arm was situated 2 mm from the central unipolar wire (200 μm diameter) used for stimulation.¹⁵⁸

The HRCEA was constructed by imbedding Teflon-insulated silver wire (125 μm diameter) in a flexible acrylic matrix (Flexacryl, Lang Industries, Chicago, IL).¹³⁹ Best results were obtained using a ratio of 2 parts Flexacryl Hard to 1 part Flexacryl Soft (personal communication, David Lang, Lang Industries). The Teflon-insulated silver wires were passed through dots on a pair of "onion skin" paper squares which had dots printed accurately to specification by a graphic composed in CorelDraw. After the acrylic matrix was carefully and slowly mixed, allowing for few air pocket bubbles to

develop in the mixture, it was poured into a wax mold of the desired size the wire between the paper squares was embedded, keeping them parallel to each other by applying opposing force at the exterior parts of the paper. The whole arrangement was then placed into a vacuum housing for curing.

After 24 hours, the matrix was cut, trimmed and sanded to achieve the proper dimensions. The opposite ends of the wires were then exposed at the tips and were soldered into 36 pin Centronics connectors, each column containing one electrode, and the other column was soldered together and connected to a single reference located on the precordial surface of the dog. Since the electrodes were closely spaced, verification of each position was verified by the following technique. The array was placed in a 0.9% NaCl (saline) solution, along with a separate silver wire. The opposite end was attached to the negative terminal of a 9 Volt battery. Another silver wire was affixed to the positive terminal of the battery, and the opposite end connected to one end of a wire with two attached alligator clips. The other alligator clip was connected to the free end of the wires, one at a time. Using a large magnifying glass, the underside of the grid was viewed to watch for hydrogen bubble formation at one site of the grid, denoting the location of the wire being tested. In this manner, each wire was soldered in a numbered connector to assure that all electrode locations were properly known and connected. After each use, the array was removed and cleaned with an enzymatic detergent, and after drying, was maintained to make sure that all

connections remained intact and operable. The underside of the grid was polished with 400 grit wet sandpaper just prior to each experiment to maximize the conductivity of the unipolar recording electrodes, and permitted only the exposed cross section of the wire to contact the myocardial tissue. It was found that this procedure results in increased recording fidelity and lower current thresholds for programmed electrical stimulation.⁴⁷

High resolution rectangular electrode array

A high resolution rectangular electrode array was constructed by imbedding Teflon-insulated silver wire (125 μm diameter) in the same flexible acrylic matrix described above.¹³⁹ The rectangular electrode array consisted of 128 unipolar recording electrodes arranged in a 16 by 8 grid configuration with an interpolar distance of 0.5 mm (Figure 22D). The acrylic matrix was trimmed so that it extended 2 mm on all sides of the outside columns and rows, with a dimension of 11.5 by 7.7 mm, and so that it was 2 mm thick. Once an arc of block was located by whole ventricle isochronal activation mapping, the high resolution grid array was positioned at sites demonstrating double potentials, signifying where arcs of conduction block occurred. The grid array was placed so that the arc would bisect the long side of the rectangle.

Needle electrodes

To make transmural recordings extending from epicardial to endocardial surfaces, small bore needles (23 gauge, 350 μm inside diameter, 640 μm outside diameter) containing a set of 8 tungsten wires (California Fine Wire Co., Grover City, CA), each 51 μm in diameter and insulated with polyurethane, were fabricated to meet design needs, and was based on a report by Kassel and Gallagher (see Figure 45).¹⁵⁹ Each needle was cut from the pointed end to a 10 mm length backwards along its barrel to remove half of the metal housing with a Dremel high-speed multipurpose drill. After deburring and sanding to a smooth surface, the needle housings were set aside.

A guide for correct wire alignment within the needle was created with a graphic produced in CorelDraw, and consisted of 8 lines, each 250 μm wide, and 4 mm long. The printed lines were taped to a flat surface on both sides, and double sided sticky tape was applied just above and just below the lines. Eight wires, each 50 cm long, were then laid across the guidelines and pressed onto both pieces of sticky tape, holding their position fixed. Pieces of transparent tape were applied across the double sticky tape, holding the wires in place, and kept their spatial distance fixed. Two more pieces of tape were then applied, this time placed 1 mm from and parallel to the outside wires, which formed a small rectangular well that was filled with a thin film of 5 Minute Epoxy (Devcon Industries, Quincy, MA). After curing, the tape

was removed, and the hardened epoxy formed a straight edge at the base of the set of wires, which were securely embedded in the film of epoxy. The wires were then carefully bent 90° in a lateral direction at the point where the wires came out of the epoxy, and the opposite ends were fed into the needle bore until the flat end of the epoxy and the bent wires fit completely into the bore. The arrangement was then fixed with another coating of epoxy and held in place by sealing wax placed at the ends. After curing, the wax was removed and another coat of epoxy was applied to securely fix the wires to the bore of the needle. The epoxy coat was trimmed and polished flush to approximate the outside diameter of the needle, and the tips of the wires were now exposed in the correct spatial sequence. The opposite end of each wire were then exposed.

Testing and correct connecting was performed utilizing the procedure described earlier. The needles were placed in saline, along with an exposed silver wire. A 9 V battery connection of the silver wire and each tungsten wire, one at a time, completed the circuit, causing bubble formation at each electrode point in the immersed needle. A magnifying glass was used to pinpoint the site of the bubbles, and the opposite ends were soldered to a DB9 male connector in the correct position with most distal electrode, which is the most endocardial site, fixed as electrode #1, and the most proximal electrode (most epicardial site) fixed as electrode #8.

Other needles with sites having varying interpolar distances were also constructed for transmural activation purposes. For example, to record from septal locations, 4 pairs of electrode sites were configured, with the interpair distance of 1 mm, and pairs separated by 2.5 mm. However, these were mainly used for transmural activation mapping, while the needles described above were used for both activation mapping and correlation of refractoriness and activation-recovery intervals. This was performed by placing needles into a 5x5x2 mm acrylic plate which had 8 holes as guides 45° apart on circles of 2 and 3 mm diameter. One needle for plane wave stimulation was placed in the center of the circle, constructed by placing a 7 mm exposed section of silver wire fixed with epoxy into a 23 gauge needle.

Cabling system

All electrode systems had connections which were soldered to male Centronics connectors. For the plunge needle electrodes, an extension was made from 36 wire flat ribbon cable, having 4 DB9 connectors soldered to one end into which the needles were connected, and a male Centronics cable on the opposite end. A row of labeled female Centronics connectors was fixed with cabling ties to metal bars which spanned the head of the surgical table where the surgery and subsequent experiments were performed. Ribbon cable was placed from the female Centronics connectors, receiving the electrode arrays, to the individual amplifiers housed in a rack in front of the table. High speed data communication between the processors and the direct

memory access computer boards was achieved by means of 2 fiber optic cables. A serial cable was also used to provide for command-based communication between the computer and the processors.

System amplification and filtering

The gain and initial filtering of the signals were performed in the amplifier section, which was bundled with two Digital Signal Conditioner (DSC) systems purchased from INET Corp. (Newark, CA). The amplifier section consists of 4 sections: isolation, differential, highpass filtering and lowpass filtering, and are diagrammed in Figure 23. Programmable gain is offered in each of the 4 sections. The amplifiers are arranged 8 to a card, with 16 cards socketed along the front panel of the DSC, for a total of 128 amplifiers per DSC. The isolated inputs offer voltage protection beyond 300 V. The amplifiers have a typical common mode rejection of 95 dB, input noise of 2 μ V RMS, and an accuracy of 0.1%.

The programmable circuit design allows for four gain and filter settings to be used by sending commands to each of the processor cards in the DSCs via the communications board. Initial gain settings ranged from 438 to 1451, which corresponded to input ranges of ± 23 mV down to ± 6.8 mV. This configuration, however, is not ideal for the unipolar mode of electrogram recording, because these signals can often be > -40 mV in amplitude. The

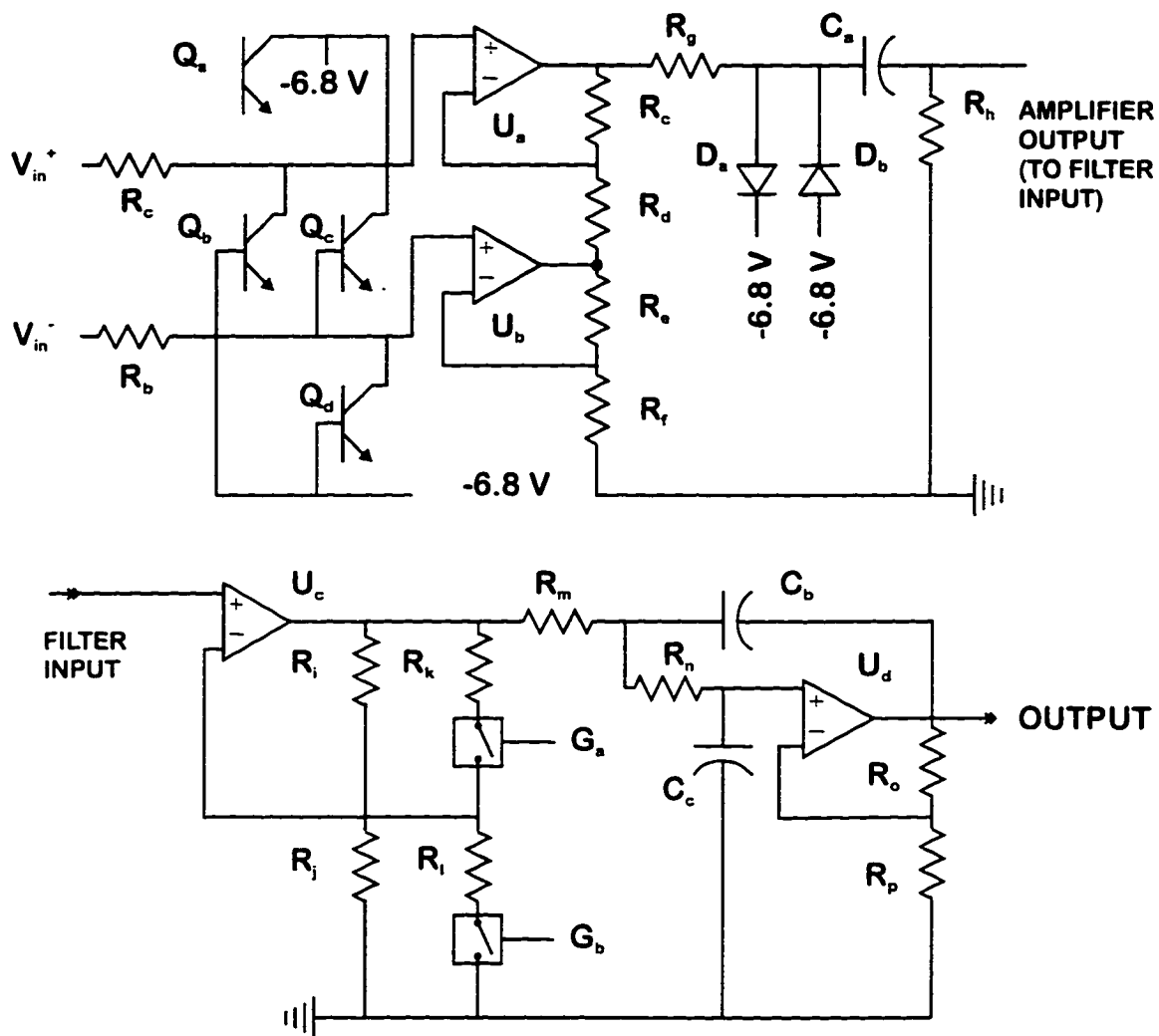


Figure 23. Circuit diagram of amplifier section

ideal gain configuration is one which allows for both unipolar or bipolar recording modes, which translates into an allowable input range of $\sim \pm 5$ to ± 50 mV. Therefore, in order to conduct experiments which were used in studies described in this paper, the amplifier design was modified.

An evaluation of the circuit design was required so that modifications of the gain settings could be achieved without deleteriously effecting the filtering sections. Analysis revealed that of the 4 gain sections, the easiest section to modify was the lowpass section. Circuit analysis of this section was then performed to determine suitable replacements. The transfer function, $H(\omega)$, was calculated as:

$$H(\omega) = \frac{1}{1 - \left(\frac{\omega}{\omega_n}\right)^2 + j2\xi\frac{\omega}{\omega_n}}$$

where ω is the frequency $\cdot 2\pi$, ω_n is $\frac{1}{\sqrt{\tau_1 \cdot \tau_2}}$, and the damping factor, ξ , is

$\frac{1}{2}((1 - \text{gain}) \cdot \tau_1 + \tau_2 + \tau_3) \cdot \omega_n$. Each τ is based on RC values from the circuit

diagram (Figure 23), with $\tau_1 = R_m C_1$, $\tau_2 = R_n C_2$, and $\tau_3 = R_m C_2$. The gain is

$\frac{R_o + R_p}{R_p}$. From these equations, it is seen that the damping factor and the

frequency response are both dependent on the gain value, so care was taken to adjust the gain upward and still maintain proper damping and frequency response.

Implementation of the new values was achieved by desoldering resistors R_n and R_o from each of the 256 amplifier sections, soldering caps into their positions on the circuit boards, and inserting 1% error resistors into them with values of 21 k Ω for R_n , and 11 k Ω for R_o . The new gain settings allowed input voltage ranges of ± 7 mV at gain setting #1 to ± 46 mV at gain setting #2, while maintaining a flat frequency response to 800 Hz. The system was then tested and calibrated by inputting 1 ms square wave pulses with amplitudes of 1 mV and 30 mV at frequencies of 10, 100, and 1,000 Hz.

Sampling rate and bit resolution

After each electrogram signal is amplified, it is fed into an analog multiplexor, capable of simultaneously acquiring 128 signals. The sampling rate is programmable, and ranges from 1 kHz to 8 kHz. For 1 kHz sampling, all 128 channels are sampled, while for higher sampling rates, fewer channels are sampled (64 channels for 2 kHz, 32 channels for 16 kHz, and 16 channels for 8 kHz sampling). The signals are then fed into a sample-and-hold circuit, and are then digitized by way of an analog-to-digital converter. The conversion employs 12-bit resolution, which is adequate for electrogram analysis. For example, with a gain setting of ± 7 mV for bipolar recordings, the full scale voltage is 14 mV, and with 2^{12} or 4096 levels, each level has a resolution of 3.4 μ V, which is equivalent to the input noise level. For unipolar mode, the resolution is 23.4 μ V/level, which is still quite adequate for electrogram analysis.

Transport to temporary storage

The digitized data is sent to the computer via fiber optic cable, and the system can send 300 k words/sec. The upper limit on this system is 256k words/second, which is well below the upper data transfer rate. The communication card on each DSC is programmed to interrogate each channel selected and send its contents into the data stream in the order specified by programmable software commands. Each word consists of 16 bits; the least significant 12 bits contain the data and the most significant 4 bits contain control data. Each DSC sends the data to an interface card in the PC, which in turn, puts the data on a bus via separate direct memory access (DMA) channels. The software reserves a portion of the PC's extended memory, which is proportional to the duration of the sampling run. For example, if all 256 channels are used at 1 kHz sampling rate, and the length of the run is 1 second, the amount of extended memory reserved is $256 \text{ channels} \cdot 1000 \text{ samples/second} \cdot 2 \text{ bytes/sample}$, or 512 Kbytes. The organization of the data stream is programmed in a format called the sample plan, and the order of the data stream is depicted in Figure 24. The figure shows that the 1st sixteen words are the first 1st channels of the 16 processor cards of DSC1, followed by all the 2nd channels of the 16 processor cards of DSC1, etc., until all channels of DSC1 have been read. This process is then repeated for the next data points in each channel of DSC1, until a block of 64 Kbytes has been filled. The next 64 Kbytes block are occupied by the same channel sequence,

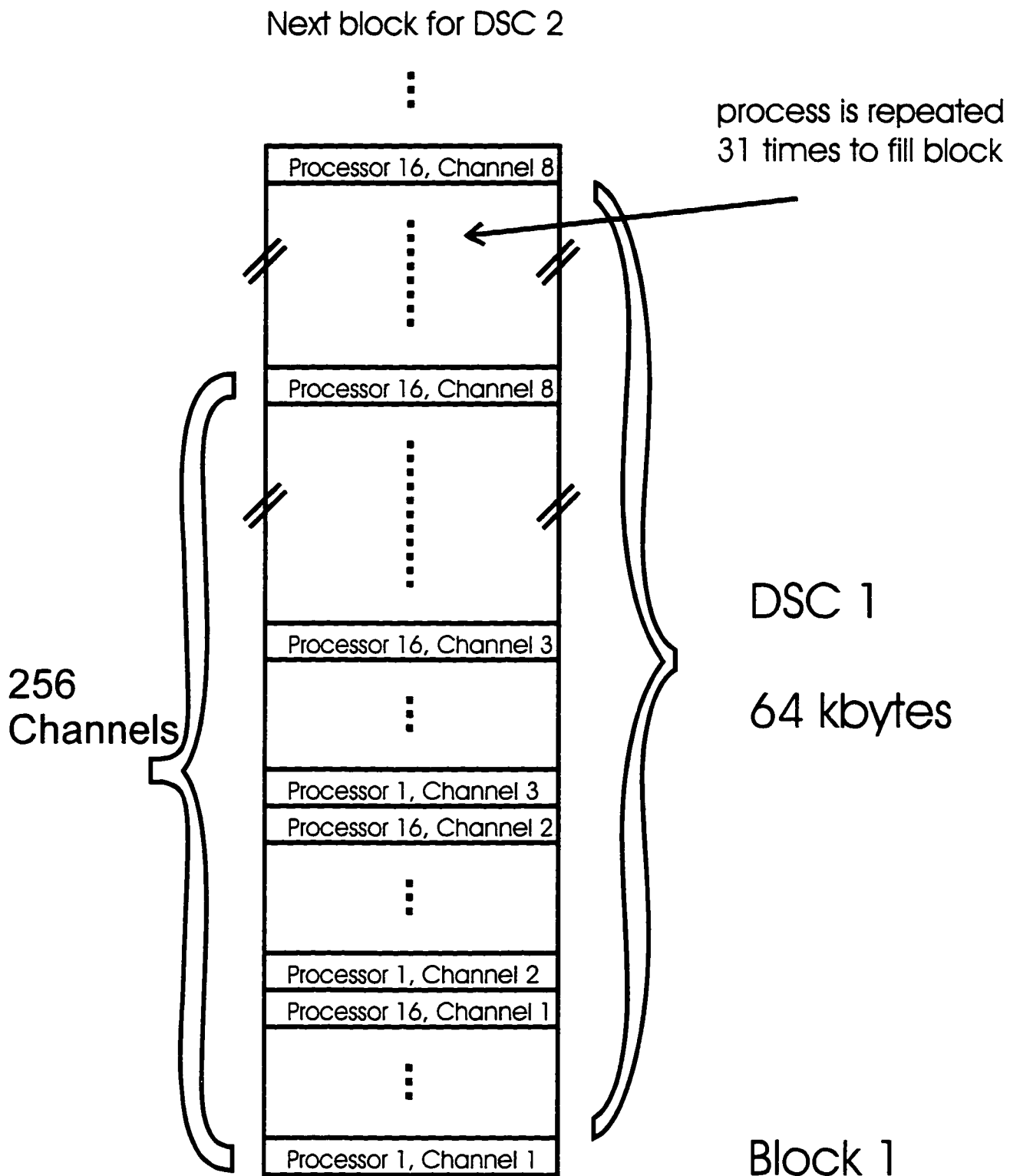


Figure 24. Flow chart of data transfer from multiplexor to temporary storage.

but for DSC2. The 3rd block will consist of DSC1 data, and the 4th block will contain DSC2 data. A total of eight blocks are required to store the 1 second run.

Of considerable use is the implementation of a double buffer to allow the capture of pretriggering data. Figure 25 illustrates this process. Two buffers of equal size are established in the memory section of the computer, and the data continuously fills them as the program monitors the buffers to prevent overfilling, and switches back and forth between them. Figure 25 shows that at Time=0 msec, the buffers are set to the bottom of the memory area. The primary buffers for DSC1 and DSC2 are the 1A and 2A blocks, respectively, while the 1B and 2B blocks represent the secondary buffers for DSC1 and DSC2, respectively. The shaded blocks are being filled with data. When the blocks are filled 250 msec later, the secondary blocks get filled with data, and the program reinitializes the buffer addresses so that the primary buffers are above the secondary ones. At Time=500 msec, the secondary buffers have filled up and the program directs data to the primary buffers once again, but recall that they have been moved upward on the memory address ladder. This process continues until the next buffer exceeds the amount of memory available, at which time the buffer is set to block 0, restarting the process in a circular fashion.

Depressing a key triggers the data acquisition process, which can currently acquire up to 15 seconds of continuous data. The implementation

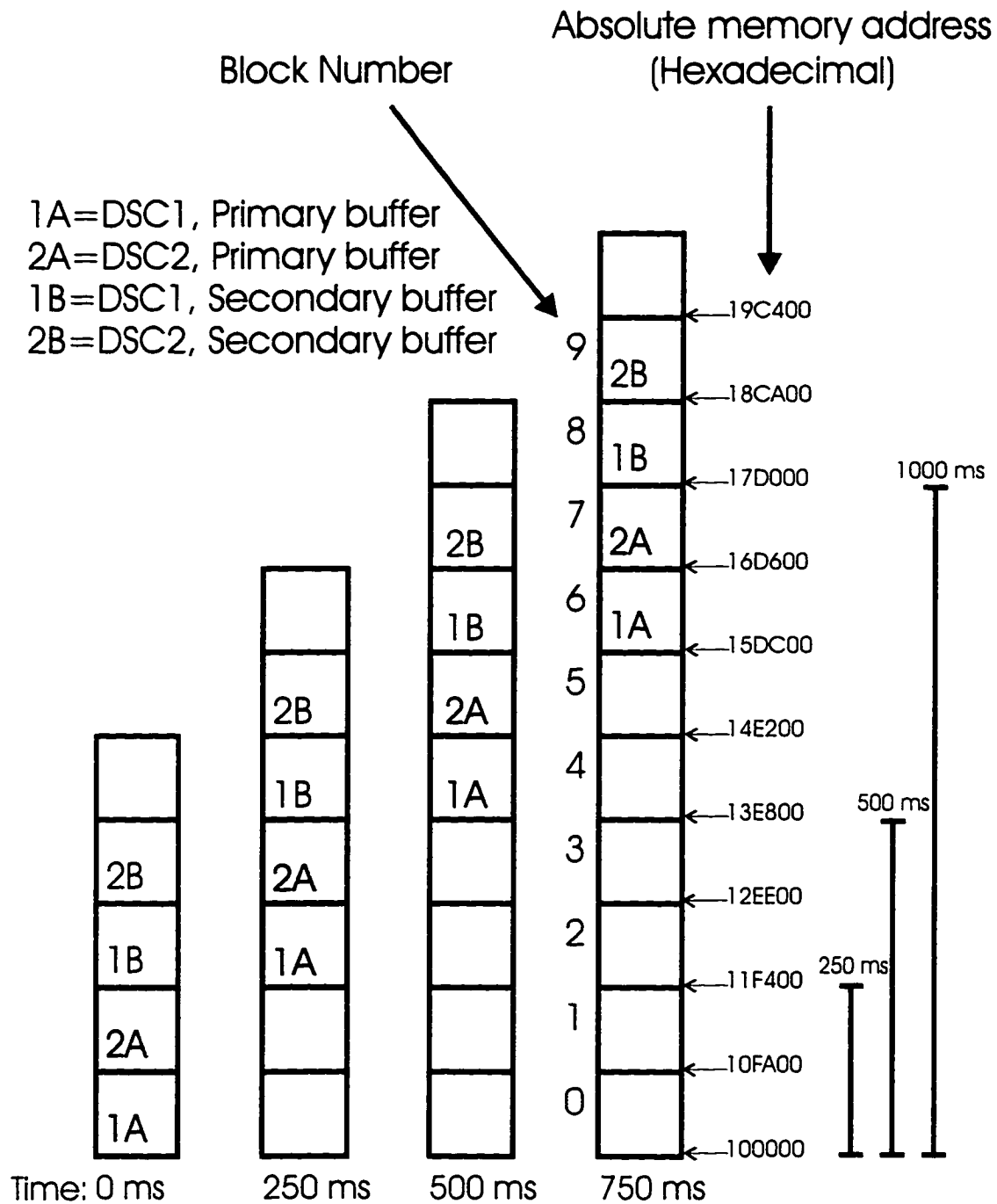


Figure 25. Graphic showing movement of data with double buffering algorithm.

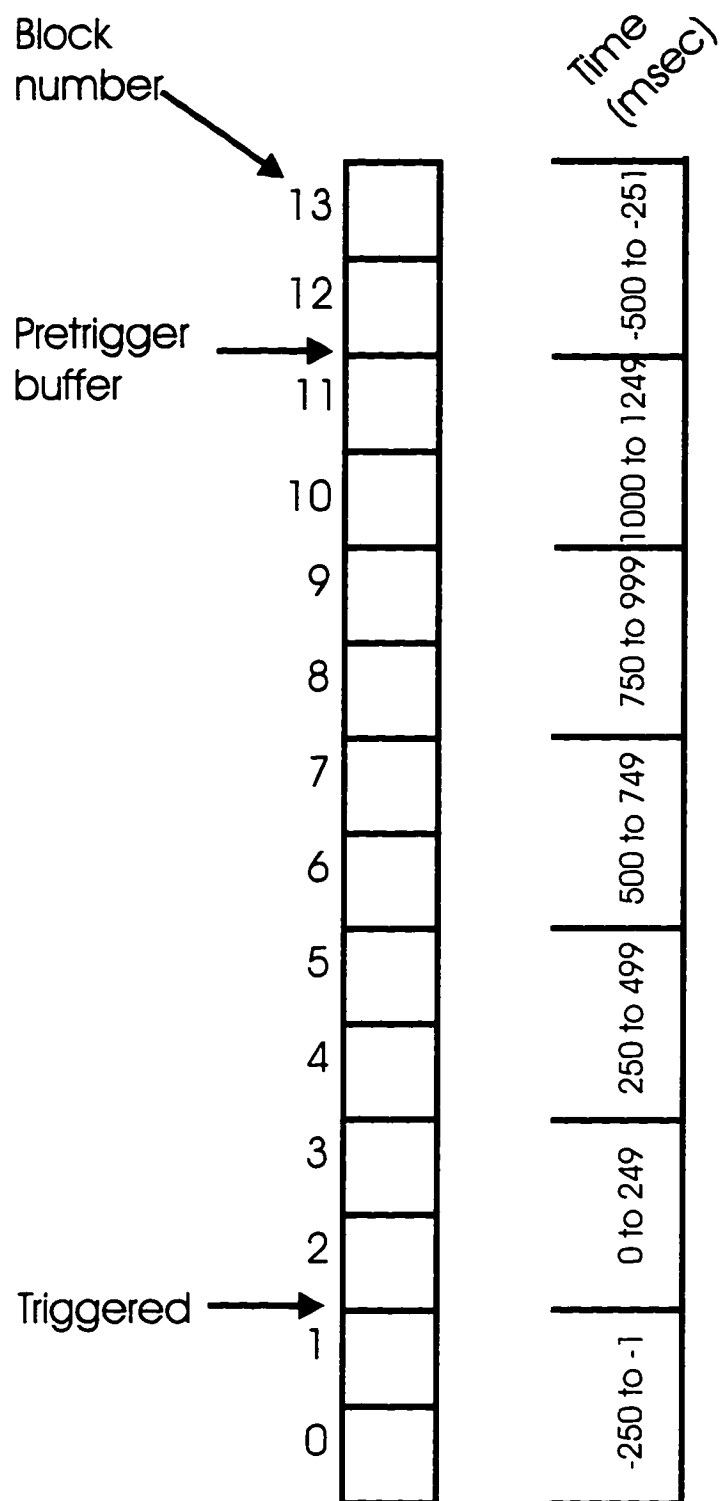


Figure 26. Illustration of pretriggering ability allowing the capture of important electrographic events.

of the double buffering technique allows for all but 250 msec of the total data acquired to be pretriggered data, and is very useful in the experimentation design. An example is shown in Figure 26. The trigger begins at Block 2, and the pretrigger data, set to 500 msec, begins at Block 12. The pretrigger data is retained and after triggering, data is collected through Block 11. If a protocol requires that termination of an arrhythmia be analyzed, the data run can be setup so that the majority of the data captured will be comprised of pretriggered data. When viewing the arrhythmia on a physiologic monitor, the data acquisition process is triggered just after the termination event occurs, and the data preceding the termination is captured to memory.

Short- and long-term storage

After the data is acquired in memory, the program prompts the user to decide whether it should be saved. If the user indicates “yes”, by typing ‘y’, then the data is transferred to the hard disk in a file named “capture.dat”. A batch program, “save.bat”, is then employed to rename the file and move it to an appropriate directory. The filing system used is based on the date and run number of each experiment. The directory is the date of the experiment, “MMDDYY”. The file name is also the date, and the file extension is the run number. Each run is also entered into a record book which describes its contents, along with any comments that are pertinent for subsequent analysis. The short-term storage process time is run-length dependent, and

lasts approximately 4 sec for a 1 sec run, to 20 sec for a 10 sec run.

Afterwards, the acquisition process can be reset in about 2 sec.

During the course of a normal experiment, between 20-80 data runs may be taken, occupying 100-300 Mbytes of hard disk space. These data are then stored onto DC2120 and 9-track data tapes for long-term storage and post-processing. Currently, our lab has several methods of storing data. After each data run is obtained, it is stored onto a hard drive which has an 800 Mbyte capacity. The runs for each experiment are then backed up onto 9-track tapes (a holdover from previous systems) and DC2120 tapes via a Colorado Jumbo Tape system (Colorado Memory Systems, Irvine, CA). Recent experiments remain on the hard disk until they are deleted to make room for new data. The system resides on a Windows for Workgroups 3.11 network, and each investigator can access the hard disk of the data acquisition computer to retrieve data over the network. Additionally, we have installed Colorado tape backup units on several of the individual investigator's computers, so that they may retrieve data from the DC2120 tapes.

Sorting routine

The data stream described above is sorted to optimize retrieval time for data analysis. The data stream is organized into blocks of 64 Kbytes, which for 1 kHz sampling translates into 125 msec of 256 channel data. This data

is sorted by establishing a record for each channel, and placing the data point for each channel into the record as it is read from the data stream. Since it is in 12 bit data format, the last 4 bits are masked to the 0 value. An area of memory is set aside for the new data set and a record is created whose size is based on the number of electrograms recorded, and the data is then placed into each record for each electrogram, one value at a time, via a loop which reads the values to the end of the block. This process continues until all the blocks have been read. The new data stream will then consist of the following order: all sequential data samples of channel #1, followed by all sequential data samples of channel #2, etc. After all the blocks have been read, the data is translated into "ASCII comma separated variable" format and written into 2 files, one for the 1st 128 channels, and one for the 2nd 128 channels. This format is consistent with the importation of ASCII data of all of most popular commercial data analysis, spreadsheet, statistical and graphic packages available. (See Appendix for Pascal programming.)

Graphic display and printing

In order to gain visual insight into acquired electrogram data, a program was written which plots the data to the monitor. The monitor viewing area is divided into 16 equal rectangles, with the width equal to the width of the monitor display, and the height 1/16th of the monitor's display height. The data from channel #1 is then written to the monitor (VGA specification) by converting it into a pixel position in its rectangle. To speed up the display

process, only every fourth point is plotted. The next 15 channels are displayed onto the monitor in similar fashion, and the remaining channels can be viewed by use of the <Page Up>, <Page Down>, and function keys, with keys F1-F10 representing the first 160 channels, and <Shift-F1— Shift-F6> representing channels 161-256. The user can jump to any page of electrograms by depressing the appropriate function key. The process is relatively quick and is data file length dependent; changing pages on the 486-33 PC with 1 Mbyte of VRAM takes < 1 sec for a 1 sec data run.

A program was also written to print the electrogram data on a laser printer utilizing HP-GL5 graphic language ¹⁶⁰ support. After the data run is selected, channel #1, which in our system always contains body surface Lead I data, it is displayed on the monitor, along with 2 vertical bar cursors at each end of the electrogram. The user then depresses the left and right cursor keys to delimit the portion of data required for printing; the <Home> key switches back and forth to each cursor. The cursor moves in 100 msec increments (for 1 k Hz sampling); fine tuning of the left cursor is accomplished by depressing the <Ctrl> + left or right arrow keys. The right cursor always rounds the data sample to the nearest 100 msec increment. When the data subsample is selected by depressing the <Esc> key, the subsample is displayed, occupying the entire width of the screen. If the subsample is judged correct, then by depressing the <Esc> key again, the user is prompted to answer questions regarding the number of electrograms

per page, the channels required, draft (every 4th data point) or high resolution mode, whether 10 or 20 ms vertical bars for timing are needed, and whether activation time markers are required. For the latter, a simple routine was written, which calculates local maximas and minimas of the first temporal derivative and places 4mm long vertical bars across the electrogram locations along with the time determinations. Other notations are included, such as the date of the run, run number, electrogram number, and if desired, markings for computer-extracted activation time of each electrogram. Additionally, if the printed page is divided into 10 or 20 msec segments, each segment number is printed at the top of each segment, providing an easily readable timing marker. (See Appendix for a sample graphing program.)

Chapter V . Electrogram analysis of unipolar and bipolar recordings obtained from normal canine epicardium

Introduction

Previously, electrographic characteristics were described for functional conduction block in the subacute phase of myocardial infarction in the canine heart of high resolution bipolar electrograms at 1 mm interelectrode spacing.⁴⁷ Using similar high resolution methods, a more systematic evaluation of the morphological characteristics of bipolar electrograms from normal myocardium and the influence of recording method on the recorded signals was undertaken. The goal this study was to identify optimal criteria for activation time determination of bipolar electrograms from normal hearts. Bipolar electrograms were synthesized from unipolar electrograms using a high resolution cross electrode array (HRCEA), comprised of 128 poles with 500 μm between each pole, during both broad wavefront propagation initiated distant from the HRCEA (B-Wave) and elliptical wavefront propagation initiated locally (E-Wave). The times of various bipolar electrogram landmarks were extracted and compared with an activation time standard - the time of the maximum negative derivative of a central unipolar electrogram. The role of interpolar distance and electrode orientation, with

respect to both fiber orientation and impulse direction, on activation time determination were also studied for both stimulated wavefront topologies. Preliminary and full reports have been recently published.^{115,161}

Methods

Surgical preparation

Experimental data were obtained from the hearts of 12 conditioned male mongrel dogs weighing 12-16 kg. The study was approved by the local institutional review board and conformed to the guiding principles of the Declaration of Helsinki. Dogs were pre-anesthetized with sodium thiopental (17.5 mg/kg, iv) and intubated with a cuffed endotracheal tube. Anesthesia was maintained by constant ventilation of a mixture of 1-2½% isoflurane, vaporized in 100% O₂, administered through an electronically controlled anesthesia ventilator (Foregger F500, The Foregger Co., Hauppauge, NY). A left sided thoracotomy was performed at the fourth intercostal space to expose the heart. Electrocardiographic lead II and aortic blood pressure (Statham, Gould, Inc., Oxnard, CA) were continuously monitored on an Electronics for Medicine VR12 monitor (PPG Co., Pleasantville, NY). Core and intrathoracic temperatures were monitored using two electronic thermometers (Yellow Spring Instruments, Yellow Springs, OH). When slowing of the sinus rate was necessary, a Grass S88 stimulator (Grass Instruments, Quincy, MA) was used to stimulate the right and left

vagosympathetic trunks through two pairs of Teflon-insulated silver wires (250 μm diameter) with square wave pulses, 0.1-0.5 msec duration, at a frequency of 20 Hz, at 1-10 volts.

High resolution cross electrode array

The high resolution cross electrode array (HRCEA) was constructed as described in the previous chapter. The HRCEA was placed on the left ventricular base with the most distal pole of the cross 4-5 millimeters from the interventricular septum. The upper panel of Figure 27 is a schematic depiction of the HRCEA placement in relation to anatomical landmarks on the anterior surface of the heart. The cross was situated on the epicardial surface parallel and perpendicular to the longitudinal fiber axis of the ventricle.¹³⁹ Correct positioning was verified by maximizing the anisotropic conduction velocity ratio, performed by measuring the ratio of activation times of transverse and longitudinal electrograms equidistant from the central stimulation site on a digital storage oscilloscope, and adjusting the position until the ratio was maximized.¹⁶² Once the HRCEA position and recording proved satisfactory, the ribs were approximated and the chest cavity closed. Once temperature was within physiologic range and stable, electrogram data were acquired.

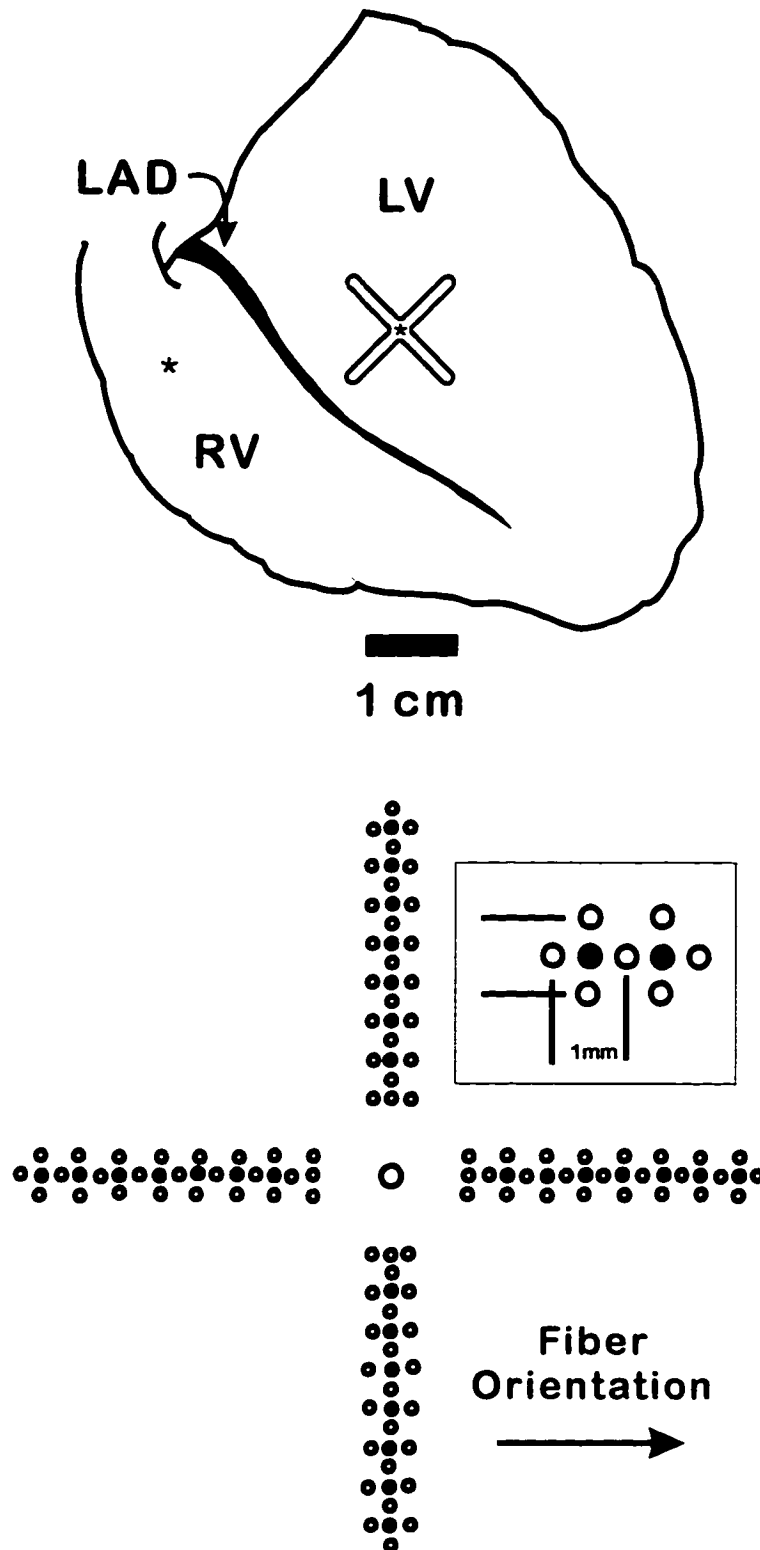


Figure 27. High resolution cross electrode array and its location on the epicardial surface. The asterisks denote the stimulation sites. LAD, left anterior descending artery; LV, left ventricle; RV right ventricle.

Multichannel data acquisition system

Unipolar electrograms were acquired using the mapping system described in the previous chapter. Signals were amplified and filtered with a fixed highpass setting of 0.05 Hz and an adjustable lowpass setting of 500-2000 Hz. The analog data were digitized with 12 bit resolution at a sampling rate of 1000-4000 samples per second per channel. The digitized signals were then stored on hard disk on an IBM compatible computer system (486PC, Touche Co., Chicago, IL).

Stimulation protocol

Programmed electrical stimulation was performed utilizing a Bloom DTU-101 digital stimulator (Bloom Co., Reading, PA). To generate B-Wave, stimulation was applied through a bipolar plunge electrode consisting of two hooked, enamel coated, stainless steel wires (125 μm diameter) placed in a 23 gauge hypodermic needle and inserted into the right ventricle near the outflow tract. To generate E-Wave, cathodal unipolar stimulation was applied at the center of the HRCEA at 1.3 times diastolic threshold. Only sites in which the stimulation threshold was ≤ 0.6 mA were included in the analysis.

The stimulation protocol consisted of pacing at cycle lengths of 600, 500, 400, 300, and 250 ms. After at least 30 consecutive captured paced beats at

each cycle length were evident, 2 sec recordings were obtained by the data acquisition system.

Data Analysis

The data was sorted with a custom written Pascal program and converted to a file format for use in Microsoft Excel 5.0 for Windows, as described in the previous chapter. Macros were written to view each electrogram and perform all necessary calculations required for analysis. The time of the maximum negative temporal derivative was chosen as the moment of activation for unipolar electrograms. A 5-point Lagrange approximation method, shown to have low error when applied to 12 bit data, ¹⁶³ was used to calculate the temporal derivative. The relation is:

$$\frac{dV_t}{dt} = \frac{V_{t-2} - 8V_{t-1} + 8V_{t+1} - V_{t+2}}{12h}$$

where h is the sampling interval of the acquired digitized data.

Bipolar electrograms were synthesized by taking the arithmetic difference between two unipolar recordings. The timing of selected landmarks in each bipolar electrogram complex was compared with the moment of activation of the unipolar electrogram situated in the center of each bipolar pair. For most portions of the study, the interpolar distance was 1 mm. The 28 black dots in the cross electrode shown in Figure 27 indicate each central unipolar reference site for 2 orthogonal bipolar electrode

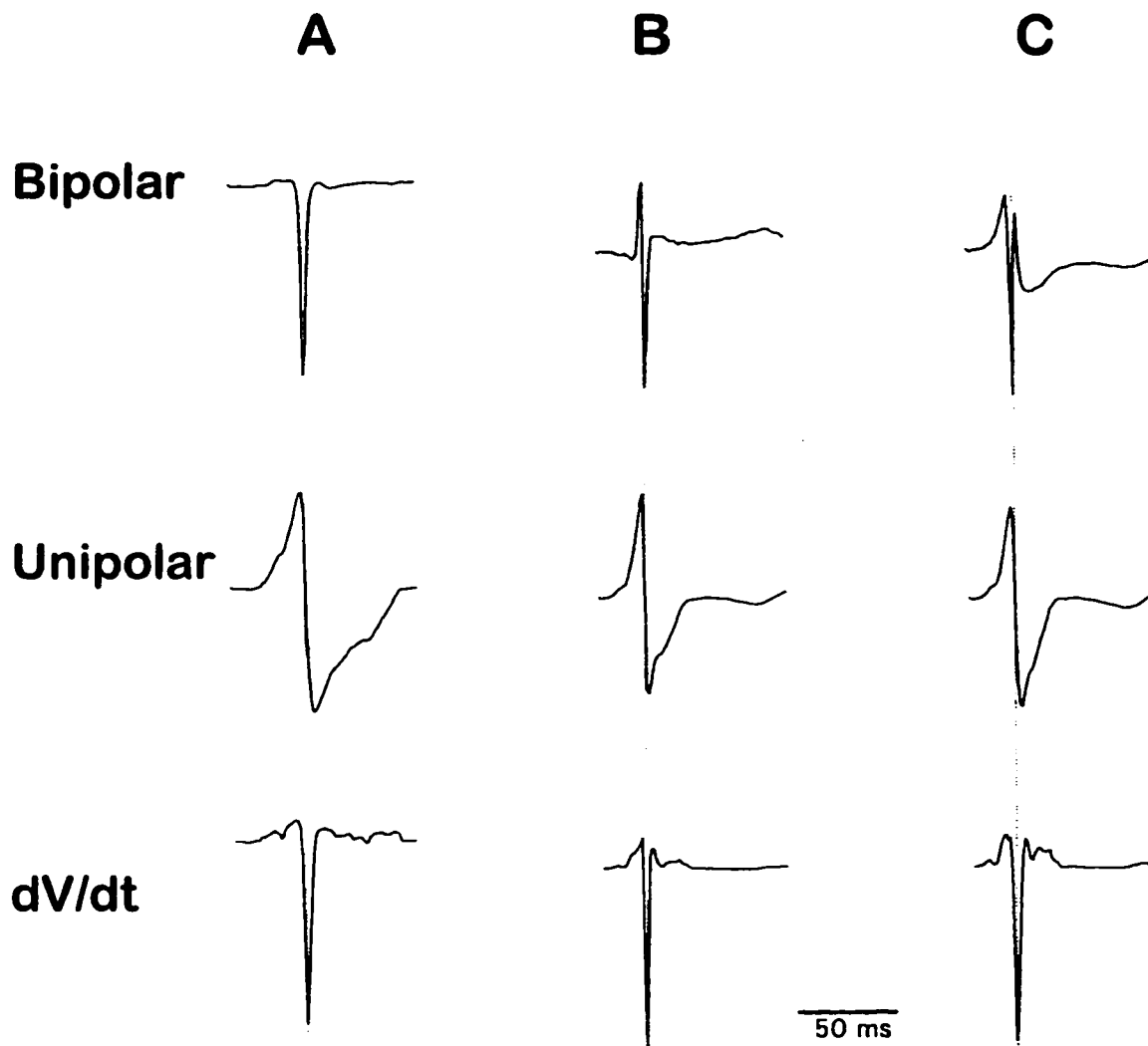


Figure 28. Bipolar electrogram morphologies: Uniphasic (A), Biphasic (B), and Triphasic (C).

configurations. A total of 56 bipolar electrograms from each HRCEA recording could be analyzed.

Bipolar electrograms were also synthesized for various interpolar distances (1-7 mm, in 1 mm increments) and for different bipole orientations with respect to fiber orientation (parallel electrode orientation and perpendicular electrode orientation). The inset of Figure 27 shows two orthogonally oriented bipolar electrode arrangements with a central unipolar reference in relation to the both activation impulse directions (longitudinal propagation and transverse propagation).

Statistical analysis

Data are presented as mean $\pm$ standard deviation. Statistical analysis was performed with Systat for Windows (version 5.2, Systat Corp., Evanston, IL). Data were compared using ANOVA and Student's *t*-test for unpaired data where appropriate. A confidence level of 95% was considered statistically significant. Figures and graphs were created with CorelDraw (version 5, Corel Corp., Ottawa, Ontario) or Origin (version 3.5, MicroCal Software Inc., Northampton, MA).

Results

Morphologic characteristics and classification of bipolar electrograms during B-Wave

The bipolar electrode configurations and associated unipolar electrode references for this portion of the study are shown in the inset of Figure 27. B-Wave was generated in the right ventricle (indicated by the star in the left panel), distant from the HRCEA. Bipolar recordings revealed three distinct electrogram morphologies which are shown in Figure 28. To facilitate grouped analysis, all bipolar electrograms were constructed by subtracting the pole activated last from the pole activated first. This produced bipolar electrograms with standard negative polarity, and allowed the analysis of fewer morphology subgroups (three groups instead of six). Along with each electrogram in Figure 28 is the associated unipolar electrogram at the center of the bipoles and the first temporal derivative of the unipolar electrogram. Panel A shows an example of a uniphasic bipolar electrogram, characterized by a single negative deflection. Electrograms with two deflections were considered biphasic (Panel B) if the smaller deflection was greater than 20% of the total electrogram amplitude, otherwise they were categorized as uniphasic. Electrograms with three deflections were considered triphasic if both smaller deflections were greater than 20% of the total electrogram amplitude, otherwise they were categorized as uniphasic if neither deflection

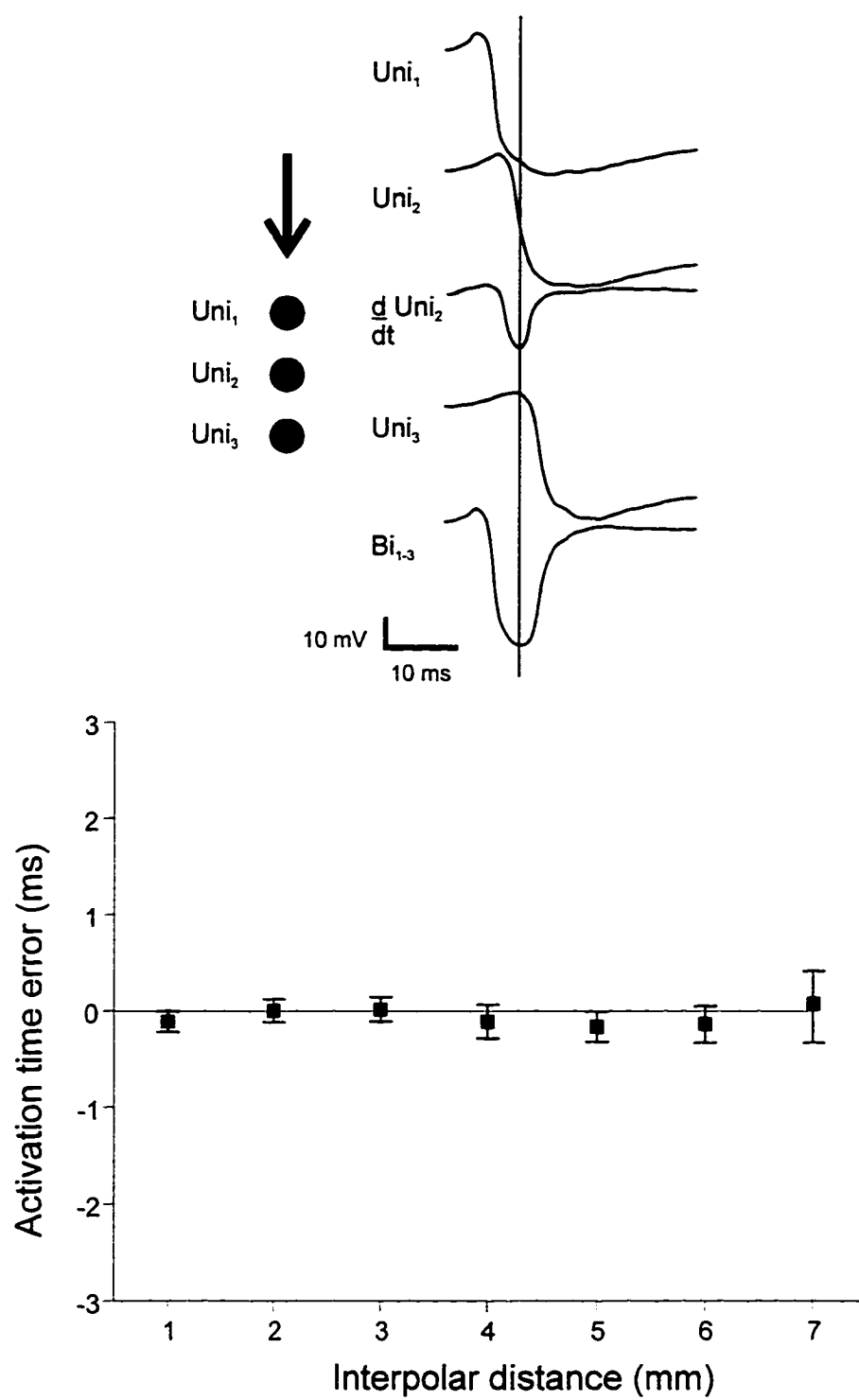


Figure 29. Orientation, morphology, and group analysis of bipolar electrograms 1-7 mm from central unipolar site

met the amplitude criteria, or biphasic if one deflection met the amplitude criteria. An example of a triphasic electrogram is shown in Panel C. The time of the maximum negative derivative of the central unipolar electrogram is indicated by the dotted vertical line in each panel.

Because of the uncertainty of absolute wavefront direction in relation to the bipolar electrode orientations during B-Wave, all electrograms were analyzed together. A total of 170 electrograms were classified for each morphology and tabulated for comparison: 104 (61%) electrograms had uniphasic morphology, while 39 (23%) electrograms showed biphasic morphology, and 27 (16%) displayed triphasic morphology.

Analysis of activation time error of constructed bipolar electrogram during E-Wave

In order to determine if the activation time of bipolar sites represents the activation time of a point midway between the poles, analysis was performed on 467 unipolar electrograms. Activation times of poles comprising bipolar recordings separated by 1mm to 7 mm were compared to the activation time of a central unipolar site. Activation time was determined by finding the maximum negative first derivative of three unipolar sites aligned as shown in the left panel of Figure 29. The error was calculated as:

$$error = t_c - \left[\frac{t_1 + t_2}{2} \right]$$

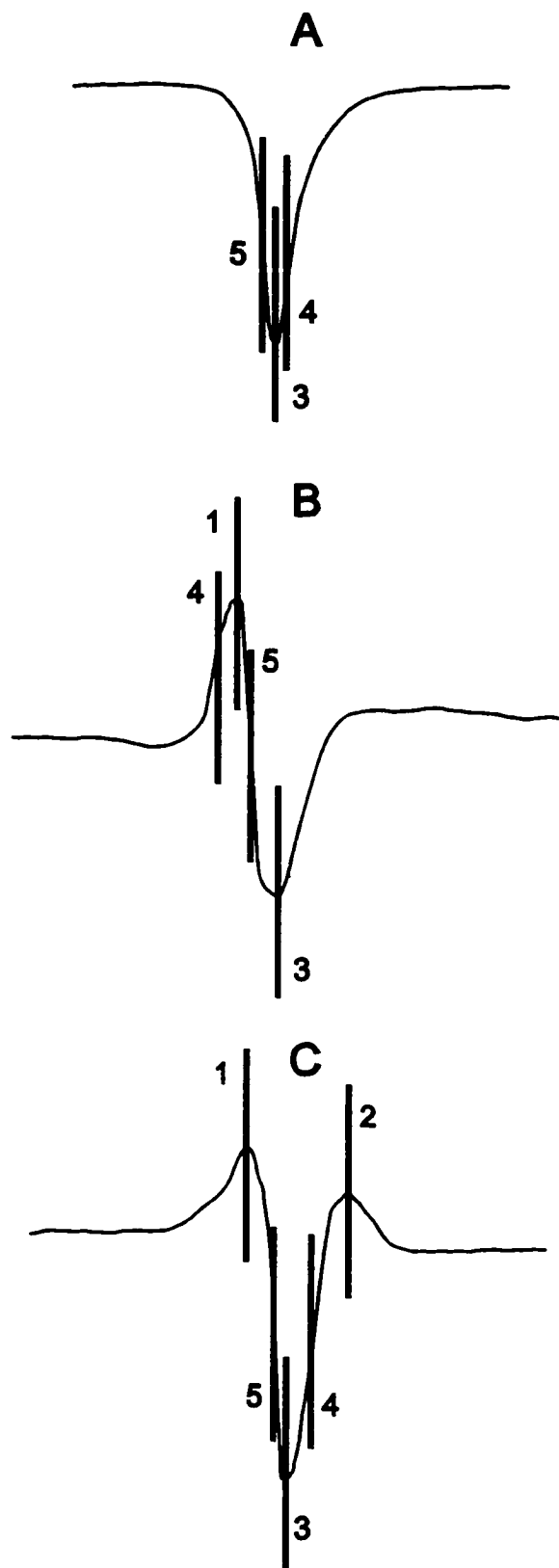


Figure 30. Bipolar electrogram landmarks

where t_c is the activation time of the central unipolar electrogram, and t_1 and t_2 are the activation times of unipolar sites 1-7 mm equidistant from the central pole. Figure 29 shows the orientation (upper left panel) of the recording sites, typical electrogram morphology and timing alignment (upper right panel), and grouped statistics (lower panel) of analyzed electrograms 1-7 mm equidistant from a central pole. The error shown is less than the time resolution of the sampling interval used (0.25 ms), and analysis of variance failed to uncover any statistical differences between bipole distances.

Analysis of activation time determination by bipolar electrogram features during B-Wave

To determine the accuracy of activation time determination in bipolar electrograms during B-Wave, the timing of several common electrogram landmarks were compared with time of activation of the central unipolar electrogram. Examples of the 3 electrogram morphologies and associated landmarks are illustrated in Figure 30. For uniphasic electrograms (Panel A), the peak negative voltage (3), maximum positive derivative (4) and time of maximum negative derivative (5) were computed; for biphasic electrograms (Panel B), the times of peak positive voltage (1), peak negative voltage (3), maximum positive derivative (4), and maximum negative derivative (5) were computed; for triphasic electrograms (Panel C), the times of both positive voltage peaks (1 and 2) were computed along with the time of the peak

Table 3 Time difference (error) between bipolar electrogram landmarks and maximum negative 1st derivative of central unipolar electrogram during broad wavefront propagation.

	n (%)	Peak negative voltage error (ms)	Peak positive voltage error (ms)	Maximum -dV/dt error (ms)	Maximum +dV/dt error (ms)	ANOVA p value <
<u>Morphology</u>						
Uniphasic	104 (61%)	0.6 ± 0.6	--	1.6 ± 1.2	1.9 ± 1.4	0.001
Biphasic	39 (23%)	5.2 ± 4.2	3.3 ± 3.4	1.5 ± 1.1	3.9 ± 3.9	NS
Triphasic	27 (16%)	0.6 ± 0.8	$4.1 \pm 4.0^*$ $5.0 \pm 3.9^{**}$	1.5 ± 0.8	1.6 ± 0.6	0.003

Legend. *, time of first positive peak voltage feature; **, time of secondary positive peak voltage feature; dV/dt, first temporal derivative; ANOVA, analysis of variance

negative voltage (3), and maximum positive and negative derivatives (4 and 5, respectively).

The difference between the time of activation of the central unipolar electrogram and the various landmarks shown in Figure 30 was computed. The summary data are shown in Table 3. During B-Wave, the optimal predictor of activation time was the peak negative voltage for uniphasic and triphasic bipolar electrograms (0.6 ± 0.6 msec, $p < 0.01$ and 0.6 ± 0.8 msec, $p < 0.005$, respectively). There was no significant difference between uniphasic and triphasic peak negative voltage as predictors of activation time. For biphasic electrograms, the maximum negative derivative was the best predictor, but this feature was not significantly better compared to the 3 other landmarks. When comparing all landmarks of the 3 electrogram morphologies, the peak positive voltage of biphasic electrograms was the least accurate predictor.

Morphologic characteristics and classification of bipolar electrograms during E-Wave

For this portion of the study, electrograms were recorded during unipolar stimulation applied at the center of the HRCEA. The bipolar electrode configuration and associated electrograms are shown in Figure 31. The left portion of the figure shows a schematic of the HRCEA in relation to elliptical isochrones of activation during anisotropic conduction arising from central

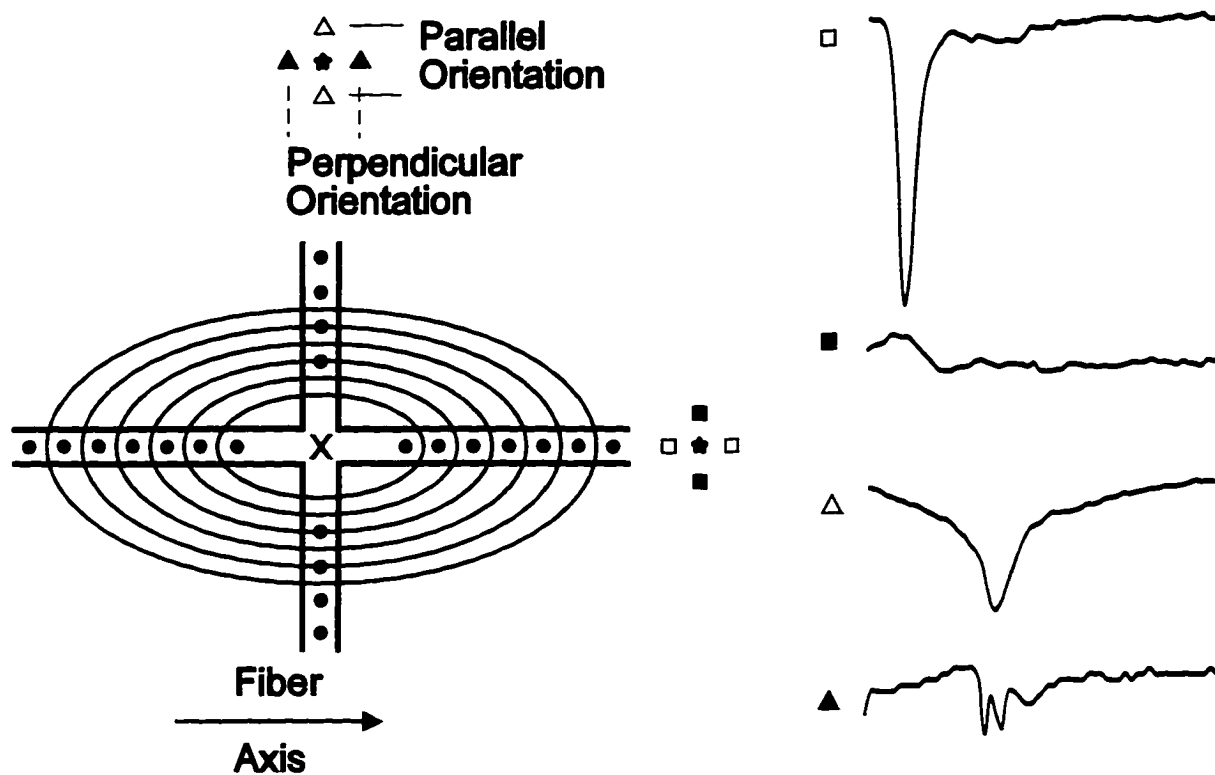


Figure 31. Parallel and perpendicular orientation of bipolar electrograms during elliptical wavefront stimulation

stimulation. The wide spaced isochrones reflect the more rapid conduction along the longitudinal axis of the myocardial fibers compared with propagation transverse to the fiber axis. For longitudinal and transverse conduction, bipolar signals for two orthogonal electrode arrangements were computed. The open symbols in Figure 31 represent a bipolar electrode pair oriented parallel to the activation wavefront direction, while the filled symbols represent perpendicular orientation of the bipole relative to the direction of the wavefront. Comparisons of electrogram morphology were made for parallel and perpendicular orientations in both propagating directions of the wavefront. For parallel electrode orientation, the electrogram morphology for wavefront propagation in both directions was uniphasic. In the examples shown in Figure 31, electrograms oriented parallel to the wavefront (1st and 3rd electrograms) have more distinct uniphasic morphology than electrograms oriented perpendicular to the propagation wavefront (2nd and 4th electrograms). Table 4 shows that for parallel bipole orientation, the electrogram morphology was uniphasic in >99% of cases. On the other hand, no definitive electrogram morphology was found for perpendicular bipole orientation for propagation along either fiber axis orientation. Still, unipolar morphology was most commonly recorded. The example shown in Figure 31 illustrates that perpendicular electrode orientations were sensitive to wavefront direction. As a result, these electrograms generally had reduced amplitude, longer duration and could

Table 4 Quantitative comparison of electrogram morphology on bipolar electrode orientation during local elliptical propagation.

Fiber Orientation	Longitudinal		Transverse	
<u>Electrogram Orientation</u>	Parallel	Perpendicular	Parallel	Perpendicular
<u>Morphology</u>				
Uniphasic	82 (99%)	43 (52%)	58 (100%)	41 (73%)
Biphasic	0	35 (43%)	0	14 (25%)
Triphasic	1 (1%)	4 (5%)	0	1 (2%)

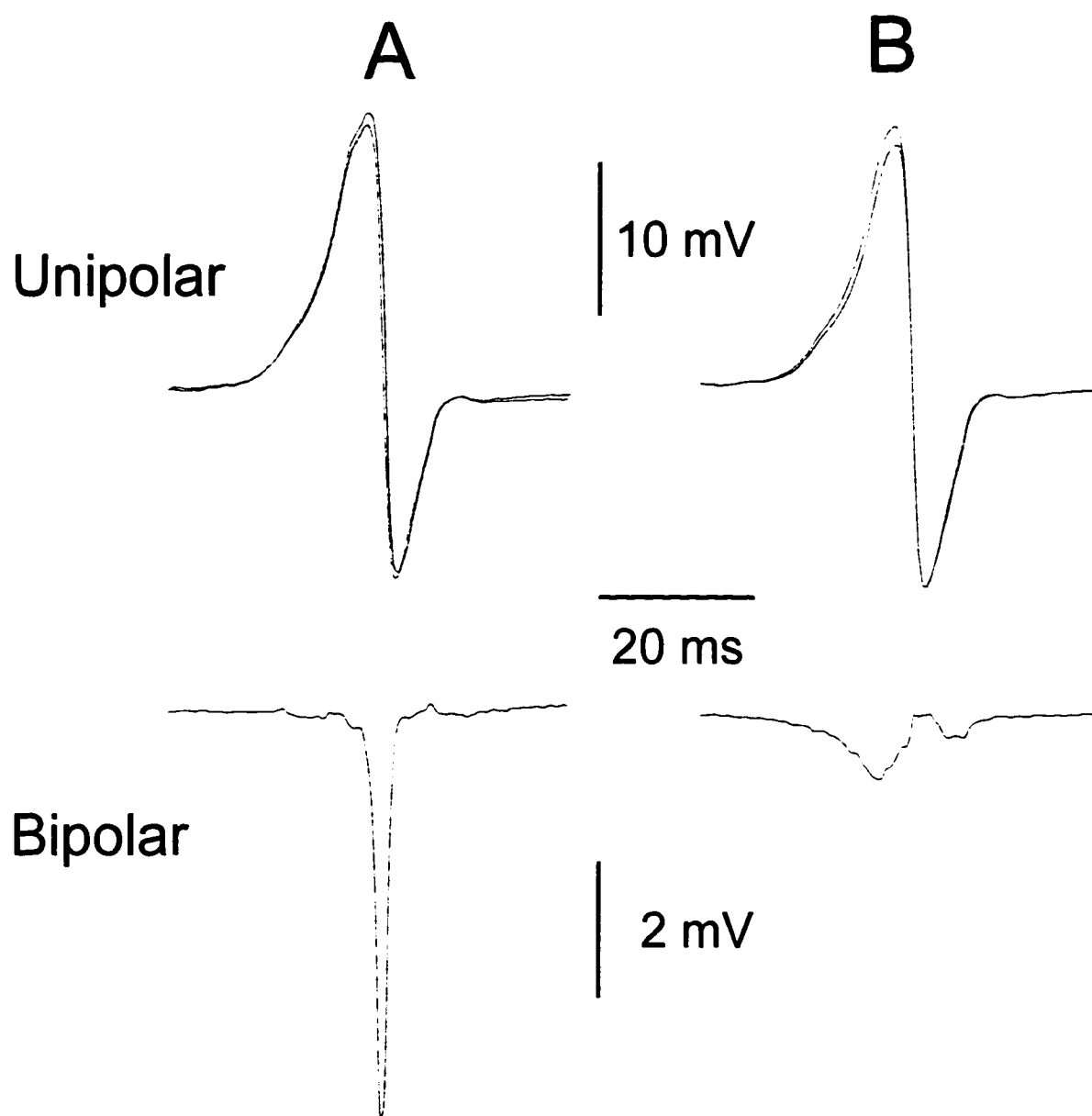


Figure 32. Unipolar and corresponding synthesized bipolar electrograms in parallel and perpendicular orientations

exhibit multiple deflections. The effect of perpendicular electrode orientation is further examined in the following example. The bipolar difference (bottom traces) and two corresponding unipolar electrograms (top traces) are shown for parallel (A) and perpendicular (B) orientation of the bipoles in Figure 32. The top portion of Panel A shows that for parallel electrode orientation (A), the rising and descending phases of the biphasic unipolar electrogram, which reflect more distant electrical activity, are essentially superimposed. The intrinsic deflections, which represent local activation, are shifted in phase and this difference accounts for the uniphasic shape of the bipolar electrogram shown at the bottom. Conversely, for perpendicular electrode orientation (B), the intrinsic deflections are superimposed while components of the rising and descending phases of the biphasic unipolar electrograms demonstrate phase shifts. For the exact same location in the heart, the resulting perpendicular oriented bipolar is of smaller amplitude and has multiple components.

Analysis of activation time determination by bipolar electrogram features during E-Wave

Electrogram characteristics (electrogram amplitude, electrogram duration and predicted activation time difference) for propagation along and across fibers, and for perpendicular and parallel bipolar orientations are shown in Table 5. There was a significant reduction in amplitude and increase in duration for perpendicular orientation for both longitudinal and

Table 5. Electrogram characteristics with respect to fiber orientation during elliptical wavefront propagation.

Fiber Orientation	Longitudinal			Transverse		
Electrogram orientation relative to propagation	Parallel	Perpendicular	p value	Parallel	Perpendicular	p value
Voltage (mV) (n)	8.8 ± 4.8 (70)	6.4 ± 3.4 (69)	0.001	8.6 ± 5.0 (45)	5.3 ± 3.8 (49)	0.0001
Duration (ms) (n)	7.5 ± 4.2 (70)	11.1 ± 8.8 (48)	0.009	5.3 ± 3.8 (41)	9.9 ± 6.4 (28)	0.0001
Error (ms) (n)	0.5 ± 0.7 (81)	0.7 ± 1.1 (82)	0.003	1.3 ± 1.4 (55)	4.0 ± 7.6 (55)	0.009

LEGEND: Voltage, peak-to-peak amplitude; Duration, time between positive and negative peaks; Error, the time difference between the optimal feature of each bipolar electrogram with respect to the activation time standard. For parallel orientation which resulted in only uniphasic electrogram morphology, peak negative voltage was the optimal feature.

transverse conduction. The values for activation time error, shown at the bottom, reflect the electrogram landmark which provided the most accurate determination of activation time for each electrogram morphology. For uniphasic and triphasic electrograms, the peak negative voltage feature was optimal, while for biphasic morphology, the maximum negative derivative or peak negative voltage landmarks had the least error. The ability to predict accurately the moment of activation between the poles was also significantly degraded for perpendicular electrode orientations compared to parallel orientations during propagation in either direction relative to fiber axis.

Effect of interpolar distance on activation time determination

The effect of interpolar distance for parallel orientation of the bipoles was examined during E-Wave stimulation and is shown in Figure 33. The top portion of Figure 33 illustrates the method by which the bipolar electrograms were computed. The open circle represents the unipolar electrode at the center of each bipolar electrode, for which the maximum negative derivative was again applied as the activation time standard. Bipolar electrograms were constructed for interpolar distances ranging between 1-7 mm, in 1 mm steps. The waveform at the top of panel A shows the center unipolar electrogram for propagation along the longitudinal axis of the myocardial fibers. The waveform immediately below is the 1st derivative of the unipolar electrogram shown above. The remaining electrograms shown are for

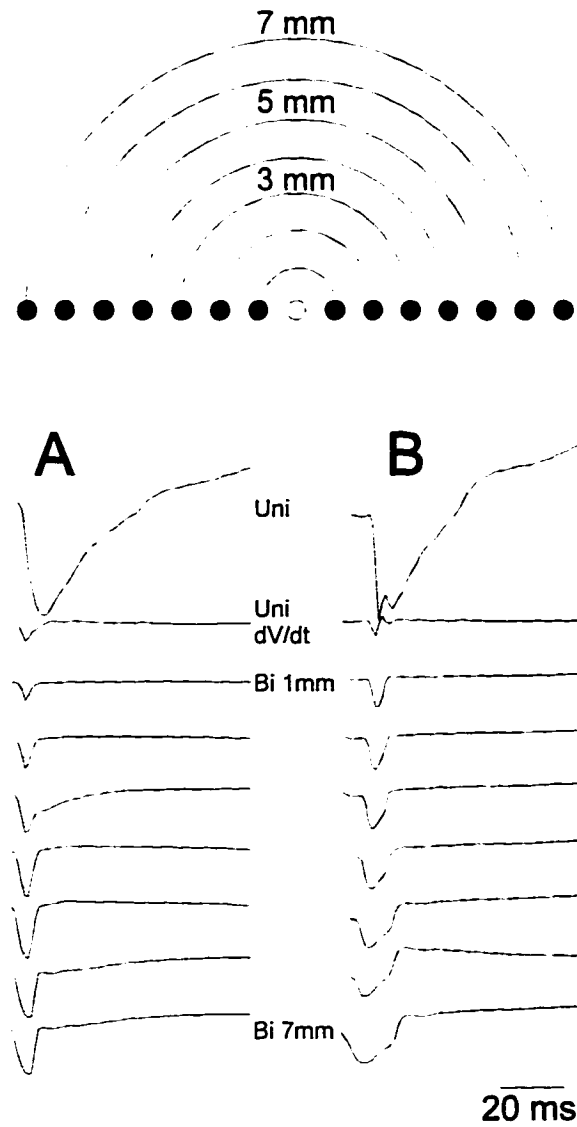


Figure 33. Effect of interpolar distance on activation time determination

successive increases in interpolar distance from 1 mm (top) to 7 mm (bottom). The dotted line corresponds to the time of peak negative derivative of the central unipolar electrogram. Increasing the interpolar distance caused an increase in both electrogram amplitude and duration. Also note that there was an obvious shift in the peak negative voltage from the activation standard as interpolar distance was increased. Electrograms recorded during transverse propagation are shown in panel B. Similar to panel A, all electrograms recorded were uniphasic. There was also a similar increase in amplitude with increasing interpolar distance. However, during transverse propagation, increasing the interpolar distance produced more marked increases in duration and shifts in peak potential from the activation time standard at the center of the bipolar electrode.

To highlight the effects of interpolar distance on the accuracy of activation time determination, the activation time shift between the peak negative voltage of the bipolar signal and the activation time standard is presented in Figure 34. The left panel of Figure 34 presents analysis for electrode configurations shown in Figure 32. For longitudinal propagation, the activation time difference ranged from 0.2 ± 0.4 msec, at an interpolar distance of 1 mm, to 2.0 ± 2.1 msec, at an interpolar distance of 7 mm. The effect was more pronounced for transverse propagation, ranging from 0.3 ± 0.6 msec to 4.9 ± 3.7 msec. Grouped analysis, comparing the activation time predictive accuracy of bipolar electrograms for B-Wave and E-Wave, is shown

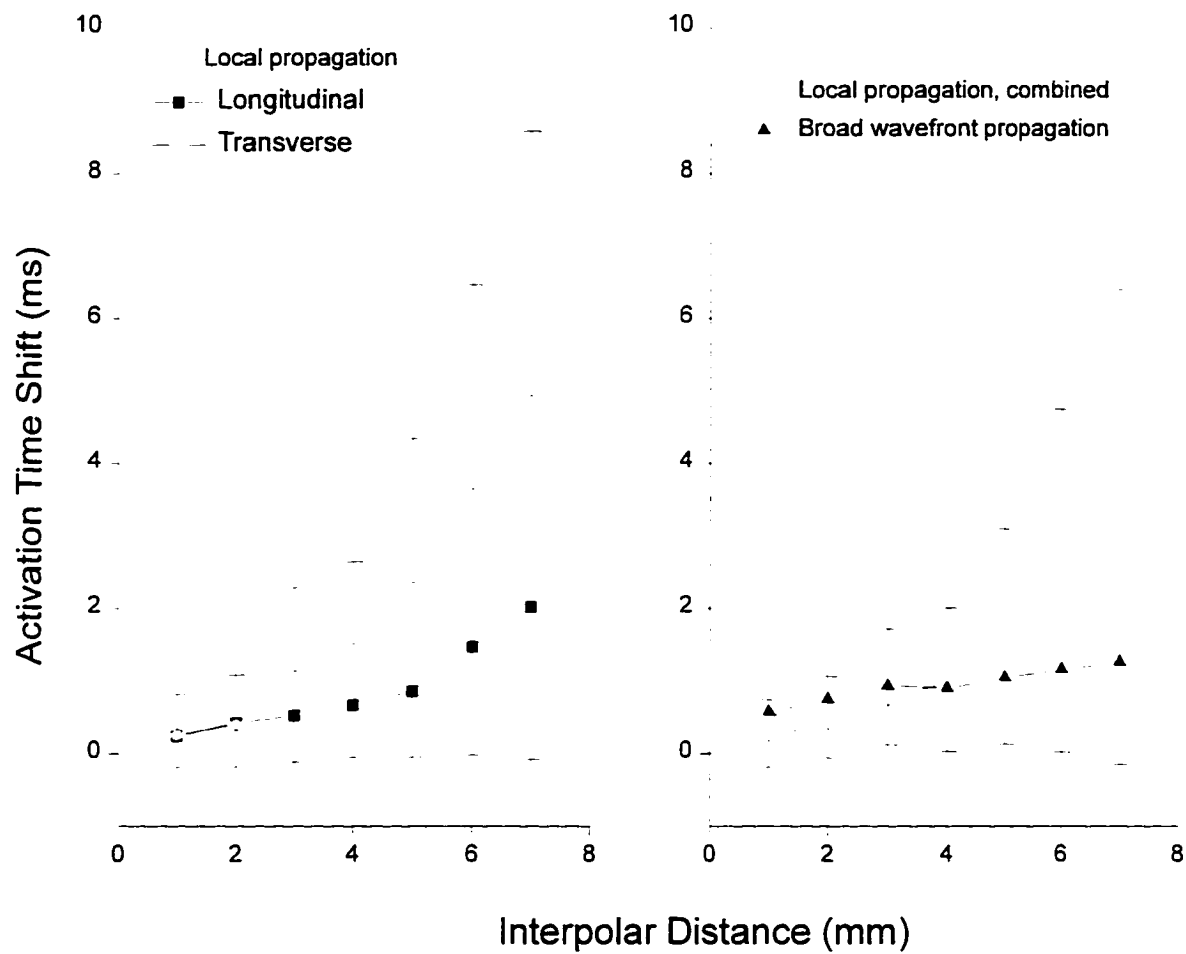


Figure 34. Statistical analysis of error in relation to interpolar distance

in the right panel of Figure 34. This graph shows that for B-Wave, as the interpolar distance increased, only small differences between the activation time standard and the optimal feature used for activation time determination were found. The activation time shift in this case ranged from 0.6 ± 0.8 msec to 1.3 ± 1.4 msec. Though the accuracy during E-Wave (0.3 ± 0.6 msec) was better than B-Wave for interpolar distances less 4 mm, the activation time accuracy was far worse for larger interpolar distances (maximum of 4.9 ± 3.7 msec at 7 mm interpolar distance).

Discussion

These results provide the first detailed analysis of activation time determination in bipolar electrograms using high resolution activation mapping techniques. Using a computerized data acquisition system, we were able to reconstruct simultaneously acquired electrogram data in order to examine the effects of electrode orientation and interpolar distance for broad wavefront propagation initiated distant from the recording site and elliptical wavefront propagation initiated near the recording site.

Maximum negative derivative of unipolar electrogram as predictor of activation time

Accurate activation time determination from bipolar electrograms should represent the moment of activation at the center of the bipole. This was confirmed by the analysis shown in Figure 29, describing the small errors in

activation time difference between 2 unipoles 1-7 mm equidistant from a central unipolar site. The results of this study present a method by which bipolar electrogram landmarks of activation time could be compared reliably with a standard of activation, namely, the maximum negative derivative of the unipolar electrode centered between the poles. The time of the maximum negative derivative has been long recognized as the most accurate indicator of activation beneath the electrode, ^{16,126,164} and is supported by both experimental and theoretical work. In an elegant study, Spach et al. found that the maximum negative derivative of unipolar extracellular waveforms occurred within less than 200 microseconds of the peak derivative of the upstroke of the intracellular action potential, recorded as close as possible to the extracellular electrode. ¹⁶

However, in diseased hearts, there are many situations in which the peak negative derivative may not be a reliable predictor of activation time. Spach and coworkers have recorded multicomponent unipolar electrograms from isolated atrial preparations for which the maximum negative derivative alone did not accurately predict activation of the cells immediately beneath the extracellular electrode. ¹²⁶ They found the maximum negative derivative sometimes reflected activation of larger cardiac bundles some distance from the recording site. The authors also found that the first derivative fell off more rapidly with distance than the amplitude of the extracellular unipolar signal and the second derivative fell off more rapidly with distance than the

first derivative. Based on these findings, Anderson et al. employed the ratio of the amplitude of the maximum negative derivative to peak-to-peak amplitude of the unipolar component and found this was the most reliable predictor of activation beneath the electrode.¹²² In a similar study, in which intracardiac atrial electrograms were recorded in humans during supraventricular tachycardia, Anderson et al. also showed that the derivative/amplitude ratio was the best predictor of activation time.¹²³ In that study, the authors were able to separate reliably local atrial activation from distant activation potentials of the larger bioelectric mass of the ventricles.¹²³

Unipolar electrograms are strongly influenced by electrical potentials arising from distant activation. Blanchard et al.,¹⁵¹ and Damiano et al.,¹⁵⁵ have demonstrated the influence of right ventricular activation on unipolar recording in the left ventricle. Though the activation sequence of the right ventricle influenced left ventricular recordings, they still found that the maximum negative derivative was not affected and was still a reliable predictor of activation. Because our measurements were made in normal ventricles and because we did not observe multicomponent unipolar electrograms, we relied only on the maximum negative derivative of the unipolar electrogram as the standard of activation time.

Characteristics of bipolar electrograms

While limitations of bipolar electrogram interpretation have long been recognized, ^{11,166} they still represent the most common recording modality for both clinical and experimental electrophysiological study. There remains almost no theoretical basis for bipolar electrogram analysis. The analysis and interpretation of bipolar electrograms which have been applied vary among investigators and is based loosely on biophysical theory. There is little data comparing the morphologies of electrograms for which activation times can be assigned to fiducial points of various bipolar electrograms morphologies.

In a study from the early 1950's, Itatsu examined bipolar and unipolar electrograms from the epicardial surface of the dog using an interpolar spacing of several millimeters. ¹⁵ In a simple theoretical treatment based on the Wilson gradient hypothesis, he concluded that the peak potential of all electrograms corresponded with the moment of activation. However, the results presented here indicate that peak voltage was a reliable predictor of activation time only for uniphasic and triphasic signals, and only for interpolar distances of 2 mm or less.

Effect of electrode orientation

A well known limitation of bipolar electrograms is the sensitivity of electrode orientation to the direction of the activation wavefront. By

stimulating from the center of the HRCEA, we were able to observe the effects of wavefront direction and fiber orientation on bipolar electrogram morphology. We found that electrograms recorded parallel to the wavefront in either fiber orientation resulted only in uniphasic morphology. The perpendicular electrogram morphology counterpart was much more variable. As illustrated in Figure 31, bipolar recordings using this electrode configuration were influenced more by distant potentials. Though we observed significant decreases in amplitude for perpendicular electrode orientations compared to the parallel arrangement, the findings were inconsistent. Many of the electrograms were reduced to < 10% of maximum amplitude of parallel orientations, while the overall decrease in electrogram amplitude was 34%. This value may be explained by the wide variance of electrogram amplitudes that were recorded here and by others.¹⁵⁰

Effect of interpolar distance

For bipolar electrograms, the most accurate determinant of activation time was for uniphasic morphology with the poles oriented parallel to activation wavefront arising from central stimulation of the HRCEA. However, the data from Figure 33 shows that this finding was significantly degraded by increasing the interpolar distance. The results were even worse during propagation transverse to the fiber axis. These findings have implications for those who determine activation properties based on the analysis of bipolar electrograms, as in routine clinical electrophysiology,

where the analysis is based on bipolar recordings spaced 0.5-1 cm apart. For broad wavefronts, the accuracy, though less than for poles oriented closely in line with the activation wavefront, was not appreciably degraded by increasing the interpolar distance.

Experimental and clinical implications

The treatment of cardiac tachyarrhythmias in man are dependent on precise analysis of electrophysiological recordings. Endocardial catheter recordings have been used for identification of the possible substrate of supraventricular and ventricular tachycardia in man for drug treatment, map guided surgical treatment, and as a guide for high energy or radiofrequency ablation of the arrhythmogenic substrate.^{141,142,150,167} In order better to identify the type of arrhythmia or location of zones critical to the arrhythmia, special consideration must be given to the analysis of signals recorded directly from the heart during arrhythmia. Recordings of fractionated multicomponent electrograms have been ascribed to slow conduction, circuitous conduction and/or conduction block by using deductive analyses based on limited or misapplied biophysical theory.^{47,50,150} Blanchard and coworkers have shown that extracellular electrograms are heavily influenced by distant activation potentials unrelated to activation in the tissue immediately beneath the electrode.¹⁵¹ This concept has also been demonstrated in mapping studies by McGuire et al., who evaluated local atrial "slow pathway" potentials recorded during AV nodal reentrant

tachycardia and found that these potentials are not pre-potentials but activation of sites distant to the recording electrode.¹⁶⁷

In a previous study, we addressed the importance of recording methodology on the interpretation of electrograms from ischemic myocardium canine heart during reentrant tachycardias.⁴⁷ We have shown using bipolar electrograms that discrete activation events may occur on a millimeter scale and cautioned that electrical activity from electrodes with wide bipolar spacing or high filter setting may produce misleading results. These problems associated with the interpretation of extracellular electrograms have been recognized by many investigators and point to the need for detailed analysis of electrical activity recorded from normal and ischemic myocardium. Dillon and coworkers have analyzed long duration multicomponent electrograms from the border zone of abnormal myocardium overlying infarcts and hypothesized that very slow circuitous conduction occurs across the longitudinal fiber axis rather than long arcs of block as previously believed.⁵⁰ The differences in interpretation of signals recordings by groups using the same animal model requires an in-depth study of the influences of recording methodology of extracellular recordings from normal and pathological states of the heart.

Still, the results in Table 3 show that for impulses initiated near the recording site in normal tissue, a biphasic or triphasic morphology indicates almost certainly that the bipolar electrode is oriented perpendicular to the

wavefront direction, irrespective of fiber orientation. Therefore, electrogram morphology can be used indirectly to determine information about the activation wavefront.

Future directions

A partial examination of the problems associated with the analysis of bipolar electrograms has been presented here. An issue not addressed in the present study is the effect of filter setting on the morphology of extracellular electrograms and the ability to determine accurately activation time with different filter settings. The effect of filtering on activation time determination in unipolar electrograms has been examined by Cabo et al.¹⁰¹ However, the effects of filter changes in electrogram parameters must be compared with a standard of activation similar to that used in the present study. This information could be utilized to develop a set of rules to for an automatic cardiac activation detector, similar to studies by Simpson et al.^{20,21} and Pieper et al.¹⁸ In addition, bipolar electrogram recordings from pathologic states such as ischemia have not been carefully examined either theoretically or experimentally. High resolution recordings techniques applied here may be a useful tool to examine the complicated waveforms in this setting.

Theoretical models have been developed for relating extracellular potentials to intracellular electrical events.^{16,168} Some of the models have been applied for normal experimental conditions and show a good correlation

with predictions. We did not provide a detailed theoretical explanation for the different electrogram morphologies observed during this study. Perhaps this indicates the need for the development of theoretical models in which bipolar electrograms can be studied.

A final comment relates to the recording of extracellular electrical potentials from diseased myocardial fibers where the recordings and their interpretation are expected to be far more complex than the results shown in the present study. These studies remain to be done.

Conclusion

Bipolar electrode configurations are sensitive to wavefront direction, bipole orientation and interpolar distance, which may affect the accuracy of activation time determination. Peak negative voltage of uniphasic and triphasic signals is a reliable predictor of activation time only for broad activation wavefronts and for parallel orientation in the longitudinal direction during elliptical propagation. Although the intrinsic deflection is the best predictor of activation time from among the features of the biphasic electrograms, it is less accurate than peak negative voltage in uniphasic or triphasic electrograms. A maximum interpolar distance of 2 mm and bipolar orientation parallel to the impulse is minimally required for accurate determination of activation time for impulses initiated near the recording electrodes.

Chapter VI . Qualitative and quantitative electrogram analysis of unipolar and bipolar recordings from ischemic canine epicardium

Introduction

It is increasingly important to develop a more scientifically sound method for the analysis of complex extracellular electrograms. Though the importance of understanding electrogram morphology from ischemic myocardium is obvious, few theoretical studies have been directed to the analysis of complex electrograms in this setting. The bipolar recording modality is still most commonly used, especially for activation mapping of ischemia related arrhythmias. There are, however, few theoretical studies which have analyzed their biophysical basis. One significant inherent limitation to bipolar recordings is their sensitivity to wavefront direction. Though justification for bipolar recordings rests mainly on the large reduction of distant electrotonic potentials, no evidence has been provided which shows this to be the case in ischemic zones where large tissue inhomogeneities coexist with small amplitude, multiphasic deflections. Electrodes of various surface area dimensions, interpolar distance, and highpass filter settings have also been used with little regard for the theoretical basis of the recorded electrical signals. The possibility of artifact

or misinterpretation due to methodological considerations has been addressed by Ideker et al.¹¹ and Waxman et al.¹⁶⁹

The majority of theoretical and experimental work on the analysis of extracellular electrograms has been reported for unipolar recordings. Mathematical derivations of an extracellular point potential relating to transmembrane potentials have been described, and their experimental confirmation performed with good results.¹⁴ Dower¹⁷⁰ and later Spach and Dolber¹⁶ showed that the intrinsic deflection of the unipolar electrogram coincided with the upstroke of action potentials recorded in close proximity to the extracellular site. Spach et al. provided data showing that the maximum negative derivative ($-dV/dt_{\text{MAX}}$) normalized for muscle bundle size could be a good predictor of activation time in normal tissue.¹²⁶ Anderson and coworkers used a statistical approach to validate Spach et al.'s prediction in atrial unipolar electrograms obtained during supraventricular tachycardia, and found the normalized derivative ($-dV/dt_{\text{MAX}}/V$) could provide better prediction than $-dV/dt_{\text{MAX}}$.¹²³ This may also be the case in preparations with more complex anatomy, because $-dV/dt_{\text{MAX}}/V$ accounts for bundles of varying diameter assuming similar conduction velocity in each bundle. However, in ischemic preparations the situation is complicated by the fact that there are bundles of cardiac fibers of varying dimension and uneven conduction velocity. Thus, the normalized derivative may not be as good a predictor of activation in this setting.

For many experimental studies designed to test the accuracy of electrogram features to predict the moment of activation compared with an activation time standard, no suitable standard was applied.^{17,18} Instead, most studies relied on the experience of investigators to manually assign activation time to electrograms, and compared features to those assignments. The goal of this study was to provide a framework for the analysis of unipolar and bipolar electrograms in the post-infarcted heart, and develop an objective, statistically based set of criteria for activation time determination using analysis based on a standard of activation related to sound biophysical theory.

Methods

Surgical preparation

Experimental data were obtained from the hearts of 10 conditioned male mongrel dogs weighing 12-16 kg. The study was approved by the local institutional review board and conformed to the guiding principles of the Declaration of Helsinki. Dogs were pre-anesthetized with sodium thiopental (17.5 mg/kg, iv) and intubated with a cuffed endotracheal tube. Anesthesia was maintained by constant ventilation with a mixture of 1-2½% isoflurane vaporized in 100% O₂, administered through an electronically controlled anesthesia ventilator (Foregger F500, The Foregger Co., Hauppauge, NY). A left sided thoracotomy was performed at the fourth intercostal space to

expose the heart. The left anterior descending artery was dissected free and ligated in one-stage, 1-2 cm from its origin. Coronary circulation and collateral blood flow were assessed by inspection, and when necessary, large epicardial branches in the anterior left ventricular free wall and apex originating from the left circumflex artery or posterior descending artery were also ligated in one-stage. After the ligation, the dog was monitored with the chest area remaining open for 20 minutes. The chest was then closed in layers and the pneumothorax evacuated. The dogs were allowed to recover receiving antibiotics (penicillin-G procaine, 20,000 U/kg i.m.) prophylactically and analgesic (buprenorphine, 0.005-0.02 mg/kg) as required.

Four to five days after the ligation procedure, the dog was again reanesthetized as was previously performed. The heart was again exposed via left-sided thoracotomy. Electrocardiographic lead II and aortic blood pressure (Statham, Gould, Inc., Oxnard, CA) were continuously monitored on an Electronics for Medicine VR12 monitor (PPG Co., Pleasantville, NY). Ventilated CO₂ was monitored (Datex CO₂ Monitor, Puritan Bennett Corp.), and core and intrathoracic temperatures were monitored using two electronic thermometers (Yellow Spring Instruments, Yellow Springs, OH). When slowing of the sinus rate was necessary, a Grass S88 stimulator (Grass Instruments, Quincy, MA) was used to stimulate the right and left vagosympathetic trunks through two pairs of Teflon-insulated silver wires

(250 μm diameter) with square wave pulses, 0.1-0.5 msec duration, at a frequency of 20 Hz, at 1-10 volts.

Whole ventricle electrode array

A sock electrode array was placed over the epicardial surface for simultaneous recording at 254 sites as described in an earlier chapter. Once the sock position and recordings proved satisfactory, the ribs were approximated and the chest cavity closed. When the core temperature was stable within the physiologic range, electrogram data were acquired.

High resolution cross electrode array (HRCEA)

The HRCEA was constructed as described in *Chapter IV*. The HRCEA was placed on the left ventricular free wall in an area overlying the infarct zone; the most distal pole of the cross was 4-5 millimeters from the interventricular septum. The top panel of Figure 35 is a schematic depiction of the HRCEA placement in relation to anatomical landmarks on the anterior surface of the heart. The heavy line represents the left anterior descending artery (LAD); the stars represent sites of stimulation in the right ventricle and at the center of the HRCEA. The HRCEA was situated on the epicardial layer, overlying the infarct (dotted line), parallel and perpendicular to the long axis of the ventricular fibers. The location of the ligation is denoted by the 'X' on the LAD. ¹³⁹ Correct positioning was verified by maximizing the

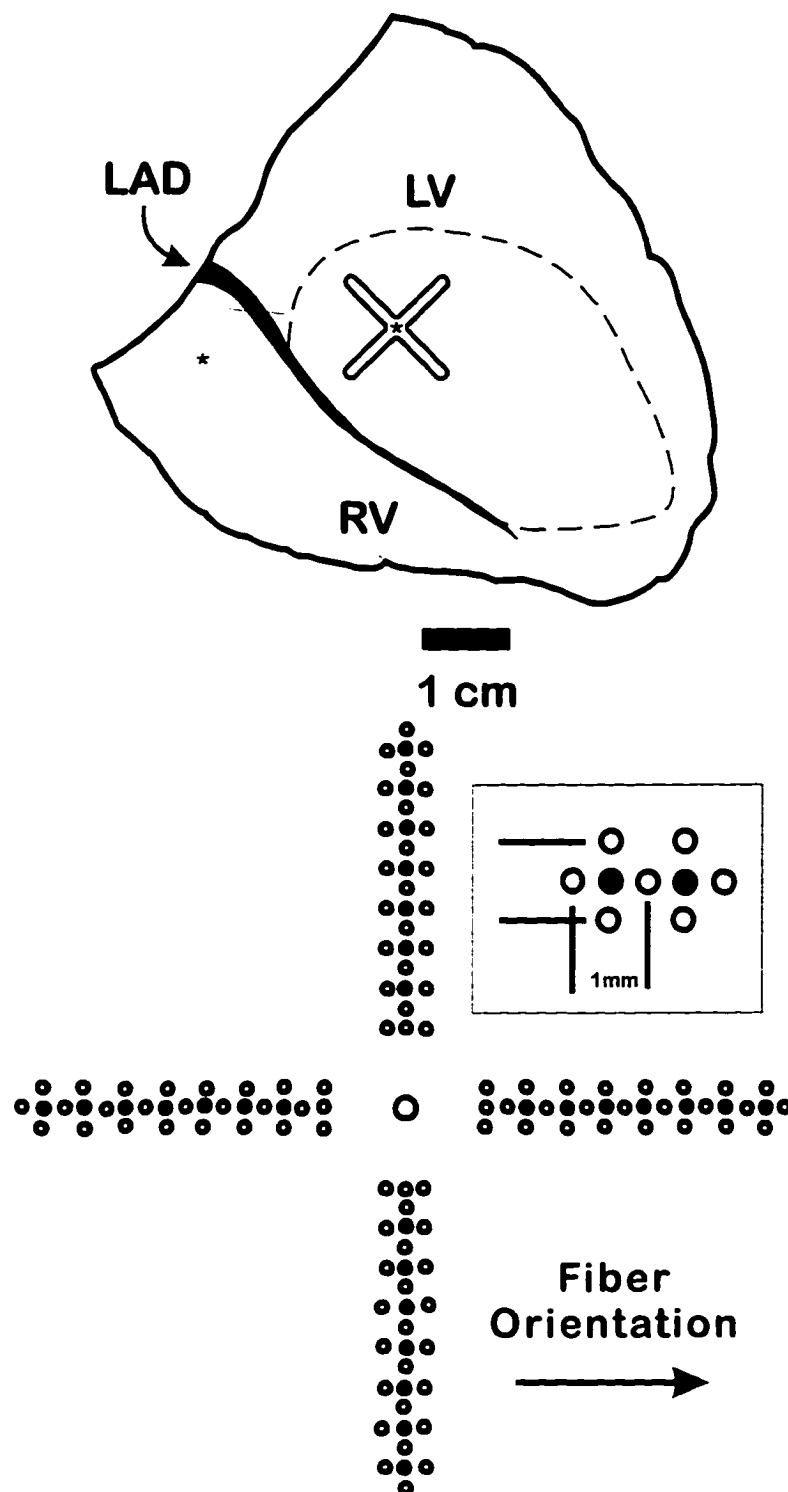


Figure 35. Schematic representation of high resolution cross electrode array and its location on ischemic epicardial surface

anisotropic conduction velocity ratio, performed by measuring the ratio of activation times of transverse and longitudinal electrograms equidistant from the central stimulation site on a digital storage oscilloscope (Model 5115, Tektronix), and adjusting the HRCEA position until the ratio was maximized.¹⁶²

High resolution rectangular electrode array

A high resolution rectangular electrode array was constructed as previously described in *Chapter IV*. Once an arc of block was located by whole ventricle isochronal activation mapping, the high resolution grid array was positioned at sites demonstrating double potentials, signifying where arcs of conduction block occurred. The grid array was placed so that the arc would bisect the long side of the rectangle.

Multichannel data acquisition system

Unipolar electrograms were acquired using 2 variable gain 128 channel multiplexed data acquisition systems (DSC 2000, INET Corporation, Newark, CA), allowing simultaneous recording of up to 256 signals. Signals were amplified and filtered with a fixed highpass setting of 0.05 Hz and an adjustable lowpass setting of 500-2000 Hz. The analog data were digitized with 12 bit resolution at a sampling rate of 1000-4000 samples per second per channel. The digitized signals were then stored on hard disk on an IBM compatible computer system (486PC, Touche Co., Chicago, IL).

Stimulation protocol

Programmed electrical stimulation was performed utilizing a Bloom DTU-101 digital stimulator (Bloom Co., Reading, PA). To generate a broad wavefront, stimulation was applied through a bipolar plunge electrode consisting of two hooked, enamel coated, stainless steel wires (125 μm diameter) placed in a 23 gauge hypodermic needle and inserted into the right ventricle near the outflow tract. To generate elliptical stimulation, cathodal unipolar stimulation was applied at the center of the HRCEA at 1.3 times diastolic threshold. Only sites in which the stimulation threshold was ≤ 0.6 mA were included in the analysis.

The stimulation protocol consisted of pacing at cycle lengths of 600, 500, 400, 300, and 250 ms. After at least 30 consecutive captured paced beats at each cycle length were evident, 2 second recordings were obtained by the data acquisition system.

Data Analysis

The data was sorted with a custom written Pascal program and converted to an ASCII file format for use in Microsoft Excel 5.0 for Windows (see Chapter IV). Macros were written to view each electrogram and perform most calculations required for analysis. A 5-point Lagrange approximation method ¹⁶³ was used to calculate the first temporal derivative, dV/dt . The relation is:

$$\frac{dV_t}{dt} = \frac{V_{t-2} - 8V_{t-1} + 8V_{t+1} - V_{t+2}}{12h}$$

where h is the sampling interval of the acquired digitized data. To estimate the second temporal derivative, d^2V/dt^2 , the difference equation used was:¹⁶³

$$\frac{d^2V_t}{dt^2} = \frac{V_{t+1} - 2V_t + V_{t-1}}{\Delta t^2}$$

Approximately 200 ms were selected from each run of data and were subjected to analysis. After calculating the derivative of each waveform, the program placed selected electrograms in a waterfall plot so they could graphically displayed. The algorithm used for analysis of unipolar electrograms is discussed in the *Results* section below.

Bipolar electrograms were recorded in two ways: 1) during whole sock isochronal activation mapping, bipolar recordings were obtained by conventional methods described in previous reports ¹³⁹; and 2) they were synthesized by taking the arithmetic difference between two unipolar recordings. ¹¹⁵ For most portions of the study, the interpolar distance was 1 mm. The 28 black dots in the cross electrode shown in Figure 35 indicate each central unipolar reference site for 2 orthogonal bipolar electrode configurations. A total of 56 bipolar electrograms from each HRCEA recording could be analyzed.

Bipolar electrograms were also synthesized for various interpolar distances (1-7 mm, in 1 mm increments) and for different bipole orientations

with respect to fiber orientation (parallel electrode orientation and perpendicular electrode orientation). The inset of Figure 35 shows two orthogonally oriented bipolar electrode arrangements with a central unipolar reference in relation to the both activation impulse directions (longitudinal propagation and transverse propagation).

Statistical analysis

Data are presented as mean $\pm$ standard deviation. Statistical analysis was performed with Systat for Windows (version 5.2, Systat Corp., Evanston, IL).¹³¹ Data were analyzed by linear regression and discriminant function analysis, where appropriate. Figures and graphs were created with CorelDraw (version 5, Corel Corp., Ottawa, Ontario) or Origin (version 3.5, MicroCal Software Inc., Northampton, MA).

Results

Bipolar recordings

Long duration, multiphasic waveform recordings are often recorded from the ischemic zone of infarcted hearts, often making precise activation time determination difficult. A typical example of this situation is presented in Figure 36, in which bipolar recordings were obtained from 254 sites situated on the left ventricle, and in this area, the sites are 2.5 mm apart, and the interpolar distance is 0.8-1.2 mm. The map and electrograms were obtained

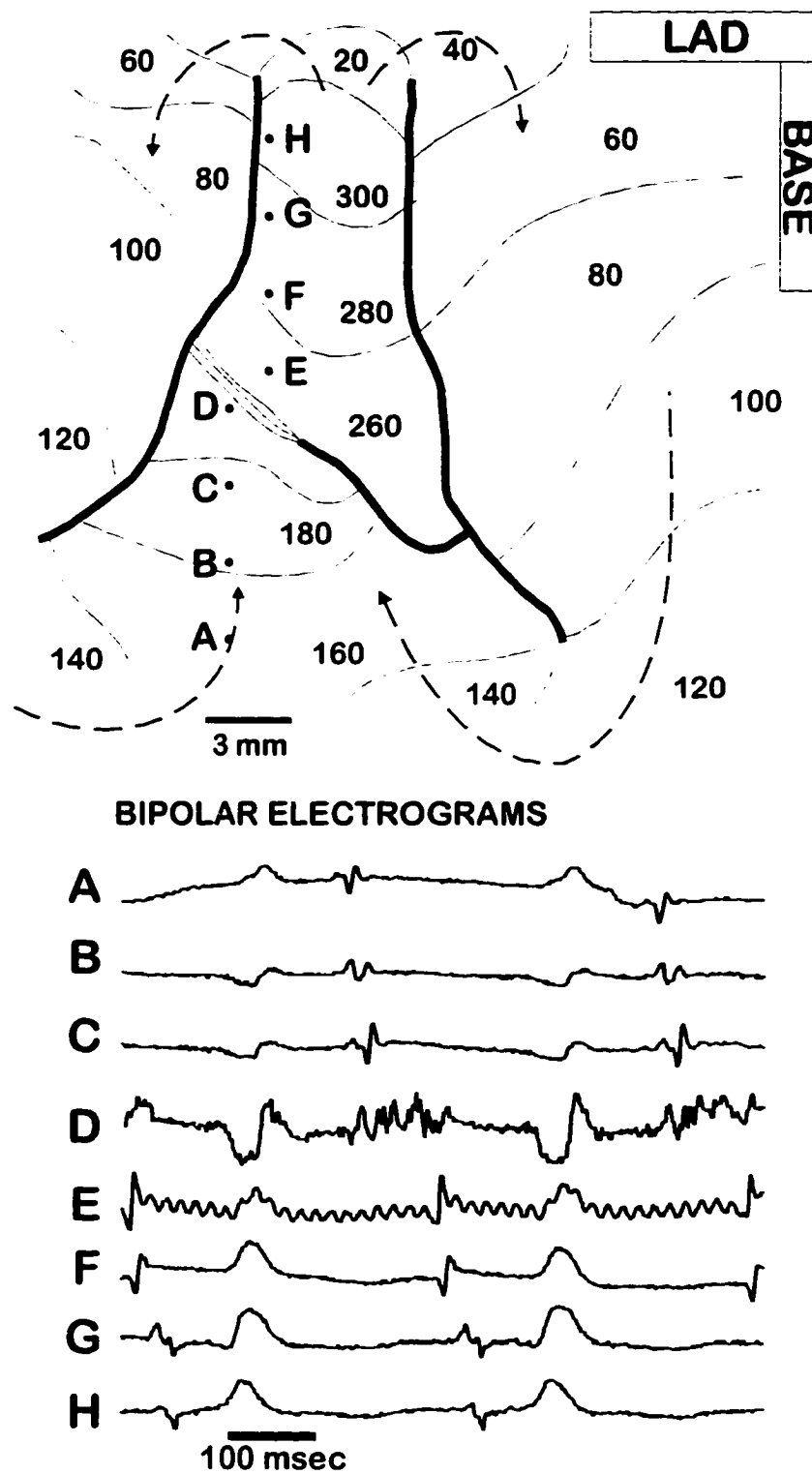


Figure 36. Typical problems associated with activation time determination in bipolar recordings from ischemic myocardium

during a sustained ventricular tachycardia with a cycle length of 300 ms. The top panel shows a high resolution activation map of the common reentrant pathway of a figure-8 ventricular tachycardia determined by whole sock activation mapping. The spatial placement of selected electrograms A-H are denoted by filled dots. Electrograms A-H are shown in the bottom panel. Activation propagates from H to A over a 140 ms period, however, site E shows multiphasic activity, making precise activation time assignment for that site difficult to assess by conventional feature extraction techniques. In this figure, site E was placed in the 260 ms isochrone, and three closely spaced isochrones are drawn between sites E and D, armed only with the understanding that the range of activation of site E was between that of sites F and D (180-260 ms), and there are few other outstanding clues from the waveform to assist in activation time assignment.

The effect of interpolar distance on bipolar electrograms and activation time accuracy during broad wavefront stimulation is displayed in Figure 37. Synthesized bipolar electrograms with poles separated by 1-7 mm were constructed by taking the arithmetic difference between unipolar recordings, centered about the unipolar electrode (UNI). The vertical dashed line is aligned to the maximum $-dV/dt$ (2nd from top), and represents the moment of activation of UNI. As the interpolar distance increases (i.e., > 2 mm interpolar distance), the waveform becomes multiphasic and if the maximum

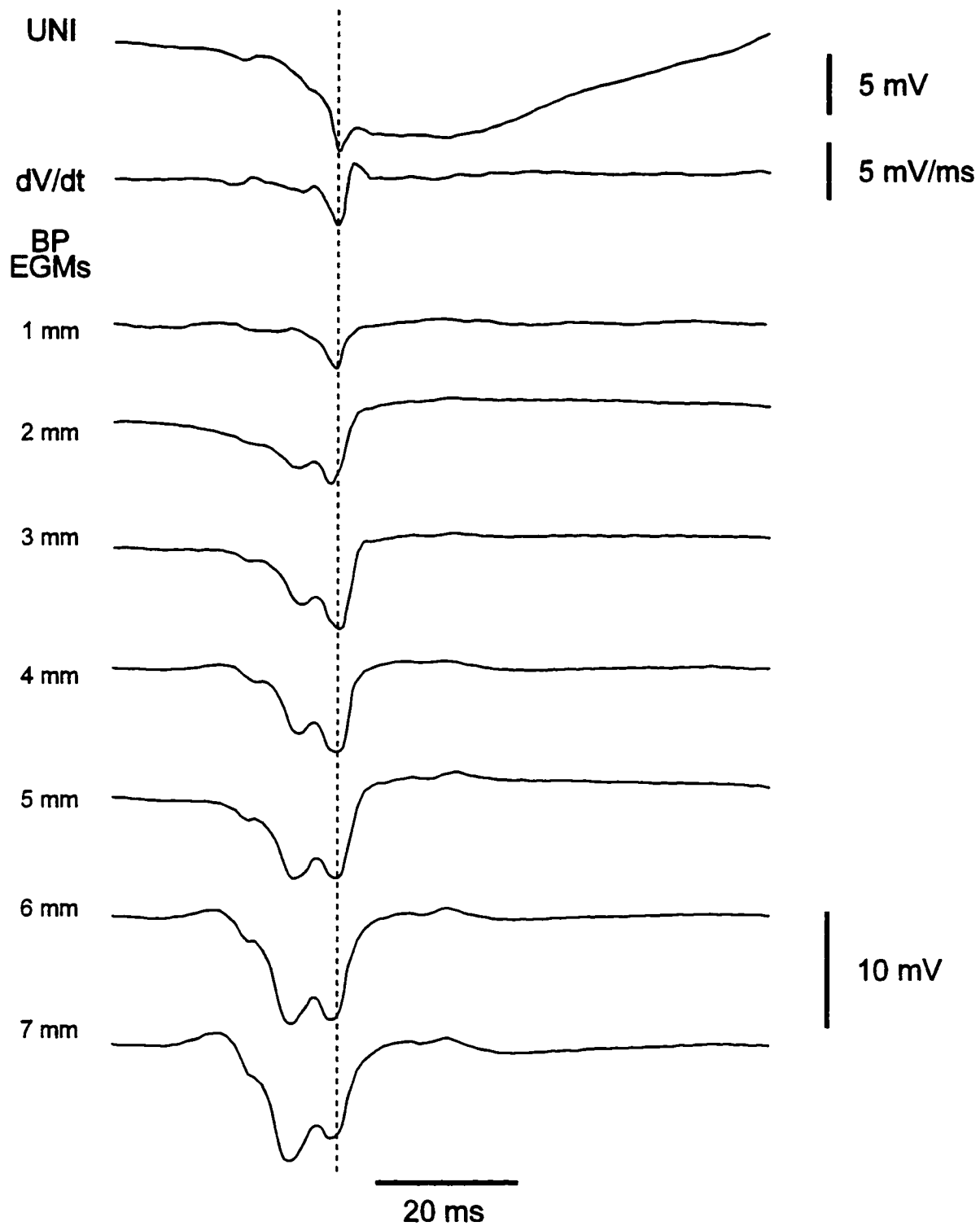


Figure 37. Effect of interpolar distance on activation time determination in ischemic bipolar electrograms during broad wavefront stimulation.

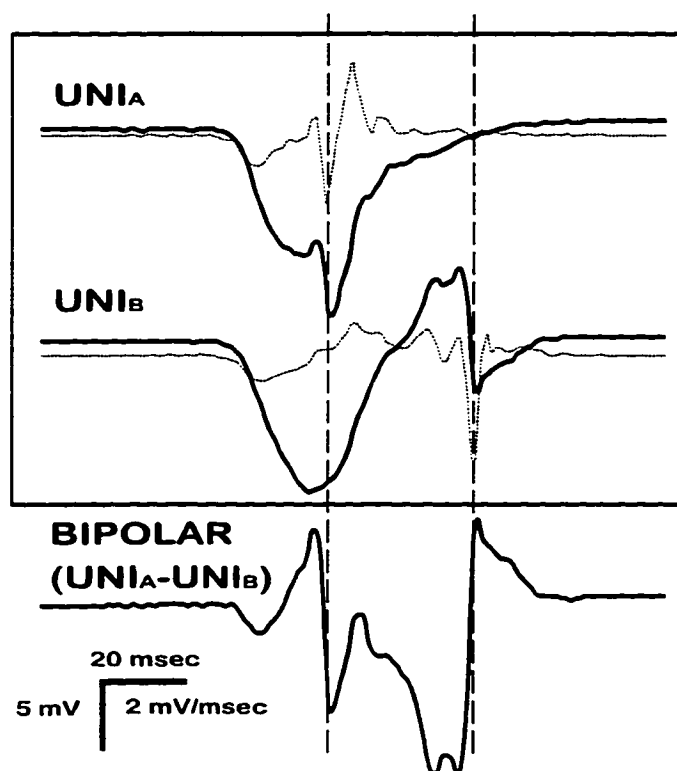
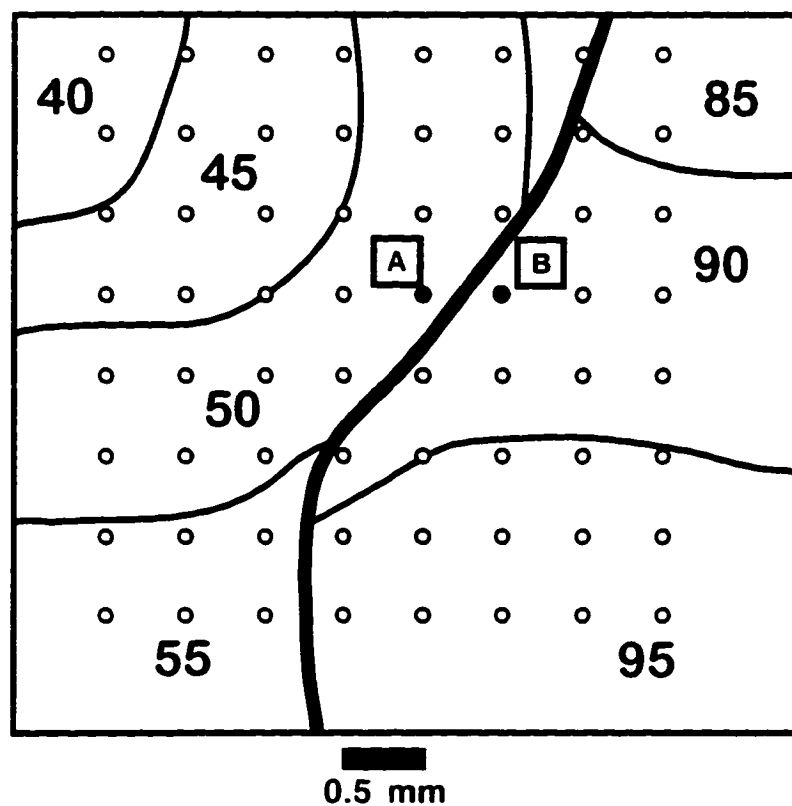


Figure 38. High resolution map with interpolated arc of block obtained during ventricular tachycardia. The 2 unipolar electrograms at bottom correspond to the sites in the map above.

negative potential is used as the feature to assign activation time, the activation time error also increases. At 7 mm interpolar distance, the error was 8 ms. This example demonstrates that distant effects can significantly bipolar recordings, especially when the interpolar distance increases >2 mm.

Multiphasic bipolar recordings could also be obtained by recording across an arc of block, as demonstrated in Figure 38. The top panel of Figure 38 shows a high resolution isochronal map realized by recording 128 unipolar sites arranged in a 16 by 8 grid with 0.5 mm separation. The site of block was initially identified with whole sock isochronal activation mapping techniques, and is displayed as a thick line interpolated between recorded electrograms having activation time differences ≥ 40 ms. The electrograms of two sites, A and B, shown in Figure 38, are shown at the bottom and in Figure 39, along with their dV/dt (dashed lines). A bipolar signal composed of the difference of the two electrograms was synthesized and is shown below the unipolar electrograms, having double potentials commonly encountered in areas of conduction block. This signal was then highpass filtered with a 8-pole, digital Butterworth implementation at cutoffs of 10, 25, and 50 Hz.¹⁷¹ The dV/dt of both sites A and B shows a clear, single, maximum negative amplitude, with a time difference of 42 ms between the sites. The dotted vertical lines represent the activation times of each unipolar electrogram. Highpass filtering increased the both number of deflections and the duration from the original signal. The characteristics of

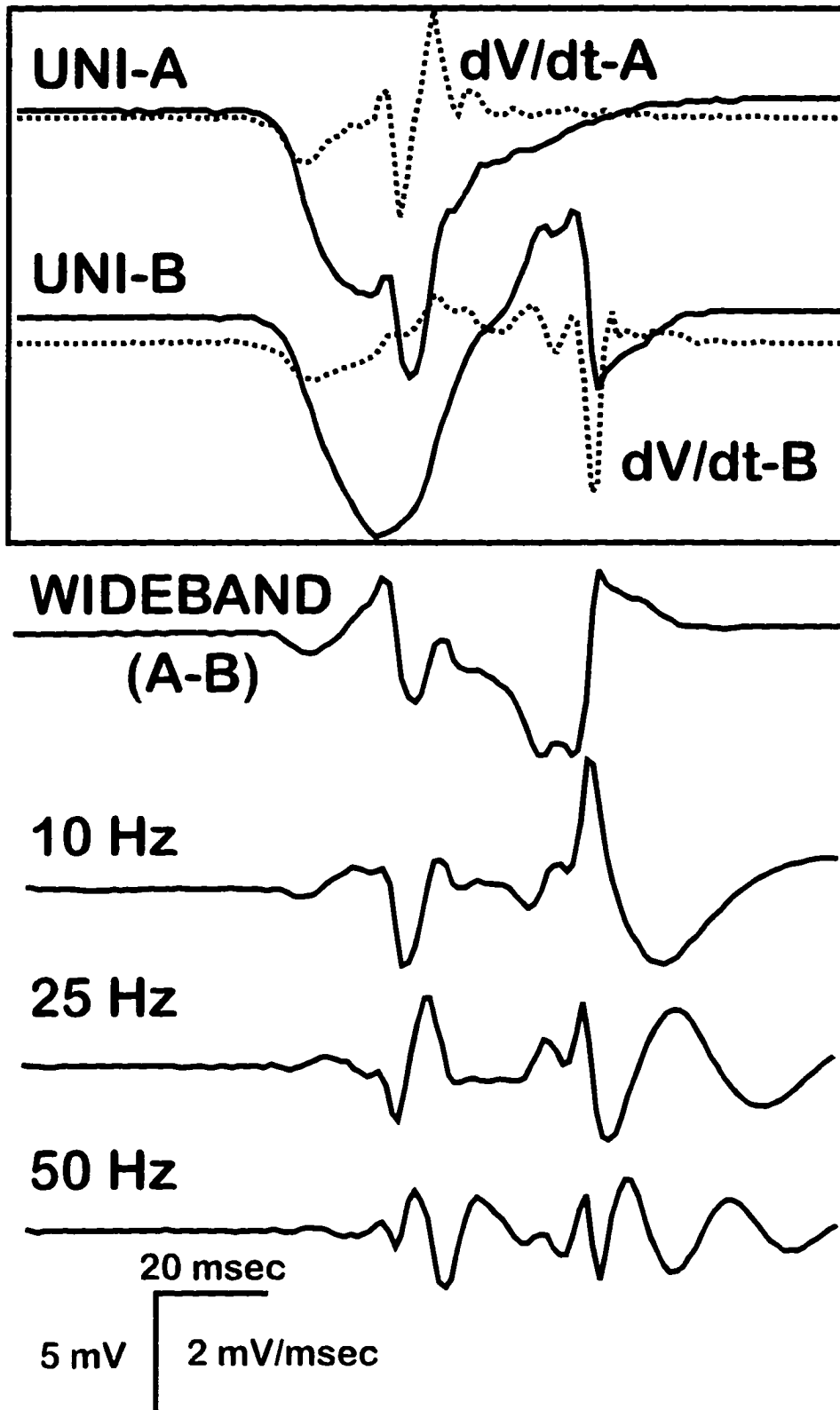


Figure 39. High pass filtering of bipolar electrograms creates multiphasic waveforms..

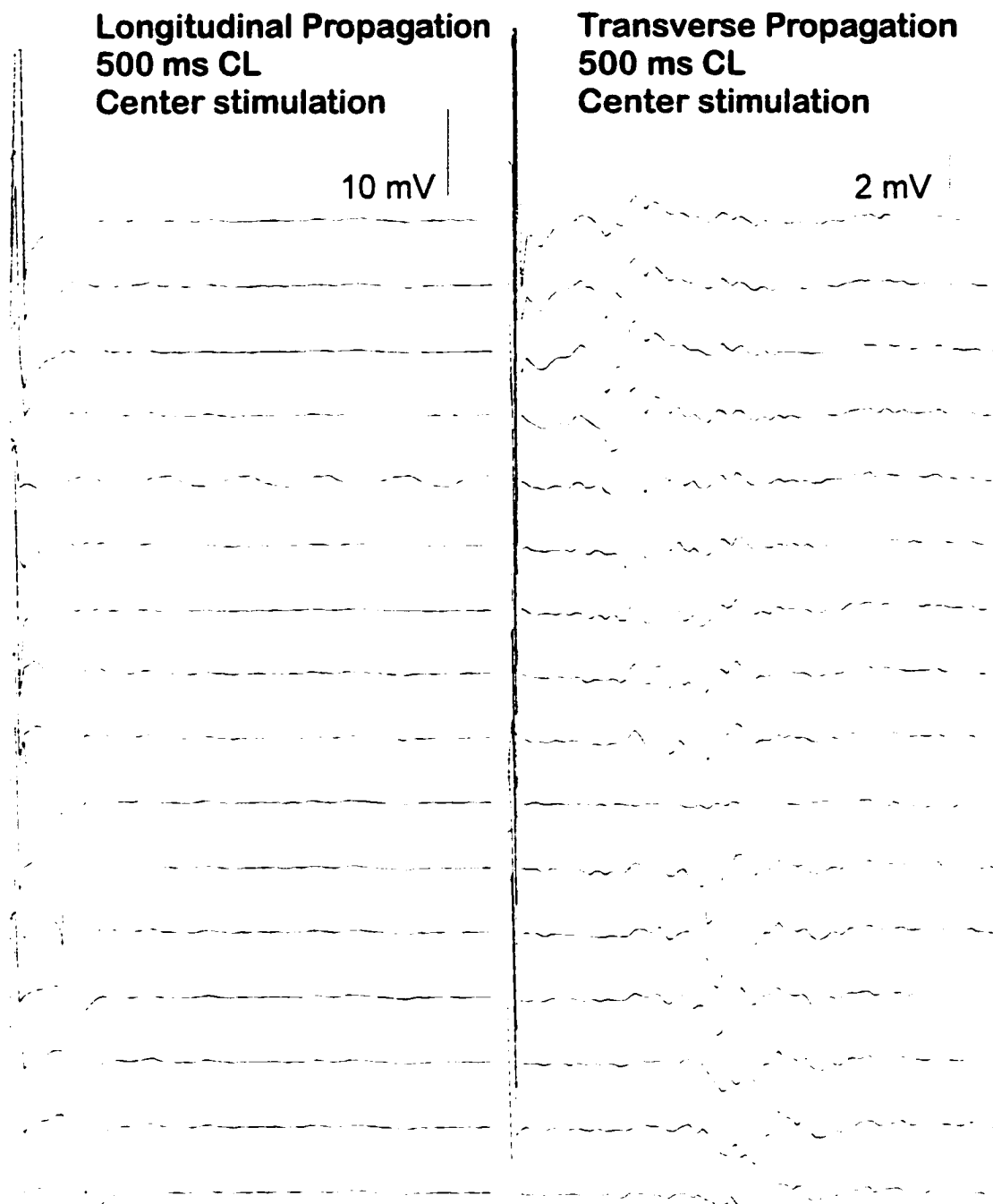


Figure 40. Effect of anisotropic conduction on ischemic unipolar electrograms

the signal at 50 Hz are similar to the fractionated potentials recorded from site D in Figure 38, with at least 4 local minimums revealed.

Unipolar recordings

The qualitative effect of anisotropic conduction on unipolar EGMs recorded from ischemic myocardium is shown in Figure 40. Stimulation was applied to the center of the HRCEA. Each column displays the dV/dt of 16 consecutive unipolar recordings separated by 0.5 mm. The electrograms at the top of each column are 2 mm from the stimulus site; the bottom electrograms are 9.5 mm from the stimulus site. The left panel shows that longitudinal (along the fiber axis) propagation at 500 ms pacing proceeds rapidly, with large amplitude deflections that remain fairly constant and have a narrow complex dV/dt . The activation in this set is completed in about 13 ms, and the conduction velocity is 6.7 cm/ms.

The recordings differ markedly for transverse propagation (across the fiber axis), shown in the right panel of Figure 40. During the same 500 ms stimulation, the recordings display progressively smaller amplitude and multiphasic components, and activation appears discontinuous between the fifth to twelfth electrograms. If only the topmost five electrograms are used, the measured conduction velocity is 2.2 cm/ms. Also note that activation time assignment is more difficult to make visually, but employing the concept of propagation from a set of closely spaced electrograms can aid in the decision making process. For example, consider the sixth electrogram from

the top of the right panel of Figure 40, which displays two clear negative deflections in the dV/dt , the first one deeper than the second. With conventional methods, the first or deeper deflection would be assigned as the activation time. However, with the aid of viewing propagation from a set of closely spaced electrograms, the second deflection is seen to occur midway between deflections of the upper and lower electrograms, while the first deflection is coincident with the deep deflection of the upper electrogram. From this, one may reasonably assume that the first deflection is an electrotonic deflection, and the second deflection is the closest accurate assignment of activation time.

Standard of activation

In order to investigate which features of the unipolar electrogram (U-EGM) achieve the best prediction of local versus distant activation, an activation time standard (ATS) was developed for comparison from a varying set (5-16) of closely spaced U-EGMs. The ATS consisted of three properties: 1) propagation of activation, evidenced by a linear temporal shift of waveforms from closely spaced U-EGMs with little or no decay in amplitude, 2) cycle length dependent changes of those propagating waveforms, and 3) evidence of electrotonic deflections, seen as basically non-propagating deflections having decaying amplitude with distance.

An example which describes how an ATS was determined is presented in Figures 41 and 42. Temporal and spatial propagation can be clearly seen in

Figure 41 by noting the progression of a waveform from U-EGM to its neighbor. In this example, stimulation at basic cycle lengths of 600 and 300 msec was introduced from the right ventricle. In both the left and right panels, deep deflections are present as the wavefront traverses in the longitudinal direction, along the long axis of the fibers. The dotted lines overlying each waveform are the dV/dt of each U-EGM. With pacing at the 600 ms (left) the $-dV/dt_{MAX}$ shows visible uniform temporal propagation. For this example, the time of each $-dV/dt_{MAX}$ was entered into a regression analysis, with the uppermost U-EGM fixed at 0 mm and the bottom U-EGM in this set 2.5 mm distant, propagation can be described as essentially linear, shown in Figure 42, ($R=0.98$) with a slope of 2.7 (Figure 41, bottom left panel). The conduction velocity (.027 cm/s) is about three times slower than conduction velocity obtained from normal tissue measurements. At 300 ms pacing, propagation is still apparent, however, depicting the $-dV/dt_{MAX}$ as the activation time is difficult, because there are multiple deflections in the dV/dt with near-equal amplitudes, particularly in EGMs 2-4. If the regression analysis is again employed, only 1 deflection from each waveform is selected to maximize linear propagation statistics; while the other deflections are labeled electrotonic. Since propagation at 300 ms pacing is slower than at 600 ms pacing, a larger slope is expected. Therefore, regression analysis

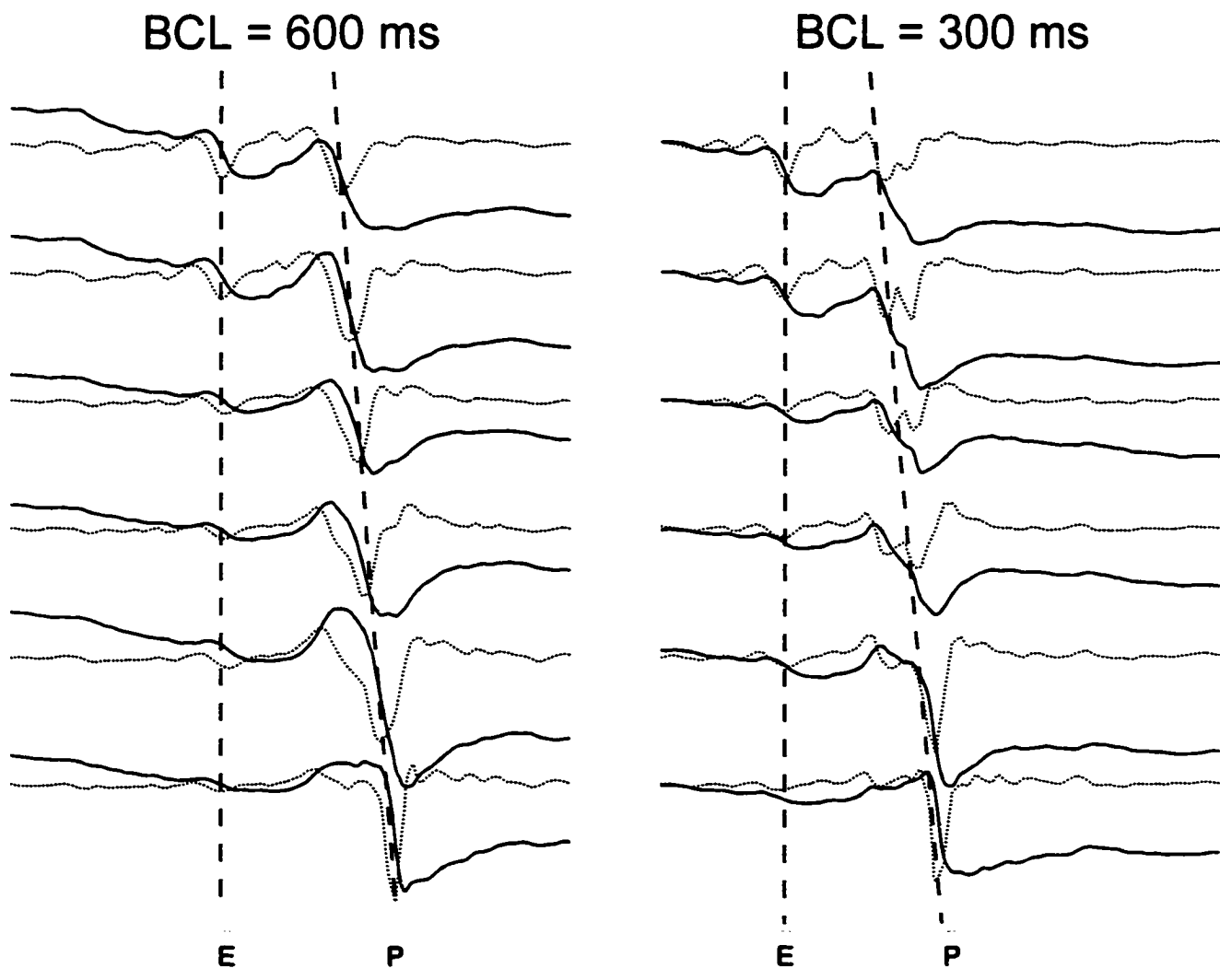


Figure 41. Determination of a standard of activation, part I

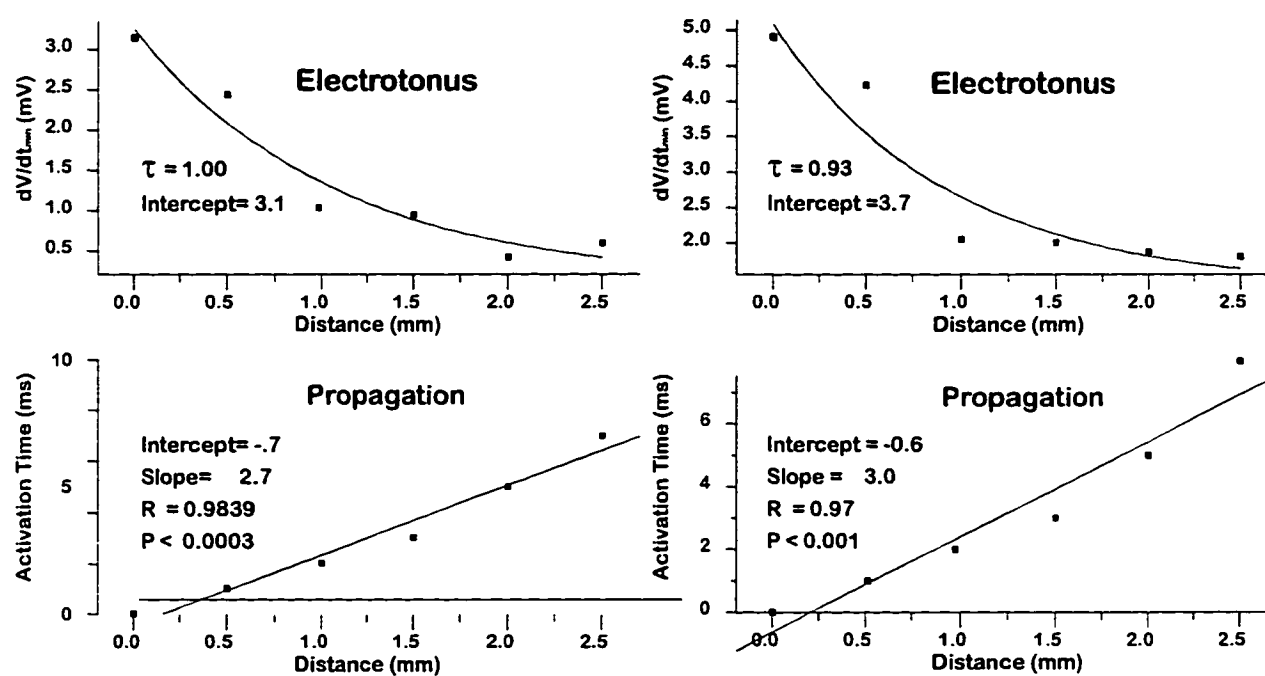


Figure 42. Determination of a standard of activation, part II

picked deflections as local activations from each U-EGM of each set which: 1) increased the slope factor from that calculated at slower pacing cycle lengths; and 2) had regression correlation coefficients (R) ≥ 0.9 . For this study, sets of U-EGMs which could not meet this criteria were excluded from further analysis. From this method of analysis, local activation could be well described.

Another important aspect contributing to the development of an accurate ATS was the ability to discern electrotonic, or distant deflections from the same sets of U-EGMs. Biophysical theory on the analysis of extracellular potentials from sources some distance away describes distant potentials which decay exponentially in amplitude with distance from the source. Using this knowledge, and combined with the understanding that distant potentials will create deflections from a set of closely spaced U-EGMs which do not propagate in time, an analysis for detection of electrotonus was applied, and is shown in the upper panels of Figure 42. These panels show plots of the amplitudes of deflections intersecting the vertical (i.e., velocity $\rightarrow \infty$) dashed line (E) in the sequential U-EGMs at the left of Figure 40, and show an exponential decay with a τ of 1.0 for the 600 ms paced tracings.

The analysis of the dV/dt of U-EGMs in the right panel of Figure 40 is more complex. Similar to the left side, the amplitudes of deflections intersecting the vertical dashed line (E) are plotted in the upper right panel of Figure 41, also decaying exponentially with a τ of 0.93. However, there are

three deflections in each dV/dt , therefore, two deflections must represent distant activation, while the third depicts local activation. Using a combination of techniques described above, an accurate picture of local and distant activation deflections can be realized. The vertical dashed line (E) line is drawn to intersect with a set of nonpropagating deflections. It should be noted that other attempts to create a different pattern of propagation utilizing other deflections either result in a lowered R value or a slope which is smaller than the slope of the 600 ms regression line.

For purposes of determining which electrogram features provided the optimal activation time determination, only neighboring electrograms in which a clear determination of ATS could be determined were subjected to analysis. A consistent ATS was defined as: 1) an ability to measure linear propagation ($R > 0.9$) from the first temporal derivatives of 5 or more neighboring electrograms, while 2) discerning waveforms between these neighbors with constant temporal characteristics, indicative of electrotonic activation, and further, that these waveforms progressively display a reduced amplitude; and 3) that slope measurements of propagation increase as the cycle length of basic drive train pacing decreases. Using this definition, it could be argued that this ATS represents the most reliable surrogate currently available for transmembrane recordings from those sites.

Electrogram feature extraction

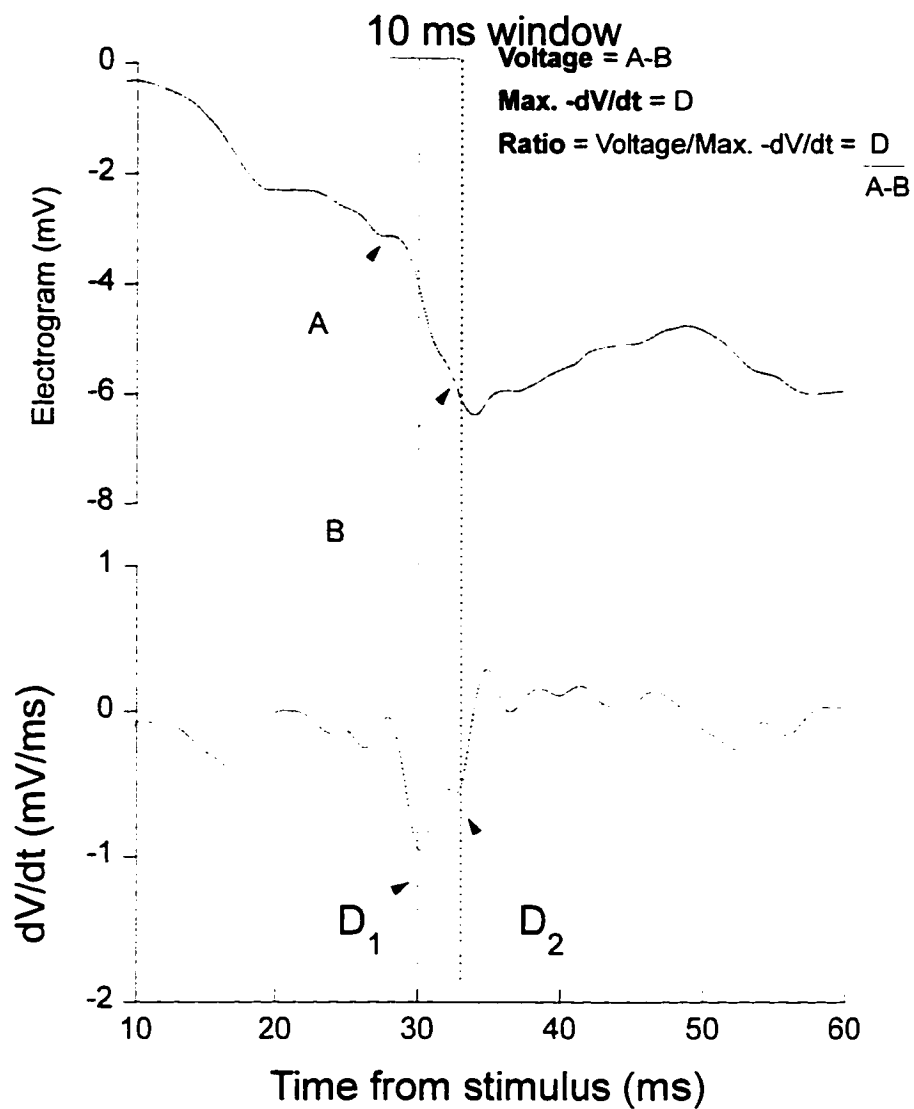
A number of electrogram features were calculated and subjected to analysis by comparing their occurrence with the ATS. Of specific interest was the finding by Spach and Dolber¹²⁶ and later by Anderson et al.¹²³ that for unipolar electrograms, the normalized $-dV/dt_{MAX}$ (ratio of the dV/dt to the peak-to-peak amplitude) could contribute to discriminating local from distant activation. The following algorithm was used for feature extraction. A 100 ms window containing the entire waveform was subjected to analysis. The $-dV/dt_{MAX}$ within the window was found by use of a maximum function, and the corresponding time was determined and tabulated. A 10 msec window centered about that time was then applied to the initial voltage signal. The maximum (Voltage), minimum and maximum-minimum values in that window were then determined. Finally, the corresponding times of the maximum and minimums were determined and tabulated for analysis. The variable, Ratio, was calculated by the ratio of $-dV/dt_{MAX}$ to the maximum-minimum values in the 10 msec window, while its temporal position remained that of $-dV/dt_{MAX}$. The algorithm was then repeated, this time for the second largest discrete $-dV/dt$ amplitude deflection in the window. A deflection was considered discrete if the second temporal derivative, d^2V/dt^2 , had at least 3 consecutive negative points reaching 0 value just before the deflection point, and at least 3 consecutive positive points just after the deflection point. Additionally, the amplitude of the second dV/dt deflection

must have been $>20\%$ of the primary deflection's dV/dt amplitude. Figure 43 provides a graphical description of the algorithm and result used to identify landmarks and tabulate their temporal parameters. In this example, D_1 would be selected as activation based on $-dV/dt_{MAX}$ and Voltage, while D_2 would be chosen as activation if Ratio were used.

Data was collected from sets of electrograms obtained from ischemic epicardial sites that: 1) had an unequivocal ATS; and 2) had both primary and secondary $-dV/dt$ deflections that could be analyzed. A total of 193 electrograms were included in the analysis, each having 6 features identified: Voltage₁, $-dV/dt_{MAX1}$, and Ratio₁ and Voltage₂, $-dV/dt_{MAX2}$, and Ratio₂. For each electrogram, the time position of the ATS was also tabulated. Figure 43 shows that the feature closest to the ATS was assigned as local activation, and the remaining features were designated as distant events (see Figures 41 and 42). Approximately 70% of electrograms were obtained from sites whose location was perpendicular to the fiber orientation, and the remaining 30% were from sites having a parallel orientation.

Statistical analysis

Discriminant function analysis was then applied to the data set, resulting in a model incorporating all 6 features, three from each deflection, to statistically determine which feature or set of features could provide the most



	D₁	D₂
Deflection (mV/ms)	1.15	0.70
A-B (mV)	3.87	2.86
Ratio (ms⁻¹)	0.34	0.40

Figure 43. Features extracted for unipolar electrogram analysis

significant discrimination between local and distant activation. Discriminant function analysis is a linear multivariate model of the form $Y=XB+E$ where Y is a matrix of dependent variables, X is a matrix of dummy variables, B is the matrix of regression coefficients, and E is the matrix of random error.¹⁷² For this study, Y consisted of 2 groups, “local” and “distant”, based on the relation of an electrogram feature to the ATS. The model created discriminant spaces for the 2 groups and scored each parameter based on the calculated probabilities of belonging to each space. Each feature is weighted by a set of calculated coefficients and constants to describe its probability of belonging to a space. The closer a feature is to the particular location of that group, the more likely it is that it belongs to that group. The model parameters were tested for significance, with the null hypothesis being that the groups were equivalent. The output are group classification coefficients and constants, comprising the Fisher discriminant space, which can be applied to new data for group prediction.

The standardized model solution provided two equations in the form of :

Local Activation = $-6.6 * dV/dt + 65.8 * Ratio + 2.1 * Voltage - 7.2$; and

Distant Activation = $-9.1 * dV/dt + 110.9 * Ratio + 3.0 * Voltage - 17.8$.

Each deflection analyzed in the future will have its features substituted in both equations, with the larger resultant determining to which group that

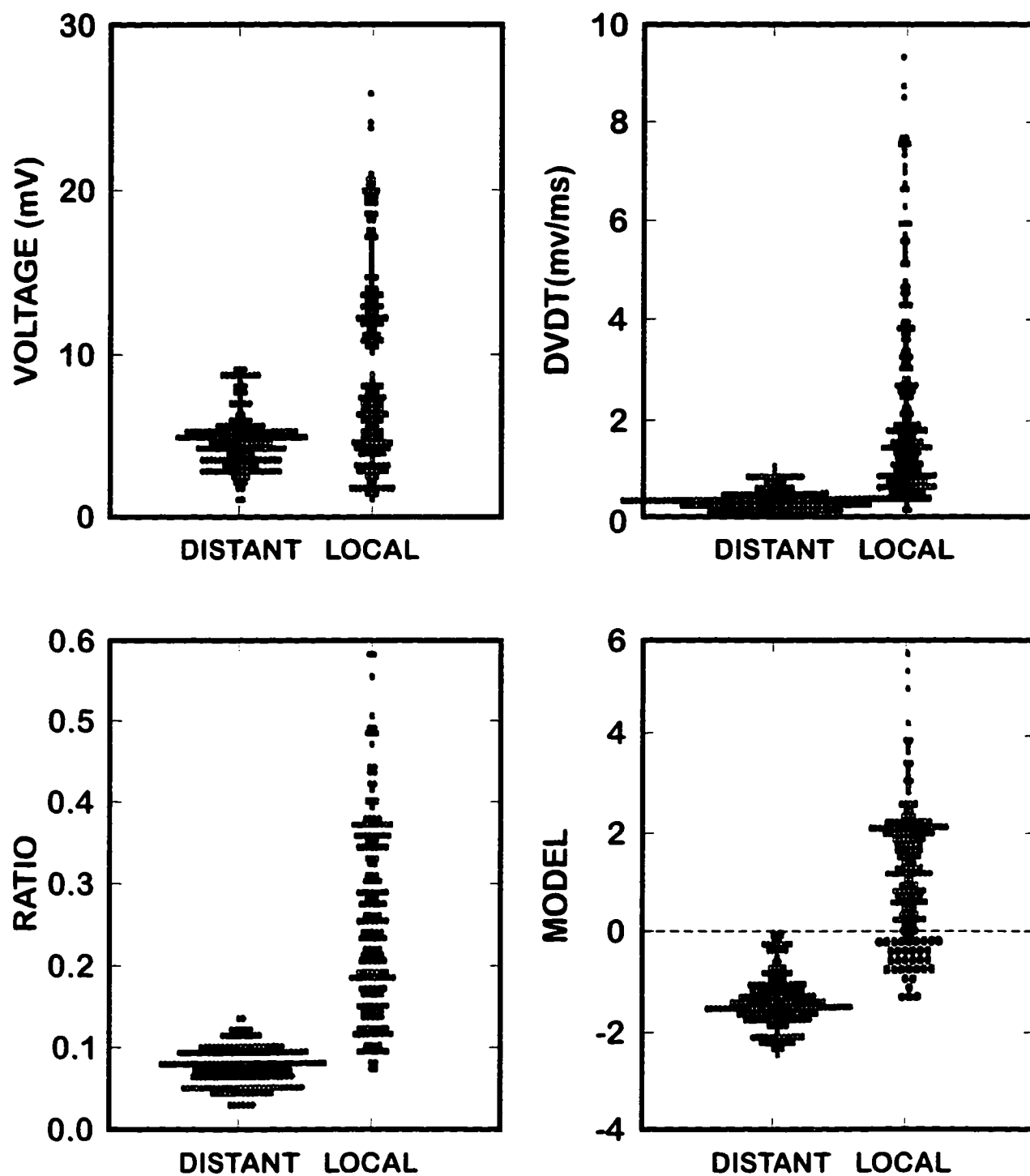


Figure 44. Feature assignment by discriminant function analysis into "local" and "distant" activation groups.

deflection belongs. This process is shown in Figure 44, which contains 4 dot plots. The Voltage, dV/dt , and ratio features are displayed separately, along with the model, incorporating all 3 features. It is readily visible that the model provides superior discrimination between distant and local groups, having the fewest number of data points which may be incorrectly categorized.

The results of the model, which incorporated all 6 features entered, was compared with the features analyzed separately or in pairs. Statistics on sensitivity, specificity, and total predictive accuracy were tabulated for comparison, and are presented in Table 6. Decisions concerning the placement of each variable were based on the following algorithm:

true positive	local activation correctly predicted as local activation;
true negative	distant activation correctly predicted as distant activation;
false positive	distant activation incorrectly predicted as local activation;
false negative	local activation incorrectly predicted as distant activation.

The table shows that the best single predictor of local and distant activation was the Ratio, or normalized derivative, with a predictive accuracy of 86%. No paired combination of variables was able to improve upon this prediction, however, the model incorporating all three variables, increased the predictive accuracy to 90%.

Table 6. Posterior prediction of variables into local and distant activation classifications by discriminant function analysis

n = 386	Sensitivity (%)	Specificity (%)	Predictive Accuracy (%)
Voltage	89	53	71
-dV/dt_{MAX}	100	57	79
Ratio	100	73	86
Voltage + -dV/dt_{MAX}	100	57	79
Voltage + Ratio	100	70	85
-dV/dt_{MAX} + Ratio	100	72	86
Voltage + -dV/dt_{MAX} + Ratio	100	80	90

Discussion

The recording of unipolar electrograms for activation mapping has not been commonly performed because the large electrical “view” often contains much waveform information which is distant from the recording site. These distant potentials make activation time assignment difficult to perform, especially upon visual inspection. The bipolar recording mode is more commonly used because distant activation potentials are significantly attenuated by the high common mode rejection ability of differential amplifiers. However, the bipolar mode is quite sensitive to wavefront direction, interpolar distance, filtering techniques, and very little biophysical theory to support interpretation of recorded waveforms. ^{51,142,151}

As shown in Figure 36, long duration, multiphasic bipolar recordings have often been recorded in ischemic areas and poses great analysis difficulties. Different laboratories have ascribed different mechanisms of reentrant rhythms in the same model of arrhythmia based on varying interpretations of these complex waveforms. The interpretation is based on intuition and lacks a systematic approach. A methodical analysis of these fractionated waveforms will help to better understand and treat these arrhythmias.

The effect of increasing interpolar distance was shown in Figure 37, and clearly shows that multiphasic activity can develop when the spacing is

greater than 2 mm. While decreasing the distance between the poles to less than 1 mm may decrease the amplitude and frequency content of the signal, it is obvious from Figure 37 that increasing interpolar distance may prove more harmful. Another problem with bipolar recordings is that in areas across or close to arcs of block, complex electrograms and double potential electrograms are often recorded, making activation time assignment difficult. In Figure 39, clear unipolar dV/dt deflections on either side of an arc of block, seen in Figure 38, were used to synthesize a bipolar signal which contained multiple deflections. Signal processing of this bipolar signal with highpass filtering made the waveform more complex and of longer duration, resembling fractionated electrograms often recorded in this setting. Restivo et al. warned that caution must be exercised when applying filtering settings to bipolar signals.⁴⁷ In addition, basic electrical theory has described how sensitive bipolar recordings are to wavefront direction; bipoles parallel to propagation wave will record deep deflections, while those perpendicular to the propagation wave will record 0 potential (see Figure 18B).

Another major issue unresolved is the fact that there are no methods yet devised which can relate the underlying transmembrane potential to an associated bipolar recording.²² While biophysical theory has described equations relating the potential at a point some distance away from a current source to the transmembrane potential, for a bipolar recording, this would have to be solved for two unipolar positions and the difference between the

two resulting potentials obtained, as was performed in this study. This relationship could not, however, be solved starting from bipolar recordings alone.²²

There is however, good biophysical theory to understand the composition of unipolar electrograms. Furthermore, Spach et al. showed good correlation between the intrinsic deflection of unipolar electrograms and the upstroke of Purkinje strands recorded in close proximity.¹⁶ Spach later showed that unipolar recordings were also sensitive to the diameter of muscle bundles, and found that for distant potentials, the amplitude of the second temporal derivative was attenuated more than the first temporal derivative, and the first temporal derivative was attenuated more than the voltage of the waveform.¹²⁶ Anderson et al. later used this information to develop a statistical method of analyzing unipolar recordings, and found the normalized first temporal derivative to be a good predictor of activation time in normal tissue.¹²³ An intent of this study was to provide unipolar data for activation time prediction utilizing biophysical and statistical information from ischemic epicardium. This study utilized a “classic” model of subacute myocardial infarction which gives an essentially two-dimensional experimental approach to investigate electrogram morphology and characteristics in ischemic areas. Unipolar recordings obtained from this in vivo preparation showed differences in amplitude and phasic activity when

comparing longitudinal and transverse orientation of sets of electrograms to the muscle fibers (Figure 40).

The development of a consistent and viable activation time standard is important to study which waveform features can provide optimal accuracy of activation time assignment. This study implemented several biophysical findings to create a suitable standard. The ability to demonstrate propagation from an ensemble of closely spaced electrodes, while at the same time, also demonstrating electrotonus which decayed over space, was a unique method of determining activation time. Several studies used potentials propagating in a temporal and spatial progression to indicate local activation.^{122,147,156,173} Anderson et al. combined the concept of propagation and electrotonus in analyzing atrial electrograms,¹²³ but used synthesized bipoles with 5mm interpolar distance, which makes uncertain assumptions out of recordings of local and distant activation.¹⁵¹ In this study, electrotonus was demonstrated by two methods: 1) temporal alignment of waveforms from a set of closely spaced sites; and 2) an exponential decay if the amplitude of electrotonic deflections. The later may occur in only part of the ensemble, but it was demonstrated in each of the electrogram sets. Furthermore, propagation was verified by recording at several basic drive train cycle lengths, which applied a known electrophysiologic phenomenon, namely, that when pacing at faster cycle lengths in ischemic tissue, the conduction velocity decreases.⁷ Evidence of this event was an increase in the

slope of the linear regression line. One limitation of this ATS was the 10 ms window used to determine the peak-to-peak voltage used for normalizing the $-dV/dt_{\text{MAX}}$, with the possibility that some inaccuracies have occurred.

The electrogram landmarks which were analyzed in this study were basically derived from the work of Spach and Dolber¹²⁶ and from Anderson et al.¹²³ Spach and Dolber plotted the peak-to-peak voltage, first and second derivatives as a function of distance, showing that while all three parameters decreased, the relationship of the decrease for distant potentials was such that the second derivative diminished more than the first, and the first derivative diminished more than the voltage signal.¹²⁶ They also showed that the amplitude could be increased if the size of the muscle bundle were large. Anderson et al. continued this logic to develop the normalized derivative, consisting of the ratio of the temporal first derivative to the voltage signal, which would account for muscle bundle size, and should be increased in amplitude for local activation.¹²³ This parameter, combined with the nonnormalized derivative and the peak voltage, were combined into a discriminant function analysis to test for optimal activation time selection criteria in the present study.

Statistical analysis was utilized to overcome subjective interpretation and provide an objective test for accurate activation time detection. Discriminant function analysis was applied to test whether a linear combination of variables could optimize detection compared to evaluation of

any variable evaluated separately. It was found that, while the Ratio variable provided a predictive accuracy of 86%, a combination of the three test variables into a discriminant model could improve the prediction to 90%. One interpretation of these results is clear, that the Ratio variable is extremely useful in determining activation time, as has been described in previous studies.¹²³ The ability of the other two test variables to add to the predictive accuracy of activation time is less well understood, however, these contributions could be due to limitations of the technique in ascribing the activation time standard, the sampling rate, or any of several unknown factors. The electrograms used in this analysis all displayed multiphasic waveforms arising out of ischemic tissue, and the ability to accurately assign activation time rigorously in this setting has been limited to date.

Based on the results of this study, it is appropriate to reanalyze the usefulness of the bipolar mode of recording to predominate over unipolar recording for activation time mapping. These results need to be validated and extended in this setting, however, they provide data which, for the first time, offers an objective and fairly accurate measure of activation time assignment in ischemic ventricular myocardium. The implementation of these results is more easily performed with the aid of computer technology, indeed, there is no reason why an ensemble of recordings can't be obtained and quickly analyzed for basic or clinical use.

Conclusions

Bipolar recordings suffer from a lack of biophysical data, sensitivity to fiber orientation, and artifactual multiphasic waveforms which make accurate analysis difficult to perform in ischemic myocardium. Unipolar EGM morphology in ischemic tissue is sensitive to fiber axis and wavefront direction, but can be analyzed for accurate activation time assignment. A standard of activation from an ensemble of closely spaced unipolar EGMs can be utilized to discern activation based on: 1) a temporal shift of a propagation potential; 2) cycle length dependent changes in regression of propagation potentials; and 3) stationary decay of non-propagating electrotonic potentials. The maximum $-dV/dt$ of unipolar EGMs can provide good prediction of activation time, but normalizing the dV/dt to the potential improves its prediction. A discriminant function incorporating multiple features (Voltage, $-dV/dt$ and Ratio) of major deflections improves prediction of activation time to 90%.

Chapter VII . Analysis of activation-recovery intervals from transmural unipolar recordings in an in vivo model of Long QT Syndrome and Torsade de Pointes

Introduction

Because of the high risk for sudden arrhythmic death in patients with Long QT Syndrome (LQTS), it is important to understand the mechanism of QT prolongation. Since dispersion of repolarization has been invoked as a primary mechanism for this arrhythmia, ⁶¹ it is necessary to study this mechanism in this setting. It is also important to understand the combined setting of disperse refractoriness as it relates to conduction of an early afterdepolarization (EAD), and its subsequent induction of the polymorphic tachyarrhythmia, Torsade de Pointes (TdP). ⁴⁷ The mechanism of drug-induced LQTS and TdP is especially important given the radical shift in pharmaceutical strategies, following the results of CAST, ¹³⁸ from Class I to Class III agents as therapy for ventricular arrhythmias. Class III agents prolong the action potential, and as such, have the propensity to induce LQTS and TdP. ¹⁷⁴ While there are several models of LQTS, the fact remains that in all of these models, the spatial sequence of activation and

repolarization, and thus the mechanism of the arrhythmia, have not been determined. A better understanding of the underlying electrophysiologic mechanism in the LQTS and TdP is a logical prerequisite for development of appropriate strategies for the management of this potentially lethal disorder. In this study, a model of LQTS and TdP with a close electrophysiological resemblance to a congenital form of LQT3 Syndrome was used to study dispersion of repolarization utilizing tridimensional mapping techniques.¹⁷⁵ Activation-recovery intervals (ARI) were calculated from transmural electrograms and used as a parameter to determine refractoriness measurements. Preliminary results have been recently published.^{59,176}

Methods

Surgical preparation

To obtain higher resolution for isochronal mapping, ten to twelve week old mongrel canine hearts were used. The protocol was approved by the local institutional review board and conformed to the guiding principles of the Declaration of Helsinki. Dogs were pre-anesthetized with sodium thiopental (17.5 mg/kg, iv) and intubated with a cuffed endotracheal tube. Anesthesia was maintained by constant ventilation with a mixture of 1-2½% isoflurane vaporized in 100% O₂, administered through an electronically controlled anesthesia ventilator (Foregger F500, The Foregger Co., Hauppauge, NY). A midsternal thoracotomy was performed, and the pericardium was cut and

sutured to the surrounding tissue to expose and cradle the heart.

Electrocardiographic leads I, II, and V1 were continuously monitored on an Electronics for Medicine VR12 monitor (PPG Co., Pleasantville, NY).

Ventilated CO₂ was monitored (Datex CO₂ Monitor, Puritan Bennett Corp.), and core and intrathoracic temperatures were monitored using two electronic thermometers (Yellow Spring Instruments, Yellow Springs, OH).

Transmural plunge needle electrodes for recording and stimulation

For ARI measurements, 16 plunge needle electrodes were constructed as described in *Chapter IV*. The needles each contained 8 electrodes of 50 μ m polyimide-insulated tungsten wire, spaced 1 mm apart. The electrode tips were sanded to expose the electrodes to the myocardial tissue. They were inserted into an "acrylic button", 2 mm thick, which had 8 equidistant holes around a circle of 2 mm radius, and each hole was just wide enough to snugly fit the needles through. The buttons were positioned according to the diagram of Figure 45.

Planar stimulation was accomplished in the center of each button via a 125 μ m polyimide-insulated silver wire embedded in a needle, and exposed for 6 mm. Thirty minutes were allowed for stabilization of the recordings after insertion of the plunge needle electrodes. Needle insertion did not result in any significant alteration of electrophysiologic parameters.

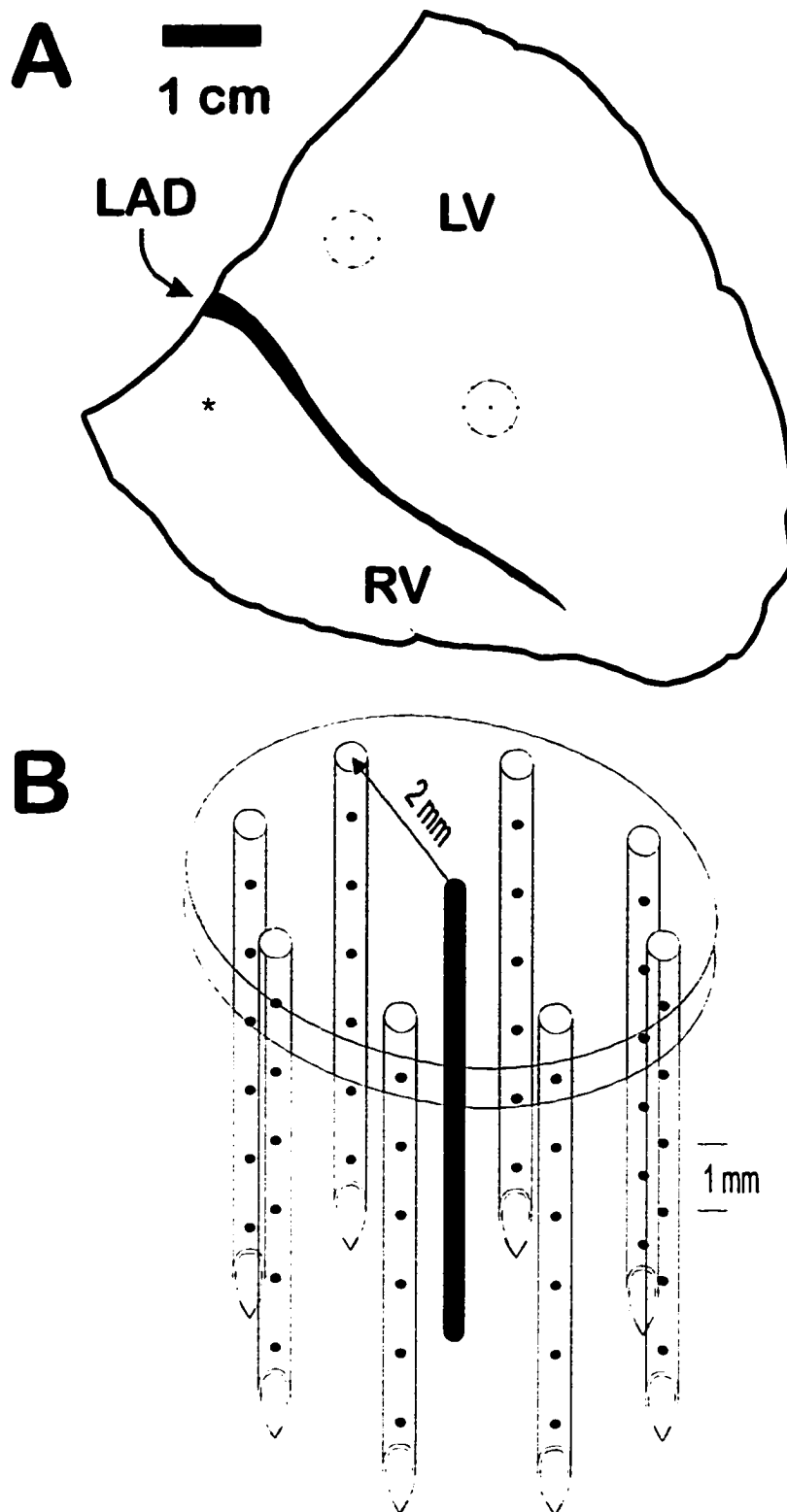


Figure 45. Diagrammatic illustration of the placement of plunge needle electrodes for ARI recordings.

ARI recordings

Anthopleurin-A (AP-A) was then administered as an i.v. bolus of 50 $\mu\text{g/kg}$ followed by a maintenance dose of 1.0 $\mu\text{g/kg/min}$ to create LQTS. To slow the heart rate, a Grass S88 stimulator (Grass Instruments, Quincy, MA) was used to stimulate the right and left vagosympathetic trunks wave pulses, 0.1-0.5 msec duration, at a frequency of 20 Hz, at 1 V to 10 V through two pairs of Teflon-insulated silver wires (125 μm diameter) with square pulses. Planar stimulation was performed cathodally at 1.3 times current threshold for capture via a stimulator (Bloom DTU-101, Bloom Co., Reading, PA). Stimulation consisted of 20-50 paced S_1 beats at a CL of 1000 ms, followed by a single premature stimulus, S_2 , which ranged from 460 ms to 600 ms. Unipolar recordings lasting 2-6 seconds were obtained by means of the mapping system described in *Chapter IV*.

Activation-Recovery Interval (ARI) determination

Selected portions of the recorded electrograms were preselected for ARI analysis. The digitized electrogram data were normalized by converting the bit level readings for each sample point into voltage values, and subsequently bandpass filtered with an eight-pole Butterworth filter with the cutoffs set at 0.5-50 Hz, performed by a program written in MathCad for Windows, version 6.0 Professional Edition (MathCad Corp., Massachusetts).¹⁷¹ The filtered data were then imported into Microsoft Excel, version 5.0 (Microsoft Corp.,

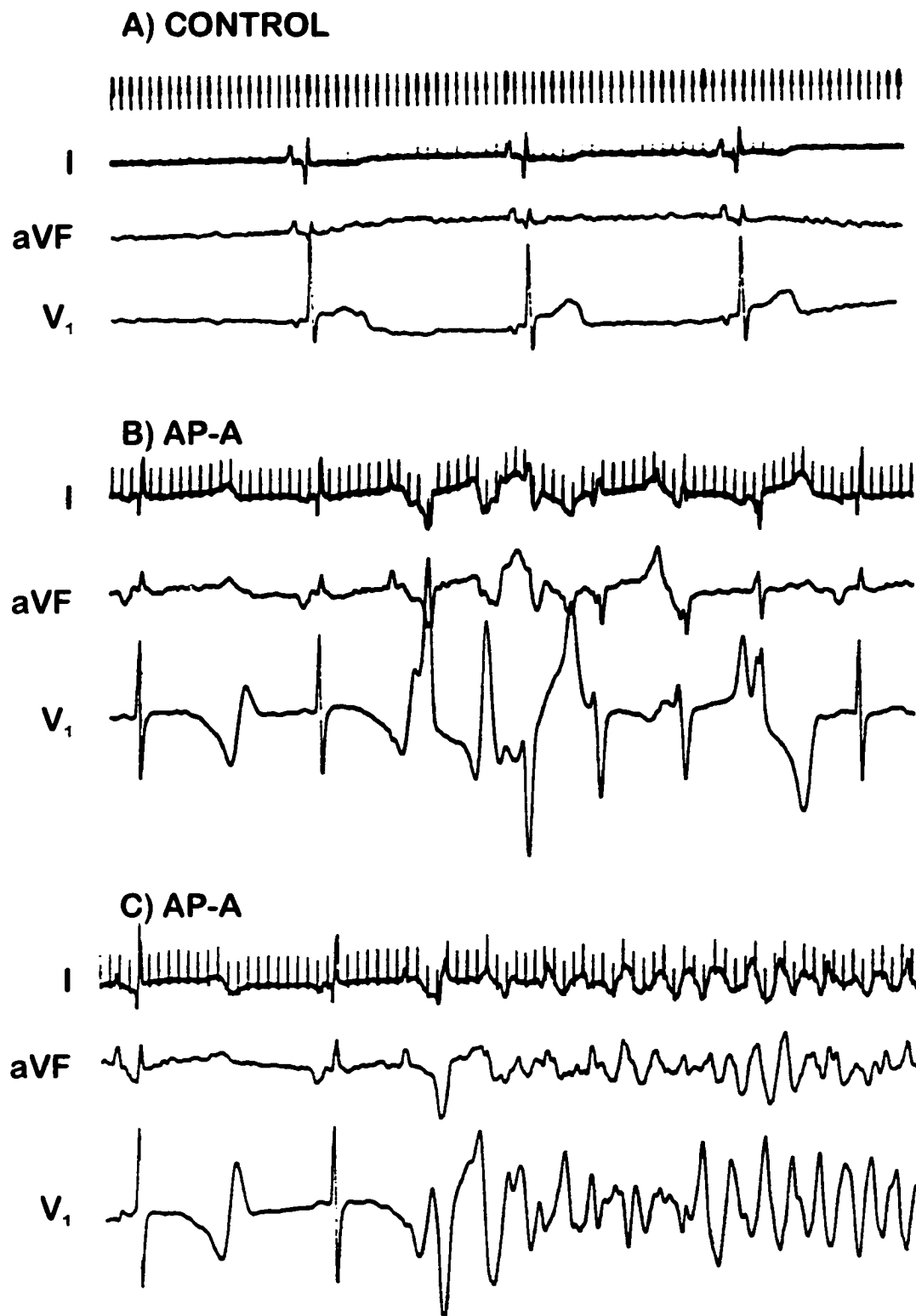


Figure 46. ECG leads I, aVF, and VI during sinus rhythm and after administration of Anthopleurin-A, with development of polymorphic ventricular tachycardia and Torsade de Pointes.

Redmond OR), ¹³² and subjected to macros which calculated the first temporal derivative of each electrogram as described in *Chapters V and VI*. The ARI of each electrogram was calculated as the time interval between the dV/dt minimum of the activation complex and the dV/dt maximum of the subsequent T-wave. ³³

Results

Figure 46 illustrates surface ECG leads I, aVF, and V₁ during control sinus rhythm at a cycle length (CL) of 1150 ms in panel A. Timing marks of 50 ms increments are shown at the top. Panels B and C were obtained 10 min after AP-A administration while a supraventricular rhythm was maintained at a CL of approximately 1000 -1100 ms. The drug resulted in marked prolongation of the QT interval (from 310 ms during control to 600-620 ms after AP-A at similar CL). Panel B shows the occurrence of couplets and triplets of ectopic ventricular beats while panel C (obtained 30 sec later) shows the onset of a polymorphic tachyarrhythmia that degenerated into ventricular fibrillation which required DC cardioversion. The QRS configuration of the couplet in panel B, as well as their isochronal activation maps, were identical to the first two beats of the succeeding triplet run.

Figure 47 shows 8 unipolar electrograms recorded across the basal-lateral free wall of the left ventricle, several millimeters below the AV groove. The most endocardial electrode, #1, was located 0.5 mm from the endocardial surface, while the most epicardial electrode, #8, was located 0.5 mm from the

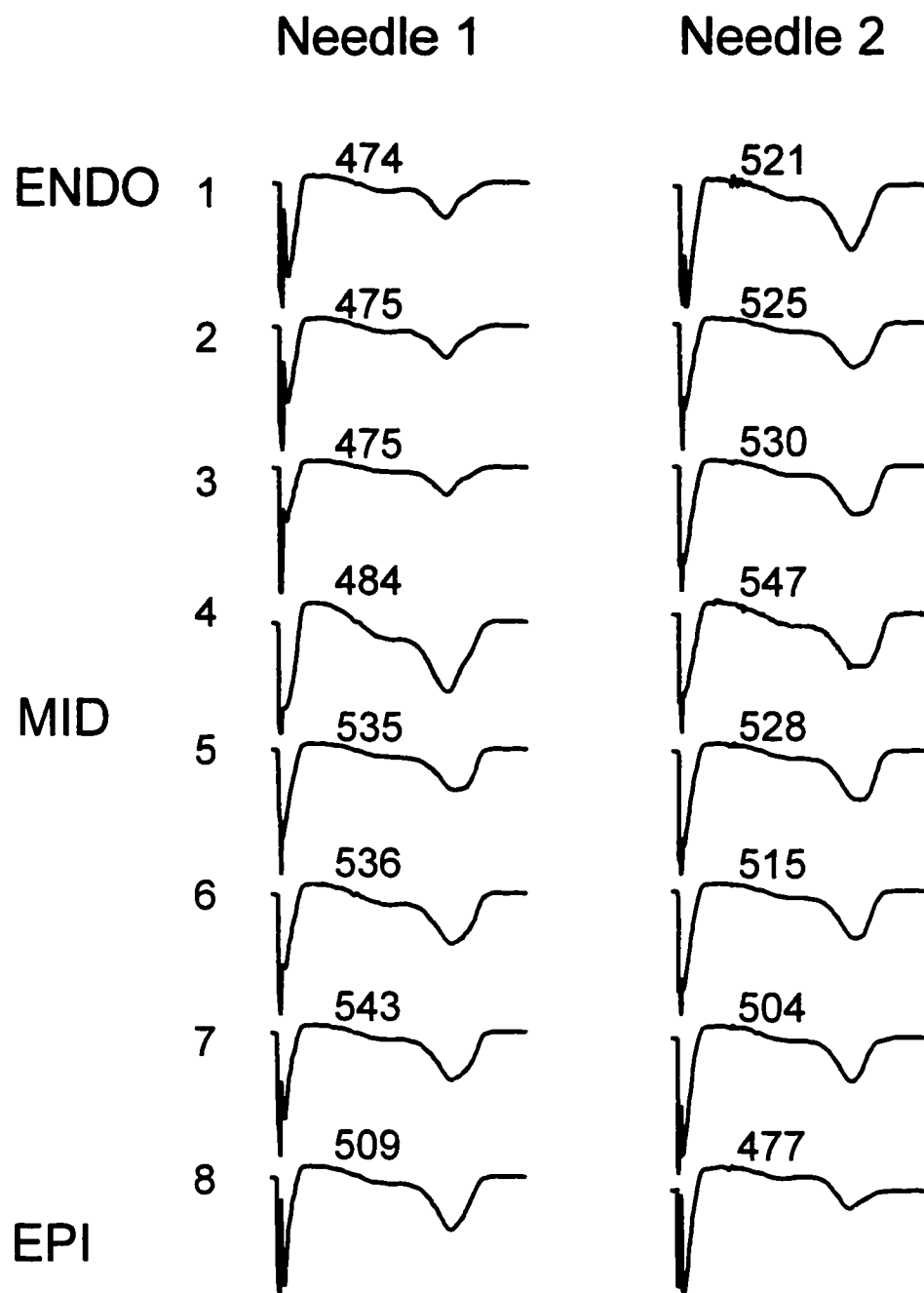


Figure 47. Unipolar electrograms recorded across the basal-lateral free wall of the left ventricle.

epicardial surface. Two of the eight plunge needle recordings are shown during pacing at 1000 ms during AP-A infusion. The numbers above each electrogram are the calculated ARIs, and show a marked dispersion of 62 ms 70 ms for Needle 1 and Needle 2, respectively. Also noteworthy is the ARI dispersion between neighboring recording sites. The maximum neighboring ARI dispersion for Needle 1 was 51 ms, between sites #4 and #5, and was 27 ms between sites #7 and #8 for Needle 2.

Figure 48 illustrates grouped data of the distribution of ARIs analyzed from 4 unipolar plunge-needle recordings (2 are shown in Figure 47). The cycle length was increased to 1400 ms to enhance the dispersion. The electrode recordings were grouped into 1 mm spatial bins along the epicardial-endocardial axis and plotted as a function of ARI. Figure 48 shows that a steep increase in ARI was apparent in midmyocardial electrodes #3 to #6 as compared to both subendocardial electrodes #1 and #2, and subepicardial electrodes #7 and #8. There was a marked variation in the dispersion of ARIs at the transitional zones between subendocardial and midmyocardial sites, as well as between the subepicardial sites and midmyocardial sites. Differences in ARIs up to 100 ms between contiguous sites at the transition zones were recorded at 1400 ms pacing (not shown). The overall maximal ARI dispersion between all sites was 300 ms, and the maximal ARI dispersion was 151 ms within a single plunge needle.

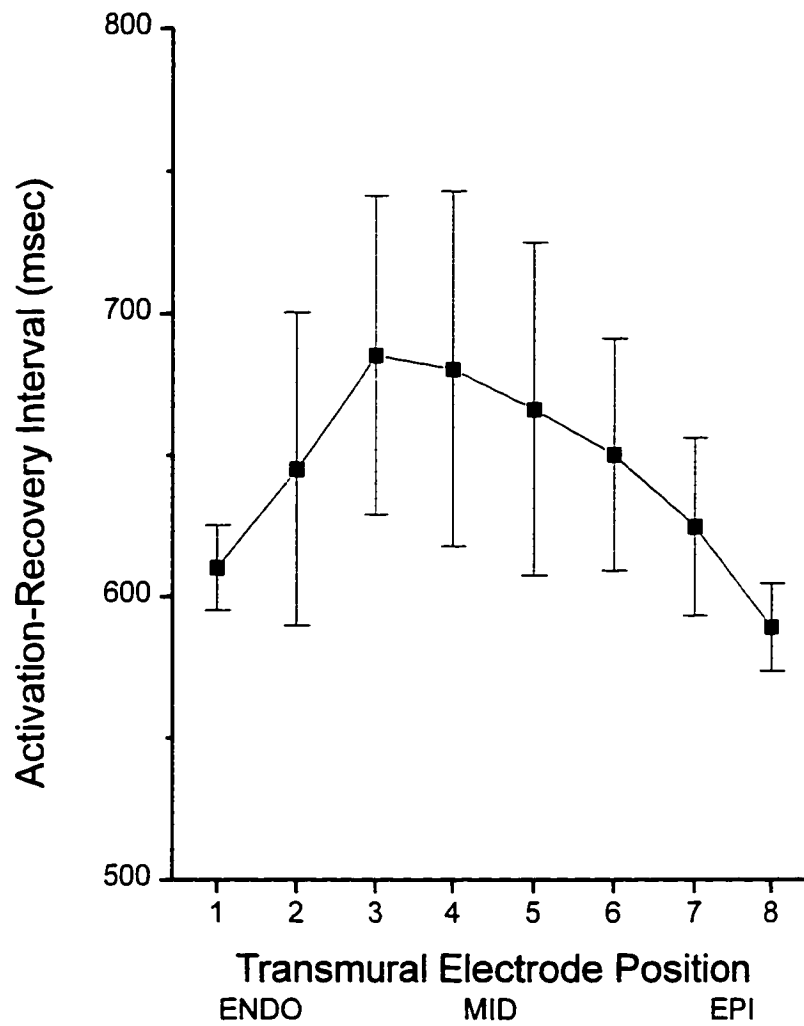


Figure 48. Grouped data of the spatial distribution of ARIs.

The relation of ARI to refractory measurements is shown in Figure 49. Each column is the same plunge needle recording of 6 electrograms, #1 through # 6, obtained at a basic pacing CL of 1000 ms followed by a single premature stimulus of 460 ms to 540 ms in 20 ms increments. The ARI values, obtained from the penultimate beat before the S₂, are shown above each electrogram. The last S₁ preceding S₂, and the S₂ beat are plotted for each S₁S₂ coupling interval. At 460 ms, the S₂ stimulation was blocked at all locations, while at 540 ms, all sites were activated. The S₂ intervals of 480, 500 and 520 ms show variable activation and block (marked by asterisks), which presents a dispersion of refractoriness pattern. The figure shows a high correlation between the dispersions of ARI and refractoriness, with electrode recordings having smaller ARI measurements (#2 and #6) also having shorter refractory periods. Conversely, electrode recordings having longer ARI measurements (#3, #4, #5, and #6) also had longer refractory periods. A linear correlation of these values is plotted in Figure 50, and shows a high correlation R value of 0.99, with a slope of 0.88 and an intercept of 60.8.

Discussion

Dispersion of myocardial refractoriness can be due to differences in active or passive membrane properties, or intercellular resistance.⁴⁷ Spatial dispersion of refractoriness is a prerequisite for reentrant excitation, a

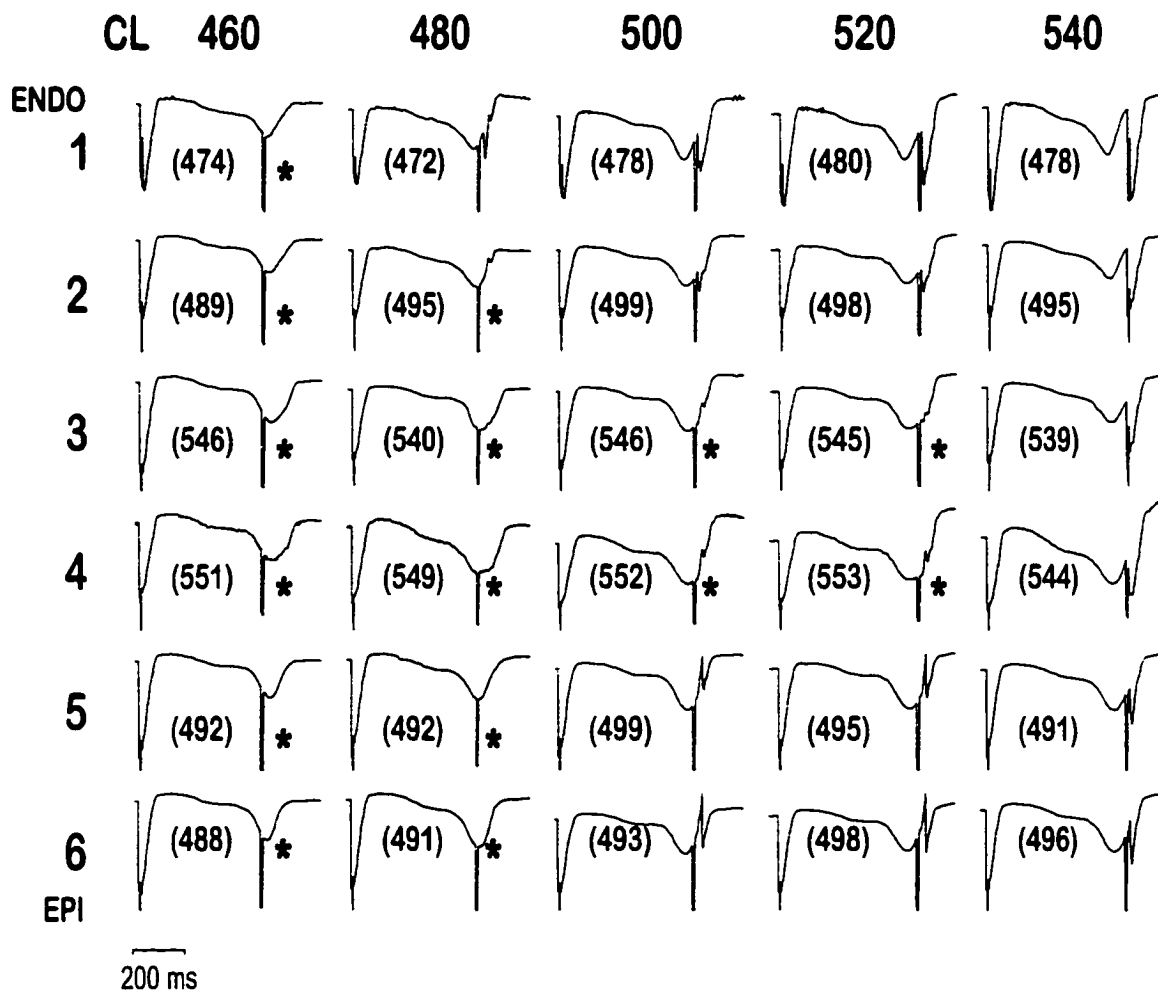


Figure 49. The relation of ARIs to refractory measurements.

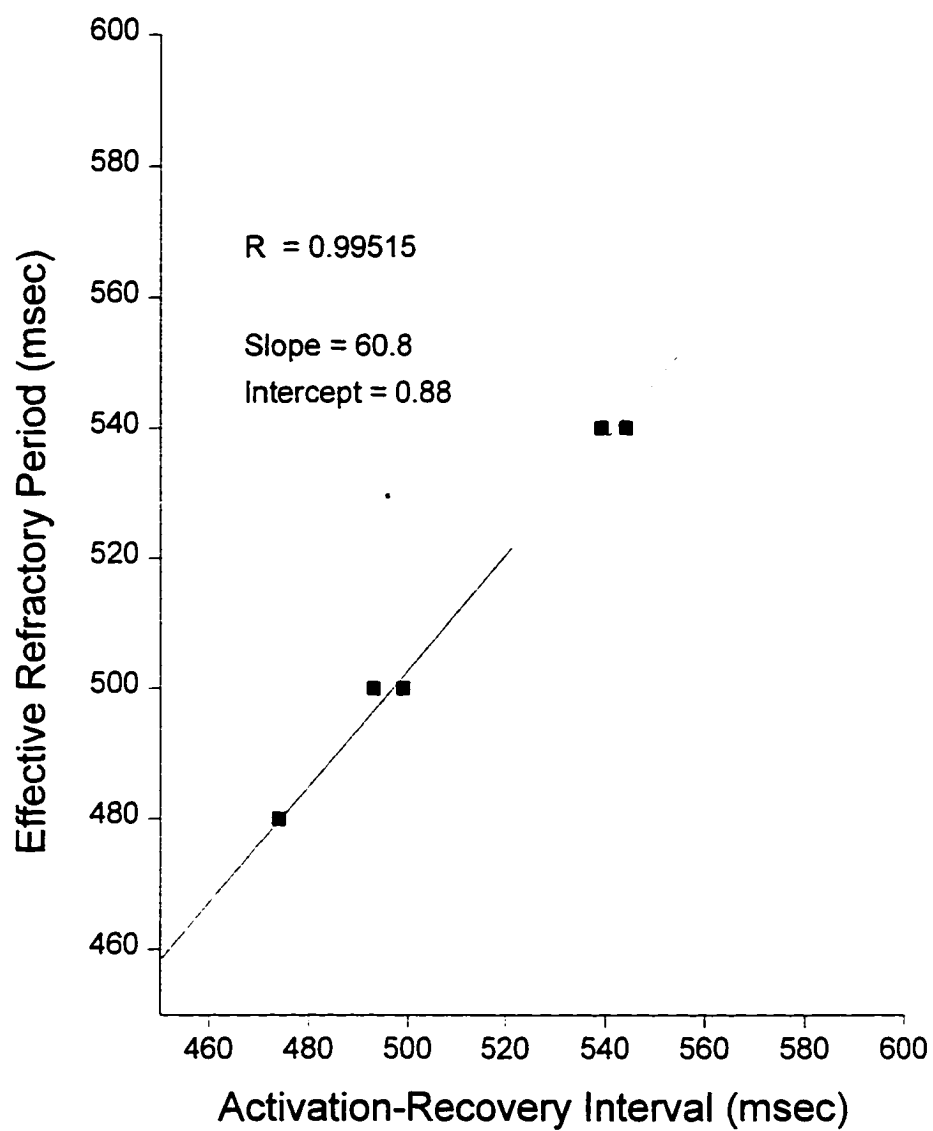


Figure 50. Regression analysis of data shown in Figure 49.

mechanism that could be involved in the LQTS and TdP. An activation wavefront encountering regions of disparate refractoriness can result in slowed conduction and functional unidirectional conduction block, setting the stage for possible circus movement reentry. However, there has been no practical technique to measure the tridimensional distribution of refractoriness in vivo with a sufficient spatial and temporal resolution. The most common approach to mapping repolarization is indirect, through measurements of refractory periods.¹⁷⁸ A disadvantage of this technique is that the measurements have to be obtained at individual sites in a sequential manner, making it unsuitable for evaluation of dynamic changes in refractoriness. Further, the definition of refractory period depends on the amplitude, duration, and polarity of the stimulating current.¹⁷⁹ Intracellular microelectrode and the surrogate in vivo technique of monophasic action potential (MAP) recording can provide accurate measurements of action potential duration,³⁰ but thus far, measurements can only be obtained from limited sites and mostly from endocardial or epicardial surfaces.

The ARI in unipolar electrograms has been proposed as a useful measure of the duration of repolarization. The validity of the measurement has also been demonstrated with respect to refractory periods. Millar et al. showed that ARIs from unipolar electrograms correlated closely with ventricular refractory periods under conditions of varying cycle length and adrenergic stimulation.³³ Blanchard et al. concluded that the ARI measures local events since the measurement was not significantly altered by changing the

timing of distant electrical events.¹⁸⁰ Wyatt examined the relation between ARIs and APDs during changes in cycle length and coronary occlusion.²⁹ Haws and Lux provided an analytic derivation of the theoretical basis for the correlation between times of dV/dt_{MIN} of the activation complex and dV/dt_{MAX} of the action potential upstroke, as well as the time of dV/dt_{MAX} of the T-wave and dV/dt_{MIN} of the action potential downstroke. They also provided evidence for good correlation between ARIs and in vivo transmembrane action potential durations under a variety of conditions.³² Stimulation studies by Steinhaus, while upholding the value of ARI measurements from unipolar and bipolar electrograms, also showed that potential errors in estimation of activation and recovery times from electrograms can occur.³⁴ Factors responsible for those errors included nonuniform coupling resistance, nonuniform membrane properties, and alterations in recording sites relative to activation sequence. The ARI technique has been applied recently to measure the dispersion of refractoriness on the epicardial surface in the human heart,¹⁸¹ from the body surface in patients with congenital LQTS,¹⁸² and from the epicardial surface in various in vivo animal models.^{183,184}

The results of this study show that in the in vivo heart: 1) a steep dispersion of ARI exists along the endocardial-epicardial axis, especially marked at the transition zones between the endo-to-mid myocardial zone, as well as the epi-to-mid myocardial zone; and 2) the ARIs at electrode sites along the endocardial-epicardial axis correlate with the refractory periods of

those sites. Studies from Antzelevitch et al. have shown that cells with different electrophysiologic characteristics exist between the endocardial, midmyocardial, and epicardial regions of the free wall of the left ventricle. This may well explain the dispersion of refractoriness seen along the endocardial-epicardial axis in this study. The correlation of ARI to refractory period appears to underlie the value of the ARI technique to measure an important electrophysiological parameter in this model, though its validation is required by more complete study.

Conclusion

ARIs from noncontiguous sites of the left ventricular free wall show a dispersion of refractoriness of up to 300 ms. Transmural recordings obtained in a plane from the endocardial-epicardial axis show ARI dispersion of up to 151 ms. A steep gradient of ARI dispersion was seen between the subepicardial layer and the midmyocardial layer, as well as the subendocardial layer and the midmyocardial layer, though the latter was not as steep as the former. The dispersion of ARIs between contiguous sites was nearly 100 ms at the transition zones. ARIs correlated well with refractory periods measured at the same sites along the endocardial-epicardial axis. These results show that ARIs may be a useful indicator to transmurally measure the dispersion of repolarization, which plays a significant role in the initiation and perpetuation of polymorphic tachyarrhythmias.

Chapter VIII . Future directions

The studies in this dissertation demonstrate the significant contribution that computer science techniques have made to the field of cardiac electrophysiology. Three specific directions were undertaken in this work: 1) development and implementation of a state-of-the-art mapping system; 2) the solving of a physiologic problem, the analysis of electrograms, which can make a significant contribution to basic and clinical electrophysiology; and 3) developing a recording and analysis technique for understanding mechanisms underlying polymorphic tachyarrhythmias. In each case a contribution was made, but there remains much work to be done in the future. A proposal for future work in these areas is outlined below.

To improve the design of the ideal mapping system, focus should be placed on two main areas: increasing the number of recording sites, and improving the speed and capabilities of graphic displays. In the former, work must be accomplished to improve and integrate computer hardware. Multiplexors can be combined in parallel to achieve a greater number of recording sites, and it should be possible to increase the total number of channels to 1024 using one Pentium-based PC, utilizing multiple direct memory access channels and motherboard slots. The simultaneous recording of > 1000 channels is feasible with proper integration of hardware available today or in the very near future.

Improvements in graphic display can also be significant, utilizing the newer technology recently introduced combined with software that takes advantage of these features. Quite often, life scientists can better understand problems through a graphic display of the data. Investigators will be no less grateful if they could appreciate their data with greater visual clarity. The study in Chapter VII, which begins to depict activation and activation-recovery intervals in three dimensions, would be greatly enhanced with a three dimensional display of the data that could, for example, zoom in and out from a variety of angles.

To enhance the development of electrogram analysis, a major benefit would be the ability to perform the activation time analysis on a real-time basis. This would greatly facilitate the clinical electrophysiologists who routinely map arrhythmias in humans, where analysis time is critical to successful procedures. Aside from validating the statistical approach taken in this study, another important direction is to assess other statistical techniques which may enhance activation time determination, such as neural networks, or artificial intelligence algorithms. Other studies of electrogram analysis such as the choice of filters and bandpass settings, have yet to be methodologically performed. Theoretical models of the bipolar electrogram must be developed which can explain their waveform structure in both the normal and pathological states.

Finally, in regards to ARI analysis, there are many studies to perform. These include validating the technique by comparing ARIs with other known techniques which measure action potential duration, such as monophasic action potential recordings or optical recordings, and transmembrane voltage recordings. Studies on the comparison of ARIs obtained from unipolar and bipolar recording modes are also warranted. The dispersion of repolarization of different regions of the heart and its correlation with different cell types, such as endocardial, midmyocardial, and epicardial cell layers, is of interest. Also intriguing is the correlation of refractory measurements with ARIs, and whether these can be consistently shown to correspond with arrhythmia development.

Appendix

```
program print_egms_on_crt;
```

```
Uses Graph,Crt,Dos,Printer;
```

```
const
```

```
  nmbr_chans      = 256;
  data_blk        = 25600;
  mask            = 4095;
  smple_per_blk   = data_blk div nmbr_chans;
  total_nmbr_smpls = nmbr_chans * smple_per_blk;
  create_out      = false;
  debug_on        = false;
  max_blks        = 200;
```

```
type
```

```
  file_name_type      = string[44];
  block_data_ptr_type = ^block_type;
  block_ptr_type       = array[1..max_blks] of
block_data_ptr_type;
  block_type           = array[1..data_blk] of word;
```

```
var
```

```
  i                  : integer;
  position            : longint;
  chan,smpl           : integer;
  eg_max,eg_min       : array[1..nmbr_chans] of integer;
  file_name,
  output_file_name_1,
  output_file_name_2,
  input_file_name     : file_name_type;
  ext_run             : string[2];
  run_number          : integer;
  data_output_file_1,
  data_output_file_2  : Text;
  data_input_file     : file;
  debug_file          : Text;
  blk_read_result     : word;
  block_data_ptr      : block_data_ptr_type;
  block_ptr           : block_ptr_type;
  block_data          : block_type;
  block_number        : longint;
  total_nmbr_blks     : integer;
  ans                 : char;
  key1,
  key2                : char;
```

```

const {GRAPHICS}
  crt_w      = 640;
  crt_h      = 480;
  graph_dir  = 'D:\BP\BGI';

var  {GRAPHICS}
  GraphDriver,
  GraphMode,
  ErrorCode   : integer;
  x_text_pos,
  y_text_pos  : integer;
  chan_string : string[3];
  page        : integer;

procedure make_names;
begin
  writeln('Enter File Name');
  readln(file_name);
  repeat
    writeln('Enter run number');
    readln(run_number);
  until (run_number > 0) and (run_number < 100);
  Str(run_number:2,ext_run);
  if run_number < 10 then
    begin
      input_file_name:='g:\inet\' + file_name + '\' +
file_name + '.c0' + ext_run[2];
      if create_out then
        begin
          output_file_name_1:= 'g:\inet\' + file_name + '\' +
file_name + '.p0' + ext_run[2];
          output_file_name_2:= 'g:\inet\' + file_name + '\' +
file_name + '.q0' + ext_run[2];
        end;
      end
    else
      begin
        input_file_name:='g:\inet\' + file_name + '\' +
file_name + '.c' + ext_run;
        if create_out then
          begin
            output_file_name_1:= 'g:\inet\' + file_name + '\' +
file_name + '.p' + ext_run;
            output_file_name_2:= 'g:\inet\' + file_name + '\' +
file_name + '.q' + ext_run;
          end;
        end;
        writeln(input_file_name);
        if create_out then

```

```

        begin
            writeln(output_file_name_1);
            writeln(output_file_name_2);
        end;
    end;

procedure open_output_file;
begin
    if create_out then
        begin
            Assign(data_output_file_1,output_file_name_1);
            Rewrite(data_output_file_1);
            Assign(data_output_file_2,output_file_name_2);
            Rewrite(data_output_file_2);
        end;
    if debug_on then
        begin
            Assign(debug_file,'g:\inet\debug.txt');
            Rewrite(debug_file);
        end;
    end;

procedure sort_data;
type
    out_string_type = string[4];
var
    out_string : out_string_type;
    pass,jump   : integer;
    index       : integer;
    key         : char;
    converted_data : word;
    i           : integer;

begin
    writeln('number of samples per block = ',smple_per_blk);
    i:= 0;
    for smpl:= 1 to smple_per_blk do
        for chan:= 1 to nmbr_chans do
            begin
                if chan <= nmbr_chans div 2 then
                    begin
                        index:= (smpl-1)*nmbr_chans + chan;
                        i:= i+1;
                        converted_data:=block_data[index] and mask;
                        Str(converted_data:4,out_string);
                        if chan = (nmbr_chans div 2) then
                            writeln(data_output_file_1,out_string)
                        else
                            write(data_output_file_1,out_string,',');
                        end
                    end
                end
            end
        end
    end

```

```

else
  if chan > nmbr_chans div 2 then
    begin
      index:= (smpl-1)*nmbr_chans + chan;
      i:= i+1;
      converted_data:=block_data[index] and mask;
      Str(converted_data:4,out_string);
      if chan = (nmbr_chans) then
        writeln(data_output_file_2,out_string)
      else
        write(data_output_file_2,out_string,',');
      end;
    end;
  end;
end;

procedure open_input_file;
begin
  make_names;
  Assign(data_input_file,input_file_name);
  Reset(data_input_file,1);
end;

procedure read_tape_file;
var
  i,j : integer;
  skip : longint;
  count_blk : word;
begin
  writeln('IOResult = ',IOResult,' first file size = ',
  FileSize(data_input_file));
  repeat until ReadKey = 'y';
  count_blk:= word(data_blk)*2;
  writeln('count = ', count_blk);
  FileMode := 0;
  Reset(data_input_file,1);
  total_nmbr_blks:= FileSize(data_input_file) div
  (data_blk*2);
  writeln('total number of blocks = ',total_nmbr_blks);
  for block_number:= 1 to total_nmbr_blks do
    begin
      New(block_ptr[block_number]);
      skip:= longint((block_number-1)*data_blk)*2;
      Seek(data_input_file,skip);

      BlockRead(data_input_file,block_data,count_blk,blk_read_resu
      lt);
      block_ptr[block_number]^:= block_data;
      if create_out then sort_data;
    end;
  end;
end;

```

```

procedure init_graphics;
begin
  (*GraphDriver:= Detect;*)
  GraphDriver:= 9;          (* VGA *)
  GraphMode:=2;             (* VGA hi 640x480 *)
  InitGraph(GraphDriver,GraphMode,graph_dir);
  ErrorCode:=GraphResult;
  if ErrorCode <> grOk then
    writeln(ErrorCode,GraphErrorMsg(ErrorCode));
  end;

procedure min_max;
var
  sample,
  test      : integer;
begin
  for chan:= 1 to nmbr_chans do
    begin
      eg_max[chan]:=block_ptr[1]^[chan] and mask;
      eg_min[chan]:=eg_max[chan];
      for block_number:= 1 to total_nmbr_blks do
        begin
          for sample:= 1 to smple_per_blk do
            begin
              block_ptr[block_number]^[chan+(sample-
1)*nmbr_chans]:=
                block_ptr[block_number]^[chan+(sample-
1)*nmbr_chans] and mask;
              test:=block_ptr[block_number]^[chan+(sample-
1)*nmbr_chans];
              if eg_max[chan] < test then eg_max[chan]:= test
              else
                if eg_min[chan] > test then eg_min[chan]:= test
              end;
            end;
          end;
        { if debug_on then
          writeln(debug_file,eg_max[chan]:8,eg_min[chan]:8);
        }
      end;
    end;
  end;

procedure plot_egm(chan_start: integer);
var
  ans                : char;
  chan_index         : integer;
  sample            : integer;
  test              : integer;
  y_pos_real        : real;
  x_pos,

```

```

y_pos,
y_last                                     : integer;
crt_blk                                  : integer;
blk_length                               : integer;
crt_blk_offset                           : real;
crt_blk_smple_real                       : real;
pixels_per_blk                           : real;
sample_mod                               : integer;
blk_index                                : integer;
begin
ClearDevice;
x_text_pos:= 10;
for chan_index:= 0 to 15 do
begin
chan:= chan_index+chan_start;
if debug_on then
begin
write(debug_file,'chan index = ',chan_index:4);
write(debug_file,'chan = ',chan:4);
write(debug_file,'max = ',eg_max[chan]:6);
write(debug_file,'min = ',eg_min[chan]:6);
writeln(debug_file);
end;
Str(chan:2,chan_string);
y_text_pos:= 30*chan_index+15;
OutTextXY(x_text_pos,y_text_pos,chan_string);
pixels_per_blk := crt_w / total_nmbr_blks;
for x_pos:=0 to crt_w-1 do
begin
crt_blk:=1 + Trunc(x_pos/pixels_per_blk);
crt_blk_offset:= (crt_blk-1) * (pixels_per_blk);
sample_mod:= Round(x_pos-crt_blk_offset) mod
Round(pixels_per_blk);
crt_blk_smple_real :=
((sample_mod)/pixels_per_blk)*smple_per_blk);
blk_index:= chan + Round(crt_blk_smple_real)*nmbr_chans;
if (eg_max[chan]-eg_min[chan]) <> 0 then
y_pos_real:=30*(1-(block_ptr[crt_blk]^[blk_index] -
eg_min[chan])/(eg_max[chan]-eg_min[chan]))
else
y_pos_real:= 0;
y_pos_real:=y_pos_real + 30 * chan_index;
y_pos:= Round(y_pos_real);
if x_pos > 0 then
Line(x_pos,y_last,x_pos+1,y_pos);
y_last:=y_pos;
if debug_on then
begin
write(debug_file,'crt_blk = ',crt_blk:4);
write(debug_file,'crt_blk_offset = ',crt_blk_offset:4);

```

```

        write(debug_file,'sample_mod = ',sample_mod:6);
        write(debug_file,'crt_blk_smple_real =
',crt_blk_smple_real:7:2);
        write(debug_file,'blk_index = ',blk_index:3);
        write(debug_file,'y_pos_real = ',y_pos_real:7:2);
        writeln(debug_file);
    end;
end;
end;
end;

procedure plot_page;
var
    done : boolean;
begin
    page:= 1;
    plot_egm((page-1)*16 + 1);
    done:= false;
    repeat
        repeat key1:= ReadKey until key1 in [#0,#27,#49];
        if key1 = #49 then writeln (#7#7);
        if key1 = #0 then
            begin
                key2:= ReadKey;
                case key2 of
                    #73: begin
                        page:= page - 1;
                        if page < 1 then page:= 1;
                    end;
                    #81: begin
                        page:= page + 1;
                        if page > 16 then page:= 16;
                    end;
                    #59: page:= 1;
                    #60: page:= 2;
                    #61: page:= 3;
                    #62: page:= 4;
                    #63: page:= 5;
                    #64: page:= 6;
                    #65: page:= 7;
                    #66: page:= 8;
                    #67: page:= 9;
                    #68: page:= 10;
                    #84: page:= 11;
                    #85: page:= 12;
                    #86: page:= 13;
                    #87: page:= 14;
                    #88: page:= 15;
                    #89: page:= 16;
                end;
            end;
        end;
    end;
end;

```

```
        plot_egm((page-1)*16 + 1);
    end
else
    begin
        if key1 = #27 then done:= true;
        end;
    until done;
end;

begin
    open_input_file;
    open_output_file;
    read_tape_file;
    min_max;
    init_graphics;
    plot_page;
    Close(data_input_file);
    if create_out then
        begin
            Close(data_output_file_1);
            Close(data_output_file_2);
        end;
    if debug_on then
        Close(debug_file);
    CloseGraph;
end.
```

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