Fever-induced type-1 Brugada pattern: A sign of revealed Brugada syndrome or just a Brugada phenocopy?

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Brugada syndrome (BrS) is a hereditary channelopathy of the right ventricular outflow tract that might potentially lead to malignant arrhythmogenesis and sudden cardiac death [1, 2]. Currently, the diagnosis of this phenomenon is largely based on detection of spontaneous or induced type- 1 Brugada pattern (manifesting as a coved ST-segment elevation [≥2 mm] in the right precordial leads) on electrocardiogram (ECG) [2]. In their recently published article, Franke et al. [1] have reported a coincidental detection of type-1 Brugada pattern in two little girls in the setting of SARS-CoV-2-related-multisystem inflammatory syndrome (MIS) presenting with a high fever. In this context, we would like to highlight potential implications of the fever-induced type-1 Brugada pattern.

In clinical practice, hyperthermia might have the potential to convert concealed BrS (with type-2 [saddleback type] or 3 ECG pattern, or rarely normal ECG at baseline) to overt BrS (with type-1 ECG pattern) [1, 2]. Importantly, hyperthermia has also been regarded as an adverse factor that should be strictly avoided in patients with an established diagnosis of BrS (regardless of whether it is overt or concealed) [1, 2]. In this setting, the adverse impact of fever might be associated with emergence of further disturbances in depolarization and repolarization currents (further inactivation of sodium and/or activation of potassium currents), all of which appear to be central to the pathogenesis of BrS [2]. Importantly, asymptomatic subjects with a fever-induced type-1 Brugada pattern (as reported in [1]) were previously suggested to have a worse prognosis due to the higher risk of future arrhythmic events [2]. Accordingly, did the authors plan further risk-stratification of the patients through advanced tests including an electrophysiological study?

As a distinct phenomenon, Brugada phenocopy is well known to constitute a variety of diverse and reversible conditions (including myocardial ischemia, myopericarditis, ionic abnormalities, hypothermia, etc.) that present with Brugada-like ECG patterns [2]. Importantly, patients with a Brugada phenocopy usually do not suffer BrS-related symptoms or have a negative drug challenge (mostly performed with sodium channel blockers including ajmaline) [2–4]. However, a portion of patients with a Brugada phenocopy might also have ambiguous genetic testing, as well as a family history of sudden cardiac death. This may suggest an overdiagnosis of BrS, particularly in those with a phenocopy [2].

In contrast to hypothermia [2], hyperthermia has been an underrecognized etiology of Brugada phenocopy in previously healthy subjects. Accordingly, the exact mechanisms of fever-induced Brugada phenocopy are still nebulous. However, this phenomenon might emerge in the presence of substantially higher body temperatures (as compared with revealed BrS) potentially suggesting alternative mechanisms other than ionic current disturbances. Specifically, febrile conditions including MIS and Kawasaki disease might serve as potential etiologies of Brugada phenocopy largely through mechanisms including right ventricular outflow tract inflammation, cytokine storm, etc. In the literature, fever-induced reversible type-1 and type-2 ECG patterns have been rarely reported and termed as "Brugada-like ECG changes" [3, 4]. Importantly, the absence of BrS-related symptoms and family history, and more importantly a negative drug

challenge emerged as important characteristics of these patients [3, 4].

Based on the above-mentioned notions, it seems necessary to differentiate between revealed BrS and Brugada phenocopy in the setting of hyperthermia. In this context, we hold the opinion that fever-induced conversion from a baseline type-2 or type-3 ECG pattern to a type-1 ECG pattern most likely suggests revealed BrS. On the other hand, fever-induced conversion from a normal baseline ECG pattern to a type-2 or type-3 ECG pattern most likely suggests a Brugada phenocopy. These conditions might not warrant a drug challenge following defervescence and restoration of

the baseline ECG pattern. However, fever-induced conversion from a normal baseline ECG pattern to a type-1 ECG pattern (as in the patients reported [1]) might suggest either a phenocopy or revealed BrS. This potentially warrants a drug challenge for the final diagnosis. Therefore, did the authors perform or plan a drug challenge for their patients? Finally, evolution of malignant arrhythmias following the fever-induced type-1 ECG pattern strongly suggests revealed BrS. In conclusion, Franke et al. [1] should be congratulated for their thought-provoking clinical vignette. Hyperthermia has important implications both in the settings of BrS and Brugada phenocopy [1–4]. However, further aspects of Brugada phenocopy associated with hyperthermia still need to be established.

Article information

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