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How personalized heart modeling can help treatment of lethal arrhythmias: A focus on ventricular tachycardia ablation strategies in post-infarction patients

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Abstract

Precision Cardiology is a targeted strategy for cardiovascular disease prevention and treatment that accounts for individual variability. Computational heart modeling is one of the novel approaches that have been developed under the umbrella of Precision Cardiology. Personalized computational modeling of patient hearts has made strides in the development of models that incorporate the individual geometry and structure of the heart as well as other patient-specific information. Of these developments, one of the potentially most impactful is the research aimed at noninvasively predicting the targets of ablation of lethal arrhythmia, ventricular tachycardia (VT), using patient-specific models. The approach has been successfully applied to patients with ischemic cardiomyopathy in proof-of-concept studies. The goal of this paper is to review the strategies for computational VT ablation guidance in ischemic cardiomyopathy patients, from model developments to the intricacies of the actual clinical application. To provide context in describing the road these computational modeling applications have undertaken, we first review the state of the art in VT ablation in the clinic, emphasizing the benefits that personalized computational prediction of ablation targets could bring to the clinical electrophysiology practice.

Keywords

computer model; image-based modeling; simulation; substrate ablation; ventricular arrhythmia

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AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

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1 | INTRODUCTION

Precision Cardiology, as part of Precision Medicine, is the targeted strategy for cardiovascular disease prevention and treatment to which the cardiovascular research community aspires. Precision Cardiology accounts for individual variability in the pathophysiology of cardiovascular disease at multiple scales. There are a number of novel approaches that are now being developed or incorporated under the umbrella of Precision Cardiology, and computational modeling of cardiac function/dysfunction is one of them (Gray & Pathmanathan, 2018; Winslow, Trayanova, Geman, & Miller, 2012). Computational modeling of the heart is a discipline that has a long history, and it has contributed tremendously in understanding the mechanisms of cardiac disease and in particular, electrical and pump dysfunction, as reviewed in a number of contemporary articles (Lopez-Perez, Sebastian, & Ferrero, 2015; Niederer, Lumens, & Trayanova, 2019; Reumann, Gurev, & Rice, 2009; Vagos et al., 2018). Studies have progressed from single myocyte models and applications (e.g., Heijman, Volders, Westra, & Rudy, 2011; Lascano et al., 2013; Luo & Rudy, 1991), particularly exploring the role of ion channel protein mutations on the functioning of the cardiac cell (Clancy & Rudy, 2002; Wu et al., 2014) and the effects of drugs (Fermini et al., 2016; Moreno et al., 2011) on cell electrical behavior, to whole-organ applications. The latter include, for example, mechanisms of atrial and ventricular arrhythmia at the organ level (Bayer, Lalani, Vigmond, Narayan, & Trayanova, 2016; Keldermann et al., 2008; McDowell et al., 2012, 2013, 2015; ten Tusscher, Hren, & Panfilov, 2007; Van Nieuwenhuyse, Seemann, Panfilov, & Vandersickel, 2017; Vandersickel, de Boer, Vos, & Panfilov, 2016; Zahid, Cochet, et al., 2016; Zahid, Whyte, et al., 2016), effects of disease remodeling on organ function (Dutta, Mincholé, Quinn, & Rodriguez, 2017; Rodríguez et al., 2004), defibrillation (Trayanova, 2001; Trayanova, Li, Eason, & Kohl, 2004) and optogenetics (Boyle, Williams, Ambrosi, Entcheva, & Trayanova, 2013; Bruegmann et al., 2016) studies, and importantly, modeling the hearts of patients to improve diagnostics and treatment of heart rhythm disorders (Boyle et al., 2019).

The latter modeling efforts are particularly important to the nascent field of Precision Cardiology. Personalized computational modeling of patient hearts has made strides in incorporating in models the individual geometry and structure of the heart, typically reconstructed from imaging modalities, as well as other patient-specific information such as structural, electrophysiological and contractile remodeling under diseased conditions. Of these developments, one of the potentially most impactful is the research aimed at noninvasively predicting the targets of ablation for a lethal ventricular arrhythmia, ventricular tachycardia (VT), using patient-specific models. The approach has been successfully applied, in proof-of-concept studies, to patients with ischemic cardiomyopathy (ICM), that is, infarction. The goal of this study is to review the strategies for computational VT ablation guidance in ICM patients, from model developments to the intricacies of the actual clinical application. To provide context in describing the road these computational modeling applications have undertaken, we first review the state of the art in VT ablation in the clinic, emphasizing the benefits that personalized computational prediction of ablation targets could bring to the clinical electrophysiology practice.

2 | STATE OF THE ART IN ABLATION OF VT IN ISCHEMIC CARDIOMYOPATHY PATIENTS

The majority of patients with sustained ventricular arrhythmias have structural heart disease, an umbrella term that encompasses ICM, nonischemic cardiomyopathy (NICM), and less common conditions such as cardiac sarcoidosis, hypertrophic cardiomyopathy, and other pathologies that result in alteration of normal myocardial structure (Dukkipati et al., 2017). In contrast to ventricular arrhythmias in structurally normal hearts, VT in patients with structural heart disease is often hemodynamically unstable (Stevenson et al., 2008). Accordingly, catheter ablation is not indicated as first-line treatment but is considered as an adjunctive therapy following placement of an implantable cardioverter-defibrillator (ICD), particularly when antiarrhythmic drugs are ineffective at reducing the frequency of appropriate ICD shocks. The most recent guidelines for the management of ventricular arrhythmia recommend catheter ablation for ICM patients with recurrent episodes of symptomatic sustained VT or VT storm who are intolerant of antiarrhythmic medications (Class I recommendation, level of evidence B) (Al-Khatib et al., 2018). Catheter ablation may be considered as first-line therapy (rather than antiarrhythmics) in ICM patients with ICD shocks for sustained monomorphic VT or with symptomatic recurrent sustained monomorphic VT (Class IIb recommendation, level of evidence C). Hemodynamic instability of the VT may limit the ability to safely identify critical VT isthmuses using entrainment and activation mapping during VT. As a result, the electrophysiologist must often rely on modification of the underlying arrhythmogenic substrate during sinus or paced rhythm. Characterizing this complex substrate and developing methods to identify locations capable of supporting VT circuits have therefore been the subject of extensive investigation.

2.1 | The arrhythmogenic substrate in ischemic cardiomyopathy

Following acute myocardial infarction, the involved myocardium is replaced by a core region of electrically inert dense fibrosis, with strands of electrically active myocardium interspersed within and surrounding the infarct, creating a peri-infarct border zone (Fenoglio et al., 1983). It is this heterogeneous substrate that allows for conduction slowing, unidirectional block, and reentry (de Bakker et al., 1988). Of those ICM patients presenting for VT ablation, 69% are reported to have hemodynamically unstable VT (Stevenson et al., 2008). Consequently, substrate ablation is frequently performed as an initial step in VT ablation in ICM. Recent evidence suggests that substrate ablation as an initial step in catheter ablation reduces procedure time, radiation exposure, and need for cardioversion compared to a protocol of VT induction and mapping before substrate ablation (Fernández-Armenta et al., 2016). Multiple studies have demonstrated that catheter ablation in ICM is effective in reducing ICD therapy (Kuck et al., 2010; Reddy et al., 2007; Sapp et al., 2016). However, despite a reduction in the frequency of appropriate ICD therapy, VT still recurs in 25–50% of ICM patients who undergo catheter ablation (Dukkipati et al., 2017). Additionally, prophylactic VT ablation (at time of ICD implantation) has no proven survival benefit (Tilz, Eitel, et al., 2019) and is currently being investigated in the BERLIN VT trial (Tilz, Kuck, et al., 2019).

2.2 | Noninvasive imaging for substrate characterization

Given the importance of characterizing the fibrotic substrate in structural heart disease, preprocedural noninvasive imaging has emerged as a valuable tool to prospectively identify potential ablation targets. Noninvasive substrate characterization has primarily been accomplished using cross-sectional imaging, such as cardiovascular magnetic resonance imaging (MRI) and cardiac computed tomography (CCT).

2.2.1 | Cardiovascular magnetic resonance imaging—MRI provides excellent tissue characterization, principally through the use of gadolinium-based contrast agents, which accumulate in fibrotic tissue. Areas on MRI with late gadolinium enhancement (LGE) correspond to scar and peri-infarct border zone, thus identifying potential ablation targets (Estner et al., 2011). Pre-procedural assessment of scar distribution can also aid in planning the access route (endocardial vs. epicardial), particularly in NICM (Bogun et al., 2009). Incorporation of MRI into electroanatomic maps (EAMs) in the EP lab has also been shown to improve ablation outcomes (Zghaib et al., 2018).

Frequently, patients with a history of VT have ICDs, which previously were contraindicated in MRI due to potential adverse effects from the strong magnetic field and radiofrequency energy involved in the scan. However, the development of MRI-conditional devices has expanded the number of patients able to safely undergo MRI prior to VT ablation (Shinbane, Colletti, & Shellock, 2011). MRI has been demonstrated to be safe even in patients with “legacy devices” that predate the development of MRI-conditional devices, so long as standardized protocols for pre-scan device programming are followed (Nazarian et al., 2017). ICDs pose another challenge to pre-procedural substrate characterization: The physical proximity of the generator to the heart can result in image artifacts that obscure visualization of the myocardium (Sasaki et al., 2011). These artifacts can be reduced (though not completely eliminated) using a modified wideband pulse sequence (Rashid et al., 2016).

The current clinical standard LGE is a 2D sequence with limited spatial resolution (1–2 mm in-plane resolution and 6–8 mm slice thickness). Recent developments in 3D imaging allow the acquisition of high resolution LGE images with reduced partial volume averaging (1–2 mm in-plane resolution and 2–4 mm slice thickness), potentially providing better information of the spatial organization of the infarct structure. However, 3D LGE MRI faces more challenges with respect to device artifact (Rashid et al., 2016) and respiratory motion artifact (Bratis et al., 2017).

2.2.2 | Cardiac computed tomography—CCT has some distinct advantages over MRI for pre-ablation substrate characterization. The artifact from an ICD generator is minimal in CCT compared to that seen with MRI (though the lead artifact is larger). Additionally, CCT has superior spatial resolution (0.5–2 mm³ isotropic resolution) compared to MRI. The main limitation of substrate characterization using delayed enhancement CCT with iodinated contrast is that the relative gray tone differences in tissue radio-opacity between infarct and normal tissue are fairly small, as opposed to LGE MRI, in which the contrast between infarct and normal tissue can be optimized by adjusting inversion times to null normal myocardium (Rodriguez-Granillo, 2017). Because of this

increased soft tissue contrast with LGE MRI, delayed enhancement CCT has been shown to be less sensitive in detecting ischemic scar (Bettencourt et al., 2013). Consequently, the presence of myocardial fibrosis has been inferred using surrogate measures such as regional LV wall thinning and abnormal wall motion (Komatsu et al., 2013; Tian et al., 2010). CCT images have been successfully integrated with EAM in the EP lab to assist in the identification of critical isthmuses, with somewhat greater success in ICM compared to NICM (Yamashita et al., 2016).

2.2.3 | Electrocardiographic imaging—The goal of preprocedural MRI and CCT is to characterize tissue structure to guide the electrophysiologist to potential ablation targets. In contrast, electrocardiographic imaging (ECGi) attempts to noninvasively reconstruct cardiac electrical activity by solving the inverse problem of electrocardiography: calculating activation, recovery, voltage, isopotential, or phase maps based on body surface potential signals recorded from the torso and patient-specific heart-torso geometry obtained from MRI or CCT (Barr, Ramsey, & Spach, 1977). Two commercial systems current exist for ECGi: Amycard 01C (EP Solutions SA, Yverdon-les-Bains, Switzerland) (Tsyganov et al., 2018) and ECVUE (CardioInsight Technologies Inc., Cleveland, Ohio) (Cheniti et al., 2019). For treatment of ventricular arrhythmias, ECGi has predominantly been used to guide ablation for premature ventricular contractions and focal VT (Cakulev et al., 2013; Jamil-Copley et al., 2014). A limited number of studies have investigated the use of ECGi for VT exit site localization in structural heart disease (Tsyganov et al., 2018; Wang, Gharbia, Nazarian, Horáček, & Sapp, 2018; Zhang et al., 2016), but validation has largely been limited to qualitative evaluation due to the lack of a clear clinical ground truth for exit site. More recently, ECGi has been used to identify targets for noninvasive cardiac radioablation (Cuculich et al., 2017).

2.3 | Novel electroanatomic mapping strategies for substrate ablation

While noninvasive imaging can provide information on tissue structure, catheter ablation involves access to the endocardial or epicardial surface, where detailed electrophysiologic information can be obtained to further aid in substrate ablation. Specifically, abnormal electrogram (EGM) characteristics can corroborate and augment findings from noninvasive imaging studies. Invasive substrate characterization has been aided by the development of catheters with small electrodes and short inter-electrode spacing, which can create high-density maps. The improved spatial resolution of these high-density maps allows for identification of high-voltage signals within heterogeneous low-voltage areas, suggestive of small channels of electrically active myocardium within scar.

The earliest work on substrate mapping was based on bipolar EGM voltage, with endocardial voltage <0.5 mV consistent with dense scar, voltage >1.5 mV consistent with normal myocardium, and voltage between 0.5 and 1.5 mV consistent with border zone. For epicardial voltages, <0.5 mV is consistent with scar, 0.5–1.0 mV consistent with border zone, and >1.0 mV with a normal EGM pattern consistent with normal tissue (Marchlinski, Callans, Gottlieb, & Zado, 2000). While voltage mapping provides a rough approximation of substrate geometry, EGM voltages can vary due to the direction of the activation wavefront relative to the catheter position, the conduction velocity (CV), catheter contact with tissue,

electrode size and spacing, and signal filtering (Anter & Josephson, 2016). For these reasons, voltage criteria alone are nonspecific for critical isthmuses (Mountantonakis et al., 2013), and the incorporation of abnormal EGM characteristics adds specificity to the identification of appropriate ablation targets.

Two abnormal EGM patterns are of particular interest in substrate ablation. Late potentials (LPs) have multiple definitions in the literature but are generally characterized as EGM potentials that occur after the QRS complex of the surface ECG, suggesting the presence of slow conducting channels (CCs) that can play a role in VT induction. Local abnormal ventricular activities (LAVAs) are stereotypical high-frequency ventricular potentials that are distinct from the far-field ventricular EGM (Jaïs et al., 2012). These signals are found in border zone and scar and signify slowly conducting tissue that have a potential to serve as VT isthmuses. Multiple approaches to substrate ablation based on both voltage and abnormal EGM characteristics have been proposed.

2.4 | Ablation of LPs and LAVAs

One approach to substrate ablation is to identify and ablate all LPs or LAVAs, as these EGM patterns localize to slowly conducting tissue. In a study of 50 patients (36 with ICM, 14 with NICM) with LPs on initial EAMs, LPs were completely ablated in 42 patients and could not be completely eliminated in eight. At the end of the procedure, VT was inducible in 5/8 with incomplete LP ablation, compared to 5/42 of those with complete LP ablation, suggesting the use of LP elimination as an endpoint for successful substrate ablation (Vergara et al., 2012). With respect to LAVA elimination, a prospective study of 70 patients (56 ICM, 14 NICM), identified LAVAs in 67. Complete ablation of LAVAs was possible in 47 of the 67 patients and in multivariable analysis was independently associated with a reduction in recurrent VT or death (Jaïs et al., 2012). More recently, in a trial of 159 patients with ICM undergoing first VT ablation, complete LAVA elimination was associated with improved VT-free survival at 1 and 5 years post-ablation (Wolf et al., 2018).

2.5 | Core isolation

Core isolation involves electrically isolating the low-voltage scar from the rest of the myocardium using a circumferential ablation around all critical VT circuit elements. This method involves voltage mapping to identify scar, border zone, and CCs, followed by entrainment and activation mapping if VT is hemodynamically stable. Ablation lesions are applied to incorporate all identified VT circuit elements within the electrically isolated region, and success of the approach is confirmed by pacing within the isolated region in locations that previously demonstrated capture. In the initial description of the method in 44 patients (32 with ICM), core isolation was successful in 37 (84%) and led to better VT-free survival than those in whom core isolation was not successful (Tzou et al., 2015).

2.6 | Scar homogenization

A more thorough approach to substrate ablation involves extension of ablation lesions throughout the entire scar. This technique involves ablation of both low-voltage areas (<1.5 mV) as well as any location with abnormal electrograms on both the endocardial and epicardial surfaces (Di Biase et al., 2012). The guiding principle behind this approach is that

substrate not participating in VT at the time of ablation could become part of a VT isthmus in the future. Therefore, the goal is to homogenize the entire scar and border zone, thus eliminating all potential VT circuit elements. This approach also provides redundancy, where a more limited approach such as core isolation may be more susceptible to failure from an incomplete ablation lesion. Scar homogenization has been shown to be effective at reducing VT recurrence in ICM (Di Biase et al., 2012) and to a lesser extent NICM (Gökolan et al., 2016).

2.7 | Scar dechanneling

In contrast to the extensive ablation approach of scar homogenization, the scar dechanneling method opts for a more targeted approach. CCs are identified as a series of contiguous high-voltage EGMs within a low-voltage area. CC entrances are defined by EGMs with the shortest delay between the local, delayed EGM and the far-field component of the surrounding border zone or normal myocardium. Targeted ablations at these CC entrances have been shown to result in VT noninducibility in over half of patients presenting for VT ablation, suggesting the role of dechanneling as an initial step that may obviate more extensive scar homogenization (Berruezo et al., 2015). The incorporation of MRI LGE imaging with scar dechanneling resulted in a reduction in VT recurrence compared to non-MRI-guided scar dechanneling, despite fewer ablation lesions in the MRI group (Andreu et al., 2017).

The above methods, while effective in reducing VT frequency, have the disadvantage that they are based on the assumption that CCs and critical isthmuses are fixed, anatomical locations. The following approaches aim to characterize the functional properties of the arrhythmogenic substrate.

2.8 | Decrement evoked potentials mapping

Decrement evoked potentials (DEEPs) are specific subtypes of LPs that demonstrate an exaggerated delay in response to a premature extra stimulus. To identify a DEEP, the interval between the surface ventricular far-field signal onset and the local LP EGM is recorded during a paced rhythm. A premature extra stimulus is delivered at a coupling interval of 20 ms above the ventricular effective refractory period. If the interval between the ventricular far-field signal and the LP is >10 ms longer than during steady-state pacing, the LP is classified as a DEEP. Locations with such decremental conduction are thought to be susceptible to unidirectional block due to alterations in CV restitution, providing a mechanism for reentry. A small study of 20 patients with ICM demonstrated that DEEPs have increased specificity over LPs in identifying VT isthmuses with no significant difference in sensitivity (Porta-Sánchez et al., 2018).

2.9 | Isochronal late activation mapping

Isochronal late activation mapping is a technique for visualization of slow conduction within scar to identify deceleration zones (DZs), which correspond to sites critical for reentry (Irie et al., 2015). Local activation times are obtained at the offset of EGMs and displayed as eight isochrones of equal time intervals on the EAM. DZ are identified as locations with >3 isochrones within a 1-cm radius. Pacing is performed in these DZs to reproduce VT

morphology (pace mapping). A prospective study of 120 patients (60 with ICM, 60 with NICM) who underwent targeted ablation of DZ demonstrated 70% 12-month freedom from VT (Aziz et al., 2019).

2.10 | How computer simulations can help guide VT ablation

Long-term outcomes of VT ablation in structural heart disease remain suboptimal despite the multitude of innovations described above. The rapid increase in imaging and electrophysiologic data have strengthened our understanding of arrhythmogenesis and have informed novel ablation techniques, but each data source has important limitations. Noninvasive imaging data does not have the spatial resolution necessary to clearly delineate precise targets for ablation. EGM data is highly dependent on a number of variables such as the direction of the activation wavefront relative to the catheter position, the CV, catheter contact with tissue, electrode size and spacing, and signal filtering (Anter & Josephson, 2016).

Computer simulations can play an essential role in guiding VT ablation by creating personalized heart models incorporating patient data to reproduce the arrhythmogenic substrate in silico and then predict the ablation targets. These patient-specific heart models allow for thorough investigation of the VTs the remodeled substrate can sustain as the model can be paced for many locations that are not accessible in the clinic. The virtual heart could identify the highest-yield critical ablation targets that have smallest lesion size, resulting in more efficient procedures by reducing excessive and unnecessary ablation lesions. Simulated ablation via modification of the substrate in silico provides pre-procedural testing of various ablation strategies and can reveal unintended consequences of particular ablation lesions, such as unmasking of a previously unidentified VT circuit. In doing so, simulations can also elucidate fundamental mechanisms behind arrhythmia induction and maintenance. A stronger understanding of these mechanisms can inspire novel, more effective ablation techniques.

3 | ADVANCES IN PERSONALIZED HEART MODEL DEVELOPMENT

Personalized 3D ventricular models utilized thus far in clinical applications for VT ablation were all reconstructed from patient's cardiac LGE-MRI imaging data (Figure 1), as these contrast-enhanced scans allow for visualization of the structural remodeling in the myocardium resulting from ICM or other structural heart disease. We refer to such personalized image-based model as the "patient's virtual heart." A number of published papers have described in detail the steps for patient-specific heart model construction.

These steps include first contouring the myocardial boundaries in the MRI image stack and reconstructing the ventricular wall geometry using a variational implicit functions interpolation methodology (Turk & O'Brien, 2005) validated with clinical data (Prakosa et al., 2014). Signal thresholding (Arevalo et al., 2016) or energy minimization based-method (Ukwatta et al., 2016, 2014) is used to segment out infarcted and non-infarcted areas within the ventricular wall. Each infarct region is further classified into scar and gray zone (GZ, a semi-viable area surrounding the non-conductive scar, also termed infarct border zone). Several widely used image thresholding methods exist for scar and GZ segmentation

including the n standard deviation and the full-width half maximum methods (Flett et al., 2011; Mesubi et al., 2015). In the personalized virtual heart models reconstruction, a previously validated full-width half maximum approach (Schmidt et al., 2007) is typically used for this segmentation. Using LogOdds method, 3D infarct geometry is then reconstructed from the infarct segmentation of the 2D clinical MRI images (Ukwatta, Arevalo, et al., 2015; Ukwatta, Rajchl, et al., 2015). In cases where the patient whose virtual heart model is being constructed has an implanted ICD device, then additional image-processing steps are conducted to overcome the presence of artifact in the image. These include extrapolation of the ventricular boundaries through the area occluded by the ICD artifact, as described in Prakosa et al. (2018). The presence of ICD shadow in the scar area, however, could in some cases severely affect the assessment of the scar distribution. In such cases, the application of a wideband LGE-MRI is used to suppress the ICD artifact. Constructing a virtual heart from wideband LGE-MRI includes the same steps as the standard LGE-MRI. Geometrical model construction next involves the generation of finite-element ventricular meshes (Arevalo et al., 2016; Arevalo, Plank, Helm, Halperin, & Trayanova, 2013; Prassl et al., 2009). Finally, fiber orientations specific to the individual ventricular geometry are assigned on a per-element basis in the mesh, typically using a rule-based (RB) approach (Bayer, Blake, Plank, & Trayanova, 2012). Recently on 4-valves bi-ventricular models, this RB approach has been extended to incorporate fiber information specific to the right ventricle and ventricular outflow tracts (Doste et al., 2019). After fiber orientation is assigned to the elements in the ventricular mesh, the corresponding “masks” of infarct scar and GZ are superimposed. This completes the generation of the patient-specific ventricular geometrical model.

To construct an electrophysiological model from the geometrical model requires assigning distinct electrophysiological properties to the different regions in the geometrical model (Arevalo et al., 2016; Prakosa et al., 2018). For constructing patient-specific models from patients with ICM, regionally uniform cell and tissue electrophysiological properties are assigned to the three regions outlined from the LGE-MRI scans: scar, GZ, and non-infarcted tissue. While scar is electrically inert, human action potential is used in non-infarcted areas and GZ, with the latter being assigned modified kinetics (Arevalo et al., 2016; ten Tusscher, Noble, Noble, & Panfilov, 2004). Overall, the GZ action potentials are characterized by a longer duration, decreased upstroke velocity, and decreased peak amplitude compared to those in the non-infarcted myocardium, based on experimental findings (Cabo & Boyden, 2003; Decker & Rudy, 2010). Tissue properties representing human ventricular cell-to-cell electrical communication are also assigned to the non-infarcted and GZ regions, with GZ characterized with a decrease in transverse conductivity to reflect connexin-43 remodeling in the infarct border zone. The uniform electrophysiological changes implemented in the GZ in the virtual hearts reflect the aggregate of the local contributions of healthy and fibrotic cells within the mixed-cell infarct border zone. This is a simplified representation of the electrophysiology of the GZ, thus avoiding complex spatially discrete considerations of local behavior, and does not reflect the presence of a single disease-state cell behavior in the infarct border zone.

Our patient-specific modeling approach does not use patient-specific electrophysiological parameters in the models; the personalized aspects in the models involve only patient-

specific ventricular geometry and distribution of structural remodeling. This is consistent with the clinical application for which these virtual hearts are intended: predicting the VT ablation targets in patients with structural cardiac disease. In the current state of the art in VT ablation, as described in this review, personalization of electrophysiological parameters would most likely necessitate invasive data acquisition in each patient. This is deliberately avoided in the simulation-guidance approach to ablation, underscoring the noninvasive aspect of this clinical translation application.

In this respect, the described approach stands apart from previous attempts at image-based modeling of ventricular electrical function to guide VT ablation, where acquiring personalized electrophysiological information is considered a priority (Relan et al., 2011). Advances in machine learning could allow the use of currently available noninvasive measurement of cardiac electrical activity such as QRS duration extracted from noninvasive 12-lead ECG (Tse & Yan, 2017) to adjust CV in patient-specific models. Zettinig et al. (2014) used polynomial regression to calibrate three diffusivity parameters of a phenomenological model by using the QRS duration and electrical axis features. A complete personalization of biophysically detailed model would require more computational resources as a large quantity of forward model simulations is required to train the machine learning algorithm. In the absence of personalized electrical properties, the potential uncertainty in the predicted targets is significantly alleviated the novel approach to predicting the targets, as described below.

Patient-specific image-based ventricular electrophysiological models developed as described above are suitable for assessing the arrhythmogenic propensity of the disease-remodeled ventricular substrate. They cannot assess spontaneous activity in the myocardium (ectopic foci, which are the ventricular triggers of arrhythmia), but can accurately evaluate rapid-pacing induced VTs, and the locations of lesions, which, when executed in the clinic, will eliminate all VTs. Typically, fairly uniformly distributed, mostly bi-ventricular locations of the pacing stimuli are used (Arevalo et al., 2016; Prakosa et al., 2018). The distribution of pacing sites throughout the ventricles ensures that the protocol covers a large range of possibilities for potential sites at which ectopic foci could emerge and captures all the possible arrhythmias that could arise from the given infarct morphology, and not only the one that is clinically manifested. Different numbers of bi-ventricular pacing sites have been used, from 19 to 26. The rationale for choosing a large number of pacing sites is based on clinical studies, which have shown a positive correlation between the number of pacing sites and inducibility of ventricular arrhythmia (Buxton, 2014; Piccini et al., 2009), and further increase in the number of pacing sites do not uncover more unique VTs (Arevalo et al., 2013). However, it remains unknown whether there is an optimal number of pacing sites that does uncover all relevant VTs. Similarly, the pacing pulse trains used in these virtual heart studies have mimicked those in the clinic (Cheng et al., 2013), however, it is unclear whether such pacing trains can be optimized for the simulations to avoid aggressive pacing that could result in arrhythmia even in healthy hearts.

4 | APPLICATION OF VIRTUAL-HEART MODELS TO VT ABLATION IN POST-INFARCTION PATIENTS

A number of simulation studies have paved the way for the application of patient-specific electrophysiological models to help clinical decision-making and guide the clinical VT ablation procedure. Several of them are noteworthy. Zhu, Wei, and Okazaki (2012) showed that models of the heart can be used to carry out noninvasive localization of accessory pathways in patients with Wolff-Parkinson-White syndrome. Ng et al. (2012) provided the initial exploration of the feasibility of using simulations to predict VT circuits. Relan et al. (2011) used a hybrid X-ray and MR environment to image a patient heart, which was further personalized with voltage measurements; the results demonstrated that the heart model could successfully be used to assess infarct-related VT inducibility from sites not accessible in the clinic. The recent study by Campos et al. (2019) used individualized models of the LV to examine the electrophysiological factors that promote block and reentry in infarcted hearts, concluding that CV slowing in the infarct border zone was the dominant factor promoting arrhythmogenesis, with a contribution from the prolongation of action potential duration (APD) in these regions. These results are consistent with the findings of Lopez-Perez et al. (2019), who used a model constructed from a post-infarction patient scan and demonstrated that reduced CV and heterogeneity in APD in the border zone are the main factors in promoting reentrant activity.

Of particular importance to the development of ventricular computational models that can be translated to the clinic was the 2016 study by Arevalo et al. (2016), who used 41 post-infarction patient-specific ventricular models to predict risk of sudden cardiac death by arrhythmias. The study demonstrated the feasibility of the use of population-based image-based models to address problems in heart rhythm disorders. The methodology was further extended to diseases other than ICM such as myocarditis (Cartoski et al., 2019) and Tetralogy of Fallot (Shade et al., 2019). A number of articles described below followed that approach, extending it to the evaluation of the VT circuits in individualized hearts for the purpose of understanding how to best target specific regions in the myocardium for ablation, eliminating the VTs.

An improved knowledge of the spatial organization of infarct structure and its contribution to VT is important for designing optimal ablation approaches. Unfortunately, clinical cardiac LGE-MRI scans are of low resolution, precluding a thorough investigation of this contribution. Historically, renditions of myocardial structure have been based on sectioning approaches (Streeter, Spotnitz, Patel, Ross, & Sonnenblick, 1969). While these approaches have produced high-resolution data of local tissue structure (Pashakhanloo et al., 2017), combining these measurements together into a registered whole-organ data sets in large animal and human hearts is extremely difficult. Pashakhanloo et al. (2016) were the first to develop a methodology to image ex vivo large animal and human hearts in a clinical MRI scanner at submillimeter resolution ($0.25 \times 0.25 \times 0.5 \text{ mm}^3$). Subsequently, the same team explored the distribution of the scar in ex vivo post-infarction hearts at that resolution (Pashakhanloo et al., 2017; Pashakhanloo, Herzka, Halperin, McVeigh, & Trayanova, 2018) and used computer simulations to evaluate the VTs formed in these ex vivo hearts, providing

a glimpse into how VTs are formed in structurally remodeled hearts, and offering a pathway towards achieving an improved interpretation of clinical recordings of electrical activity in the zone of infarct, and thus a better ablation targeting.

Examples of the distribution of scar in these hearts are shown in short-axis slices of high-resolution LGE-MRI in Figure 2. Regions of non-enhanced (viable) tissue interdigitates with scar patches, either adjacent to the scar subendocardially or subepicardially, or located intramurally traversing the scar. In Figure 2A, top row, there is a thin layer of subendocardial surviving tissue of varying thickness. In Figure 2B, top row, surviving tissue is located predominately at the midwall, potentially providing a conductive pathway across the wall. In Figure 2C, top row, a region of viable myocardium is observed adjacent to the scar at the subepicardium. In contrast to the low-resolution clinical LGE-MRI scans where the admixture of normal tissue and scar manifest itself as a “gray zone” (border zone), here we see a clear distinction between viable and non-viable tissue (scar).

Simulations executed with high-resolution models reconstructed from these images reveal different types of arrhythmias in each of these cases. The VT in Figure 2A, bottom row, is a subendocardial VT; the infarct spans the septum and the anterior wall. As the transmembrane voltage maps demonstrate, the reentrant circuit is primarily located on the endocardial side of the scar. As the analysis revealed (Pashakhanloo et al., 2018), the heterogeneity in the thickness of the surviving subendocardial tissue creates tortuous pathways for the activation during reentry. The reentry in Figure 2B, bottom row, involved propagation that traversed the scar transmurally through a region of surviving tissue in the infarct zone (green in bottom panel) that made a breakthrough on the epicardium. Figure 2C, bottom row, presents a subepicardial reentry that encompasses propagation through a tube-like structure of viable tissue that runs inside the infarct subepicardially. The channel has an irregular zig-zag shape with total length of ≈ 30 mm. Overall, in all ex vivo models analyzed in the study, the majority of the VT pathways were completely or partially subendocardial (52 and 78%, respectively), whereas 26% of the simulated VTs traversed the scar transmurally with breakthroughs at the epicardium or the endocardium; finally, 22% of the pathways were located entirely on the epicardial side of the scar. Importantly, this study showed that the critical parts of VT reentrant circuit do not involve all surviving tissue in the zone of infarct (i.e., all channels). The results suggest that even if channels are identified through the scar on the endocardial surface during a clinical electrophysiology procedure, these may be passive conduits of propagation during VT rather than critical pathways, and thus not appropriate targets for ablation.

High-resolution models reconstructed from ex vivo data could help investigate the effect of image resolution on the VT pathways in patient-specific models. This can be done by downsampling of the high-resolution images to lower resolution images and then simulating and comparing VTs in the models constructed at different resolutions. Such analysis could, therefore, provide a means to assess the accuracy of the patient-specific models from clinical MRI for the prediction of VT pathways. A step in this direction was provided by the study of Deng et al. (2015). In four individualized ex vivo post-infarction heart models, high-resolution original images (resolution 390 μm) were downsampled into two lower resolutions in order to replicate image quality obtainable in the clinic (medium resolution,

$1.5 \times 1.5 \times 4 \text{ mm}^3$, and low resolution $1.5 \times 1.5 \times 8 \text{ mm}^3$). This was achieved by eliminating the high-frequency components in the Fourier space of the original images using a 3D rectangular mask; an inverse FFT was then applied to reconstruct the downsampled images. Models were reconstructed from the three image stacks for each heart. Simulation results demonstrated that induced VTs in the medium- and low-resolution models were located close to those in high-resolution models. Importantly, all models, regardless of image resolution, accurately predicted the VT morphology and circuit location. These results demonstrate that MRI-based computer models of hearts with ICM could provide a unique opportunity to predict and analyze VT resulting from specific infarct architecture, and thus may assist in clinical decisions to identify and ablate the reentrant circuit(s).

As described above, only a small subset of CCs sustain VT in patients with myocardial infarction, although there is an abundance of such channels. As described above, identifying these critical CCs (CCCs) in the clinic, so that they can be targeted by ablation, remains a significant challenge. The study by Deng, Prakosa, Shade, Nikolov, and Trayanova (2019a) used a personalized virtual-heart approach to conduct a 3D assessment of CCCs sustaining VTs of different morphologies in such patients, to investigate their 3D structural features, and to determine the optimal ablation strategy for each VT. To achieve these goals, ventricular models were constructed from LGE MRIs of six post-infarction patients in a retrospective study. Rapid pacing induced VTs in each model, and CCCs that sustained different VT morphologies were identified and their structure examined. Ablation was performed at the optimal part of each CCC, aiming to terminate each VT with a minimum lesion size, and the predicted ablation locations were compared to clinical.

Analyzing the simulation results, the study found that there were 1 to 4 VT morphologies (2.7 ± 1.2) induced in each model, sustained by propagation through CCCs. Consistent with the findings by Pashakhanloo et al. (2018) reviewed above, there were other CCs in the models as well, but those were conduits of propagation during VT and not critical structures for VT maintenance. Further, three types of CCCs sustaining VTs were identified (Figure 3, top row): I-type and T-type channels, with all channel branches bounded by scar, and functional-reentry channels, which were fully or partially bounded by conduction block surfaces. The three different types of CCCs accounted for 43.8, 18.8 and 37.4%, respectively, of all CCCs in the six patients. Figure 3, middle row, provides examples of VTs in each case. The I-type CCC was part of a single 3D reentrant pathway, often of convoluted shape. In the T-type CCC, the wavefront propagated through a 3D channel that split into 2, often unequal, branches. The VT morphology through the I- or T-type CCCs could be either figure-of-eight or circular reentry, depending of the 3D structure of the specific CCC. In each of these cases the VT morphology, whether figure-of-eight or circular, depended on the presence or absence, respectively, of symmetry in the 3D structure of the CCC. In the third type of VT (partially or fully functional reentry), rotational activity was around an area (3D surface) of functional block between GZ and non-infarcted tissue, formed because non-infarcted tissue was refractory at the time of wave propagation through the slower-conducting GZ. Again, asymmetry of CCC boundaries was the determinant factor in the type of reentry.

In this study, the authors also performed ablation of the narrowest part of each CCC and found it was sufficient to terminate VT. The mean narrowest width of a CCC or a branch of a CCC was 9.7 ± 3.6 mm. Figure 3, bottom row, shows the predicted ablation sites (the narrowest parts of the channels) and the (blind) comparison with the clinical ablation. The correspondence to the clinical ablation sites was excellent in these patients, as demonstrated by the co-registered simulation targets and ablation locations in the clinical CARTO maps. The results of this study provide comprehensive information regarding the individualized 3D structure–function relationship in regard to VT maintenance in the post-infarction patient heart. The study was also the first to characterize the functional-reentry VTs and their relation to the surrounding scar. Finally, the results demonstrated that a personalized virtual-heart approach is capable of determining the VT morphologies in each patient and identifying the CCCs which sustain reentry. Interestingly, this study also clearly demonstrated that lesions predicted by simulations are smaller than those executed in the clinic. This is consistent with the findings of Ashikaga et al. (2013), who demonstrated, in a retrospective analysis of 13 patients, that the prediction of ablation targets for infarct-related VT could result in lesions that are much smaller than those executed in the clinic.

The study by Prakosa et al. (2018) was the watershed study that demonstrated the utility of virtual-heart simulations in determining noninvasively the optimal (i.e., minimum lesion size) VT ablation targets and guiding the clinical procedure of VT ablation. The authors termed the noninvasive approach VAAT (virtual-heart arrhythmia ablation targeting). The capability of the approach to determine the minimum-size ablation targets that eradicate all VTs was first assessed in retrospective studies, both animal ($n = 5$) and human ($n = 21$), including a human study where image construction was carried out from clinical images with device artifacts. Finally, in a proof-of-concept prospective study ($n = 5$), the feasibility of using VAAT to guide clinical VT ablation was demonstrated, in an approach where sites predicted by the VAAT approach were targeted directly. After ablation, programmed stimulation was repeated. Acute success was defined as the inability to induce clinical VT at the end of the procedure.

Importantly, in a significant departure from all current VT ablation procedures, as described in the first part of this review, the VAAT approach targets termination not only of VTs that are clinically manifested or induced at the time of procedure, but of all VTs that could arise from the given post-infarction substrate, including those that might arise following initial ablation. This approach thus could eliminate the need for repeated ablations and thus offer long-term freedom from VT.

Figure 4 illustrates results from the retrospective patient study in the study. The top row (panel A) illustrates the technology as applied in two of the 21 patients. Following reconstruction of the patient-specific models, all VTs that the remodeled substrate can sustain were evaluated from the results of rapid pacing. In these two patients, there is one induced VT in each model, illustrated by the activation map images. Ablation targets were then predicted from the VT analysis (using a minimum-cut algorithm; Zahid, Whyte, et al., 2016) and blind to any clinical data (the only input is the LGE-MRI patient data), which rendered, with minimum lesion size, each heart not inducible for VT from any ectopic site. Once the simulation results were completed, the comparison with clinical data (following

co-registration of MRI surfaces with ablation targets and CARTO surfaces with ablation sites) demonstrated excellent predictive capability of the VAAT approach.

In the VAAT approach, once the ablation lesions were incorporated back in the corresponding virtual-heart model and the VT inducibility protocol was repeated, a new VT was inducible in the modified-by-ablation ventricular substrate, indicating that the patient had a high probability of have a new VT emerge from that location post-ablation. In such cases, the VAAT protocol is repeated until all VTs are terminated by the virtual lesions and complete VT noninducibility is achieved. The set of ablation targets that achieve this are the final (optimal) set of VAAT ablation targets. They represent the targets that would be directly approached during the clinical procedure, without any electrical mapping. The set of VAAT ablation lesions is expected to result in the complete elimination of the ability of the infarct-remodeled ventricular substrate to sustain VT.

The ablation target prediction in the patient shown in Panel B consisted of three targets. When compared with the clinical ablation lesion, it becomes apparent that the patient had two VTs manifested clinically, which were ablated, and their locations coincided with two of the VAAT targets. However, the patient returned for repeat ablation 7 months later, and was ablated at another location, which coincided with the remaining VAAT target. This retrospective analysis demonstrated that should the ablation procedure had executed the VAAT-predicted targets, there would have been no need for repeat ablation. Panel C in Figure 4 illustrates the case of a patient with an existing ICD, which generated a large artifact on the LGE-MRI image. The study showed that as long as the artifact does not cover the zone of infarct, a virtual heart can be constructed and used to determine the VAAT targets. In this case, one target was predicted located centrally on the mid LV wall. Comparison with the executed clinical lesions revealed a complete overlap between the VAAT and the clinical lesion. However, the patient was additionally ablated in a manner surrounding the infarct resulting in a large lesion and potentially decreased contractile function of the heart. Should the VAAT prediction have been followed, the patient would have been spared this additional large ablation lesion.

The most important aspect of this study was its prospective study of five patients at two different clinical centers. In the prospective study, VAAT was executed during the brief time interval (<24 hr) between the acquisition of patient MRI and the clinical ablation procedure. Once calculated, the set of predicted ablation targets were exported, then uploaded and co-registered in the clinical electroanatomical navigation system before the procedure commenced. Figure 5 presents two cases, one from each clinical center, of successful VAAT-guided ablations in a post-infarction patients with inducible sustained VT. Model-generated ventricular images with the VAAT targets were imported into the clinical electroanatomical navigation system (Figure 5), so that the ablation catheter could be directly steered towards the targets. After ablation of the VAAT targets, a clinical VT inducibility pacing was executed to confirm that VT was no longer inducible. The promising results from the proof-of-concept prospective study (five patients) at two clinical centers demonstrate the feasibility of conducting a large prospective patient study and underscore the VAAT potential for translation to the clinic for guidance of VT ablation in patients. VAAT overcame significant additional technical challenges in combining virtual-heart output with the clinical

electroanatomical navigation system, thus presenting the first direct integration of computational modeling in cardiac patient care.

The VAAT approach did not use patient-specific electrophysiological parameters in the models. Currently, personalization of electrophysiological parameters would necessitate invasive data acquisition in each patient, as described earlier in this review. Invasive acquisition was deliberately avoided in the VAAT approach, since noninvasive target assessment is one of its major advantages. Interpatient variability in electrophysiology could affect ablation target location predictions. To assess that, Deng, Prakosa, Shade, Nikolov, and Trayanova (2019b) conducted a study in five patient-specific post-infarction ventricular models to determine the accuracy of ablation target prediction when electrophysiological parameters are altered. Both APD and CV were changed, in both directions, from the average human values used in the VAAT technology. The study found that majority of reentrant circuits' locations did not change when electrophysiology was changed within physiological bounds, although in a number of cases new targets arose. However, it was found that these new targets were also captured by the VAAT methodology, as they appeared as emergent VTs upon the repetition of the stimulation protocol. Thus, the potential uncertainty in target locations due to the use of average human ventricular electrophysiology was significantly alleviated by the use of virtual ablations and repeated VT inducibility protocols in the models. These findings demonstrate that the VT ablation target uncertainty in patient-specific ventricular models with an average representation of VT-remodeled electrophysiology is relatively low and the ablation targets stable, as the localization of the induced VTs was primarily driven by the remodeled structural substrate.

5 | OUTLOOK AND CONCLUDING REMARKS

Personalized computational modeling of the heart to predict VT ablation targets, such as the VAAT technology, holds the promise to radically change infarct-related VT ablation, and usher new approaches in precision cardiology. Should such approaches be successful, they would result in swift and precise delivery of ablation without prior electrical mapping, also having the ability to eradicate all possible VTs the substrate can sustain, thus eliminating or at least reducing the need for redo procedures. This could result in a dramatic improvement in the efficacy of and tolerance for the therapy, as well as in reduction of post-procedure complications. As we have previously discussed (Prakosa et al., 2018), since early use of VT ablation post-infarction has been shown to result in much improved patient outcomes (Reddy et al., 2007; Tung, Josephson, Reddy, Reynolds, & SMASH-VT Investigators, 2010), an accurate and easily executed VT ablation will lead to significant widening of the therapeutic potential of the procedure: the latter could become first line therapy for infarct-related VT, in contrast to its current administering after drugs have failed.

In order to make approaches like VAAT a clinical reality, a number of obstacles have to be overcome. One of them is the availability of MRI acquisition in patients with ICD devices, which remains a challenge. As scar and GZ cannot be reliably acquired from contrast-enhanced CTs as of yet (Esposito et al., 2016), MRI scans remain the imaging input for patient-specific model generation. As of late, attempts have been made to use wall thinning on CT as an indicator of scar distribution (Komatsu et al., 2013; Takigawa et al., 2019), but

the accuracy of such models has not been confirmed. An initial attempt to use the distribution of penetrating fat in the zone of infarct has also been made (Sung, Prakosa, Zimmerman, & Trayanova, 2019). Additional challenge includes the accurate computational representation of electrophysiological changes associated with fibrotic remodeling overall, and specifically in the infarct border zone, which remains far from settled (Costa, Plank, Rinaldi, Niederer, & Bishop, 2018); the resolution to this issue will depend on the acquisition of electrophysiological data in patients with ischemic and other cardiomyopathies. The importance of using personalized ventricular fiber distribution also remains unclear, although simulations with models incorporating local alterations in fiber orientations of up to 25° from a control atlas have demonstrated small effects on activation times and VTs (Bayer et al., 2012).

Furthermore, the issue of what constitutes a VT ablation target is far from settled. Thus far, simulation protocols either follow clinical approaches ablating exit sites and isthmuses or propose where to ablate based on the narrowest region of the CCC, as described above. While these are ad hoc decisions, a better approach would be to have an automatic detection of the ablation targets using an algorithm. In VAAT, the “min-cut” algorithm was used (Zahid, Whyte, et al., 2016), however it could be very time consuming, which is an issue when issues such as the clinical workflow are considered. Attempts have been made to detect organizing centers of reentry in atrial fibrillation using directed graphs (Vandersickel et al., 2019), however, the algorithm needs to be extended to 3D for ventricular arrhythmias use. A different approach would be to account for differences in activation and repolarization times within the 3D myocardium (Campos et al., 2019), however it remains unclear how these will be mapped during the ablation procedure. Furthermore, the issue of the uncertainty in predicting the ablation targets is a subject of emerging research (Dhamala et al., 2017; Dhamala et al., 2018) and will need to be accounted for in clinical implementations. Finally, machine learning and other artificial intelligence will likely be combined with computational modeling to account for clinical parameters other than the remodeled myocardial substrate.

Finally, in order for VAAT and similar approaches to become adopted in the clinic, most or all components of the pipeline will need to be automated, allowing for execution with minimum operator intervention. That will include approaches for automatic segmentation, a direction that has undergone a number of new developments using deep learning (Bai et al., 2018), as well as automation in the execution of the individual modules. The computation time will also need to be significantly decreased; new methodologies towards this end are being already implemented (Neic et al., 2017). Nonetheless, preprocedural noninvasive personalized ablation targeting, such as VAAT, holds high promise for becoming a critical component in clinical arrhythmia management. Importantly, if combined with the novel noninvasive ablation by stereotactic radiation therapy (Cuculich et al., 2017), it could lead to a radical change in the way arrhythmias are treated in the clinic.

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FIGURE 1.

MRI-based virtual heart reconstruction workflow. A, Contrast-enhanced cardiac MRI stack (left), with delineation of endocardial and epicardial surfaces (middle), respectively, and the resulting ventricular segmentation (right) into non-infarcted myocardium, gray zone and scar. B, High-resolution ventricular structure model (left) with estimated fiber orientation (middle). Action potential traces from the non-infarcted myocardium (red) and gray zone (green) are in right panel. (Reprinted from Arevalo et al. (2016). Copyright 2016 Springer Nature. Permission exempt per copyright transfer agreement.)

FIGURE 2.

Distribution of viable tissue in the zone of infarct, shown in short-axis slices of high-resolution LGE-MRI in three infarcted hearts. A, top row, Thin subendocardial layer of surviving tissue (red arrows); B, top row, Intramural viable tissue (yellow arrows); C, top row, Subepicardial layer of surviving myocardium (blue arrows). A, bottom row, Transmembrane voltage maps in one cycle of reentry. White arrows indicate wave propagation direction. The reentry is primarily located in the subendocardial layer. B, bottom row, A breakthrough on the epicardium. Below, delineation of a portion of an intramural surviving tissue embedded inside the infarct (green) that participates in the reentry. The arrows point to the locations of wave entrance and exit from the surviving tissue. C, bottom row, Wave traverses the channel. A border layer around the scar has been

rendered semitransparent to visualize channel position. (Reprinted from Pashakhanloo et al. (2018). Copyright 2018 Wolters Kluwer Health. Permission exempt per copyright transfer agreement.)

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FIGURE 3.

Types of reentry in post-infarction hearts. Top row, schematic diagram of the three types of VTs sustained by propagation through a CCC. Different colors represent different tissue types: non-injured (red), core scar (yellow), and GZ (green). The white arrows show the predominant direction of reentrant wave propagation for each type of CCC. The black line in the functional reentry schematic represents conduction block. The optimal ablation lesion that terminated each type of reentry is shown schematically in purple. Middle row, examples of VTs in each case shown by the activation map in the LV. Bottom row shows the ablation targets predicted (blue) and the clinical ablation lesions (red). (Reprinted with permission from Deng et al. (2019a). Copyright 2019 Elsevier)

FIGURE 4.

Prediction of the VT ablation targets using the VAAT approach in a retrospective study. Representative examples of in silico models and predictions from three patients (A–C). Panels a, Reconstructed ventricular computational models with different structurally remodeled regions. Panels b, Electrical activation maps of the induced VT on the epi- or endocardial surfaces. The white arrows show the direction of propagation of the excitation wave. The color scale indicates activation times and black indicates tissue regions that did not activate. Panels c, Predicted ablation sites by VAAT. The purple regions correspond to VAAT-predicted ablation targets on the endocardial surface, and insets show the zoomed-in VAAT predictions. Panels d, Co-registration of VAAT targets with the CARTO 3 endocardial surface (blue) showing clinical ablations corresponding to red dots representing locations of

the tip of the catheter during ablation. In C, the patient had ICD. The myocardial wall artifact burden was 59%. Panel a in this case shows, in addition, the LGE-MRI scans with ICD artifact burden. (Reprinted from Prakosa et al. (2018). Copyright 2018 Springer Nature. Permission exempt per <https://www.nature.com/nature-research/reprints-and-permissions/permissions-requests>)

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FIGURE 5.

Application of the VAAT technology in a prospective study for two patients from two different clinical centers (top and bottom rows). A,D, Reconstructed ventricular models with different remodeled regions. B,E, Activation maps corresponding to the two VT morphologies induced in the patient models. White arrows depict the direction of propagation of the excitation wave. The color scale indicates activation times and black indicates tissue regions that did not activate. C,F, Co-registration of the VAAT-predicted targets (purple) with the CARTO 3 endocardial surface (green). The red dots correspond to locations of the tip of the catheter during ablation. The left ventricular endocardial surface is shown in green and the total infarct region is shown in gray. Non-injured and scar tissues are shown in red and yellow, respectively. (Reprinted from Prakosa et al. (2018). Copyright 2018 Springer Nature. Permission exempt per <https://www.nature.com/nature-research/reprints-and-permissions/permissions-requests>)