Electrocardiogram Reconstruction from High Resolution Voltage Optical Mapping

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Abstract—Electrocardiogram recordings during optical mapping experiments in heart tissue are commonly used to monitor the health of the preparation and to obtain dominant frequencies during arrhythmic and defibrillatory studies. However the use of ECG reconstructed from optical mapping is seldom used and to date it has not been strictly validated. In this manuscript we present the first detailed validation and comparison of Optical Mapping ECG, or OM-ECG, with standard ECG recordings by calculating the electrostatic potential in space as a function of the voltage measured optically and describe the different approximations that can be used to obtain unipolar or bipolar ECG recordings. We found that in small/medium hearts, such as rabbits, leads that are aligned apex to base only require activation recording from one surface (anterior or posterior) for the OM-ECG to match the ECG while leads aligned left to right may require both an anterior and posterior optical mapping recording. The discrepancy between leads is due to symmetries in the ventricular activations. In the case of ischemic hearts where activations even-out more, the match between the OM-ECG and standard ECG may require only one surface recording for both left-right and base-apex leads. We believe that this methodology has two main and direct applications in the study of cardiac dynamics. The first is during studies of defibrillation where information after the shock may be crucial in the development of new strategies, OM-ECGs do not suffer the current artifacts of standard ECGs during shocks and can be calculated during the entire activation. We present examples in rabbit ventricles where even low amplitude pacing artifacts are captured by the ECG but do not appear in the OM-ECG. The second use of this technique is for reconstructions of intramural dynamics in larger hearts where differences between the ECG and OM-ECG obtained from anterior and posterior recordings can be used to derive the intramural activation.

I. INTRODUCTION

The heart is an excitable system through which depolarizing waves propagate in a coordinated manner to initiate mechanical contraction. These waves give rise to a measurable change in electric potential in the outer-cardiac medium. By tracing the resulting electric potential over time, the electrocardiogram (ECG) can quickly identify anomalous electrical pathways. Electrocardiography has therefore proven itself an invaluable tool in cardiac electrophysiology. Trained medical professionals can quickly diagnose pathological conditions such as ventricular hypertrophy, life-threatening arrhythmias, and myocardial infarctions [1]. The ECG remains the medical standard for quick and powerful diagnoses; however, it is a global measurement and therefore cannot determine specific information pertaining to individual cellular regions of depolarization and repolarization within the heart [6]. In this paper, the term electrocardiogram, or ECG, will be used to refer to the general idea of the electrocardiogram. Pseudo-ECG will refer to ECG obtained from in-vitro experiments by means of conductive leads and circuitry, and OM-ECG will refer to ECG reconstructed from optical mapping data. It is commonplace in cardiac research to obtain a pseudo-ECG from isolated hearts to monitor the healthy condition of the preparation. However, it is not possible to determine the physiological response immediately following the application of an electric shock with the true ECG or pseudo-ECG as the electric field from the stimulus will generate large DC and commonmode signal that will saturate the long-pass filter, amplifier, and instrumentation commonly used as ECG front end. Post-shock saturation can inhibit the ECG/pseudo-ECG for a short period of time and mask important cardiac events. For example, Wu et al. [7] found in their experiments that early recurrence of ventricular fibrillation always occurred before their pseudo-ECG recovered. This effect is particularly important during defibrillation studies where it is vital to track tissue responses to electric stimuli in order to develop new and better anti-arrhythmic strategies.

Voltage sensitive dyes allow for tracking the polarization and depolarization across the heart’s surface in high spatial and temporal resolution by optical mapping. When voltage propagation across intramural tissue and the surface are similar, optical mapping data should allow for accurate reconstruction of the ECG even in the case of high stimulus or shocks. A handful of optical mapping studies have obtained what we have defined as an OM-ECG from their recordings, however no direct correlation has been done with pseudo-ECGs [11] or they have been shown not to match [10]. This paper aims to establish a direct link between measured surface transmembrane voltages and the ECG by attempting to reconstruct the ECG from optical mapping data. The OM-ECG produced will be compared to the pseudo-ECG to evaluate the model used.

II. METHODS

All experiments conformed to the current Guide for Care and Use of Laboratory Animals published by the National Institute of Health (NIH Publication No. 85-23, revised 1996) and were approved by the Office of Research and Integrity Assurance at Georgia Tech. New Zealand white rabbits (4) were anesthetized with ketamine/xylazine/acepromazine (17/9/0.9 mg/kg) and then injected with heparin (300 U/kg). After five minutes, euthanasia was induced with pentobarbital (120 mg/kg). Hearts were quickly removed via a left thoracotomy and perfused retrogradely via the aorta with cardioplegic solution gassed with 95% O2 and 5% CO2. Then the heart was immersed in a chamber kept at 37.0±0.3°C and perfused at a...
pressure of about 60 mmHg with a peristaltic pump and Tyrode’s solution gassed with 95\% O2 and 5\% CO2 and also kept at 37.0±0.3°C. The hearts were then stained for 15-20 minutes with a solution of Tyrode and 40 \mu mol/L voltage-sensitive dye di-4-ANBDQBS (JPW-6033) dissolved in ethanol (24.4 mg/mL). Heart motion was suppressed by perfusing the hearts with Tyrode’s solution containing 2-5 \mu mol/L blebbistatin for 20-30 min. Hearts were fixed in a glass imaging chamber containing Tyrode’s solution and illuminated by three LEDs each with 640/10nm 905 filter (EDMUND). Epicardial voltage signals were recorded using a back-illuminated, EMCCD (Photometrics Evolve 128) at a spatial resolution of 128 × 128 pixels (∼250 \mu m per pixel) and 500 Hz framerate through a 700nm long pass filter [3]. Optical mapping signals were analyzed using stacking[8] of up to 400 beats to increase signal to noise ratio without filtering.

A. Electrocardiogram

Two pairs of electrodes, right-left (R-L) and base-apex (B-A), connected to an Arduino Due development board with two ECG shields by Olimex were placed around the hearts in a plane perpendicular to the camera’s vantage. The two channel ECG signal was digitized with Arduino Due board (internal 12bit A/D converter) and each channel was sampled at the rate of 2000 Hz. The pseudo-ECGs were recorded concurrently with the optical mapping.

B. Optical Mapping Electrocardiogram Construction

Consider the heart occupying a volume $\Omega_H$ within an extracardiac medium $\Omega_0$. The transmembrane potential $V_m$ at point $r$ in the tissue and time $t$ may be expressed

\[ V_m(r, t) = u_i(r, t) - u_e(r, t), \]

where $u_i$ and $u_e$ are the intra- and extracellular myocardial potentials, respectively. Let the current densities be of the form

\[ j_r = -g_i \nabla u_i \]

for the intra-, extracellular, and extracardiac regions, respectively. There are no current sources or sinks within the body, so the continuity equation requires

\[ \begin{aligned}
0 &= \nabla \cdot \{ j_i + j_e \} \mid_{r \in \Omega_H}
0 &= \nabla \cdot j_0 \mid_{r \in \Omega_0}.
\end{aligned} \]

Flux continuity across the boundary between the heart and extracardiac medium requires

\[ \begin{aligned}
u_e &= u_i \\
j_0 \cdot \hat{n} &= (j_i + j_e) \cdot \hat{n}
\end{aligned} \]

along the boundary $\partial \Omega_H \cup \partial \Omega_0$. Within the heart, transmembrane potential differences $V_m(r, t)$ provide an equivalent cardiac source when related as

\[ j(r) = -g_i \nabla V_m, \]

where $g_i$ is the intracellular membrane conductance. We may then express the total current density as a sum including both the transmembrane potential $V_m$ and the total electric potential $\varphi(r, t)$

\[ j = -\sigma_0 \nabla \varphi - g_i \nabla V_m. \]

Since the divergence of the total current density is zero according to equation 4,

\[ 0 = -\nabla (\sigma_0 \nabla \varphi) - \nabla (g_i \nabla V_m), \]

It is possible to write a Poisson equation for the electric potential in terms of the transmembrane potential

\[ \nabla^2 \varphi(r) = -\frac{g_i}{\sigma_0} \nabla^2 V_m. \]

From the boundary conditions associated with the system, there exists a unique solution for $\varphi(r)$ throughout space. To reduce computational costs associated with solving this elliptic problem for all points within a computer generated mesh, we favor an integral formulation. From the form of equation 7, there exists a Green’s function $G(r; r')$ satisfying Neumann boundary conditions that yields an integral form for the electric potential

\[ \varphi(r) = -\frac{g_i}{\sigma_0} \int_{\Omega_H} d^3r' \nabla' \left( G(r; r') \cdot \nabla' V_m(r') \right). \]

Integration by parts yields the form

\[ \frac{g_i}{\sigma_0} \varphi(r) = -\int_{\Omega_H} d^3r' \left\{ \nabla' \left[ G \nabla' V_m \right] - G \nabla'^2 V_m \right\} = \int_{\Omega_H} d^3r' G \nabla'^2 V_m - \int_{\partial \Omega_H} dS \cdot G \nabla' V_m \]

Since the ECG probe is located external to the heart, $r \notin \Omega_H$. By the Neumann boundary conditions imposed upon the Green’s function, the surface term is zero if we take the approximation that the conducting medium has equal anisotropy ratios, or $g_e \propto g_i$. For an infinite and homogeneous extracardiac medium $\Omega_0$, we have the free space Green’s function

\[ G(r; r') = -\frac{1}{4\pi |r - r'|}. \]

Substitution of this Green’s function, assuming equal anisotropy ratios, and utilizing the divergence theorem yields an integral formulation for the electric potential at point $r$ in terms of the transmembrane potential

\[ \varphi(r) = \frac{g_i}{4\pi \sigma_0} \int_{\Omega_H} d^3r' \nabla'^2 V_m(r') \frac{1}{|r - r'|}. \]

Since the dimensional scales associated with the transmembrane potential difference and ECG amplitude are known, the important characteristic involved in OM-ECG calculation is the relationship between its amplitude and time.

III. RESULTS

OM-ECGs were calculated using equation 11 from voltage optical mapping recordings and compared to pseudo-ECGs for three different sets of rabbit experiments. The first set of experiments consisted of recording the pseudo-ECGs and optically mapping voltage from normal sinoatrial (SA) pacing. Figure 1 shows a sequence of the ventricular activation where the top panel, first row illustrates the wave front (excitation),
Fig. 1. Voltage optical mapping, OM-ECG, and pseudo-ECG from rabbit heart during normal sinoatrial activation. Top panel shows the activation (first row) of the ventricles from the Purkinje network and the de-activation (second row). Color bar indicates the normalized voltage signal from 0 to 1, originally -85mV to 20mV. Lower panels show the OM- and pseudo-ECG for Right-Left (left) and Base-Apex (right) leads. Notice that the activation starts sooner in the apex than at the base but the de-activation follows the inverse trend and terminates at the base instead of the apex, which produces the positive T-wave deflection in the OM- and pseudo-ECGs for the L-R lead. While the OM- and pseudo-ECG match well for the L-R leads, there are some differences for the B-A leads, most likely due to intramural dynamics, see discussion.

Fig. 2. Voltage optical mapping, pseudo-ECG, and OM-ECG from rabbit heart during normal sinoatrial activation in an ischemic heart. Top panel shows the activation (top row) of the ventricles from the Purkinje network and the de-activation (second row). Color bar indicates the normalized voltage signal from 0 to 1, originally -85mV to 20mV. Lower panels show pseudo-ECG and OM-ECG for Right-Left leads (left) and Base-Apex leads (right). Notice that compared to the healthy heart, the activation and deactivation are somehow more homogeneous and the pseudo-ECGs are less complicated with only a clear activation and deactivation upstroke. In this case both leads (L-R and B-A) match for the pseudo-ECG and OM-ECG compared to the healthy heart where only the L-R matched well.

The optical mapping data during normal SA-node shows how the activation of the ventricles is slightly uneven at the surface due to the different activation breakthroughs from the Purkinje network and also a complex de-activation sequence as the action potential duration is much larger at the base compared to that at the apex. For the first set of experiments (normal heart), the R-L and B-A OM-ECGs resulted similar to those measured in vitro on a rabbit heart with the R-L showing a well defined QRS and T wave in both the pseudo- and OM-ECG; however, the pseudo- and OM-ECG for the B-A differ. This discrepancy is due to the activation being less symmetric with respect to the B-A than L-R. Additionally, there is an expected difference in that the pseudo-ECG measures the internal activation but the OM-ECG is calculated from surface activations. For the ischemic heart the wave length is decreased and the tissue activation is more homogeneous intramurally, thus there is a much closer correlation between the pseudo- and OM-ECG for both leads L-R and B-A as shown in figure 2. During electrical stimulation, regular and pseudo-ECGs will measure the electric field from the stimulus and will reflect that interference in the signal, a disadvantageous artifact when trying to study the immediate effects following shocks. Reconstructed OM-ECGs do not have this spurious effect as shown in figure 3, where the signal from the stimulus that initiates the activation in the apex is clearly visible in the pseudo-ECG but not in the OM-ECG.

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The OM-ECG had no significant deviation from what we would expect to see in an ordinary ECG and was remarkably similar to the conventionally recorded pseudo-ECG so long as there is little difference in intramural and surface activation. Sources of error were minimized by shock absorption, high frame rates, high resolution, and noise reduction. As expected, we found that it is possible to generate an OM-ECG with arbitrary reference points and that the OM-ECG produced was dependent on their orientation about the heart as well as the separation distance between them. That is, with optical
recordings it is possible to reconstruct ECG signals from any leads in any direction. Regular and pseudo-ECGs recorded with electrodes are limited by interference during pacing or when applying defibrillation shocks. We have shown that the OM-ECG is free of that limitation and therefore makes an excellent contender for in-vitro defibrillation studies. The fact that differences can be obtained between the pseudo-ECG and OM-ECG when intramural activations are different will also allow this methodology to be used to quantitatively characterize these intramural dynamics. That is, it would be possible to use numerical simulations to reconstruct the wave propagation observed at the surface and then use variational or intramural forecasting methods[9] to obtain an intramural activation that would make the OM-ECG match the real ECG.

The methodology developed here is generic and can easily be applied to other types of hearts. In future work it would be desirable to record the whole surface of the heart using at least two cameras for panoramic optical mapping signal of the whole heart.

We will improve this process by testing more and different types of hearts. It is desirable to construct the OM-ECG in near real-time for use as a tool in diagnosing heart conditions, including many types of tachycardia and fibrillation, while performing electrically paced in-vitro experiments.

A. Limitations

This study contains a series of limitations, primarily we have recorded optical signals only form the epicardium and from one side. Ideally a panoramic mapping would provide more information, however it seems that activation along the anterior and posterior of the heart are similar. Higher temporal resolution would allow for less noisy OM-ECG signals.

Multiple assumptions were made in the derivation of equation 11, namely the isotropic conductivity in the extracardiac medium. Although this assumption may not be accurately claimed in noninvasive electrocardiography, the hearts in our experiment are submerged in a bath of Tyrode’s solution.

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Fig. 3. OM-ECG and pseudo-ECG from a healthy rabbit heart obtained when the activation is generated by a wave initiated at the apex by an electrode stimulus. Notice that both unipolar L-R recordings are similar except for the large “artifact” pulse current measured by the pseudo-ECG shown by the solid line box. The OM-ECG does not include this effect and thus displays the ECG from only the heart’s electrical sources.