Available online at www.sciencedirect.com

SciVerse ScienceDirect

Journal of Electrocardiology 44 (2011) 656–661

JOURNAL OF Electrocardiology

www.jecgonline.com

J-wave syndromes. From cell to bedside☆,☆☆

Charles Antzelevitch, PhD,[a,*] Gan-Xin Yan, MD, PhD[b,c]

[a]Masonic Medical Research Laboratory, Utica, NY, USA
[b]Main Line Health Heart Center and Lankenau Institute for Medical Research, Wynnewood, PA, USA
[c]Jefferson Medical College, Philadelphia, PA, USA

Received 16 April 2011

Abstract The J wave, a deflection that follows the QRS complex of the surface electrocardiogram, is usually partially buried in the R wave in humans, appearing as a J-point elevation. An early repolarization (ER) pattern characterized by J-point elevation, slurring of the terminal part of the QRS, and ST-segment elevation has long been recognized and considered to be totally benign. Recent studies have presented evidence demonstrating that an ER pattern in inferior leads or inferolateral leads is associated with increased risk for life-threatening arrhythmias, named *early repolarization syndrome*. Early repolarization syndrome and Brugada syndrome share similar electrocardiographic characteristics, clinical outcomes, risk factors, as well as a common arrhythmic platform related to amplification of I_{to}-mediated J waves. Although Brugada syndrome and early repolarization syndrome differ with respect to the magnitude and lead location of abnormal J wave manifestation, they can be considered to represent a continuous spectrum of phenotypic expression, termed *J-wave syndromes*. Early repolarization syndrome has been proposed to be divided into 3 subtypes: type 1, displaying an ER pattern predominantly in the lateral precordial leads, is prevalent among healthy male athletes and rarely seen in ventricular fibrillation survivors; type 2, displaying an ER pattern predominantly in the inferior or inferolateral leads, is associated with a higher level of risk; whereas type 3, displaying an ER pattern globally in the inferior, lateral, and right precordial leads, is associated with the highest level of risk for development of malignant arrhythmias and is often associated with ventricular fibrillation storms.

Keywords: Cardiac arrhythmias; Sudden cardiac death; Sudden cardiac arrest; Transient outward current; J-point elevation; Early repolarization syndrome; Brugada syndrome; Idiopathic ventricular fibrillation; Hypothermia; STEMI

Introduction

The J wave is a deflection that follows the QRS complex on the surface electrocardiogram (ECG). When partially buried in the R wave, the J wave appears as a J-point elevation and may be accompanied by an ST-segment elevation, an ECG feature referred to as an early repolarization (ER) pattern. Recent studies have provided evidence in support of an association of ER pattern with life-threatening arrhythmias, designated as ER syndrome (ERS) or Brugada syndrome (BrS) based on the region of the heart responsible for the arrhythmogenic substrate. Although BrS and ERS differ with respect to the magnitude and lead location of abnormal J-wave manifestation, they are thought to represent a continuous spectrum of phenotypic expression termed *J-wave syndromes*.[1]

The ER pattern, 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 predominantly found in healthy young males and has traditionally been viewed as benign.[2,3] Our observation in 2000 that an ER pattern in the canine coronary-perfused wedge preparation can easily convert to one in which phase 2 reentry gives rise to polymorphic ventricular tachycardia/ventricular fibrillation (VT/VF) prompted the suggestion that ER may in some cases predispose to malignant arrhythmias in the clinic.[1,4,5] A number of case reports and experimental studies have suggested a critical role for the J wave in the pathogenesis of idiopathic ventricular fibrillation (IVF).[6-14] A definitive association between ER and IVF was presented in the form of 2 studies published in the *New England Journal of Medicine* in 2008.[15,16] These were followed by another

☆ Supported by HL47678 from the National Heart, Lung, and Blood Institute (CA), Masons of New York State and Florida (CA).

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

* Corresponding author. Gordon K. Moe Scholar, Masonic Medical Research Laboratory, 2150 Bleecker Street, Utica, NY 13501, USA.
E-mail address: ca@mmrl.edu

0022-0736/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.jelectrocard.2011.07.026

study from Rosso et al[17] that same year and 2 large population association studies in 2009 and 2010.[18,19]

Based on the available clinical data, we recently suggested a classification scheme that attempts to risk stratify patients with ER.[1] An ER pattern that manifests 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. Early repolarization pattern in the inferior or inferolateral 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.[1] Brugada syndrome represents a fourth variant in which ER is limited to the right precordial leads.

Ionic and cellular basis for the J wave and associated arrhythmogenesis

Transmural differences in the early phases of the action potential have long been recognized as the basis for inscription of the electrocardiographic J wave.[20,21] The ventricular epicardial action potential, particularly in the right ventricle, displays a prominent transient outward current (I_{to})–mediated notch or spike and dome morphology. The presence of a prominent I_{to}-mediated action potential notch in ventricular epicardium but not endocardium produces a transmural voltage gradient that registers as a J-wave or J-point elevation on the ECG. Direct evidence in support of this hypothesis was first obtained in arterially perfused canine ventricular wedge preparations[7] as illustrated in Fig. 1. Factors that influence I_{to} kinetics or

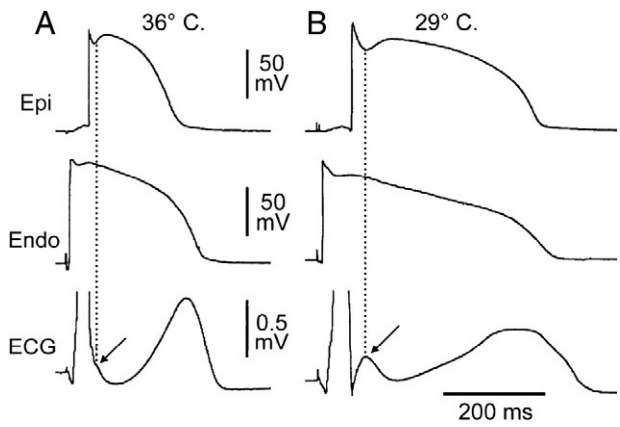

Fig. 1. Hypothermia-induced J wave. Each panel shows transmembrane action potentials from the epicardial and endocardial regions of an arterially perfused canine left ventricular wedge and a transmural ECG simultaneously recorded. A, The relatively small action potential notch in epicardium but not in endocardium is associated with an elevated J point at the R-ST junction (arrow) at 36°C. B, A decrease in the temperature of the perfusate to 29°C results in an increase in the amplitude and width of the action potential notch in epicardium but not endocardium, leading to the development of a transmural voltage gradient that manifests as a prominent J wave on the ECG (arrow) (modified from Yan and Antzelevitch[7] with permission).

ventricular activation sequence can modify the manifestation of the J wave on the ECG. Whether reduced by I_{to} blockers such as 4-aminopyridine or premature activation or augmented by exposure to hypothermia, changes in the magnitude of the epicardial action potential notch parallel those of the J wave.[22,23]

Augmentation of net repolarizing current, secondary to a decrease of inward currents or an increase of outward current, accentuates the notch leading to augmentation of the J wave or appearance of ST-segment elevation. A further increase in net repolarizing current can result in partial or complete loss of the action potential dome, leading to a transmural voltage gradient that manifests as accentuation of the J wave or an ST-segment elevation.[5,22,23] In regions of the myocardium exhibiting a prominent I_{to}, such as the right ventricular epicardium, marked accentuation of the action potential notch and a coved-type ST-segment elevation diagnostic of BrS (Fig. 2B). A further outward shift of the currents active during the early phase of the action potential can lead to loss of the action potential dome, thus creating a dispersion of repolarization between epicardium and endocardium as well as within epicardium, between the region where the dome is lost and regions at which it is maintained (Fig. 2C). Sodium channel blockers such as procainamide, pilsicainide, propafenone, flecainide, and disopyramide cause a further outward shift of current flowing during the early phases of the action potential and therefore effective in inducing or unmasking ST-segment elevation in patients with concealed J-wave syndromes.[24-26] Sodium channel blockers such as quinidine, which also inhibits I_{to}, reduce the magnitude of the J wave and normalize ST-segment elevation.[5,27] Loss of the action potential dome is usually heterogeneous, resulting in marked abbreviation of action potential at some sites but not others. The dome can then propagate from regions where it is maintained to regions where it is lost, giving rise to a very closely coupled extrasystole via phase 2 reentry (Fig. 2D).[28] The phase 2 reentrant beat can then initiate a polymorphic VT or VF (Figs. 2E and F).

The outward shift of current may extend beyond the action potential notch and thus lead to depression of the dome in addition to accentuating the J wave. Activation of the ATP-sensitive potassium current ($I_{K\text{-}ATP}$) or depression of inward calcium channel current (I_{Ca}) can effect such a change (Figs. 3A and B). This is more likely to manifest in the ECG as an ER pattern consisting of a J-point elevation, slurring of the terminal part of the QRS, and mild ST-segment elevation. The ER pattern can facilitate loss of the dome due to other factors and thus lead to the development of ST-segment elevation, phase 2 reentry, and VT/VF. (Fig. 3C and D).

Clinical manifestations of J-wave syndromes

In both ERS and BrS, the manifestation of the J wave or ER is dynamic,[14,29,30] with the most prominent ECG changes appearing just before the onset of VT/VF.[7-14,29-31] Other ECG characteristics of ERS also closely match those of BrS, including the presence of accentuated J waves, pause