Haissaguerre syndrome – a new clinical entity in the spectrum of primary electrical diseases?

Zespół Haissaguerre'a – nowa jednostka kliniczna wśród pierwotnie elektrycznych chorób serca?

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Sudden cardiac death and channelopathies

Sudden cardiac death (SCD) is an important issue worldwide and occurs at a rate of 0.36 to 1.28 per 1000 persons/year in the US [1]. Approximately 10% of SCD cases occur in patients with no evidence of structural heart disease. Channelopathies are primary electrical diseases that are responsible for the majority these SCD cases. At the end of the 20th century, two new arrhythmic syndromes were identified as channelopathies – Brugada syndrome (BrS) (1992) and short QT syndrome (2000) – and these have received considerable interest in recent years [2, 3]. Although specific electrocardiographic hallmarks are present in channelopathies, often these ECG signs can be transient and difficult to detect. A SCD caused by ventricular fibrillation (VF) in a patient without a specific ECG sign is described as an idiopathic VF (IVF). Recently, some IVF episodes or SCDs have been reported to be associated with the presence of prominent J-waves or J-point elevation in inferior and/or lateral leads [4-15].

J-wave aetiology and association with ventricular fibrillation

A J-wave (also called an 'Osborn wave') is a deflection that appears at the QRS-ST junction on a surface ECG. The shape and magnitude of the J-wave varies from J-point elevation with horizontal ST-segment elevation or small ST-segment hump to large dome-shaped waves (Figures 1 and 2). Moreover, a J-wave might be hidden in the QRS complex, and therefore slurring (notch) of the terminal part of the QRS complex might be a J-wave equivalent (Figure 3). Kui et al. recently reported that presence of a J-wave on the ECG of apparently healthy people is not a rare phenomenon, with a prevalence of 7.26% in a cohort of 1817 Chinese subjects [16]. In this study the J-wave was more common in men than women (10.5 vs. 1.9%), and occurred in inferior, lateral and anterior leads in descending order of frequency (4.6 vs. 2.2 vs. 0.5% respectively). The J-wave has been observed in a variety of clinical conditions including early repolarisation syndrome (ERS), hypothermia, hyperkalaemia, hypercalcaemia, stroke, subarachnoid haemorrhage, variant angina, acute ischaemia, BrS and IVF.

Myocytes in the ventricular epicardium present an action potential with a prominent Ito-mediated notch (spike and dome morphology). This prominent I_{to}-mediated notch present in the epicardium but not in the endocardium may produce a transmural voltage gradient during the early ventricular repolarisation phase that can appear as a J-wave or J-point elevation on the ECG [17]. I_{to} plays an important role in J-wave aetiology, so any factors influencing I_{to} can modulate J-waves on the ECG. Quinidine can result in reduced J-wave size and normalization of ST-segment elevation, probably due to inhibition of I_{to}. Potent sodium channel blockers such as ajmaline or flecainide, which reduce the epicardial action potential dome, can augment J-wave size and are used to detect a latent BrS. An increase in the heart rate during pacing or isoprenaline administration can also reduce the I_{to}, resulting in a reduced J-wave magnitude. It might be sometimes difficult to differentiate between the terminal QRS notch due to conduction delay and a J-wave (Figure 4). However, the terminal notched part of the QRS complex due to depolarisation delay can increase its magnitude during higher heart rate or is a stable phenomenon, while a true

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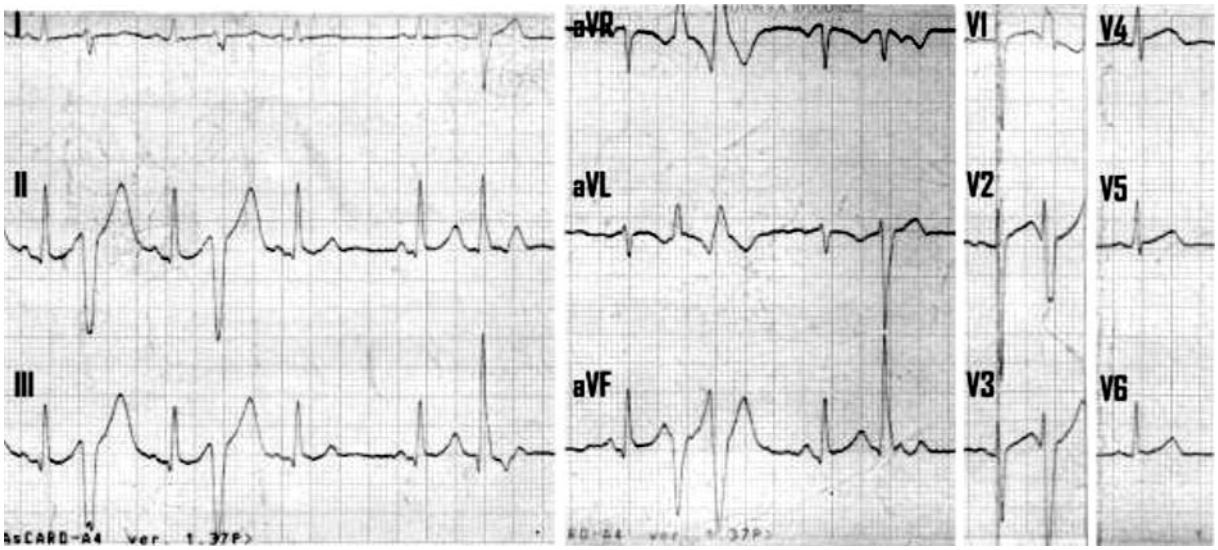

Figure 1. ECG of a 20-year old woman who survived an episode of idiopathic ventricular fibrillation. After admission episodes of fast polymorphic ventricular tachycardia quickly degenerating to VF were observed. After ICD implantation she suffered multiple appropriate interventions for VF. Note the small J-waves and ST-segment elevation in inferior and lateral leads and short-coupled ventricular premature beats originating from inferior-apical part of left ventricular wall

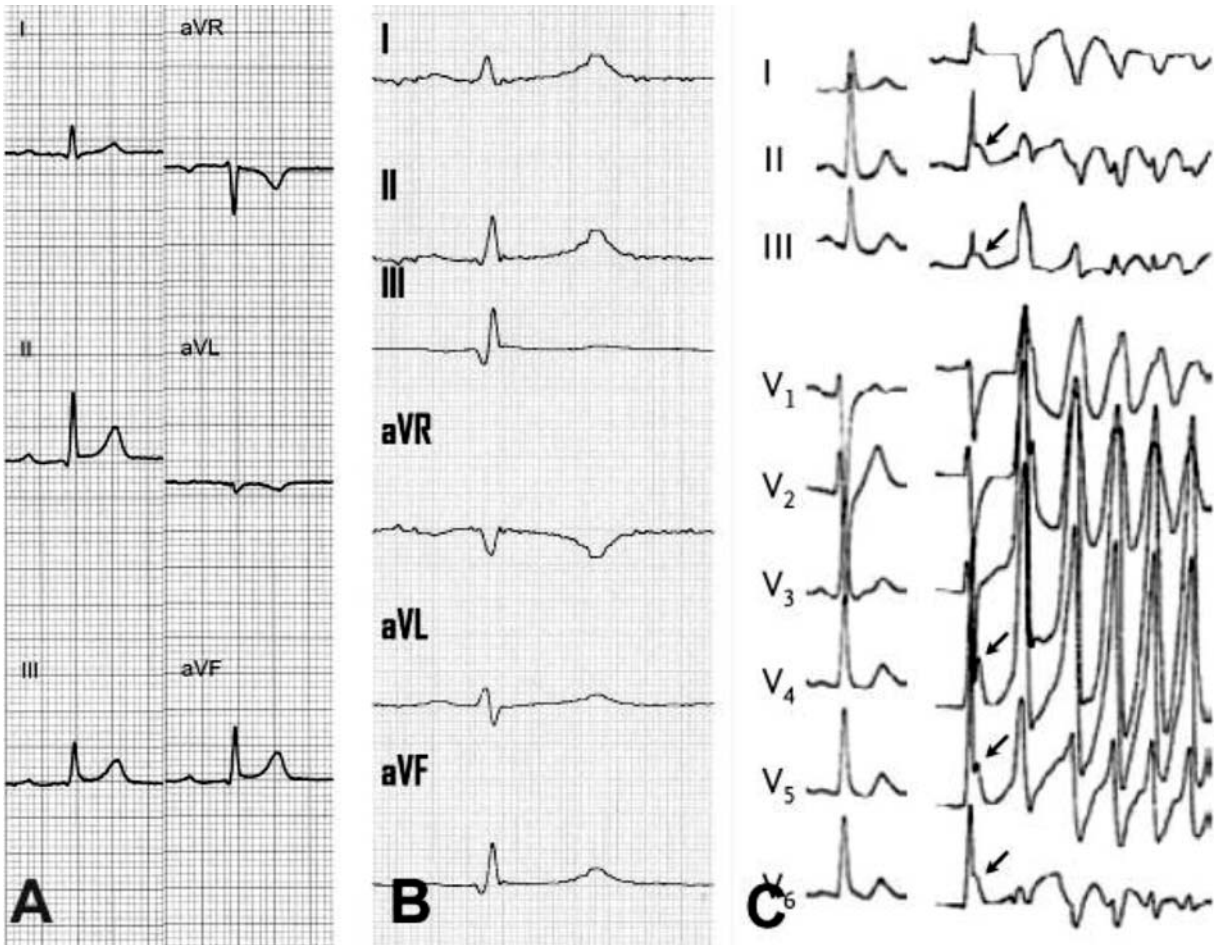

Figure 2. A – ECG with persistent ST-segment elevation in inferior leads registered in a 48-year old male who survived aborted SCD. Subsequently, after ajmaline test he was diagnosed with BrS. **B** – Tiny, hump-like J-wave in inferior leads registered in a 23-year old woman with recurrent syncopal episodes due to very fast polymorphic ventricular tachycardia/VF. Paper speed 50 mm/s. **C** – Prominent J-wave before VF initiation (courtesy of Prof. Michel Haissaguerre)

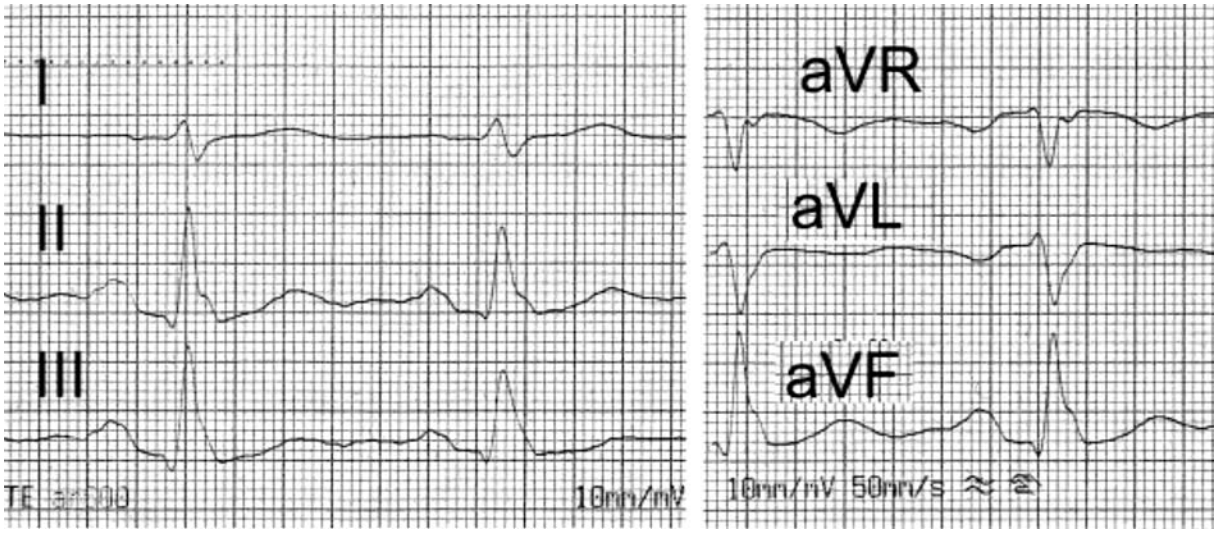

Figure 3. Admission ECG showing J-waves superimposed on the terminal part of QRS complexes in inferior leads in a 51-year old man who survived an aborted sudden death. On the following days these J-waves disappeared; however, 1 mm ST-segment elevation in inferior leads was present

J-wave is augmented during bradycardia, diminished during tachycardia, and is often a transient phenomenon with considerable amplitude changes that accompany ST-segment changes rather than QRS morphology changes, suggesting that it is a deflection of repolarisation rather than a depolarisation phase.

The action potential shape is relevant in arrhythmogenesis. The deeper the action potential notch between phase 1 and phase 2 of repolarisation the greater the predisposition to complete loss or depression of the dome shape in the epicardium [17]. This complete loss or depression produces a transmural voltage gradient during the entire repolarisation phase 2 that manifests as ST elevation on the ECG. Each pathological or pharmacological factor that increases outward currents (mainly I_{to}) or decreases inward currents (mainly I_{Ca} and I_{Na}) that are active at the end of phase 1 can accentuate the notch to a greater negative potential, at which point L-type I_{Ca} fails to activate or activates only partially, leading to a shortening of action potential duration and ST elevation in a mechanism similar to 'systolic current of injury' during acute ischaemia.

J-wave and ST-segment elevation in ischaemia

The classic theory for ST-segment elevation is 'the injury current' concept. The injury current is the result of the difference in the resting membrane potential between injured and uninjured myocardial tissues. However, no injury zone is identified in ERS, IVF or BrS, suggesting that other mechanisms are involved in ST-segment elevation in these syndromes [18]. Indeed, today even the concept of the injury current in the early phase of acute myocardial infarction (AMI) is evolving to include similar mechanisms to those operating in BrS [17, 19]. Yan et al. provided evidence that AMI can lead to loss of an I_{to}-mediated epicardial action potential dome, contributing in part to the development of ST-segment elevation similar to that observed in BrS [17, 19]. Complete loss of action potential dome in the epicardium is often heterogeneous, meaning the dome shape can be lost in one place and still remain normal in other places. This heterogeneous loss of the dome-shaped action potential is able to produce a marked difference in repolarisation, leading to local reexcitation, which is termed phase 2 re-entry. On a surface ECG, phase 2 re-entry manifests as a closely coupled R-on-T extrasystole that can initiate the development of poly-VT or VF [19]. In AMI, similarly to IVF, VF onset is almost always initiated by such closely coupled R-on-T extrasystole, further promoting the concept of similar electrophysiological mechanisms of arrhythmogenesis in these two conditions.

AMI studies show that the incidence of VF in AMI is greater in patients with right ventricular involvement compared with those with inferior AMI without right ventricular involvement and those with anterior AMI (8.4 vs. 2.7 vs. 5.0%, respectively) [20]. These observations are concordant with the fact that I_{to} is more prominent in the epicardium of the right than the left ventricle. What is more, I_{to} is greater in males than in females, and this is consistent with the higher incidence of BrS, IVF and the rate of SCD in coronary artery disease in men [21].

Lambda-like ST segment ST elevation in acute myocardial infarction – a risk factor for primary ventricular fibrillation?

We have also observed that ST elevation shape resembling the Greek letter λ ('lambda wave'), which also bears resemblance to a giant J-wave, is often present in patients with AMI complicated by VF (Figure 5) [22, 23].

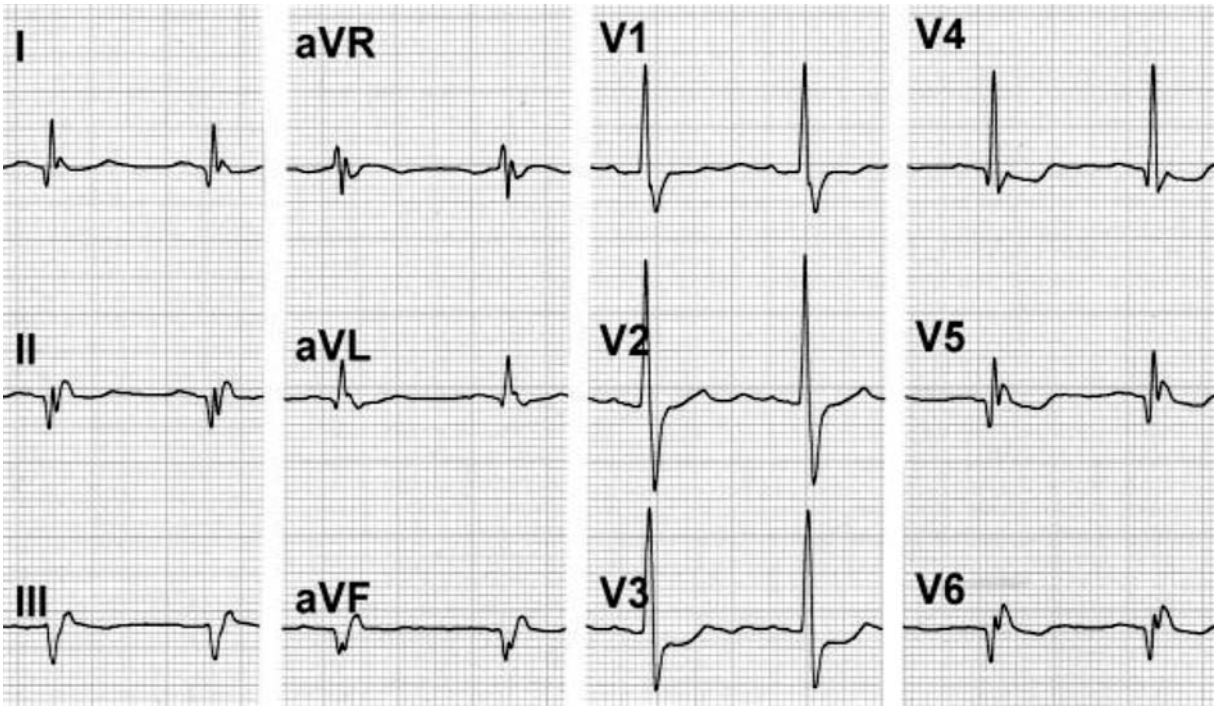

Figure 4. Resting 12-lead ECG registered in a 59-year old male, with multi-vessel disease (occluded right and circumflex coronary artery, 99% stenosis of left anterior descending branch, however, with a patent arterial bypass to that vessel) who suffered two myocardial infarctions (inferior and infero-lateral). Now with an enlarged left ventricle and a left ventricular ejection fraction of 25%. Conduction delay, especially over lateral and inferior wall, resulted in a notched terminal part of the QRS complex that resembles a J-wave; however, this pseudo J-wave was a stable part of QRS morphology and not influenced by heart rate, most likely resulting from depolarisation rather than repolarisation abnormality

A partial explanation for this observation might be that the arrhythmogenesis and ST segment elevation in BrS and AMI have a similar pathophysiological basis. Intriguingly, patients with primary VF during AMI do not differ in respect to age, classic risk factors, infarct size and location, culprit coronary artery, and presence of multivessel disease from patients without primary VF [24]. Dekker et al. showed that the risk of primary VF in AMI is determined by cumulative ST deviation and family history of sudden death [24]. Furthermore, Hu et al. recently showed that VF in AMI, particularly occurring in the setting of an electrical storm, may be, similarly to BrS, genetically predisposed owing to a missense mutation in the SCN5A gene [25].

J-wave syndromes

Clinical syndromes associated with J-wave and ST elevation include ERS, IVF and BrS. These syndromes show similar ECG features but have different clinical consequences. ERS is considered a clinically benign syndrome, whereas IVF and BrS are associated with episodes of SCD and syncope owing to poly-VT degenerating to VF. These syndromes have a number of common features. 1) They predominantly occur in males. 2) The decrease in heart rate can accentuate J-point and ST-segment elevation. 3) For IVF and BrS, quinidine can normalize ST elevation and prevent VF. 4) In some BrS and IVF cases gene mutations responsible for these diseases are found in the SCN5A gene. In addition to these similarities, the syndromes also have distinguishing features. 1) In terms of anatomical locations, J-point and ST elevation are observed in the lateral side of the left ventricle (LV) in ERS, in the infero-posterior area of the LV in IVF, and in the right ventricle in BrS. 2) The clinical manifestations of all these syndromes are probably related to the Ito density in the epicardium; Ito density is small in ERS, medium in IVF and large in BrS. Consequently, the J-wave amplitude is small in ERS, medium in IVF, and large in BrS [26, 27].

J-waves in clinical cases

In recent years several authors have reported SCD and/or ventricular arrhythmia cases associated with the presence of J-waves in the lateral and/or inferior leads.

Aizawa et al. were first to draw attention to the association between terminal QRS notching in inferior and lateral leads and IVF. They presented the ECGs of four such patients. However, they ascribed this ECG sign to

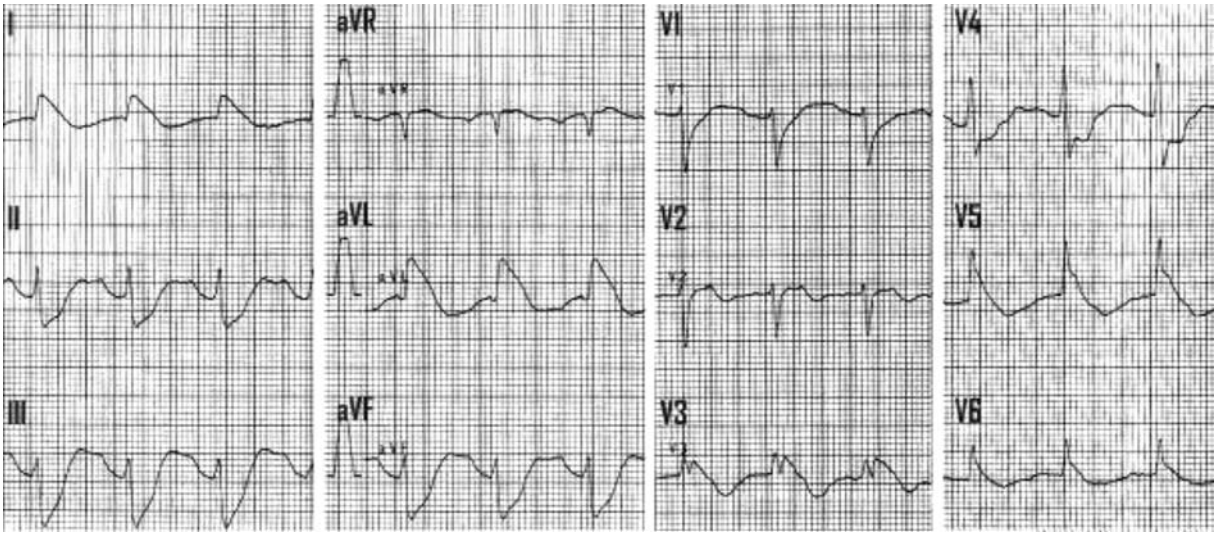

Figure 5. ECG from a 73-year-old man with occlusion in the first diagonal artery and an electrical storm requiring seven defibrillations for ventricular fibrillation in the acute phase of AMI. The QRS complex/ST-segment elevation shape in leads I, aVL, V_4-V_6 resembles the Greek letter lambda or a giant J-wave

a bradycardia-dependent intraventricular block rather than to a repolarisation abnormality [13].

Garg and coworkers described an 18-year old man with J-wave and aborted sudden cardiac death due to ventricular fibrillation [4]. J-wave was observed in leads II, III, aVF, I, aVL and V_3-V_6. This deflection on the terminal part of QRS complexes corresponded to an abnormal signal-averaged ECG, demonstrating a late potential. The patient had easily inducible polymorphic VT during the electrophysiological study, which was suppressed by quinidine but not procainamide and beta-blockers. During oral quinidine therapy J-waves were eliminated and the patient had no other further arrhythmia during 6 years until he inexplicably discontinued his medication and died suddenly shortly thereafter.

Takagi et al. reported three patients with J-wave and ST-segment elevation in inferior leads and clinical characteristics similar to BrS. They considered it a variant BrS despite a lack of spontaneous or induced J-waves in leads V_1-V_3. The magnitude of ST-elevation varied from day to day; disopyramide augmented ST-elevation while exercise test demonstrated disappearance of J-waves [12].

Maruyama described a case of a 52-year-old man with vasospastic angina and VF associated with J-waves predominantly in the lateral leads (maximum amplitude up to 7 mm) and leads I, II, aVL, aVF and V_1-V_6. During coronary vasospasm the ECG revealed ST depression in leads V_3-V_6 but no J-wave. VF occurred approximately 20 minutes after identification of the J-wave in the ECG [28].

Ogawa et al. reported on a 52-year-old patient with syncope and J-waves in the inferior leads but no ST-segment elevation in the right precordial leads [8]. Ventricular extrasystoles with a short coupling interval were observed and all had left bundle branch-like morphology with a superior axis including the extrasystole initiating spontaneous episodes of VF. Although coronary angiography revealed no stenosis, infusion of acetylcholine induced coronary spasm. Intravenous pilsicainide caused ST-segment elevation in the inferior leads and coved-type ST elevation in the right precordial leads. Isoproterenol infusion did not reduce the ST elevation in the inferior leads. VF was induced during the electrophysiological (EP) study. An ICD was implanted and the patient remained free of VF recurrence during a 12-month follow-up without antiarrhythmic therapy. A similar case of IVF, spontaneous J-waves in inferior/lateral leads and inducible BrS sign in V_1-V_3 was reported by Daimon et al. [14].

A report by Ozeke et al. described the case of a 23--year-old man who experienced palpitations mainly during exercise [9]. An exercise stress test provoked stable VT with a left bundle branch block pattern and an inferior axis, suggesting that the origin was the right ventricular outflow tract (RVOT). Propafenone was administered to terminate repetitive VT and suppressed the arrhythmia and caused a moderate J point elevation in inferior leads II, III and aVF. In the EP study, VT was induced from the right ventricular apex and RVOT. The patient remained free of symptoms in the absence of any medication over the 12-month follow-up period.

In 2004, Riera et al. described an interesting case of a 26--year-old man with a history of brief fainting and convulsive-like episodes [10]. Two members of the patient's family had died from SCD at 31 and 39 years of age, respectively. The patient presented with a peculiar ECG showing J-wave and ST-segment elevation in the inferior II, III, aVF and V_6 leads. ST-segment elevation had an atypical shape with down-sloping, and a terminal negative T wave in the infero-lateral leads. Additionally, ST depression was observed in: V_1-V_5, I, aVR and aVL leads. This patient died

suddenly during Holter monitoring, which revealed a short run of poly-VT in the early morning, which quickly evolved into asystole and SCD.

Recently, we described two patients with J-wave (point) elevation and aborted SCD. In both cases, the J-wave in the infero-lateral leads normalized after ajmaline administration, in one case it normalized during exercise testing, and one case showed ST elevation typical for BrS during the ajmaline test. One patient (with Brugada abnormalities) refused quinidine treatment and ICD therapy, but an ICD was implanted in the second patient [5, 7].

The Haissaguerre syndrome

The circumstantial evidence from the published case reports resulted in a search for more solid scientific evidence for J-wave association with ventricular arrhythmias. Haissaguerre et al. were the first to show an association between early repolarisation pattern (ERP) and SCD based on observation of 206 patients with IVF [29]. The ERP was more frequent in patients with IVF than in controls (31 vs. 5%, $p < 0.001$) and was greater in magnitude in IVF patients too. Arrhythmogenic J-waves in case subjects had statistically higher amplitude than benign J-waves in control subjects, 2.0 vs. 1.2 mm, respectively. In patients with VF, those showing ERP were more likely to be males, to have frequent syncope or experience sudden death during sleep and to have shorter QTc than those without ERP. Furthermore, patients showing an ERP in ECG had more arrhythmic episodes in ICD (implantable cardioverter-defibrillator) memory than in those without one (41 vs. 23%, hazard ratio – 2.1). These results were corroborated by Abe et al., who showed almost 10-fold increase in J-wave occurrence in 222 patients with syncopal episodes as compared to 3915 healthy controls (18.5 vs. 2%), and by Rosso et al., who found J-point elevation in 42% of 45 IVF cases and in 13% of 124 matched controls [30, 31]. Importantly, J-point elevation in leads V_5-V_6 occurred with similar frequency in both groups, while in leads I and aVL it was much more frequent in patients with IVF (13 vs. 1%), also in leads II, III, and aVF it was more frequent in patients with IVF (27 vs. 8%). Similarly, Nam et al. observed J-wave augmentation in patients with IVF, especially in patients with electrical storm [32]. The ERP was observed in 60% of patients with IVF, and in all with electrical storm. In healthy control subjects ERP was seen in 3.3%. The J-wave became accentuated across precordial and limb leads before episodes of electrical storm. In these patients in contrast to patients with Brugada syndrome the J-wave was not limited to the right precordial leads and flecainide could not provoke these ECG abnormalities. BrS quinidine and isoproterenol suppressed these J-waves. Interestingly, arrhythmic events recorded in 18 patients showed accentuation of the J-wave amplitude prior to VF. What is more, three subjects with J-wave elevation of over 5 mm had more than 50 episodes of VF, leading in one case to death. In eight patients, localization of the ectopy during mapping of the arrhythmia was concordant with the location of the repolarisation abnormalities. These studies indicate the need to re-define ERS and IVF. Recently Haissaguerre described a case of a 14 year-old girl with a typical J-wave and a history of over 100 episodes of VF, and genetic screening showed, for the first time, the missense mutation in KCNJ8, a subunit of the K_{ATP} channel [33].

Conclusions

The electrocardiographic J-wave seems to be very important in understanding arrhythmogenesis both in structurally normal hearts and in ischaemia. Michael Haissaguerre and coworkers were first to show in a large series of patients an association between unexplained ventricular fibrillation and the J-wave in the ECG in leads II, III, aVF and/or V_5-V_6. Therefore, we propose the eponym 'Haissaguerre syndrome' for this new clinical entity. We should no longer use for such patients the term idiopathic ventricular fibrillation because as in the Brugada, long QT or short QT syndromes an ECG hallmark for this condition is present: J-wave in inferior and/or lateral leads. The term IVF should be reserved for cases of VF without any electrocardiographic arrhythmia-related abnormalities. As such, fewer conditions can now be considered true IVF. Currently, a major limitation of this new ECG sign is its low specificity due to high prevalence of asymptomatic cases with ERS. Possibly, in the future, this limitation might be overcome with more refined ECG criteria and/or with pharmacological tests.

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