

## Early Repolarization in Athletes

### A Review

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Early repolarization (ER) on ECG was initially described in 1936 and has been considered a benign ECG finding for more than half a century.<sup>1,2</sup> However, in 2008, a seminal study by Haïssaguerre et al<sup>3</sup> challenged this view by demonstrating an association between ER and an increased risk of idiopathic ventricular fibrillation (VF). To reconcile these apparently contradictory views, as well as to better understand the potential implication of ER in athletes, it is necessary to first understand the semantic confusion that has arisen around the term ER.<sup>4</sup>

#### Original Definition of ER

The original definition of ER is based on  $\geq 0.1$ -mV concave ST-segment elevation (STE), with or without accompanying J waves (defined as a deflection after the QRS that seems as a late delta wave or a small secondary R wave), in  $\geq 2$  anterolateral leads (Figure 1A and 1B). This ECG pattern is present in 1% to 2% of the general population, with a higher prevalence in young athletes and blacks. Historically, it has chiefly constituted a benign differential diagnosis to STE myocardial infarction and pericarditis.<sup>5</sup> In fact, several large recent studies have confirmed that this type of ER carries no negative prognostic implications in the general population.<sup>6,7</sup> Indeed, because ER is so common in young athletes, some have even considered it an ECG sign of good health.<sup>2</sup> For the purpose of this review, we will refer to this type of ER as benign ER.

#### Emerging Definition of ER

The emerging definition of ER, which was introduced by Haïssaguerre et al,<sup>3</sup> is defined as inferolateral J-wave notching or slurring at the end of the QRS complex (Figure 1C and 1D). It is more common than benign ER, with prevalence estimates ranging from 3% to 13% in the general population.

The J waves seen in this definition of ER bear resemblance to Osborn waves, which were first described in 1953 as a harbinger of ventricular arrhythmia during experimental hypothermia.<sup>8</sup> Later, other investigators suggested that the increased risk of malignant ventricular arrhythmias in the presence of J waves may also extend to normothermic conditions.<sup>9</sup> This hypothesis was confirmed in the 2008 case-control study by Haïssaguerre et al,<sup>3</sup> which showed an association between inferolateral J waves and an increased risk of idiopathic VF. Several subsequent case-control studies<sup>10-13</sup> and general

population studies<sup>14-16</sup> have corroborated the association between inferolateral J waves and an increased risk of malignant ventricular arrhythmia. Although there are studies with conflicting results,<sup>17,18</sup> a recent meta-analysis, summarizing all studies to date, reported that individuals with inferolateral J waves have a relative risk of 1.7 (95% confidence interval, 1.19–2.42) to have arrhythmic death.<sup>19</sup>

Importantly, the risk of malignant ventricular arrhythmia seems to vary across different ER patterns. J waves involving multiple leads,<sup>20</sup> particularly inferior leads,<sup>14</sup> and higher J-wave amplitudes ( $\geq 0.2$  mV) have been associated with higher risk.<sup>14</sup> Furthermore, a horizontal or downsloping ST segment (ie, the absence of STE) after the J wave is also associated with higher arrhythmia risk.<sup>21</sup> For the purpose of this review, we will refer to the ER pattern(s) described in this section as malignant ER. Of note, the ability of the ST segment to discriminate between high- and low-risk patients is particularly important in athletes, who have ascending ST segments in the majority of cases.<sup>22</sup>

Thus, the term ER is used today to describe 2 different ECG morphologies. Hence, the semantic confusion alluded to earlier. The benign form of ER is characterized by anterior STE, whereas the potentially malignant form mainly involves inferolateral J waves followed by a horizontal or downsloping ST segment. A recent consensus article, authored by several researchers that have been instrumental in investigating ER during the past decade, was recently published.<sup>23</sup> The authors' objective was to attempt to establish an agreed terminology, including recommendations for measurements of J waves and ST-segment slope, to facilitate future studies in this area.

#### ER in Athletes

It has been known for decades that the benign ER pattern is common in athletes. Prevalence estimates in athletes range from 10% to 90%, which are several folds higher than in the general population (Table).<sup>10,24</sup> In athletes, this ECG pattern is thought to result from higher vagal tone, and it is, thus, considered training related and benign.<sup>25,26</sup> This concept is fairly uncontroversial among experts in sports cardiology.<sup>25,26</sup> Therefore, this review mainly focuses on the implications of the presence of a malignant ER pattern on an athletes' ECG.

As mentioned above, the malignant ER pattern is also more common in athletes. Prevalence estimates vary from

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8% to 44%, which is considerably higher than in the general population (Table).<sup>10,18,21,27-30</sup> In an elegant study design, Noseworthy et al<sup>28</sup> demonstrated that exercise training can induce both the benign and the malignant ER pattern. In college athletes who returned to intense training, ER was present in 37% before, and in 53% after, an intense 90-day training period ( $P < 0.01$ ). Although the vast majority of athletes developed ER with ascending ST segments, the prevalence of the malignant ER pattern also increased, including a significant increase in subtypes associated with higher risk of arrhythmias in the general population, such as inferior J waves and J waves followed by a horizontal or downsloping ST segments. Of note, the increased prevalence of ER after the 90-day training period was driven by an increase in endurance athletes (rowers), whereas ER prevalence remained stable in strength athletes (football players), suggesting that endurance training is a more powerful inducer of ER than strength training.

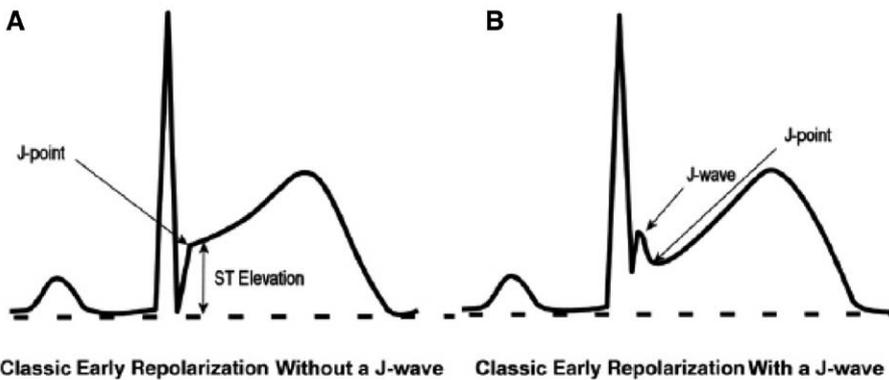
Furthermore, in the study by Noseworthy et al,<sup>28</sup> ER was significantly more common in men and in black athletes, which is consistent with other data. There was also a high correlation between ER and other ECG signs of physiological adaptation to training, that is, athletes' heart, such as voltage criteria for left ventricular hypertrophy and bradycardia. However, ER was not associated with increased left ventricular chamber dimensions or wall thickness on echocardiogram, suggesting that ER represents cardiac electric remodeling that occurs independently of the structural remodeling commonly seen in athletes' heart.

Importantly, no adverse clinical events occurred during 2 years of follow-up, including in individuals with inferior J waves followed by a horizontal or downsloping ST segment (the pattern that has been associated with the highest risk in the general population). The authors, therefore, concluded that ER should be considered benign in athletes and not, when present in isolation, trigger additional diagnostic work-up.

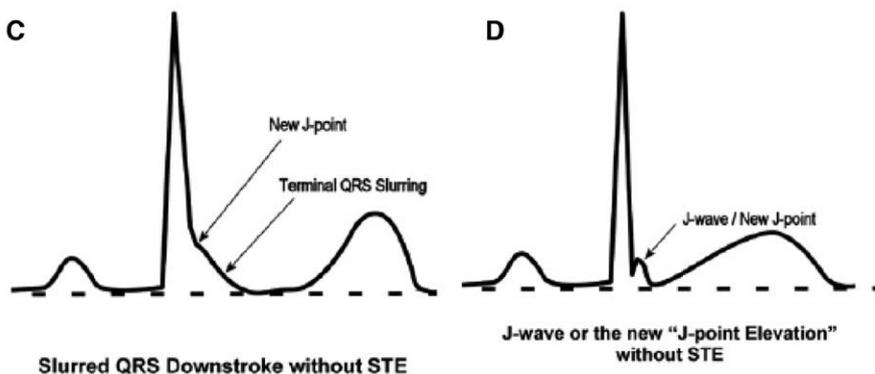
However, an Italian case-control study by Cappato et al<sup>34</sup> raised concern over the implications of the malignant ER pattern in athletes. In this study, inferolateral ER followed by a horizontal or downsloping ST segment was significantly more common in athletes who had unexplained sudden cardiac death (SCD), compared with in that control athletes (38.1% versus 15.6%;  $P = 0.04$ ). However, it should be noted that the athletes in the control group had a lower prevalence of ER than reported in other athlete cohorts. It has subsequently been suggested that the difference in ER prevalence between cases and controls in this study may have related to a lower proportion of endurance athletes in controls compared with cases.<sup>47</sup> Therefore, the findings from this study should be interpreted with caution.

It is interesting, however, that in the study by Cappato et al,<sup>34</sup> ER did not disappear after sports discontinuation in any of the athletes with previous cardiac arrest on serial ECG monitoring during 3 years of follow-up. This contrasts with findings in healthy elite athletes, where the ER pattern disappears in >50% after detraining.<sup>30</sup> Furthermore, it is intriguing that there were no further arrhythmic events after sports

### Classic Definition of Early Repolarization: ST Elevation



### New Definitions of Early Repolarization



**Figure 1.** Examples of the original benign and new malignant definitions of early repolarization. **A** and **B**, Original definition based on ST-segment elevation (STE), with or without J waves. New definition, based on J-wave slurring (**C**) and notching (**D**) followed by a horizontal or downsloping ST segment. Reprinted from Perez et al<sup>4</sup> with permission of the publisher.

**Table. Prevalence and Prognostic Significance of Early Repolarization in Athletes**

Study	n	Age, y	Men, %	J Waves, %	STE, %	Follow-Up
Balady et al <sup>31</sup>	289	21–35	100	...	13	...
Bianco et al <sup>32</sup>	155	31±10	100	...	89	...
Pelliccia et al <sup>33</sup>	32 652	22±13	80	...	7*	...
Rosso et al <sup>10</sup>	121	17–19	100	22	...	...
Crouse et al <sup>24</sup>	77	18±1	100	...	33.8	...
Tikkanen et al <sup>21</sup>	62	13±1	100	44	...	...
Cappato et al <sup>34</sup>	365	28±8	90	7.9	21.6	No events 36 mo (IQR, 31–119)
Noseworthy et al <sup>28</sup>	879	18±1	62	25.1	...	No events during 21±13 mo†
Junttila et al <sup>27</sup>	503	17–22	51	30	...	...
Quattrini et al <sup>29</sup>	704	25±5	62	14	84	No events during 6±4 y
Muramoto et al <sup>18</sup>	1114	19±2	57	13.1	21.9	No events during 3 y
Aagaard et al <sup>35</sup>	151	50±5	100	30	13	...
Sera-Grima et al <sup>30</sup>	299	20±6	66	31	...	No events during 24±8 y

IQR indicates interquartile range; and STE, ST-segment elevation type early repolarization.

\*Exact percentage not given.

†Follow-up limited to a subgroup of 146 athletes.

discontinuation in the sudden cardiac arrest survivors. This is not in keeping with the findings from the original study by Haïssaguerre et al,<sup>3</sup> where recurrent arrhythmic events were common in patients with ER during follow-up. The persistence of the malignant ER pattern, coupled with the absence of ventricular arrhythmias after detraining, thus, raises some concern that strenuous exercise may have played a role as an arrhythmia trigger in these young athletes. Therefore, on the basis of these data, it cannot be excluded that the ER pattern in the athletes who had survived sudden cardiac arrest was truly malignant, rather than training induced and benign. However, except for 1 case report,<sup>36</sup> there are, to the authors' knowledge, no other studies linking ER to SCD in athletes. On the contrary, several studies have demonstrated a lack of an association between J waves and malignant arrhythmias in athletes during medium to long-term follow-up.<sup>28–30,37</sup> However, given the rarity of SCD in athletes (annual incidence of 1/75 000 to 1/200 000 per year),<sup>38,39</sup> it should be pointed out that these longitudinal studies, although some are of considerable size and length, remain underpowered. Nevertheless, after taking all of the above into account, several international expert consensus documents categorize ER, of all subtypes, as a benign ECG finding in athletes.<sup>25,26</sup>

Given the large increase in participation of middle-aged and older individuals in sporting events (eg, Marathon running), so-called master athletes,<sup>40</sup> it should be emphasized that ER may develop not only in young elite athletes but also with recreational training at an older age. For example, in a study of middle-aged men training for a first-time participation in a long-distance running race, the malignant ER pattern was present in 30%.<sup>6</sup> The study participants had a training history that was generally <1 year and an average training load of 2.4±1.9 hours per week. Therefore, they are perhaps better characterized as recreational runners, rather than athletes. In addition to a 12-lead ECG, all subjects in this study underwent a thorough cardiovascular examination that included history and physical, echocardiography, and blood laboratory work,

including cardiac biomarkers, without any alarming findings in individuals with ER. On the contrary, participants with ER were characterized by results indicating a higher degree of physical fitness, such as lower resting heart rates, lower body mass index, and faster runtimes. Similar to young athletes, there was no correlation between the presence of ER and left ventricular hypertrophy on echocardiogram. Data from this study are, thus, consistent with the concept that ER may occur early in the course of training and before, or independent of, structural cardiac changes.<sup>28</sup> However, the exact degree of training necessary to induce ER remains unknown, and the interindividual variation is likely large. Based on available data, we agree with current expert consensus that ER in athletes should be viewed as part of physiological cardiac adaptation to strenuous physical activity.<sup>25,26</sup>

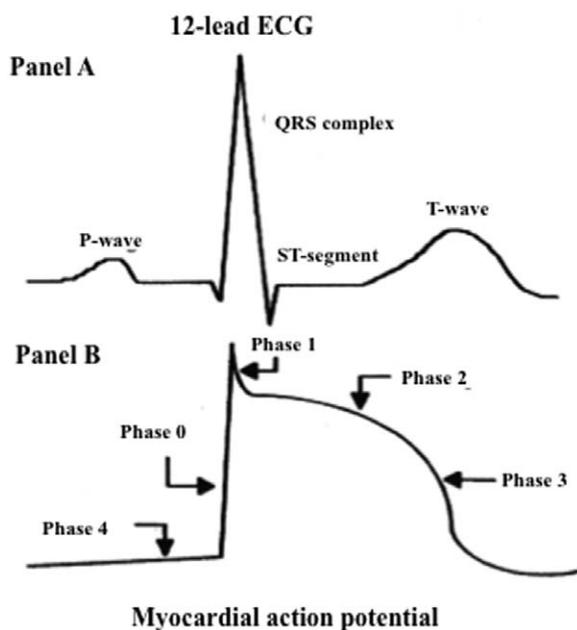
### Electrophysiological Mechanisms

There are several potential explanations as to why ER with STE is benign, whereas ER with J waves followed by a horizontal or downsloping ST segment is associated with an increased arrhythmia risk. In athletes, it has been suggested that a training-induced elevation of vagal tone causes regional dispersion of repolarization, which manifests as ER on ECG.<sup>41,42</sup> More specifically, the STE seen in ER is thought to originate from a transmural repolarization gradient caused by a vagally mediated inward potassium current during the plateau phase of the action potential (phase 2).<sup>43</sup> The association between STE and vagal activity offers an explanation to the benign nature of this ECG pattern, as a high vagal tone generally protects against malignant ventricular arrhythmias.<sup>44,45</sup> This hypothesis is supported by the association between ER and other markers of an elevated vagal tone, such as bradycardia. Furthermore, ER tends to disappear during and immediately after strenuous exercise (a state of vagal withdrawal and heightened sympathetic tone), as well as with administration of sympathomimetic agents.<sup>35,46</sup> However, ER does not disappear with complete autonomic nervous system blockade using

concomitant atropine and propranolol administration,<sup>47</sup> suggesting that factors other than autonomic activity also play a role in the development of this type of ER pattern.

J waves, on the other hand, at least in carefully performed myocardial wedge preparation experiments, originate from a transient outward potassium current ( $I_{to}$ ) during the early phase (phase 1) of the cardiac action potential (Figure 2).<sup>43</sup> Transmural heterogeneity, because of an endoepicardial ion voltage gradient during the early phase of repolarization in individuals with J waves, could theoretically increase arrhythmia susceptibility caused by local re-excitation (phase-2 re-entry). A causal link between J waves and arrhythmias is also supported by reports of increased J wave amplitudes before the onset of arrhythmia (Figure 3).<sup>12</sup> Cardiac ion channel function interplays with several other factors, such as body temperature and sex hormones, which can influence the 12-lead ECG appearance. In fact, a dose–response relationship between higher testosterone levels and more pronounced ER has been demonstrated.<sup>48</sup> This can likely explain, at least some of, the sex differences in ER prevalence.

A concept known as repolarization reserve, which holds that normal hearts have several redundant repolarization currents, may explain why arrhythmias remain rare even in individuals with prominent J waves.<sup>49,50</sup> Because of repolarization reserve, defects in one of the repolarization currents may not suffice to produce phase-2 re-entry. However, when other factors affecting repolarization, such as autonomic nervous system perturbances, ischemia, drugs, and inherited or acquired ion channel deficiencies, are also present, the repolarization reserve may become exhausted, resulting in arrhythmia.



**Figure 2.** The myocardial action potential and early repolarization. **A**, An example of a 12-lead ECG lead. **B**, Corresponding phases of the myocardial action potential. The figure illustrates how changes in phase 1 of the action potential can lead to changes at the end of the QRS complex (eg, J waves). Correspondingly, changes during phase 2 of the action potential can be seen as ST-segment changes (eg, ST-segment elevation).

With regard to athletes, exercise induces significant autonomic nervous system changes and can also induce ischemia in certain individuals, particularly middle-aged and older athletes with underlying coronary artery disease. Furthermore, performance-enhancing drugs or medications are used by some in the athletic community. Finally, although rare, primary ion channel deficiencies are also present in the athletic population. It can, therefore, not be excluded that ER may play a role in arrhythmias in some athletes.

However, it should be emphasized that the electrophysiological mechanisms underlying ER are still incompletely understood and remains an area of controversy. It has even suggested that ER in the form of J-wave notching or slurring at the end of the QRS complex may not represent ER at all but rather indicate late depolarization.<sup>51</sup>

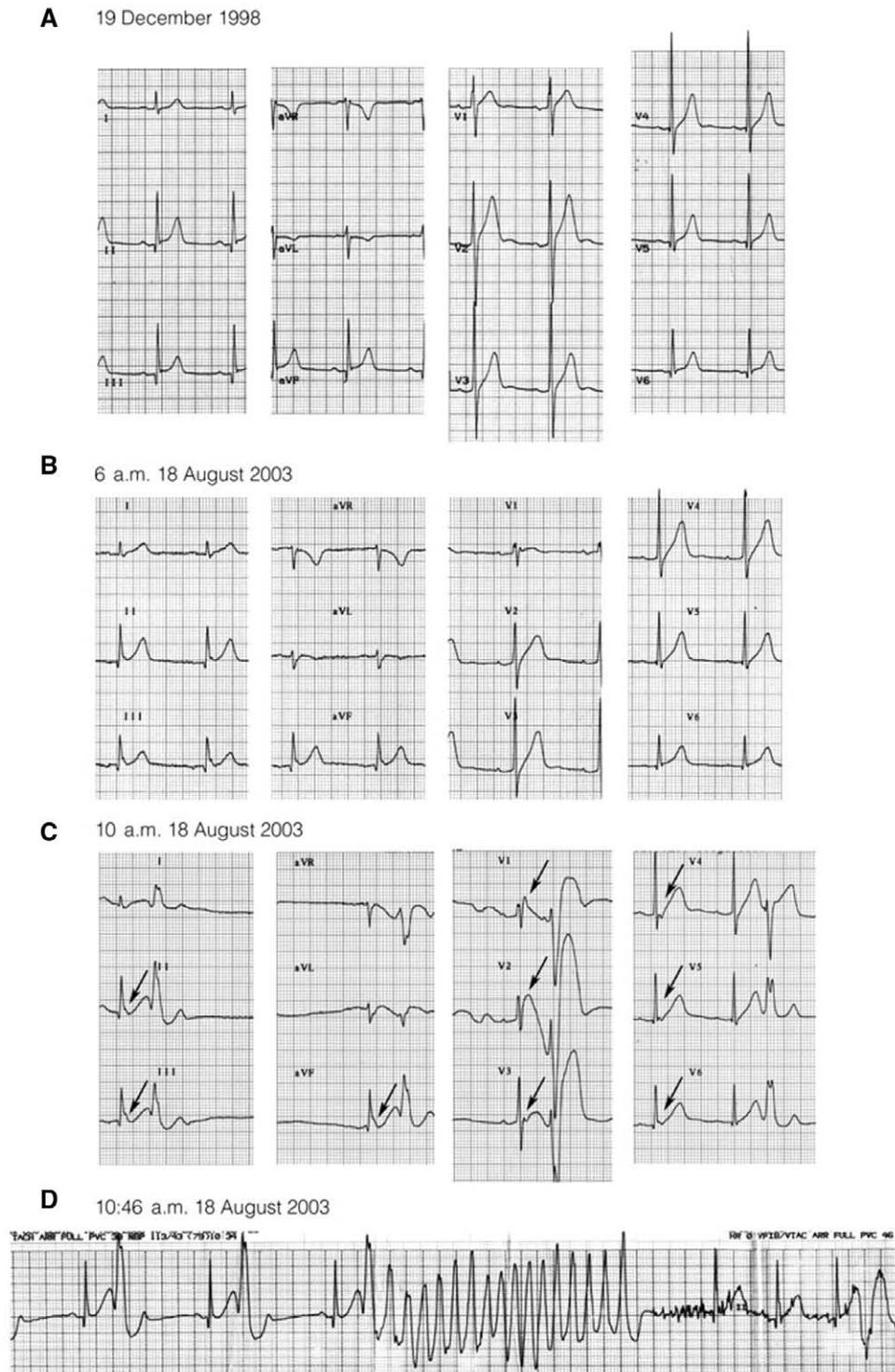
### Risk Stratification and Clinical Implications

Although the statistical association between the malignant ER pattern and SCD is concerning, we agree with Viskin et al<sup>52,53</sup> that it is still too early to risk stratify asymptomatic individuals with ER for SCD in clinical practice. This is perhaps best illustrated by borrowing an example from the named authors: the risk of idiopathic VF in individuals aged <45 years is  $\approx 3/100\,000$  per year.<sup>10</sup> This risk increases to 11/100 000 when J waves are present on ECG and to 30/100 000 in individuals with the ER pattern currently associated with the highest risk (inferolateral J waves followed by a horizontal or downsloping ST segment).<sup>54</sup> Thus, the absolute risk is still low, and there are currently no tools available to further improve risk stratification. Therefore, until algorithms that better predict individuals at risk become available, it is not feasible to use the presence of ER on 12-lead ECG in asymptomatic individuals to guide further diagnostic work-up or treatment.

This concept also applies to the athletic population, and there are currently no data to support further diagnostic testing or sports discontinuation in asymptomatic athletes with ER pattern and a negative family history of SCD. Although pre-participation ECG screening of athletes remains controversial, it is becoming more common. Therefore, it is important for physicians overseeing such screening programs, as well as for any physician caring for athletes, to be aware of the implications of ER in this population.

Asymptomatic patients with Brugada syndrome or short-QT syndrome and concomitant malignant ER pattern are an exception, as the presence of ER seems to negatively affect prognosis in this population.<sup>55</sup> Therefore, in such cases, further diagnostic work-up (eg, an invasive electrophysiology study) may be warranted. However, this concept plays a limited role with regard to sports cardiology, as athletes with Brugada ECG or short-QT syndrome should be counseled on their high risk of arrhythmic events during strenuous physical activity based on these conditions alone (ie, even without the concomitant presence of J waves).

It is also important to differentiate between the presence of inferolateral J waves in asymptomatic individuals and J-wave syndrome. J-wave syndrome can only be diagnosed in individuals with inferolateral J waves and a history of sudden cardiac arrest, VF, or polymorphic ventricular tachycardia.<sup>56</sup> In such individuals, including athletes, implantable cardioverter



**Figure 3.** Twelve-lead ECG from an individual with suspected J-wave syndrome. **A**, An ECG from December 19, 1998, with mild inferior J waves. **B**, ECG from August 18, 1998, 4 hours before the patient had ventricular fibrillation (VF). J waves are now more pronounced. **C**, ECG recorded 10 minutes before the onset of VF. The inferior J waves are now even more pronounced, and J waves have developed also in lateral leads. **D**, One of several episodes of VF that followed. Of note, all arrhythmia episodes were preceded by ventricular extra systoles after a short-long cardiac cycle. Reprinted from Nam et al<sup>12</sup> with permission of the publisher.

defibrillator implantation should be strongly considered to prevent SCD. Although most individuals with sudden cardiac arrest, VF, or polymorphic ventricular tachycardia qualify for secondary prophylactic implantable cardioverter defibrillator implantation, it is still clinically relevant to diagnose J-wave syndrome, as this patient population tends to have more

frequent implantable cardioverter defibrillator shocks, which seems to be reduced with concomitant quinidine treatment.<sup>56,57</sup> In individuals with high-risk ER patterns and suspected cardiac syncope but no documented arrhythmia, an implantable loop recorder can be considered as part of the diagnostic work-up.<sup>53</sup>

Athletes with asymptomatic ER, but with a strong family history of SCD, represent a clinical challenge. No clear recommendations on how to manage these patients currently exist although it has been suggested that further diagnostic testing is reasonable to rule out J-wave syndrome.<sup>58</sup> Several genes have been associated with ER, and J-wave syndrome seems to cluster in some families.<sup>59,60</sup> However, so far, none that predict malignant arrhythmias have been identified. Given the high prevalence of ER in the general population, as well as in athletes, ER is likely polygenetic and, as discussed above, influenced also by nongenetic factors.<sup>56</sup> Therefore, until genetic testing becomes more refined at risk stratification, it is currently unclear what the optimal treatment strategy is for athletes with ER and a strong family history of SCD. Potential options include sports discontinuation, prophylactic quinidine, and implantable cardioverter defibrillator implantation.<sup>56</sup>

In conclusion, it is clear that the large majority of asymptomatic athletes with ER, even those with inferolateral J waves followed by a horizontal or downsloping ST segment, are at low risk of SCD. The challenge going forward will be to develop better risk stratification tools that allow us to determine which athletes with ER are at high enough SCD risk to justify intervention.<sup>61</sup> The secondary challenge is then to identify which interventions actually reduce mortality without imparting excessive morbidity to this patient population.

## Disclosures

None.

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