Journal of Electrocardiology 51/4 (2018) 725–733

Contents lists available at ScienceDirect

Journal of Electrocardiology

journal homepage: www.jecgonline.com

Image-based modeling of acute myocardial ischemia using experimentally derived ischemic zone source representations

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ARTICLE INFO

Article history:
Received 6 March 2018
Received in revised form 22 April 2018
Accepted 10 May 2018
Available online xxxx

Keywords:
Myocardial ischemia
ST deviation
Computer modeling
Subject-specific modeling
Border zone
Ischemic zone

ABSTRACT

Background: Computational models of myocardial ischemia often use oversimplified ischemic source representations to simulate epicardial potentials. The purpose of this study was to explore the influence of biophysically justified, subject-specific ischemic zone representations on epicardial potentials.
Methods: We developed and implemented an image-based simulation pipeline, using intramural recordings from a canine experimental model to define subject-specific ischemic regions within the heart. Static epicardial potential distributions, reflective of ST segment deviations, were simulated and validated against measured epicardial recordings.
Results: Simulated epicardial potential distributions showed strong statistical correlation and visual agreement with measured epicardial potentials. Additionally, we identified and described in what way border zone parameters influence epicardial potential distributions during the ST segment.
Conclusion: From image-based simulations of myocardial ischemia, we generated subject-specific ischemic sources that accurately replicated epicardial potential distributions. Such models are essential in understanding the underlying mechanisms of the bioelectric fields that arise during ischemia and are the basis for more sophisticated simulations of body surface ECGs.

Introduction

The electrocardiogram (ECG) is the most commonly used clinical tool for detecting and diagnosing myocardial ischemia, yet errors in ECG-based diagnosis [1] suggest a general lack of understanding regarding its underlying electrophysiology. Myocardial ischemia is a potentially life-threatening condition [2] that arises in response to a blood supply deficit within cardiac tissues leading to electrophysiological changes within the heart. Reduced blood flow within ischemic tissues inhibits the ability of cells to produce ATP. Reductions in available ATP, in turn, lead to depressed Na^+/K^+ and Ca^{++} pump activity—resulting in altered local ionic concentrations and causing subsequent changes in tissue electrophysiology, such as reduced action potential amplitude, decreased action potential duration, and less-negative resting membrane potential [3,4]. The resulting extracellular potential differences that arise between healthy and ischemic tissues cause ECG recordings that deviate from normal. Clinically, ST segment shift is used as a marker for detecting the presence of ischemia [5-7]; however, ECG-based detection exhibits wide sensitivity and specificity ranges [1], resulting in diagnostic error. In an effort to avoid the potentially severe consequences of misdiagnosis [2], medical professionals have adopted aggressive admissions policies at the expense of elevated false positives, with only 50–60% of admitted patients actually experiencing an ischemic event [1,8].

Errors associated with the clinical detection of myocardial ischemia stem, at least in part, from an incomplete understanding of its mechanistic origins. Current clinical dogma assumes that ischemia develops as geometrically simple, contiguous regions of injured tissue that are anchored along the endocardial wall [7]. While the presence of a single, fixed ischemic region provides a simple approach for interpreting ischemic disease, it is often a gross oversimplification of a far more complex condition. Recent experimental studies, for example, showed that subendocardial patterns of ischemia were not common—appearing in only 6% to 13% of all observed cases [9]. In all other cases, ischemia formed over numerous, spatially distributed regions within the thickness of the

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https://doi.org/10.1016/j.jelectrocard.2018.05.005
0022-0736/

myocardium, creating multiple isolated zones that expanded independently of each other under conditions of prolonged stress [9].

These novel findings led us to develop an equally novel, experiment-based simulation pipeline to more fully elucidate the effects of ischemic disease on cardiac potentials [10]. To this end, we previously constructed a subject-specific, image-based model of the heart, using, as a source, measured **intracardiac** potentials sampled from the anterior left ventricle, to simulate **epicardial** potential distributions during the ST segment for multiple ischemic episodes. Simulated epicardial potentials correlated strongly with those measured during experimentation [10]. However, a partial sampling of the extracellular potentials of the intramyocardial space is only one possible representation of the ischemic source, and, although it closely resembles our experimental findings, a more natural and potentially more powerful option is to represent the injury in terms of ischemic zones. Once adequately characterized, such zones offer a path to parametrization, forming a much simpler representation of ischemia than a distributed set of potentials in space, much like a propagating wave encapsulates important behavior that is both intuitive and more easily interpreted than a set of electrograms. The result would be a reduction in complexity of the ischemic source descriptions from our previous model [10] that offers a completely novel, physiologically motivated approach to locating and visualizing the impact of ischemic stress on the heart. The goal of this study, therefore, became to characterize ischemic zone sources, based on measured intramyocardial potentials, and to evaluate the ability of zone-based simulations to replicate measured epicardial potentials.

We, therefore, augmented our original simulation pipeline [10] to explore the influence of biophysically justified, subject-specific ischemic zone representations on computed epicardial potentials. Using experimental measurements from canine models of induced ischemia, we extracted subject-specific ischemic zone geometries from measured intramural extracellular potentials during conditions of elevated ischemic stress. We imposed these zones within our image-based cardiac models, which we tuned to replicate measured epicardial potentials. This tuning consisted primarily of semi-empirically adjusting the various parameters of the ischemic border zone, *i.e.*, the thin layer of hypoperfused tissue that separates healthy from ischemic tissues. Border zone tuning led to consistent and predictable changes in simulated outcomes. Our results showed improved accuracy in terms of epicardial potential distributions for simulations using zone-based source representations when compared to our previous studies, which incorporated directly measured, distributed, intracardiac potential values as boundary conditions [10]. These results suggest that it is, indeed, possible, and in many ways preferable, to represent ischemia in terms of discrete zones. These findings encourage further exploration of zone-based modeling approaches, particularly with respect to the parameter space used to define them, in order to increase our understanding of the underlying biophysical mechanisms that drive myocardial ischemia and, consequently, to improve noninvasive localization and monitoring of acute myocardial ischemia.

Material and methods

The overall approach in this study was to simulate static epicardial potentials associated with subject-specific ischemia models using an augmented implementation of our previously defined image-based modeling pipeline [10,11]. Fig. 1 illustrates our overall approach in which image-based geometries, physical properties, and time-signal data were extracted from experimental canine models of acute ischemia [9]. These were used to create subject-specific computational models, from which simulated epicardial potentials were computed and validated [10].

Experimental methods and data processing

Unipolar intramural and epicardial electrograms were collected from open-chest canine models in which controlled, acute ischemia was induced, as described previously [9,12]. In brief, we regulated coronary blood flow through the left anterior descending artery (LAD) of anesthetized canine models (supply ischemia) while independently elevating heart rate and metabolic demand (demand ischemia), via right atrial pacing, to generate episodes of acute, transient ischemia. Our data includes examples of both supply and demand ischemia, which, for purposes of simulation, we consider to be equivalent. Electrogram recordings were concurrently captured using both a high-resolution customized sock (epicardial potentials) [13] and plunge needle electrodes (intramural potentials) [14] placed within the anterior portion of both ventricles. Potential values were extracted from each electrogram, using the Pfeifer open-source software package [15], at ST40%—a lead-independent time point defined as 40% of the interval between the end of the QRS complex (QRS_{off}) and the peak of the T wave (T_{peak}) of the global root mean squared signal, which considered all sock and needle electrograms together. ST40% was chosen to capture deflections in the ST segment while avoiding interference from T wave upstroke. Six distinct episodes, or interventions, of induced ischemia, acquired from two canine subjects, were considered for this study. Each episode lasted 6–8 min and consisted of stepwise increases in ischemic stress. ST40% potentials were corrected against control recordings taken prior to each induced ischemic episode to isolate the acute affects of ischemia [9,12].

Each heart was excised postexperiment and scanned using magnetic resonance imaging (MRI) and Diffusion Weighted MRI (DW-MRI) modalities (7 Tesla Bruker BIOSPEC 70/30, Billerica, MA) to identify cardiac geometries and fiber directions, respectively [10].

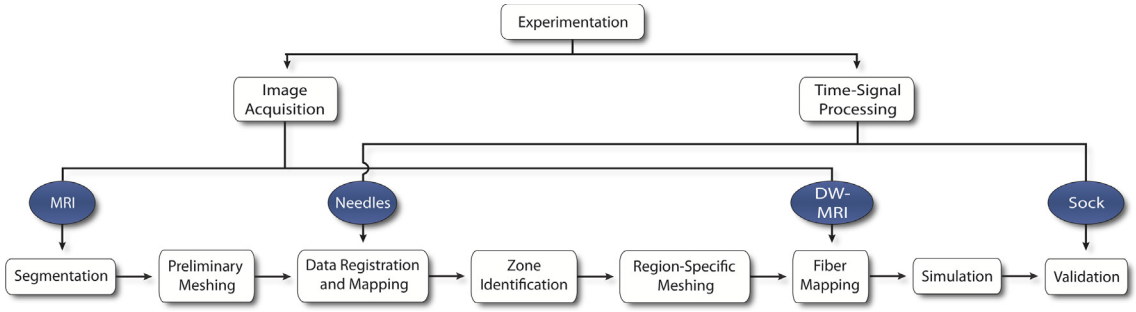

Fig. 1. Ischemia simulation pipeline. Electrogram and imaging data were extracted from experimental preparations of induced acute ischemia in dogs. From imaging data, subject-specific geometric models were generated that contained conforming, subject-specific cardiac fibers definitions and ischemic zone geometries. Intramural electrical potentials were mapped within the geometric models. Intramural and epicardial electrical potentials (recorded from plunge needle and sock electrodes) were also mapped in order to define subject-specific ischemic regions and to validate simulation results, respectively.