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The Electrophysiological Substrate of Early Repolarization Syndrome: Noninvasive Mapping in Patients

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Abstract

Background—The early repolarization (ER) pattern is a common ECG finding. Recent studies established a definitive clinical association between ER and fatal ventricular arrhythmias. However, the arrhythmogenic substrate of ER in the intact human heart has not been characterized.

Objectives—To map the epicardial electrophysiological (EP) substrate in ER syndrome patients using noninvasive Electrocardiographic Imaging (ECGI), and to characterize substrate properties that support arrhythmogenicity.

Methods—Twenty-nine ER syndrome patients were enrolled, 17 of which had a malignant syndrome. Characteristics of the abnormal EP substrate were analyzed using data recorded during sinus rhythm. The EP mapping data were analyzed for electrogram morphology, conduction and repolarization. Seven normal subjects provided control data.

Results—The abnormal EP substrate in ER syndrome patients has the following properties: (1) Abnormal epicardial electrograms characterized by presence of J-waves in localized regions; (2) Absence of conduction abnormalities, including delayed activation, conduction block, or fractionated electrograms; (3) Marked abbreviation of ventricular repolarization in areas with J-waves. The action potential duration (APD) was significantly shorter than normal (196 ± 19 vs. 235 ± 21 ms, $p < 0.05$). Shortening of APD occurred heterogeneously, leading to steep repolarization gradients compared to normal control (45 ± 17 vs. 7 ± 5 ms/cm, $p < 0.05$). Premature ventricular

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contractions (PVCs) were recorded in 2 patients. The PVC sites of origin were closely related to the abnormal EP substrate with J-waves and steep repolarization gradients.

Conclusions—Early Repolarization is associated with steep repolarization gradients caused by localized shortening of APD. Results suggest association of PVC initiation sites with areas of repolarization abnormalities. Conduction abnormalities were not observed.

CONDENSED ABSTRACT

Early repolarization syndrome (ERS) is associated with fatal ventricular arrhythmias. Its arrhythmogenic substrate in the intact human heart remains ill-defined. This paper reports the results of cardiac EP mapping using noninvasive Electrocardiographic Imaging (ECGI) in 29 ERS patients. The maps showed no evidence for delayed activation. However, there was marked abbreviation of ventricular repolarization in localized areas with J-wave epicardial electrograms, causing steep repolarization gradients. PVC initiation sites were closely related to areas of J-waves and repolarization abnormalities. These observations have implications to the diagnosis and mechanism-based therapy of ERS arrhythmias.

Keywords

early repolarization; sudden cardiac death; idiopathic ventricular fibrillation; mapping

Introduction

The early repolarization (ER) pattern on the ECG is characterized by a J-wave ≥ 0.1 mV in inferior and/or lateral leads (1). It resolves during exercise and fast pacing, but accentuates during bradycardia. The prevalence of ER pattern in the general population is estimated to range between 1% and 13% (2–3). It is thought to be more common in males, young athletes and people of African descent. For decades, the ER pattern was considered a benign ECG manifestation. Since the 1980s, this view has been challenged based on sporadic observations that linked the J-wave with ventricular arrhythmia (4–6). In a recent study with a large cohort of patients, the prevalence of ER pattern was significantly higher in patients with idiopathic ventricular fibrillation (VF) compared to control subjects (1). This was the first study that provided clinical evidence supporting a definitive association between the ER pattern and an increased risk of ventricular arrhythmia. Following this study, additional population-based studies provided corroborating evidence (2,7–9). The critical role of the ER pattern in initiating ventricular fibrillation has been supported by observations of a consistent and marked J-wave accentuation preceding the onset of arrhythmia (1,10) and by electrophysiology (EP) mapping data that suggested an association between the origin of ectopy that initiated VF and the location of repolarization abnormalities (1). Meta-analysis on 16 studies involving 334524 subjects suggests that the ER pattern is associated with an increased risk for sudden cardiac arrest, cardiac death, and death from any cause (11).

Studies in patients with ER syndrome (ERS) have been so far confined to investigation of the body-surface ECG characteristics and extrapolating possible mechanisms. However, ECG characteristics have been shown to be inadequate measures of underlying repolarization properties (12). Reports of invasive catheter mapping in patients with ERS

provide limited information about the abnormal EP substrate (1,13). Understanding the mechanism of ER and how it may predispose patients to an increased risk of arrhythmias requires detailed characterization of the EP substrate in the intact heart of ERS patients. Similarly, risk stratification for arrhythmia and differential diagnosis between benign and malignant ERS require noninvasive mapping of the EP substrate in individual subjects. Recent developments in noninvasive Electrocardiographic Imaging (12,14–21) (ECGI) have demonstrated its ability to obtain high-resolution panoramic EP data of epicardial activation, repolarization and their alteration by disease and interventions in humans (17–21). In the current study, we characterize the epicardial EP substrate in ERS patients based on high-resolution ECGI data obtained during sinus rhythm (SR), in an effort to provide insights into the substrate properties that support arrhythmogenicity in these patients.

Methods

Patient Population

ERS patients from Washington University and Bordeaux University Hospital were enrolled. The clinical diagnosis is ER pattern on the ECG, defined as an elevation of the J-point (J-wave) $>0.1\text{mV}$ in at least two contiguous leads. The J-wave is manifested either as QRS slurring or notching in the inferior lead, lateral lead, or both. The patients should have at least one of the following: idiopathic VF, unexplained syncope and familial incidence of unexplained sudden cardiac death. Patients with structural heart disease, coronary artery disease or other conditions, including long QT syndrome, short QT syndrome and Brugada syndrome (BrS) were excluded. All patients had structurally normal hearts and normal ventricular function. Data from seven healthy subjects provided normal control (14). These were healthy adults, ranging in age from 21 to 43 years. All control subjects had normal 12-lead ECG and no known history of heart disease. Protocols were approved by the Institutional Review Boards at both centers; written informed consent was obtained from all patients.

Noninvasive Mapping

During ECGI, body surface ECG potentials were acquired simultaneously from 256 electrodes using a multichannel data acquisition system (Biosemi, the Netherlands). Next, the patient underwent thoracic computed tomography (CT) with ECG-gating to obtain the epicardial geometry and torso electrode positions. Body surface potentials were baseline corrected and bandpass filtered (0.05–400 Hz) to remove high frequency noise and DC component. If necessary, a 60 Hz notch filter was applied to remove power-induced noise. The pre-processed signals and the patient-specific heart-torso geometry were processed with ECGI algorithms to reconstruct epicardial potentials, unipolar electrograms (EGMs), and maps of epicardial activation and repolarization. ECGI has been validated extensively in torso-tank and canine experiments, and in human studies. It provides high accuracy and high-resolution (4 to 6 mm) panoramic data for noninvasive evaluation of EP properties. In order to further evaluate ECGI's accuracy of determining ARI noninvasively in the in-situ heart of human subjects, an additional experiment was performed in patients undergoing cardiac surgery. In this experiment, epicardial electrograms were recorded with 240 evenly

distributed electrodes, mounted in an epicardial sock. Details of the validation method and results are provided in Section 1 of the Online Supplement.

Data Analysis

Characteristics of the abnormal EP substrate in ERS patients were analyzed by using data recorded during SR. The EP mapping data were analyzed for EGM morphology, conduction and repolarization. The J-wave on local epicardial unipolar EGM is defined as J point elevation of > 5% of peak-to-peak QRS amplitude. The area of the epicardium with J-waves on the EGMs was measured as a percentage of the total epicardial surface area. Conduction was evaluated by activation time (AT), activation duration (AD), EGM fractionation and voltage. AT was determined by the maximum negative slope of the EGM during QRS inscription (22–23). All ATs were referenced to the beginning of QRS in ECG lead II. Epicardial activation isochrone maps were created from ATs. AD was defined as the interval between the earliest and latest AT, considering all epicardial EGMs. Repolarization was assessed by recovery time (RT) and activation-recovery interval (ARI). Local RT was determined from the maximum positive slope of the EGM T-wave, which reflects the sum of local AT and local action potential duration (APD) (22–23). Steep RT dispersion has been shown to provide substrate for unidirectional block and reentry. ARI was defined as the difference between RT and AT. ARI is independent of AT and a surrogate for local APD (23). From the RT map and ARI map, epicardial dispersion of repolarization was measured as the maximum difference RT and ARI between two adjacent EGM sites on the epicardium. Epicardial RT and ARI gradients (RT/x and ARI/x) were computed through division by the distance x between the two adjacent sites.

Statistical Analysis

All continuous data are presented as mean±SD. Continuous variables were analyzed by unpaired t-test. The Satterthwaite modified t-test was used for variables with unequal variances. The Mann-Whitney U test was used for variables with non-normal distribution. To account for potential influences of combining subjects from two health care systems on the results, we applied a multivariable linear regression model with two independent, dichotomous variables: study group (normal/ERS) and health care system (Washington University/Bordeaux University). All tests with $P<0.05$ were considered statistically significant. Statistical analysis was performed by using SPSS v19.

Results

Twenty-nine ERS patients (26 men, 3 women) were enrolled in this study. Seventeen (59%) had previous aborted SCD or arrhythmic events (idiopathic VF), 10 of which received implantable cardioverter-defibrillator (ICD). Fourteen (48%) experienced unexplained syncope. Ten (34%) had a family history of SCD or ERS. Detailed characteristics for individual patients are provided in Table 2 and 3 of the online supplement.

EGM Characteristics and Localization

Figure 1 shows epicardial EGM characteristics and localization for representative examples in 3 ERS patients. ECGI data for all patients are shown in the online supplement (Figure 8 to

36). Patient ER-11 was an asymptomatic patient with a family history of sudden death. He had ER pattern in lateral leads. Patient ER-14 experienced previously aborted sudden death, and had ER pattern in both inferior leads and lateral leads. Patient ER-20 did not have clinical arrhythmic events, but experienced unexplained syncope. His ER pattern was found in inferior leads. The 12-lead ECGs of these patients are provided in the online supplement (Figure 5 to 7). Data from a normal subject is provided for reference. Epicardial J-wave was observed in EGMs from all 29 ERS patients (0.68 ± 0.25 mV vs. 0 mV in control, $p < 0.05$); 8 in the anterior wall, 19 in the lateral wall and 23 in the inferior wall (most patients had epicardial J-wave in multiple locations). The proportion of epicardium that presented J-wave ranged from 23% to 57%, with a mean value of $39\% \pm 9\%$. EGMs with abnormal low-voltage and fractionation, indicative of slow discontinuous conduction, were not found in any ERS patient.

Epicardial Activation

Figure 2 shows ECGI epicardial activation isochrone maps for a control subject and 3 ERS patients (same patients as in Figure 1). The epicardial activation pattern during SR in ERS patients was characterized by a normal epicardial breakthrough (white asterisks) in the right ventricle (RV). The excitation wavefront spread uniformly and rapidly to activate both ventricles. The left ventricular (LV) base was the latest region to activate. The activation pattern was not affected by the presence of the J-wave; regions of slow conduction (isochrone crowding) or conduction block (adjacent activation times differ by more than 50 ms) were not found in ERS patients. A similar activation sequence was observed in the normal control subjects, as well as in the isolated human heart from individuals with no history of cardiac disease (24). AD, the time needed for activation of both ventricles, was 54 ± 7 ms for ERS patients, comparable with 47 ± 9 ms for normal control.

Epicardial Repolarization

Representative maps of RT (Figure 3) and ARI (Figure 4) from a normal subject and 3 ERS patients (same patients as in Figure 1) demonstrate marked local changes in repolarization in ERS patients compared with normal control. Abnormal repolarization was observed primarily in regions with a prominent J-wave. Steep epicardial RT gradients and ARI gradients occurred mostly at the border of regions where J-wave EGMs were present (Figure 3, Panel B–D, white arrows). Figure 4-E shows EGMs with prominent J-wave (location 1) and EGMs without J-wave from an adjacent location (location 2) for 3 ER patients. In patient ER-11 for example, ATs at location 1 and 2 were similar ($AT(1) = 66$ ms, $AT(2) = 61$ ms), but repolarization dispersion was observed between the two locations: RT was 65 ms ($RT(1) = 232$ ms, $RT(2) = 297$ ms) and ARI was 70 ms ($ARI(1) = 166$ ms, $ARI(2) = 236$ ms). This resulted in steep gradients of RT and ARI ($RT/x = 43$ ms/cm; $ARI/x = 46$ ms/cm), much steeper than those of control (typically 5–8 ms/cm and 4–10 ms/cm, respectively, in the same region). Patients ER-14 and ER-20 also had shortened RT and ARI, as well as increased gradients of RT and ARI, but the location of abnormal repolarization varied.

Table 1 summarizes the ECGI-derived parameters, adjusted for differences between the two participating centers. Compared with normal control, ERS patients had shortened RT (223 ± 28 vs. 265 ± 30 ms, $p < 0.05$) and ARI (196 ± 19 vs. 235 ± 21 ms, $p < 0.05$), increased

repolarization dispersion RT (52 ± 15 vs. 18 ± 14 ms, $p < 0.05$) and ARI (53 ± 15 vs. 16 ± 10 ms, $p < 0.05$), and increased repolarization gradients RT/x (48 ± 18 vs. 8 ± 6 ms/cm, $p < 0.05$) and ARI/x (45 ± 17 vs. 7 ± 5 ms/cm, $p < 0.05$). Table 4 of Online Supplement shows that there is no significant difference between health care systems for all parameters.

Ventricular Arrhythmias

Premature ventricular contractions (PVCs) were recorded in two patients, ER-1 and ER-11. Figure 5 shows substrate maps (J-wave and ARI) and PVC activation maps for patients ER-1 and ER-11. Panel A shows that in patient ER-1, a large portion of epicardium (54%) was affected by abnormal EGMs with J-waves, including anterior RV, anterior LV, lateral LV, apical LV and inferior LV (not shown). In patient ER-11, about 32% of the epicardium had J-waves in the EGMs, located in the antero-lateral and apical LV. Panel B shows that in patient ER-1, the anterior RV had the shortest ARI (about 140 ms), and the majority of LV had ARI less than 180 ms, significantly below the normal range. Patient ER-11 had shortened ARI (about 160 ms) in the antero-lateral and apical LV. Panel C shows the PVC activation patterns. In patient ER-1, the PVC originated from the apical LV region, then propagated towards the basal RV. In patient ER-11, the PVC initiation site was located in mid anterior LV near the septum. The inferior LV was the latest region to activate during a PVC. In both cases, locations of the EP substrate with J-wave EGMs, shortened ARIs and steep ARI gradients correlated with the PVC sites of origin.

Discussion

Based on studies in the canine ventricular wedge preparation (4), differences in the magnitude of the transient outward current, I_{to} , in epicardium and endocardium result in different configurations of the action potential (AP) phase-1 notch across the ventricular wall. The resulting AP transmural gradient is thought to be responsible for the J-wave on the ECG. Augmentation of a repolarizing current by mutation can result in accentuation of the AP notch and loss of the AP dome, leading to the development of arrhythmias due to a mechanism termed phase-2 reentry (4).

The clinical ERS phenotype is defined based on body-surface ECG morphologies. These include presence of a J-wave in the form of a positive deflection or slurring of the QRS waveform as it transitions to the ST segment. These late QRS characteristics could reflect delayed activation or early repolarization; these two possibilities cannot be differentiated from the body-surface ECG. The name Early Repolarization Syndrome was given based on a hypothesis, not on a confirmed underlying mechanism. Therefore, the first obvious question we tried to answer with ECGI was: are the ECG abnormalities in ERS patients due to delayed activation in regions of the ventricles, or indeed due to early regional ventricular repolarization. The high-resolution panoramic mapping was essential for characterizing the properties of the EP substrate and answering this question. The maps showed no evidence for delayed activation in any of the patients. J-waves were found in epicardial EGMs, indicative of the presence of voltage gradient during phase-1 of the AP at the EGM location, similar to J-waves recorded with pseudo-ECG leads from the ventricular wedge preparation. In contrast, J-waves in body surface ECG leads are not location specific, because each lead

records a signal that reflects integrated electrical activity over the entire heart. There was marked abbreviation of ventricular repolarization in areas with J-wave epicardial EGMs, suggesting that loss of the AP dome gave rise to transmural voltage gradient at the EGM location. The results are consistent with observations of a recent experimental study (25) and provide evidence in support of the early repolarization mechanism in patients.

Figure 3 and 4 demonstrate that there is significant regional abbreviation of the AP (based on reconstructed ARIs) on the ventricular epicardium of ERS patients compared with normal control. As shown in Figure 4-E, in regions with abnormal EGMs, the epicardial J-wave is followed by shortening of RT. These regions were located in close proximity to regions with relatively longer RT. The regional differences in RT gave rise to steep repolarization gradients. Given the fast and uniform conduction, the difference in ATs between two adjacent locations is too small to account for the difference in RTs. Thus, RT and RT dispersion are primarily determined by ARI and ARI dispersion, independent of conduction. With ARI being the surrogate for local APD, shortened ARI suggests abbreviated AP. The formation of regions with steep gradient of repolarization is caused by spatially heterogeneous abbreviation of the AP over short distances. In contrast, the apex-to-base ARI dispersion (about 42 ms) and inter-ventricular ARI dispersion (about 32 ms) result in much shallower gradients in normal subjects (14). Results from this study are consistent with a previous case report that presented preliminary data from 2 ERS patients mapped by ECGI (19).

Since the establishment of a link between the ER pattern on the ECG and fatal cardiac arrhythmias (1), numerous studies have been conducted in an effort to stratify risk of ventricular arrhythmias in patients with the ER pattern. Risk stratification in this population is of clinical importance, given the prevalence of the ER pattern in the general population. Importantly, young otherwise healthy individuals with ER may have increased vulnerability to idiopathic VF. Surface ECG markers, including the amplitude and distribution of the J-wave, morphology of the ST segment and the presence of ventricular ectopy have very limited success in risk stratification, although they have been shown to associate with arrhythmic risk in patients presenting with unexplained syncope (2,8–9,26–27). A recent study investigated the role of invasive EP studies in risk stratification in ERS patients (28). Results indicate that VF inducibility does not have a role in risk stratification in ERS patients; it neither predicts arrhythmic risks, nor correlates with the ECG markers listed above. Better understanding of the EP substrate and a capability for its noninvasive mapping can help with the development of effective diagnostic and risk stratification approaches. We will examine this possibility with ECGI in a future study. ER and BrS are often collectively referred to as “J-wave syndromes”, because the two conditions share similar ECG characteristics and a number of clinical features. Both are associated with vulnerability to VF in young adults without apparent structural heart disease, and have a higher prevalence in males than females (29). The J-wave and associated ST-segment elevation are accentuated before the arrhythmic event, and VF is often initiated during bradycardia. Their responses to quinidine and isoproterenol are ameliorative (normalization of the J-wave and inhibition of VF) (25,30). Nevertheless, there are several key characteristics that distinguish ERS from BrS, suggesting different underlying mechanisms for the ECG phenotype and arrhythmogenesis. Moderate structural abnormalities (RV interstitial derangement), though

undetectable by noninvasive clinical imaging, have been found in endomyocardial biopsies of BrS patients (31). In a recent study, ECGI was performed in 25 BrS patients (20). Altered or delayed epicardial activation in the RVOT was found in 20 patients. EGMs with abnormally low voltage and fractionation were found in all patients. The abnormal EGMs in the setting of BrS can reflect slow discontinuous conduction, as well as abnormal repolarization as demonstrated in a recent experimental study (32). Prolonged repolarization and steep repolarization gradients were also observed. These findings demonstrate the coexistence of conduction and repolarization abnormalities in BrS. The abnormal EP substrate was confined to the RVOT. In contrast, the wide-spread distribution of J-waves in ERS patients indicates that the EP substrate may not be localized to a specific region of the heart. The current study identifies additional differences between ERS and BrS. Conduction delays and EGMs indicative of slow discontinuous conduction were not found in ERS patients. The location and size of the abnormal EP substrate varied among ERS patients. Instead of ARI prolongation in BrS patients, shortened ARIs were observed in ERS patients during SR.

There is a paucity of EP mapping data of ERS-related arrhythmias, given the small number of ERS patients who have experienced aborted sudden cardiac death. Catheter mapping was performed in 8 ERS patients with a history of idiopathic VF (1). In 6 patients with ER pattern only in the inferior ECG leads, all ectopies were mapped to the inferior ventricular wall. In 2 patients with ER pattern in both inferior and lateral leads, ectopy originated from multiple locations. In the current study, PVCs were recorded in 2 patients. The PVC sites of origin were located in an epicardial region with marked J-waves, short ARIs and steep ARI gradients. Proximity of areas with steep ARI gradients to PVC sites of origin supports the hypothesis that reactivation of early-repolarizing cells by local currents could generate the ectopy (33). The timing of the J-wave did not change before the onset of PVC compared to baseline SR beats and beats following the PVC. In addition, the T-wave morphology of the preceding SR beat was not altered prior to the PVC. This suggests lack of or minimal coupling between the J-wave and PVC, consistent with the view that the J-wave is a marker of steep phase-1 repolarization gradients (30,33). The localization of the PVC origin in regions with steep repolarization gradients suggests that local PVC initiation could be a trigger of reentrant arrhythmia. A recent study using ECGI in an ERS patient during VF identified rotors in the inferior-lateral LV wall (26).

Limitations

The control data were not obtained at the time of this study; they were recorded previously with the same ECGI methodology. The ability to generalize the results and draw a quantitative conclusion regarding ECGI sensitivity in detecting and localizing J-waves is limited by the relatively small number of 29 patients.

In this first study, not all patients had a malignant form of ERS. Subjects with ECG ER pattern and a broad spectrum of evidence for arrhythmogenic substrate (idiopathic VF, syncope, family history of sudden cardiac death) were included. ER subjects without evidence of arrhythmogenesis in them or their family were excluded. Properties of the abnormal EP substrate (J-wave EGMs and regional APD shortening with steep

repolarization gradients) were consistent across the patient population. Future large-scale studies are needed to differentiate between subgroups (e.g. based on symptoms and genotype) and to establish the potential of ECGI for noninvasive diagnosis and risk stratification in ERS patients.

Changes in heart rate are known to affect the ER pattern on the ECG, but the present study was conducted only at resting heart rate. Similarly, several drugs (including quinidine, isoproterenol, milrinone, and cilostazol) have been shown to have ameliorative effects on the ER pattern. It will be constructive to characterize the effects of increased heart rate and of these drugs on the EP substrate in terms of spatial repolarization patterns and dispersion in future studies using ECGI.

It is well established that the J-point amplitude increases significantly at the onset of an arrhythmic event. However, polymorphic VT or VF was not recorded during ECGI in any of the patients in this study. The two patients (ER-1 and ER-11) in Figure 5 had isolated PVCs that were not followed by VT. The study characterizes the EP substrate and records isolated PVCs, but does not provide direct recordings of VT in ERS patients.

ECGI can reconstruct epicardial dispersion of repolarization. Experimental studies (25) have shown that in addition to markedly elevated epicardial dispersion of repolarization, transmural dispersion of repolarization is an important component of the arrhythmogenic substrate. However, transmural dispersion of repolarization throughout the heart cannot be measured directly with ECGI.

Conclusions

Noninvasive ECGI revealed the presence of abnormal EP substrate in ERS patients, characterized by spatially heterogeneous APD shortening, steep repolarization gradients, and regional distribution of J-wave EGMs on the epicardium. Steep repolarization gradients provide a substrate that is susceptible to the development of asymmetrical conduction and reentrant arrhythmias. Conduction abnormalities in the form of slow conduction or conduction block were not present. PVC sites of origin co-localized to the regions of J-wave presence and steep repolarization gradients mapped during SR.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

AD	Activation Duration
APD	Action Potential Duration
ARI	Activation-Recovery Interval
AT	Activation Time
BrS	Brugada Syndrome
CT	Computed Tomography
ECGI	Electrocardiographic Imaging
EGM	Electrogram
EP	Electrophysiology
ER	Early Repolarization
ERS	Early Repolarization Syndrome
ICD	Implantable Cardioverter-Defibrillator
LV	Left Ventricle
PVC	Premature Ventricular Contraction
RT	Recovery Time
RV	Right Ventricle
SR	Sinus Rhythm
VF	Ventricular Fibrillation

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Perspectives

Competency in Medical Knowledge

The arrhythmogenic substrate of early repolarization syndrome (ER) in the intact human heart has not been characterized. Noninvasive EP mapping with ECGI demonstrates that ER is associated with localized shortening of the action potential duration, giving rise to steep repolarization gradients that provide a substrate for reentrant arrhythmia.

Translational Outlook

Being noninvasive, ECGI is a promising tool for arrhythmic risk stratification in ER patients based on EP substrate properties; this possibility requires evaluation in a larger study. With its single-beat mapping capability, ECGI could be used to locate the origin of frequent arrhythmic PVCs for possible intervention.

Epicardial J-wave Distribution and Magnitude

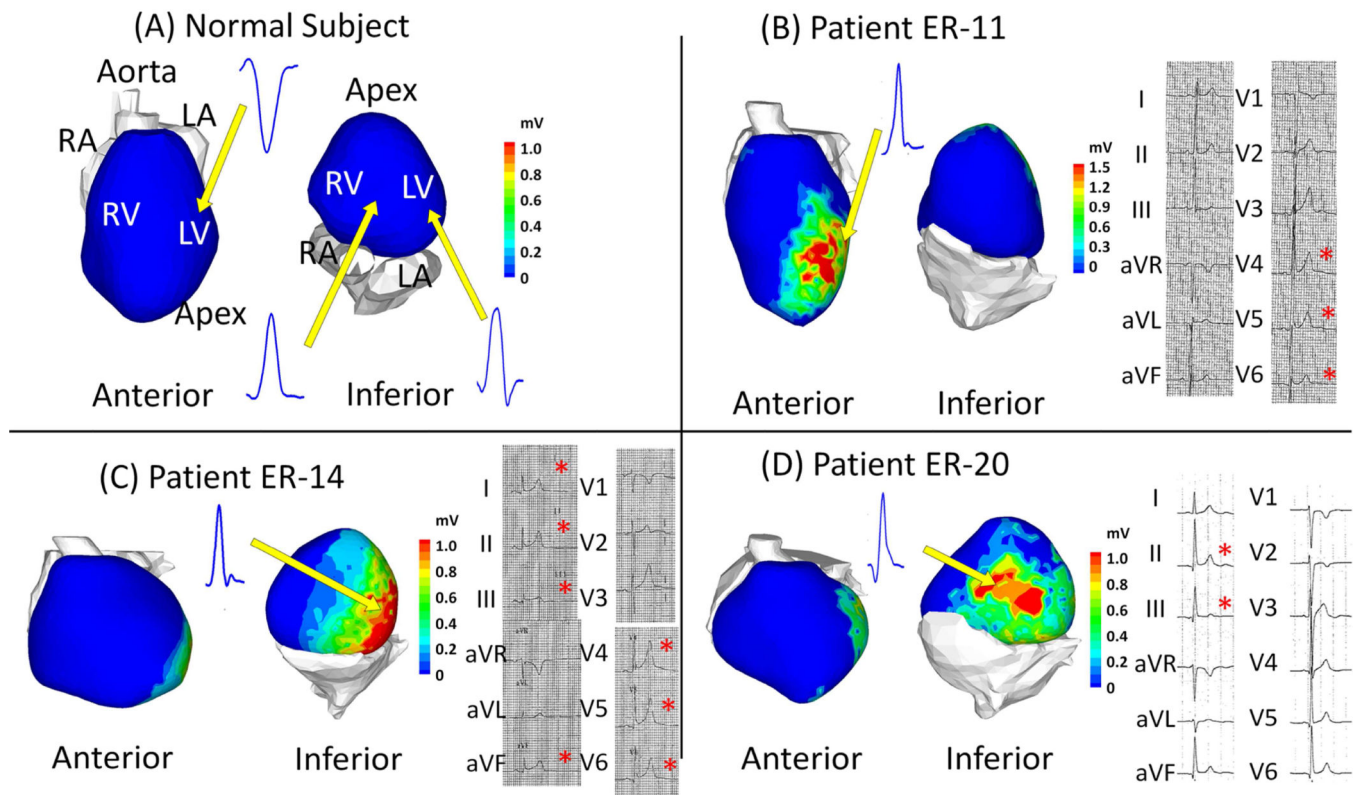


Figure 1. Epicardial J-wave Distribution and Magnitude

Abnormal epicardial EGMs with a J-wave that resemble the ER pattern (terminal-QRS notch or slurring) on the surface ECG are observed in ERS patients, but not seen in normal subjects. Example maps of epicardial J-wave magnitude in 3 ERS patients are shown. The maps are shown in anterior view and inferior view for each subject. The locations of epicardial J-waves are ER-11: lateral and apical left ventricle (LV); ER-14: lateral and inferior LV; ER-20: lateral and inferior LV. Inset: representative EGMs with a J-wave (QRS only) in ERS patients (Panels B, C, D) and EGMs from corresponding locations in the normal control subject (Panel A). 12-lead ECGs for ERS patients are shown to the right of the epicardial maps. A red asterisk indicates the presence of early repolarization pattern. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

Sinus-Rhythm Activation Isochrone Map

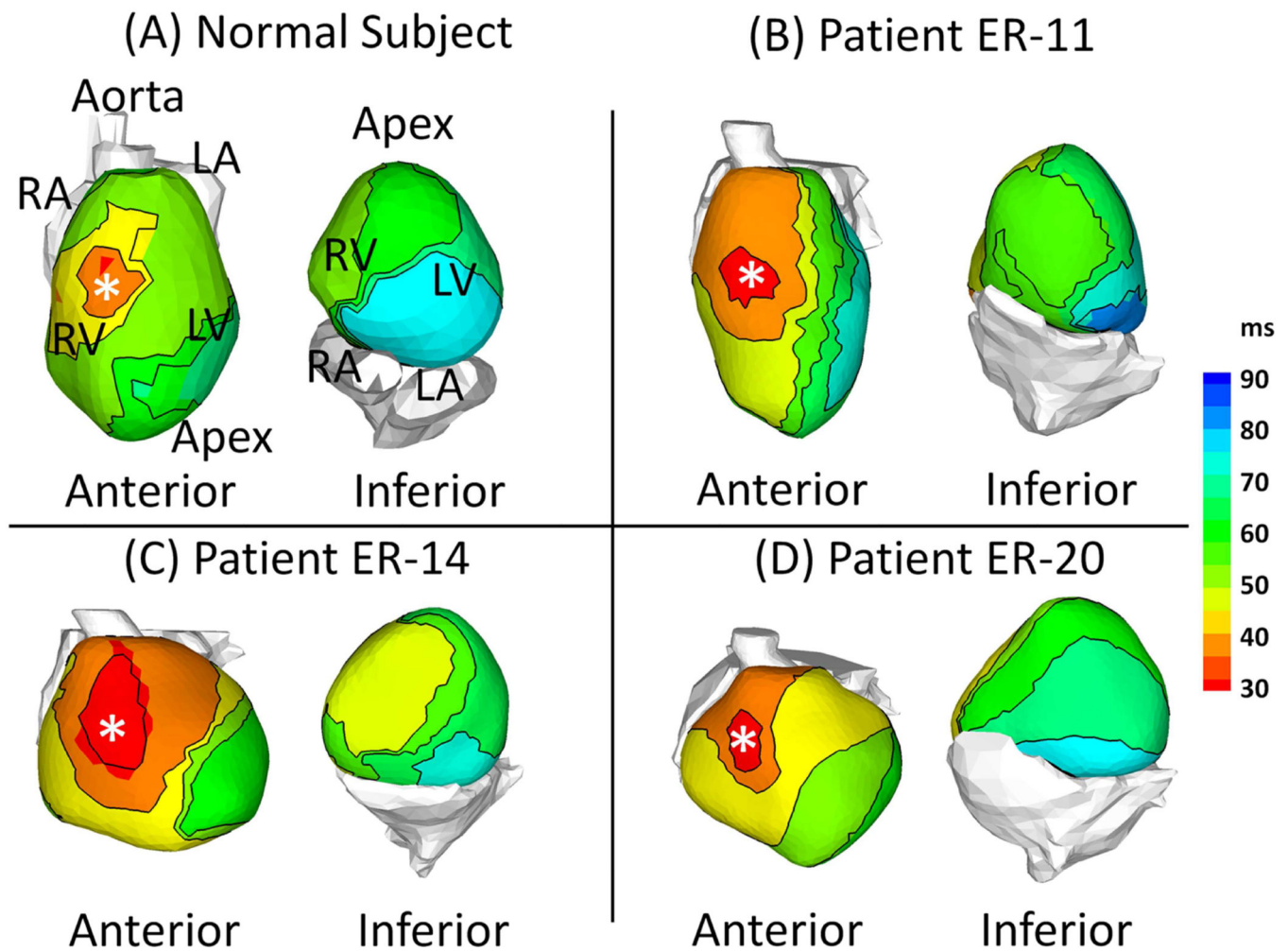


Figure 2. Activation Isochrone Maps

Examples of activation during sinus rhythm (SR) are shown for a normal control subject and 3 ERS patients. The maps are shown in anterior view and inferior view for each subject. ERS patients and the normal subject have similar activation patterns. After breakthrough in the anterior right ventricle (asterisk), the wavefront propagates uniformly to activate both ventricles. The LV base is the latest region to activate. Conduction block and slow conduction were not observed in the ERS patients.

Sinus-Rhythm Recovery Time Map

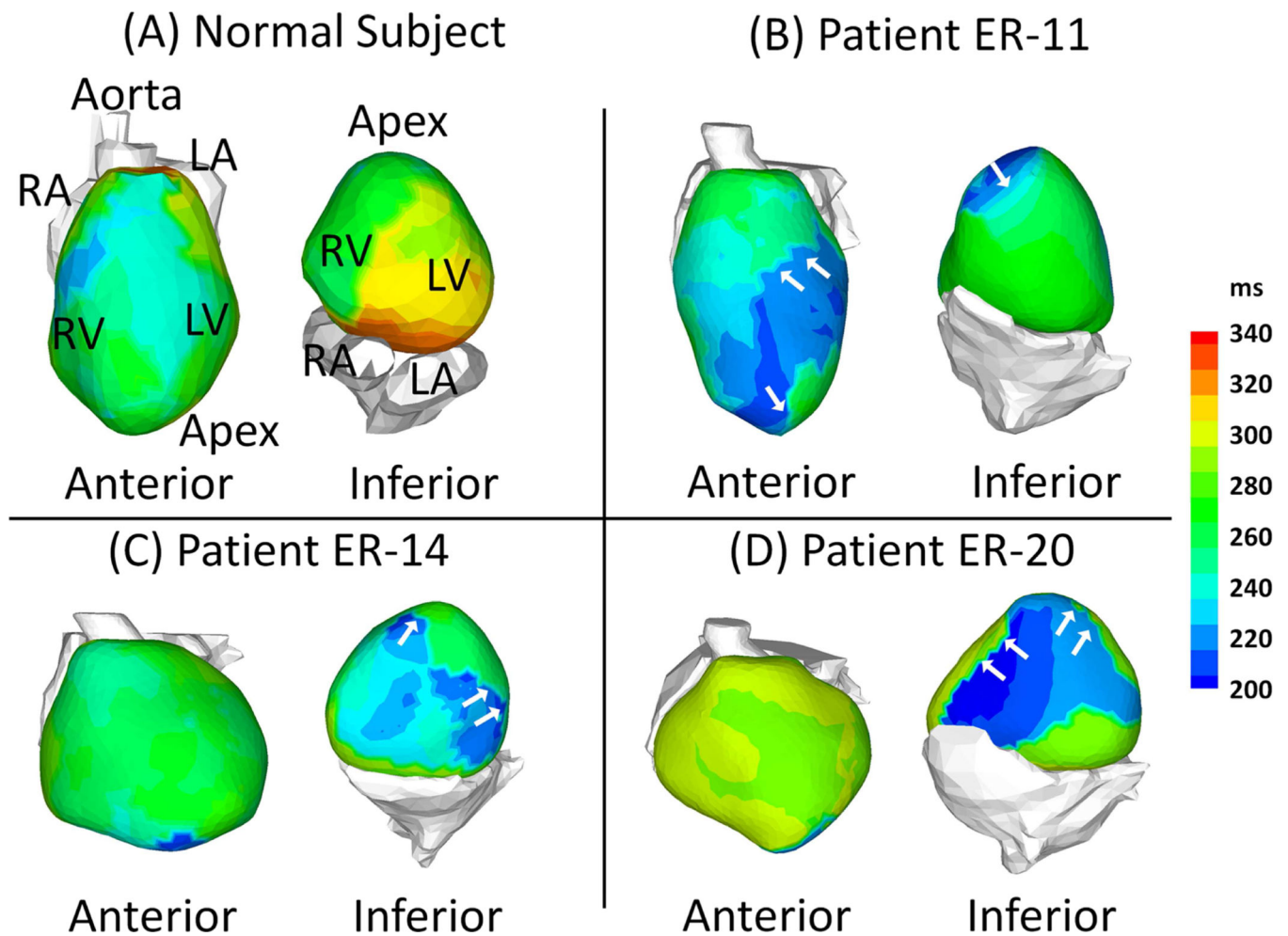


Figure 3. Recovery Time (RT) Maps

Examples of epicardial RT during SR are shown for a normal control subject and 3 ERS patients. Maps are shown in anterior view and inferior view for each subject. ERS patients have regions with abnormally short RT (dark blue). White arrows in Panels B-C point to regions with steep RT gradients.

Sinus-Rhythm Activation-Recovery Interval Map

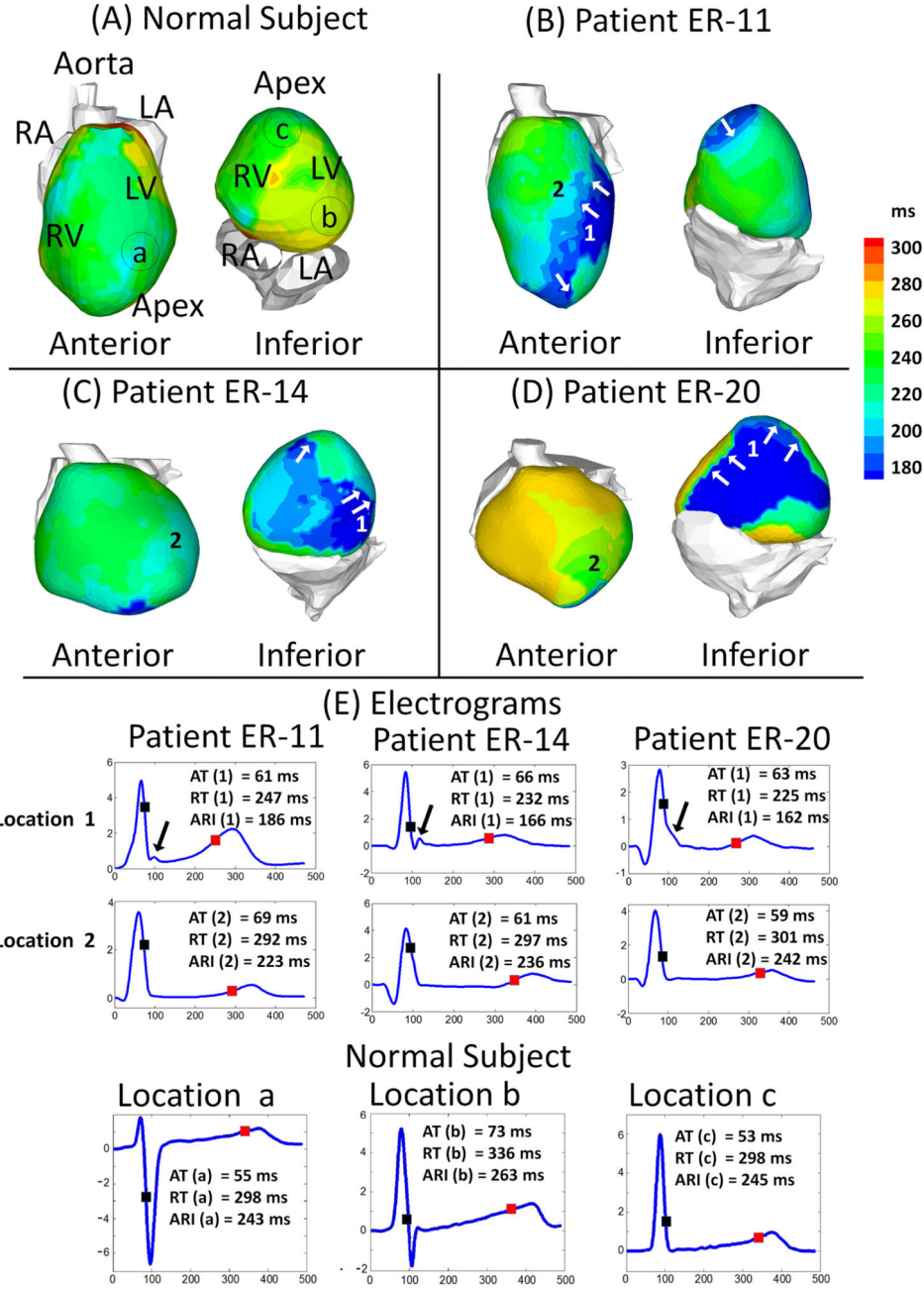


Figure 4. Activation-recovery Interval (ARI) Maps

Panels A to D: ARI maps for a normal control subject and 3 ERS patients. Maps are shown in anterior view and inferior view for each subject. ERS patients have regions with abnormally short ARI (dark blue). White arrows in Panels B-C point to regions with steep ARI gradients. Top two rows of Panel E show ECGI reconstructed electrograms (EGMs) from two adjacent location in each ERS patient. Location 1 (top row): prominent J-wave and short ARI; location 2 (middle row): absence of J-wave and normal ARI. There is a steep gradient of repolarization across these two locations. Bottom row of Panel E shows 3 EGMs

from the normal subject, from locations marked in Panel A. The time instances of activation (AT; black square), recovery (RT; red square) and corresponding ARIs are indicated.

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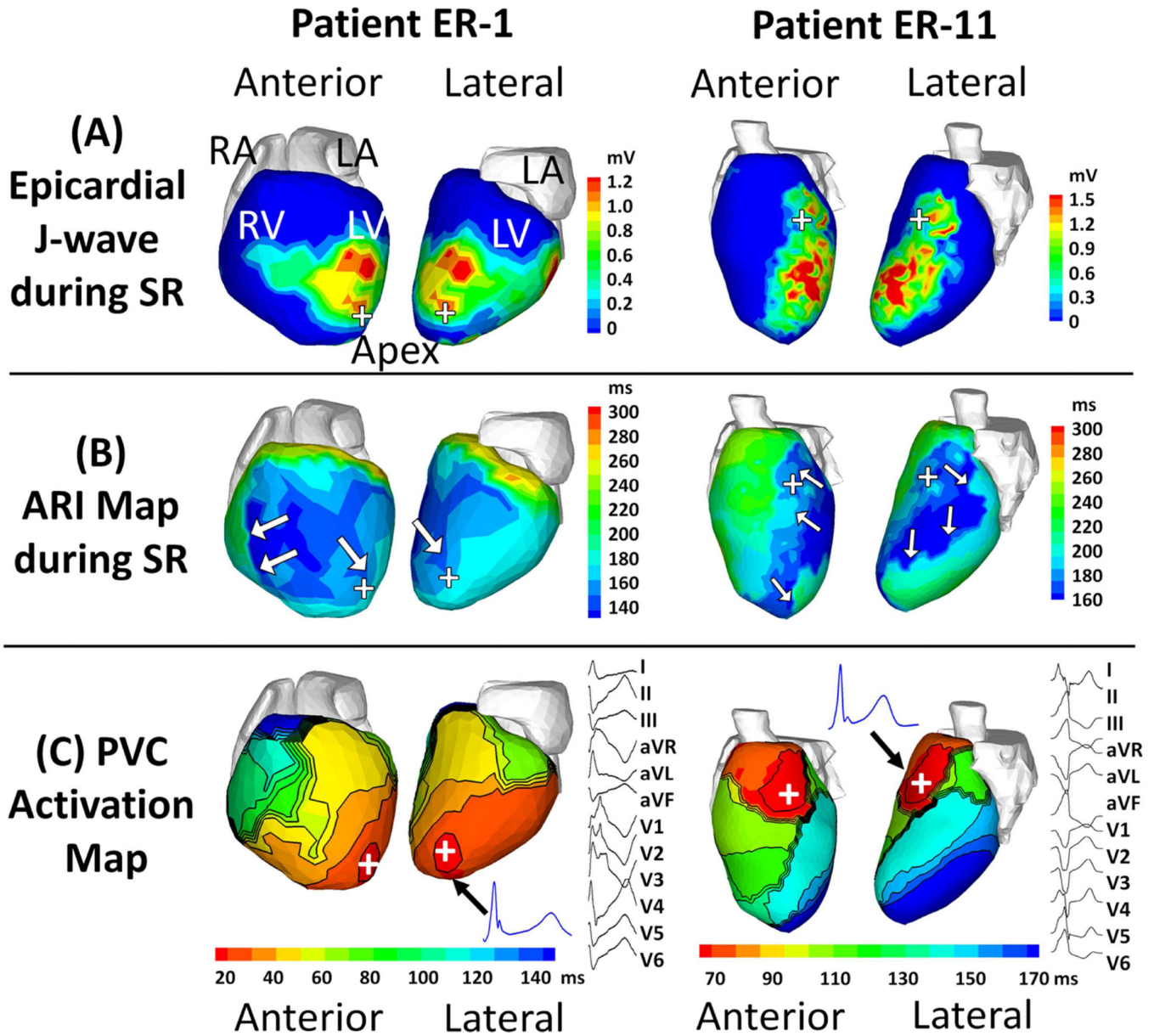


Figure 5. The electrophysiological substrate in relation to premature ventricular contractions (PVCs)
 (A) Epicardial J-wave magnitude and (B) Activation-recovery interval (ARI) maps during sinus rhythm (SR). (C) PVC activation map and 12-lead ECG. Each panel shows maps for 2 patients, ER-1 (left, PVC coupling interval =635 ms) and ER-11 (right, PVC coupling interval = 520 ms). The hearts are displayed in anterior and lateral views. White arrows in Panels B point to regions with steep ARI gradients. In panel C, J-wave electrograms (EGMs) from the PVC site of origin are shown (black arrow); 12-lead ECG depicting the PVC is shown to the right of the map. The PVC initiation sites are indicated by plus signs “+”. Note that an EP substrate with abnormal EGMs, shortened ARIs and steep ARI gradients correlated with the PVC site of origin in both cases.

Table 1

Comparison of ECGI Parameters between ERS Patients and Normal Subjects

Parameters	Normal Control (N=7)	ERS Patients (N=29)
J-wave Magnitude (mV) *	0	0.68±0.25
AD (ms)	47±9	54±7
Mean RT (ms) *	265±30	223±28
RT (ms) *	18±14	52±15
RT/ x (ms/cm) *	8±6	48±18
Mean ARI (ms) *	235±21	196±19
ARI (ms) *	16±10	53±15
ARI/ x (ms/cm) *	7±5	45±17

* : P<0.05

AD = Activation Duration; ARI = Activation-Recovery Interval; ERS = Early Repolarization Syndrome; RT = Recovery Time; ARI = ARI Dispersion; ARI/ x = ARI Gradient; RT = RT Dispersion; RT/ x = RT Gradient.