Pathophysiological mechanisms of arrhythmogenic right ventricular disorders
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Citation for published version (APA):
Hoogendijkstra, M. G. (2013). Pathophysiological mechanisms of arrhythmogenic right ventricular disorders

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CHAPTER 5

The J-wave conundrum: early repolarization and Brugada syndrome

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Heart Rhythm 2013;10:540-541
In this issue of *Heart Rhythm*, Takagi and colleagues evaluated the prognostic value of inferolateral J-point elevation in a large cohort of Brugada syndrome (BrS) patients. Inferolateral J-point elevation followed by a horizontal ST-segment was associated with an increased risk of arrhythmic events in both patients groups with and without a history of aborted sudden cardiac death by ventricular fibrillation (VF). The authors conclude that the combination of electrocardiographic patterns may help identify BrS patients with a highly arrhythmogenic substrate. The paper by Takagi once more shows the intertwinement of BrS and early repolarization syndrome.\(^1\)

The intricate interrelation between the two syndromes has invoked the idea that the pathophysiological mechanisms underlying the syndromes is the same.\(^2\)

The identification of ECG anomalies in idiopathic VF victims has enabled their differentiation into subgroups with a presumably shared arrhythmogenic substrate. It was the Brugada ECG pattern that set BrS patients apart from other idiopathic VF victims at the initial description of the syndrome.\(^3\) This has sparked great interest in the mechanism underlying both the ECG pattern and arrhythmogenesis in BrS.\(^4\) Recently, a high prevalence of J-point elevation in the inferolateral leads, termed early repolarization, was reported in idiopathic VF patients.\(^5\) Subsequent reports on this so-called early repolarization syndrome indicated that inferolateral J-point elevation followed by horizontal or descending ST segment in particular is associated with an increased risk of arrhythmic death at a population level\(^6\) as well as with idiopathic VF.\(^7\)

A degree in overlap in patient characteristics and modulators of arrhythmic events has prompted some to consider the BrS and early repolarization syndrome the result from a single pathophysiological mechanism and grouped them under the term “J wave syndromes”.\(^2\) Indeed, inferolateral J-point elevation has a higher prevalence in BrS patients (~11%)\(^8,9\) than in either their unaffected relatives (~6%)\(^8\) or the general population (~5%).\(^5,6\) The study by Takagi et al takes this idea a step further by looking at the prognostic value of the early repolarization pattern in a BrS population.

Although their study obviously was not designed to address the pathophysiological mechanism(s) underlying early repolarization syndrome and BrS, the paper by Takagi et al. raises several questions. First, in what aspect does the arrhythmogenic substrate differ between Brugada syndrome patients with and without inferolateral J-point elevation? One explanation may be that the arrhythmogenic substrate encompasses a larger myocardial area in patients with inferolateral J-point elevation than in other BrS patients. Support for this notion can be found in body surface mapping studies that demonstrated that a larger body surface area of ST-elevation after sodium channel blockade is related with inducibility of ventricular arrhythmias in the BrS.\(^10\) Furthermore, the Brugada ECG pattern is not always confined to the right precordial leads\(^11\) and can be pro-
voked quite frequently in the inferior leads of BrS patients with inferolateral J-point elevation by sodium channel blockade.\textsuperscript{8}

Second, if a single mechanism accounts for the Brugada ECG pattern and for inferolateral J-point elevation in idiopathic VF patients how does this explain the differential pharmacological modulation of the ECG features in these patient groups? Sodium channel blockade augments or provokes the Brugada ECG pattern\textsuperscript{12} and is considered such a pivotal modulator of BrS that such provocation tests have been incorporated in its diagnostic criteria.\textsuperscript{13} In contrast, sodium channel blockers attenuate the inferolateral J-point elevation observed in idiopathic VF patients.\textsuperscript{14,15} Likewise, isoproterenol, which enhances the L-type calcium current ($I_{\text{CaL}}$), also has a differential effect in these two conditions: normalization of the J-point elevation was achieved in the majority of idiopathic VF patients with inferolateral J-point elevation, whereas normalization of the Brugada ECG pattern was not achieved in any patient by Roten et al.\textsuperscript{16}

It will be a challenge to determine the pathophysiological mechanism(s) in these patient groups. One first step is to determine whether the Brugada ECG pattern and inferolateral J-point elevation are caused by a conduction or repolarization anomaly. Differentiation based on modulation of these ECG patterns by the $I_{\text{CaL}}$ and transient outward current ($I_{\text{to}}$) is not possible as these currents can influence both conduction\textsuperscript{17} as well as shape of the action potential.\textsuperscript{18} In conditions of local conduction slowing, the current available for conduction depends not only on the cardiac sodium current but on the sum of all inward (depolarizing) and outward (repolarizing) currents during the early phase of the action potential. A reduction in repolarizing $I_{\text{to}}$ or increase in depolarizing $I_{\text{CaL}}$ will increase the current available for conduction and have been demonstrated to reduce the Brugada ECG pattern in a model based on local conduction disturbances by current-to-load mismatch.\textsuperscript{17} Similarly, a reduction in $I_{\text{to}}$ and an increase in $I_{\text{CaL}}$ determine the early repolarization phase (phase 1 of the action potential) which has been suggested to be altered in these conditions.\textsuperscript{18} Local recordings at the site of the arrhythmogenic substrate may therefore be essential for gaining mechanistic insight in these conditions. Thus far, only one clinical study reported ST-segment elevation in epicardial unipolar electrograms of BrS patients indicating that these electrograms originated from the myocardial area responsible for the Brugada ECG pattern.\textsuperscript{19} This myocardial area showed low voltage areas containing marked fractionation of activation indicative of a local conduction disturbance. Similar unipolar electrograms were previously provoked by sodium channel blockade in the explanted heart of a loss-of-function mutation carrier in SCN5A undergoing cardiac transplantation for heart failure in dilated cardiomyopathy.\textsuperscript{20} These electrograms in this heart were located at sites where fibrous and fatty tissue interspersed the myocardium which suggest that conduction abnormalities based on current-to-load mismatch is the pivotal mechanism in BrS.
From a mechanistic point of view there is at present insufficient basis to group BrS and early repolarization syndrome as “J wave syndromes” with a repolarization anomaly as a common mechanism. More direct measurements of the arrhythmogenic substrate will be required to solve the J wave conundrum.
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References


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