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Yvonne Cristoforetti MD, Luigi Biasco MD, Carla Giustetto, Ole De Backer MD PhD, Davide Castagno MD, Piero Astegiano MD, Gianpasquale Ganzit MD, Carlo Gabriele Gribaudo MD, Marco Moccetti MD, Fiorenzo Gaita MD

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J wave duration and slope as potential tools to discriminate between benign and malignant Early Repolarization

Running title: Is J wave amplitude the J key to Early Repolarization?

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Key words: Early repolarization syndrome; athlete; sudden cardiac death; J point elevation.

Abbreviations:

ER : Early Repolarization

SQTS: Short QT syndrome

LQTS: Long QT syndrome
Introduction

Interest towards Early Repolarization (ER) rose after the theoretical proposal\(^1\) and the clinical demonstration\(^2\) that certain electrocardiographic patterns characterized by an elevation of the J point were associated with an increased risk of sudden cardiac death in otherwise healthy individuals. Previous studies showed that only the rare pattern characterized by a significant J point elevation (≥ 2 mm) in the inferior leads associated with a slurred J wave and a horizontal/descending ST segment was associated with an increased risk of death (whether arrhythmic, from cardiac or any cause).\(^3^\)\(^-^\)\(^6\) Whether this pattern may constitute a real primary arrhythmic disorder rather than a predisposing substrate facilitating arrhythmias during ischemic episodes is still a matter of debate.

Moreover, those findings are somehow in contrast with the clinical evidence of patients presenting with idiopathic ventricular fibrillation and several different morphologies of the J wave and ST segment, questioning what is the real ECG marker able to distinguish between a malignant and a benign form of ER.

Thus, the aim of the present study is to compare the amplitude of J waves by measuring slope and duration in ER syndrome patients and healthy athletes with ECG evidence of J point elevation associated with J wave and to evaluate
its potential role as an electrocardiographic marker of increased arrhythmic risk.

**Methods**

**Cases**

A systematic review was performed to select those manuscripts reporting good quality, undistorted, preferably 12 leads ECG tracings of patients with episodes of idiopathic ventricular fibrillation and ECG evidence of J point elevation associated with J wave commonly accepted and referenced in contemporary works as patients with ER syndrome.

Only manuscripts reporting data and ECG of patients with isolated ER syndrome, not associated with any other form of congenital (Brugada syndrome, SQTS, LQTS, structural heart disease) or acquired causes of J point elevation (ER in the setting of acute myocardial ischemia) were taken into account.

Ovid MEDLINE, PubMed, CENTRAL, and Excepta Medica (EMBASE) were searched up to February 2014 for suitable works, bibliographies of pertinent articles were also reviewed to search for relevant publications.

Detailed references of the selected manuscripts and tracings are reported in table 1. For all cases, the index clinical event was obtained through the
manuscript while J wave’s morphology, localization, entity of J point elevation, were derived from available data (description and/or ECG) while duration and slope of the J wave were electronically measured from the published ECG tracings with an electronic caliper by two independent cardiologists. For both athletes and cases the (available) lead showing the wider J wave was chosen for measurements.

Controls

Controls were selected from our database comprising clinical, electrocardiographic, echocardiographic and long term follow up data of 338 male professional elite athletes, members of soccer clubs participating in the Italian national football championships, who were screened for a first pre-participation evaluation between June 1980 and April 2008 at the Turin Institute of Sport Medicine. A detailed description of this population was previously published.27

Briefly, the incidence of J point elevation in this population was 35.6% and at a median follow up of 13.3 years no episodes of sudden cardiac death were observed.

From this initial population only subjects with a significant J point elevation (≥0.2mV) and evidence of J wave either with a notched or a slurred appearance, whatever the morphology of the ST segment
(horizontal/descending or ascending), were selected. A J point elevation ≥0.2mV was selected as an inclusion criteria in both cases and controls in order to obtain reliable measurements of the slope and duration of the J wave. Subjects with the traditional form of early repolarization characterized by J point elevation and upward displacement of the ST segment but without evidence of J wave were excluded.

**ECG analysis.**

All electrocardiograms were digitally acquired and analyzed by two independent reviewers who were blinded to all subjects characteristics. In ambiguous cases final adjudication was achieved by consensus with a third reviewer.

All measurements were performed using a digital caliper and protractor at a 400% magnification.

Measurements were performed following the recent recommendations on J point identification and measurement provided by the consensus paper published in July 2015 by Macfarlane et al. in the Journal of the American College of Cardiology\(^28\).
In both cases and controls the duration of the J wave was measured as the interval comprised between the J point (J onset or $J_o$) and the intersection of the tangent to the J wave with the isoelectric line or the change of slope of the J wave into the ST/T wave, whatever come first. To assess the slope of the J wave, the “J angle” (the angle between an ideal line drawn from the J point ($J_o$ point) perpendicular to the isoelectric line and the tangent to the J wave) was digitally measured. Angle measurements are expressed in sexagesimal degrees ($^\circ$). A graphic description of how measurements were preformed is provided in figure 1.

According to previously proposed morphological classifications of J waves, a notched J wave was defined by the presence of a sharp and well-defined hump immediately after the R-wave, while a slurred J wave was identified when the QRS-ST transition was characterized by a change in the slope of the terminal portion of the R wave.\textsuperscript{3,4} To estimate the entity of J point elevation the height of the $J_o$ point was measured, with the isoelectric line considered as a baseline.

Statistical analysis

Descriptive analysis was performed using mean±standard deviation for continuous variables and counts and percentages for categorical variables. Comparisons between groups were performed with the Student’s t-Test, one way ANOVA and Yates corrected or uncorrected Chi-squared method when
appropriate. All probability values were considered to be significant at a value ≤ 0.05. All the analyses were performed with SPSS software (SPSS, Chicago, IL).

Results

Out of 1523 papers evaluated only 21 works reported original, non-distorted, interpretable ECG tracings of 27 different patients with idiopathic ventricular fibrillation due to early repolarization syndrome.

Table 1 reports the clinical and ECG data obtained from original reports.

Out of 338 healthy, professional top series football players only 24 showed a J point elevation ≥0.2 mV (and a clearly identifiable J waves with a notched or slurred appearance). Table 2 reports the clinical characteristics of controls.

J point elevation was 0.307±0.125 mV in cases and 0.269±0.103 mV in controls (p=0.243) with a wide overlap of measurements between the two populations (Fig 2, left panel).

Cases showed a significantly longer duration of the J waves if compared to controls (69.48±27.93 vs 35.05±10.33 ms; p<0.001). None of the controls showed a duration greater than 60 ms while 15 out of 27 cases (55.5%) showed a J wave duration longer than 60 ms (Fig 2, central panel).
When compared to controls, cases showed a significantly wider J angle (32.59±10.4° vs 20.00±6.84°; p<0.001), with only 2 out of 24 controls (8.3%) showing a J angle >30°(Fig 2, right panel).

Figure 3 shows the plot of J wave duration as expressed in millimeters (horizontal axis) and J angle (vertical axis). As shown in the graph controls, characterized by a short and steep J waves, are clusterized in the left inferior corner. None of the healthy athletes showed a duration longer than 60 ms in combination with an angle greater than 30°. On the other hand, cases showed a wide dispersion of measurements. Few of them had a short and steep J wave, while the majority showed, alone or in combination, a long and delayed J wave.

**Discussion**

The main finding of this work is that patients reported in contemporary literature with episodes of idiopathic ventricular fibrillation deemed to be related to ER syndrome show a slow and delayed J wave if compared to healthy controls, representing a new potential tool to discriminate between benign and malignant early repolarization.

Despite the recent rise of interest, clear electrocardiographic criteria to stratify the arrhythmic risk of subjects with ER are still missing. Several previous retrospective, population based works identified the rare pattern characterized by significant J point elevation (≥0.2 mV) in the inferior leads
concomitant with a J wave and a horizontal/descending ST segment as associated with an increased risk of (late) death, from cardiac or any cause. Subjects with a slurred J wave showed an increased risk if compared to those with a notched J wave. Those works failed to solve the issue whether deaths were effectively related to primary arrhythmic episodes, fatal arrhythmias in the setting of ischemic events or other causes.

As for the Brugada syndrome, the electrophysiological mechanism deemed to be responsible for the arrhythmogenicity of ER is a I_to-mediated loss of the epicardial action potential dome causing transmural dispersion of repolarization, a trigger for phase 2 reentry mediated short coupled ventricular extra beats, a potential cause of ventricular arrhythmias. Thus the basic idea supporting our work is that J wave’s amplitude by impacting on the persistence of the J wave (i.e., longer duration and wider angle) will prolong the transmembrane dispersion of repolarization, thus enhancing the arrhythmogenic potential. Similarly, subjects with Brugada type II or III ECG patterns with a drug elicited type I pattern showed a delayed and slurred J wave, evident with an ample angle between the upslope of the S wave and the downslope of the r’wave as compared to subjects with a negative drug challenge, supporting the hypothesis that the amplitude of the J wave may be an effective
electrocardiographic marker of increased arrhythmic risk. To the best of our knowledge, this is the first paper to systematically describe J wave’s duration and slope in patients with ER syndrome and controls with ECG evidence of ER, a characteristic that has been advocated, but not yet evaluated, as a potential marker of increased risk.

Our data are hypothesis generating: the amplitude of the J wave, regardless of the morphology (slurred/notched) or location (inferior/lateral/combined) could represent an electrocardiographic marker able to distinguish between a benign and a malignant form of ER.

Lessons learned from other primary electrical disorders such as Brugada syndrome and LQTS or other ion channel diseases taught that beside the presence of an electrocardiographic pattern, its extent and persistence may constitute a useful prognostic marker, further supporting our hypothesis. Moreover prominent J waves are known to anticipate arrhythmic episodes in patients with ER syndrome, another evidence supporting our hypothesis.

In line with previous works, J point elevation as itself doesn’t seem to play a real role as a ECG marker of increased arrhythmic risk, being slightly, but not significantly increased in cases versus controls.

As evident figure 3, while controls are grouped in the right inferior corner of the plot, ER cases showed a true disorder of the early repolarization process,
evident as a wide dispersion of measurements. None of the controls showed a
duration longer than 60 ms while a minority showed a slope greater than 30°.
Only cases showed J waves >60 ms and a slope exceeding 30°, this representing
a potential discriminant between a malignant and a benign form of ER that will
be prospectively evaluated in a large population study planned to start in the
next future.

Several limitations should be mentioned. First, the hypothesis was only derived
but not yet validated in an independent large volume population. Second, the
target of this work was not to definitely solve the ultimate question on how to
stratify the risk of subjects with early repolarization, but rather to rise the
interest toward a poorly investigated aspect such as the morphology of the J
wave. Third, cases were evaluated only on ECG obtained from literature. Even if
only high quality, non distorted, clearly interpretable tracing were selected,
the editorial process could have introduced some minor distortions that could
eventually impact on the results. Moreover, none of the evaluated works
reported an accurate description of the filters used when recording the ECGs,
this limitation mostly attributable to a lack of methodological accuracy of the
original works. Finally, ER has both in the benign and malignant form a waxing
and waning appearance, that is known to alter its electrocardiographic
characteristics, and thus the evaluated parameters. Nevertheless, prominent J
waves are known forerunners of incumbent arrhythmic events, thus ultimately supporting our hypothesis.

In conclusion, this is the first paper to report the potential role of J wave’s duration and slope as ECG markers of an increased arrhythmic risk. A delayed and prolonged J wave, marker of a transmural dispersion of repolarization may represent the new discriminant able to distinguish between benign and malignant ER. A prospective validation of this hypothesis is needed.

References


9. Nam GB. Idiopathic ventricular fibrillation, early repolarization and other J wave-related ventricular fibrillation syndromes: from an


Table legends

Table 1. References, clinical and electrocardiographic characteristics of cases.

Table 2. Clinical and electrocardiographic characteristics of control athletes.

Figure legends

Figure 1. Measurement of slope and duration of the J wave. Panel A: notched J wave in a control subject; B: slurred J wave in a control subject; C notched J wave in a case; D: slurred J wave in a case.

Figure 2. Plot of J point elevation, duration and slope of the J wave in control subjects and cases.

Figure 3. Scatter plot of J wave duration (mm, horizontal axis) and slope (degrees, vertical axis).
Fig 1.
Fig 2.
Fig 3.

![Duration vs. Slope scatter plot](image-url)
### Table 1. References, clinical and electrocardiographic characteristics of cases.

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IVF = idiopathic ventricular fibrillation; SD = sudden death; HR = heart rate (bpm); N = notched; S = slurred; Inf = inferior; Lat = lateral; Inf-Lat = inferolateral; n.a. = not available; *on showed lead; †Circ Arrhythm Electrophysiol; ‡J Cardiovasc Electrophysiol.
Table 2. Clinical and electrocardiographic characteristics of control athletes.

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