Cellular basis for the monophasic action potential.
Which electrode is the recording electrode?

Masahiko Kondo, Vladislav Nesterenko, Charles Antzelevitch*

Gordon K. Moe Scholar, Masonic Medical Research Laboratory, 2150 Bleecker Street, Utica, NY 13501-1787, USA

Received 17 February 2004; received in revised form 8 April 2004; accepted 4 May 2004
Available online 15 July 2004
Time for primary review 28 days

Abstract

Background: The cellular basis for the monophasic action potential (MAP) has long been a matter of debate. At the center of the controversy is the issue as to which of the two electrodes is the recording electrode and which is the indifferent electrode. The present study is designed to address this issue. Methods: Transmembrane action potentials (TAPs) and either intramural MAPs or contact (Franz-like) MAPs were recorded from adjacent sites in canine arterially perfused ventricular wedge preparations. Intramural MAPs were recorded using thin wire electrodes referenced to a KCl electrode. Results: Local cooling or injection of ATX-II into the region subtending the inactivating (contact or KCl) electrode did not affect the MAP. Similar maneuvers at the site of the noninactivating electrode always prolonged the MAP. The intramural MAP always prolonged in proportion to the TAP, whereas the contact MAP did not, often displaying apparent early afterdepolarizations (EADs) or delayed afterdepolarizations (DADs) due to its much wider field of view, which captured activity from the region of prolonged repolarization as well as the remote normal regions. Conclusions: Our results suggest that (1) it is not the contact or MAP electrode that records the MAP, but rather the noninactivating “indifferent” electrode and (2) intramural MAPs provide more accurate recordings of local activity. The data provide compelling evidence in support of the hypothesis that the MAP represents the extracellular potential difference between active and inactive sites within the heart rather than injury currents flowing at the boundary of the active and inactive zone under the inactivating electrode.

Keywords: Electrophysiology; MAP; Franz electrode; Extracellular potentials

1. Introduction

The cellular basis for the monophasic action potential (MAP) has long been a matter of debate. At the center of the controversy is the issue of which of the two electrodes is the recording electrode and which is the indifferent electrode [1–5]. As early as the 1930s, it was suggested that the MAP represents the extracellular potential difference between an active and inactive (injured) site on the heart [6]. This simple and straightforward theory, which stems from the basic laws of electricity and has been shown to be consistent with core conductor theory for the two-dimensional and three-dimensional myocardium [7–10], was considered by Franz [11] as not sufficient to explain the MAP recordings obtained with the Franz contact electrode. Instead, the MAP signal was suggested by Franz [11] to be the result of current flowing between inactivated and noninactivated tissues under the contact electrode at the inactivated site. The two concepts while different in their terminology are unified in their appreciation of the fact that flow of current within the functional syncytium that makes up the myocardium is based on the voltage difference between the two electrode sites. The disagreement between these concepts is centered around the issues of which electrode is the recording electrode, or more accurately, activity near which electrode is responsible for the shape and duration of the recorded monophasic signal?

Recent computer simulation and experimental studies from our laboratory suggested that the contribution of the signal from the inactivating electrode is relatively small and...
that the Franz-like catheter (contact electrode) may have a wide field of view causing it to record a variety of artifactual early afterdepolarization (EAD)-like deflections when positioned near a region of heterogeneous repolarization [12–16]. Based on these observations, we developed an intramural MAP recording technique in which one or more thin wire recording electrodes are referenced to a remote indifferent electrode that inactivates local tissue using KCl [12–15]. This electrode configuration permitted the recording of stable discrete MAP signals from multiple sites, including transmural sites. The spatial separation of recording and indifferent electrodes also permits independent variations of electrical activity under each electrode.

The present study uses both MAP recording methodologies to examine the two hypotheses for the basis of the MAP and to catalog the artifacts recorded when various configurations of the two electrodes are positioned in regions of heterogeneous repolarization.

2. Methods

2.1. Arterially perfused canine left ventricular wedge preparation

Adult mongrel dogs weighing 20–25 kg were anticoagulated with heparin and anesthetized with sodium pentobarbital (30–35 mg/kg IV). Their hearts were excised rapidly through a left thoracotomy and immersed in a cardioplegic solution consisting of cold (4 °C) Tyrode’s solution containing 12.0 mmol/l [K+]o. Transmural wedges with dimensions of ≈ 2 × 1.5 × 0.9 cm to 3 × 2 × 1.5 cm were dissected from the posterior walls of left ventricles. The preparations were cannulated via a small (diameter 0.9 cm) branch of the left m) branch of the left coronary. Intramural MAP recordings were obtained between the indifferent electrode connected to the positive input of differential amplifier and the recording electrode made of a small syringe needle (24 gauge) inserted near a region of heterogeneous repolarization[12–16]. This electrode configuration permitted the recording of stable discrete MAP signals from multiple sites, including transmural sites. The spatial separation of recording and indifferent electrodes also permits independent variations of electrical activity under each electrode.

The present study uses both MAP recording methodologies to examine the two hypotheses for the basis of the MAP and to catalog the artifacts recorded when various configurations of the two electrodes are positioned in regions of heterogeneous repolarization.

2.2. Recordings of intracellular action potentials

The preparations were electrically stimulated using bipolar silver electrodes insulated except at the tips and applied to the endocardial surface to create a normal endocardium to epicardium sequence of ventricular activation. Basic cycle length (BCL) was 2000 ms.

Transmembrane action potentials (TAPs) and intramural MAPs were simultaneously recorded at adjacent sites of the preparation (Fig. 1). TAPs were recorded using floating glass microelectrodes filled with 2.7 M KCl (20–30 MΩ DC resistance) connected to a high input-impedance amplifier (Electro 705, WPI). Ag–AgCl electrode in the bath served as a reference for both TAP and unipolar electrogram (UEG) recordings.

2.3. Recording of monophasic action potentials

Intramural MAPs were recorded using electrodes made of a thin silver wire (120 μm in diameter) insulated except for at the tip (recording electrode). Several recording electrodes were inserted in the wedge preparation at various depths (1–7 mm). Negative MAP-like injury potentials appeared immediately after the recording wires were inserted. The myocardium “healed-over” within 5–10 min yielding an “electrogram-like” signal. An indifferent electrode made of a small syringe needle (24 gauge) insulated except at the tip was inserted 2–3 mm below the tissue surface at a site >5 mm from recording electrodes. A small volume of 1 M KCl (≈ 30–60 μl) was injected into the tissue through the syringe to depolarize the myocardium. Intramural MAP recordings were obtained between the indifferent electrode connected to the positive inputs of all differential amplifiers and the recording electrodes connected to the negative inputs of corresponding amplifier (Fig. 1). To avoid possible influence of nonuniform myocardial electrical resistivity, indifferent and recording electrodes were placed along the midmyocardial axis of the wedge preparation. In some experiments, a contact MAP catheter (BARD electrophysiology, 006248, 6 F, interelectrode distance 5 mm) was used for MAP recordings. The catheter was fixed to a micromanipulator via a flexible spring and placed separately under a calibrated pressure on the transmural surface of the wedge to obtain a stable MAP recording between the two electrodes of the catheter (distal and proximal). The contact (distal) electrode was connected to the positive input and another electrode to the negative input of differential amplifier. MAP signals were filtered (0.05–1000 Hz) and processed as described for the TAP recordings above.

2.4. Measurement of monophasic action potential duration

MAP duration (MAPD) was measured at 90% (MAPD90) or 100% repolarization (MAPD100). MAP amplitude was defined as the voltage difference between the baseline and
the peak plateau of the AP. MAP recordings with amplitude less than 25 mV were discarded. Activation time of MAP was defined as the time of the notch of the intrinsic deflection of phase 0. In cases with no clear intrinsic deflection, activation time was defined as the moment of the minimum first derivative of the unipolar electrogram, recorded between the same wire MAP electrode and the bath ground (Fig. 1, left panel).

Local APD prolongation was achieved using two different methods. In the first series of experiments, local surface cooling was induced by perfusing cooled Tyrode’s solution into an open well created by placing a circular barrier (4 mm diameter, 2 mm high) on the transmural surface of the preparation. The level of perfusate in the chamber was lowered just enough to prevent any mixing of the normal warm solution and the cold solution inside the well. Cooling continued until the temperature at the site 4 mm away from the well fell below 37.5°C. During the course of experiment, the temperature at the site 5 mm away from cooled site never fell below normal temperature in the chamber (38.0 ± 0.5 °C) indicating that cooling was truly local. MAP and TAP were continuously recorded during the period of gradual cooling. In a second series of experiments, local APD prolongation was achieved by injection of 30–60 μl of 50 nmol/l ATX-II solution just below the tissue surface. Recordings were made immediately before and after ATX-II injection. ATX-II prolongs APD by enhancing late sodium current.

3. Results

3.1. Correlation between transmembrane and monophasic action potentials

Fig. 1 schematically illustrates a typical recording arrangement. Intramural MAPs and TAPs were recorded approximately 10 mm away from the KCl indifferent electrode. The recording MAP wire electrode was inserted 1 mm below the surface of the wedge to avoid direct contact of the uninsulated portion of the wire with the bath solution. Duration of intramural MAPs and TAPs from adjacent sites on the transmural surface were similar over a wide range of stimulation rates (Fig. 1C).

3.2. Effect of local cooling of the tissue surface

Fig. 2 illustrates the result of an experiment in which site 1 was selectively cooled. Prior to cooling (Fig. 2A left, 37.5 °C), simultaneously recorded intramural monophasic action potentials (MAPK1 and MAPK2) and transmembrane action potentials (TAP1 and TAP2) were nearly identical. When the surface at site 1 was cooled to 33.2 °C, TAP1 and MAPK1 recorded at that site were prolonged proportionally, whereas TAP2 and MAPK2 remained unchanged (panel A, right traces). The graph below the scheme (Fig. 2B) shows the changes in action potential duration in all four recordings during the gradual cooling process.
Throughout the cooling period, the duration of MAPK1 closely followed that of TAP1 recorded at the same site. In contrast, when cooling was applied at the site of the indifferent (KCl) electrode, the MAPK1 signal at site 1 did not prolong (Fig. 3, panel A). TAP recorded site 1 did not prolong, but a TAP recorded near the cooled site showed a prominent prolongation (panel A, bottom traces). Time-dependent changes in the duration of the recorded signals are graphically illustrated in Fig. 3B.

In the next series of experiments we investigated the spatial resolution of the contact MAP technique under conditions of heterogeneous repolarization (Fig. 4). The contact electrode was placed either 2 or 5 mm from the cooled site (see schematic in Fig. 4). The upper left panel shows results obtained with the contact electrode positioned 2 mm to cooled site (site 1). Prior to cooling, the morphology and duration of TAP at sites 1 and 2 and those of the MAP were similar. When the temperature at site 1 was reduced to 31°C, TAP1 recorded at that site significantly prolonged, whereas the duration of TAP2 10 mm away remained unchanged. The MAPC signal recorded using the contact electrode positioned near site 1 displayed duration similar to that of TAP1, but with a distinctly different morphology characterized by the appearance of a prominent apparent early afterdepolarization (EAD), as if this signal was composed of two action potentials of different durations overlaying each other. No abnormalities of repolarization were observed in the TAP traces at either of the recording sites.

The lower left panel of Fig. 4 shows results obtained with the contact electrode positioned 5 mm from the cooled region. Gradual cooling of site 1 from 38 to 30°C was attended by a progressive prolongation of TAP1; the duration of TAP2 remained unchanged. At 38°C (no spatial heterogeneity of APD), the duration of MAPC signal was the same as that of TAP1 and TAP2. With gradual cooling of site 1, MAPC developed an apparent delayed afterdepolarization (DAD) or very negative EAD. Once again, the morphology of MAPC resembles the weighted sum of TAPs from the cooled and normal sites. The amplitude of the apparent EAD is smaller due to the greater distance of the MAP electrode from the cooled site. Accordingly, there is a close correlation between the duration of MAPC (MAPD100) and the APD100 recorded simultaneously at the cooled site (TAP1) (Fig. 4, graphic plot).

Similar results were obtained when local prolongation of the action potential was produced by injecting ATX-II immediately below the surface. In this series of experiments, intramural and contact MAPs were recorded near the ATX-II injection site (Fig. 5); the KCl indifferent electrode was positioned 10 mm away. Before ATX-II, the two intramural MAPs recorded at sites 2 mm apart displayed a similar
duration. After ATX-II, MAPK1 displayed a marked prolongation, increasing to the duration of TAP1 (Fig. 5A).

TAP2 and MAPK2 located a mere 2 mm away remained unchanged after ATX-II, indicating that the ATX effect was truly local. Next, the contact electrode of MAP catheter was placed 3 mm from the site of ATX-II injection. ATX-II injection resulted in prolongation of TAP1 at the injection site, but also of MAPC recorded 3 mm away (Fig. 5B). It is noteworthy that TAP2 recorded near the contact electrode showed no prolongation whatsoever. The duration of the contact MAP was always longer than that of TAP2, but shorter than that of TAP1. In some experiments, MAPC recorded with contact catheter electrode displayed apparent EADs (humps) when placed near the ATX-II-injected site (within 5 mm from the site). This set of experiments (n = 3) served to demonstrate the very narrow field of view of the intramural electrode in contrast to the wide field of view of the contact electrode.

The volume conductor hypothesis proposed by Franz [11] maintains that the signal recorded by the contact MAP electrode is exclusively determined by the current flow between the inexcitable tissue under the contact (pressure) electrode and the tissue that immediately surround inactivated area, especially the excitable regions subtending the inexcitable zone under the electrode. As a test of this hypothesis, we conducted a series of experiments in which we altered the duration of the action potential in a region 4 mm under the contact electrode by injecting ATX-II into that region (Fig. 6). In the first series of experiments, the contact electrode of MAP catheter was placed on the transmural surface of preparation, and three intramural electrodes were inserted at an angle into the tissue so that their tips aligned along the vertical axis below the contact electrode at depths 1, 4 and 7 mm (MAPK1, MAPK2, and MAPK3). Under baseline conditions, the intramural MAP signal from the electrode positioned 1 mm below the contact electrode (MAPK1) showed no activity since the pressure of the contact electrode had rendered this tissue inexcitable. MAPK2 and MAPK3 recorded at depths of 4 and 7 mm, respectively, displayed action potentials with durations similar to those recorded with the contact MAP electrode (MAPC) and intracellular microelectrode (TAP) at the surface (Fig. 6A).

Injection of ATX-II into the region adjacent to the MAPK2 (4 mm below the contact electrode) caused a marked prolongation of MAPDk2, but no change in the action potential duration recorded by the MAPC electrode or the other electrodes. This series of experiments showed unequivocally that activity under the contact electrode does not determine or influence the signal recorded by the contact electrode at the surface.

The MAPK3 recording electrode was next shifted closer to the KCl indifferent electrode. Fig. 6B illustrates that prolongation of activity under the indifferent electrode does
not affect the MAP recorded with any of the other MAP electrodes, including the contact electrode (MAPc). Only the activity near the MAP+3 recording electrode shows a prolonged action potential.

In its standard configuration, it is difficult to ascertain which of the two electrodes that make up the Franz-like contact catheter is the recording electrode and which is the indifferent (reference) electrode. To address this issue, we modified a contact catheter recording scheme by incorporating two “indifferent” electrodes connected to a single contact electrode (Fig. 7). The contact (distal) electrode of the MAP catheter was connected to the positive inputs of two differential amplifiers and MAP signals were recorded between the contact electrode and two “indifferent electrodes”: One was the usual proximal electrode of the MAP catheter (site 1) and the other was placed 30 mm away (site 2). The “indifferent” electrodes were connected to the negative inputs of the amplifiers. This experimental setup permitted the recording of two MAP signals simultaneously.

According to the prevailing theory, because the contact electrode is the “recording” electrode, the two signals should be identical under all conditions. Under baseline conditions, the two MAP signals and the two transmembrane action potentials recorded at sites 1 and 2 were similar in duration (Fig. 7A). Injection of ATX-II in the region under MAPc2 resulted in prolongation of MAPc2 and TAP2 at the same site, but not MAPc1 or TAP1. The prolongation of MAPc2 was accompanied by development of apparent EAD. The duration of MAPc2 waveform was nearly identical to the TAP2, indicating that the “indifferent” electrode of the contact catheter is actually the recording electrode.

4. Discussion

The mechanism underlying the monophasic action potential (MAP) has been a matter of debate for over seven decades. At the heart of the controversy is the issue of which of the two electrodes is the recording electrode and which is the indifferent electrode [1–5]. Or more accurately, electrical activity at which site determines the essential characteristics (shape and duration) of the MAP signal. Our results are inconsistent with the conventional view [4] of the MAP but concordant with the hypothesis proposed by early investigators [1–3]. Although, the controversy has been a long standing, a definitive experimental study to resolve this problem has been lacking. The success of our approach is attributable to the availability of an experimental model, in the form of an arterially perfused wedge preparation [17], that permits the simultaneous recording of intracellular and monophasic (contact and intramural)
action potentials in three dimensions with the capability of easily and selectively altering action potential duration at discrete sites. With both the contact and intramural MAP techniques, it seems clear that the recording electrode is not the contact (pressure) or KCl electrode, but the opposite electrode (Figs. 2, 3 and 7). In the case of the conventional Franz-like contact catheter, the recording entity is the electrode commonly referred to as the “indifferent” electrode (Fig. 7).

The MAP signal recording is based on the core conductor theory [7–10]. According to this concept, the theoretical extracellular potential in a limited extracellular space of uniform resistivity mirrors the TAP in morphology but has a reduced amplitude and opposite polarity. The extracellular potential \( \Phi_0(z) \) at site \( z \) is:

\[
\Phi_0(z) = -\frac{r_o}{r_1 + r_o} \times V_m(z)
\]

where \( r_o \) and \( r_1 \) are the external and internal resistance per unit length, and \( V_m \) is intracellular potential [10]. However, according to the definition of the electrical potential in physics, actual recordings can be made only between two sites. To discuss the shape of a voltage signal on the basis of at a single recording electrode is therefore theoretically counterintuitive. The use of Earth as a common ground is theoretically possible for a very strong current source, e.g., power line, a large charged object, when one input of an amplifier is connected to the source and another one—directly to the Earth. On the other hand, biological signals are so weak, that recording relative to the Earth generates little more than noise. A second connection is needed between Earth and some point close to the biological source. Thus, recording is made between the two close sites even in the case of so called unipolar recordings when one electrode is placed at the site of interest and another one in the bath or inactive tissue. This second electrode is essentially connected to all sources in the active area. This is the reason why unipolar electrogram in a restricted space has a biphasic shape. Thus, the only way to answer the question of which electrode is the recording one, is to alter electrical activity near each of the two electrodes and to register observed changes in the recorded waveform. Because the contact electrode serves to inactivate the subtending tissues, no external influences in its vicinity can affect its activity. Thus, an electrode positioned in an inactive (depolarized) region can serve as a reference for another electrode and recorded voltage difference becomes monophasic. This is the basis for the MAP recording technique.

Fig. 5. Narrow field of view of intramural MAP vs. wide field of view of contact MAP. (A) Simultaneous recordings of intramural monophasic (MAP\(_{x1}\) and MAP\(_{x2}\)) and transmembrane (TAP1 and TAP2) action potentials at the ATX-II-injected site (site 1) and a site 2 mm away (site 2). MAP\(_{x1}\) and TAP at each site are similar in duration under baseline conditions (○) as well as after injection of ATX-II (●), thus demonstrating ability of intramural MAP to accurately record local activity. Similar results were obtained in three other experiments. (B) Simultaneous recordings of transmembrane action potentials at the ATX-II-injected site (site 1) and TAP and contact MAP (MAP\(_C\)) recordings at a site 3 mm away (site 2). The duration of MAP\(_C\) is similar to that of TAP2 before (○), but not after injection of ATX-II at site 1 (●). Because of its wide field of view, MAP\(_C\) is not able to faithfully reproduce local activity at site 2. Similar results were obtained in five other experiments.
In the case of either intramural or contact MAP recordings, cells surrounding the indifferent electrode are depolarized by KCl or pressure, respectively. Activity at this site would be expected to consist of a very low amplitude electrotonic image of activity of surrounding excitable tissue decayed in accordance with the space constant of the inexcitable zone under the KCl or pressure electrode. In the case of the intramural MAP, the recording electrode

Fig. 6. Transmembrane activity under the contact catheter does not influence the MAP recorded using the catheter. (A) Traces depict monophasic action potentials (MAP) recorded using a contact electrode (MAPc) and three intramural-MAP electrodes positioned 1, 4 and 7 mm under the contact electrode (MAPk1, MAPk2, and MAPk3) before (○) and after (●) ATX-II injection near the region of the MAPk2 recording electrode. (B) Electrode positions are as in panel A except for the MAPk3 electrode which was shifted to a position approximately 3 mm under the KCl electrode. Recordings were obtained before (○) and after (●) ATX-II injection at the region of the MAPk3 recording electrode. Calibrations are as described in Fig. 2. Similar results were obtained in three other experiments.

Fig. 7. The “indifferent” electrode of the contact catheter is the recording electrode. A standard Franz-like contact catheter was modified such that an MAP could be recorded simultaneously with the “indifferent electrode” in its usual position (MAPc1; 5 mm proximal to the contact electrode) as well as at a remote site 30 mm away (site 2, MAPk2). Transmembrane action potentials were simultaneously recorded at the two sites (TAP1 and TAP2). Under baseline conditions the two MAP and TAP recording displayed similar durations. Injection of ATX-II at site 2 produced no change in MAPc1 but prolonged MAPc2 and TAP2 by a similar amount. Calibrations are as described in Fig. 2. Similar results were obtained in four other experiments.
consists of a thin silver wire insulated except at the tip placed inside the tissue. Because the extracellular field that it senses is relatively limited, the electrode has a narrow field of view resulting in a truly local recording of cellular activity. In the case of the contact catheter, the recording electrode is positioned in the extracellular fluid 5 mm away from the tissue. Because it senses a relatively large extracellular space, the electrode has a wide field of view. Such interference by far-field potentials cannot be avoided in highly heterogeneous system when contact electrode is used for MAP recording. The voltage difference between the indifferent and recording electrode yields a waveform similar to that of the TAP at the site of the recording electrode.

Although both MAP techniques provide an accurate representation of the time course of local intracellular activity in the absence of electrical heterogeneities, the two methodologies yield very different results when placed in close proximity to a region of heterogeneous repolarization as a result of the dramatically different fields of view. The intramural MAP technique provides an accurate measure of local APD (Figs. 1–3, 5 and 6) when placed within a region of dispersed repolarization, whereas the contact MAP technique yields a grossly inaccurate measure of local activity under these conditions (Figs. 4, 5, and 7). The signals recorded in the case of the contact MAP represent a weighted sum of activity at the different regions, often yielding apparent EAD and even DAD-like activity (Figs. 4 and 7). Neither EAD nor DAD activity was ever observed in the adjacent TAP recordings under these conditions. EAD activity similar to that depicted in Figs. 4 and 7 has at times been interpreted as being representative of genuine EADs [18,19].

Previous studies have hypothesized that the signal recorded using the intramural-KCl-MAP technique reflects an injury current exclusively at the site of the KCl electrode [20,21]. Our results showing the lack of an effect of ATX-II injection under the KCl electrode on the MAP response, clearly demonstrate that the intramural-MAP is not influenced by activity within the region surrounding the KCl electrode (Figs. 3 and 6).

A similar hypothesis has been proposed for the contact MAP electrode, specifically that the MAP signal recorded using a contact MAP catheter is generated by the boundary current flowing between active cells and inactivated cells subjacent to the contact electrode [4,20]. Because MAP recordings from thicker segments of tissue yield greater amplitudes than recordings from thin-walled tissues, it has been suggested that the field of view of the contact electrode extends into the deep myocardial layers under the contact electrode [20]. A direct test of this theory failed to provide evidence in its support (Fig. 6) ATX-II injection into the active region under the contact electrode (3–4 mm deep) produces a prominent prolongation of local APD but no change in the MAP, clearly indicating that activity of excitable tissue directly under the contact catheter is not responsible for the MAP signal (Fig. 6). These results suggest that the true recording electrode in the case of the contact MAP technique is the “indifferent electrode”. Direct evidence in support of this hypothesis is provided in Fig. 7, which shows that prolongation of APD in the region of the “indifferent electrode” (separated from the contact electrode) prolongs the MAP. The induction of apparent EADs under these conditions is due to the wide field of view of “indifferent electrode” which permits it to capture the prolonged action potential in the ATX-II-injected area as well as briefer responses in the surrounding tissue.

In conclusion, our data provide evidence in support of the hypothesis that the MAP signal generated in the case of both MAP techniques reflects the activity around the electrode at the uninjured (active) site rather than the electrode at inactivated site and that the purpose of the contact or KCl electrode is to inactivate the tissues underneath and thus to provide a relatively time-independent reference voltage. Taken together, the data provide compelling support for the hypothesis that the MAP represents the extracellular potential difference between an active and inactive site within the heart and is not exclusively the result of injury currents flowing at the boundary of the active and inactive zone under the inactivating electrode.

Acknowledgements

We are grateful to Dr. Yoram Rudy for his reading of the manuscript and suggestions and acknowledge Di Hou and Bob Goodrow for their expert technical assistance. This study is supported by grants from the National Institutes of Health-HL47678 (CA), American Heart Association, New York State Affiliate (CA and VVN) and the Masons of NYS and Florida.

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