Quantitative Assessment of the Effects of Therapeutic Hypothermia on Early Repolarization in Idiopathic Ventricular Fibrillation Survivors

A 7-Year Cohort Study

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Background—The early repolarization (ER) pattern on ECG is associated with an increased risk of idiopathic ventricular fibrillation (ID-VF). Hypothermia is known to result in similar electrocardiographic changes. In this retrospective cohort study, we examine the impact of therapeutic hypothermia on ER in survivors of cardiac arrest attributed to ID-VF and draw comparisons with a control group who experienced coronary artery disease–related VF (CAD-VF).

Methods and Results—All patients who had cardiac arrest and were treated with therapeutic hypothermia over a 7-year period were considered for inclusion in the study. Forty-three patients were identified with ID-VF or CAD-VF arrest. ECGs were obtained during cooling and again after rewarming. ECGs were digitized and assessed for the presence of ER by 2 independent observers. Cooling significantly increased the prevalence (74% during cooling versus 51% at baseline temperature; \( P=0.044 \)) and mean amplitude (0.78±0.10 mV during cooling versus 0.56±0.09 mV at baseline temperature; \( P=0.038 \)) of ER in the overall cohort. During cooling, ER was more common among survivors of ID-VF than of CAD-VF (100% versus 67%; \( P=0.043 \)). ER magnitude was significantly greater among ID-VF survivors than CAD-VF survivors both during cooling (1.16±0.18 versus 0.70±0.11 mV; \( P=0.044 \)) and at baseline temperature (1.02±0.21 versus 0.42±0.09 mV; \( P=0.005 \)).

Conclusions—Hypothermia increases both the prevalence and magnitude of ER in cardiac arrest survivors. Despite the association of ER with ID-VF, therapeutic hypothermia only increases ER amplitude in CAD-VF survivors. (Circ Arrhythm Electrophysiol. 2014;7:120-126.)

Key Words: arrhythmias, cardiac death, sudden, cardiac hypothermia, paroxysmal ventricular fibrillation ventricular fibrillation

Early repolarization (ER) is a common electrocardiographic finding, being seen in 5% to 13% of Europeans.2 Although long thought to be a benign variant or even a marker of cardiovascular health, robust data now point to such changes as a marker of elevated risk of ventricular fibrillation (VF) and cardiac arrest. This is true in both otherwise healthy individuals (so-called idiopathic [ID]-VF)3,5,7 and in those with coronary artery disease (CAD).6,10 Risk seems to vary markedly with the degree of ER, quantified as the magnitude of J-point elevation (JPE). Thus, patients with a JPE magnitude >0.2 mV are at about twice the risk of cardiac arrhythmic death as compared with those with JPE defined using a more conventional cut-off of ≥0.1 mV.1 Furthermore, patients with ER who have experienced an episode of ID-VF have a mean JPE magnitude of around twice that seen in those without arrhythmia.11

Clinical Perspective on p 126

ER syndrome is one of a broader set of conditions, including the Brugada syndrome, collectively termed the J-wave syndromes.12 These conditions are defined by an elevation of the J-point, slurring of the terminal part of the QRS complex, and ST-segment elevation. All seem to be attributable to a similar ionic mechanism: an enhanced net repolarizing
current gives rise to a marked epicardial action potential notch and hence a J-wave. The resulting transmural dispersion of repolarization leads to an increased propensity to ventricular arrhythmia. Such J-waves are also a well-established feature of hypothermia. Although similarities and differences to investigate the potential interactions between ER and hypothermia have not previously been studied in a clinical context.

In this study, we hypothesized that therapeutic hypothermia (defined as core temperature of 33°C–36°C) would have a greater effect on the magnitude of JPE in ID-VF than in CAD-related VF (CAD-VF) arrest survivors. We, therefore, used data obtained from a population of adult early survivors treated with therapeutic hypothermia after cardiac arrest to investigate the potential interactions between ER and hypothermia.

Methods

All survivors of sudden cardiac arrest with an initial rhythm of VF treated at the critical care unit at St Thomas’ Hospital between 2005 and 2012 were assessed for inclusion. Data collection and analysis for this study were part of ongoing real-time data collection processes during physician-directed patient care.

Patient Selection

Cases were eligible for inclusion if: (1) their management included therapeutic hypothermia; (2) ECGs obtained at baseline temperature and during cooling were available; and (3) sufficient data (echocardiograms, coronary angiograms, cardiac MRI studies, or electrophysiology studies) were available to determine whether the arrest was attributable to myocardial ischemia. Cases were excluded if ventricular conduction abnormalities, other underlying arrhythmic disorders, or clear confounding factors, such as recent cardiothoracic surgery or cocaine use, were present.

Cases were classified as ID-VF if criteria specified in guidelines were met, that is, there was no structural heart disease (as indicated by an echocardiogram showing normal biventricular dimensions and function), no CAD (as indicated by a normal coronary angiogram), and no known repolarization abnormalities. Cases were classified as CAD-VF if (1) there was a pre-existing diagnosis of CAD; or (2) significant CAD was demonstrated on an angiogram, a significant troponin rise from baseline was observed, and regional wall motion abnormalities were present either on echocardiography or MRI.

Data Collection and Analysis

ECGs were obtained close to the midpoint of the period of therapeutic hypothermia (cooled ECG), during which patients’ core temperatures fell to between 32°C and 34°C, and again before discharge (baseline ECG). Records were digitally scanned (300 dpi, 24-bit color) and read at ×4 magnification by 2 independent observers. ECGs (ECGs) obtained at baseline temperature and during cooling were available; and (3) sufficient data (echocardiograms, coronary angiograms, cardiac MRI studies, or electrophysiology studies) were available to determine whether the arrest was attributable to myocardial ischemia. Cases were excluded if ventricular conduction abnormalities, other underlying arrhythmic disorders, or clear confounding factors, such as recent cardiothoracic surgery or cocaine use, were present.

Cases were classified as ID-VF if criteria specified in guidelines were met, that is, there was no structural heart disease (as indicated by an echocardiogram showing normal biventricular dimensions and function), no CAD (as indicated by a normal coronary angiogram), and no known repolarization abnormalities. Cases were classified as CAD-VF if (1) there was a pre-existing diagnosis of CAD; or (2) significant CAD was demonstrated on an angiogram, a significant troponin rise from baseline was observed, and regional wall motion abnormalities were present either on echocardiography or MRI.

Table 1. Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>ID-VF (n=10)</th>
<th>CAD-VF (n=33)</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
<td>42.9±4.7</td>
<td>61.5±2.3</td>
<td>0.0004*</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>8 (80%)</td>
<td>31 (94%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Women</td>
<td>2 (20%)</td>
<td>2 (6%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (10%)</td>
<td>14 (42%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0 (0%)</td>
<td>11 (33%)</td>
<td>0.043*</td>
</tr>
<tr>
<td>Pre-existing CAD (previous MI or stent)</td>
<td>0 (0%)</td>
<td>11 (33%)</td>
<td>0.043*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0 (0%)</td>
<td>5 (15%)</td>
<td>0.320</td>
</tr>
<tr>
<td>Family history of ischemic heart disease</td>
<td>0 (0%)</td>
<td>2 (6%)</td>
<td>1.000</td>
</tr>
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</table>

*Statistical significance.
In contrast, JPE of magnitude $\geq 0.1$ mV was present significantly more frequently in the ID-VF group than in the CAD-VF group at baseline (70.0% versus 27.3%; Figure 2C), but the significance threshold was not met during cooling (80.0% versus 42.4%; Figure 2D). Finally, there was no significant difference in the prevalence of ER between ID-VF and CAD-VF at baseline (20.0% versus 3.0%) or during cooling (40.0% versus 15.2%) when defining ER with JPE magnitude $>0.2$ mV (Figure 2E and 2F). Cooling was not associated with the de novo development of ER in patients with either ID-VF (8 of 10 versus 10 of 10; $P=0.480$) or CAD-VF (14 of 33 versus 22 of 33; $P=0.061$) arrest.

**Temperature-Dependent Amplitude of JPE**

Mean and maximum JPE amplitude were significantly greater among patients in the ID-VF group, as compared with the CAD-VF group, both at baseline and during cooling.
Maximum, but not mean, JPE magnitude increased significantly on cooling in the ID-VF group (Figure 4A). Both mean and maximum JPE magnitude increased on cooling in the CAD-VF group (Figure 4B). There was no difference in the proportion of patients in the ID-VF group as compared with the CAD-VF group in whom JPE magnitude increased on cooling (6 of 10 versus 16 of 33; \( P = 0.72 \) for mean; 9 of 10 versus 18 of 33; \( P = 0.063 \) for maximum). Similarly, there was no difference in the magnitude of increase in either mean or maximum JPE on cooling between the groups (\( \Delta \)JPE; Table 2).

**QRS Duration and QTc Intervals**

QRS duration and QTc interval increased significantly on cooling in both the ID-VF and CAD-VF groups (Table 3). There were no differences in QRS duration or QTc interval between ID-VF and CAD-VF groups either during cooling or at baseline (all \( P > 0.20 \)).

**Discussion**

The main findings of this study are as follows. (1) Overall, ER was more common and of greater amplitude during cooling than at baseline. (2) ER amplitude was significantly greater in survivors of ID-VF arrest than survivors of CAD-VF arrest at all temperatures. (3) Although the prevalence of ER was not significantly increased in either group on cooling, mean JPE was increased by cooling only in survivors of CAD-VF arrest.

In recent years, robust population-based studies have established an association between the ER pattern and VF, whether idiopathic in nature or secondary to ischemia. At the same time, the tendency for hypothermia to result in similar electrocardiographic changes is well established. Furthermore, in isolated cases, therapeutic hypothermia itself has been described as potentially proarrhythmic. The now common use of therapeutic hypothermia after cardiac arrest presents an important opportunity to examine systematically the impact of cooling on ER morphology in patients who have either ID-VF or CAD-VF. This retrospective cohort study, therefore, assessed the impact of therapeutic hypothermia on the prevalence, morphology, and
Magnitude of ER in all VF patients receiving therapeutic hypothermia at our critical care unit over a 7-year period.

Several differences exist between this cohort and previously published descriptions of ER. First, the overall frequency of ER in our study population is rather higher than that reported elsewhere. At baseline temperature, 51% showed morphological ER. Even limiting to those patients with JPE ≥0.1 mV, a widely accepted definition, the overall prevalence of ER in this cohort at baseline was still 37.2%. This prevalence is substantially higher than that seen in the European population overall (5%–13%) and also markedly higher than that described in a recent study by Rolfast et al22 on patients (3%) who had cardiac arrests attributable to a variety of causes. The former likely reflects the high-risk nature of patients in our study population, and the latter reflects differences in the underlying causes for VF between our cohort and that reported in Rolfast et al. During cooling, 74% of our study population showed the ER pattern (51.2% at 0.1 mV JPE threshold). The prevalence of ER is well established to vary with core temperature; case series of patients with accidental hypothermia suggest that, given the relatively mild degree of hypothermia used in a therapeutic setting, the prevalence of ER would be expected to be close to zero.23,24 Rolfast et al22 reported a 30% prevalence in their study population during cooling.

Second, similarities and differences emerge between patients whose arrest was attributable to ID-VF as compared with CAD-VF. Perhaps unsurprisingly, patients who had an episode of ID-VF were younger and apparently healthier than those who experienced CAD-VF. There were no differences in QRS duration or QTc between the groups, though both parameters increased significantly on cooling. The latter finding has previously been established,25 with increased QTc being described in the context of therapeutic hypothermia.22 The ER pattern was more common among survivors of ID-VF, as compared with CAD-VF, during cooling, though not at baseline temperature. Furthermore, JPE was of a greater magnitude in patients with ID-VF at both temperatures studied. Large-magnitude JPE was seen more frequently among patients with ID-VF. This finding reached significance at baseline temperature but became less marked with the compounding influence of cooling. These observations are in keeping with a previous suggestion that the presence of ER in patients resuscitated after cardiac arrest is suggestive of a nonischemic cause and that large-magnitude JPE is associated with a particularly high risk of ID-VF.1,25

The present study was intended to discern differences in response to cooling between patients with ID-VF and CAD-VF. In this regard, we note that cooling-related increases in JPE were significant in the CAD-VF group but not the ID-VF group. It is tempting to speculate that this surprising finding is attributable to differences in the specific ion channel disruptions giving rise to ischemic or idiopathic ER. On one hand, ischemic ER is most likely attributable to the local activation of ATP-sensitive K+ currents by ischemic mediators.23,24 Hypothermia is generally also thought to produce ER as a result of the activation of K+ currents, most importantly the transient outward current.27 On the other hand, idiopathic ER may arise as a result of dysfunction of one

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<td></td>
</tr>
<tr>
<td>Mean</td>
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<tr>
<td>ΔJPE</td>
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<td>Maximum</td>
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CAD-VF indicates coronary artery disease–related ventricular fibrillation (VF); ID-VF, idiopathic VF; and JPE, J-point elevation. *Statistical significance.

Figure 4. J-point elevation (JPE) among patients with ID-VF and CAD-VF at baseline temperature and during hypothermia. Mean (circles) and maximum (triangles) JPE at normothermia and during cooling in (A) ID-VF and (B) CAD-VF cases are shown as individual data points. Baseline/normothermic ECGs were obtained after rewarming after the period of therapeutic hypothermia. CAD-VF indicates coronary artery disease–related ventricular fibrillation (VF); and ID-VF, idiopathic VF. *Indicates statistical significance.
of several depolarizing or repolarizing ion currents, and hence interactions with hypothermia may be less predictable.16

**Limitations**

Although we report the association between ER and both idiopathic and CAD-related VF, these data provide no clear ideas as to the mechanisms underlying arrhythmia in either setting. Traditionally, ER has been associated with arrhythmia initiated by phase II re-entry.13,20 It is certainly possible, however, that patients in the CAD-VF group who had previously experienced a myocardial infarction (one third of this group) might, in fact, have had an episode of scar-related VT, which subsequently deteriorated into VF. Patients in the ID-VF group were younger than those in the CAD-VF group. Because the prevalence of ER decreases with age,29,30 it is possible that this confounding factor could have contributed to some of the differences observed between the ID-VF and CAD-VF groups. Finally, the baseline (normothermic) ECGs were obtained after rewarming. Whether the same results would have been seen had pre-morbid baseline ECGs been available is not known.

**Conclusions**

ER is more strongly associated with ID-VF than with CAD-VF. Hypothermia increases both the prevalence and magnitude of ER in cardiac arrest survivors; however, the mean amplitude of JPE is increased in survivors of CAD-VF, but not of ID-VF.

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**Disclosures**

None.

**References**


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**CLINICAL PERSPECTIVE**

Electrocardiographic changes seen during hypothermia, characterized in the 1950s by Osborn, are similar to those seen in patients with the more recently described early repolarization (ER) syndromes. Although the retrospective association between idiopathic ventricular arrhythmia and ER change on the 12-lead ECG is now well established, the clinical significance of an ER pattern ECG remains poorly understood. We tested the hypothesis that therapeutic hypothermia would have differential ECG manifestations according to the cause of ventricular arrhythmia and that these manifestations could potentially confirm a diagnosis of true ER syndrome. This study, therefore, examines the impact of therapeutic hypothermia on ER in survivors of cardiac arrest attributable to idiopathic ventricular fibrillation (ID-VF) and draws comparisons with a control group who experienced coronary artery disease (CAD)-related VF. Our results indicate that ER during hypothermia is most prominent in ID-VF. Although hypothermia increases both the prevalence and magnitude of ER changes in cardiac arrest survivors overall, the mean magnitude of ER increases only in the CAD group. Therefore, therapeutic hypothermia seems to be an inexact diagnostic aid to the interpretation of the significance of ER electrocardiographic change.
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