Supplemental Material

Supplemental Methods

MRI acquisition

Cardiac MRI was performed using a 3T Philips Achieva magnet (Philips Healthcare, Best, Netherlands) and a 32 channel coil for patients without an ICD or CRT. A Siemens Magnetom Aera 1.5T magnet (Siemens, Munich, Germany) with wideband sequences was used in those with an ICD or CRT. Standard sequences were obtained during breath-holds using white blood steady state free precession sequences (SSFP) and black blood turbo spin echo (TSE), with ECG signal gating.

In addition, a 3D LGE enhanced sequence was obtained following the standard images. Images were obtained 8-10 minutes following the administration of a 0.15mmol/kg intravenous bolus of gadobutrol (Gd-BT-DO3A) (Gadovist). The optimal inversion time (TI) was identified by performing a T1 look-locker scan and selecting the TI with maximum nulling of healthy left ventricular myocardium. Free-breathing images were acquired using Spectral Presaturation with Inversion Recovery (SPIR) turbo field echo (TFE) sequence with respiratory navigator motion correction, a 12 degree flip angle and a 360 x 360mm field of view. Acquired voxel resolution was 1.8 x 1.8 x 3.6mm^2, which was reconstructed to 1.3 x 1.3 x 1.8mm^2. Acquisition window was 154ms and images were obtained in diastole. Typically, 80 slices were obtained to ensure full acquisition of the ventricular myocardium. Images were analysed, anonymised and exported using cvi42 version 5.14 (Circle Cardiovascular Imaging Inc, Calgary, Canada).

Structural heart model generation

The exported LGE-MRI images were reconstructed into geometrical models of the individual patient's ventricular myocardium. The images were resampled into short axis at an isotropic resolution of 0.35 x 0.35 x 0.35 mm. The myocardium was semi-automatically segmented as reported in previous publications.[20,22,23] In brief, landmark control points were placed along the left ventricular endocardium and epicardium using CardioViz3D.[38] From these points, the 3D myocardial wall geometry was reconstructed using a method based on variational implicit functions interpolation which has been previously validated.[24] Dense scar and borderzone were identified in the myocardium using the full-width half-maximum methods. Areas of > 50% of the maximal signal intensity in the myocardium were assigned as dense scar. Areas of between 35% and 50% maximal signal intensity were designated as borderzone. All remaining areas are designated as healthy tissue. The 3D geometry of the infarcted areas is integrated into the geometric model. For a patient with an ICD *in situ*, additional processing was required. The ventricular geometry was extrapolated from the unaffected areas, through the region occluded by the ICD artefact. The myocardium within the ICD artefact was assumed to have normal tissue properties.

Next, from the reconstructed ventricular geometries, finite-element, tetrahedral meshes were generated using a commercial meshing software Materialize Mimics (Materialise NV, Leuven, Belgium) with a previously described meshing procedure.[39] On average, 4 million individual nodes form this mesh per patient, giving an average resolution of 400μm.[28] Finally, personalised fibre-orientation was applied to the computational mesh using a Laplace-Dirichlet rule-based approach which defines the transmural and apicobasal directions of the fibres for each point in the ventricles[40]. It then uses bi-directional spherical linear interpolation to assign fibre orientation which is based on a set of rules derived from previous histological analysis and diffusion tensor MRI data.[18,29,41]

Application of electrophysiological parameters to create the heart digital twin

Once the ventricular mesh was created, cell and tissue electrophysiological properties were assigned based on the three different tissue types (healthy, borderzone and dense scar). Dense scar was considered electrically inert. Healthy areas were modelled based on previous modelling data by Tusscher.[30] Grey zone mechanics represent a modification of healthy ionic model based on previous patch clamp studies from cells taken from an infarct borderzone. The changes include a 62% reduction in peak sodium current, 69% reduction in L-type calcium current and a 70% and 80% reduction in the I_{Kr} and I_{ks} potassium currents respectively.[18] Compared with healthy tissue, these changes combine to give a reduced upstroke velocity of the action potential (6.7 vs 11.6 V/s), longer action potential duration (360 vs 310ms), and reduced peak AP amplitude (20 vs 35mV). Longitudinal and transverse conductivity in healthy tissue is set at 0.08 S/m and 0.00889 S/m respectively based on studies on human tissue.[42–45] In the borderzone, there is a 90% reduction in transverse conductivity based on the observed reduction in connexin-43, reduced conduction velocity and other gap junction alterations observed in the post-infarct borderzone areas.[46]

Electrical propagation was simulated by solving a reaction-diffusion partial differential equation, which represents the spread of the electrical wavefront through the model, as well as the ordinary differential and algebraic equations representing myocyte membrane dynamics at each node in the mesh.[47] Simulation of electrical propagation using these equations was performed using the software package openCARP (https://opencarp.org) using a parallel computing system.[33] This software has been used to solve other computational EP problems in both animal and human subjects and has been validated in several publications.[25,48–50]

VT induction protocol

Each patient's heart digital twin was subjected to multi-site pacing in order to induce re-entrant rhythms. The aim is to simulate the degeneration of the electrical signal following a PVC into re-entrant VT within the diseased myocardium. Seven segments are used for the simulated pacing, which are derived from the 17-segment American Heart Association (AHA) model and the pacing stimulus was delivered to an area of 1mm.[3] If scar is present in that particular segment, the pacing location was projected to the scar area, in order to increase the chance of inducing a VT. Seven segments were chosen to balance the computational resources required for the modelling against the chances of inducing a VT, which increase with more pacing sites.[51,52]

A pacing train (S1) of 6 beats was delivered at a 1 x 1 x 1mm spot at 600ms followed by an extrastimulus (S2) 300ms after S1. If this fails to capture, the S1-S2 interval is increased by 50ms until capture is achieved. Following capture of S2, the S1-S2 interval was shortened in 10ms intervals to find the shortest S1-S2 capture interval, which is then observed for the presence of re-entry. If no VT was induced with S2, a second (S3) or third (S4) extrastimulus was added. Sustained arrhythmia was defined as exhibiting two full rotations at a fixed location. Previous studies have shown that a longer observation period of up to 5 seconds does not reveal significantly more sustained VTs than a 2 second monitoring period.[19] Furthermore, the iterative in-silico ablation procedure makes sure that the heart digital twin is non-inducible of VT at the final iterations.

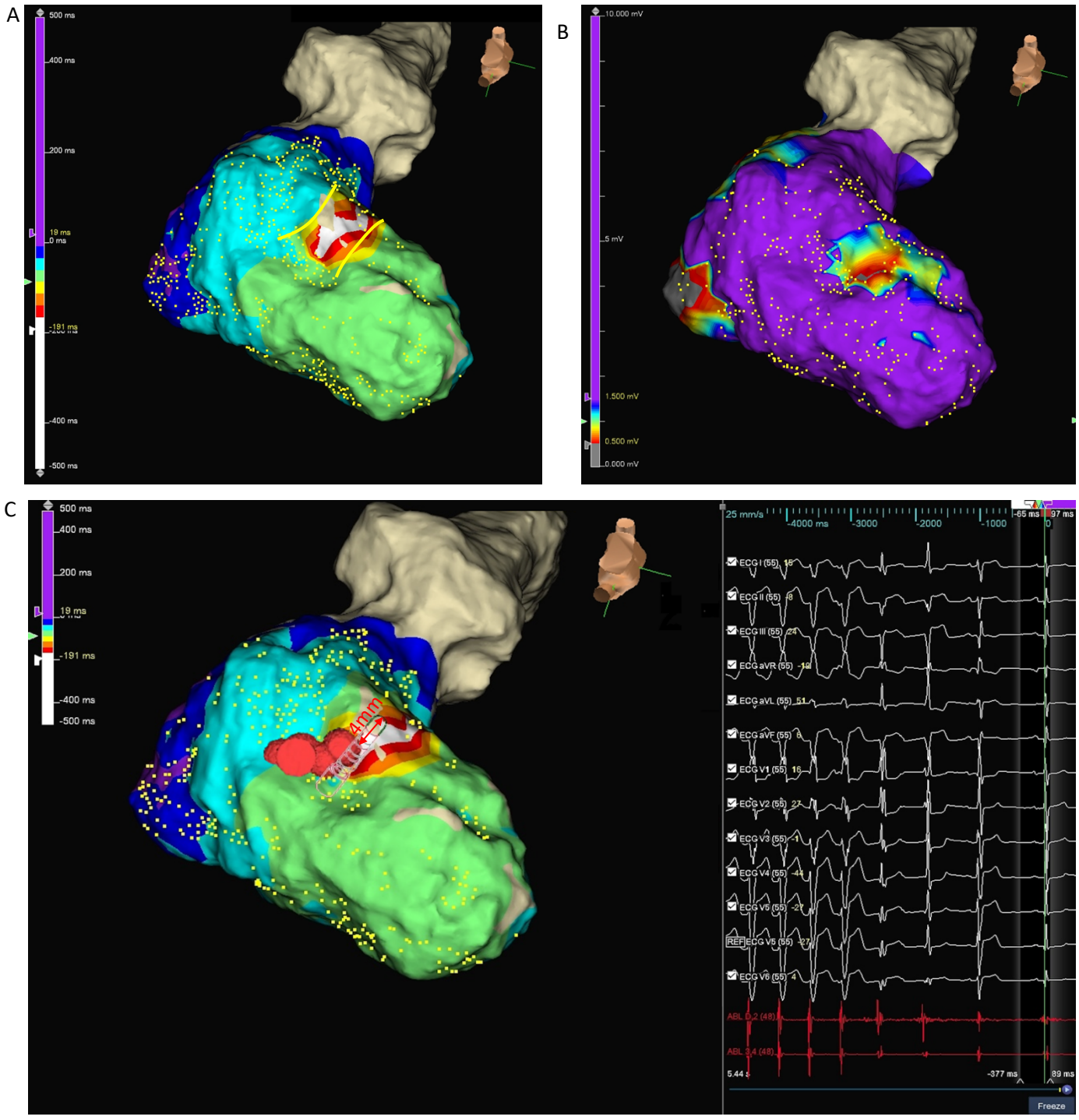
Supplemental Tables

Supplemental Table 1: diagnostic accuracy of digital twin primary predicted sites to predict critical VT components.

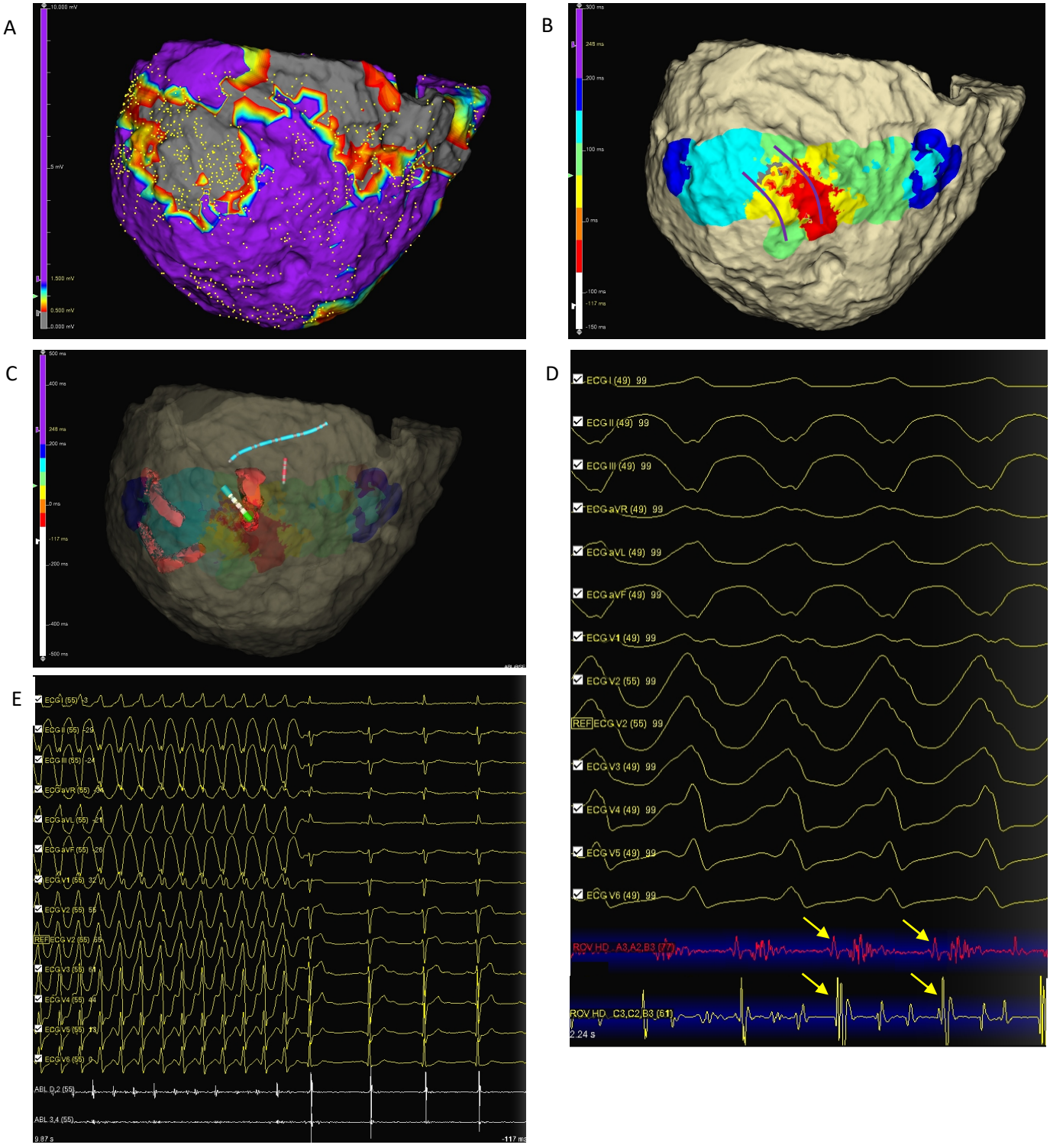
Parameter	TP	FP	TN	FN	Sensitivity	Specificity	PPV	NPV
Mid-diastolic potentials	13	47	243	3	81.3%	83.8%	21.7%	98.8%
Entrainment with concealed fusion	3	57	254	1	75.0%	81.7%	5.0%	99.6%
VT termination with ablation	4	56	245	1	80.0%	81.4%	6.7%	99.6%
Deceleration zones	18	42	238	8	69.2%	85.0%	30.0%	96.7%

TP = true positive, FP = false positive, TN = true negative, FN = false negative, PPV = positive predictive value, NPV = negative predictive value

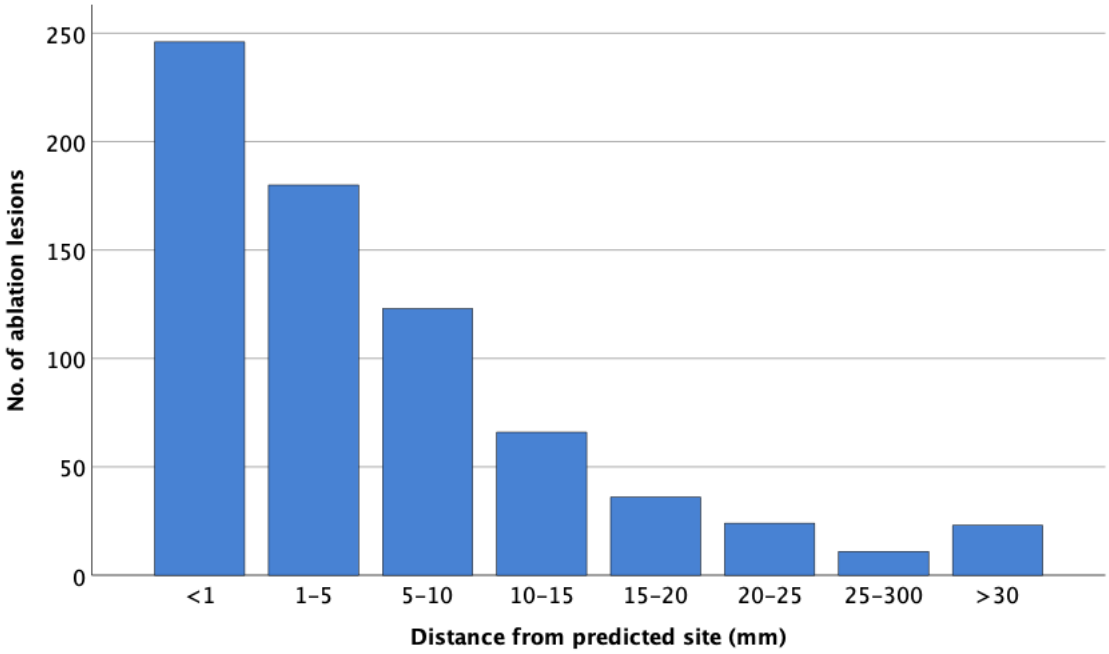
Supplemental Figures



Supplemental Figure 1: ICM patient with inferior and septal scar. A: VT activation map showed isthmus at mid septal region. B: Small area of scar seen on endocardial mid-septal surface. C: Ablation at VT isthmus was 4mm from predicted target site (red area) and lead to termination of tachycardia within 5 seconds of onset of radiofrequency energy.



Supplemental Figure 2: Epicardial map of ICM patient exhibiting basal to mid inferolateral and lateral wall scar. A: Substrate map showing epicardial scar. B: VT activation map showing VT channel (purple borders) along borderzone area. C: correlation of VT isthmus with predicted target site and ablation catheter placement at predicted target site. D: 12-lead ECG (100 mm/s speed), demonstrating right bundle, left-superior axis VT, TCL 348ms, with MDPs (yellow arrows) found at predicted target site. E: Slowing and termination of VT with ablation at predicted target site.



Supplemental Figure 3: Histogram demonstrating geodesic distance of each ablation lesion from the nearest predicted target site.