Some Controversies about Early Repolarization: The Haïssaguerre Syndrome

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Controversy has followed the groundbreaking and cornerstone paper of Haïssaguerre et al. Much of this controversy has been due to the use of the term “early repolarization pattern” and possible waveform morphologies on the standard 12-lead ECG (it is 10-second strip) that could predict who will manifest the malignant arrhythmogenic syndrome described by Haïssaguerre et al. The standard ECG definition of early repolarization pattern (ERP) or early repolarization variant (ERV) since then has changed its clinical meaning for a surface electrocardiographic waveform from benign to malignant. The new definition of ERP/ERV contains only J wave but ST-segment elevation is no more obligatory.

In the old definition, early repolarization pattern (ERP) or early repolarization variant (ERV) is a well-recognized idiopathic electrocardiographic phenomenon considered to be present when at least two adjacent precordial leads show elevation of the ST segment, with values equal or higher than 1 mm. In the new electrocardiographic ERP concept, the ST segment may or may not be elevated and can be up-sloping, horizontal or down-sloping while in the old ERP/ERV concept it must be elevated at least 1 mm in at least two adjacent leads and the variant is characterized by a diffuse elevation of the ST segment of upper concavity, ending in a positive T wave of V2 to V4 or V5 and prominent J wave and ST-segment elevation predominantly in left precordial leads. The phenomenon constitutes a normal variant; it is almost a rule in athletes. ERP or ERV is a well-recognized idiopathic electrocardiographic phenomenon considered to be present when at least two adjacent precordial leads show elevation of the ST segment, with values equal or higher than 1 mm. In the new electrocardiographic ERP concept, the ST segment may or may not be elevated and can be up-sloping, horizontal, or down-sloping whereas in the old ERP/ERV concept it must be elevated at least 1 mm in at least two adjacent leads and the variant is characterized by a diffuse elevation of the ST segment of upper concavity, ending in a positive T wave of V2 to V4 or V5 and prominent J wave and ST-segment elevation predominantly in left precordial leads. The phenomenon constitutes a normal variant; it is almost a rule in athletes (present in 89% of the cases in this universe).
cases in this universe). However, it is found in a 36% of sedentary men.\textsuperscript{4} Therefore, since that time the ERP is not ERP anymore. Because the J wave is electrocardiographic sign associated with different arrhythmogenic disorders, Antzelevitch proposed to call arrhythmogenic syndromes presenting with J waves (Brugada syndrome, ER syndrome) as "J wave syndromes." However, in our opinion, the current definition of ERP/ERV only introduces confusion and should be reserved for its old meaning as proposed by Wasserburger and Alt in early 1960s last century.\textsuperscript{3}

**THE J WAVE CHRONOLOGICAL HISTORY**

**Others Denominations**

J wave is also referred to as the J deflection, "the camel's hump"/camel-hump sign,\textsuperscript{5} "late delta wave,"\textsuperscript{6} elevated J-point, hooked J-point, hathook junction, hypothermic wave, K wave, H wave,\textsuperscript{7} current of injury,\textsuperscript{8} or with the unjust eponym Osborn wave.\textsuperscript{9}

The J wave has been observed in hypothermia but can also be observed in numerous conditions of normothermia such as athlete heart,\textsuperscript{10} hypercalcemia,\textsuperscript{11} obstructive coronary heart disease,\textsuperscript{12} Prinzmetal variant angina,\textsuperscript{13} takotsubo cardiomyopathy,\textsuperscript{14} injuries in the central nervous system: subarachnoid hemorrhage,\textsuperscript{15} post-heart arrest and in cervical sympathetic system dysfunction,\textsuperscript{16} epileptic hemiplegia,\textsuperscript{17} early repolarization syndrome, Brugada "entities,"\textsuperscript{18} familial cases [≈17%]: true Brugada disease; sporadic cases [≈63%]: Brugada syndrome,\textsuperscript{19} and Brugada phenocopies,\textsuperscript{20} congenital short QT syndrome, idiopathic ventricular fibrillation, concealed forms of arrhythmogenic right ventricular cardiomyopathy/dysplasia,\textsuperscript{21} and hypertrophic cardiomyopathy.\textsuperscript{22}

In 1953, Osborn studied the effect of hypothermia on cardiac and respiratory conditions in dogs.\textsuperscript{25} In his model of hypothermia, ECG revealed a novel deflection at the J point, which he called "current of injury." Interestingly, he noted the association of the occurrence this peculiar wave and the occurrence of ventricular fibrillation.

In 1957, Fleming and Muir were the first who confirmed this electrocardiographic phenomenon as prognostic for ventricular fibrillation (VF) in hypothermic patients.\textsuperscript{26}

In 1959, Emsli-Smith et al. following the Osborn's research of hypothermia found the differences between the endocardium and the epicardium in response to hypothermia.\textsuperscript{27} They documented that the Osborn wave was more prominent in the epicardium than in the endocardium. In the same year, West et al. confirmed that a notch in action potential of epicardium was accentuated by hypothermia.\textsuperscript{28}

In 1993, Aizawa et al. reported a case series of patients with idiopathic VF who presented with ECGs showing a notch at the J-point or on the descending arm of R wave.\textsuperscript{29} The authors attributed the notches to bradycardia-dependent intraventricular block because they were accentuated by a longer preceding cycles.

In 1996, Yan and Antzelevitch elegantly confirmed the correlation between the amplitude of a notch of epicardial action potential and J wave registered on surface ECG.\textsuperscript{30} Heterogeneous distribution of a transient outward current-mediated spike-and-dome morphology of the action potential across the ventricular wall underlies the manifestation of the electrocardiographic J wave. The presence of a prominent action potential notch in epicardium but not endocardium is shown to provide a voltage gradient that manifests as a J (Osborn) wave or elevated J-point in the ECG.

In 1998, Garg et al. reported a case with a family history of sudden cardiac death associated with a large terminal QRS abnormality and positive late potentials. Quinidine therapy made the notches and the late potentials disappear and the patient died suddenly after discontinuing quinidine.\textsuperscript{31}

Following these reports, several other cases of SCD/syncope/ventricular arrhythmia related to Aizawa ECG pattern were reported by Kalla et al.,\textsuperscript{32} Takagi et al.,\textsuperscript{33} Riera et al.,\textsuperscript{34} and Shinohara et al.\textsuperscript{35}

In 2008, Haissaguerre et al. reported the largest cohort of idiopathic ventricular fibrillation (IVF)
patients with similar ECG pattern, unfortunately labeling it “ER.”

**WHY NOT “EARLY REPOLARIZATION”?**

Our position is not to use the name “early repolarization” in clinical situation described by Haïssaguerre et al. As previously proposed by our team and Viskin, we support calling the new arrhythmogenic syndrome with the eponym “The Haïssaguerre syndrome.”

In our opinion, the Haïssaguerre syndrome is obligatory associated with J waves and additionally with different patterns of ST-segment running, but not with the classical ECG pattern of ERP/ERV based on ST elevation. Below, we would like to present arguments to support our opinion.

1. Hypothermia is a clinical model condition for the true J wave. The J wave observed in hypothermia can be a positive deflection (lateral and inferior leads as only the QRS complex is of positive amplitude) and is a negative deflection in 2 leads: aVR and V₁ (Fig. 2B).

The presence of negative true J waves in leads aVR and V₁ can be helpful in making the differential diagnosis between the presence of unspecific depolarization disturbances and the true J wave. A J wave in severe hypothermia (<28°C) appears in almost all ECG leads, similar to the extreme cases of “malignant ER” (Haïssaguerre pattern) associated with electrical storm. Ito et al. published recently a very striking case of a patient with electrical storm and diffuse J waves in all leads (Fig. 1). In both clinical scenarios, the global abnormal response of ion channels due to an inherited disorder or hypothermia seems to be responsible for diffuse electrocardiographic changes that are not localized in a given territory (e.g., not only seen in the inferior but widespread all over ECG leads). In malignant ER Haïssaguerre pattern (Fig. 2A) and in advanced hypothermia (Figs. 2B and 5), a J wave is positive in all leads except aVR and V₁ where it is a negative deflection.

Higuchi et al. showed that J waves were found in 50% of a series of hypothermic patients. All the patients whose body temperature was less than 30.0°C developed J waves. Furthermore, the amplitude of the J waves and the number of sites where J waves appeared was related to the severity of hypothermia. What is interesting in advanced hypothermia is that J waves were observed in the inferior leads in all patients, in lateral leads in 92% patients, and right precordial leads in 50% patients. This is a similar distribution of J wave in mainly inferior leads in “malignant ER Haïssaguerre pattern.”

In recent paper by Kim et al., J waves developed in 35% of patients with therapeutic hypothermia. All J waves developed on the inferior leads II, III, aVF, and in 10% additionally in lead I, aVL, V₅, and V₆. Ventricular fibrillation appeared in one patient with a J wave in all leads. Okada et al. demonstrated in 50 patients with accidental hypothermia the following results: (i) J waves were observed in 80% patients, (ii) J waves were recorded most frequently in leads II or V₆ in 85% cases, and (iii) the size of the J wave appeared to be related to body temperature. Below 30°C, large J waves were often observed; above 30°C, the J wave decreased in size along with rise of the body temperature. However, a small J wave persisted in many cases even after normothermia was restored.

The J wave in hypothermia and in “malignant ER Haïssaguerre pattern” behaves in the same way. When both deteriorate, the hypothermia gets very severe in the first one and electrical storm develops.
in the second one, the J wave is related not only to inferior territory but spreads to all over regions of the heart reflecting the global and diffuse pathology (Fig. 2B).

2. The J wave and ST-segment in hypothermia can present a wide spectrum of morphology (see Fig. 3A–F) as similar as in IVF patients with the Haïssaguerre pattern:
   (a) a small wave; deflection up to 1 mm, described as a notch after end of QRS (Fig. 3A),
   (b) a high-amplitude notch >2 mm arising from the J point (end-point of QRS) on the descending portion of the R-wave (Fig. 3B),
   (c) a very large wave, sometimes as tall as the R-wave in left precordial leads simulating LBBB (pseudo R′ wave), presenting with visible ascending and descending arms of the wave (Fig. 3C).

Note that a small J wave (as seen in Fig. 3A) is generally observed in classic ERP. For comparison, Figure 1 is an example of a J wave in hypothermia and a J wave in a patient with IVF presented by Sacher et al. (Fig. 2A and B). The ECGs from both clinical situations look similar.

In a model of hypothermia, the J wave often follows ST segment running as horizontal or upsloping; however, in advanced hypothermia, the most frequent ST segment pattern is downsloping (Fig. 3D–F). The rule observed in ECG is: the lower the body temperature, the higher is the amplitude of J wave. When the J wave amplitude gets more higher, the ST segment becomes to run downsloping (Fig. 5).

3. A large J wave mimicking the R′ wave especially in left precordial leads, followed by the downsloping or horizontal ST segment depression (Fig. 3C), even with deep negative T waves (Fig. 1) simulates a left bundle branch block (LBBB). Considering the morphological similarity with a LBBB raises the question “Why does the ST segment polarity become opposite to a J wave one”? Maybe it is the same electrophysiological phenomenon as observed in true LBBB, when the depolarization process produces the
opposite “graphic effect” on repolarization one registered on a surface electrocardiogram (QRS complex polarity versus opposite ST–T complex polarity; Figs. 2, 3C, and 5). It is only a speculation but increasing of J wave amplitude can reflect the escalation of depolarization abnormalities. This hypothesis can be supported by the cases described by Aizawa et al.\textsuperscript{29} and Garg et al.\textsuperscript{12} They documented the association of J wave or notch on downsloping R wave as reflection of depolarization abnormalities due to presence of the late potentials.

There are suggestions that the J wave could be considered as a repolarization abnormalities rather than late depolarization abnormalities because of its slower inscription, rate-dependent fluctuation in morphologic pattern and amplitude in the face of the stable QRS complexes.\textsuperscript{1, 41, 42} However, a study of Abe et al.\textsuperscript{43} showed that the incidence of late potential was higher in patients with VF and ERP than in patients with VF and without ER pattern (86% vs 27%), showing circadian variation with night ascendency.\textsuperscript{44} In contrast, the markers of repolarization did not differ between the two groups. The investigators concluded that J waves are more closely associated with a depolarization abnormality and autonomic modulation than with a repolarization abnormality. In opposite to most recently published studies, the study of Abe et al. suggests that pathogenesis of J wave could be more complex than previously reported and depolarization abnormalities could also play a role in some patients with IVF and ERP.\textsuperscript{44} We should not specify the cases with IVF and Haïssaguerre pattern as IVF associated with early repolarization. Antzelevitch proposed to include it to “J wave syndromes family” as the one of its subtype and we support it. It could be argued that the term J wave syndrome is not appropriate because of diverse ECG patterns and different associated mechanisms. Postema and Wilde suggested not use the term J wave syndromes but to describe phenotypes instead.\textsuperscript{45} We think that describing many different phenotypes will create even more confusion.

4. In high-risk patients with IVF/*new ER* (Haïssaguerre pattern), before electrical storm, a pronounced J wave follows the ST segment running as downsloping pattern.\textsuperscript{38, 45, 46} In this
scenario, the J wave and ST segment create a special morphology pattern called "a lambda wave" resembling a Greek letter lambda (Fig. 6). It was firstly introduced in 2004, in editorial comment by Gussak et al.\textsuperscript{47} to described a.

an interesting case of a 26-year-old man by Riera et al.\textsuperscript{34} with a history of fainting and convulsive-like episodes. The patient presented with a peculiar ECG showing J wave and ST-segment elevation in the inferior II, III, aVF, and V\textsubscript{6} leads. ST-segment elevation had an atypical shape with downsloping, and a terminal negative T wave in the infero-lateral leads. In addition, ST depression was observed in: V\textsubscript{1}–V\textsubscript{5}, I, aVR, and aVL leads. This patient died suddenly during Holter monitoring, which revealed a short run of polymorphic-VT in the early morning, which quickly evolved into asystole and sudden cardiac death. The almost identical pattern with a J wave and downsloping ST segment that resembles a lambda wave was registered in a Finnish patient resuscitated from VF, and it is shown in a paper by Tikkanen et al.\textsuperscript{48} and Huikuri\textsuperscript{49} (their figure 2). The "Lambda wave" was for the first documented by our team and proposed as a marker of susceptibility to ventricular fibrillation in acute coronary syndrome (STEMI)\textsuperscript{50, 51} (Fig. 6C). This observation with a lambda-like J wave–ST pattern was supported by Aizawa et al.\textsuperscript{29} and Maruyama et al.\textsuperscript{52} (Fig. 6B). The lambda-like J wave marker in IVF patients with Haissaguerre pattern can present the last stage of J wave continuum, the most arrhythmogenic and malignant marker. Curiously enough a common denominator of all cases with "a malignant lambda wave" described by Haissaguerre et al.\textsuperscript{1, 42} Riera et al.\textsuperscript{20} and Tikkanen et al.\textsuperscript{48} is the presence of negative "mirror reflection" lambda wave in right precordial leads or lateral limb leads (Fig. 6A and B). In addition, such a negative "mirror reflection" lambda wave.
is observed in leads V₁–V₃ in patients with ischemic J wave. This negativity of lambda wave makes it similar to negative “mirror” J waves in leads aVR and V₁ in hypothermia.

The ST segment in Haïssaguerre syndrome is rather playing a secondary role—only of a bystander phenomenon. Consider the examples of ST-segment elevation in long QT syndrome (LQTS) patient [Fig. 7B] or the hypertrophic cardiomyopathy patient [Fig. 7A]. In both these disorders the ST segment is only a bystander. The changes of ST segment could be “a secondary changes,” resulting from the changes in abnormalities of depolarization process as seen in bundle branch block. Such changes can be observed immediately before electrical storm or after a sudden cycle length changes. In these situations when a J wave amplitude dramatically and suddenly grows up, the ST segment changes its morphology from upsloping to downsloping and T wave from positive to negative polarity [Figs. 1, 3–6].

The classic ERV, as described by Wasserburger and Alt, presents dynamic alternations but only of ST-segment amplitude relative to heart rate, most elevated at bradycardia and disappearing with tachycardia. There can be alternations in the ST-segment pattern with Holter monitoring, exercise, or beta-adrenergic stimulation [Fig. 6].52, 53 Stern showed that ER pattern appeared at heart rates <70 bpm in 93% subjects and ER patterns “come and go” 10–20 times a day.54 The important information concerning the dynamic changes in patients with ERP and Haïssaguerre pattern brings study by Baestianen et al.55 They showed that during the both, ajmaline provocation test and exercise test, there was a complete loss of ER pattern in patients with rapidly upsloping ST segment but no with ST segment downsloping/horizontal. In addition, there was a complete loss of ER in the lateral but not the inferior and infero-lateral leads during ajmaline provocation and exercise. Upon these results it can be concluded that ST-segment elevation in lateral leads with upsloping pattern as described as typical for classic ER seems to be a different pattern from infero-lateral/inferior ST-segment downsloping/horizontal pattern. The last pattern persists with the both provocation tests with an increase in heart rate, and this may add further evidence to disordered depolarization. The next interesting information coming from Baestianen et al. study is that 50% patients with persistent J wave during ajmaline test had late
potentials and mild biventricular dilatation on MRI. During exercise, 60% patients with persistent J wave had evidence of subtle myocardial abnormality. The late potential was more likely to be abnormal in patients with persistent J wave during ajmaline testing and exercise. Thus, in some patients, inferior and infero-lateral J-point elevation with horizontal/descending ST segment may represent a disorder of depolarization rather than repolarization.

**SUMMARY**

We have argued that the controversial electrocardiographic changes in IVF population first described by Haïssaguerre are similar to the J wave of hypothermia rather than the early repolarization (ER) introduced by Wasserburger and Alt. In many of the cases of IVF, the ECG recorded just before the VF episode is similar to the ECG in advanced hypothermia.

Dividing the ECG pattern of ER into “benign” or “malignant” or “typical” or “atypical” results in more confusion. The ER is but one ECG pattern and should be consider only as a normal variant in young and otherwise healthy individuals (predominantly males and athletes). When a patient presents with clinical symptoms (e.g., syncope or palpitations), they should undergo investigations, particularly a family tree for sudden death, with the understanding that the classic ER pattern can be “a bystander phenomenon.” Our point of view is that ER term should be associated with only the traditional, classic ER definition proposed by Wasserburger and Alt. ER pattern should be classified in cases with mid-precordial, lateral, and rarely infero-lateral leads ST segment—J-point elevation with rapidly/upsloping ST segment and normal T waves as a sine qua non,
and additionally a small J wave (a notch or slur) can be seen but this finding is optional.

The new channelopathy, preferably called the Haïssaguerre or J wave syndrome, is a rare new condition characterized by death during sleep and most notably the dynamic appearance of large J waves with or without ST elevation before idiopathic VT/VF. Unfortunately, it has been labeled early repolarization by researchers and electrophysiologists, causing much confusion among clinicians who have been taught that early repolarization is physiological ST elevation occurring in an otherwise normal ECG. It is sad that lack of consideration of established definitions will probably cause more harm than good due to the ‘J wave-ICD reflex’.

The Haïssaguerre syndrome should be defined as a syndrome consisting of: clinical symptoms (aborted sudden cardiac death, documented malignant ventricular arrhythmias) and electrocardiographic markers:

A. obligatory: aberrant terminal R waves, different spectrum of J wave morphology [notch, slur, including extreme scenario with a lambda wave], J point elevation;
B. additional, strengthening diagnosis: horizontal or downsloping ST segment.

REFERENCES


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