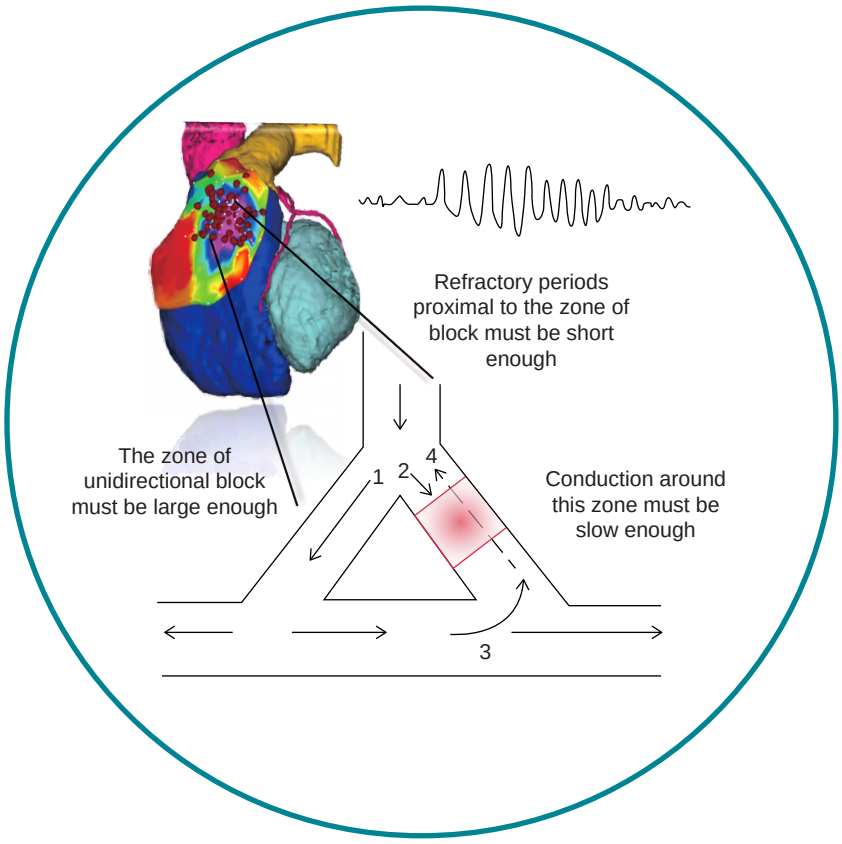

Figure 1 The combined effect of three variables that must compete together and exceed a threshold for the initiation of re-entry.

Gregory Dendramis *
Cardiovascular Department, Clinical and Interventional Arrhythmology, ARNAS Ospedale Civico Di Cristina Benfratelli, Piazza Nicola Leotta 4, Palermo 90127, Italy
*Corresponding author. Tel: +0039 0916665010. *E-mail address*: gregorydendramis@libero.it

https://doi.org/10.1093/europace/euac249

Prognostic value of right ventricular refractory period heterogeneity in Brugada syndrome. Independent predictor or part of something more complex? Author's reply

This is a response to the Letter to the Editor, 'Prognostic value of right ventricular refractory period heterogeneity in Brugada syndrome. Independent predictor or part of something more complex?' by Gregory Dendramis https://doi.org/10.1093/europace/euac248, about the article, 'Prognostic value of right ventricular refractory period heterogeneity in Type-1 Brugada electrocardiographic pattern' by Rossi *et al.* https://doi.org/10.1093/europace/euac168

We thank Dendramis[1] for the interest in our work[2] and for arising shareable additional comments around some of the potential mechanisms necessary to induce life-threatening arrhythmias in patients with Brugada syndrome (BrS).[1]

The main finding of our work was the original observation that the presence of a difference in the endocardial ventricular effective refractory period (VERP) between right ventricular outflow tract (RVOT) and right ventricular (RV) apex ($\Delta RP_{RVOT\text{-}apex}$) > 60 ms was able to predict adverse events (a composite of sudden cardiac death, resuscitated cardiac arrest, or appropriate intervention by the implantable cardioverter-defibrillator) in patients with BrS. This is somehow in line with the observation made in the PRELUDE study, in which a reduced VERP in the apex was associated with a higher risk of arrhythmias in BrS patients.[3] At least in our cohort, this novel metric easily assessed during the electrophysiological study seemed to outperform the prognostic power of ventricular tachycardia/fibrillation inducibility during programmed ventricular stimulation. As we did not perform a RV high-density electroanatomical mapping, we cannot unveil at this time the underlying potential pathophysiological mechanisms (i.e. low voltage areas or slow conductive zones) behind the genesis of BrS-related arrhythmias in subjects with a higher $\Delta RP_{RVOT\text{-}apex}$. Still, this seems an important finding should our work be confirmed by larger observational studies.

BrS has been suggested as an electrical epicardial disease characterized by a difference in the action potential (AP) plateau size among cells within the RVOT and by a loss of AP dome in the epicardium rather than the endocardium. This 'repolarization theory' was able to explain the BrS electrocardiographic phenotype and the arrhythmogenic mechanism. Previous research on animal model showed a strong correlation between higher VERPs and prolongation of AP duration specifically in RVOT in association with a greater transmural voltage gradient dispersion and arrhythmogenic predisposition in mice carrying SCN5a mutation.[4] The potential role of heterogeneity in the repolarization pattern of BrS patients was also investigated by endocardial non-contact mapping and, more recently, by

electrocardiographic imaging techniques[5] demonstrating a strong association and co-localization of activation–repolarization interval dispersion with RV conduction slowing and functional blocks in BrS subjects, specifically in RVOT. More recently, RV high-density electroanatomical mapping techniques provided new insights into arrhythmic risk prediction evaluating endocardial low-voltage areas and abnormal or crowded conduction in RVOT.[5,6]

Overall, it seems that arrhythmogenesis in BrS (as highlighted by Dendramis[1]) is a complex scenario in which the classical components of arrhythmogenic 'reentrant model' (dimension of the zone of unidirectional block, conduction velocity around this zone, refractory periods proximal to the zone of block) are dynamically influenced by endo-epicardial electrical gradients and the presence of anatomical substrate alterations (fibrosis, as potentially reflected by low voltage areas). Furthermore, the arrhythmogenic mechanisms may be also influenced in each patient by vagal tone, pyrexia, and genetic background (gene mutations and gene modifiers). To what extent all those pathophysiological mechanisms may determine or interact with the VERP heterogeneity observed in some patients presumed to be at higher risk is a matter of great interest and will hopefully be disentangled in the next future.

Conflict of interest: None declared.

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Andrea Rossi [1], Alberto Giannoni [1,2]*, and Marcello Piacenti [1]

[1]Fondazione Toscana Gabriele Monasterio, via Moruzzi 1, Pisa 56124, Italy; and [2]Health Science Interdisciplinary Center, Scuola Superiore Sant'Anna, piazza Martiri della Libertà 33, Pisa 56127, Italy

*Corresponding author. Tel: +39-050-3152189, Fax: +39-050-3152109; *E-mail addresses*: a.giannoni@santannapisa.it; agiannon@ftgm.it