The process of cardiac excitation involves generation of the action potential (AP) by ionic membrane currents and propagation of the AP through the multicellular structure of cardiac tissue. The properties of excitation and the development of cardiac arrhythmia are determined by the interaction between the source of electric activation (membrane depolarization) and the electric load (sink) that the tissue presents. In the normal heart, the source and sink are properly matched and excitation is robust. With pathology, electrophysiological (EP) and structural changes (remodeling) can occur that alter the source–sink relationship, creating a mismatch between source and load that promotes arrhythmic behavior. Pathological changes can affect the membrane excitability (eg, via downregulation of the fast sodium current), modify the tissue structure (eg, by affecting gap–junctions expression and distribution, and by causing fibrosis), or both. In many cases, the remodeling process is dynamic and progressive, creating an arrhythmogenic substrate that changes with time.

Most studies of arrhythmia mechanisms and arrhythmogenic substrates have been conducted in animal models, which may differ in important ways from the human pathologies they are designed to represent. Electrocardiographic imaging is a noninvasive method for mapping the electric activity of the heart in humans in real-world conditions. This review summarizes results from electrocardiographic imaging studies of arrhythmogenic substrates associated with human clinical arrhythmias. Examples include heart failure, myocardial infarction scar, atrial fibrillation, and abnormal ventricular repolarization. (Circ Res. 2013;112:863-874.)

**Key Words:** atrial fibrillation ■ cardiac arrhythmia ■ electrophysiology ■ heart failure ■ myocardial infarction
Nonstandard Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
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<td>AF</td>
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<td>AP</td>
<td>action potential</td>
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<td>ARI</td>
<td>activation recovery interval</td>
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<td>CRT</td>
<td>cardiac resynchronization therapy</td>
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<td>ECGI</td>
<td>electrocardiographic imaging</td>
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<td>EP</td>
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<td>HF</td>
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<td>MV</td>
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<td>PVC</td>
<td>premature ventricular complex</td>
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The electric potential field $\phi$, generated by excitation of the heart in the surrounding torso volume between the epicardium and the body surface, obeys Laplace equation:

$$\nabla^2 \phi = 0$$  \hspace{1cm} (1)

where $\phi = \phi_T$ on the torso surface and $\phi = \phi_E$ on the epicardium. $\nabla^2$ is the Laplacian operator. $\phi_T$ can be measured noninvasively by electrodes placed on the body surface. The objective of ECGI is to compute $\phi_E$ from the measured $\phi_T$.

Application of the Green second theorem and discretization of the epicardial and torso surfaces into triangular elements provide the following matrix equation relating $\phi_T$ to $\phi_E$:

$$\phi_T = \Lambda \phi_E$$  \hspace{1cm} (2)

where $\phi_T$ is a vector of (measured) torso potentials and $\phi_E$ is a vector of (unknown) epicardial potentials. The matrix $\Lambda$ contains the geometric information that relates the 2 (heart and torso) surfaces. Equation 2 computes $\phi_T$ from given $\phi_E$, a formulation that defines the forward problem of electrocardiography. ECGI requires, to invert this problem and compute $\phi_E$ from a known $\phi_T$, a procedure that constitutes the inverse problem of electrocardiography. The inverse problem is ill-posed, meaning that even small errors in the measured $\phi_T$ data (measurement noise, electrodes positions) can result in very large (unbounded) errors in the computed $\phi_E$. To suppress such errors, we have applied 2 different computational schemes in the ECGI application: Tikhonov regularization (a method that imposes constraints on $\phi_E$) and the generalized minimal residual iterative technique.

The ECGI algorithm requires 2 sets of data: the electrocardiographic potential over the entire torso surface ($\phi_T$) and the geometries of the heart and torso surfaces (matrix $\Lambda$). To obtain $\phi_T$, 250 electrodes mounted on strips are applied to the patient’s torso (both anterior and posterior) and connected to a portable mapping system (Figure 1). Each electrode contains a marker that is visible on a CT scan. The patient undergoes thoracic noncontrast gated CT with axial resolution of 3 mm, providing the epicardial geometry and torso electrode positions in the same image. The torso surface potentials, recorded by the 250 electrodes, are sampled at 1-ms intervals. The recorded torso potential and CT-derived geometric information provide the input data for the ECGI algorithm, which constructs noninvasively epicardial potentials, electrograms, activation sequences (isochrone maps), and repolarization patterns. The reconstruction is performed during a single beat and does not require accumulating data from many beats. This property makes it possible to image nonsustained and polymorphic arrhythmias and arrhythmias that are not hemodynamically tolerated.

At present, CT is the method of choice for obtaining noninvasively the individual heart–torso geometric relationship in a given patient. We use noncontrast CT at very low radiation (<2 rads), and this has been decreasing with advances in CT technology. We only obtained 1 CT scan at the first ECGI study. In follow-up studies, we reapplied the body surface electrode strips at the same positions as in the first study (using anatomic and external markers), eliminating the need for a repeat CT. In principle, other anatomic imaging methods can be used to obtain the geometry. MRI could be used once it has been developed for human application (both research and clinical) recently developed electrocardiographic imaging, (ECGI, mapping of cardiac electrophysiology and arrhythmia. We have been hampered by the unavailability of noninvasive imaging methods (similar to computed tomography (CT) or magnetic resonance imaging (MRI)) for high-resolution mapping of cardiac electrophysiology and arrhythmia. We recently developed electrocardiographic imaging, (ECGI, also called electrocardiographic mapping) as a noninvasive modality for human application (both research and clinical) and used it to study arrhythmogenic substrates and arrhythmias in patients. ECGI reconstructs potentials, electrograms, activation sequences (isochrones), and repolarization patterns on the heart surface. The reconstruction is performed simultaneously over the entire heart and is performed continuously on a beat-by-beat basis.

In this review, insights from ECGI studies of human EP substrates associated with clinical arrhythmias are summarized. The article focuses on ECGI substrate imaging, not on the basic mechanisms of cardiac arrhythmias. After a brief description of the ECGI methodology, the following representative examples are provided:

2. Progressive remodeling in atrial fibrillation (AF).
3. The EP substrate associated with abnormal AP repolarization.
made safe to apply in patients with implanted devices (a large segment of the cardiac patients population). Ultrasound probably also could replace CT, once high-quality 3-dimensional echocardiography becomes available.

ECGI has been validated extensively under different physiological and pathological conditions in animal models and human studies. In particular, the torso–tank experimental set-up provided well-controlled experimental conditions that mimicked the clinical situation. This preparation consisted of a tank in the shape of a 10-year-old boy’s torso filled with an electrolytic solution, with a perfused dog heart suspended within the torso volume in the correct anatomic position. The system included 384 torso surface electrodes and 384 rods with electrodes at their tips. The rods were pushed toward the heart so that their tips created an epicardial envelope. Potentials measured by the torso surface electrodes were used as input data to compute noninvasively epicardial potentials. These were then compared with the gold standard of directly measured epicardial potentials by the rod-tip electrodes. Validation protocols were conducted in normal and infarcted canine hearts during sinus rhythm, multiple-site pacing, and re-entrant ventricular tachycardia (VT). Correlation coefficients between noninvasively reconstructed and directly measured epicardial electrograms were >0.9 for 72% of all epicardial locations, indicating very good agreement. In infarcted hearts, ECGI reconstructed accurately low potentials and low-amplitude fractionated electrograms within the infarct scar region. ECGI also was shown to reconstruct repolarization properties accurately and to localize areas of increased dispersion of repolarization (induced by myocardial warming and cooling) noninvasively. Validation in humans included comparison with direct intraoperative mapping in open heart surgery patients during sinus rhythm and right ventricular (RV) epicardial and endocardial pacing. Unlike the tank–torso experiments, ECGI and direct epicardial mapping could not be performed simultaneously and under identical conditions in the intraoperative study. Despite this limitation, it was shown that ECGI-reconstructed isochrones captured the sites of earliest activation, areas of slow conduction, and the general excitation pattern. Through comparison with simultaneous invasive catheter mapping and localization of pacing electrodes by CT, it was determined that the spatial accuracy for determining initiation sites (induced by pacing) noninvasively with ECGI was ≈6 mm.

The ECGI method for computing epicardial potentials from body surface potentials relies on the assumption that Laplace equation (1) holds in the torso volume conductor between these 2 bounding surfaces (the torso surface and the epicardium). This reflects the fact that there are no active electric sources (no excitable cardiac tissue) in this volume. Extension of the approach to the endocardium violates this assumption because, during cardiac excitation, there are active sources within the myocardium. Therefore, reconstruction of endocardial excitation requires additional assumptions (that may bias the solution in a nonphysiological way) or the application of alternative approaches. One alternative approach is the model-based method (using a bidomain model of the heart) that computes only local activation times (isochrones) but not the entire electrograms. This approach was used successfully to image preexcitation in Wolff–Parkinson–White patients and to reconstruct activation sequences in congestive HF patients undergoing cardiac resynchronization therapy (CRT).

The data presented here were published previously. All protocols were approved by the Washington University Human Research Protection Office, and informed consent was obtained from all patients.

**EP Substrate and CRT in HF**

HF is a progressive disease that is highly prevalent and associated with high mortality. Up to 50% of deaths in HF patients are sudden, and a majority of the deaths are from ventricular tachyarrhythmias. However, arrhythmias can contribute to HF by causing cardiomyopathy through remodeling processes. In HF, abnormal cellular EP processes and calcium cycling are superimposed on structurally remodeled tissue, resulting in compromised AP propagation (slow conduction, conduction block). Through abnormal calcium cycling and AP repolarization, HF also promotes arrhythmia triggers in the form of delayed and early afterdepolarizations. Much is known (and is being intensely researched) regarding the molecular basis for the cellular EP and calcium cycling (contractile) changes in HF. At the level of the whole heart, human data for mechanical contraction are available from tagged...
MRI and echocardiographic noninvasive imaging studies.\textsuperscript{29,30} Body surface electrocardiographic characteristics in many HF patients include a wide QRS complex and left bundle branch block pattern, indicative of delayed and dysynchronous activation, predominantly of the left ventricle (LV).\textsuperscript{31} However, detailed understanding of the spatiotemporal excitation pattern in the failing human heart has been lacking. We have used ECGI, taking advantage of its noninvasive nature, to fill some of this gap and to provide insight into the substrate-related ventricular activation patterns in HF patients.\textsuperscript{32}

Figure 2 shows ECGI epicardial activation (isochrones) maps of native (nonpaced) rhythm from 4 HF patients.\textsuperscript{32} In all cases, RV epicardial activation started from a breakthrough site (circular isochrones), in a location consistent with activation of the normal, nonfailing human heart.\textsuperscript{5} This property indicates normal RV activation via the right bundle of the specialized conduction system. From the breakthrough site, activation spreads radially and uniformly in the RV, with latest activation occurring at the basal or anterior/inferior paraseptal regions, as in normal hearts. Mean duration of RV activation (8 patients) was 25 ms.

In contrast to RV activation, LV activation was abnormal and delayed in all patients, accounting for the left bundle branch block pattern of the body surface ECG. Importantly, and different from RV, details of the LV activation patterns were heterogeneous and differed between patients, with variability in the location of the latest activation (blue). In patient 7 (Figure 2A), LV conduction was from apex to lateral base; inferior to anterolateral conduction was the pattern in patient 5 (Figure 2B); and combined activation from apical, inferior, and superior LV was mapped in patient 1 (Figure 2C). In patient 3, conduction was anterior to inferoposterior. In the patients represented in Figure 2, anterior line(s)/region(s) of block (black; defined by >50-ms activation delay across) prevented the activation from spreading further into the LV after crossing the septum from the RV; it spread in a U-shape pattern to reach the lateral wall by way of the apical or inferior LV (as observed by endocardial catheter mapping, also).\textsuperscript{33} Interestingly, during subsequent pacing protocols some of the block regions shifted, indicating their functional nature, whereas others remained unchanged, suggesting the presence of an anatomic obstacle. Consistent results, but with less interpatient variability, were obtained by Berger et al\textsuperscript{20} using the activation time reconstruction approach. In their study, congestive HF patients showed right-to-left septal activation with the latest activation epicardially in the lateral wall of the LV. Biventricular pacing resulted in resynchronization of the ventricular activation sequence and decrease of total LV activation duration compared with intrinsic conduction.

CRT uses biventricular pacing to restore ventricular synchrony; it attempts to advance in time electric activation of the greatly delayed region of late LV activation. CRT improves patients’ symptoms, LV performance, and long-term survival.\textsuperscript{34} For reasons that are not clear, ≈33% of cases do not respond to CRT. Short-term improvement is likely attributable to more efficient pumping action of the synchronized LV. Long-term improvement involves reverse remodeling of molecular components and processes.\textsuperscript{35} The ability to image the EP substrate with ECGI and the interpatient heterogeneity of the substrate have implications for CRT. The degree of resynchronization that is achieved with CRT depends on the site of LV lead placement. On the basis of the ECGI-imaged sequence of native activation (Figure 2), the region of most
delayed LV activation could be determined in a patient-specific manner for placing the pacing lead to maximize synchrony. In addition, information on the EP properties of the substrate in a given patient’s heart could also be considered. For example, lead placement in areas of unexcitable tissue and regions of conduction block or slow conduction could be avoided. We conducted an ECGI study in pediatric HF patients with congenital heart disease undergoing evaluation for CRT. The study demonstrated that ECGI could be used to evaluate ventricular electric dys synchrony and identify suitable candidates for CRT. In addition, ECGI was able to guide resynchronization lead placement to the area of latest electric activation. The potential role of ECGI in CRT should be evaluated in a large prospective study in the adult population of HF patients.

Finally, the observation that RV activation used the specialized conduction system suggested that in some cases, biventricular pacing can be replaced by LV pacing alone for CRT. We demonstrated that with optimal atrial-ventricular delay, in 3 of 4 patients with atrioventricular conduction synchroniza tion was achieved by fusion between intrinsic excitation from the RV and paced excitation from the LV-placed electrode. The possibility of LV pacing alone for CRT has the RV and paced excitation from the LV-placed electrode. In addition, ECGI was able to guide resynchronization lead placement to the area of latest electric activation. The potential role of ECGI in CRT should be evaluated in a large prospective study in the adult population of HF patients.

EP Substrate After MI
MI triggers a progressive remodeling process that is associated with high incidence of ventricular arrhythmias in survivors in the days and weeks that follow the initial ischemic event. The time progression of electric changes has been divided into the acute ischemia phase (first 10–15 minutes after ischemia onset), the sub acute phase (hours after onset), and the healing and healed infarct (days to years after the original ischemic event, once infarct has formed). Many studies of EP and structural properties of the healing and healed MI have been conducted in a canine model in which a transmural infarct was created. Late potentials, reflecting delayed activation during sinus rhythm, were present in subsets of electrograms from within the scar region. Examples are shown in Figure 4 (late potentials) and from regions outside the scar (blue). Scar electrograms are of very low magnitude, as emphasized when plotted on the same voltage scale together with nonscar electrograms in the bottom row of Figure 3B. They are also characterized by fragmentation (fractionation), clearly observed on the expanded scale of Figure 3C. Based on the electrograms, the scar maps in Figure 3A were constructed (red). Two images are shown: the top map was based on the low-voltage criterion alone and the bottom map added the criterion of electrogram fractionation, which eliminated the basal part of the scar. Delayed-contrast MRI has been used to image anatomic scars. Figure 3D compares the ECGI-reconstructed electric scar (red; based on the low-voltage criterion) with the MRI-imaged anatomic scar (yellow). There is good agreement between the 2 images. The basal portion of the electric scar that was removed by the fractionation criterion is included in the MRI image. It is possible that this portion reflects epicardial fat, rather than true scar substrate (epicardial fat attenuates electrogram voltages but does not cause fractionation; it also appears as a bright region, suggesting scar tissue, in delayed contrast MRI). Inclusion of the fractionation criterion (not detectable by MRI, which does not image electric properties) removes this portion of the substrate from the electric scar image (bottom of Figure 3A).

Late potentials, reflecting delayed activation during sinus rhythm, were present in subsets of electrograms from within the electric scar. Examples are shown in Figure 4 (late potentials are highlighted by boxes). The presence of scar altered the pattern of epicardial activation during sinus rhythm (Figure 3; compared with normal activation in the absence of scar). Asymmetrical electric loading of a propagating wavefront at scar borders created lines of conduction block. Scar-related slow conduction regions also were mapped by ECGI. The combination of asymmetrical (unidirectional) block and slow conduction provides conditions for formation of re-entry circuits and re-entrant arrhythmias.

Scar-Related VT
ECGI can image the electric activation sequence over the entire ventricular surfaces in a single beat. This ability to map noninvasively and continuously the dynamic pattern of excitation during an arrhythmia facilitates the study of clinical VT characteristics in the human heart. A study of 25 patients undergoing catheter ablation for a broad range of VT provided...
information on VT initiation and continuation and, in the context of this review article, on the relationship of VT to the ventricular substrate (anatomic scars and myocardium with abnormal EP properties). Five patients had re-entrant VT, with re-entry activation patterns related to regions of myocardial scar. An example is shown in Figure 5. Single-photon emission CT images identified an area of scar from a previous MI in the inferior septum (dark blue in Figure 5C). ECGI activation map during VT is shown in Figure 5B; activation movie is provided as Online Movie I. Earliest activation is in the inferior basal septum at the scar border (red in the map), where the wavefront exits at the start of the VT beat and re-enters at the end of the beat to complete the LV epicardial clockwise reentry pattern (white arrows). In this region, ECGI reconstructed low-amplitude, highly fractionated electrograms, consistent with electric scar substrate. Immediately before each VT beat, localized presystolic activity was observed at sites along the inferior scar border (Online Movie I), indicating exit sites of activation fronts that propagated slowly through viable pathways in the scar substrate. The high curvature re-entrant wavefront rotates around the scar (white arrows in Figure 5B; Online Movie I).

It should be noted that determination of activation times in a region of scar is a challenging task. The time of local activation is determined from the electrogram as the instant of steepest negative deflection (so-called intrinsic deflection). As shown, electrograms within a scar substrate could be fractionated with multiple deflections, sometimes of similar magnitude and steepness. These deflections reflect activation of neighboring regions (islands) of surviving myocardium. The global activation sequence can be constructed by assigning a single (average) activation time. However, high-resolution isochrones within the scar should consider each deflection distinctly. This requires careful interpretation and editing of the electrogram, considering not only its temporal properties but also the spatial/temporal relationships to its neighbors.

Atrial Fibrillation
The substrate for AF is dynamic, with AF itself inducing remodeling and substrate changes that promote AF (AF begets AF). Structural
remodeling, in particular interstitial fibrosis, contributes to AF by providing a heterogeneous substrate that supports slow discontinuous conduction and development of conduction block, and can lead to break-up and fragmentation of propagating wavefronts.\(^5^5\) Abnormal calcium cycling in remodeled atrial cells could underlie focal ectopic activity in AF.\(^5^4\) As remodeling progresses, these multifactorial changes interact to form a complex substrate for atrial excitation during AF.

In a recent study, ECGI activation maps of AF in 26 patients were analyzed in terms of complexity of patterns.\(^5^6\) Within a diverse population of AF patients (including paroxysmal, persistent, and long-standing persistent AF),\(^5^7\) activation patterns were variable. The most common epicardial pattern during AF consisted of multiple wavelets together with activity from focal sites near the pulmonary veins. In general, complexity of the activation pattern (classified in terms of number of wavelets and focal sites) increased with longer clinical history of AF (ie, with increased AF duration, implying longer, more progressed remodeling). Examples are provided in Figures 6 and 7; they serve to illustrate the effect of substrate remodeling progression on the complexity of the AF activation pattern rather than provide insights into the basic mechanisms of AF. For discussion of mechanisms, the reader is referred to the original report on the ECGI AF study.\(^5^6\)

Figure 6 shows the activation pattern of paroxysmal nonsustained AF in a young patient with a structurally normal heart. AF was induced during an EP study. The pattern is relatively simple; it is that of a single spiral wave (rotor); 100 ms of AF is depicted in the map (right posterior and anterior views). Black line marks the interatrial septum. A similar example of paroxysmal AF is shown in Online Movie II. In comparison, the pattern of long-standing persistent AF in Figure 7 and Online Movie III is of much greater complexity. The movie shows 900 ms of continuous AF imaging. There are at least 4 coexisting wavelets, characterized by a high degree of wavefront curvature and wave breaks. Focal sites are seen near pulmonary veins.

The time-lapsed ECGI maps of Figure 7 are representative of similar complexity at other times during AF. Of course, the activation pattern is dynamically changing.

![Figure 5. Scar-related re-entrant ventricular tachycardia (VT). The scar is inferobasal. A, Epicardial activation isochrones for a sinus capture (SC) beat. B, The activation pattern during VT beat. A clockwise re-entry loop (white arrows in left lateral and LAO inferior views) is anchored to the scar. Pink arrows depict a wavefront propagating in a clockwise fashion into the right ventricle (RV). ECG lead V2 (inset) shows 2 VT beats (red, B) interrupted by SC beat (blue, A), followed by another VT beat (VT is monomorphic). Online Movie I shows this entire sequence as imaged by electrocardiographic imaging. C, Single-photon emission (left) computed tomography (SPECT) of inferobasal scar (blue). Endocardial activation (right) during VT mapped with a NavX catheter (red is early; blue is late). Right column presents (top) 12-lead body surface ECG of VT and signals (bottom) recorded by the ablation catheter. LA, left atrium; LAD, left anterior descending artery; RA, right atrium; and RAO, right anterior oblique. See Online Movie I. Adapted from Wang et al,\(^5^2\) with permission.](http://circres.ahajournals.org/doi/abs/10.1161/CIRCRESAHA.107.149932)

![Figure 6. Paroxysmal atrial fibrillation (AF). A, A single biatrial spiral wave (rotor) drives the arrhythmia (white arrows); 100 ms of AF is depicted in the map (right posterior and anterior views). Black line marks the interatrial septum. B, Body surface potential maps at the 2 instances during AF marked on the ECG lead II at the bottom. Note the low voltages and simple (single-maximum) potential distribution, a consequence of the smoothing effect of the torso volume conductor. ECGI, electrocardiographic imaging; LA, left atrium; LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; MV, mitral valve; RA, right atrium; RAA, right atrial appendage; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; and TV, tricuspid valve. Online Movie II shows this repetitive pattern. Adapted from cuculich et al,\(^4^6\) with permission.](http://circres.ahajournals.org/doi/abs/10.1161/CIRCRESAHA.107.149932)
The observations rely on the ability of ECGI to map the AF activation sequence continuously on both atria with sufficient resolution. This can be difficult to achieve in some cases, because the body surface signals generated by AF are typically of low amplitude and body surface potential distributions are smoothed out by the torso volume conductor (Figure 6). In the examples of Figures 6 and 7 (and for the other patients in the original AF study), a clear signal from atrial activation during AF was present in the body surface ECG (see lead II tracings). Several minutes of data were recorded from each patient. T-Q segments were used for analysis of AF. By considering at least 5 AF activation movies (ranging from 500–1000 ms) for each patient, nonphysiological artifacts were minimized. Because ventricular signals are typically of much greater magnitude than the atrial signals, it might be necessary in some cases of AF with normal atrioventricular conduction to remove the ventricular signals by QRS(T) subtraction algorithms, or to apply atrioventricular blocking drugs to produce long continuous recordings of atrial signals of adequate quality.

Dispersion of Repolarization
Abnormal repolarization of the cardiac AP can be the result of genetic mutations in ion channel proteins or other auxiliary proteins (eg, the long QT syndrome),58 disease processes (eg, ischemia),59 or the effects of various drugs. It can produce the 2 components that generate cardiac arrhythmias: the substrate and the trigger. A trigger associated with abnormal repolarization is early afterdepolarization. The substrate is steep regional repolarization gradients, or dispersion of repolarization, that create spatial asymmetry of excitability and conditions for unidirectional block and reentry. Unlike the electric substrate associated with a scar, where conduction properties are affected by pathological structural changes, steep dispersion of repolarization can exist in structurally normal myocardium. ECGI can image, noninvasively, not only the sequence of activation (examples in previous sections) but also the pattern of epicardial repolarization. The time of activation and the time of repolarization at a given location are determined from the ECGI-reconstructed electrogram. Activation time is determined as the time of maximum negative derivative on the QRS segment. Recovery time is the time of maximum derivative on the T-wave. Recovery times are determined by both the activation sequence and the local repolarization. Activation recovery interval (ARI) is the difference between recovery time and the time of maximum derivative on the T-wave. Recovery times are determined by both the sequence of activation and the local repolarization. Activation recovery interval (ARI) is the difference between recovery time and the time of maximum derivative on the T-wave. Recovery times are determined by both the activation sequence and the local repolarization. Activation recovery interval (ARI) is the difference between recovery.
time and activation time; ARI reflects intrinsic repolarization properties and is a surrogate for local AP duration.\textsuperscript{60,61}

Early repolarization syndrome is defined in terms of its electrocardiographic signature, that is, significant elevation of the QRS–ST-segment junction in the inferior or lateral precordial leads.\textsuperscript{62–64} It has long been considered to be benign.\textsuperscript{65} However, it was recently shown to be more prevalent in patients with a history of idiopathic ventricular fibrillation (31.1\% vs 5\% in control).\textsuperscript{65,66} Because of its nonspecificity, the ECG signature does not provide a conclusive definition of the ventricular electric substrate and QRS prolongation and J-point elevation could reflect delayed activation and not necessarily early repolarization. ECGI was used to image the early repolarization substrate and to test the hypothesis that it involves accelerated repolarization rather than delayed activation; an example is provided in Figure 8.\textsuperscript{66}

Figure 8, top panel, shows the ECGI activation map during sinus rhythm, with activation starting from the superior anterior septum (a variant of normal ventricular activation), followed by activation of the anterior RV and LV in an apex to base fashion. This activation sequence is normal and excitation spreads uniformly; there is no evidence for slow conduction or regions of abnormal delayed activation. Figure 8, middle panel, depicts the ECGI repolarization ARI map for the same sinus beat. Strikingly, there are regions of very short ARI in midanterolateral RV (ARI=140 ms, dark blue, marked by 1 in right anterior oblique view) and inferior basal RV (ARI=160 ms, light blue, marked by 3 in LPO view). These short ARIs reflect short APs in these regions. Corresponding ARI values in normal human ventricles are 235±21 ms. Importantly, for arrhythmogenesis, there are very steep repolarization gradients in these regions; 107.4 ms/cm in region 1 and 102.2 ms/cm in region 3. For comparison, ARI gradients in normal hearts range from 4.5 ms/cm to 11.3 ms/cm. ECGI-reconstructed electrograms from the regions of short ARI show marked elevation of the QRS–ST segment junction (inset 1), whereas those from neighboring regions do not show any evidence of early repolarization (inset 2).

During the ECGI procedure, the patient had several premature ventricular complexes (PVC) of identical morphologies. The bottom panel of Figure 8 shows ECGI-imaged epicardial potential maps for early activation (left) and repolarization (right) during a PVC. The local negative potential minimum of early activation (asterisk, dark blue) locates the PVC origin. Note that the PVCs originated from the apical region, remote to the area of steep dispersion of repolarization. If the PVC excitation wave interacts with the substrate of steep dispersion in a specific way (at a particular velocity, direction, orientation, and time window), unidirectional block can occur and reentrant arrhythmia induced. This, of course, is a probabilistic event that requires co-occurrence of multiple specific conditions.

In summary, ECGI of early repolarization identified normal ventricular activation during sinus rhythm but abnormal repolarization with areas of very short ARIs (reflecting the short APs) as the substrate in this case. The resulting local dispersion of repolarization creates steep excitability gradients that provide the substrate for unidirectional block and reentry. The PVC excitation wave could provide the trigger for initiation of arrhythmic reentrant excitation in this substrate.

An ECGI study showed that repolarization abnormalities also occur in patients with the Wolff–Parkinson–White syndrome.\textsuperscript{67} In the preexcited rhythm, ARI was prolonged (349±6 ms) in the area of preexcitation, leading to high base to apex ARI dispersion of 95±9 ms (normal is ±40 ms). The ARI dispersion remained the same 45 minutes after ablation of the accessory pathway, although the activation sequence was restored to normal. ARI dispersion was still high (79±9 ms) 1 week later and returned to normal (45±6 ms) 1 month after ablation, demonstrating cardiac memory. The 1-month time course is consistent with transcriptional reprogramming and remodeling of ion channels. Similar observations were made in conjunction with RV pacing.\textsuperscript{68} It should be added that the ECGI-determined preexcitation sites were consistent with sites of successful ablation in all cases. Accurate noninvasive determination of preexcitation in Wolff–Parkinson–White syndrome patients was also reported with the model-based activation time method.\textsuperscript{19}

Conclusions

The topic of this review is the noninvasive imaging of EP substrates using ECGI. The article therefore is limited to examples of substrate reconstructions and does not address the broader applications of ECGI in the study of arrhythmia mechanisms and in clinical practice. Being a noninvasive method, ECGI can serve both as a research tool for investigating the basic mechanisms of human cardiac arrhythmias and as a clinical tool for diagnosis and guidance of therapy. We have published examples of both; the reader is referred to the research section of http://rudylab.wustl.edu for additional information and a list of references.

The examples of EP substrate imaging in this article are representative of data from several studies. These data demonstrate the variability of substrate properties and characteristics between individual patients with similar diagnoses and pathologies. This is evident in the HF data of Figure 2, in which native LV activation was heterogeneous among patients, with different spatial patterns of slow conduction and conduction block and different regions of latest activation. This variability has important clinical consequences because optimal LV lead placement for CRT depends on the substrate properties. The choice of lead location should consider the sequence of activation (ie, pacing from the region of most delayed activation to maximize synchrony) and the EP properties of the substrate (avoiding electrode placement near extensive block regions and regions of slow conduction). This information could be obtained noninvasively with ECGI before CRT implantation for guidance of electrode placement in a substrate-dependent individualized manner.

Similarly, the AF study highlights the coexistence of a variety of mechanisms and variable complexity among patients. ECGI can map the dynamically changing activation sequence of AF and may have a role in guidance of therapy. It could help to identify AF patients who are likely (or unlikely) to benefit from catheter or surgical ablation, depending on the complexity of their atrial activation during AF. It could also help to plan a patient-specific ablation strategy, tailored to repetitive activation patterns in the individual patient’s heart.
Variability also exists in the post-MI scar substrate. The substrate is characterized by heterogeneous scar with surviving myocardial fibers that support slow, discontinuous conduction. However, most patients with ischemic cardiomyopathy never have VT. Efforts to quantify VT risk in this population have shown associations with scar burden and QRS fragmentation. A useful role for ECGI could be in noninvasive risk stratification for VT in ischemic cardiomyopathy patients. To this end, we compared ECGI from ischemic cardiomyopathy patients with or without history of VT. Preliminary results\(^6\) show that patients with VT had a larger total electric scar burden, greater electrogram fragmentation (reflecting greater heterogeneity of the substrate), and more late deflections (late potentials) on the electrograms.

The noninvasive nature of ECGI makes it well-suited for follow-up repeated studies over time. In the context of electric substrate imaging, it could be used to assess the progression of substrate remodeling (eg, degree of electric heterogeneity of scar, steepness, and extent of dispersion of repolarization) and the consequences of interventions, such as ablation, reverse remodeling with CRT, or changes to the repolarization gradients attributable to drug therapy.

As explained in the Methods section, our approach to ECGI (reconstruction of epicardial potentials) limits solutions to the epicardial surface of the heart. This choice stems from several considerations. First, the solution can be validated by comparison with directly recorded raw data (as in the tank–torso experiments and intraoperative mapping studies), without additional data processing (eg, determination of activation times) that in itself could be a source of error. Second, extension to the endocardium or intramural myocardium requires additional assumptions that may not be consistent with properties of excitation in a given patient’s heart, thus biasing the results. Third, epicardial potentials contain information on intramural and endocardial activation even before the epicardium is activated. As we have demonstrated,\(^1\) from the evolving pattern of epicardial potentials and electrogram morphology (presence or absence of r-wave), the intramural depth of an ectopic arrest point on the QRS; it does not consider all other information that electrograms contain, including repolarization. In the context of electric substrate imaging with ECGI, reconstructing entire electrograms is of particular importance. As shown by the examples of this review, post-MI scar substrate is reflected in the electrogram magnitude, multiple deflections along its entire time course, and presence of delayed deflections (late potentials). Also, imaging the substrate of steep repolarization gradients requires reconstruction of repolarization and ARIs, not only activation.

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Noninvasive Electrocardiographic Imaging of Arrhythmogenic Substrates in Humans
Yoram Rudy

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