Advances in Arrhythmia and Electrophysiology

Imaging-Based Simulations for Predicting Sudden Death and Guiding Ventricular Tachycardia Ablation

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Simulation-driven engineering has put rockets in space, airplanes in the sky, and self-driving cars on the road. Computational approaches have also contributed to advancements in clinical medicine and human health.1–3 In the arena of cardiac care, the recent emphasis on personalized medicine has provided a significant impetus for the development of predictive approaches combining imaging and computational modeling that can be applied to the diagnosis and treatment of heart rhythm disorders. A major advance in this direction is the creation and translation into clinical practice of novel imaging- and simulation-based strategies for predicting an individual’s risk of sudden cardiac death (SCD) and for the noninvasive planning of optimal personalized antiarrhythmia therapies. Clinical decisions about the stratification of patients for SCD risk resulting from arrhythmia and for determining the optimal targets for antiarrhythmia ablation therapies could greatly benefit from such targeted developments because current approaches, although life saving, remain suboptimal, often increase the burden on the healthcare system, and could lead to increased patient morbidity.

SCD resulting from ventricular arrhythmias is a leading cause of death in the industrialized world, particularly among patients with prior myocardial infarction (MI).4 For patients at high risk of SCD, mortality is reduced by the prophylactic insertion of implantable cardioverter defibrillators (ICDs).5 To determine the level of SCD risk, clinical cardiology practice still relies on the one-size-fits-all metric of left ventricular ejection fraction (LVEF) <35% to identify high-risk patients. Mechanistically, in hearts with structural disease, arrhythmia results from the heterogeneously distributed remodeled tissue, which can promote the initiation and maintenance of electric instability. Global LVEF poorly reflects these mechanistic factors and, hence, its use to determine the level of SCD risk and stratify patients for ICD implantation results in a low rate of appropriate ICD device therapy, only 5% per year.6 Thus, many patients are exposed to ICD risks—infecions, device malfunctions, and inappropriate shocks—without deriving any health benefit.7 Furthermore, the LVEF metric only targets a relatively small subgroup of individuals at high risk for SCD, failing to identify the majority of SCD victims (ie, the Myerburg conundrum). Personalized risk assessment could ensure life-saving timely intervention in patients at high risk while limiting unnecessary ICD implantations in patients with low risk.

In patients with ventricular tachycardia (VT), particularly those with structural disease (eg, MI), catheter-based ablation offers the possibility of permanent cure. However, it is associated with modest levels of success in eliminating infarct-related VT, 50% to 88%,8,9 and with complication rates as high as 8% of the treated population.10 The insufficient efficacy of the procedure stems from limitations in current voltage and pace mapping techniques used to identify the target locations for ablation.11–15 There is a need for new approaches that can result in swift and accurate identification of optimal ablation targets and thereby improve the efficacy of and increase the tolerance for the therapy and reduce postprocedure complications. Finally, because early use of VT ablation postinfarction has been recently shown to result in much improved patient outcomes (SMASH-VT trial [Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia]16), an accurate and easily executed VT ablation will lead to significant broadening of the therapeutic potential of the procedure.

Novel noninvasive imaging- and simulation-based strategies have been recently developed to address these clinical needs in patients with structural heart disease. They are based on personalized information about the distribution of structural remodeling in the patient’s ventricles as obtained from clinical imaging scans and on the biology and physics of heart cells and the electric current flow patterns through the cardiac syncytium, resulting in the construction of a virtual replica of the patient’s heart (ie, the patient’s virtual heart). Using a virtual heart, the patient’s unique lethal heart rhythm disorder can be studied in silico, and personalized treatment devised. Researchers can poke and prod the virtual organ in ways that are simply not possible with a flesh-and-blood heart. The hope is that with such models at the patient bedside, therapies could be improved, invasiveness of diagnostic procedures minimized, and healthcare costs reduced.

The goal of this article is to review recent developments of the personalized virtual heart methodology in determining risk of SCD and predicting the optimal targets for infarct-related
VT ablation in patients with MI. We present the methodology fundamentals based on cardiac imaging and computational modeling, outlining important assumptions, followed by a review of validation studies. We discuss the potential impact this approach could have on treatments for arrhythmias and how this can bring personalized medicine to the arena of cardiac care.

How to Construct a Virtual Heart
For both SCD risk stratification and ablation planning, a 3-dimensional (3D) computer model of MI patient’s individual heart is constructed from contrast-enhanced clinical cardiac magnetic resonance (CMR) data. The heart model incorporates the patient’s ventricular geometry and MI structural remodeling (the personalized part of the model), as well as electric functions from the subcellular to the organ level (based on the known biology of myocytes and the physics of current flow). The model is thus capable of representing the interplay between abnormal MI myocardial structure and electric instability in the heart that results in the generation and maintenance of ventricular arrhythmias. A virtual multisite delivery of electric stimuli from a large number of ventricular locations at different distances to remodeled tissue ensures that the ventricular substrate’s propensity to develop infarct-related ventricular arrhythmias can be comprehensively evaluated.

Personalized Geometric Model Construction
Patient-specific geometric models of 3D ventricular structure are reconstructed from the late gadolinium enhanced (LGE) CMR scans (Figure 1). For information on CMR acquisition, please refer to the methods description in Arevalo et al.17 For each patient, the myocardial boundaries in the CMR stack are contoured using landmark points, and the patient-specific 3D ventricular wall geometry is reconstructed.18 The myocardial regions are then classified as infarcted and noninfarcted by means of signal thresholding. The cut-off thresholds were determined on the basis of a percentage of the maximum intensity of the scar (such as full-width half-max method);17 alternatively, a methodology based on SDs above the remote normal tissue could be used. Although the ICD artifact can obscure part of the image, the geometry of the ventricles could nonetheless be reconstructed from the partially missing data using landmark-based interpolations.19 The presence of ICD shadow in the scar area, however, could in some cases severely affect the assessment of the scar distribution. The application of a wideband LGE–magnetic resonance imaging (MRI)20 has shown promising results in suppressing the ICD artifact in the heart and could be used in future applications of the virtual heart imaging simulation methodology.

Previous research has indicated that the presence and extent of the infarct border zone (termed also gray zone [GZ] because of its intermediate CMR signal intensity) contribute to arrhythmia propensity, thus pixels belonging to infarcted tissue are further subclassified as scar or GZ. In creating the patient’s heart model, the 3D geometries of the infarct zones are segmented and reconstructed and then merged with the ventricular geometry. Next, the 3D finite element mesh is generated using an approach developed for image-based meshes.21 Each finite element ventricular mesh has an average resolution of 350 μm as needed to adequately resolve wavefront propagation.22 Mesh generation is automatic and produces boundary-fitted, locally refined, and smooth conformal meshes, preserving the boundaries of scar and GZ as reconstructed from the MRI.

The final step in model construction is determining the fiber orientation in each element of the ventricular mesh. Patient myocardial fiber orientations cannot be currently acquired in vivo although a recent study demonstrated significant
progress toward in vivo diffusion tensor (DT) MRI. As an alternative approach, 2 methodologies have been developed to date for assigning fiber orientations on the basis of the individual geometry of the ventricles. The first is an atlas-based approach using ex vivo MRI and DT-MRI of a human heart (the atlas). Using image transformation algorithms, the atlas ventricular geometry is deformed to match that of the patient. The same deformation field is then applied to the atlas fiber orientations to obtain an estimate of patient fiber orientations. Computational simulations of ventricular activation maps and pseudo-ECGs in sinus rhythm and VT in animal hearts closely matched those using DT-acquired fiber orientations, validating the approach. The approach has been used to assign fiber orientations in a study of 2 patient-specific ventricular models. The downside of the methodology is its computational expense, limiting the approach in cases where time is crucial, as in ablation targets prediction where the time period between CMR scan and procedure is ≤24 hours. A much faster rule-based fiber orientation estimation has been developed, also assigning fiber orientations based on the individual ventricular geometry; it interpolates fiber orientations based on rules derived from fiber orientation histological and DT-MRI data. Bayer et al compared simulations of ventricular activation in a model with rule-based fibers to those in the same geometric model but with DTI-derived fiber orientation. The results demonstrated that activation patterns were nearly indistinguishable, with relative differences <6% and positive correlations >0.99, indicating a robust algorithm.

After fiber orientations were assigned, the corresponding GZ and scar masks are superimposed. The scar is considered nonconductive, thus no electrophysiological parameters, including anisotropy arising from fiber orientation, is of any consideration there. Fiber orientation in GZ, as estimated by the methodology described above, was the subject of concern because there could be some level of fiber rearrangement not captured by those methodologies. The high-resolution imaging study by Pashakhanloo et al used submillimeter resolution DT and LGE-MRI on a clinical scanner to examine the detailed organization of the infarct structure in the ventricles. The study demonstrated that the epi-to-endo progression of the DT primary eigenvector is preserved in infarcted parts of the wall in human (Figure 2) and in porcine hearts, justifying the adoption of a rule-based approach to fiber orientation estimation in the zone of infarct.

**Nonpersonalized Electrophysiological Model Parametrization**

Once the ventricular mesh is generated, average human cell and tissue electrophysiological properties are assigned to scar, GZ, and noninfarcted tissue. Scar region is considered electrically nonconductive while finite elements that belonged to noninfarcted tissue and GZ are assigned regionally uniform human ventricular cell action potential dynamics. Remodeled GZ ionic properties are represented by modifying the human action potential model with data from experimental recordings; detail can be found in recent publications showing GZ action potentials characterized by longer durations, decreased upstroke velocity, and decreased peak amplitude. Tissue properties representing human ventricular cell-to-cell electric communication are also assigned to the noninfarcted and GZ regions, with values of conductivities as described previously. GZ region is characterized with a decrease in transverse conductivity to reflect connexin-43 remodeling in the infarct border zone.

The propagation of electric activity in a virtual heart is simulated by solving, using the finite element method, a reaction–diffusion equation representing the spread of current in the ventricular myocardium, together with the ordinary differential and algebraic equations representing myocyte membrane dynamics at each node in the mesh. This approach has been experimentally validated and used in several mechanistic arrhythmia studies.

The approach to personalize virtual hearts with respect to only heart geometry and regional distribution of structural remodeling, and not with respect to the values of electrophysiological properties, as reviewed here, stands apart from previous attempts at image-based modeling of ventricular function. In such studies, personalization of electrophysiological properties was also performed, either in porcine models or in small studies of 1 to 7 patients, based on voltage measurements, demonstrating good correspondence between simulation results and VT circuit measurements. Instead, the approach reviewed here enables the construction of a virtual heart model based on noninvasive information only. It is suitable for the noninvasive assessment of the ventricular substrate arrhythmogenic propensity in patients with structural heart disease, where structural remodeling plays a major role in arrhythmogenicity. In its current form, the virtual heart approach lends itself to applications, such as the prediction of the infarct-related VT ablation targets and post-MI risk stratification for arrhythmia. As the approach evolves, the expectations are that tests will be performed to determine whether additional personalization (presence of antiarrhythmic drugs; genetic information, etc.) can further improve its predictive capability and broaden its applicability to arrhythmias resulting from different heart diseases.

**Protocol for Evaluating the Arrhythmogenic Propensity of the Ventricular Substrate**

To evaluate the arrhythmogenic propensity of the structurally remodeled substrate, each post-MI virtual heart is subjected to pacing from multiple locations to elicit reentrant arrhythmias; information about the specific pacing protocol can be found in Arevalo et al. In this way, the potential of the disease-remodeled ventricles to cause degeneration of propagation into arrhythmia after premature beats that originate at different locations in the heart can be fully assessed. Because all pacing sites are assigned automatically, typically using American Heart Association nomenclature for segment locations, the number of pacing sites uniformly distributed throughout the left and right ventricles can be chosen. In recent publications, each virtual heart was paced from at least 19 different locations. The distribution of pacing sites throughout the ventricles, and particularly the left ventricle, 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 structural remodeling distribution.
Validation of Post-MI Arrhythmia Modeling

Do arrhythmias calculated by a virtual heart, as described above, mimic the actual arrhythmias in the patient? This question is difficult to address in the clinical setting because specific pacing locations (typically in the right ventricle) during an electrophysiological study are difficult to be exactly reproduced in the model. Given a distributed morphology of GZ and scar and the propensity for arrhythmogenesis, often even small differences in pacing locations between a clinical study and model could result in a different morphology of the elicited arrhythmia, making such comparisons difficult. To do so, a prospective validation study needs to be carefully designed to ensure the pacing sites could be matched. Initial attempts in this direction have already been made, but a larger patient cohort is needed to confirm model predictions in the clinical setting.

Validation of the virtual heart approach has been instead performed in a swine model. Deng et al used sock epicardial data for infarct-related VT, obtained from 4 swine hearts, and demonstrated that models reconstructed from clinical-resolution MRI data of the corresponding hearts were able to predict fairly accurately the morphology of each VT circuit and its organizing center (eg, isthmus). Figure 3 shows VT results from 2 of the swine models and the corresponding experimentally recorded epicardial map. The simulations also reveal the nature of the transmural ventricular activity that manifests itself into epicardial activity mimicking the experimental findings. Furthermore, the study also compared models reconstructed from high-resolution ex vivo MRI of the same swine hearts with those of clinical resolution (low resolution). The organizing centers of the reentrant circuits induced in the low-resolution models closely matched...
those in the high-resolution models (difference of 11.3±4.1 mm). Because a given location is targeted by several ablations, the predicted organizing centers for the VT circuits in the low-resolution models were, for all practical purposes, colocated to the true VT circuit location predicted in the high-resolution models. Because clinical ablation usually involves the delivery of multiple lesions in 1 area, the study concluded that MRI-based computer models of MI hearts could indeed provide a unique opportunity to predict and analyze VTs resulting from specific infarct architectures.

Deng et al\(^{32}\) demonstrated that the geometric morphologies of scar and GZ, as well as the representation of differences in electrophysiological properties in noninfarcted tissue and GZ, have a primary role in determining VT inducibility and the location(s) of its organizing center. This is consistent with the findings by Arevalo et al,\(^{31}\) where a parameter sensitivity analysis of the GZ model representation was conducted. The research found, using post-MI canine ventricles models, that inclusion of small scar heterogeneities in a physiological density did not alter inducibility of infarct-related VT or its morphology. In the study, first microregions of scar were randomly distributed throughout the GZ at varying densities. After pacing from several sites, the locations of the resulting organized centers of reentrant activity (filaments) were compared with those in the corresponding homogeneous GZ model. Incorporation of microregions of scar in the GZ (Figure 4A shows the 60% case) resulted in some conduction slowing within the GZ (Figure 4B). For the typical heterogeneous cases where GZ was composed of up to 40% scar, all induced VT morphologies were fully identical to the control, and the filaments remained in the same spatial position. The study next incorporated random microregions at increasing density in the GZ, but this time these were composed of normal myocardium. The simulations revealed that models with unchanged GZ conductivities but GZ composition incorporating up to 80% normal tissue exhibited the same VT morphology as in control; VT cycle lengths also did not differ significantly from the control. This study provided the justification for the use of uniform GZ properties in the virtual heart models and established that even fairly substantial changes in model parameters had minimal effects on model predictions.

**Feasibility of Using Virtual Hearts to Estimate Ablation Targets**

Figure 5 presents the concept of using patient-derived virtual hearts to predict optimal ablation targets. It substitutes the invasive mapping to determine the arrhythmia critical

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**Figure 3.** Comparison of simulation and experimental results in 2 infarcted pig hearts. A, Reconstructed models with the epicardium rendered semitransparent. Scar and gray zone (GZ) appear in red and purple, respectively. B, Activation maps of simulated ventricular tachycardias with breakthrough patterns on the epicardium. C, Endocardial views showing reentrant source. D, Experimentally recorded epicardial activation map. Pink arrows denote propagation direction. Adapted with permission from Deng et al\(^{32}\) under the Creative Commons license. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

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**Figure 4.** Sensitivity of electric activity in the canine ventricular model to gray zone (GZ) electrophysiological properties. A, Model with 60% scar in GZ (white speckles). Myocardium is colored in red, scar and GZ are yellow and green, respectively. B, Time needed to fully activate GZ by propagation as a function of scar density in GZ. Adapted with permission from Arevalo et al\(^{31}\) under the Creative Commons license. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
pathways with evaluation of model VT circuits. From the simulated VTs, ablation targets can be determined and then implemented in the virtual heart as nonconductive lesions to simulate ablation and determine whether the lesions result in VT noninducibility from any pacing site. It is possible that after ablation new VT circuits could be formed in the virtual heart. They will then be evaluated and the appropriate ablation targets determined. The process can be repeated until complete noninducibility is achieved. The resulting set of ablation targets could then be loaded into the 3D electroanatomic mapping system so that the ablation catheter is navigated during the procedure to the model-predicted targets. VT ablation would then be swift and precise, eliminating VT circuits with minimum lesions and maximum chance of VT noninducibility.

Although such an approach has not yet been prospectively implemented clinically, initial steps toward it have already been made. Ashikaga et al. conducted a retrospective study in 13 patients who had preablation MRI for infarct-related VT ablation. Simulations with patient-specific models induced VTs and estimated targets according to the simulated circuits. Comparisons between simulation results and clinical recordings were made in 11 patients. In 5 patients, VT circuits were of the figure-of-8 reentry pattern (Figure 6A and 6B). The central common pathway was located over the GZ or the superficial layer of the viable myocardium over the scar. In this type of circuit in the virtual hearts, the target region was estimated to be an area bordered by 2 facing lines of conduction block that compose the isthmus (Figure 6A and 6B, green area in right-most column). An ablation line between the 2 facing conduction block lines was expected to prevent VT recurrence, and the minimum length of this hypothetical ablation line (ie, narrowest isthmus width) was quantified. In 7 patients, virtual heart VT circuits were of unidirectional reentry pattern (Figure 6C), and the target region was estimated to be a triangular area that connects the closer end of the conduction block line to an adjacent anatomic barrier (eg, mitral annulus); the minimum length of this hypothetical ablation line was also quantified.

The comparison between the estimated ablations in simulations and in the standard clinical approach showed that these are highly consistent (82%); in 9 of 11 cases, ablation within the estimated target region was associated with acute success (n=8), and ablation outside the estimated target region was associated with failure (n=1). The results of this study indicated that virtual heart simulations could be used to estimate ablation targets. The simulation results also determined that the narrowest width of the target region that an ablation line should span to prevent VT recurrence was relatively small (5.0±3.4 mm). This indicated that the preprocedural estimation of the location and the size of the target region by simulation would likely help reduce procedure time.

Although the study did not perform model ablation and postablation tests of VT noninducibility, it demonstrated that this approach could have value in the clinic. To fully ascertain the potential of the virtual heart approach in predicting the optimal ablation targets, research needs to demonstrate its ability to determine, using a verified operator-independent algorithm, the optimal ablation targets that terminate all VTs, rather than applying the currently clinical decision-making process to the VT circuits in the virtual heart. Such an approach was recently undertaken in predicting the ablation targets for macro-reentrant atrial tachycardia and could also be applied to infarct-related VT ablation. Noninducibility studies after the in silico ablation will need to also be conducted to verify that no new VTs arise postablation, and if they do, to determine the additional ablation targets. Importantly, the use of the approach can only be verified in a prospective study, requiring the overcoming of technical barriers associated with merging the predicted targets with the 3D electroanatomical navigation system. Finally, research will need to validate that the lesions specified by the in silico studies can actually be generated in a patient. Imaging methods can validate this directly. It has been shown that the extent of ablation lesions can be determined with LGE MRI, as well as with noncontrast methods, during or just after an actual ablation procedure. Prospective studies are needed, therefore, to compare directly the results from in silico predictions, with those of actual ablation, where lesion extent is quantified with MRI.

Using Virtual Hearts to Stratify Arrhythmia Risk in Post-MI Patients

In this application of the virtual heart approach to post-MI patients, the multisite delivery of ventricular stimuli was used to determine the patient’s heart propensity to develop infarct-related ventricular arrhythmias. Arevalo et al. termed this noninvasive SCD risk assessment approach virtual heart.
arrhythmia risk predictor (VARP). Because the goal of electrically stressing out the ventricular substrate is to only determine presence of reentrant arrhythmia (or the lack thereof) as the result of pacing from at least 1 site, this application is conceptually simpler and less computationally demanding than the ablation guidance described above, allowing for evaluation of the predictive capability of the approach in a larger patient cohort, and for comparison with other clinical metrics.

The retrospective proof-of-concept study by Arevalo et al.17 used data from 41 patients with prior MI and LVEF <35%, chosen randomly from those enrolled in the CMR-Prospective Observational Study of Implantable Cardioverter Defibrillators.38 Patients were followed for the primary end point of appropriate ICD firing because of ventricular arrhythmia or cardiac death. Follow-up time averaged 4.8±2.9 years. VARP predictive capabilities were compared with LVEF, as well as to other clinical metrics, that have been used to predict arrhythmic risk, such as GZ volume,49 scar volume,50 and left ventricular mass.51 Furthermore, 32 of the 41 patients in the cohort underwent, at the time of ICD implantation, clinical electrophysiological testing; for these 32 patients, VARP assessment was also compared with the outcome of the clinical testing. Figure 7 presents 7 reconstructed patient heart models; induced arrhythmia is shown in 2 models (transmembrane

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Figure 6. Magnetic resonance imaging (MRI)–based simulation approach for estimating infarct-related ventricular tachycardia (VT) ablation targets. Each row represents a different patient (A–C). The simulation column shows calculated isochrone maps of VT. Green arrows indicate direction of propagation. Lines of conduction block are in blue. MRI-based model column presents models constructed from preablation MRIs (scar: orange; GZ: yellow; noninfarcted myocardium: gray). The lines of conduction block (blue lines) from the simulations and the ablation sites (red circles) from the clinical approach are coregistered on the model geometry. The estimated target region column shows a potential target region (green area) estimated from the simulations. The shortest possible line of ablation that spans the target region (ie, narrowest width of the isthmus) is shown in cyan color. Clinical ablation sites that fell within the green area are indicated by yellow circles. The first 2 simulation results in this figure (patients A and B) show a figure-of-8 pattern, and the last simulation result (patient C) shows a unidirectional reentry. Adapted with permission from Ashikaga et al.45 Copyright © 2013, Elsevier. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
potential and activation maps), with reentrant waves often propagating through isthmuses in the scar. In the 5 models shown at Figure 7, bottom, no arrhythmia was induced from any pacing site, despite the presence of infarcted tissue.

Statistical analysis demonstrated that a positive VARP test was significantly associated with the primary end point, with a 4-fold higher arrhythmia risk than patients with negative VARP test. The comparison of VARP with LVEF, as well as with GZ volume, scar volume, and left ventricular mass, revealed that only VARP outcome was significantly associated with arrhythmic risk in this small cohort. When only appropriate ICD shock was used as a secondary end point, the hazard ratio for VARP increased from 4.05 to 5.0. Among the 32 patients who had both VARP and invasive testing, the hazard ratio for VARP was 10.4 versus 1.7 for clinical electrophysiological testing. For the appropriate shock end point, the hazard ratio for VARP remained significant at 8.60 versus 2.60 for clinical testing. It is important to note that the noninvasive nature of VARP offers an additional advantage over clinical testing, which entails risks of vascular access, sedation, and induction of ventricular arrhythmias requiring defibrillation in already tenuous cardiomyopathy patients.

The superiority of the VARP approach, as demonstrated by Arevalo et al., stems from its ability to comprehensively evaluate the arrhythmogenic propensity of the MI substrate as probed by triggers acting at locations of different geometric position with respect to remodeled tissue. Should the predictive capability of the approach be demonstrated in larger studies, VARP has the potential to radically change the process of SCD risk assessment and patient selection for prophylactic ICD implantation, potentially eliminating many unnecessary ICD implantations and their associated complications (infections, device malfunctions, and inappropriate shocks).

Importantly, as acknowledged by Arevalo et al., VARP could be applied to patients with prior MI but preserved LVEF >30% to 35%, who could also be at significant risk for arrhythmia because of their remodeled myocardium, but are generally not targeted for therapy under current clinical recommendations. Because current guidelines for ICD placement target low LVEF patients who constitute only one third of SCD victims, VARP has the potential to identify increased SCD risk in a much larger number of at-risk patients. The first step in this direction was recently made by Deng et al., who applied VARP in the analysis of data from 4 patients with MI and average LVEF of 44.0±2.6%. VARP correctly predicted the occurrence of VT in 1 patient and the lack thereof in the remaining 3, as shown in Figure 8.

Concluding Remarks and Outlook
The immense potential of simulation-driven applications in cardiac patient care has been recognized in several recent reviews, arguing that clinical translation of physiological models will transform medical practice. However, getting to the
point of translation is a long road, and success has been variable depending on the specific applications. In this review, we examined recent advances in using physics-based physiological models in the diagnosis and treatment of cardiac arrhythmias. Initial applications have focused on structural heart disease, necessitating the development of geometric models from clinical images so that structural remodeling of the ventricular substrate could be adequately represented. It is important to note that these models do not and cannot fully reflect the biology of remodeling. The goal is to create a clinically useful tool that, while having mechanistic underpinnings, can also be successfully used in the clinic to improve diagnostics (SCD risk) or noninvasively guide therapies (VT ablation). This requires a balance between model execution time and the level of model detail. As further progress is made, such balance will need to be disease specific, and decisions about model complexity will need to be made within the constraints of the given clinical application.

Although initial successes of the virtual heart approach provide a glimpse into the potential of the technology, its development to full potential and use in the clinic are dependent on several current limiting factors; overcoming these will ensure easy and straightforward implementation in the clinic. Some of these include:

1. Contrast-enhanced image quality and standardization. The quality and resolution of clinical images is paramount to image-based model construction. Improvements in the quality of cardiac MR and standardization of image acquisition across clinical centers will ensure consistently high quality of the patient-specific virtual hearts. Alternatively, computed tomographic scans could be used, should there be a possibility for acquiring contrast-enhanced images of remodeled heart structure at high signal-to-noise ratio.

2. Accelerated image processing with minimum manual input. Image processing of clinical-quality cardiac scans is a dynamic field, with major advancements made particularly in reconstructing ventricular shape over just minutes. Reconstruction of enhanced regions of remodeling has seen less advancement, but remains crucial to model construction, and in need of new algorithms that will decrease time and manual input.

3. Algorithmic developments to decrease model execution times. The need to execute calculations of VT circuits and ablation targets in a limited interval of time consistent with procedure and patient care timelines imposes major constraints on the simulation process because the electrophysiological simulation code is computationally demanding. Additional speed up and development of lightweight application-adjusted electrophysiological simulators would relieve this burden.

Further developments of the virtual heart approach are expected to extend to diagnosis and arrhythmia risk stratification in other disease conditions, such as tetralogy of Fallot and nonischemic and hypertrophic cardiomyopathies, as recent preliminary data demonstrate. Importantly, the approach is also extendable to predicting ablation targets for atrial arrhythmias. A retrospective study using the virtual heart approach to predict targets for atypical atrial flutter ablation in 10 patients with atrial fibrotic remodeling demonstrated excellent correspondence to clinical targets. Finally, although the approach has not yet been used to find ablation targets for persistent atrial fibrillation, a recent study by Zahid et al demonstrated the ability to create atrial patient-specific models from CMR-LGE scans that predicted atrial fibrillation reentrant drivers consistent with clinical recordings. Advancements in the virtual heart methodology and its applications could thus

Figure 8. Ventricular models for 4 patients with myocardial infarction and preserved left ventricular ejection fraction. Virtual heart from patient 1 (top; model shown on left and in semitransparent view in middle) had inducible ventricular tachycardia (isochronal map top right; purple arrows show direction of propagation of reentrant arrhythmia). Models from patients 2 to 4 (bottom) demonstrated no inducible arrhythmia. Adapted with permission from Deng et al. Copyright © 2016, Oxford University Press. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
10  Trayanova et al  Simulations to Stratify VT Risk and Guide Ablation

help usher several personalized medicine approaches in cardiac patient care.

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