

A feasibility study of arrhythmia risk prediction in patients with myocardial infarction and preserved ejection fraction

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Aim

To predict arrhythmia susceptibility in myocardial infarction (MI) patients with left ventricular ejection fraction (LVEF) >35% using a personalized virtual heart simulation approach.

Methods and results

A total of four contrast enhanced magnetic resonance imaging (MRI) datasets of patient hearts with MI and average LVEF of $44.0 \pm 2.6\%$ were used in this study. Because of the preserved LVEF, the patients were not indicated for implantable cardioverter defibrillator (ICD) insertion. One patient had spontaneous ventricular tachycardia (VT) prior to the MRI scan; the others had no arrhythmic events. Simulations of arrhythmia susceptibility were blind to clinical outcome. Models were constructed from patient MRI images segmented to identify myocardium, grey zone, and scar based on pixel intensity. Grey zone was modelled as having altered electrophysiology. Programmed electrical stimulation (PES) was performed to assess VT inducibility from 19 bi-ventricular sites in each heart model. Simulations successfully predicted arrhythmia risk in all four patients. For the patient with arrhythmic event, *in-silico* PES resulted in VT induction. Simulations correctly predicted that VT was non-inducible for the three patients with no recorded VT events.

Conclusions

Results demonstrate that the personalized virtual heart simulation approach may provide a novel risk stratification modality to non-invasively and effectively identify patients with LVEF >35% who could benefit from ICD implantation.

Keywords

Personalized virtual heart • Ejection fraction >35% • Ventricular tachycardia • Myocardial infarction • Computational modelling

Introduction

Sudden cardiac death (SCD) is a leading health problem worldwide, accounting for over 300 000 deaths per year in the USA alone.^{1,2} A large proportion of SCDs result from ventricular arrhythmia, particularly amongst patients with prior heart damage from myocardial infarction (MI). Implantable cardioverter defibrillators (ICDs) are the first line of therapy for preventing SCD in high-risk individuals.³ Optimal deployment of this expensive resource remains a major clinical challenge because of the lack of robust strategies for identifying patients that would and would not benefit from this lifesaving

therapy.⁴ Current clinical criteria for selecting patients for ICDs rely on a 'one-size-fits-all' metric representing global reduction in heart pumping function: left ventricular ejection fraction (LVEF) <35%.⁵ This single metric poorly reflects the mechanisms underlying cardiac arrhythmias in MI and hence, its use as a risk stratifier results in a low rate of appropriate ICD device therapy, only 5%/year.³ Thus, many patients are exposed to ICD risks (e.g. infections, device malfunctions, and inappropriate shocks), without deriving any health benefit.^{6–8} Importantly, the low LVEF criterion only targets a relatively small subgroup of individuals at risk for SCD, failing to identify the majority of SCD victims. Thus, inadequate SCD risk stratification poses

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What's new?

- Using computational modelling to non-invasively predict arrhythmia risk in myocardial infarction patients with preserved left ventricular ejection fraction (LVEF).
- The methodology used in our simulation is totally automatic, is reproducible and can be applied to image stacks obtained from different centres.
- Our model can accurately detect VT arrhythmia susceptibility in patients with LVEF >35% who do not have implantable cardioverter defibrillators (ICDs) implanted. Thus, our technique may help clinicians identify patients that could benefit from ICD implantation.

a large socioeconomic burden.⁹ Despite extensive research on risk prediction strategies, none have proved sufficiently discriminative for use in general clinical practice.¹⁰ Given the complex pathophysiology of SCD and MI, a strategy is needed that incorporates the underlying mechanisms, namely the myocardial arrhythmogenic substrate, in an individualized way. A robust, readily available, non-invasive, personalized arrhythmia risk predictor will not only identify individual patients in need of lifesaving therapy, but will reduce unnecessary ICD implantation and the associated complications.

In a recent study in *Nature Communications*,¹¹ we presented a novel, non-invasive, and accurate test for SCD risk stratification in MI patients with LVEF <35%, which we termed the virtual-heart arrhythmia risk predictor (VARP). The VARP approach is based on personalized magnetic resonance imaging (MRI)-based computational modelling of the patient heart that non-invasively assesses the individual's susceptibility to lethal ventricular arrhythmias. In that study, we demonstrated VARP's predictive capability using data from 41 patients with LVEF <35%, and compared it to that of other clinical metrics. The results demonstrated that VARP significantly outperformed clinical metrics in predicting future arrhythmic events.

This feasibility study aims to extend the VARP approach to the arrhythmia risk stratification of patients with MI and LVEF >35%, for whom prophylactic ICD implantation is not clinically indicated. The goal here is to demonstrate that the approach can be applied to such patients, and to compare the VARP prediction for this small cohort with clinical outcomes.

Methods

Study population

For this retrospective study, we used data from four patients who were diagnosed with ischaemic cardiomyopathy between 2008 and 2013 at the University of Pennsylvania Hospital. *Table 1* summarizes the baseline characteristics for the four patients. The patients had mean \pm standard deviation (SD) LVEF of $44.0 \pm 2.6\%$ and were thus not clinically indicated for prophylactic ICD implantation. All patients underwent MRI performed on a 1.5 T scanner using post-gadolinium perfusion and inversion-recovery-prepared delayed enhancement ($1.77 \times 1.77 \times 8 \text{ mm}^3$ resolution). One of the patients had spontaneous stable monomorphic ventricular tachycardia (VT) prior to the MRI. The other three patients had no spontaneous or inducible arrhythmia pre- or post-MRI.

Image processing

The MRI image stacks were segmented using our recently published segmentation and interpolation method,^{12,13} an updated methodology in comparison to what was previously used in the VARP approach.¹¹ CardioViz3D (INRIA, Sophia-Antipolis, France) was used to seed points and obtain the surfaces for the epi- and endo-cardial boundaries of the ventricles (*Figure 1A*). The grey-level thresholding method described in our previous paper¹³ was used to further segment the myocardium into three tissue types, non-infarcted tissue, border zone (also termed grey zone, because of its intermediate level of signal intensity in the MRI), and scar. The mean and SD of the voxel intensities in the region outside the infarct were calculated. The grey-level value corresponding to mean + 3 SD was assigned as the upper limit for normal tissue ($\text{normal}_{\text{max}}$), and the range of intensities within the infarct tissue ($\text{infarct}_{\text{range}}$) was calculated by obtaining the difference between the maximum intensity within the infarct region ($\text{infarct}_{\text{max}}$) and $\text{normal}_{\text{max}}$. Voxels with intensity between $\text{normal}_{\text{max}}$ and $(\text{normal}_{\text{max}} + 30\% \text{ of } \text{infarct}_{\text{range}})$ were classified as grey zone. Voxels with intensity more than $\text{normal}_{\text{max}} + 30\% \text{ of } \text{infarct}_{\text{range}}$ were classified as scar (*Figure 1B*).

Discretization and fibre orientation generation

The tetrahedral meshes were constructed directly from the segmented images using a previously described approach, which uses the dual mesh of an octree applied directly to segmented 3D image stacks.¹⁴ The procedure preserved the fine geometric details of the ventricles and the different infarct zones (*Figure 1C*). Finally, fibre orientations were assigned in the mesh using a previously validated rule-based method (*Figure 1D*).¹⁵ It uses the Laplace–Dirichlet method to define transmural and apicobasal directions at every point in the ventricles, and then employs bi-directional spherical linear interpolation to assign fibre orientations based on a set of fibre orientation properties (rules) derived from a large amount of histological and diffusion tensor MRI data.¹¹

Electrophysiological properties

Assigning electrophysiological (EP) properties in the model was done as previously described.¹¹ Briefly, mathematical description of electrical conduction in cardiac tissue was based on the monodomain representation.¹⁶ The scar was modelled as passive tissue. The non-infarcted tissue and grey zone were assigned human ventricular cell action potential dynamics.¹⁷ Modifications to the ionic model based on experimental recordings were implemented to represent EP remodelling in the grey zone, as we have previously described (*Figure 1E*),¹³ namely: peak sodium current, peak L-type calcium current, peak potassium currents IKr, and IKs were decreased to 38%, 31%, 30% and 20% of the original values in the Ten Tusscher model, respectively. As a result, the grey zone action potential was characterized by a longer duration, decreased upstroke velocity, and decreased peak amplitude compared to that in the non-infarcted myocardium (360 vs. 310 ms, 6.7 vs. 11.6 V/s, and 20 vs. 35 mV, respectively), similar to what has been previously reported.^{18,19}

As implemented previously in VARP,¹¹ the values of the non-infarcted tissue conductivities used in this study were 0.255 and 0.0775 S/m in the longitudinal and transverse directions, respectively. Tissue in the grey zone region was characterized with a 90% decrease in transverse conductivity to reflect connexin-43 remodelling in the infarct border zone.²⁰

Stimulation protocol

All simulations were performed using the software package CARP (CardioSolv, LLC) on a parallel computing platform.^{16,21} To examine the arrhythmogenic propensity of the post-MI ventricular models,

Table 1 Baseline characteristics of patients and the normal, grey zone, and scar volumes in the reconstructed heart models

Patient	Age(y)	Sex	EF (%)	Clinical VT	Tissue classification	Reconstructed volume (cm ³)	% of total ventricular volume
1	38	F	47	Y	Normal	149.7	92.0
					Grey zone	9.9	6.1
					Scar	3.1	1.9
2	60	F	45	N	Normal	88.4	90.1
					Grey zone	2.4	2.4
					Scar	7.3	7.5
3	59	F	43	N	Normal	125.4	91.1
					Grey zone	9.7	7.1
					Scar	2.5	1.8
4	56	F	41	N	Normal	105.5	91.6
					Grey zone	9.3	8.1
					Scar	0.3	0.3
Mean ± SD					Normal	117.3 ± 26.4	91.2 ± 0.8
					Grey zone	7.8 ± 3.6	5.9 ± 2.5
					Scar	3.3 ± 2.9	2.9 ± 3.2
					Total	128.4 ± 28.0	

programmed electrical stimulation, similar to the protocol used in the standard clinical protocols,²² was simulated; the same protocol was used in the original VARP study.¹¹ Specifically, each patient-derived ventricular model was subjected to pacing from multiple locations in an attempt to elicit reentrant arrhythmias, thus assessing the potential of the disease-remodelled ventricles to cause degeneration of electrical signal propagation into arrhythmic activity following premature beats that originate at different locations in the heart. The stimuli were delivered at 17 locations in the LV, one in each American Heart Association (AHA) segment,²³ and at the apex and near the outflow tract of the right ventricle. The rationale for choosing a large number of pacing sites was based on clinical studies, which have shown a positive correlation between the number of pacing sites and inducibility of ventricular arrhythmia.²⁴ The distribution of pacing sites throughout the LV ensured that the protocol covered a large range of possibilities for potential sites at which ectopic foci could emerge.

All models were paced endocardially from each of the 19 locations for 6 beats (S1) at a cycle length of 600 ms followed by a premature stimulus (S2) initially given at 90% of S1 cycle length. The timing between S1 and S2 was progressively shortened until VT was induced. If VT was not induced, a second premature stimulus (S3) was delivered after S2. If VT was not induced either, a third premature stimulus (S4) was delivered after S3 (Figure 1F). Three seconds of VT were simulated.

Results

Table 1 summarizes the volumes of the normal myocardium, grey zone, and scar in the reconstructed hearts. The mean value of ventricular volumes for the four patients is 128.4 cm³. The normal tissue occupies more than 90% of the ventricular volumes in all the patients, but the fractional volume of grey zone within the infarct ranged from 24.7 to 96.9%.

Virtual-heart arrhythmia risk predictor, the execution of which was blinded to clinical outcome, accurately predicted arrhythmia

susceptibility in all four patients. Figure 2 summarizes the arrhythmia inducibility simulation results for the only patient that reported clinical VT (Patient 1). In this patient model, the infarcted tissue is located at the inferolateral and posterior area near the base, and the core scar occupies 24% of the infarct volume (Figure 2A). Activation and voltage maps in Figure 2B and 2C, respectively, show that the reentrant circuit in the model is an epicardial figure of eight, with an isthmus located within the inferolateral grey zone at the base. These results are consistent with clinical recordings obtained as part of the EP study performed during the ablation procedure for this patient, which revealed that the reentry conducted through an isthmus located in the lateral and basal scar border zone.

Figure 3 shows the reconstructed geometry for patients 2–4. In the ventricular model of Patient 2, the infarcted tissue is located at the middle anterior and lateral wall of left ventricle, and the core scar occupies 75% of the infarct. In the Patient 3 model, the infarct is located mainly at the arterial and septal wall, with the core scar occupying 20% of it. In Patient 4 model, the infarcted tissue is located at the lateral wall from base to apex, and the core scar occupies only 3% of the infarct. These three patients had no inducible VT as predicted by VARP, which is consistent with the patient's clinical histories. All of these patients had no recorded case of arrhythmia prior to MRI procedure.

Discussion

In this article, we present a feasibility study for the use of computational modelling in identifying patients with LVEF >35% who could potentially benefit from prophylactic ICD implantation. Currently, the LVEF <35% metric is used to stratify patient risk for SCD and identify candidates for preventive ICD implantation. However, patients with LVEF <35% account for only one-third of all SCD

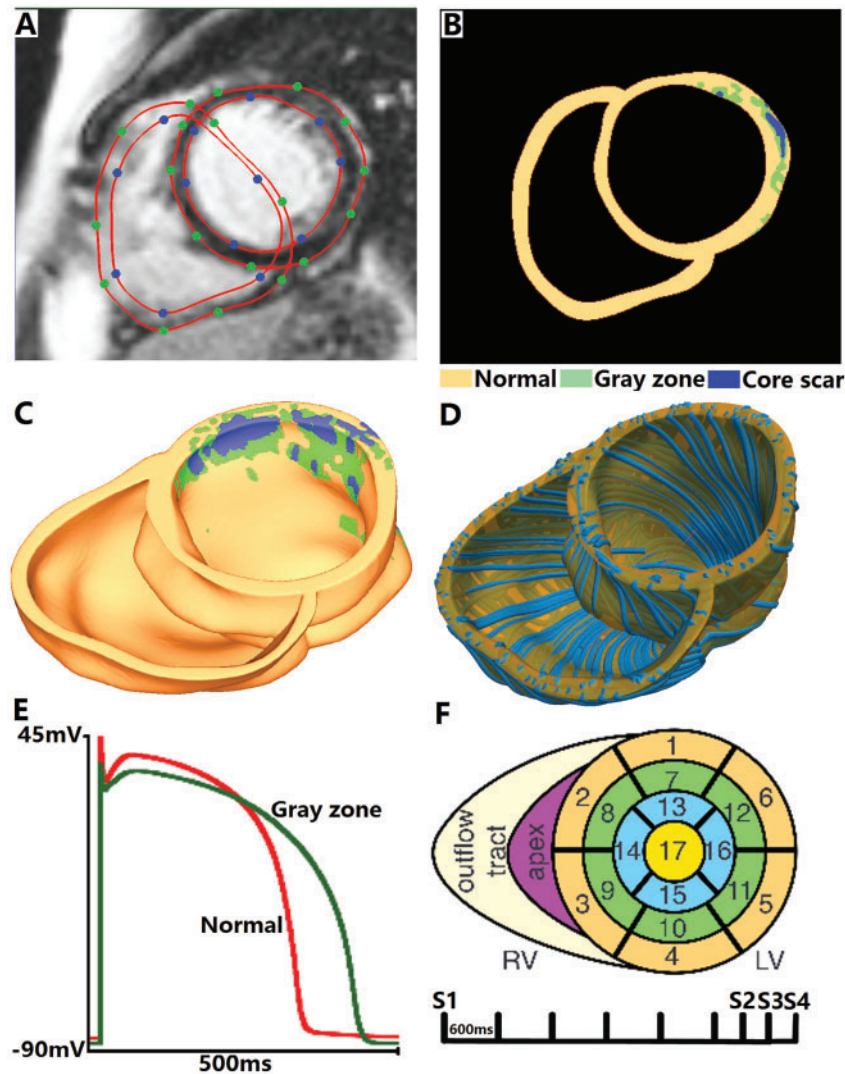


Figure 1 Virtual-heart arrhythmia risk predictor methodology. Contrast-enhanced cardiac MRI stack with landmark points and splines delineating the endocardial and epicardial surfaces (A), and the resulting ventricular segmentation into normal tissue, grey zone, and core scar (B). High-resolution ventricular structure model (C) with estimated fibre orientations (D). Action potential (E) for non-infarcted tissue (red) and grey zone (green). Virtual-heart arrhythmia risk predictor pacing sites (F).

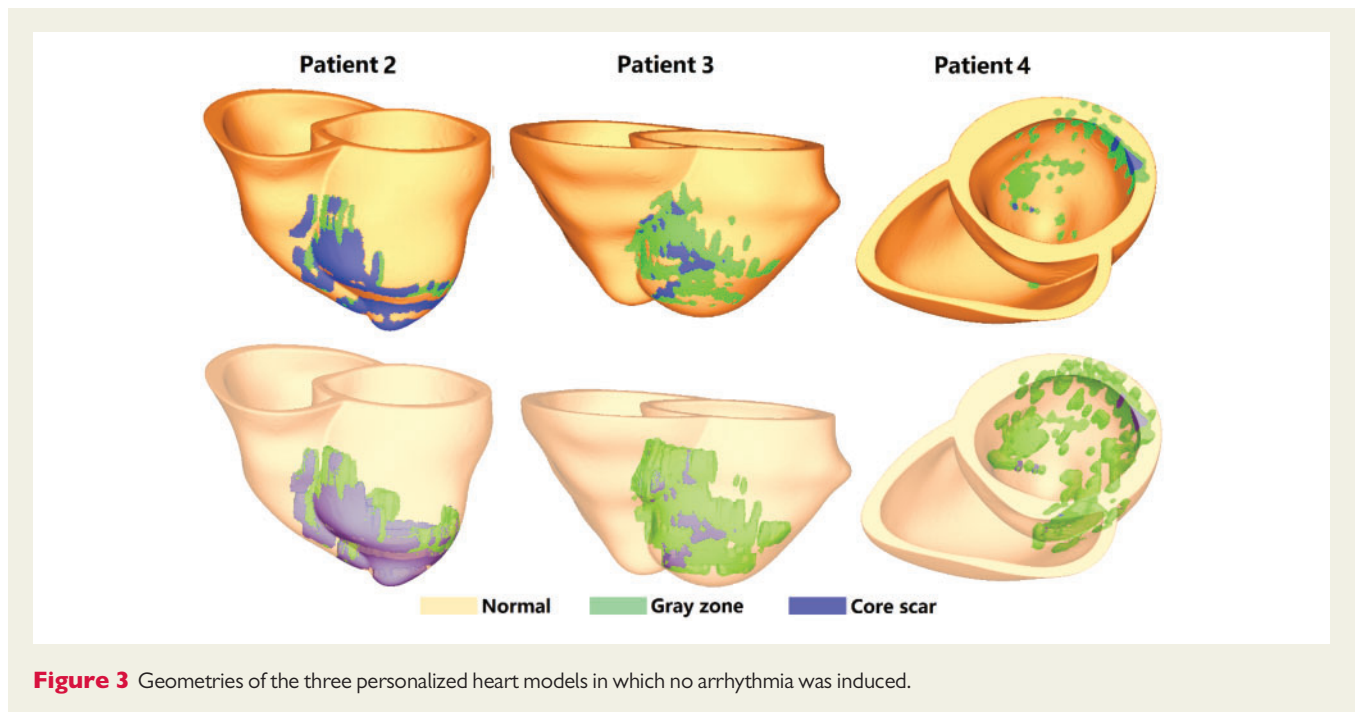
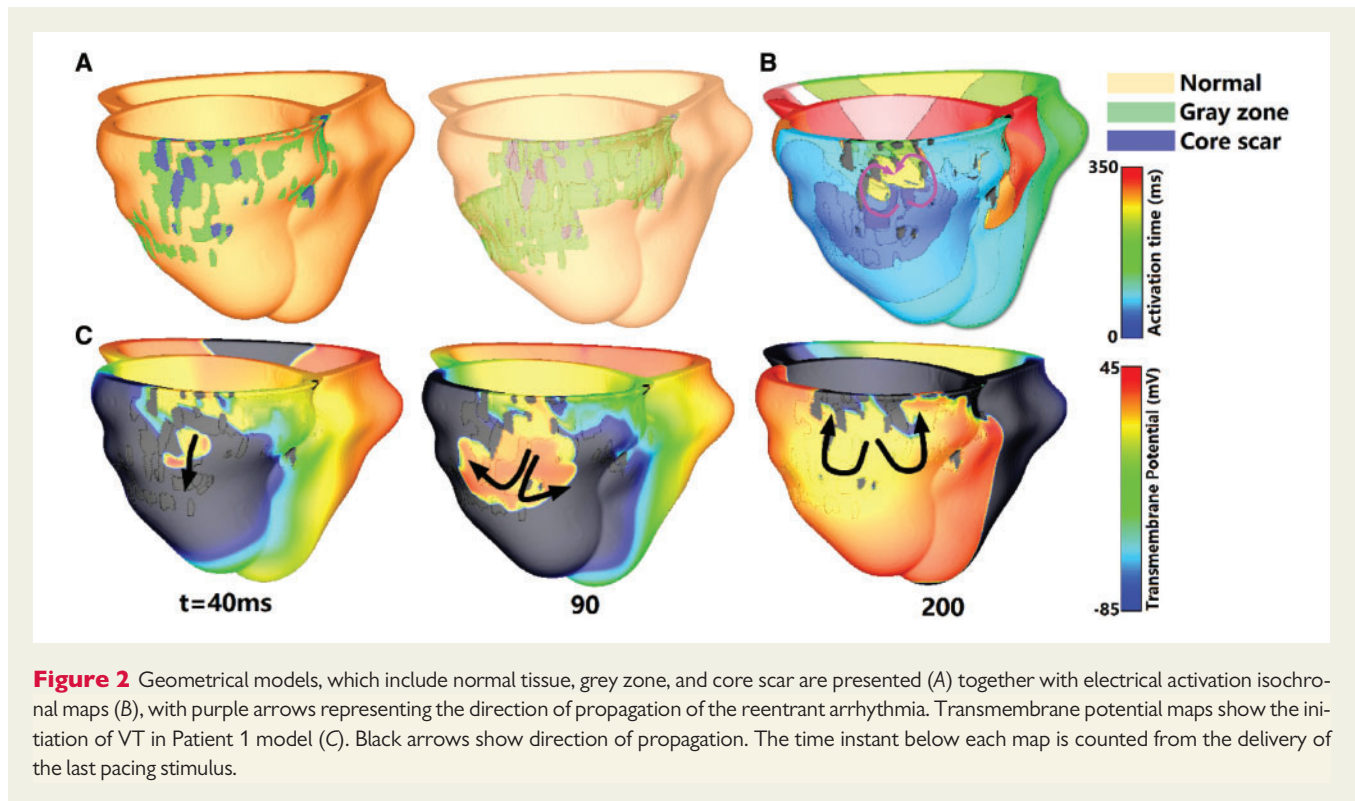
events.²⁵ Thus a large proportion of patients who are susceptible to SCD are not indicated for prophylactic ICD insertion.

We recently demonstrated that VARP computational simulations could be used to predict arrhythmia susceptibility in patients with MI and LVEF <35%.¹¹ That retrospective study demonstrated that VARP results are superior to other current non-invasive clinical metrics, such as LVEF, grey zone volume,²⁶ scar volume,²⁷ or left ventricular mass,²⁸ as well as to the invasive EP testing. These results point to the translational potential of VARP in being used as an effective patient selection tool for prophylactic ICD implantation.

The case studies presented here demonstrate that VARP can also be used to identify MI patients with preserved LVEF who are nonetheless at risk for arrhythmias and who could benefit from

prophylactic ICD implantation. Virtual-heart arrhythmia risk predictor is of low burden to patients since it requires only a single MRI scan and would not significantly alter the current standard of care for these patients. The simulations presented here show that the method is robust for personalized arrhythmia risk stratification in patients with LVEF >35%.

Among the four patients in this article, the grey zone and scar volume did not differ significantly between the VT-inducible and not inducible hearts. This is consistent with the findings from the 41 patients with LVEF <35% examined in our previous study¹¹: in that cohort, neither grey zone nor scar volume were found predictive of arrhythmia events. The reentrant circuit in the inducible model had an isthmus located within the grey zone, which is consistent with our



previous findings of VT organizing centres in grey zone,^{12,13,29,30} and experimental data which showed that the infarcted border served as the isthmus and a centrifugal pathway in different VT morphologies.^{26,31}

The VARP approach entails a complex simulation methodology, validated over a number of studies.^{13,27,29–31} Accurate reconstruction of ventricular geometry has been validated with *ex-vivo* and *in-vivo* imaging datasets.^{12,32} The approach to construct a model of the

infarcted ventricles by thresholding the infarct into only scar and (homogeneous) grey zone, as done in the present study, without accounting for additional small-scale heterogeneities in the grey zone, has been recently validated with experimental data. Specifically, Deng *et al.*¹³ used sock epicardial data for infarct-related VT, obtained from *in-vivo* swine heart, and demonstrated that ventricular models reconstructed from MRI data of the corresponding hearts were able to predict fairly accurately the morphology of each VT reentrant circuit and its organizing centre (e.g. isthmus). This approach to account for the contribution of the grey zone to ventricular arrhythmogenesis has been instrumental in enabling us to perform a large number of simulations of patient hearts.¹¹ Similar personalized virtual heart simulation methodologies are now being implemented to assess arrhythmogenesis and predict optimal ablation strategies for atrial arrhythmias in patients with fibrotic remodelling.^{33,34}

Limitations

A limitation of the current study is the small sample size of only four patients. The predictive capability of VARP for MI patients with preserved LVEF needs to be assessed in large retrospective and ultimately, prospective studies.

Conclusions

This study presents for the first time the use of virtual heart computational modelling to predict the arrhythmia risk in patients with LVEF >35%. The results demonstrate that personalized heart models can accurately detect VT arrhythmia susceptibility in those patients who are usually not candidates for prophylactic ICD implantation. Our proposed methodology has the potential to aid clinicians in preventing SCD in these patients.

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