Available online at www.sciencedirect.com

ScienceDirect

Journal of Electrocardiology 46 (2013) 510–518

JOURNAL OF Electrocardiology

www.jecgonline.com

J wave syndromes: Molecular and cellular mechanisms☆,☆☆

Charles Antzelevitch, PhD, FHRS, FACC, FAHA*

Masonic Medical Research Laboratory, Utica, NY, USA

Abstract An early repolarization (ER) pattern in the ECG, consisting of J point elevation, distinct J wave with or without ST segment elevation or slurring of the terminal part of the QRS, was long considered a benign electrocardiographic manifestation. Experimental studies a dozen years ago suggested that an ER is not always benign, but may be associated with malignant arrhythmias. Validation of this hypothesis derives from recent case–control and population-based studies showing that an ER pattern in inferior or infero-lateral leads is associated with increased risk for life-threatening arrhythmias, termed early repolarization syndrome (ERS). Because accentuated J waves characterize both Brugada syndrome (BrS) and ERS, these syndromes have been grouped under the heading of J wave syndromes. BrS and ERS appear to share common ECG characteristics, clinical outcomes, risk factors as well as a common arrhythmic platform related to amplification of I_{to}-mediated J waves. However, they differ with respect to the magnitude and lead location of abnormal J waves and can be considered to represent a continuous spectrum of phenotypic expression. Recent studies support the hypothesis that BrS and ERS are caused by a preferential accentuation of the AP notch in right or left ventricular epicardium, respectively, and that this repolarization defect is accentuated by cholinergic agonists. Quinidine, cilostazol and isoproterenol exert ameliorative effects by reversing these repolarization abnormalities. Identifying subjects truly at risk is the challenge ahead. Our goal here is to review the clinical and genetic aspects as well as the cellular and molecular mechanisms underlying the J wave syndromes.

Keywords: Cardiac arrhythmias; Sudden cardiac death; Early repolarization syndrome; Brugada syndrome; Idiopathic ventricular fibrillation

Introduction

The electrocardiographic J wave was first described in 1938[1] in an ECG recorded from an accidentally frozen human. It was referred to as the Osborn wave for many years after being reported by Osborn in hypothermic dogs in 1953.[2] The appearance of prominent J wave in humans is encountered in cases of hypothermia,[3–5] hypercalcemia[6,7] and more recently has been suggested as a marker for a substrate capable of generating life-threatening ventricular arrhythmias.[8] In humans, the J wave more commonly appears as a J point elevation, with part of the J wave buried inside the QRS.

An early repolarization (ER) pattern on the ECG was first described in 1936 by Shipley and Hallaran, who studied four-lead ECGs of 200 healthy young men and women and described J deflection as slurring or notching of the terminal part of QRS complex and considered it as a normal variant.[9] In subsequent years, ST segment elevation was added to these electrocardiographic manifestations and the complex was designated "early repolarization" based on the presumption that early repolarization was responsible,[10] although no data were available to support this assertion. Experimental data in support of the hypothesis were first advanced with the identification of the cellular basis for the J wave in 1996.[11]

An ER pattern in the ECG, consisting of a distinct J wave or J point elevation, a notch or slur of the terminal part of the QRS and an ST segment elevation, is generally found in healthy young males and has traditionally been viewed as benign.[12,13] In 2000, we challenged this view on the basis of experimental data showing that an ER pattern in the canine coronary-perfused wedge preparation predisposes to the development of polymorphic ventricular tachycardia and fibrillation (VT/VF).[8,14,15]

Validation of this hypothesis was provided eight years later in the New England Journal of Medicine by Haïssaguerre et al.[16] and a letter to the editor by Nam et al.[17] These reports together with numerous additional case control and population based studies provided clinical

☆ Conflicts of Interest: There are no conflicts of interest to disclose.

☆☆ Support: Supported by grants HL47678 from NHLBI, NIH, C026424 from NYSTEM, and the Masons of New York State, Florida, Massachusetts Connecticut, Maryland, Rhode Island and Wisconsin.

* Gordon K. Moe Scholar, Masonic Medical Research Laboratory, 2150 Bleecker Street, Utica, NY 13501.

E-mail address: ca@mmrl.edu

0022-0736/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jelectrocard.2013.08.006

evidence that there is an increased prevalence of ER pattern, particularly in the inferior and infero-lateral leads, among patients with a history of idiopathic ventricular fibrillation, thus confirming a link between ER pattern in the ECG and life-threatening cardiac arrhythmias (see[18,19] for review).

The poorer prognosis of subjects with inferior or infero-lateral ER was confirmed in numerous population based studies (see[18,19] for references). We recently suggested a classification scheme for ER (Table 1).[8] An ER pattern manifest exclusively in the lateral precordial leads was designated as Type 1; this form is prevalent among healthy male athletes and is thought to be associated with a relatively low level of risk for arrhythmic events. ER pattern in the inferior or infero-lateral leads was designated as Type 2; this form is thought to be associated with a moderate level of risk. Finally, an ER pattern appearing globally in the inferior, lateral and right precordial leads was labeled Type 3; this form is associated with the highest level of risk and in some cases has been associated with electrical storms.[8] Type 3 ER may at times be very similar to that of Type 2, exhibiting infero-lateral ER, except for brief periods immediately before the development of VT/VF when pronounced J waves are also observed in the right precordial leads (see [20] for an example). BrS represents a fourth variant in which ER is limited to the right precordial leads.

Genetics basis for the J wave syndromes

BrS has been associated with mutations in twelve different genes, accounting for approximately 40% of probands. Greater than 300 mutations in *SCN5A* ($Na_v1.5$, BrS1) have been reported by centers worldwide accounting for 11–28% of BrS probands. Mutations in *CACNA1C* ($Ca_v1.2$, BrS3), *CACNB2b* ($Ca_v\beta2b$, BrS4) and *CACNA2D1* ($Ca_v\alpha2\delta$, BrS9) are reportedly found in ~13% of probands. Mutations in glycerol-3-phophate dehydrogenase 1-like enzyme gene (*GPD1L*, BrS2), *SCN1B* (β_1-subunit of Na channel, BrS5), *KCNE3* (MiRP2; BrS6), *SCN3B* ($\beta3$-subunit of Na channel, BrS7), *KCNJ8* (BrS8) and *KCND3* (BrS10) are more rare. Mutations in these genes lead to loss of function in I_{Na} and I_{Ca}, as well as to a gain of function in I_{to} or $I_{K\text{-}ATP}$. MOG1 was recently described as a new partner of $Na_V1.5$, playing a role in its regulation, expression and trafficking. A missense mutation in MOG1 was also associated with BrS (BrS11). Mutations in sarcolemmal membrane-associated protein (SLMAP), a protein of unknown function localizing at T-tubules and sarcoplasmic reticulum, have recently been associated with BrS (BrS12). Preliminary reports indicate an important association with *SCN10A*, a neuronal sodium channel that co-associates with *SCN5A*, with a yield as high as 20%. Mutations in *KCNH2* and *KCNE5*, although not causative, have been identified as capable of modulating the substrate for the development of BrS. Loss-of-function mutations in *HCN4* causing a reduction in the pacemaker current, I_f, have the potential to unmask BrS by reducing heart rate[21] (see [18] for references).

The familial nature of ER pattern has been demonstrated in a number of studies.[22–24] ER pattern and ERS have been associated with mutations in 6 genes. Consistent with the findings that $I_{K\text{-}ATP}$ activation can generate an ER pattern in canine ventricular wedge preparations, a rare variant in *KCNJ8*, responsible for the pore forming subunit of the $I_{K\text{-}ATP}$ channel, has been reported in patients with ERS as well as BrS.[25–27] Loss of function mutations in the $\alpha1$ and $\beta2$ and $\alpha2\delta$ subunits of the cardiac L-type calcium channel (*CACNA1C*, *CACNB2*, and *CACNA2D1*) have been uncovered in patients with ERS.[28] The most recent addition to the genes associated with ERS is *SCN5A*, the gene that encodes the α subunit of the cardiac sodium channel.[29] Interestingly, it appears that the *SCN5A* mutations are associated with a Type 3 ERS in which a J point or ST segment elevations is present in the right precordial leads as well as in the inferior and lateral leads under baseline conditions or following a sodium block challenge.[29]

It is noteworthy that only a small fraction of identified genetic variants in the numerous genes associated with BrS and ERS have been investigated functionally to establish causality or a plausible contribution to pathogenesis. Very few have been studied in genetically engineered animal models or native cardiac cells. Computational strategies have been developed to predict the functional consequences of mutations, but none of these methods have been rigorously tested. The lack of functional or biological validation of mutation effects remains the most severe limitation of genetic test interpretation.[30] This limitation is further extended to those cases in which a susceptibility gene has been identified on the basis of a single proband and with the absence of familial segregation data.

Ionic and cellular mechanisms

The J wave in the ECG is inscribed as a consequence of the presence of a prominent I_{to}-mediated action potential notch in epicardium, but not endocardium giving rise to a transmural voltage gradient.[31,32] Direct evidence in support of this hypothesis derives from data first reported using the arterially-perfused canine ventricular wedge preparation.[11]

Factors that augment or reduce I_{to} or that speed or slow the kinetics of the current can importantly modify the manifestation of the J wave on the ECG. Whether augmented by exposure to hypothermia, I_{Ca} and I_{Na} blockers or I_{to} agonists such as NS5806 or reduced by I_{to} blockers such as 4-aminopyridine, quinidine or premature activation or changes in the magnitude of the epicardial AP notch parallel those of the J wave.[33,34]

Brugada syndrome

The proposed cellular mechanism for the Brugada syndrome is summarized in Fig. 1. Most studies support the hypothesis that the Brugada syndrome results from amplification of heterogeneities intrinsic to the early phases of the action potential among the different transmural cell types. An increase in net repolarizing current due to either a decrease of inward currents such ands I_{Na} or I_{Ca} or an increase of outward current such as I_{to} or $I_{K\text{-}ATP}$, accentuates the notch leading to augmentation of the J wave or