ESC European Society of Cardiology

Europace (2025) **27**, euaf094
https://doi.org/10.1093/europace/euaf094

EDITORIAL

Diagnosing Brugada syndrome: look for right ventricular outflow tract conduction delay

Pieter G. Postema *

Heart Center, Department of Clinical and Experimental Cardiology, Amsterdam UMC, University of Amsterdam, Cardiovascular Sciences, Meibergdreef 9, Amsterdam, 1105 AZ, the Netherlands

Online publish-ahead-of-print 13 June 2025

This editorial refers to 'Assessment of activation delay in the right ventricular outflow tract as a potential complementary diagnostic tool for Brugada Syndrome' by C. Monaco *et al*., https://doi.org/10.1093/europace/euaf093.

Brugada syndrome (BrS) is known as a potentially inheritable disease entity with characteristic electrocardiographic (ECG) changes in the (high) right precordial leads—namely a coved type STT segment (known as the type-1 BrS ECG)—and a propensity for cardiac arrhythmias and sudden cardiac death by ventricular fibrillation.[1,2] In the past decades, the criteria needed for a diagnosis of Brugada syndrome (BrS) have changed several times, with the current view that a solid diagnosis should contain both these ECG changes (either spontaneously or provoked by sodium channel blockers) in combination with either symptoms or a familial occurrence.[3] Patient management can often be conservative with life style advices but may include implantation of a defibrillator (ICD), the use of drugs like quinidine, and also ablation (but only in severe cases).[4–6,1] Not surprisingly, a BrS-diagnosis impacts on patients' wellbeing.[7,8]

In the past decades, there has also been debate on the pathophysiological background of BrS.[9] Currently, the dominant opinion is that conduction delay in the right ventricle (RV), in particular, the right ventricular outflow tract (RVOT), causes these characteristic ECG changes and its associated malignant arrhythmias.[10–12] These electrophysiological alterations appear to be predominantly located in the RVOT epicardium,[13] while there are probably multifactorial causes of this RV(OT) conduction delay. Not surprisingly, from the body surface ECG, such alterations can be detected.[12,14,15] In this edition of *Europace*, Monaco and colleagues from Brussels, Belgium, share with us their insights in the evaluation of RV conduction delay from the body surface with a special technique known as *electrocardiographic imaging* or ECGi.[16] Particularly, they pose the hypothesis that even in the absence of a unequivocal typical type-1 BrS ECG, a typical pattern of RV conduction delay captured by ECGi possibly recapitulates a BrS-diagnosis and hence would suffice for a similar patient management. Interestingly, this might also shed more insights in patients with conduction delays caused by, e.g. right bundle branch block (RBBB) or *SCN5A* mutations as in these latter patients, a wide variety in the severity and location of conduction delay may exist and may pose different reactions to sodium channel blockers such as ajmaline.[17,18]

Assessment of activation delay in the right ventricular outflow tract as a potential complementary diagnostic tool for Brugada Syndrome

In their study, Monaco and colleagues approached this problem as follows. They studied 104 patients with ECGi, over two study-phases, who either had a spontaneous type-1 BrS ECG or a type-1 BrS ECG that was provoked by ajmaline provocation testing, or who did not reach a type-1 BrS ECG upon ajmaline provocation testing (controls). Interestingly, they specifically also included patients RBBB to evaluate the overlap or difference between the *location* of conduction delay in patients with or without the development of a type-1 BrS ECG.

For ECGi evaluations, they used the 252 electrode CardioInsight Noninvasive 3D Mapping System technology (Medtronic Inc, Minneapolis, MN, USA) in combination with computed tomography (CT) scans to both be able to locate different segments of the right ventricle (see their *Figure 3*) and the position of the cardiac anatomy in relation to the position of electrodes of the CardioInsight vest. Subsequently, an in-house developed software script (not yet released by the authors) was utilized to evaluate the mean activation times (and repolarization times) in each segment.

In summary, they found that a $\geq 45\%$ relative conduction delay in the RVOT in comparison to the conduction delay in the anterior RV was characteristic of patients with either a spontaneous or provoked type-1 BrS ECG, with quite promising test characteristics. Moreover, they found that this metric was still appropriate in patients with RBBB. The importance of this finding is that, in this latter group, the differentiation between the presence or absence of a type-1 BrS ECG can

The opinions expressed in this article are not necessarily those of the Editors of *Europace* or of the European Society of Cardiology.

* Corresponding author. Tel: +31-20-5663072, *E-mail address*: p.g.postema@amsterdamumc.nl

© The Author(s) 2025. Published by Oxford University Press on behalf of the European Society of Cardiology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.

be even more difficult than without RBBB.[19] In addition, they found that this metric was useful in determining the test outcome in patients in whom a type-1 BrS ECG was not that clear.

Discussion

First, I must say that the colleagues from Brussels did a good job on trying to find complementary tools to (i) further characterize electrocardiographic signs of BrS and (ii) provide further insights in the pathophysiological mechanisms underlying BrS. They found that RVOT conduction delay is the most important feature of BrS and, in particular, its relative relation to other RV segments like the anterior RV, which nicely fits with previous research in this field (which is way too much to adequately refer to).[1,10,12,13,19] Their ECGi collection in more than 100 patients surely represents an impressive amount of work.

Despite its elegance and perfect fit in the current view on BrS, there are, however, several comments to be made. First, I would say that this work is hypothesis generating. Why? Because the call is made that ECGi can be used to diagnose BrS when standard ECGs are not conclusive. It is important to recognize that the gold standard is at stake here. Despite that I also believe that the characteristic ECG of BrS might not always be present in cases that seem to have a similar electrophysiological background, this is an important limitation. While particularly the RVOT epicardial substrate is the location of interest, currently the closest we can get non-invasively is with ECGi. However, ECGi on its own has quite some drawbacks, among which are its dependency on numerous assumptions. In addition, the authors chose to use mean values from segments—which is understandable but (another) simplification. In addition, they did not test the *incremental value* of ECGi in relation to other parameters (such as the beta-angle)—which already provides pretty good pre-test likelihood characteristics.[14] Moreover, the implications of a BrS diagnosis by ECGi vs. a standard BrS diagnosis remains unresolved—particularly regarding its value to differentiate the rare malignant forms of BrS vs. the predominant benign forms (provided appropriate measures are taken). Of course, the appropriate way to do the latter would be a prospective analysis—which will be extremely cumbersome due to the relative low incidences of events. Certainly, computer models including artificial intelligence, maybe aided by polygenic risk scores, might further enhance both our understanding as well as recognition of the several BrS subtypes and that might also be important to, e.g. differentiate the different subtypes *and the prognosis* of patients with *SCN5A* mutations.

So, in conclusion, congrats to the authors on providing this work, while we recognize that there still is more work to be done in this corner of inheritable arrhythmia syndromes to further stratify and advise our patients and their families.

Funding

Dutch Heart Foundation grant *03-003-2021-T061.*

Conflict of interest: none declared.

References

1. Hoeksema WF, Amin AS, Bezzina CR, Wilde AAM, Postema PG. Novelties in brugada syndrome: complex genetics, risk stratification, and catheter ablation. *Card Electrophysiol Clin* 2023;**15**:273–83.
2. Crotti L, Brugada P, Calkins H, Chevalier P, Conte G, Finocchiaro G *et al.* From gene-discovery to gene-tailored clinical management: 25 years of research in channelopathies and cardiomyopathies. *Europace* 2023;**25**:euad180.
3. Behr ER, Winkel BG, Ensam B, Alfie A, Arbelo E, Berry C, *et al.* The diagnostic role of pharmacological provocation testing in cardiac electrophysiology. A clinical consensus statement of the European heart rhythm association (EHRA) and the European association of percutaneous cardiovascular interventions (EAPCI) of the ESC, the ESC working group on cardiovascular pharmacotherapy, the association of paediatric and congenital cardiology (AEPC), the paediatric & congenital electrophysiology society (PACES), the heart rhythm society (HRS), the Asian Pacific heart rhythm society (APHRS), and the Latin American heart rhythm society (LAHRS). *Europace* 2025;**27**. doi: 10.1093/europace/euaf067.
4. Postema PG, Neville J, de Jong JSSG, Romero K, Wilde AAM, Woosley RL. Safe drug use in long QT syndrome and Brugada syndrome: comparison of website statistics. *Europace* 2013;**15**:1042–9.
5. Bouzeman A, Traulle S, Messali A, Extramiana F, Denjoy I, Narayanan K *et al.* Long-term follow-up of asymptomatic Brugada patients with inducible ventricular fibrillation under hydroquinidine. *Europace* 2014;**16**:572–7.
6. Konigstein M, Rosso R, Topaz G, Postema PG, Friedensohn L, Heller K *et al.* Drug-induced Brugada syndrome: Clinical characteristics and risk factors. *Heart Rhythm* 2016;**13**:1083–7.
7. Six S, Theuns P, Libin P, Nowe A, Pannone L, Bogaerts B *et al.* Patient reported outcome measures (PROMs) on mental health and psychosocial factors in patients with Brugada Syndrome. *Europace* 2023;**25**:euad205.
8. van der Werf C, Postema PG. The psychological impact of receiving a Brugada syndrome diagnosis. *Europace* 2023;**25**:euad293.
9. Wilde AA, Postema PG, Di Diego JM, Viskin S, Morita H, Fish JM *et al.* The pathophysiological mechanism underlying Brugada syndrome. Depolarization versus repolarization. *J MolCell Cardiol* 2010;**49**:543–53.
10. Postema PG, van Dessel PF, de Bakker JM, Dekker LR, Linnenbank AC, Hoogendijk MG *et al.* Slow and discontinuous conduction conspire in Brugada syndrome: a right ventricular mapping and stimulation study. *Circ Arrhythm Electrophysiol* 2008;**1**:379–86.
11. Hoogendijk MG, Potse M, Linnenbank AC, Verkerk AO, Den Ruijter HM, Van Amersfoorth SC *et al.* Mechanism of right precordial ST-segment elevation in structural heart disease: excitation failure by current-to-load mismatch. *Heart Rhythm* 2010;**7**:238–48.
12. Postema PG, van Dessel PF, Kors JA, Linnenbank AC, van Herpen G, Ritsema van Eck HJ *et al.* Local depolarization abnormalities are the dominant pathophysiologic mechanism for the type-1 ECG in Brugada syndrome. A study of electrocardiograms, vectorcardiograms and body surface potential maps during ajmaline provocation. *J Am CollCardiol* 2010;**55**:789–97.
13. Nademanee K, Veerakul G, Chandanamattha P, Chaothawee L, Ariyachaipanich A, Jirasirirojanakorn K *et al.* Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. *Circulation* 2011;**123**:1270–9.
14. van der Ree MH, Vendrik J, Verstraelen TE, Kors JA, Amin AS, Wilde AAM *et al.* The β-angle can help guide clinical decisions in the diagnostic work-up of patients suspected of Brugada syndrome: a validation study of the β-angle in determining the outcome of a sodium channel provocation test. *Europace* 2021;**23**:2020–8.
15. van der Ree MH, Vendrik J, Kors JA, Amin AS, Wilde AAM, Tan HL *et al.* Left axis deviation in Brugada syndrome: vectorcardiographic evaluation during ajmaline provocation testing reveals additional depolarization abnormalities. *IJMS* 2021;**22**:484.
16. Monaco C, Eltsov I, Del Monte A, Aglietti F, Pannone L, Rocca DD *et al.* Assessment of activation delay in the right ventricular outflow tract as a potential complementary diagnostic tool for Brugada Syndrome. *Europace* 2025.
17. Amin AS, Reckman YJ, Arbelo E, Spanjaart AM, Postema PG, Tadros R *et al.* SCN5A mutation type and topology are associated with the risk of ventricular arrhythmia by sodium channel blockers. *Int J Cardiol* 2018;**266**:128–32.
18. Tuijnenburg F, Proost VM, Thollet A, Barc J, Groffen AJA, Veerman CC *et al.* Long-term prognosis of patients with an SCN5A loss-of-function variant and progressive cardiac conduction disorder or Brugada syndrome. *Heart Rhythm* 2024;**S1547-5271**:03518–5.
19. Perez Riera AR, Filho CF, de Abreu LC, Ferreira C, Yanowitz FG, Femenia F *et al.* Do patients with electrocardiographic Brugada type 1 pattern have associated right bundle branch block? A comparative vectorcardiographic study. *Europace* 2012;**14**:889–97.