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EDITORIAL

Arrhythmogenic vulnerability of reentrant pathways in post-infarct ventricular tachycardia assessed by advanced computational modelling

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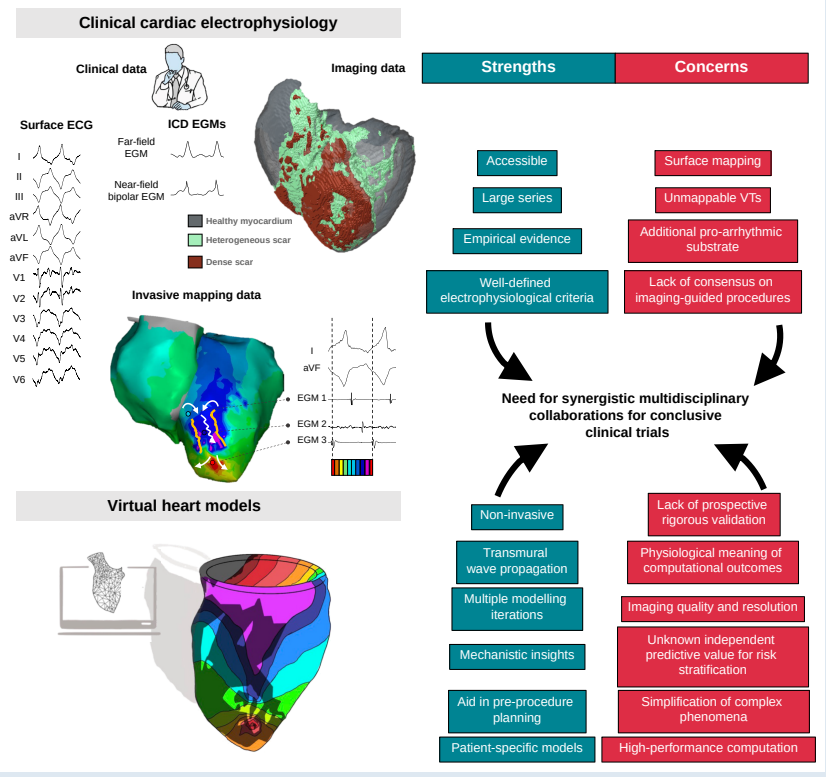
Graphical Abstract



Keywords Ventricular arrhythmia • Computational modelling • Virtual heart simulations • Risk stratification

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Ventricular tachycardia (VT) episodes in patients with infarct-related scarring constitute the clinical paradigm of reentry. The reentry mechanism is based on channels of conducting healthy tissue within non-conducting scar tissue that allow a complex interplay between activation wavefronts (e.g. after a premature focal beat) and may result in a self-sustaining arrhythmia.[1] In the clinic, complete characterization of reentrant VT circuits using classical electrophysiological criteria and state-of-the-art high-density mapping during VT is complex[1] and often cannot be completed because of haemodynamic instability during the mapping procedure. This common limitation has motivated the implementation of mapping strategies during sinus rhythm or ventricular pacing aiming to identify scar regions associated with VT isthmuses or potential arrhythmogenicity.[2,3] Complementary imaging-based strategies including advanced analyses of scar tissue characteristics have been also proposed for procedure planning and identification of potential arrhythmogenic regions.[4]

Despite substantial advances in invasive mapping, ablation, and imaging, clinical outcomes on VT ablation continue to be suboptimal with recurrences on the range of 25–40% after 1 year of follow-up.[5] This may be related to several limitations of current electrophysiological tools for VT characterization (Graphical abstract): (i) electrophysiological mapping data are mainly two-dimensional on the epicardial or endocardial surface.[6] Therefore, intramural patterns of wave propagation can only be estimated.[1] (ii) Mapping and ablation of all clinical and inducible VT morphologies during an invasive procedure does not exclude recurrences from other scar areas potentially sensitive to reentry in real-life conditions. (iii) Poorly tolerated unmappable VTs are common in VT ablation procedures and make it challenging to identify (all) critical isthmus sites.[2,3] (iv) Identification and interpretation of the potential proarrhythmogenic substrate from 3D imaging is still challenging and is sensitive to the method used to identify scar or the criteria to define arrhythmogenicity.[7]

Over the last decade, a more personalized assessment of the proarrhythmogenic substrate has been proposed by using virtual (computational-based) heart models that include the individual-specific anatomical substrate and electrophysiological properties adjusted to the underlying substrate.[8,9] Most results have been reported with models incorporating a cardiac magnetic resonance (CMR) imaging–based substrate of patients with ischaemic cardiomyopathy.[10] Multiple studies and groups have shown the potential clinical value of virtual heart models to aid physicians and interventional cardiologists in the prognosis, diagnosis, and treatment of complex ventricular arrhythmia.[10] For example, patient-specific computational heart modelling has shown promising results in patients undergoing VT ablation to localize effective ablation targets and prevent further VT recurrences.[8] Fine-tuning adjustment of the individual-specific substrate and electrophysiological properties of computational models has also enabled investigators to reproduce the surface electrocardiogram (ECG) morphology of the clinical VT and further localize the protected isthmus site documented during the invasive mapping procedure.[11] Moreover, in a retrospective series of patients with implantable cardioverter defibrillators (ICDs), ventricular arrhythmia prediction using virtual heart models has also shown to improve risk stratification compared with other clinical variables.[12] However, these approaches are time-consuming as both the creation of the personalized computational models and their assessment in a 'virtual stress test' is labour-intensive and computationally demanding.

In this issue of *Europace*, Bhagirath *et al.*[13] report the clinical value of an efficient, real-time reentrant pathway finding algorithm that provides simulation metrics for non-invasive assessment of the VT substrate complexity and predicting post-ablation VT recurrence. The algorithm, termed 'Virtual Induction and Treatment of Arrhythmias' (VITA), was tested in a retrospective study and compared with the electrophysiological data of 20 patients undergoing VT mapping and ablation. Invasive electrophysiological data for evaluation included the number of ablation lesions and the extension of the ablated area. Volumetric models for computational simulations were generated from 2D late gadolinium enhancement CMR images, which were segmented with the commercial software ADAS 3D (ADAS3D Medical, Barcelona, Spain). Four different signal intensity threshold configurations based on the full width at half maximum algorithm were used for each segmented heart to evaluate the influence of scar thresholds on computed metrics. Rule-based fibres were also assigned to the virtual myocardial model. Virtual Induction and Treatment of Arrhythmias–based simulations then provided the total number of inducible VTs and their corresponding round-trip times. The latter served as a surrogate of the reentry cycle length. Duplicate reentry VT circuits induced from different pacing locations were filtered out to provide the number of unique VTs and represent the main reentrant pathways.

The results reported by Bhagirath and colleagues show that the total number of inducible VTs was the main predictor of VT recurrence after the ablation procedure. Slightly lower values of area under the curve (AUC) on receiver operator characteristic analyses were obtained with the number of inducible unique VTs (AUC: 0.820 vs. 0.770). The results were relatively independent of the applied scar thresholds. Other non-simulation imaging-based metrics also showed similar predictive values for post-ablation recurrences. More advanced stages of the underlying cardiomyopathy, reflected by lower left ventricular ejection fraction values and higher left ventricular end-systolic and end-diastolic volumes, were present in patients with post-ablation VT recurrences compared with those patients without recurrences. The number of ablation lesions and the extension of the ablated area during the invasive procedure also showed a statistically significant positive correlation with the number of unique VTs on the VITA-based simulations. Moreover, more extensive ablated areas and a larger number of ablation lesions were also associated with VT recurrences, which suggest a more complex underlying substrate.

Overall, these simulations support the increasing complementary value of computational modelling in modern cardiac electrophysiology. Moreover, VITA-based algorithms claim to provide rapid computation on conventional hardware. However, the approach still requires careful creation of personalized computational models from individual CMR data. Additionally, computational modelling still needs to be interpreted as an experimental approach that requires proper validation in prospective and randomized studies. Such studies have yet to be reported. The independent predictive value of computational metrics for ventricular arrhythmic events or post-ablation VT recurrences needs to be addressed in large clinical series with relevant clinical variables. Notwithstanding, virtual heart technologies have shown the potential to overcome some of the limitations of state-of-the-art clinical and invasive cardiac electrophysiology to identify and target the substrate associated with complex VT. They can provide 3D (transmural) information of wave propagation patterns during VT, explore multiple pacing sites and substrate configurations for VT inducibility, simulate the ablation outcome of specific lesions delivered at the target sites, and uncover previously dormant channels that may dominate after ablation of the first critical channel. Importantly, this information could be obtained before the procedure and may aid clinicians and cardiac electrophysiologist in procedure planning and potentially decrease the intervention time.

It should be noted that computational outcomes from virtual heart models are not exempt of potential bias and limitations (*Graphical abstract*). The minimum imaging quality and resolution to obtain reliable results need to be addressed. Most of computational models have used 2D CMR images, which overestimate the scar volume compared with 3D sequences.[14] Moreover, the extension of scar borderline zones has shown to significantly affect computational outcomes.[10] The latter is highly relevant since there is a lack of agreement on the preferable signal intensity cut-off values for assessment of tissue heterogeneity and scar areas.[7] Cellular electrophysiological properties

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and myocardial fibre orientation assigned to current virtual heart models represent a simplification of the actual underlying electrophysiology and the specific disease condition. New imaging advances in diffusion tensor imaging sequences and non-invasive information from body surface mapping may help to individualize these parameters in the near future.[15] At the same time, prospective studies should also evaluate the required complexity of virtual heart models, as any further personalization will complicate the clinical implementation as well and may not necessarily improve procedure success.

As exemplified by the current study of Bhagirath et al. and many previous studies, future success of computational modelling in routine cardiac electrophysiology requires a close interaction between computational scientists and expert clinicians in the field. For cardiac electrophysiologists, proper identification of a critical VT isthmus site is demonstrated with VT termination upon radiofrequency delivery. Therefore, from an electrophysiologist's perspective, a meaningful validation of virtually predicted VT targets requires multiple steps. First, the potential target site needs to be identified on the computational model before the procedure; second, the VT needs to be induced and fully mapped to identify the critical isthmus site, *both* pre-procedurally in the virtual heart model and invasively during clinical procedure; and third, the ablation at the electrophysiologically defined target site needs to terminate the VT and render it not inducible both *in silico* and *in vivo*. This type of prospective validation is challenging since complete characterization of critical VT isthmus sites *in vivo* can only be done in well-tolerated VT episodes[3] and thus limits generalizing these findings to non-tolerated VTs. However, a well-conducted small prospective series combining rigorous electrophysiological demonstration with the corresponding computational outcomes will represent a major milestone in the field. Furthermore, reproducing clinical VT morphologies and their average cycle lengths will increase confidence of the clinical electrophysiology community on virtual heart simulations. Only after building this trust, it is worthwhile to implement efficient, clinically ready computational workflows that reliably incorporate patient-specific imaging data and pre-procedurally predict effective ablation targets.

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Data availability

As this is an editorial, the authors confirm that the data supporting the current article are available within the articles and/or its supplementary materials, cited.

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