Rev Port Cardiol. 2017;xxx(xx):xxx–xxx

Revista Portuguesa de Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

REVIEW ARTICLE

Induced Brugada syndrome: Possible sources of arrhythmogenesis

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KEYWORDS
Brugada syndrome;
Fever;
Exercise;
Iatrogenic drugs;
Ventricular arrhythmia;
Brugada phenocopy

Abstract Brugada syndrome is an inherited cardiac condition with the potential for development of life-threatening arrhythmias in relatively young individuals without significant structural cardiac abnormalities. The condition is characterized by a distinct coved-type ST segment elevation in the right precordial leads (V1-V3). This hallmark pattern (type 1) is often dynamic and sometimes concealed, and may be unmasked in certain conditions or under the effect of certain agents, which include variation of sympathovagal balance, hormones, metabolic factors and drugs. These factors may not only modulate electrocardiographic morphology and induce the characteristic type 1 pattern, but also predispose to ventricular arrhythmias. The risk of malignant arrhythmias in acute events with induced type 1 pattern may be imminent, particularly if the patient in fact has Brugada syndrome. The physician should be aware of the modulating factors that may underlie a Brugada pattern, and be able to recognize, identify and promptly correct them. The mechanisms responsible for the type 1 pattern and possible associated ventricular arrhythmias induced by these modulating factors have attracted growing attention and interest. Furthermore, not all induced Brugada ECG patterns are observed in patients with Brugada syndrome, existing the possibility for acquired Brugada patterns/syndrome and Brugada phenocopies. This paper reviews the modulating factors associated with induced type 1 pattern as possible causes of arrhythmogenesis, particularly in Brugada syndrome patients, describes some of the probable underlying mechanisms, and discusses the concepts of acquired Brugada syndrome and Brugada phenocopies.

PALAVRAS-CHAVE
Síndrome de Brugada;
Febre;
Exercício;
Iatrogenia farmacológica;

Síndrome de Brugada induzida: possíveis fontes de arritmogénese

Resumo A síndrome de Brugada é um distúrbio cardíaco congénito com o potencial para o desenvolvimento de arritmias fatais em indivíduos relativamente jovens sem anomalias estruturais cardíacas grosseiras. Essa condição é caracterizada por uma distinta elevação do segmento-ST com concavidade superior (tipo 1) nas derivações precordiais (V1-V3). Esse peculiar padrão tipo 1 é frequentemente dinâmico e por vezes dissimulado, podendo ser desmascarado

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https://doi.org/10.1016/j.repc.2017.06.015

Please cite this article in press as: Tomé G, Freitas J. Induced Brugada syndrome: Possible sources of arrhythmogenesis. Rev Port Cardiol. 2017. https://doi.org/10.1016/j.repc.2017.06.015

Arritmia ventricular;
Fenocópias

em certas condições ou sobre o efeito de alguns agentes que coletivamente envolvem e incluem o equilíbrio simpatovagal, hormonas, fatores metabólicos e agentes farmacológicos. Não só esses fatores podem modular a morfologia eletrocardiográfica e induzir o característico padrão tipo 1, como também predispor a arritmias ventriculares. Esse risco de arritmias malignas em eventos agudos pode ser iminente e possivelmente presente, particularmente se o paciente apresentar uma efetiva síndrome de Brugada. O clínico deverá estar ciente, reconhecer, identificar e prontamente corrigir esses possíveis fatores modeladores que possam estar subjacentes a um padrão de Brugada. Os mecanismos responsáveis por esses padrões induzidos do tipo 1 e possíveis arritmias ventriculares associadas por esses fatores moduladores têm igualmente trazido crescente atenção e interesse. Ademais, nem todos os padrões de Brugada induzidos ocorrem em pacientes com síndrome de Brugada, existindo a possibilidade para padrões/síndrome adquirida e fenocópias de Brugada. Este artigo faz uma revisão dos fatores moduladores associados ao padrão tipo 1 induzido, como possíveis fontes para arritmogénese, particularmente em pacientes com síndrome de Brugada, descreve alguns dos prováveis mecanismos subjacentes e aborda os conceitos de síndrome de Brugada adquirida e fenocópias.

Introduction

Brugada syndrome (BrS) was first described as a distinct clinical entity in 1992 by Pedro and Josep Brugada[1]. Considered a primary electrical heart disease, BrS is an inherited cardiac condition electrocardiographically characterized by a distinct coved-type ST segment configuration (type 1) in the right precordial leads in the absence of significant structural heart disease, and typically presents a high risk of sudden cardiac death (SCD) secondary to polymorphic ventricular tachycardia (PVT) and/or ventricular fibrillation (VF)[2,3]. It is estimated to be responsible for at least 4% of all sudden deaths and at least 20% of sudden deaths in patients with structurally normal hearts[3]. However, this concept of the structurally normal heart in BrS has been challenged[4,5].

The prevalence of BrS with a type 1 electrocardiogram (ECG) in adults is much higher in East Asian countries, where the syndrome is endemic, but in western countries the prevalence is lower[5]. It typically manifests during adulthood and is 8-10 times more prevalent in males than in females[3,5]. Most BrS patients are asymptomatic, representing a majority (around 63%) of newly diagnosed Brugada patients. When present, symptoms include ventricular tachycardia (VT)/VF or aborted SCD, syncope, nocturnal agonal respiration, palpitations, or chest discomfort. Unfortunately, sudden cardiac arrest (SCA) or SCD can be the first manifestation, frequently occurring without any preceding clinical sign[5–8]. These symptoms and arrhythmic events are more frequently observed at rest and during sleep, typically between 12 am and 6 am, and less frequently during the daytime[9].

BrS displays autosomal dominant inheritance with incomplete penetrance. The *SCN5A* gene, which codes for the alpha subunit of the cardiac sodium channel Nav1.5, was the first gene found to be linked to BrS[10]. To date, more than 300 *SCN5A* gene variants related to BrS have been described, accounting for 18-28% of BrS cases. Soon, variants in other genes were found to be related to BrS, now making up a total of 18 genes. Mutations in these genes may result in a loss of function in cardiac sodium (INa) or calcium (ICa) channel currents, or in a gain of function in transient outward (Ito) or adenosine-triphosphate-sensitive (IK-ATP) potassium currents[5].

The type 1 BrS ECG is often dynamic and sometimes concealed, and may be unmasked during febrile states, due to electrolyte imbalance, or under vagotonic conditions such as at rest or during sleep (but rarely during exercise), or under the effect of certain agents, such as sodium channel blockers (class IA and IC antiarrhythmic drugs). These modulating factors may not only induce a type 1 pattern but also predispose to associated malignant ventricular arrhythmias (VAs)[3,5,11–15]. Recently, many other drugs, including antidepressants, antipsychotics, anesthetics, antihistamines and cocaine, have also been implied in the induction of Brugada patterns, which represents a considerable challenge for physicians in clinical practice because of their potential for arrhythmic events[16–19]. Moreover, not all induced Brugada patterns occur in patients with BrS, existing the possibility for acquired Brugada patterns/syndrome and Brugada phenocopies (BrPs)[5,7,16–20].

The purpose of this paper was to review the literature on the modulators (agents and conditions) associated with induced type 1 Brugada pattern, as possible causes of adverse events and arrhythmogenesis, particularly in BrS itself, and to describe some of the possible underlying mechanisms. It also presents some of the confounding factors that could account for an ECG abnormality similar to type 1 Brugada pattern, and discusses the concepts of acquired BrS and BrPs.

Methods

The survey was conducted by searching the PubMed database for relevant Portuguese- and English-language studies published between January 1, 2012 and December 31, 2016, using the following search terms: ((''adverse effects''[Subheading] OR ''acquired''[All Fields] OR ''induced''[All Fields] OR ''modulating''[All Fields] OR ''iatrogenic disease''[MeSH] OR ''drug-induced''[All Fields] OR ''fever''[MeSH] OR ''exercise''[MeSH] OR

Please cite this article in press as: Tomé G, Freitas J. Induced Brugada syndrome: Possible sources of arrhythmogenesis. Rev Port Cardiol. 2017. https://doi.org/10.1016/j.repc.2017.06.015