It follows that the discriminatory power of programed ventricular stimulation (PVS) would be limited in this context. While not extensively studied, the writing committee of the consensus document suggested that the induction of a SMVT may be considered an indicator of further VA.[2] However the significance of a negative study or indeed the induction of VF is less clear.

A central pillar of the consensus document was the definition of the various AMVP phenotypes. First among them is severe degenerative mitral regurgitation (MR), often accompanied by left ventricular dysfunction. The value of early mitral valve surgery in cases with at least moderate to severe MR is well established, including a reported decrease in mortality and SCD.[5] The novelty in our document was the acknowledgment of the elevated risk of SCD associated with severe myxomatous MVP phenotype irrespective of MR severity. We strive to emphasize both the critical importance of MR severity and the fact that absence of hemodynamically significant MR provides no reassurance in this unique population.

The role of mitral valve surgery in the prevention of malignant arrhythmia, in the absence of a conventional indication for surgery, is an important gap in our current understanding of AMVP. While one may conceive multiple mechanisms by which mitral valve surgery may reduce the arrhythmic risk, without solid data this is mere conjecture. Likewise, there are no robust data describing the incidence or the type of VA observed in post mitral surgery patient. It would be reasonable to assume that most would be the result of scar related reentry or bundle branch reentry, yet we may not dismiss the possibility of non-reentrant VA as a relevant mechanism. Furthermore pre-existing scar in the left ventricular myocardium is common among patient with severe MR and may support reentrant arrhythmia irrespective of surgery.

At this time, we would recommend to consider the known predictors of risk, chiefly overt arrhythmia, unexplained syncope, and the described echo/CMR features and to follow the suggested risk stratification. While it is possible that PVS yield may be notable in post mitral surgery patients, the available evidence does not support to recommend it widely or adopting a different approach in this population. We do recognize the validity and importance of the question and encourage further research.

Conflict of interest: None declared.

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

This Letter to the Editor refers to 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.

A response to this letter is available 'Prognostic value of right ventricular refractory period heterogeneity in Brugada syndrome. Independent predictor or part of something more complex?—Authors' response' by Alberto Giannoni *et al.* https://doi.org/10.1093/europace/euac249.

We have recently read with great interest the article by Rossi *et al.*[1] entitled 'Prognostic value of right ventricular refractory period heterogeneity in Type-1 Brugada electrocardiographic pattern'.

A prognostic stratification with electrophysiological study (EPS) was performed in 198 patients of a cohort of 372 Brugada syndrome (BrS) patients with spontaneous or drug-induced type-1 electrocardiogram (ECG) with symptoms. The primary endpoint of the study was a composite of sudden cardiac death (SCD), resuscitated cardiac arrest, or appropriate intervention by the implantable cardioverter-defibrillator. Family history of SCD, syncope, and a spontaneous Type-1 ECG pattern were univariate predictors of the primary endpoint in the whole population. From results obtained by the authors, in patients undergoing EPS, the primary endpoint was not only predicted by ventricular tachycardia (VT)/ventricular fibrillation (VF) inducibility but also by a difference in the refractory period between right ventricular outflow tract (RVOT) and right ventricle apex (ΔRPRVOT-apex) > 60 ms. For the authors, the eterogeneity of right ventricular refractory periods represents a strong, independent predictor of life-threatening arrhythmias in BrS patients, beyond VT/VF inducibility at EPS and common clinical predictors.[1]

As reported in some research, differences between shortest and longest refractory periods are not the sole indicators of the risk of developing re-entry, and the shape of the blocked zone may also be important.[2] The combined effect of three variables must compete together and exceed a threshold: the zone of unidirectional block must be large enough, conduction around this zone must be slow enough, and refractory periods proximal to the zone of block must be short enough (*Figure 1*). Even in the presence of large disparities in refractory periods but when the size of sites of prolonged refractory period is small, re-entry will not occur unless conduction is also significantly slowed.[3,4] Considering that the electrogenic alterations at the base of BrS are mainly epicardial and that EPS provide data about endocardial refractory periods is interesting to know by the authors what is in their cohort of patients the role of the other two variables listed above, so that right ventricular refractory period heterogeneity may be considered 'a strong independent predictor of life-threatening arrhythmias'. Dispersion of refractory period is a necessary but not sufficient condition for initiation of re-entry.[3]

Conflict of interest: None declared.

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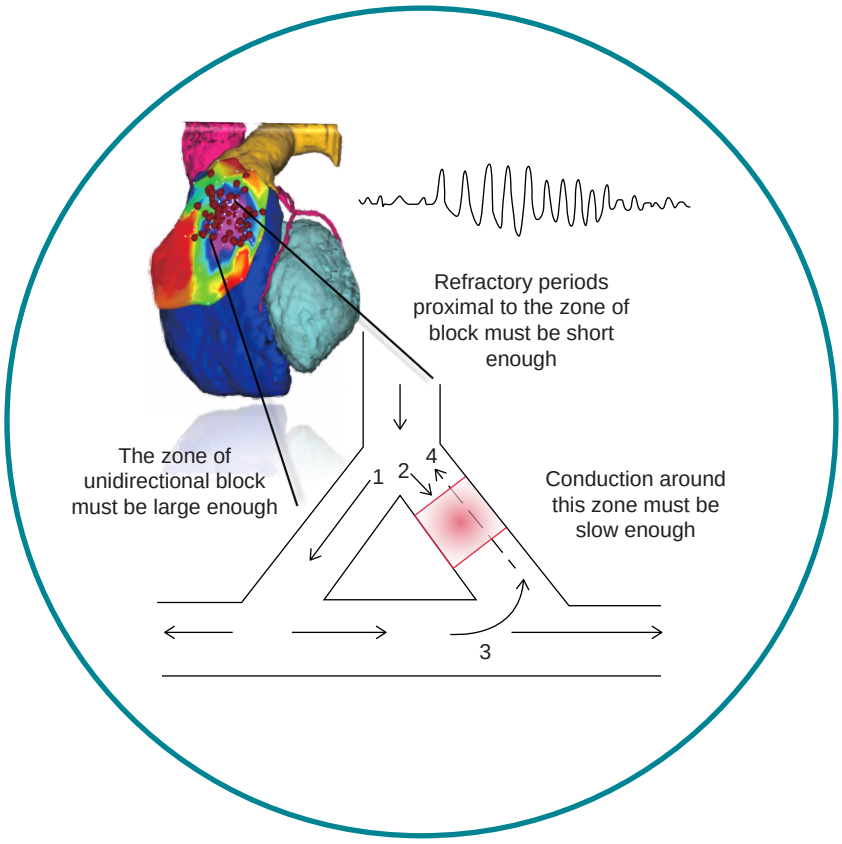

Figure 1 The combined effect of three variables that must compete together and exceed a threshold for the initiation of re-entry.

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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