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**Evaluation of electrocardiographic parameters able to distinguish between
a benign and a malignant form of early repolarization.**

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Introduction

Early repolarization represents one of the most puzzling conundrums of contemporary cardiology.

For more than 70 years, Early Repolarization (ER) has been considered to be a common normal variant (1). Population studies have demonstrated that its prevalence ranges between 5 and 13% in healthy subjects while in athletes rises from 20 to 90% (2). Nevertheless, from the latter half of the 1990s, a growing number of case reports, series, observational and retrospective studies reported that the presence of various electrocardiographic patterns attributed to early repolarization may constitute a potential marker of increased risk of sudden death in otherwise normal individuals, casting a dark shadow on this ECG peculiarity. In the last ten years, the interest towards early repolarization rose meaningfully among researchers, this being significantly enhanced by the input give from the seminal work by Haissaguerre et al published in the new England Journal of Medicine in 2008 (3).

Nowadays, the clinical entity defined as Early Repolarization Syndrome (ERS) lacks definite and conclusive diagnostic criteria, nonetheless this entity has been grouped together with Brugada Syndrome in the so called "J wave syndromes", a group of disorders sharing clinical manifestations, electrocardiographical

characteristics and with similar pathophysiologic mechanisms. To better clarify this clinical entity, a first consensus document, derived from the expert meeting held in Shangai in 2015, reporting on both syndromes has been published on the official Journal of the European Heart Rhythm association in 2017 (4).

Table 1 Shangai Criteria for the diagnosis of ERS

Expert Consensus Recommendations on Early Repolarization Syndrome (ERS) Diagnosis
ER syndrome is diagnosed in the presence of J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG in a patient resuscitated from otherwise unexplained VF/polymorphic VT
ER syndrome can be diagnosed in an SCD victim with a negative autopsy and medical chart review with a previous ECG demonstrating J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG
ER pattern can be diagnosed in the presence of J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG

Table 2. Proposed Shangai Score for the diagnosis of ERS

Proposed Shanghai Score System for diagnosis of early repolarization syndrome	
	Points
I. Clinical History	
a. Unexplained cardiac arrest, documented VF or polymorphic VT	3
b. Suspected arrhythmic syncope	2
c. Syncope of unclear mechanism/unclear etiology	1
II. 12-lead ECG	
a. ER ≥0.2 mV in ≥2 inferior and/or lateral ECG leads with horizontal/descending ST segment	2
b. Dynamic changes in J-point elevation (≥0.1 mV) in ≥2 inferior and/or lateral ECG leads	1.5
c. ≥0.1 mVJ-point elevation in at least 2 inferior and/or lateral ECG leads	1
III. ECG monitoring	
a. Short-coupled PVCs with R on ascending limb or peak of T wave	2
IV. Family History	
a. Relative with definite ERS	2
b. ≥2 first-degree relatives with a "IIa" ECG pattern	2
c. First-degree relative with "IIa" ECG pattern	1
Unexplained sudden cardiac death <45 years in a first-or second-degree relative	0.5
V. Genetic Test Result	
a. Probable pathogenic ERS susceptibility mutation	0.5
Score (with at least 1 ECG finding): ≥5 points: Probable/Definite ERS 3-4.5 points: Possibile ERS <3 points: Non diagnostic	

Historical background

The electrocardiographic pattern defined as ER has been considered for a long time to be a common normal variant, since its first description by Shipley and Hallaran in 1936 (1). These authors described the common presence in medical students and young nurses' ECGs of a terminal QRS slurring or notching, defined, respectively, as 'a momentary retardation of string movement' or 'an actual change in direction of the string movement' (Figure 1A of paper #1). In the same years, some patterns, subsequently associated to ERP due to their electrocardiographic appearance, were described. Following reports were relatively imprecise and inconsistent in describing the same ECG finding. In 1938, Tomaszewski presented the case of an accidently frozen man whose ECG demonstrated a very slowly inscribed deflection between the QRS complex and the earliest part of the ST segment, representing a J wave (5). In 1953, Osborn described a "current of injury" later named "the Osborn wave" in acidotic and hypothermic dogs at rectal temperatures < 25 °C (6). In 1961, Wasserburger et al. further defined ER as a 1-4 mm takeoff of the ST-segment at the end of the QRS complex, with a distinct notch or slur on the downslope of the R wave, in the mid to left precordial leads (7) (Figure 1B of paper #1). In 1977, Friedman et al. defined the early repolarization as a normal variant characterized by the presence

of a notch at the transition of the QRS complex into the ST segment, the latter with a concave upward displacement of 2 or even 3 mm in the precordial leads and, occasionally, in the peripheral leads and tall, broad-based and upright T waves (8) (Figure 1C of paper #1). In 1988, Schamroth used the term "early repolarization syndrome, vagotonia, the athlete's heart" to indicate a common normal pattern characterized by the presence of a thickening or slurring of the terminal part of the QRS that may appear as a distinct notch or 'hook' on the distal limb of the QRS complex, associated with concave upward elevated ST segment, tall and symmetrical T waves and other minor characteristics (9) (Figure 1D of paper #1).

The interest towards early repolarization was mainly oriented in differentiating this common, and possibly misleading pattern, from other conditions such as acute myocardial infarction, pericarditis, hyperkalemia or hypothermia sharing a ST segment displacement at ECG. Finally, a milestone works confirmed the benign nature of the classical form of early repolarization pattern together with the characteristic features of a prevalent manifestation in male, black, young and physically active individuals (10,11)

Abnormal QRS–ST segment transitions as a possible marker of increased arrhythmic risk

Few sporadic papers, published from mid 80's, started to report cases of patients with idiopathic ventricular arrhythmias associated with uncommon morphologies of the QRS-ST junction. In 1984, Otto et al. (12) described the features of three young male immigrants from south-east Asia with idiopathic recurrent ventricular fibrillation occurred during the early hours of the morning. Their ECGs showed a broad slurring of the terminal portion of the QRS complex, that was interpreted as a possible sign of ischemia or intraventricular conduction defect. At electrophysiological testing, rapid polymorphous ventricular tachycardia was induced, not suppressed by procainamide infusion, whereas oral quinidine prevented the reinduction of ventricular arrhythmias. Some years later, Aizawa et al.(13) published a series of eight young Japanese patients with idiopathic ventricular fibrillation. Their ECGs were characterized by the presence of an unusual terminal QRS notching in the inferior and lateral leads. Authors highlighted as this terminal notching became more marked in post-extrasystolic depolarizations. This phenomenon was attributed to a bradycardia-dependent intraventricular block (Fig. 2a of paper #1).

In 1998, Garg et al. (14) reported the case of an 18-year-old boy with family history of premature sudden death, who was resuscitated after an episode of idiopathic ventricular fibrillation. At ECG an abnormal low-amplitude terminal QRS deflection (labeled for the first time as ' J wave') in the inferior (II, III, aVF) and anterolateral leads (V3–V6, I and aVL) (Fig. 2b of paper #1), that persisted on serial ECG tracings was evident. Neither intravenous procainamide nor oral atenolol could prevent the induction of the ventricular arrhythmias. Oral quinidine caused the disappearance of the abnormal J waves and prevented further induction of ventricular arrhythmias.

Kalla et al. described in 2000 case of a 29-year-old Vietnamese patient resuscitated after a nocturnal episode of ventricular fibrillation (15). The electrocardiogram recorded a prominent J wave (labeled by the author Osborn wave, like the terminal QRS slurring commonly observed during hypothermia) with ST-segment elevation mainly evident in leads II, III, and aVF. Of note, the authors described dynamic changes of the ECG pattern observed at serial monitoring during hospitalization. The authors interpreted this electrocardiographic pattern as a Brugada syndrome variant (15). In the same year Takagi et al. (16) reported two cases of nocturnal idiopathic ventricular fibrillation and one case of nocturnal syncope with inducible ventricular fibrillation in

otherwise healthy young men. The ECGs were characterized by a terminal

slurring of the QRS complex (labeled J wave) in the inferior leads. A 24-h ECG

recording revealed infrequent or no PVCs in all three patients. Intravenous

disopyramide increased ST-segment elevation in the inferior leads, whereas

treadmill testing caused the ST-segment elevation to decrease or disappear at peak

exercise. Also in this article, the similarities with the clinical and the dynamic

electrocardiographic presentation of Brugada syndrome were highlighted (16).

While from a clinical standpoint some initial clinical evidences supported the

hypothesis that an an abnormal QRS-ST transition might represents an

electrocardiographic marker of increased arrhythmic susceptibility, initial in vitro

tests confirmed that the transition between depolarization and repolarization is a

crucial and potentially lethal phase of ventricular activation.

In 2000, Gussak and Antzelevitch analyzed the similarities between the early

repolarization and the Brugada ECG pattern not only from a clinical but

also from an mechanicistic perspective (17). The cellular mechanism proposed for

the J-point and ST-segment elevation in both syndromes, derived from studies in

hypothermic canine models with Osborn wave, is an Ito-mediated loss or

reduction of the transmembrane voltage gradient during phase 2 of the myocardial

action potential, leading to a transmural voltage gradient between the epicardial

and endocardial layers. As this could be a substrate for phase 2 reentry, the authors proposed the hypothetical possibility that early repolarization may not be as benign as generally believed particularly if associated with conditions characterized by an increased dispersion of refractoriness such as myocardial ischemia.

This hypothesis, based on in-vitro studies, found its first clinical confirmation in 2008, when three distinct groups leaded by Haïssaguerre et al, Nam et al and Rosso et al finally identified ER as a new arrhythmic disorder, describing a strong relationship between J-waves and many different forms of ventricular arrhythmias in the absence of known heart disease (3,18,19).

Haissaguerre et al. published a case–control retrospective study that compared the electrocardiographic characteristics of 206 patients with idiopathic ventricular fibrillation with those of 412 controlled healthy individuals. In this work a new definition of early repolarization was proposed representing a turning point from previous classical descriptions. Haissaguerre et al. also adopted the definition of early repolarization as a J-point elevation more than 1 mm in inferior and/or lateral leads. No other ECG features were deemed necessary to identify the presence of ER at ECG, not even the morphology of the ST segment, the presence of a J wave or the morphology of the T wave. The prevalence of this redefined ER was significantly higher in cases with idiopathic ventricular fibrillation than in healthy matched controls (31% versus 5%, P<0.001). Moreover, cases showed a significantly higher J-point elevation that became even more evident in

concomitance of an arrhythmic event. Haissaguerre's patients also were more frequently men, they had frequent arrhythmic events in the early hours of the morning and were protected from recurrences by oral quinidine.

In the same year, Rosso et al. added to the complexity by defining the transition of the QRS-ST segment as 'J-point elevation or J wave', when a positive notch was evident during the terminal portion of the QRS complex (Figure 2 A) or 'slurred' when the R wave gradually merged into the ST segment, with upright concavity without a clearly evident J point (Figure 2 B of paper #1). The presence of a J-point elevation was confirmed to be more common in patients with idiopathic ventricular fibrillation than in young control individuals or athletes. The 'J-point elevation or J wave', but not the morphology of the ST segment or the location of the J waves (anterolateral versus inferior leads), was recognized as a possible marker of increased arrhythmic risk.

Some recent large-scale retrospective and prospective studies have identified a particular sub-group of individuals with clinical (young, man) and ECG characteristics (a markedly anomalous transition of the QRS complex into the ST segment defined by a significant, dynamic J-point elevation in the inferior leads, occasionally associated with inverted T waves), that may be at increased risk for sudden death if compared with the general population. This risk has also estimated to be 3.4 of 100 000 in the normal population, 11 of 100 000 in participants with

J-point elevation and 34 of 100 000 in the presence of J-point elevation and horizontal ST segment (20).

Cellular background

The JWSs (BrS and ERS) are characterized by the presence of a prominent J wave.

Some studies have shown that the J wave is related to a transmural voltage gradient caused by the manifestation of an action potential (AP) notch in epicardium, but not endocardium, due to a heterogeneous transmural distribution of Ito (21). An end of QRS notch, similar to a J wave, has been was proposed to be due to intraventricular conduction delays. The 2 ECG manifestations can be distinguished based on their response to rate, with the latter showing accentuation at faster rates (22). Differences between J wave and intraventricular conduction delay (IVCD)-mediated syndromes are summarized in Table 3.

Table 3. Differential diagnosis of JWSs vs IVCD from Antzelevitch et al (4)

	JWSs	IVCD
Male predominance	Yes	No
Average age at clinical presentation	Young adults	Old adults
Common morphology	Dome-like appearance	Sharp appearance
Response to heart rate	Bradycardia-dependent augmentation of J wave (+/- T-wave inversion)	Tachycardia-dependent augmentation of the notch
Concomitant structural heart disease	Rare	Common (CAD)

When analyzing the cellular background of ERS, it is mandatory to consider the ERS as a part of JWS, so studying it together with BrS.

Two principal electrophysiological mechanism have been formulated to explain the ECG and clinical manifestations of BrS: (1) the repolarization hypothesis, that asserts an outward shift in the balance of currents in RV epicardium, that can lead to repolarization abnormalities leading to development of phase 2 reentry, which generates closely coupled premature beats able to trigger VT/VF; and (2) the depolarization hypothesis, that suggests the presence of slow conduction area in the RVOT, secondary to fibrosis and reduced connexin 43 (Cx43), leading to discontinuities in conduction, plays a primary role in the development of the ECG and arrhythmic manifestations of the syndrome (23). The typical response of BrS to acceleration of rate is diminution of ST-segment elevation, opposite to that expected at a site of discontinuous conduction. The diminution of ST-segment elevation is consistent with the reduced availability of Ito at faster rates, due to slow recovery of the current from inactivation.

These two theories are not mutually exclusive and could act together in the development of the clinical manifestations.

The strongest evidence in support of the depolarization hypothesis derives from the observational studies showing that radiofrequency ablation (RFA) of

epicardial sites displaying late potentials and fractionated bipolar electrograms in the RVOT of patients with BrS, significantly reduced the arrhythmia vulnerability as well as the ECG manifestation of the syndrome (24). Similar results were reported by Brugada et al and by Sacher et al (25,26) who also observed in an isolated case that accentuation of the Brugada ECG by ajmaline was associated with an increased area of low-voltage and fragmented electrogram activity. A wider area of low-voltage activity was associated with a more prominent ST-segment elevation. These authors concluded that the late potentials and fractionated electrogram activity are due to conduction delays within the RVOT/RV anterior wall and the ablation of the sites of slow conduction is the basis for the ameliorative effect of ablation therapy.

Similarly to the mechanisms of BrS, an accentuation of transmural gradients in the LV wall are responsible for the repolarization abnormalities present in ERS, leading to J-point elevation, J wave or slurred QRS (27). This repolarization defect is accentuated by cholinergic agonists and reduced by quinidine, isoproterenol, cilostazol, and milrinone, accounting for the ability of these agents to reverse the repolarization abnormalities responsible for ERS (28). Higher intrinsic levels of Ito in the inferior LV were also shown to underlie the greater vulnerability of the inferior LV wall to VT/VF.

Conduction delay is known to give rise to notching of the QRS complex; when it occurs on the rising phase of the R wave, it is due to a conduction defect within the ventricle, when it occurs at the terminal portion of the QRS, thus masquerading as a J wave, it may be due to either a conduction defect or a repolarization defect (29). The response to prematurity or to an increase in rate can differentiate between the two (30). Delayed conduction becomes greater at faster heart rates or during premature beats, thus leading to accentuation of the QRS notch, whereas repolarization defects usually are mitigated, resulting in diminution of the J wave at faster rates.

The prognostic value of a fragmented QRS has been demonstrated in BrS (31) but fragmentation of the QRS is not associated with increased risk in the absence of cardiac disease. The congruence between BrS and ERS with respect to clinical manifestations and response to therapy lends further support to the repolarization hypothesis.

Genetic background

An ERP has been shown to be familial (32) and associated with variants in 7 different genes (Table 4).

Table 4. Genetic mutations associated with ERS

Gene Defects Associated with ERS				
	Locus	Gene/Protein	Ion channel	% of proband
ERS1	12p11.23	KCNJ8, Kir6.1	$\uparrow I_{K\text{-}ATP}$	Rare
ERS2	12p13.3	CACNA1C, Cav1.2	$\downarrow I_{Ca}$	4.1%
ERS3	10p12.33	CACNB2b, Cavß2b	$\downarrow I_{Ca}$	8.3%
ERS4	7q21.11	CACNA2D1, Cava2δ1	$\downarrow I_{Ca}$	4.1%
ERS5	12p12.1	ABCC9, SUR2A	$\uparrow I_{K\text{-}ATP}$	Rare
ERS6	3p21	SCN5A, Nav1.5	$\downarrow I_{Na}$	Rare
ERS7	3p22.2	SCN10A, Nav1.8	$\downarrow I_{Na}$	Rare

According to the experimental evidence that activation of the IK-ATP current can generate an ERP in canine ventricular wedge preparations, variants in KCNJ8 and ABCC9, responsible for the poreforming and ATP-sensing subunits of the IK-ATP channel, have been reported in patients with ERS (33). Loss-of-function variations in the α1, β2, and α2δ subunits of the cardiac L-type calcium channel (CACNA1C, CACNB2, CACNA2D1) and the α1 subunit of NaV1.5 and NaV1.8 (SCN5A, SCN10A) have been also reported in patients with ERS (34,35).

It is mandatory to specify that only a small fraction of identified genetic variants in the genes associated with JWSs have been studied using functional expression tests to assess causality and establish a probable contribution to pathogenesis, this knowledge in this field has to be considered as preliminary.

Therefore genetic testing in ERS is thus restricted to the research field since it does not have clear utility yet (36).

Pathophysiology of ERS

As in the case of Brugada syndrome, hypotheses to justify the presence of prominent J waves on ECG explored both repolarization as well as depolarization abnormalities.

According to the classical theory explaining the ECG appeareance in Brugada syndrome, also for ERS the repolarization hypothesis asserts that J waves might be associated with an increased transmural heterogeneity of ventricular repolarization which might increase the vulnerability to VF (37)

Repolarizing gradients across diffent layers of the left ventricular wall might be due to the presence of increased outward currents (mediated either by Ito, IK-Ach or IK-ATP), or a decreased inward depolarizing currents (thus implying a role for INa or ICaL). This repolarization defect is accentuated by cholinergic agonists and reduced by quinidine, isoproterenol, cilostazol, and milrinone, accounting for the ability of these agents to reverse the repolarization abnormalities responsible for ERS (38). Higher intrinsic levels of Ito in the inferior LV were also shown to underlie the greater vulnerability of the inferior LV wall to VT/VF.

On the other hand, the depolarization hypothesis suggests that the presence of a delayed conduction of ventricular depolarization might be the cellular mechanism at the base the disease. This hypothesis originated by the evidence that in a small serie of patients with idiopathic ventricular fibrillation and ERS evidence of late potential was significantly greater than in patients without ER (39). Nonetheless, in the original observation of Haisaguerre and coauthors, the prevalence of late potentials in patients with resuscitated IVF was similar in those with and without ERS, somehow disconfirming this hypothesis. Moreover, the typical response of BrS and ERs to rise in heart rate is the diminution of ST-segment elevation, opposite to that expected at a site of discontinuous conduction. The diminution of ST-segment elevation is consistent with the reduced availability of Ito at the faster rate, due to slow recovery of the current from inactivation.

The congruence between BrS and ERS with respect to clinical manifestations and response to therapy lends further support to the repolarization hypothesis.

Risk stratification

Great efforts have been devoted by several groups in the evaluation of clinical and electrocardiographic markers of increased arrhythmic risk in patients with early repolarization. Nonetheless, identification of otherwise healthy subjects with a

clear increased risk of arrhythmic episodes according to certain ECG features still represents a dilemma.

The incidental discovery of a J wave on routine ECG should not be interpreted as a marker of increased risk of sudden cardiac death. In fact, even in the subpopulation of subjects with J waves at ECG, this remains an extremely rare phenomenon, being the odds for a fatal event estimated to be 11:100000 as compared to 3.4:1000000 in the general population without J wave (20). Nonetheless, according to data derived from case control and prospective studies several ECG characteristics might be associated with increased likelihoods of idiopathic ventricular fibrillation, cardiac deaths or total mortality.

While the seminal case control study by Haissaguerre and colleagues recognized the presence of any J point elevation ≥1mV as being associated with a 10.9 hazard ratio of idiopathic ventricular fibrillation, subsequent analyses pointed out several other associated characteristics that might furtherly stratify the arrhythmic risk. Initially, the works by Rosso et al identified the presence of J point elevation in the inferior and lateral (I/aVL) leads as being significantly associated with an increased risk of arrhythmic events. Interestingly, the presence of J point elevation in the precordial lateral leads (V4-V6) was not associated with an increased arrhythmic risk (19). Subsequently, Cappato et al., while confirming the

observations made by Rosso, pointed out that the morphology of the J wave might have played a role in risk stratification (40). The presence of a QRS slurring in any lead was in fact associated with a statistically significant risk of arrhythmic events as compared to other morphologies.

The two large, prospective population studies published by Tikkanen et al in 2009 and 2011 proposed two additional electrocardiographic markers able to risk stratify patients. First the height of the J point (as defined as a J point elevation $\geq$2 mm in the inferior leads), then the presence of a horizontal/descending ST segment were both demonstrated to be significantly associated respectively with arrhythmic death or sudden death (41,42).

The large prospective population based study published by Rollin et al in 2012, while confirming the role of an horizontal-descending ST segment, recognized the presence of a notched J wave as significantly associated to the risk of total and cardiovascular mortality (Odds ratio 3.11 95% CI:1.72-5.6; p=0.001 and 8.32 95% CI: 3.32-20.8 p=0.001, respectively) (43).

It is worth to mention that the aforementioned ECG criteria seems to predict potentially lethal events in caucasian, while their presence doesn't seem to play a significant role in black individuals (44,45). No additive role have been

recognized by other tools, in particular pprogrammed ventricular stimulation hasn't shown any role in risk stratifying ERP patients (46).

Patient management

Current evidences do not support any kind of warning, limitation or treatment to healthy individuals with any kind of early repolarization pattern, even those considered to be at high risk of arrhythmic events. Clinical follow up is nonetheless warranted by current guidelines (47). Accordingly, in those asymptomatic subjects with high risk ECG patterns (prominent J waves, horizontal ST segment, high dynamicity) and strong family history of unexplained sudden death at young age, prophylactic implant of an cardioverter defibrillator might be considered after weighting the risks associated with the implant (47). Paradoxically, the treatment of patients who survived an episode of idiopathic ventricular fibrillation and in whom the only alteration discovered with a multimodality approach is the presence of a J-point elevation is somehow easier than the management of more ambiguous situations.

After an episode of successfully resuscitated idiopathic ventricular fibrillation or episodes of ventricular arrhythmias/electrical storms an implantable cardioverter device is indicated (Class I indication). In case of arrhythmia recurrences, to reduce the number of appropriate shocks, therapy with ora quinidine or cilostazol

has shown to be effective. Some initial evidences in small series support the use of intravenous isoproterenol infusion in the management of patients presenting with arrhythmic storms. Adrenaline also showed to be effective in two patients whereas procainamide, lidocaine, verapamil, amiodarone, nifekalant, dofetilide, b-blockers, and magnesium sulfate failed to control recurrent arrhythmic episodes (48).

The management of those patients with other symptoms such as syncope, seizure, nocturnal agonal respiration or palpitations with ECG evidence of an early repolarization pattern should start from a careful personal and family history taking, to rule out/in the presence of a familial predisposition to sudden cardiac death. No common protocols exists on how to manage those patients. While current guidelines drive the choice on the estimated probability of arrhythmic origin of symptoms, our approach is to obtain at index evaluation a good quality 12-lead ECG with standard leads position and with V1–V2 in the second intercostal space and a 24-h Holter ECG monitoring (preferentially a 12-lead recording). In those cases with recurrent episodes, implant of a loop recorder could be considered to obtain a definite diagnosis, with ICD implant considered only as a second option (Class IIb in current ESC guidelines).

Aim of the study

The present research project started back in 2012 after a dramatic event.

During that year, the seminal work of Haissaguerre, followed by the reports by

Rosso and Tikkanen were the only initial and somehow cryptical evidences about

the potential malignant role of early repolarization pattern. The cardiological

community was puzzled by the contradiction between the traditional benignity of

this electrocardiographic pattern, its common presence in active, otherwise healthy

individuals and the findings of the aforementioned original reports.

While the academic discussion went on, the Italian public opinion was shocked

by the sudden death of a professional athlete, Piermario Morosini (July the 5th

1986 – April the 14th 2012), occurred during a professional football match.

Even if the post-mortem examination proposed an alternative cause for his death,

this dramatic event gave us the input to our group to get involved in this research

field with the aim in clarifying the role of Early Repolarization, with three

particular focuses:

- Clarify the historical evolution of early repolarization from the initial
  description to the renewed definitions.

- Investigate the prevalence of J point elevation, its clinical,
  electrocardiographic and echocardiographic characteristics in a population

of elite soccer players, to search for correlations with the classical structural and electrocardiographic features of the athlete's heart and to describe the outcome at long-term follow-up.

- Investigate whether additional electrocardiographic markers, beside J point elevation, its localization, the morphology of the ST segment might help in risk stratifying patients. In particular amplitude of J waves by measuring slope and duration were evaluated as markers of increased arrhythmic risk.

Those three focuses have been in depth analysed in three different papers published in peer reviewed journals:

1) Biasco L, Cristoforetti Y, De Backer O, Castagno D, Giustetto C, Orzan F, Gaita F. Early repolarization: an evolving concept for the past 70 years. J Cardiovasc Med. 2016;17:4-10. doi:10.2459/JCM.0000000000000276.

2) Biasco L, Cristoforetti Y, Castagno D, Giustetto C, Astegiano P, Ganzit G, Gribaudo CG, Gaita F. Clinical, electrocardiographic, echocardiographic characteristics and long-term follow-up of elite soccer players with J-point elevation. Circ Arrhythm Electrophysiol. 2013;6:1178-84.

3) Cristoforetti Y, Biasco L, Giustetto C, De Backer O, Castagno D, Astegiano P, Ganzit G, Gribaudo CG, Moccetti M, Gaita F. J-wave

duration and slope as potential tools to discriminate between benign and

malignant early repolarization. Heart Rhythm. 2016;13:806-11.

Paper # 1.

Biasco L, Cristoforetti Y, De Backer O, Castagno D, Giustetto C,

Orzan F, Gaita F.

Early repolarization: an evolving concept for the past 70 years.

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FIC Federazione Italiana di Cardiologia
Italian Federation of Cardiology

Early repolarization: an evolving concept for the past 70 years

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For more than 70 years, early repolarization has been considered to be a common normal variant. In the general population, the prevalence ranges between 5 and 13%, and in athletes, a rising trend is observed from 20 to 90%. Nevertheless, from the latter half of the 1990s, a growing number of case reports, series, observational and prospective studies reported that the presence of various electrocardiographic patterns attributed to early repolarization may constitute a potential marker for the increased risk of sudden death in otherwise normal individuals, casting a dark shadow on this ECG peculiarity. This review provides a historical summary of the evolution of the concept of early repolarization from its original description to the latest works and a guide to help physicians in evaluating individuals with this common electrocardiographic pattern.

Introduction

For more than 70 years since its original description in 1936,[1] the electrocardiographic pattern defined as 'early repolarization', 'unusual RT-segment deviation', 'juvenile ST variant' or 'normal RS-T segment elevation variant' has been unanimously considered to be a common normal variant.

In the general population, its prevalence ranges between 5% and 13%, while in athletes from 20 to 90%.[2–4] Nevertheless, from the latter half of the 1990s, a growing number of case reports, series, observational and prospective studies reported that the presence of various electrocardiographic patterns attributed to early repolarization may constitute a potential marker for the increased risk of sudden death in otherwise normal individuals, casting a dark shadow on this ECG peculiarity.

Historical background

Classical definition

The first available electrocardiographic description of an early repolarization pattern as a normal variant dates back to the work by Shipley and Hallaran.[1] These authors described the common presence in medical students and young nurses' ECGs of a terminal QRS slurring or notching defined, respectively, as 'a momentary retardation of string movement' or 'an actual change in direction of the string movement' (Fig. 1a).

Early reports from the 1950s to 1970s used relatively imprecise and inconsistent definitions to describe the same ECG finding. In 1961, Wasserburger et al.[5] defined a 'normal precordial RS-T segment elevation variant'

characterized by '(1) an elevated take off of the ST segment at the J junction of the QRS complex, varying from 1 to 4 mm... (2) a downward concavity of the ST segment; and (3) symmetrically limbed T waves...' (Fig. 1b).

In 1977, Friedman defined the early repolarization as a normal variant characterized by the presence of a notch at the transition of the QRS complex into the ST segment, the latter with a concave upward displacement of 2 or even 3 mm in the precordial and occasionally in the peripheral leads, and tall, broad-based and upright T waves[6] (Fig. 1c).

In 1988, Schamroth used the term 'early repolarization syndrome, vagotonia, the athlete's heart' to indicate a common normal pattern characterized by the presence of a thickening or slur of the terminal part of the QRS that may appear as a distinct notch or 'hook' on the distal limb of the QRS complex associated with concave upward elevated ST segment, tall and symmetrical T waves and other minor characteristics[7] (Fig. 1d).

The interest toward early repolarization was mainly oriented in differentiating this common, and possibly misleading pattern, from other conditions such as acute myocardial infarction, pericarditis, hyperkalemia or hypothermia also characterized by a displacement of the ST segment.

Milestone works confirmed the benign nature of the early repolarization pattern together with the characteristic features of a prevalent manifestation in male, black, young and physically active individuals.[5,8,9]

DOI:10.2459/JCM.0000000000000276
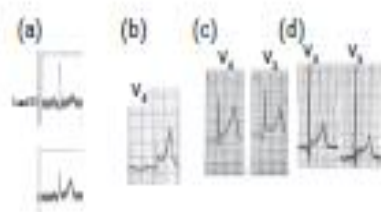
(a) ECG published by Shipley and Hallaran[1] with terminal QRS 'notching' (up) or 'slurring' (down) in leads II and III (modified); (b) ECG pattern defined as 'normal RS-T segment elevation variant' from Wasserburger et al.[5]; (modified); (c) early repolarization pattern presented by Friedman[6]; (d) 'early repolarization syndrome, vagotonia, the athlete's heart' ECG pattern as defined by Schamroth (modified).[7]

Abnormal QRS–ST-segment transitions as a possible marker of increased arrhythmic risk

In 1984, Otto *et al.*[10] described the features of three young male immigrants from south-east Asia with idiopathic recurrent ventricular fibrillation occurred during the early hours of the morning. Their ECGs showed a broad slurring of the terminal portion of the QRS complex, that was interpreted as a possible sign of ischemia or intraventricular conduction defect. At electrophysiological testing, rapid polymorphous ventricular tachycardia was induced, not suppressed by procainamide infusion, whereas oral quinidine prevented the reinduction of ventricular arrhythmias.

Some years later, Aizawa *et al.*[11] published a series of eight young Japanese patients with idiopathic ventricular fibrillation. Their ECGs were characterized by the presence of an unusual terminal QRS notching in the inferior and lateral leads. The terminal QRS notching became more marked in post-extrasystolic depolarizations. This phenomenon was attributed to a bradycardia-dependent intraventricular block (Fig. 2a).

In 1998, Garg *et al.*[12] reported the case of an 18-year-old boy with family history of premature sudden death, who was resuscitated after an episode of idiopathic ventricular fibrillation. At ECG an abnormal low-amplitude terminal QRS deflection (labeled for the first time as 'J wave') in the inferior (II, III, aVF) and anterolateral leads (V3–V6, I and aVL) (Fig. 2b) that persisted on serial ECG tracings was evident. Neither intravenous procainamide nor oral atenolol could prevent the reinduction of the ventricular
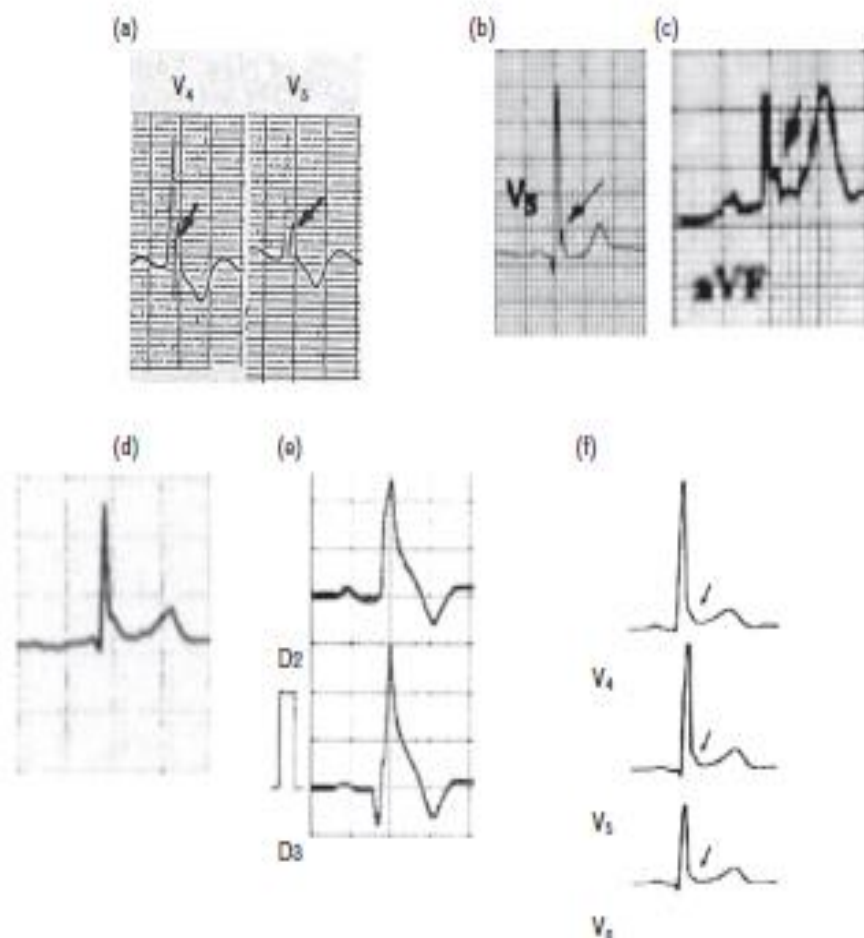
Morphologies of the QRS–ST transition in patients with ventricular arrhythmias as presented (modified from): (a) Aizawa *et al.*[11], (b) Garg *et al.*[12], (c) Kalla *et al.*[13], (d) Takagi *et al.*[14], (e) Riera *et al.*[15], and (f) Haïssaguerre *et al.*[16]

arrhythmias. Oral quinidine caused the disappearance of the abnormal J waves and prevented further induction of ventricular arrhythmias.

Kalla et al.[13] described in 2000 the similar case of a 29-year-old Vietnamese patient resuscitated after a nocturnal episode of ventricular fibrillation. The electrocardiogram recorded a prominent J wave (labeled by the author Osborn wave, like the terminal QRS slurring commonly observed during hypothermia) with ST-segment elevation mainly evident in leads II, III, and aVF (Fig. 2c). Of note, the authors described dynamic changes of the ECG pattern observed at serial monitoring during hospitalization. The authors interpreted this electrocardiographic pattern as a Brugada syndrome variant.

In the same year Takagi et al.[14] reported two cases of nocturnal idiopathic ventricular fibrillation and one case of nocturnal syncope with inducible ventricular fibrillation in otherwise healthy young men. The ECGs were characterized by a terminal slurring of the QRS complex (labeled J wave) in the inferior leads (Fig. 2d). A 24-h European Society of Cardiology recording revealed infrequent or no ventricular extrasystoles in all three patients. Intravenous disopyramide increased ST-segment elevation in the inferior leads, whereas treadmill testing caused the ST-segment elevation to decrease or disappear at peak exercise. Also in this article, the similarities with the clinical and the dynamic electrocardiographic presentation of Brugada syndrome were highlighted.

All these early reports have some aspects in common:

(1) all those patients had idiopathic ventricular fibrillation with structurally normal heart, but at ECG an abnormal transition between the QRS complex and the ST segment was evident, variously labeled by the authors;
(2) similarities with other entities characterized by an abnormal QRS–ST transition such as the Brugada syndrome or the hypothermic Osborn wave were underscored;
(3) no relation proposed between the described electrocardiographic abnormalities and the classical early repolarization pattern.

In 2000, Gussak and Antzelevitch[16] analyzed the similarities between the early repolarization and the Brugada ECG pattern not only from a clinical but also from an electrophysiological point of view. The mechanism proposed for the J-point and ST-segment elevation in both syndromes, derived from studies in hypothermic canine models with Osborn wave, is an I_{to}-mediated loss or reduction of the transmembrane voltage gradient during phase 2 of the myocardial action potential, leading to a transmural voltage gradient between the epicardial and endocardial layers. As this could be a substrate for phase 2 reentry, the authors proposed the hypothetical possibility that early repolarization may not be as benign as generally believed particularly if associated with conditions characterized by an increased dispersion of refractoriness such as myocardial ischemia.

The interpretation of Gussak and Antzelevitch appeared to be contradicted by the results of a study by Klatsky et al. in 2003,[18] where the authors reviewed the medical history and ECG recordings of 2234 individuals obtained during screening examinations from 1983 to 1985. In line with classical definitions, the presence of a ST-segment elevation more than 1.0 mm was required. After a follow-up of 14 years the authors concluded that there was no evidence that early repolarization was associated with a greater likelihood of fatal or nonfatal cardiovascular events.

Redefined concept of early repolarization

In 2008 Haissaguerre et al.[15] published a case–control retrospective study that compared the electrocardiographic characteristics of 206 patients with idiopathic ventricular fibrillation with those of 412 controlled healthy individuals. In this work a new definition of early repolarization was proposed representing a turning point from previous classical descriptions. Haissaguerre and coworkers adopted the definition of ER as a J point elevation >1 mm in inferior and/or lateral leads irrespective of the morphology of the ST segment that was not taken into consideration. As evident, when comparing provided images, the difference between Haissaguerre's tracings (Fig. 2f) and those reported by Wasserburger, Friedman and Schamroth (Fig. 1b–d) is obvious. The prevalence of this redefined early repolarization was significantly higher in ventricular fibrillation cases versus controls (31 versus 5%, $P < 0.001$). Moreover, cases showed a significantly higher J-point elevation that became even more evident in concomitance of an arrhythmic event. Haissaguerre's patients also were more frequently men, had frequent arrhythmic events in the early hours of the morning and were protected by oral quinidine.

In the same year, Rosso et al.[3] added to the complexity by defining the transition of the QRS-ST segment as 'J-point elevation or J wave' when a positive notch was evident during the terminal portion of the QRS complex (Fig. 3a) or 'slurred' when the R wave gradually merged into the ST segment, with upright concavity without a clearly evident J-point (Fig. 3b). The presence of a J-point elevation was confirmed to be more common in patients with idiopathic ventricular fibrillation than in young control individuals or athletes. The 'J-point elevation or J wave', but not the morphology of the ST segment or the location of the J waves (anterolateral versus inferior leads), was thus recognized as a possible marker of increased arrhythmic risk.

Fig. 3
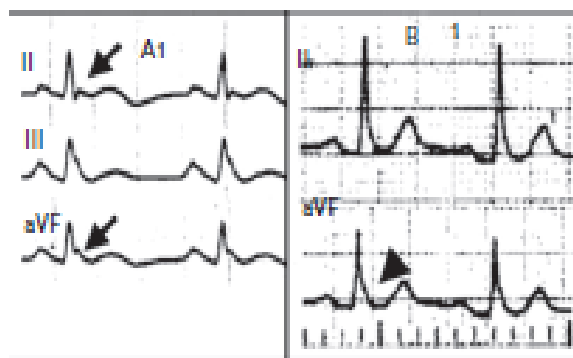
Morphologies of the QRS–ST transition presented (modified from) Rosso *et al.*[a] and defined as: (a) J-point elevation and (b) slurring.

In 2009, Tikkanen *et al.*[19] published an analysis of 10864 ECGs recorded in adult individuals at a mean age of 44.0 ± 8.5 years enrolled in the Finnish Social Insurance Institution's Coronary Heart Disease Study between 1966 and 1972. Using the definition proposed by Klatsky,[18] they reported a 5.8% prevalence of J-point elevation. This work moved a step forward in the recognition of an electrocardiographic pattern associated with an increased risk of arrhythmic events. A J-point elevation at least 2 mm in the inferior leads (recorded only in 0.3%) was associated with an increased risk of death, whether arrhythmic, from cardiac causes or from any cause. A subsequent reanalysis of this population[2] introduced the concept that not only a marked J-point elevation in the inferior leads but also a horizontal/descending ST segment is associated with an increased arrhythmic risk. This finding was subsequently confirmed by Rosso *et al.*[20]

In 2012, the group of Aizawa *et al.*[11] noted that the presence of a 'pause dependency phenomenon', that is a striking accentuation of the J waves after a sudden prolongation of the R–R interval, originally described in 1992, could be an adjunctive electrocardiographic marker of increased arrhythmic risk, being manifest in 55.6% of ventricular fibrillation cases but not in any of the controls.[21]

In summary, recent large-scale retrospective[2,3,16,19] and prospective[22] studies have identified a particular subgroup of individuals with clinical (young, man) and ECG characteristics (a markedly anomalous transition of the QRS complex into the ST segment defined by a significant, dynamic J-point elevation in the inferior leads, occasionally associated with inverted T waves) that may be at increased risk for sudden death if compared with the general population. This risk has also been estimated to be 3,4/100.000 in the normal population, 11/100.000 in subjects with J point elevation and 34/100.000 in case of J point elevation associated with horizontal ST segment.[3,20]

Need for a time out

Despite the above-mentioned acquisitions great uncertainties still exist. These are mainly related to the electrocardiographic definitions and terms used to describe this pattern, to its role as a predictor of arrhythmic events in the various subgroups of the general population in terms of age, sex and level of physical activity and to its arrhythmic potential during situations predisposing to a marked dispersion of refractoriness such as myocardial ischemia.

Electrocardiographic definitions

As evident from the historical background section, the electrocardiographic definition of early repolarization has varied considerably. For years any deflection noted at the transition between the QRS complex and the ST segment, independently from its morphology, has been identified as J wave (comprising the traditional early repolarization, the Brugada ECG pattern, the slurred and prominent wave described in the reports of idiopathic ventricular fibrillation, and the Osborn wave).

Clearly, the morphology of the transition between the QRS complex and the ST segment plays a pivotal role in the differentiation between normal and abnormal ECG patterns, but unfortunately univocal and codified terms are still unavailable.

In a commentary entitled 'Inappropriate and confusing electrocardiographic terms. J wave syndrome and early repolarization' Surawicz and Macfarlane[23] made an appeal for not using in publications the terms 'J-wave syndromes' and 'early repolarization' until such terms were properly defined by appropriate task forces. The need for a careful description of the transition between QRS complex and ST segment in terms of J-point elevation, terminal QRS abnormalities and ST-segment elevation was stressed.[23]

Surawicz and Macfarlane defined the 'J (junction) point' as the point of transition between the QRS complex and the ST segment. As such, it is present in every electrocardiogram. It is often situated above the isoelectric line both in healthy individuals and in pathological conditions (e.g. acute myocardial infarction, pericarditis). The degree of J-point elevation may also vary according to sex, age, race and recording lead.[24–26] Considering the wide variability of the J-point elevation in healthy participants, it is not known how elevated a normal J point can be.

The 'J wave', originally identified in hypothermic patients (Osborn wave), is a discrete slow deflection at the end of the QRS complex of uncertain genesis that is rarely encountered. In the presence of a J wave, the correct identification of the J point and the evaluation of the QRS duration become challenging.

Since its original description the terms 'notched' or 'slurred' have been used. Not only the morphological

differentiation between these two entities is often subtle, but notched and slurred morphologies can be recorded in different leads of the same ECG tracing.

In 2004, Gussak et al.[27] proposed the term 'λ (lambda) wave' to describe an anomalous morphology of the QRS–ST-segment transition characterized by the presence of a positive QRS complex, J-point elevation, descending ST segment and negative T waves in inferior and lateral leads[16] (Fig. 2f). The term 'λ wave' together with other proposed terms such as 'terminal delta waves' – preferred by our group – points the attention to the final portion of the QRS complex that shows an enlargement and a change in the slope of the descending limb of the R wave. These terms appear as being less confusing and more informative than those currently used.

'Early repolarization' in the athletes

The classical early repolarization pattern appears to be the rule in the athletes, being manifest in a large percentage of the athletic population. From a historical perspective, the surge of interest toward early repolarization in athletes is evident from the second half of the 1960s.[28–30]

Of interest, for more than 40 years some characteristics associated with early repolarization, such as a male prevalence, the increased incidence in athletes of black ethnicity, the heart rate dependency of its appearance and the possible effect of an increased vagal tone as a mechanistic determinant of the pattern were almost unanimously adopted by researchers as a dogma.

The necessity of a clear discrimination between training-related ECG changes and pathological findings was even more perceived in that historical setting in whom the only noninvasive imaging technique available was limited to the chest radiograph.

Nonetheless nowadays, despite the significant development of imaging techniques, very little is changed from what Lichtman et al.[31] described in 1973: 'routine medical evaluations of well trained endurance athletes frequently disclose electrocardiographic abnormalities suggestive of organic heart disease. First- and second-degree atrioventricular block, altered ventricular conduction, criteria for atrial enlargement or ventricular hypertrophy, and repolarization abnormalities are commonly found. On the basis of such abnormal tracings, the athlete may be advised to refrain from his customary strenuous exertion, even though the results of physical examination are normal and there is no history suggesting cardiovascular disease.'

Renewed interest in early repolarization arose in the 1990s after the description of the Brugada syndrome, interest justified by substantial analogies in terms of possible overlapping electrocardiographic appearances,

shared electrophysiological mechanism (i.e. an increased transmural dispersion of repolarization) and the modulating effects of β-blockers.

Bianco et al.[32] in 2001 showed that a more accurate differential diagnosis between traditional early repolarization pattern and suspected Brugada morphology was necessary only in a small percentage of top-level athletes (about 8%, i.e. those with ST elevation limited to the right precordial leads with a 'convex toward the top morphology').

As stated before, after the work published on the *New England Journal of Medicine* by Haissaguerre et al. the introduction of a newly defined early repolarization had a groundbreaking effect causing the complete collapse of the common belief about its benign significance.

Noseworthy et al.[33] were the first that reevaluated the problem of early repolarization in athletes facing this new scenario. Using Haissaguerre's definition of early repolarization, they reported a prevalence of J-point elevation of 25.1% in 879 US collegiate athletes. The pattern was primarily evident in the lateral leads (V4–V6, I and aVL) rather than in the inferior leads (21.3 versus 2.5%); J-point elevation was rarely more than 2 mm in two or more contiguous leads (2% of the population studied). An ascending elevation of the ST segment was evident almost universally (99% in lateral leads and 55% in inferior leads), whereas a horizontal or descending ST segment was rare (1.7%).

Another remarkable feature in athletes is that early repolarization is substantially stable; it only becomes less evident during exercise and disappears in the case of prolonged detraining,[33] while waxing and waning of the abnormalities of the QRS–ST transition are known to occur in patients with ventricular arrhythmias.[11,13,14,16]

Our group recently published a retrospective analysis performed in a relatively large population of 332 elite professional football players. In this series the incidence of J-point elevation was 35.6%, and no cardiovascular deaths were observed at a long-term follow-up (median of 13.3 years). At multivariable analysis, the known inverse association with heart rate was confirmed while a strong signal in the direction of a potential mechanistic role of left ventricular hypertrophy was also evident.[34]

The classical morphology of early repolarization has not been recognized as a marker of risk in the general population.[2,3,19,20] On the contrary, the electrocardiographic features associated with an increased arrhythmic risk[2,3,19,20] (marked J-point elevation, inferior leads presentation, horizontal/descending ST segment) occur very rarely in the athletes.[33,34] Thus, by inference from the general population,[2] from short-term[33] and long-term[34] follow-up studies the classical early repolarization pattern in the athlete is considered a benign phenomenon. This notion is also supported by the ESC Recommendations

QRS–ST segment abnormal transition as a marker of arrhythmic potential in the course of increased dispersion of refractoriness

Most authors have approached the problem of early repolarization as a pure electrical disorder capable *per se* of causing ventricular arrhythmias. This concept is in keeping with the absence of a structural cardiac abnormality, the young age of the patients and with some analogies with other ion channel diseases such as the Brugada syndrome. A genetic base for the 'malignant' form of early repolarization is slowly coming into better focus: a rare variant of KCNJ8 responsible for the pore forming subunit of the I_{KATP} channel and loss of function mutations in the $\alpha1$, $\beta2$ $\alpha2\delta$ subunits of the cardiac L-type calcium channels have been reported in patients with J-point elevation and malignant ventricular arrhythmias.[37–39]

In addition, recent reports added a possible and unexplored characteristic. In accordance with the hypothesis proposed by Gussak, early repolarization itself may serve as a promoter or modulator of ventricular arrhythmias in the setting of structural heart disease and myocardial ischemia.[17] Patel *et al.*[39] have shown an association between the terminal QRS notching and ventricular arrhythmias in patients with stable coronary artery disease and implantable cardioverter devices, suggesting that early repolarization in the inferior leads is associated with the occurrence of ventricular tachyarrhythmias independently of left ventricular ejection fraction. Rudic *et al.*[40] found an increased prevalence of J-point elevation in patients with ischemic ventricular fibrillation compared with a control group of patients with acute myocardial infarction and no ventricular arrhythmias (47 versus 13%, $P = 0.005$). This perhaps could explain why patients with J-point elevation more than 2mm in the population of Tikkanen *et al.* had a higher mortality from the fifth decade onward, and not earlier as a channelopathy would have implied.

Practical clinical approach to participants with early repolarization

Uncertainties upon early repolarization puzzle not only the diagnostic criteria but also the management instead the original subjects.

When assessing an individual with electrocardiographic evidence of early repolarization, good advice to keep in mind is to evaluate not only the electrocardiogram but to apply a holistic approach, adding all available data to complete the puzzle.

Current evidence does not support any kind of warning, limitation or treatment to healthy individuals with any kind of early repolarization pattern.

Paradoxically, the treatment of patients who survived an episode of idiopathic ventricular fibrillation and in whom the only alteration discovered with a multimodality approach is the presence of a J-point elevation is somehow easier than the management of more ambiguous situations.

After an episode of successfully resuscitated idiopathic ventricular fibrillation an implantable cardioverter device is indicated. In case of arrhythmia recurrences, to reduce the number of appropriate shocks, therapy with oral quinidine has been shown to be effective.

Some initial evidences in small series support the use of intravenous isoproterenol infusion in the management of patients presenting with arrhythmic storms. Adrenaline also has been shown to be effective in two patients whereas procainamide, lidocaine, verapamil, amiodarone, nifekalant, dofetilide, β-blockers, and magnesium sulfate failed to control recurrent arrhythmic episodes.[41]

The management of those patients with other symptoms such as syncope or palpitations with electrocardiographical evidence of an early repolarization pattern should start from careful personal and family history taking, to rule out/in the presence of a familial predisposition to sudden cardiac death. No common protocols exists on how to manage those patients, but our approach is to obtain at index evaluation a good quality 12-lead ECG with standard leads position and with V1–V2 in the second intercostal space and a 24-h Holter ECG monitoring (preferentially a 12-lead recording). In those cases with recurrent episodes, implant of a loop recorder could be considered to obtain a definite diagnosis.

In conclusion, an increasing burden of evidence supports the concept that the classically defined early repolarization and the presence of J-point elevation/J waves are not two sides of the same coin but two distinct electrocardiographic patterns. Even if some analogies exist, important differences are recognized as markers of increased risk, such as the dynamicity, the localization of the J-point elevation in the inferior leads and the association with horizontal descending ST segment or inverted T waves, markers of a diffuse abnormality of the repolarization process.

The new hypothesis that the presence of a J-point elevation itself may also serve as a promoter or modulator of ventricular arrhythmias in the setting of structural heart disease and myocardial ischemia opens new and unexplored research fields.

Nonetheless, novel data, originally presented by our group and confirmed by subsequent studies[14,42] support the hypothesis that early repolarization in athletes is not

Paper#2

Biasco L, Cristoforetti Y, Castagno D, Giustetto C, Astegiano P, Ganzit G, Gribaudo CG, Gaita F.

Clinical, electrocardiographic, echocardiographic characteristics and long-term follow-up of elite soccer players with J-point elevation.

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Original Article

Clinical, Electrocardiographic, Echocardiographic Characteristics and Long-Term Follow-Up of Elite Soccer Players With J-Point Elevation

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Background—J-point elevation is common in athletes; nevertheless, the influence of structural changes associated with the athlete's heart and its prognostic impact are still debated. Our aim was to investigate the prevalence of J-point elevation, the associated clinical, electrocardiographic, and echocardiographic characteristics and its impact on long-term outcome in elite soccer players.

Methods and Results—Clinical, electrocardiographic, and cardiopulmonary exercise test data from 332 male professional soccer players were retrospectively analyzed. For 235 (70.7%) athletes echocardiographic data were also available. J-point elevation was defined as an elevation ≥1 mm in ≥2 contiguous leads. Long-term follow-up data were obtained for all athletes, whereas univariate and multivariable analyses were performed to assess the associated characteristics. Overall, 118 (35.6%) athletes showed a J-point elevation ≥1 mm. At multivariable analysis a significant direct association of interventricular septum thickness (odds ratio for 1 SD increase, 1.361; 95% confidence interval, 1.019–1.817; P=0.036) and Sokolow–Lyon index (odds ratio for 1 SD increase, 1.367; 95% confidence interval, 1.026–1.822; P=0.033) and an inverse association of baseline heart rate (odds ratio for 1 SD increase, 0.686; 95% confidence interval, 0.508–0.927; P=0.011) with J-point elevation were observed. During a long-term follow-up (median, 13.3 years; first and third quartiles, 10.1–17.0 years), a low mortality rate was observed, not related to cardiovascular causes.

Conclusions—The correlation between J-point elevation and interventricular septum thickness suggests a possible mechanistic role of exercise-induced left ventricular hypertrophy as the basis for J-point elevation. After a long-term follow-up, no cardiac death was observed. (*Circ Arrhythm Electrophysiol*. 2013;6:1178-1184.)

Key Words: death, sudden ■ electrocardiography ■ electrophysiology ■ exercise

For >70 years since its original description,[1] the electrocardiographic pattern defined as early repolarization (ER) or juvenile ST variant, characterized by an elevated take off of the ST segment at the J junction of the QRS complex and an upward concavity of the S-T segment, has been considered as a normal common variant.

Clinical Perspective on p 1184

In the general population, its prevalence ranges between 5% and 13%, whereas in athletes it increases from 20% to 90%.[2–4] From the second half of the 1990s, a growing number of case reports, case series, observational and prospective studies reported that the presence of various electrocardiographic patterns attributed to ER, but defined only by the presence of a J-point elevation with or without ST-segment displacement, may constitute a potential marker of increased risk of sudden death in otherwise normal subjects, casting a dark shadow on this ECG peculiarity.[5–8] Doubts about its real prognostic impact

were emphasized even more during the preparticipation screening of competitive athletes, prompting the need for a broad cardiological evaluation, often including also an arrhythmological consultation with subsequent increase in costs.

The classical ER morphology characterized by the combination of J-point elevation and elevated ST segment with an upward concavity is not considered a marker of risk in the general population.[2,3,7,8] For this reason, the classical ER pattern found in athletes, by inference from the general population[2] and from short-term follow-up studies,[9] is considered benign. In contrast, evidence of an increased risk for sudden death exists for ER patterns characterized by J-point elevation associated with a horizontal/descending ST segment. Two main questions remain unanswered: (1) Is J-point elevation observed in competitive athletes somehow linked to structural changes associated with the athlete's heart or is it a mere electrophysiological phenomenon? (2) Does J-point elevation really imply an ominous prognosis in competitive athletes?

Recent studies have investigated the prevalence of J-point elevation and the clinical, electrocardiographic, and structural left ventricular (LV) characteristics associated with this ECG finding in various types of competitive athletes (from intercollegiate to Olympic), reporting only short-term follow-up data.[2,9]

The aim of this work is to investigate the prevalence of J-point elevation, its clinical, electrocardiographic, and echocardiographic characteristics in a population of elite soccer players, to search for correlations with the classical structural and electrocardiographic features of the athlete's heart and to describe the outcome at long-term follow-up.

Methods

Study Design and Population

Overall, 338 male professional elite athletes, members of soccer clubs participating in the Italian national soccer championships, who underwent the first preparticipation screening between June 1980 and April 2008 at the Turin Institute of Sport Medicine were screened and retrospectively evaluated. Six subjects with negative T waves with a voltage >0.2 mV in >2 contiguous leads were excluded. The final cohort consisted of 332 subjects with an age between 15 and 37 years. The preparticipation screening consisted in the collection of a detailed clinical and training history and physical examination. All subjects underwent a 12-lead ECG recording and a symptom-limited cardiopulmonary exercise test (Bruce protocol) with expired gas analysis. In subjects evaluated from 1989 to 1995 (n=87), echocardiography was performed at discretion of the evaluating physician (n=25), afterward all athletes (n=245) underwent echocardiography. The study protocol was approved by the institutional ethics committee. A written informed consent was obtained by all subjects.

ECG Analysis

All electrocardiograms were retrospectively analyzed by 2 independent reviewers who were blinded to subjects' characteristics. In ambiguous cases adjudication was achieved by consensus with a third reviewer.

All measurements were obtained with the use of 4× magnification lens. For all voltage measurements, the isoelectric line was considered to be the PR segment.

Heart rate, P wave duration, PR interval, QRS duration, and QT interval were measured in lead II. In case of J-point elevation evident in lead II, QRS duration was measured in lead I. Correction of the QT interval was obtained using the Bazett formula ($QTc=QT/\sqrt{RR}$). Left atrial enlargement, first and second degree type I atrioventricular block, left anterior fascicular block, left posterior fascicular block, complete/incomplete, right and left bundle block were defined according to the American Heart Association/American College of Chest Physicians/Heart Rhythm Society recommendations.[10–12] QRS amplitude was recorded as a continuous variable using both the Sokolow–Lyon (S in V1+R in V5 or V6 whichever greater) and the Cornell voltage index (R in aVL+S in V3). Voltage criteria for LV hypertrophy were defined by the presence of ≥1 between the Sokolow–Lyon ≥35 mm and the Cornell voltage index ≥28 mm.

The ECG was deemed consistent with a J-point elevation if an elevation ≥1 mm of the J point was evident in ≥2 contiguous leads. The height of J-point elevation was measured in the lead showing the greatest elevation. The presence of J-point elevation was categorized in each of the 12 leads separately and by territory (anterior [V1 to V3], inferior [II, III, aVF], lateral [V4 to V6, I, and aVL]). In line with the original definition of ER,[1,13–15] J-point elevation in the anterior leads (from V1 to V3) was not excluded.

In subjects with J-point elevation, the QRS-ST transition was classified into 3 groups according to its morphology in each lead. ER without J wave was defined by the combined presence of J point and ST-segment elevation in the absence of any J wave. As previously reported,[23] a notched J wave was defined by the presence of a sharp and well-defined hump immediately after the R wave, whereas 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 (Figure 1). To estimate the entity of J-point elevation in this subgroup of subjects, the J-point elevation at the intersection between the tangents of the descending limb of the QRS complex and the J wave was measured.

The morphology of the ST segment was classified into concave/rapidly ascending (elevation of the ST segment >1 mm within 100 ms after the J point or after the change in slope of the terminal portion of the QRS complex) and horizontal/descending (ST-segment elevation ≤1 mm within 100 ms after the J point or after the change in slope of the terminal portion of the QRS complex).[2]

Echocardiography

A complete echocardiographic assessment, performed during their first evaluation by a single experienced cardiologist, was available for 235 athletes. For 35 athletes an incomplete echocardiographic examination was available, but deemed inadequate because of mainly descriptive reports. Echocardiography was performed to obtain cardiac chamber measurements and to exclude the presence of structural heart disease. Measurements of left atrial anteroposterior diameter, LV wall thickness, LV systolic and diastolic diameters, volumes, and ejection fraction were obtained in compliance with contemporary guidelines.[16]

Follow-Up

For 269 (81.0%) athletes repeated clinical and electrocardiographic evaluations were available. The vital status was ascertained on 100% of the athletes as of October 2012 looking through Turin's Institute of Sport Medicine archive, the soccer club's databases, and the National Soccer Player Association online database. Follow-up started from the date of the first preparticipation screening and lasted until October 2012.

Statistical Analysis

Descriptive analysis was performed using mean±SD for continuous variables and counts and percentages for categorical variables. Comparisons between groups were performed with the Student t test, 1-way ANOVA, and Yates corrected or uncorrected χ^2 method when appropriate. All probability values were considered to be significant at a value ≤0.05. Only data of athletes who underwent echocardiographic examination were used for univariate and multivariable logistic regression analysis with a stepwise approach to identify characteristics associated with the presence of J-point elevation. Odds ratio (OR) were calculated per 1 SD increment and are expressed in the respective measure value. Using the entire population follow-up data, Kaplan–Meier survival curves were plotted, stratifying by the presence/absence of J-point elevation. All the analyses were performed with SPSS software (SPSS, Chicago, IL).
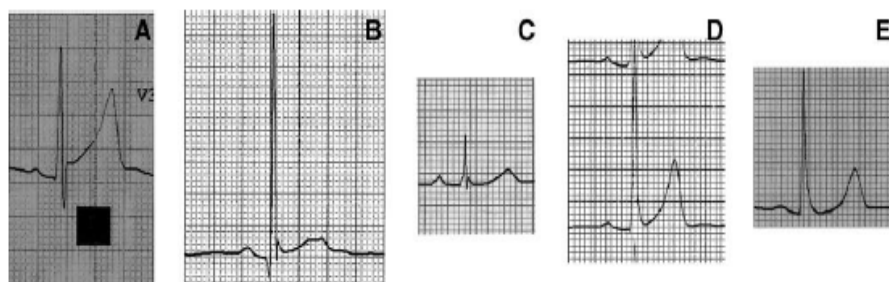

Figure 1. Morphologies of the QRS-ST transitions. **A**, Early repolarization without J wave. **B**, Notched J wave with ascending ST segment. **C**, Notched J wave with horizontal/descending ST segment. **D**, Slurred J wave with ascending ST segment. **E**, Slurred J wave with horizontal/descending ST segment.

Results

Clinical characteristics of athletes are shown in Table 1. Mean age at the time of ECG recording was 23.6±5.3 years; black athletes represented the 8.1% of the population. Average maximal oxygen consumption and maximal workload achieved during symptom-limited cardiopulmonary exercise test were 53.5±11.0 mL/(kg·min) and 237.7±41.4 Watts, respectively, consistent with a top-level physical training for soccer players.

Two hundred fourteen (64.4%) athletes showed an isoelectric J point (ISO J group), whereas in 118 (35.6%) a J-point elevation (ELE J group) at basal ECG was present. Excluding the anterior leads (from V1 to V3) any other type of J-point elevation was evident in 85 (25.6%) subjects.

The presence of J-point elevation was more frequent in black than in white athletes (62.9% versus 33.1%; RR, 1.901; 95% confidence interval [CI], 1.366–2.647; $P=0.003$). No significant differences in terms of age, weight, height, and body surface area were evident between athletes with and without J-point elevation. Exercise capacity and maximal aerobic capacity did not significantly differ between athletes with and without J-point elevation.

Electrocardiographic Characteristics

Basal ECG parameters are shown in Table 2. J-point elevation was more frequently observed in subjects with slower heart rate (ISO J group: 59.8±13.6 beats per minute versus ELE J group: 54.6±10.0 beats per minute; $P<0.001$) and increased voltage of the precordial leads evaluated with Sokolow–Lyon index (ISO J group: 30.3±9.1 versus ELE J group: 34.2±11.3; $P<0.001$; RR for positive Sokolow index, 1.392; 95% CI, 1.045–1.853; $P=0.034$). Moreover, subject with J-point elevation showed shorter QRS duration (ISO J group: 85.1±9.7 versus ELE J group: 82.5±9.4 ms; $P=0.019$) and shorter corrected QT interval (ISO J group: 391.8±30.3 versus ELE J group: 384.4±29.1 ms; $P=0.032$).

In ELE J group, average J-point elevation was 1.9±0.9 mm (range between 1 and 6 mm) and J-point elevations >3 mm were rarely found (5.1% of subjects; Figure 2, left). Mean number of leads showing a J-point elevation (including V1-V3) was 3.4±1.4 (range between 2 and 8; Figure 2, right).

QRS-ST Transition Morphology

Distribution of different QRS-ST transition morphologies in ELE J group is shown in Table 3. Subjects with notched, slurred J waves, and ER without J wave showed a progressive lengthening of the QRS complex duration (notched J waves, 78.8±8.8 ms; slurred J waves, 81.3±8.3; ER without J wave, 85.7±9.9; $P=0.005$).

J-Point Elevation Distribution

Considering only athletes with a single morphology of the QRS-ST transition, 40 (33.8% of the ELE J group) subjects showed a J-point elevation in the lateral (V4 to V6) leads, 26 (22.0% of the ELE J group) in the anterior (V1 to V3) leads, 17 (14.4% of the ELE J group) in the inferior (II, III, and aVF) leads, 7 (5.9% of the ELE J group) in the both anterior and lateral leads, and only 5 (1.5% of the ELE J group) in the inferior and lateral leads.

Considering the morphologies and distribution of QRS-ST transition in any single lead in the ELE J group (Figure 3), ER without J wave was more common in the anterior leads, whereas the presence of a notched or slurred J waves was more frequently observed in lateral or inferior leads, respectively.

ST-Segment Morphology

Description of the different ST-segment morphologies is shown in Table 3. The combined presence of J-point elevation, slurred J wave, and horizontal/descending ST segment in the inferior leads recognized in the general population as a possible marker of arrhythmic risk was rare and manifests only in 4 (1.2%) athletes.

Echocardiography

Complete echocardiographic data were available for 147 athletes of the ISO J group and for 88 of the ELE J group (Table 4). No significant differences were observed between groups in terms of LV diameters, ejection fraction, or left atrial anteroposterior diameter. Interventricular septum resulted significantly thicker in subjects with J-point elevation compared with those without J-point elevation (ISO J group: 10.2±1.4 mm versus ELE J group: 10.8±1.6 mm; $P=0.002$), whereas LV posterior wall thickness was almost significantly thicker in the former group (ISO J group: 9.3±1.1 mm versus ELE J group: 9.6±1.3 mm; $P=0.06$).

Univariate analysis revealed that black race, lower heart rate, Sokolow–Lyon index, and interventricular septum thickness were

Table 1. Clinical Parameters

	Total Population (N=332)	Isoelectric J Point (n=214)	Any J-Point Elevation (n=118)	P Value
Mean age at first ECG, y	23.6±5.3	23.6±5.2	23.5±5.5	0.869
Weight, kg	75.7±7.2	75.6±7.2	75.8±7.2	0.808
Height, cm	180.0±5.9	180.2±5.7	179.6±6.1	0.371
BSA, m²	1.9±0.1	1.9±0.1	1.9±0.1	1
Race, n (%)				
White	305 (91.9)	204 (95.3)	101 (85.6)	0.003
Black	27 (8.1)	10 (4.7)	17 (14.4)	
Exercise capacity				
Vo₂ max, mL/(kg·min)	53.5±11.0	53.3±12.3	54.0±8.4	0.582
Maximal workload, W	237.7±41.4	236.8±40.5	239.2±43.1	0.614
Follow-up, person-years	4531.5	2999.0	1532.5	

Table 2.   Basal ECG Parameters

ECG Parameters	Total Population (N=338)	Isoelectric J Point (n=214)	Any J-Point Elevation (n=118)	P Value
Rhythm				
Sinus rhythm, n (%)	324 (95.9)	208 (97.2)	110 (93.2)	
Atrial rhythm, n (%)	13 (3.8)	5 (2.3)	8 (6.8)	0.150*
Junctional rhythm, n (%)	1 (0.3)	1 (0.5)	0 (0)	
Heart rate, beats per minute	57.9±12.7	59.8±13.6	54.6±10.0	<0.001
P wave duration, ms	87.3±15.4	87.2±15.3	86.9±15.6	0.865
ECG criteria for left atrial enlargement, n (%)	1 (0.3)	0 (0)	1 (0.8)	
PR interval, ms	163.8±27.2	161.5±24.9	166.3±29.0	0.114
AV conduction*				
Normal, n (%)	320 (94.7)	206 (96.3)	110 (93.2)	
I degree AV block, n (%)†	16 (4.7)	7 (3.3)	7 (6.0)	0.236‡
II degree type 1 AV block, n (%)	1 (0.3)	0 (0)	1 (0.8)	
QRS duration, ms	84.3±9.7	85.1±9.7	82.5±9.4	0.019
QRS axis, °	65.1±24.1	64.8±23.9	66.2±23.5	0.608
Not determinable†	4 (1.2)	0 (0)	1 (0.8)	
Intraventricular conduction defect, n (%)†	15 (4.5)	9 (4.2)	5 (4.2)	
Anterior fascicular block, n (%)†	2 (0.6)	0 (0)	1 (0.9)	
Posterior fascicular block, n (%)	1 (0.3)	0 (0)	1 (0.9)	
Complete RBBB, n (%)	1 (0.3)	1 (0.5)	0 (0)	0.786§
Incomplete RBBB, n (%)	11 (3.3)	8 (3.7)	3 (2.5)	
Complete LBBB, n (%)	0 (0)	0 (0)	0 (0)	
QT interval, ms	401.0±34.8	397.3±35.9	406.1±31.5	0.026
Corrected QT interval, ms	389.3±30.0	391.8±30.3	384.4±29.1	0.032
Sokolow–Lyon index, mm	31.8±10.2	30.3±9.1	34.2±11.3	<0.001
Positive Cornell voltage index, n (%)†	22 (6.5)	16 (7.5)	4 (3.4)	0.209
Negative T waves, n (%)	6 (1.8)	. . .	. . .	

LBBB indicates left bundle branch block; and RBBB, right bundle branch block.

*Sinus rhythm (SR) vs other than SR.

†In the second and third column, data of subjects with negative T waves were not considered.

‡Normal AV conduction vs I/II type 1 AV block.

§Normal vs intraventricular conduction defect.

significantly associated with the presence of J-point elevation. After adjusting for all these significant variables, lower heart rate (OR for 1 SD increase, 0.686; 95% CI, 0.508–0.927; $P=0.011$), increased interventricular septum thickness (OR for 1 SD increase, 1.361; 95% CI, 1.019–1.817; $P=0.036$), and Sokolow–Lyon index (OR for 1 SD increase, 1.367; 95% CI, 1.026–1.822; $P=0,033$), but not black race (OR, 0.424; 95% CI, 0.147–1.224; $P=0.113$), were significantly associated with J-point elevation.
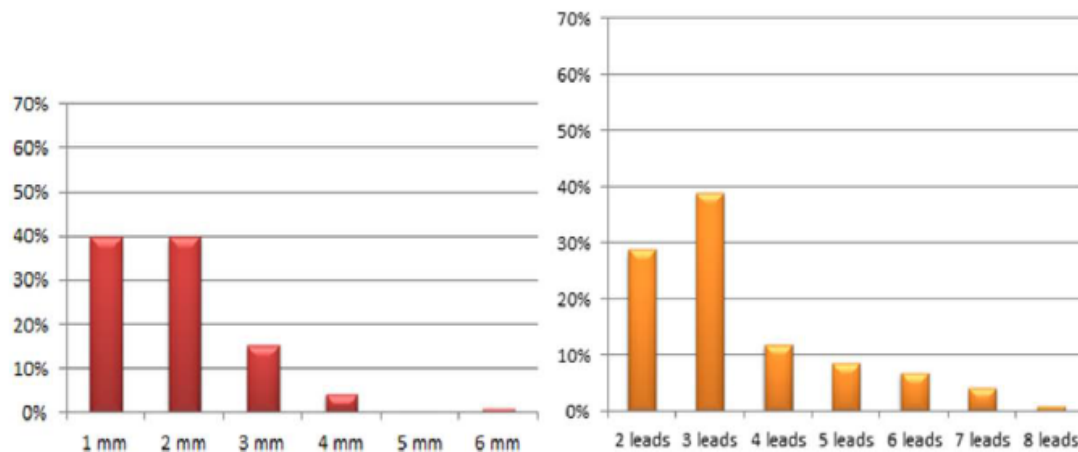

Figure 2. Left, Distribution of the amplitudes of J-point elevation. **Right**, Distribution of the number of leads with a J-point elevation ≥1 mm.

Table 3. Morphologies of the QRS-ST Transition and ST Segment

	N
QRS-ST transition	
Single, n (%)	95 (80.5)
ER without J wave	53
Notched J waves	34
Slurred J waves	8
Combined, n (%)	23 (19.5)
Notched+slurred J waves	7
Notched+ER without J wave	12
Slurred+ER without J wave	1
Notched+slurred + ER without J wave	3
ST segment	
Ascending ST segment, n (%)	95 (80.5)
Horizontal descending ST segment, n (%)	23 (19.5)
Notched J waves	13
Inferior leads	9
Lateral leads	3
Inferior+lateral leads	1
Slurred J waves	4
Inferior leads	4
Lateral leads	0
Inferior+lateral leads	0
Notched+slurred J waves*	6

ER indicates early repolarization.

*All shown in the inferior+lateral leads.

Follow-Up

Follow-up data were available for the entire cohort of athletes. During follow-up (median, 13.3 years; first and third quartiles, 10.1–17.0 years), 2 deaths, because of noncardiovascular reasons, were observed (0.67 deaths/1000 person-years in the ISO J group versus 0 deaths/1000 person-years in the ELE J group; Figure 4). One subject died at the age of 23 years from acute leukemia. Another subject died in a road accident at the age of 28 years. In none of the ECGs available for these 2 athletes, a J-point elevation was ever observed.

Discussion

This retrospective analysis of a cohort of elite soccer players provided the opportunity to examine the clinical significance of J-point elevation in the competitive sport setting, a field in which this ECG sign has been less investigated to date.

The main findings of our study are (1) the significant association between J-point elevation and markers of LV structural remodeling (eg, increased interventricular septum thickness and Sokolow–Lyon index), as well as with lower resting heart rate; (2) after a long-term follow-up, no cardiovascular deaths were observed in athletes with J-point elevation.

Previous studies recognized, in the general population or in nonprofessional athletes, the association between the presence of J-point elevation and young age, men, black race, slower heart rate, increased voltage of the QRS complexes, and enhanced aerobic fitness.[9,13–15,17] A recent work by Noseworthy et al[9] reported that, in a subgroup of football and rowing athletes, J-point elevation on surface ECG was not significantly associated with any parameter of structural remodeling typical of the athlete's heart, supporting the hypothesis that the evidence of J-point elevation is a mere electrophysiological phenomenon and that it is not related to any form of exercise-induced LV remodeling.

Our work has confirmed the association, already found in previous studies, between J-point elevation, slower heart rate, and increased QRS voltages in the precordial leads. Interestingly, a significant association between J-point elevation and a thicker intraventricular septum was also observed both at univariate and multivariable analyses. The homogeneous sample of elite athletes under study, practicing the same type of high-intensity training, may have favored this observation. Posterior wall thickness was not considered as a covariate in multivariable analysis because it is not significant at univariate analysis. The presence of a mild form of LV hypertrophy is a cornerstone of the athlete's heart and our findings suggest exercise-induced LV remodeling as the potential structural basis for J-point elevation at surface ECG. Marked echocardiographic LV hypertrophy has been demonstrated in athletes of black ethnicity. However, only interventricular septum thickness, but not black race, was retained in our multivariable model, supporting the hypothesis of a mechanistic link between cardiac remodeling and J-point elevation. A possible explanatory mechanism, based on animal studies[18] and sporadic case reports in human, linking mild LV hypertrophy and QRS shortening was proposed by Boineau. According to this hypothesis, an increased LV endocardial trabeculation and a greater endocardial invagination depth may be associated with a deeper localization (into the mid myocardium) of the Purkinje fibers and may provide the anatomic basis for a faster activation of the thickened LV walls.[19] The same mechanism was also recently proposed to explain the high prevalence of J-point elevation in a population of patients with LV noncompaction cardiomyopathy.[20] An increased LV
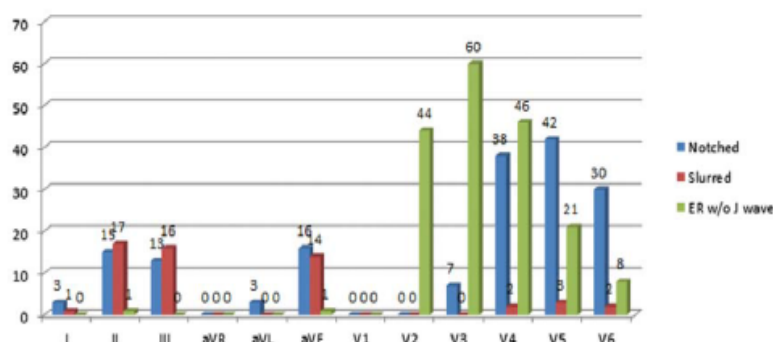

Figure 3. Distribution of the different QRS-ST transition morphologies in different leads. ER indicates early repolarization.

Table 4. Echocardiographic Parameters

Characteristics	Isoelectric J Point (N=147)	Any J-Point Elevation (n=88)	P Value
Interventricular septum thickness, mm	10.2±1.4	10.8±1.6	0.002
Posterior wall thickness, mm	9.3±1.1	9.6±1.3	0.06
LVEDD, mm	54.8±4.1	54.4±4.0	0.466
LVESD, mm	35.3±3.4	34.8±3.6	0.287
EF, %	64.2±3.2	64.3±4.5	0.843
Left atrial AP diameter, mm	35.2±3.9	35.4±4.4	0.717
Left ventricular mass/BSA, g/m²	106.8±19.8	111.1±20.6	0.113

AP indicates anteroposterior; EF, ejection fraction; LVEDD, left ventricular end diastolic diameter; and LVESD, left ventricular end systolic diameter.

trabeculation is associated with physical training. In fact, a recent MRI study comparing soccer players of European versus African descent reported a greater degree of myocardial trabeculation in the latter. According to in vitro studies,[21] small gradients in ventricular repolarization (ie, small differences in action potential duration in contiguous myocardial regions) exist in the normal LV and are responsible for the J-point elevation; as this dispersion of repolarization increases in magnitude, increasingly taller J waves become manifest on the surface ECG. The presence of a mild form of ventricular trabeculation associated with hypertrophy may allow for a more rapid ventricular activation (evident as a shorter QRS complex) revealing the presence of J-point elevation and J waves. QRS duration and coupling time between QRS complexes and J waves may influence both J-point appearance and the morphology of the transition between QRS and ST segment. As a matter of fact, in our population, the duration of QRS complex not only differed between subjects with and without J-point elevation, but a trend for a progressively longer QRS complex was also observed in subjects with notched, slurred J waves, and ER without J wave.

Interestingly and apparently in contrast with previous studies conducted in nonprofessional athletes, in our population of elite athletes the presence of J-point elevation was not associated with an increased aerobic fitness or maximal workload.

This finding may be because of a ceiling effect in the incidence of J-point elevation in highly trained athletes.

In our work, the presence of a J-point elevation was evident in >1 of 3 professional top-level soccer players; in this population, after a long-term follow-up, no deaths related to cardiovascular causes were observed. This finding, in combination with future data, should reassure Sport Medicine physicians performing preparticipation screening of athletes with unremarkable clinical history, avoiding unnecessary subsequent evaluations.

Some limitations of our study should be acknowledged. The estimated risk of sudden cardiac death of subjects with J-point elevation is low, approximating 11 in 100 000 >10 years in the general population.[8] Even if the risk of sudden cardiac death is more than doubled in active compared with sedentary subjects, the population included in the present study is too small to draw definite conclusions on the real prognostic impact of J-point elevation in athletes. Nevertheless, to the best of our knowledge, to date this is the largest, long-term follow-up study investigating clinical features associated with J-point elevation in elite athletes.

Between 1989 and 1995, a possible selection bias of athletes evaluated with echocardiography could have occurred. We tested the association between ECG signs of LV hypertrophy and J-point elevation that showed a significant direct
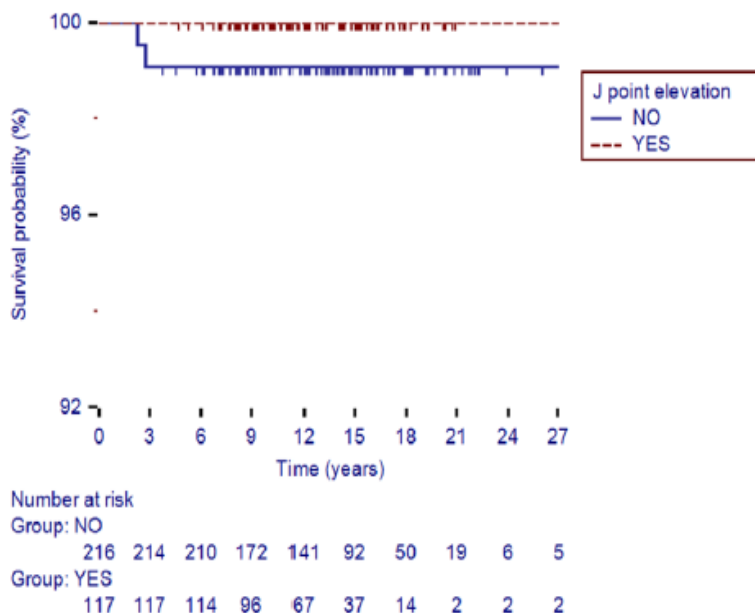

Figure 4. Kaplan–Meier survival curves of athletes with and without J-point elevation.

Number at risk
Group: NO

| 216 | 214 | 210 | 172 | 141 | 92 | 50 | 19 | 6 | 5 |

Group: YES

| 117 | 117 | 114 | 96 | 67 | 37 | 14 | 2 | 2 | 2 |

association also in the whole population (Appendix in the online-only Data Supplement).

In conclusion, in our series of elite soccer players enrolled for 3 decades, >1 of 3 showed a J-point elevation confirming its high prevalence among physically active subjects. The correlation between J-point elevation and increased interventricular septum thickness suggests a possible mechanistic role of exercise-induced LV hypertrophy in the genesis of ER.

Disclosures

None.

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CLINICAL PERSPECTIVE

Starting from the first description by Shipley and Hallaran in 1936, the electrocardiographic definition of early repolarization (ER) and the prognostic significance of different ECG patterns attributed to ER have been a matter of debate. The uncertainties on the ability to distinguish clearly between a benign and a malignant form of ER increased the number of healthy subjects with a negative clinical history referred for cardiac evaluation because of evidence of ER on a baseline ECG. This process together with the lack of data about the ECG characteristics and long-term follow-up of elite athletes with ER classified according to current definitions prompted this retrospective analysis. In this series of elite soccer players, >1 of 3 showed J-point elevation, confirming its high prevalence among physically active subjects. The evidence of a direct correlation between J-point elevation and increased interventricular septal thickness suggests a possible mechanistic role of exercise-induced left ventricular hypertrophy as a basis for the electrocardiographic evidence of J-point elevation. At long-term follow-up, a low mortality rate was observed, not related to cardiovascular causes, supporting the hypothesis of a benign finding in athletes.

Paper#3

Cristoforetti Y, Biasco L, Giustetto C, De Backer O, Castagno D, Astegiano P, Ganzit G, Gribaudo CG, Moccetti M, Gaita F.

J-wave duration and slope as potential tools to discriminate between benign and malignant early repolarization.

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J-wave duration and slope as potential tools to discriminate between benign and malignant early repolarization

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Introduction

Interest in early repolarization (ER) increased after the theoretical proposal[1] and the clinical demonstration[2] that certain electrocardiographic (ECG) 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 aims of the present study were to compare the amplitude of J waves by measuring slope and duration in patients with ER syndrome and healthy athletes with ECG evidence of J-point elevation associated with J wave and to evaluate its potential role as an ECG marker of increased arrhythmic risk.

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Methods
Cases

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

Only articles reporting data and ECG of patients with isolated ER syndrome, not associated with any other form of congenital (Brugada syndrome, short QT syndrome, long QT syndrome, and 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, and bibliographies of pertinent articles were also reviewed to search for relevant publications.

Detailed references of the selected articles and tracings are listed in Table 1. For all cases, the index clinical event was obtained through the article, while J-wave morphology, localization, and 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 2 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, ECG, 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 preparticipation

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

Subject no.	Author	Year	Journal	Age (y)	Event	Morphology	Localization	J-point elevation (mm)	Duration (ms)	Slope (deg)	Lead of measurement	HR (beats/min)
	Publication			Patient characteristics		J-wave characteristics						
1	Haïssaguerre[2]	2008	N Engl J Med		IVF	S	NA	3	72	33	NA	
2	Derval[7]	2011	J Am Coll Cardiol		IVF	NS	Inf-Lat	3	58	30	II	48
3	Derval[7]	2011	J Am Coll Cardiol	29	IVF	S	NA	2.5	53	35	NA	
4	Merchant[8]	2009	Am J Cardiol		IVF	N	Lat	2	50	33	V₄	
5	Merchant[8]	2009	Am J Cardiol		IVF	S	Inf-Lat	2	70	45	aVF	
6	Nam[9]	2012	Circ J	53	IVF	N	Lat	3	35	34	V₅	
7	Nam[9]	2012	Circ J	50	IVF	N	Lat	5	70	45	aVL	75
8	Riera[10]	2004	J Electrocardiol	29	IVF	S	Inf-Lat	6	126	30	aVF	
9	Rosso[3]	2008	J Am Coll Cardiol		IVF	S	Inf	2	67	37	III	82
10	Rosso[3]	2008	J Am Coll Cardiol		IVF	S	Inf	2	60	32	aVF	78
11	Watanabe[11]	2013	Int J Cardiol	29	IVF	S	Inf	2	45	40	II	55
12	Amara[12]	2012	Ann Cardiol Angeiol (Paris)	61	IVF	S	Inf-Lat	2.5	59	48	V₄	62
13	Sacher[13]	2014	J Electrocardiol	14	IVF	NS	All leads	4	167	45	II	
14	Ohukbo[14]	2012	J Cardiol	41	IVF	N	Inf		59	31	II	
15	Ohukbo[14]	2012	J Cardiol	27	IVF	N	Lat		73	33	V₆	
16	Nakagawa[15]	2014	Heart Rhythm	42	IVF	NS	Inf-Lat	5	84	15	V₅	
17	Aizawa[16]	2013	J Am Coll Cardiol	34	IVF	N	Lat	4.5	87	14	V₆	
18	Garg[17]	1998	J Cardiovasc	18	IVF/SD	N	Lat	4	56	10	V₅	45
19	Bastianen[18]	2010	Heart Rhythm	38	IVF	N	Inf	3	83	29	III	85
20	Katsuumi[19]	2014	Int J Cardiol		IVF	S	Inf-Lat	1.5	30	30	V₆	
21	Watanabe[20]	2011	Circ Arrhythm†	36	IVF	S	Inf	3	91	41	aVF	
22	Nam[21]	2010	Eur Heart J	31	IVF	NS	Lat	5	71	23	V₄	55
23	Hu[22]	2014	Int J Cardiol	20	IVF	N	All leads	6	48	19	V₆	
24	Talib[23]	2013	J Cardiovasc*	57	IVF	NS	Inf-Lat	4	60	36	aVF	
25	Shinohara[24]	2006	Heart Rhythm	37	IVF	N‡	NA	3	60	22	NA	55
26	Takagi[25]	2000	J Cardiovasc*	27	IVF	S	Inf	3	59	42	aVF	
27	Takagi[25]	2000	J Cardiovasc*	29	IVF	S	Inf	3	84	48	aVF	

HR = heart rate; Inf = inferior; Inf-Lat = inferolateral; IVF = idiopathic ventricular fibrillation; Lat = lateral; N = notched; NA = not available; S = slurred; SD = sudden death.

*J Cardiovasc Electrophysiol.

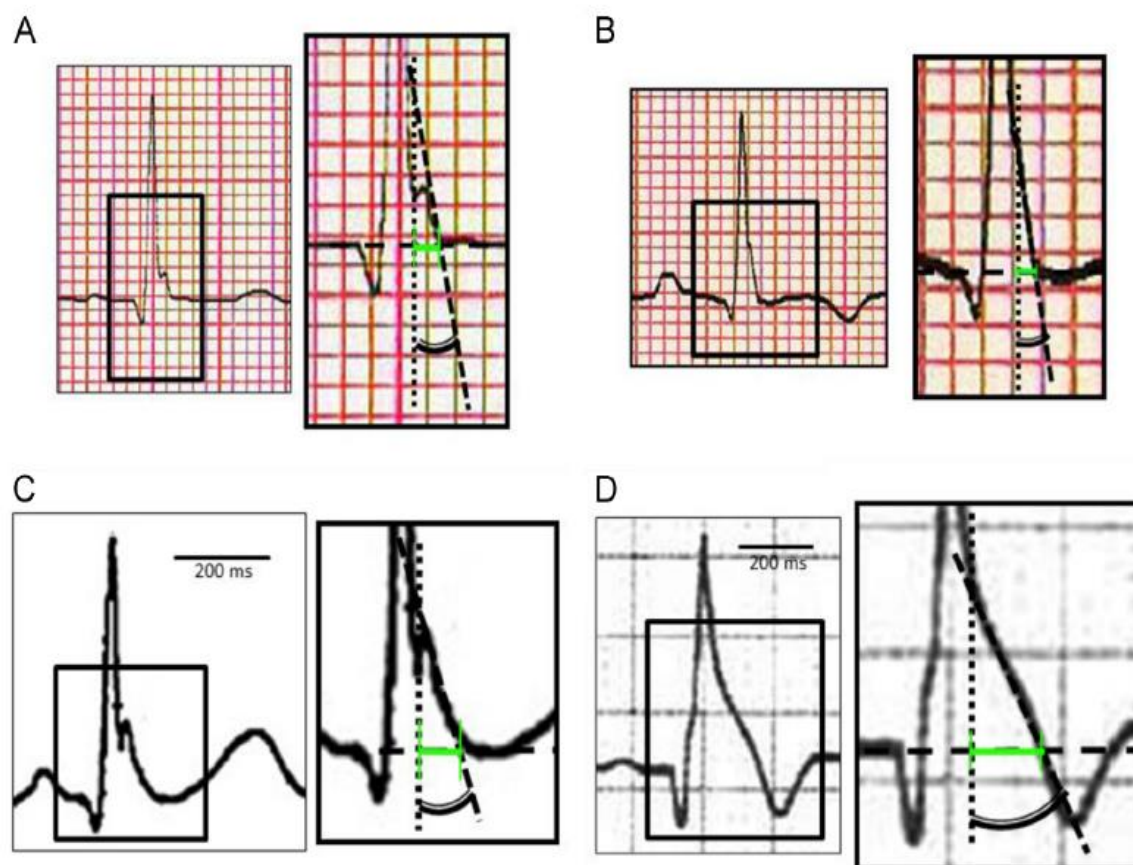†Circ Arrhythm Electrophysiol.

‡On showed lead.

Figure 1 Measurement of slope and duration of the J wave. **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.

evaluation between June 1980 and April 2008 at the Turin Institute of Sport Medicine. A detailed description of this population was previously published.[26]

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 (≥ 0.2 mV) 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 of ≥ 0.2 mV was selected as an inclusion criterion 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 ER characterized by J-point elevation and upward displacement of the ST segment but without evidence of J wave were excluded.

ECG analysis

All ECGs were digitally acquired and analyzed by 2 independent reviewers who were blinded to all subject 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 magnification of 400%.

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.*[27]

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 in slope of the J wave into the ST/T wave, whichever comes 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 measured digitally. Angle measurements are expressed in sexagesimal degrees. 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.[3,4] To estimate the entity of J-point elevation, the height of the J_o point was measured, with the isolectric line considered as a baseline.

Statistical analysis

Descriptive analysis was performed using mean $\pm$ standard deviation for continuous variables and counts and percentages for categorical variables. Comparisons between groups were performed using the Student t test, 1-way analysis of variance, and Yates-corrected or -uncorrected χ^2 test, when appropriate. All probability values were considered to be significant at a value of $\leq .05$. All the analyses were performed with SPSS software (SPSS, Chicago, IL).

Table 2 Clinical and electrocardiographic characteristics of control athletes

Subject no.	Age (y)	Morphology	Localization	J-point elevation (mm)	Duration (ms)	Slope (deg)	Lead of measurement	HR (beats/min)
		J-wave characteristics						
1	30	N	Inf-Lat	2	33	18	II	51
2	24	N	Lat	4	41	17	II	62
3	18	S	Inf	3	34	12	aVF	50
4	23	N	Lat	2	34	21	III	40
5	25	S	Inf	3	37	20	III	41
6	28	N	Inf-Lat	2	51	32	V_5	38
7	29	N	Lat	3	17	13	V_4	46
8	23	N+S	Inf-Lat	4	37	21	V_5	54
9	25	N+S	Inf-Lat	4	34	13	V_5	44
10	16	N	Lat	3	17	18	V_4	75
11	28	N+S	Inf-Lat	2	27	23	V_4	52
12	25	N	Lat	3	31	30	II	75
13	33	N+S	Inf-Lat	2	47	28	II	44
14	26	N+S	Inf-Lat	4	47	20	V_5	47
15	30	N+S	Inf-Lat	2	37	33	II	58
16	22	N+S	Inf-Lat	2	27	15	V_6	53
17	37	N	Lat	2	24	19	V_5	57
18	22	N	Lat	2	31	29	V_4	63
19	28	N+S	Inf-Lat	3	17	13	V_4	66
20	17	N+S	Inf	3	53	22	III	54
21	14	N	Inf	3	47	14	III	72
22	20	N	Lat	6	44	9	III	55
23	14	N	Inf	2	38	12	III	62
24	29	N	Lat	4	37	14	V_4	50

HR = heart rate; Inf = inferior; Inf-Lat = inferolateral; Lat = lateral; N = notched; S = slurred.

Results

Of 1523 articles evaluated, only 21 works reported original, nondistorted, interpretable ECG tracings of 27 patients with idiopathic ventricular fibrillation due to ER syndrome.

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

Of 338 healthy, professional top series football players, only 24 (7.1%) showed a J-point elevation of ≥0.2 mV (and a clearly identifiable J waves with a notched or slurred appearance). Table 2 presents 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=.243), with a wide overlap of measurements between the 2 populations (Figure 2A).

Cases showed a significantly longer duration of J waves as compared with controls (69.48 ± 27.93 ms vs 35.05 ± 10.33 ms; P<.001). None of the controls showed a duration of >60 ms, while 15 of 27 cases (55.5%) showed a J-wave duration of >60 ms (Figure 2B).

Compared with controls, cases showed a significantly wider J angle (32.59° ± 10.4° vs 20.00° ± 6.84°; P<.001), with only 2 of 24 controls (8.3%) showing a J angle of >30° (Figure 2C).

Figure 3 shows the plot of J-wave duration and J angle. As shown in the graph, controls, characterized by short and steep J waves, are clustered in the left inferior corner. None of the healthy athletes showed a duration of >60 ms in combination with an angle of >30°. In contrast, cases showed a wide dispersion of measurements. A 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 as compared with healthy controls, representing a new potential tool to discriminate between benign and malignant ER.

Despite the recent increased interest, clear ECG 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 as compared with those with a notched J wave.[5] Those works failed to solve the issue of whether deaths were effectively related to primary arrhythmic episodes, fatal arrhythmias in the setting of ischemic events, or other causes.

As for Brugada syndrome, the electrophysiological mechanism deemed to be responsible for the arrhythmogenicity of ER is an 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.[28–30] Thus, the basic idea supporting our work is that J-wave amplitude will prolong the transmembrane dispersion of repolarization by affecting the persistence of
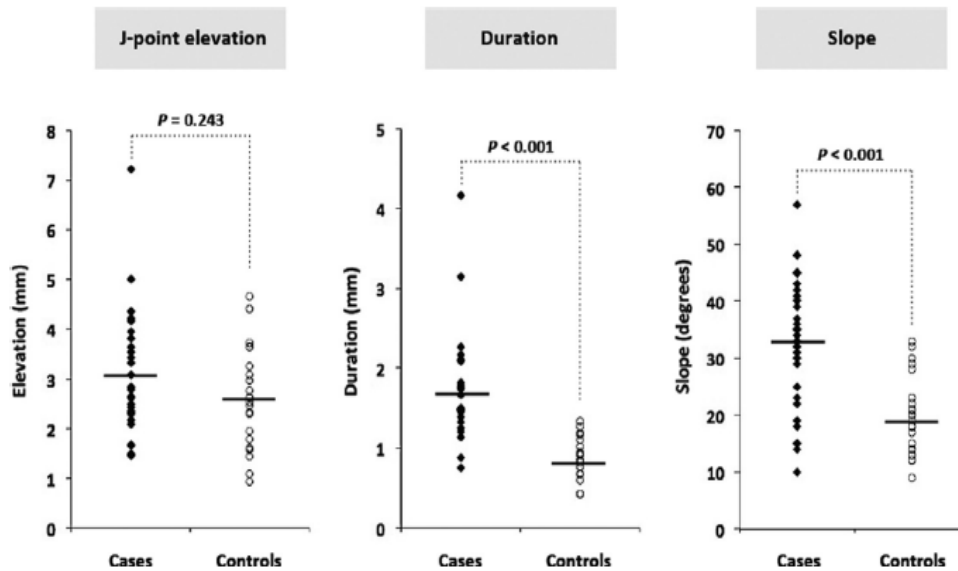
Figure 2   Plot of (**A**) J-point elevation, (**B**) duration, and (**C**) slope of the J wave in control subjects and cases.

the J wave (ie, longer duration and wider angle), 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 with subjects with a negative drug challenge, supporting the hypothesis that the amplitude of the J wave may be an effective ECG marker of increased arrhythmic risk.[31] To our knowledge, this is the first article to systematically describe J-wave 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.[30]

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 ECG 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 long QT syndrome or other ion channel diseases taught that beside the presence of an ECG 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,[2] another evidence supporting our hypothesis.

In line with previous works,[2–6] J-point elevation as itself does not seem to play a real role as a ECG marker of increased arrhythmic risk, being slightly, but not significantly, increased in cases as compared with controls.

As evident from Figure 3, while controls are grouped in the right inferior corner of the plot, ER cases showed a true *disorder* of the ER process, evident as a wide dispersion of measurements. None of the controls showed a duration of >60 ms, while a minority showed a slope of >30°. Only cases showed a J-wave duration of >60 ms and a slope of
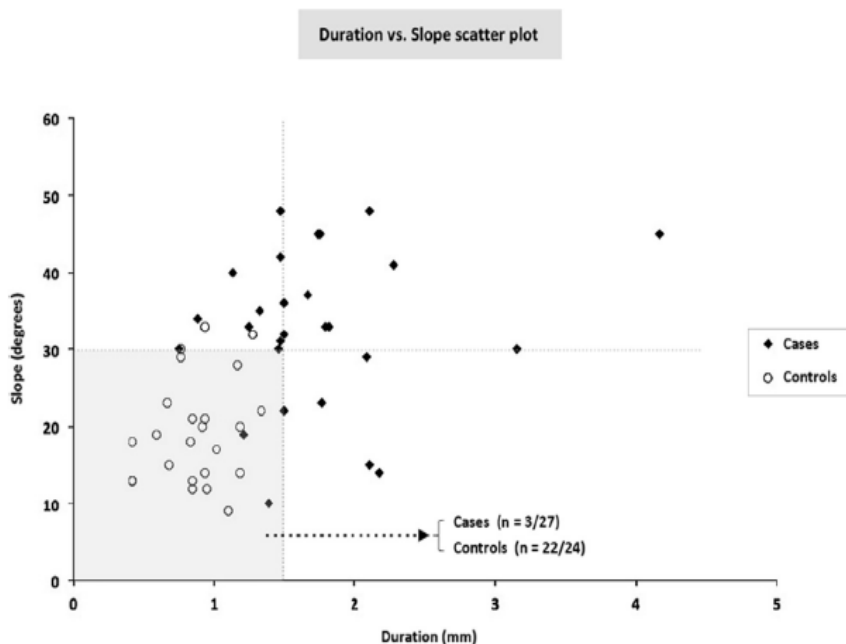

Figure 3   Scatterplot of J-wave duration) and slope.

>30°, 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.

Study limitations

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

Conclusion

This is the first article to report the potential role of J-wave 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.

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Discussion

Early repolarization still represents one of the most puzzling conundrums in clinical cardiology. Despite great efforts made by researcher aiming at clarifying the clinical characteristics, electrocardiographic features and pathophysiological mechanism behind this entity, few certainties and significant shadows casts over physicians while trying to make sense out of this. Both ESC guidelines on the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death (47) as well as the recent expert consensus (4) clearly states that several gaps in current knowledge still represents the main obstacle in the complete understanding of this phenomenon.

The main gaps in the knowledge are represented by the lack of validated diagnostic criteria (4), a clear explanation of the cellular mechanism behind both ECG manifestations and arrhythmogenesis as well as clear indications for the management of asymptomatic subjects.

In this light, the works presented in the present doctoral dissertation might represent a contribution, probably limited in terms of quantity of informations and pubblications, but certainly clear in terms of messages, that can contribute on the discussion on this topic.

With the paper #1, our aim was to achieve an in depth analysis of the evolution of the concept of early repolarization, from the original description of Shipley and Hallaran (1), to the more contemporary analysis.

The main message that arose from this historical analysis is that the traditional early repolarization, characterized from an electrocardiographical perspective as an elevation of the J point associated with a concave upward ST segment elevation is intrinsically different from that shown in the ECGs published by Haissaguerre et al (4). This original misunderstanding about terminology, was the main responsible for the great confusion that rose after the seminal publication in 2008. The original aspect, shared with other opinion leaders in the field (49), of our

first paper presented in the present dissertation is to have recognized and stressed that the term Early Repolarization was clearly used inappropriately when referring to several different abnormalities of the QRS-ST transition evident in patients with ventricular arrhythmias in otherwise healthy hearts.

Starting from this consideration and favoured by the collaboration with the Turin Institute of Sport Medicine, we aimed at evaluating whether Early Repolarization observed in competitive athletes was somehow linked to structural changes associated with the athlete's heart or, on the other hand, an electrocardiographic marker of a mere electrophysiological phenomenon. In addition, having the possibility of a retrospective analysis with long term follow up, if J-point elevation really implied an ominous prognosis in competitive athletes.

The original data presented in paper #2 clearly demonstrated that some peculiar, and still unknown aspects of early repolarization in elite athletets.

Despite the common believe that ER was a marker of increased aerobic performance, our data clearly demonstrated that in elite athletes, exercise capacity and maximal aerobic capacity did not significantly differ between athletes with and without J-point elevation. Moreover, the combined presence of J-point elevation, slurred J wave, and horizontal/descending ST segment in the inferior leads recognized in the general population as a possible marker of arrhythmic risk was rare, being manifest only in 4 (1.2%) athletes. In addition, our data demonstrated that subjects with notched, slurred J waves, and ER without J wave showed a progressive lengthening of the QRS complex duration. This might imply that both the morphology of the J wave at ECG as well as its presence might in part be related to the presence of a shorter vs longer QRS duration. A short QRS will in fact uncover the presence of a J wave, while the longer the QRS the higher the probability for a J wave to be buried into the terminal phase of the ventricular depolarization.

One of the prominent aspects of paper #2 was in fact the recognition of the correlation between a mild form of LV hypertrophy with Early

repolarization. This original finding highlights how exercise-induced LV, a known cornerstone of the athlete's heart, could represent the potential structural basis for J-point elevation at surface ECG.

Finally, the long term follow up available, even if probably underpowered to finally assess the prognostic impact of this ECG feature, at least reassured on the intrinsic benignity of this ECG feature in athletes.

The possibility of analysing the published ECG of patients with idiopathic ventricular arrhythmias deemed related to ER as well as the ECG of elite athletes with ER lead us to the conviction that the two phenomena were intrinsically different and that a careful analysis of the ECG, performed through innovative tools, might have had a role in differentiating between a benign and a malignant form of ER.

This was the hypothesis that guided the development of paper #3 presented in the present dissertation. After careful comparison between the group of patients with episodes of idiopathic ventricular fibrillation and ECG evidence of J-point elevation associated with J wave who were commonly

accepted and referenced in contemporary works as patients with ER syndrome and the tracings derived from elite athletes analysed in paper #2, we demonstrated that the malignant form is characterized by a slow and delayed J wave as compared with healthy controls, representing a new potential tool to discriminate between those two entities.

Despite several achievement obtained during development of the present research, several limitation should be mentioned:

As a first, the population included in paper #2 is definitely too small to draw definite conclusions on the real prognostic impact of J-point elevation in athletes. Moreover, while being fascinating from an clinical and cellular perspective, the hypothesis proposed in paper #3 was only derived but not yet validated in an independent large volume population.

Conclusions

In summary, few final conclusions can be drawn from the present research:

- Traditional early repolarization and the newly defined early repolarization syndromes are clearly two distinct entities with different clinical, ecg, and prognostic characteristics.

- Early repolarization in elite athletes is common and possibly related to a mild form of left ventricular hypertrophy, one of the cornerstones of athlete heart. The ECG features associated with an increased arrhythmic risk in the general population is rare in atheletes. Long term follow up reassures on the traditional benignity reported in active individuals.

- Beside the presence of a prominent J wave elevation associated with a notched J wave in the inferior leads as well as an horizontal/descending ST segment, the presence of a delayed and Jwave, marker of a transmural dispersion of repolarization, may represent a new discriminant able to distinguish between benign and malignant ER.

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