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# Noninvasive Electrocardiographic Imaging (ECGI) of Arrhythmogenesis: Insights from Modeling and Human Studies

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## Abstract

**Background—** Sudden cardiac death remains the leading cause of death claiming more than 1000 lives per day in the US alone. Noninvasive means to diagnose rhythm disorders of the heart have relied heavily on the 12-lead ECG and to a lesser extent on higher resolution body surface mapping. These suffer from lack of sensitivity and specificity due to the smoothing effect of the torso volume conductor. In contrast, noninvasive Electrocardiographic Imaging (ECGI) reconstructs potentials, electrograms and activation sequences directly on the heart surface from body surface ECGs and has been applied in animal as well as clinical studies. This presentation summarizes the application of ECGI for imaging epicardial arrhythmogenic substrates and associated properties; in particular dispersion of myocardial repolarization, fractionated electrograms and heterogeneous multipolar potential distributions.

**Methods—** ECGI was evaluated in a canine model of temperature induced dispersion of myocardial repolarization through localized warming and cooling and in three patients with preserved left ventricular ejection fraction (≥50%) undergoing open heart surgery. Noninvasively reconstructed epicardial potentials, electrograms (and derived measures) as well as activation sequences were compared to their measured counterparts.

**Results—** Epicardial measures of dispersion of repolarization (activation recovery intervals [ARIs] and QRST integrals) accurately reflected the underlying repolarization properties; prolonged ARIs and increased QRST (warming), shortened ARIs and decreased QRST (cooling) and gradients of adjacent prolonged and shortened ARIs (increased and decreased QRST) during simultaneous warming and cooling. In open heart surgery patients, ECGI reflected the underlying arrhythmogenic substrate by noninvasively reconstructing fractionated electrograms (cross correlation with measured electrograms = 0.72 ± 0.25), regions of heterogeneous multipolar potential distributions and areas of slow conduction.

**Conclusion—** These studies demonstrate that ECGI can capture and localize noninvasively important electrophysiological properties of the heart. Its clinical significance lies in mapping arrhythmogenic substrates, evaluation and guidance of therapy, and risk stratification.

## Introduction

Cardiac arrhythmias remain a leading cause of death and disability with over 300,000 annual deaths in the US alone. Cardiac electrical activity is generally assessed using electrocardiography (ECG) or vectorcardiography (VCG)[1], both of which are noninvasive yet lack sensitivity and specificity. This is due to the fact that each electrode on the body surface reflects at each time instant the distance weighted integration of the entire cardiac sources.

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Consequently, one to one relationships between body surface ECGs and a specific location on the heart do not exist. Additionally, the torso volume conductor consisting of fat, skeletal muscle, sternum, lungs and spine acts as a spatial low pass filter resulting in a smoothed distribution of body surface potentials for a given distribution of cardiac sources. Therefore, geometrical relationships between cardiac sources are not preserved on the body surface[1].

Electrocardiographic Imaging (ECGI) is a noninvasive imaging modality that reconstructs noninvasively potentials, electrograms and isochrones on the epicardial surface of the heart from body surface ECGs. Clinical application of ECGI requires the acquisition of body surface ECGs as well as the geometrical relationships between the epicardial surface and the location of recording ECG electrodes[2]. To date, ECGI has been validated extensively in controlled torso-tank and canine experiments in normal[3,4] and abnormal hearts[5–7] and during ventricular arrhythmias[5,8]. More recently, ECGI has been applied in humans[9,10] to reconstruct epicardial activation and repolarization during normal sinus rhythm, right bundle branch block, ventricular pacing and atrial flutter and open heart surgery patients[11] and in patients receiving devices for cardiac resynchronizations therapy[12]. Here, we present observations on the ability of ECGI to reconstruct arrhythmogenic properties and substrates in canine and human hearts. Specifically, examples of imaging dispersion of myocardial repolarization as well as fractionated electrograms, and potential gradients will be presented.

## Electrocardiographic Imaging (ECGI)

Noninvasive ECGI methodology in humans has been described previously[10]. Briefly, ECGs are acquired from 224 electrodes on the body surface. The geometrical relationship relating the epicardial surface to the location of the recording ECG electrodes is determined using high resolution computed tomography (CT). Following segmentation of the epicardial surface and digitization of the body surface ECG electrodes, a model of the human torso is constructed using boundary element methods[13]. The transfer matrix relating the triangulated epicardial and body surfaces is computed. Using the transfer matrix and the body surface ECG recordings as inputs, epicardial potentials are reconstructed using regularized inverse solutions such Tikhonov zero-order[14] or the Generalized Minimal Residual methods[15]. Regularization is necessary because of the ill-posed nature of the inverse problem (that is, large noise fluctuations in the input data [noise on the ECGs or inaccurate electrode locations] may precipitate large errors in the solution).

## Imaging Dispersion of Myocardial Repolarization

Dispersion of myocardial repolarization is highly arrhythmogenic. Adjacent myocardial regions with repolarization heterogeneity create substrates for unidirectional block leading to reentry[16,17]. Mechanistic optical mapping studies in isolated ventricular wedge preparations have confirmed the role of spatial gradients of transmural repolarization in the genesis and maintenance of polymorphic VT in heart failure[18] and long QT syndrome[19] models. In the clinical setting, noninvasive body surface measures of dispersion of repolarization such as QT dispersion have met with limited success[20–22]. Additionally, we have shown in a torso-tank model with realistic geometries, and using temperature induced dispersion of repolarization, that body surface measures of dispersion, specifically QT dispersion and QRST integrals lack sensitivity[23]. Paradoxically, body surface QT dispersion is decreased during left ventricular warming compared to control, whereas corresponding epicardial measures of ARIs dispersion is markedly increased. It is therefore concluded that epicardial measures of dispersion of repolarization reflect the underlying myocardial properties more accurately than body surface measures.

We subsequently applied ECGI to noninvasively reconstruct these measures from the body surface. The noninvasively reconstructed epicardial measures of repolarization dispersion

(ARIs and QRST integral maps) were compared to their measured counterpart. Figure 1 shows measured, noninvasively reconstructed and body surface QRST integral maps during control, LV warming, LV cooling and simultaneous LV warming and cooling. While the measured epicardial QRST integral maps (Figure 1, top row) captured accurately the changes in intrinsic repolarization properties (increased QRST integrals during warming, decreased QRST integrals during cooling and both increased and decreased QRST integrals during adjacent warming and cooling of the LV), the body surface QRST integrals (Figure 1, bottom row) showed a similar distribution with a local maximum on the anterior chest throughout all the interventions. The power of ECGI, therefore, was in the ability to reconstruct and localize noninvasively the corresponding spatial dispersion of QRST integrals (Figure 1, middle row) albeit with some smoothing (Figure 1, middle row, third and last columns) starting with these seemingly identical body surface distributions.

## Imaging Arrhythmogenic Substrates in Humans

ECGI was more recently applied in three patients undergoing open heart surgery[11]. Two patients (OR1 and OR2) had ischemic cardiomyopathy and underwent bypass surgery to repair coronary circulation with one patient having undergone prior stent placement. The third patient (OR3) had an ascending aortic arch aneurysm for which he underwent surgery. All patients had preserved LV ejection fraction (LVEF>50%). During surgery, epicardial potentials were recorded intraoperatively from the exposed heart using a 200 electrode sock. Patients underwent the ECGI procedure (CT scan and ECG recording) pre- and post- surgery. Note that CT was performed *only* during the pre-operative mapping procedure. Noninvasively reconstructed potentials, electrograms and isochrones using ECGI were compared to their measured counterparts during sinus rhythm, endocardial and epicardial pacing. Noninvasively reconstructed electrograms were well correlated to those measured intraoperatively. In addition, ECGI successfully localized the pacing site to within 5–20mm error. The ability of ECGI to image pacing sites provided implications for its potential application for the localization of arrhythmogenic foci.

It is worth noting that patient OR1 has multiple occluded arteries including a *severe* within-stent restenosis in the proximal right coronary artery (RCA) and patient OR2, while having normal LVEF, suffers from mildly impaired systolic RV function with moderate enlargement of the RV. Indeed, examination of the noninvasively reconstructed electrograms using ECGI reveals negative S-wave electrograms with superimposed small deflections in the mid to basal region and the right margin of the right ventricle for OR1 (Figure 2A). These deflections have been shown to reflect slow conduction in a thin layer of surviving myocardium in an otherwise infarcted tissue. In contrast, electrograms recorded from more remote sites exhibit a normal RS morphology (Figure 2B). These are invasively measured and confirmed with intraoperative mapping. Additionally, invasively measured potentials for patient OR2, show a bipolar potential distribution on the left ventricle (Figure 2C, right column) during repolarization (T-peak), while those measured over the right ventricle show multiple dispersed islands of maxima and minima (Figure 2C, first column). These potential patterns are captured noninvasively, albeit with smoother potential gradients due to the smoothing effect of the mathematical methodology of ECGI. The potential gradient measured and noninvasively reconstructed on the LV is consistent with those observed in healthy volunteers[9]. This is also consistent with the fact that patient OR2 had preserved LVEF. It can be speculated, on the other hand, that the multipolar potential distribution during T-peak on the right ventricle is indicative of substrate remodeling due to RV cardiomyopathy.

## Clinical Implications

Imaging focal activity is critical for characterizing arrhythmia mechanism and guiding ablation therapies. Additionally, imaging epicardial activity during a single beat can provide insight into the mechanisms of ventricular tachycardia with epicardial components. With close to 30% of ventricular tachycardia having epicardial circuits[24], and with the advent of transthoracic catheter ablation of epicardial targets[25,26], the role for ECGI in mapping noninvasively cardiac electrical activity and guiding ablation therapy will be emphasized further. In fact, noninvasively reconstructed ECGI maps of activation during a single premature ventricular complex with QRS morphology similar to that measured during VT, uncovered and localized the site of earliest activation in an athlete with focal tachycardia and guided ablation therapy[27]. Because CT imaging is unavailable in the electrophysiology (EP) laboratory where mapping and ablation procedures are performed and in order to render the ECGI procedure more practical for mainstream adoption, new methods for obtaining patient specific geometry using biplane fluoroscopy[28] or pseudo-3D ultrasound[29] have been developed and successfully tested in the context of ECGI in the EP laboratory. The ability to image noninvasively regions of dispersion of repolarization in the form of QRST integral maps (or other metrics of repolarization dispersion) during a single beat provides a feasible and computationally efficient method for evaluating the severity of the substrate in patients at risk of developing arrhythmias. Noninvasive reconstruction of epicardial measures of repolarization dispersion can therefore provide a tool for rapid screening of patients at risk of sudden death. The significance of applying ECGI for risk stratification is amplified by the lack of sensitivity of body surface measures (such as QT dispersion) at reflecting underlying dispersion of repolarization.

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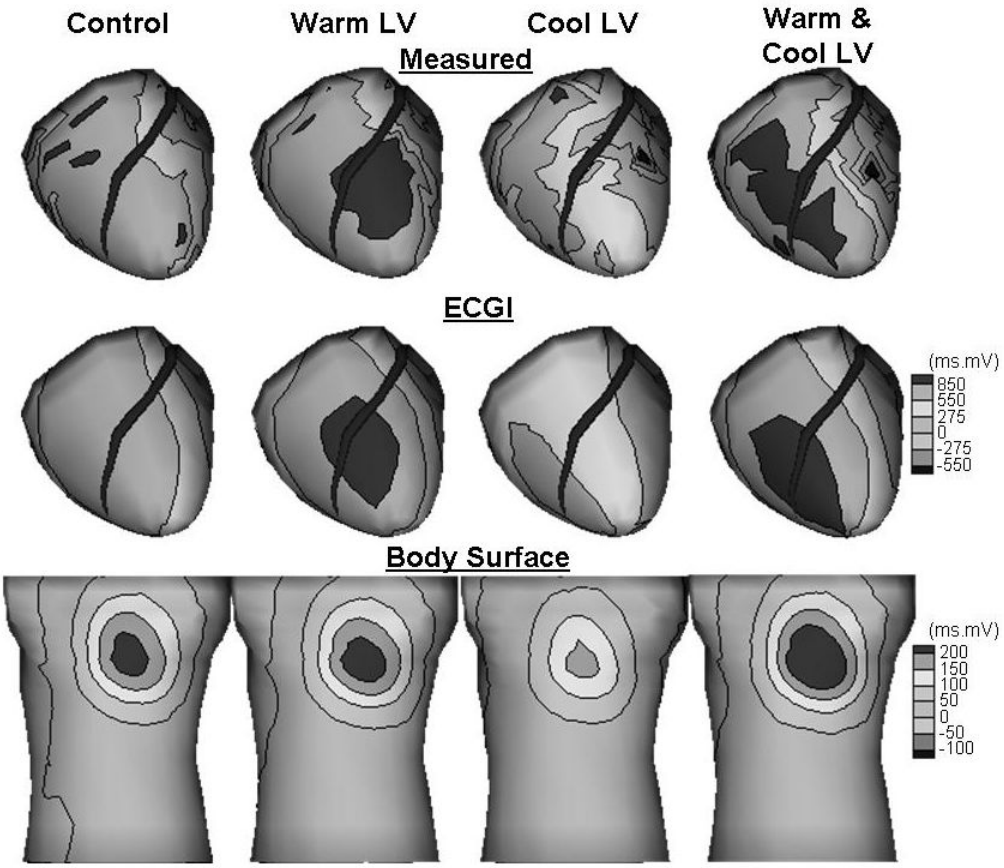


**Figure 1.**
Measured (top), noninvasively reconstructed (middle) and body surface (bottom) QRST integral maps during control, LV warming, LV cooling and simultaneous LV warming and cooling.

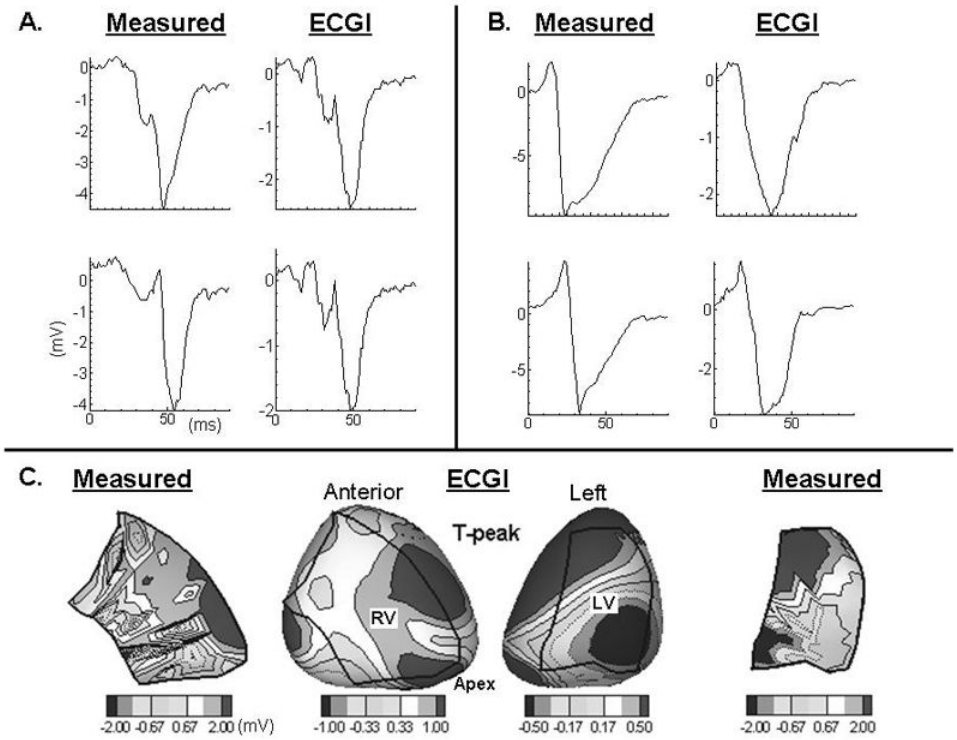


**Figure 2.**

**Panel A**, invasively measured and noninvasively reconstructed electrograms from the mid to basal region and the right margin of the RV. **Panel B**, invasively and noninvasively reconstructed electrograms from remote sites closer to the interventricular septum. **Panel C**, invasively measured (first and last column) and noninvasively reconstructed epicardial potentials during repolarization. Boundaries of the intraoperative 200 electrode sock are overlaid over the RV and LV.