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Request for Information on the National Digital Twins R&D Strategic Plan

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Up digital and personal: How heart digital twins can transform heart patient care

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ABSTRACT

Precision medicine is the vision of health care where therapy is tailored to each patient. As part of this vision, digital twinning technology promises to deliver a digital representation of organs or even patients by using tools capable of simulating personal health conditions and predicting patient or disease trajectories on the basis of relationships learned both from data and from biophysics knowledge. Such virtual replicas would update themselves with data from monitoring devices and medical tests and assessments, reflecting dynamically the changes in our health conditions and the responses to treatment. In precision cardiology, the concepts and initial applications of heart digital twins have slowly been gaining popularity and the trust of the clinical community. In this article, we review the advancement in heart digital twinning and its initial translation to the management of heart rhythm disorders.

KEYWORDS Heart digital twins; Arrhythmia; Atrial fibrillation; Sudden cardiac death risk prediction; Ablation

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Precision medicine is envisioned to provide therapy tailored to each patient. The rapidly increasing ability to capture extensive patient data, coupled with machine learning, a powerful tool for processing massive amounts of data and identifying correlations in it, is a pathway to achieve this vision. A different pathway toward precision medicine is the increasing ability to encode known physics laws and physiology knowledge within mathematical equations and to adapt such mechanistic models to represent the behavior of a specific patient.

The expectation is that it will be highly beneficial to have a digital representation of ourselves. A digital doppelgänger that is tailored to represent our own unique physiology, structure, biophysical processes and even diseases could allow health care professionals to simulate our personal medical history and health conditions using relationships learned both from data and from biophysics knowledge. That virtual replica of ourselves would integrate data-driven learning and multiscale physics-based modeling and will update itself, either continuously with data from monitoring devices, or intermittently with data from health care provider (hospital or physician) visits and tests. It will thus reflect the changes in our health conditions because of interactions with the environment, changes in lifestyle, and changes in response to medical interventions These *digital twins* (DTs) would forecast the trajectory of a patient's disease, estimate the risk of adverse events, and predict treatment response so that the potential outcome would inform treatment decision.

A DT is a virtual replica of a physical object, person, or process that can be used to simulate its behavior. This dynamic model represents both the components of a system and their ongoing interaction. Digital twinning is not a new concept—DTs have been used to replicate many real-world entities, from equipment life cycles through to entire manufacturing processes,[1] as they allow one to oversee the performance of an asset, identify potential faults, and make well-informed decisions about maintenance and global performance. In health care, the DT represents the vision of a virtual tool that integrates dynamically clinical and/or tracked data acquired over time for an individual and predicts behavior using comprehensive multiscale mechanistic simulations based on physiology knowledge and physics laws.

In precision cardiology, over the last decade, the concepts and initial applications of heart DTs have slowly been gaining popularity and the trust of the clinical community. Pathways forward have been charted,[2,3] and current developments[4–7]

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have been assessed. Figure 1 presents a flowchart of the clinical workflow using heart DTs and their envisioned applications for clinical decision support in the diagnosis and prognostication of the patient's disease trajectory as well as for guiding treatment that is optimized by considering the patient's response to the potential therapy.

One of the most advanced heart DT applications is in the management of heart rhythm disorders, with major developments in the field reviewed in this article. The present article is the review of the body of work of each year's recipient of the Gordon Moe lectureship presented by the Cardiac Electrophysiology Society. Dr Trayanova was this year's recipient, and this review article summarizes her work and that of her team at Johns Hopkins University on the development and application of heart DTs for the management of atrial and ventricular arrhythmias (VAs).

DTs for atrial arrhythmia management

Atrial fibrillation (AF) is the most common heart rhythm disorder, having a prevalence of 1%–2% worldwide. It is associated with embolic stroke, heart failure, and cardiovascular hospitalization and death.[8] Patients with AF have increased rates of cognitive impairment and a diminished quality of life.[9] The growing burden of AF and the high rate of health care expenditures associated with its management have led to a large body of basic and clinical research aimed at uncovering both a permanent cure of AF and an improved AF management strategy. Computational modeling of the atria and personalized atrial DT technologies have been and continue to be an integral part of these developments.

An important focal point in these efforts, including ours, has been the representation, in personalized DTs, of fibrotic remodeling that takes place in the atria of (aging) patients, and particularly in those experiencing the persistent form of AF (PsAF). In these patients, the mechanisms giving rise to AF shift from electrical abnormality in the pulmonary veins (PVs) to recirculating electrical waves (reentries) perpetuated by the fibrotic substrate. Personalized DT technologies have provided understanding of how fibrotic remodeling results in the turbulent propagation associated with AF and have suggested management strategies, some of which have been tested in prospective studies. Before this review, we and others have reviewed different aspects of computational modeling of the human atria.[6,10–12]

Abbreviations

AF: atrial fibrillation

ARVC: arrhythmogenic right ventricular cardiomyopathy

CT: computed tomography

DT: digital twin

Geno-DT: genotype-specific heart digital twin

inFAT: penetrating adipose tissue

MRI: magnetic resonance imaging

OPTIMA: OPtimal Target Identification via Modelling of Arrhythmogenesis

SCD: sudden cardiac death

VT: ventricular tachycardia

In developing a personalized atrial DT that represents the patient-specific fibrosis remodeling, the process commences with the assessment of the patient's clinical contrast enhanced (late gadolinium enhancement [LGE])–magnetic resonance imaging (MRI) scan, typically a 3-dimensional scan of higher resolution to resolve the thin atrial walls.[13,14] In addition to providing information on atrial shape, MRI imparts excellent heart tissue characterization, as gadolinium-based contrast agents accumulate in scar and fibrotic tissue.[15] Areas on LGE-MRI scans correspond to areas of scar and fibrotic remodeling, with the high image intensity corresponding to deep scar. Reconstruction of atrial geometry requires segmenting the chambers and the remodeled tissue from the LGE-MRI scan; the study by McDowell et al[16] was the first to reconstruct a personalized DT incorporating fibrotic remodeling. The threshold for fibrosis segmentation is not well established and remains controversial. We have used a version of the image intensity ratio since it uses ratiometric values instead of raw voxel intensities. Our team also reconstructed, for the first time, the personalized fibrotic remodeling in the right atrium (RA) of patients; we adapted the image intensity ratio for RA fibrosis.[17] Figure 2A presents a number of reconstructed biatrial models of patients with PsAF and fibrosis. In addition, atrial DTs incorporate fiber orientations to ensure realistic conduction patterns. Reconstruction of personalized atrial DTs in our translational research has involved the use of atlas human fiber orientations,[18] acquired from explanted human hearts using diffusion-tensor MRI[19] (Figure 2B), which visualize the fiber tracts in the myocardium. These are then assigned in the patient-specific geometric model with the use of a universal atrial coordinate system.[20]

In our translational work aimed at improving AF management, personalization of atrial DTs was done predominantly on the basis of patient-specific disease remodeling, where distinct electrophysiological (EP) properties are assigned in different regions on the basis of image intensity. This has been a deliberate choice, as our intention has been strategically down the road, to develop noninvasive technologies for the prognostication and treatment of AF. Several research groups have instead chosen to personalize the EP properties from invasive intraprocedural measurements.[21,22] Instead, we developed, on the basis of clinical measurements in patients with AF, a set of baseline EP properties[23] that could be modified, when needed, to explore different arrhythmogenic mechanisms. These included, but were not limited to, exploration of the effect of potential myocyte-fibroblast interactions[24,25] and arrhythmogenesis related to calcium-driven alternans in AF.[26,27] For instance, in the latter study, we found that elevated Ca^{2+} alternans propensity due to decreased ryanodine receptor inactivation, and development of repolarization alternans at slower heart rates, resulted in increased ectopy-induced arrhythmia vulnerability, complexity, and persistence because of increased repolarization heterogeneity and wavebreak.

Our atrial modeling studies strongly support the notion that the extent and distribution of atrial fibrosis are critical determinants of AF initiation, maintenance, and reentrant driver dynamics during AF. Although presence of a certain amount of fibrosis is sufficient for the initiation of AF in simulations, we found that patient-specific fibrosis distribution determines

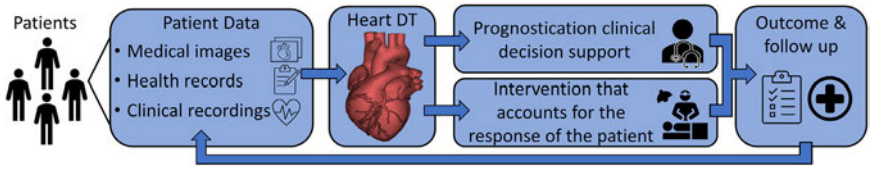

Figure 1
Flowchart of the clinical workflow using heart digital twins (DTs).

reentrant driver dynamics.[28] The study by Zahid et al[29] took this understanding further, demonstrating, in a cohort of 20 patients, that reentrant drivers induced in the fibrotic substrate by rapid pacing persist only in areas with highly specific spatial patterns of fibrosis. The study was the first to construct atrial DTs of both the left atrium (LA) and the RA. Fibrotic spatial patterns were characterized by calculating, from the 3-dimensional LGE-MRI scans, maps of fibrosis density and fibrosis entropy. Local fibrosis density indicates the proportion of fibrotic elements among all elements surrounding the given location, while local fibrotic entropy quantifies the degree of disorganization between fibrotic and nonfibrotic elements in the local neighborhood. All the reentrant drivers that could be induced in each remodeled substrate persisted in the zone of fibrotic boundaries characterized by high fibrotic density and fibrotic entropy. Fibrotic patterns with such specific regional fibrosis metrics correspond to atrial areas with a high degree of intermingling between fibrotic and nonfibrotic tissue. The findings of this atrial DT study were subsequently validated[30] with clinical data (electrocardiographic imaging).

Potentially the most transformative clinical application of atrial digital twinning is the development of personalized PsAF ablation strategies, tailored to each patient's unique (fibrotic) atrial substrate. While PV isolation (PVI), the electrical isolation of PV arrhythmia triggers, is the standard of care for patients with symptomatic AF,[31,32] in patients with PsAF and atrial fibrosis, AF recurrence rates after PVI are high,[33,34] resulting in freedom from AF of only 40%–50% 1-year postprocedure. The presence of regions of fibrosis that extend beyond the traditional wide-area PVI and have arrhythmogenic propensity could explain PVI's ineffectiveness in patients with atrial fibrosis. Establishing noninvasively whether PVI will result in subsequent AF recurrence in a patient with atrial fibrosis, and if so, determining before the ablation procedure the custom-tailored extra-PVI ablation targets that will deliver long-term freedom from AF could result in dramatically improved treatment efficacy and reduce the need for

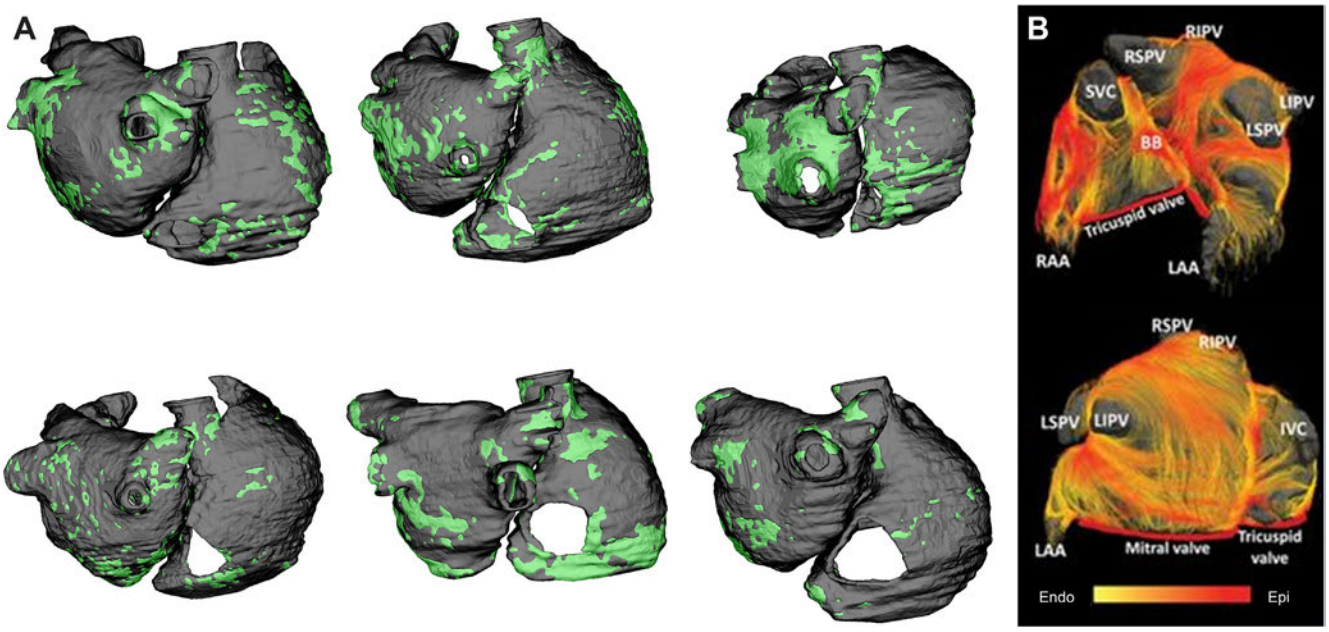

Figure 2
Developing personalized atrial digital twins (DTs). **A:** Reconstructed biatrial geometries from 6 patients with persistent atrial fibrillation. Fibrosis distribution is in *green*. **B:** Human fiber orientation acquired from explanted human hearts and used as fiber atlas for DT construction. BB = Bachman bundle; Endo = endocardium; Epi = epicardium; IVC = inferior vena cava; LAA = left atrial appendage; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RAA = right atrial appendage; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein; SVC = superior vena cava. Modified with permission from Pashakhanloo et al.[19]

repeated ablation procedures. In this, atrial digital twinning has found its calling.

McDowell et al[28] was the first study to demonstrate, as a proof of concept, that LA DTs reconstructed from the patient's LGE-MRI scans (n = 4) can be used to predict ablation targets in the fibrotic substrate. The targets were the locations in the fibrotic substrate where reentrant drivers (rotors) form after rapid pacing from locations in the substrate. Executing this virtual ablation strategy in the LA DTs rendered the atrial model noninducible for reentry. Having demonstrated the potential utility of atrial DTs in predicting ablation targets, we also assessed whether the predicted targets would be affected by different baseline cellular EP properties. In a sensitivity analysis,[35] we varied atrial action potential duration or conduction velocity to address this question. These changes resulted in different likelihoods that a location in the fibrotic substrate would sustain a reentrant driver. However, Hakim et al[36] demonstrated that this uncertainty was mitigated by first executing reentrant driver ablation procedures followed by repeat inducibility tests to evaluate the occurrence of any emergent reentrant drivers postablation. In other words, depending on the baseline EP properties in the patient's atria, locations in the fibrotic substrate will give rise to rotors either on the first inducibility test or on the subsequent inducibility tests probing for emergent rotors postinitial ablation, with the sequence determined by the patient's EP properties. Thus, as long as both initial and emergent drivers were captured, the DT with the baseline AF EP properties would be a useful clinical tool to provide personalized guidance in AF ablation.

Boyle et al[17] pioneered a prospective ablation study for patients with PsAF and fibrosis entirely guided by personalized atrial DTs. In this landmark study termed OPTIMA (OPtimal Target Identification via Modelling of Arrhythmogenesis), 10 patients were enrolled. The locations of reentrant drivers were determined following a reentrant driver inducibility test. These locations in the DT atrial substrate were then ablated virtually. In essence, the OPTIMA DT approach for guiding AF ablation is a targeted substrate ablation approach, where locations in the fibrotic substrate capable of sustaining reentrant drivers are discerned and ablated to eliminate that capability. After ablation, the DT inducibility test was repeated, and if there were aroused new locations that were capable of sustaining reentrant activity in the new (fibrosis plus initial ablation) substrate, then these emergent activities were also targeted with ablation until a set of optimal ablation targets was found that results in a complete arrhythmia noninducibility of the substrate. The proposed ablation targets were then used to steer patient treatment during the procedure, eliminating not only the clinically manifested AF but also any potential emergent AF drivers. Figure 3 shows the OPTIMA flowchart, illustrated with one of the patients in the prospective clinical study. While very

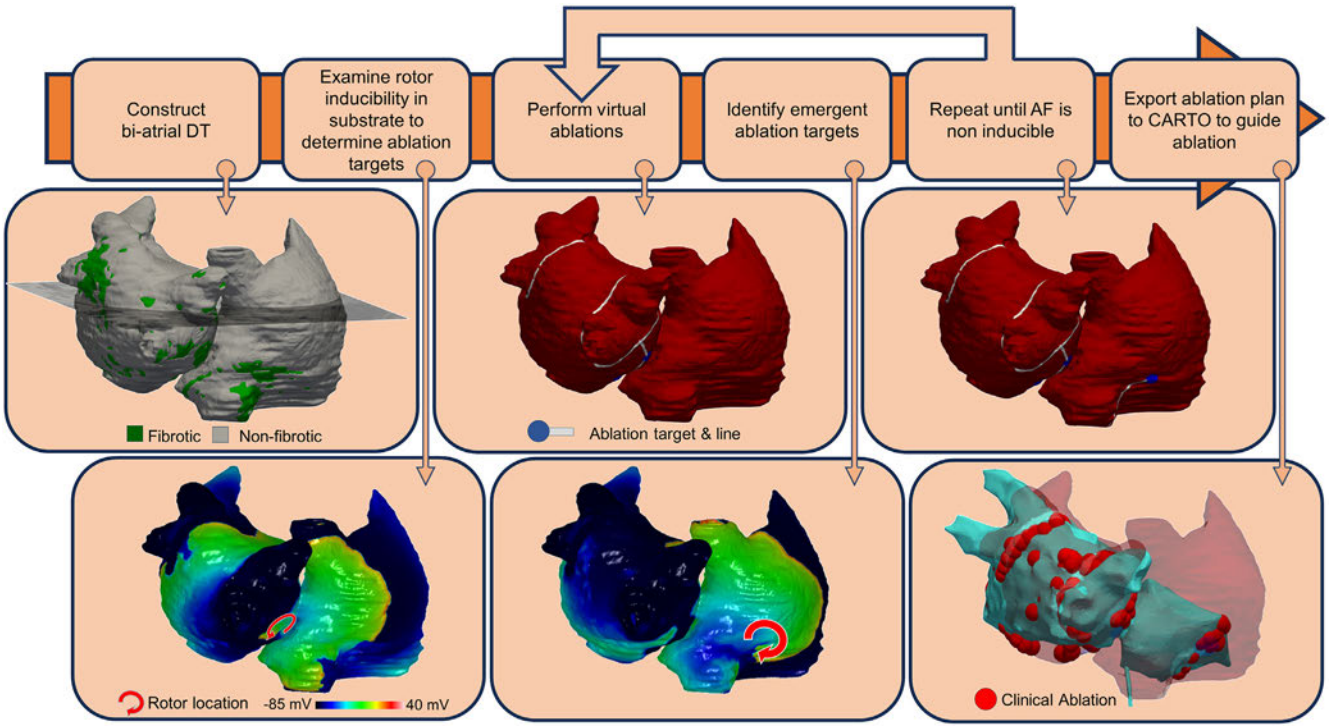

Figure 3
Flowchart of the OPtimal Target Identification via Modelling of Arrhythmogenesis approach using personalized heart digital twins (DTs). The individual steps are illustrated with the DTs of one of the participants in the study. Late gadolinium enhancement–magnetic resonance imaging scans were used to construct the patient's biatrial geometry and fibrosis distribution. After a baseline inducibility test, one location at the left atrial anterior septal wall was determined to have a high likelihood of sustaining a rotor (**bottom left**). After virtual ablation procedures targeting the detected location, a repeat inducibility test identified an emergent rotor location at the right atrial posterior region (**bottom middle**), which was then ablated. The final optimal ablation targets resulted in a complete arrhythmia noninducibility of the substrate. The proposed targets were imported to the CARTO system to guide the ablation procedure. AF = atrial fibrillation.

successful, the efficacy of this study is now being tested in a Food and Drug Administration–approved randomized controlled clinical trial (ClinicalTrials.gov identifier NCT04101539). Atrial DTs have also been used to determine how to ablate patients with atypical flutter.[37] The use of atrial DT-driven ablation has also been compared to other approaches, such as focal impulse and rotor mapping or electrocardiographic imaging.[38–40]

Inadequate modification of the atrial rotor-sustaining fibrotic substrate may explain AF recurrence after failed PVI. In a retrospective longitudinal study of 12 patients with AF who underwent pre- and postablation LGE-MRI, Ali et al[41] aimed to evaluate, using LA DTs, the postablation changes in arrhythmogenic substrate and to establish whether failure of AF ablation resulted from inadequate termination of preablation rotors or emergence of new rotors postablation. The research demonstrated that recurrent AF after PVI in the fibrotic atria may be attributable to both the existence of locations in the substrate capable of sustaining rotors that were not modified/eliminated by ablation and the emergence of new rotor-sustaining locations after ablation. The same levels of fibrosis entropy and density that underlie propensity to rotor formation in the preablation substrate hold true for the postablation substrate as well, providing a uniform framework to understand fibrosis-induced arrhythmogenesis. These conclusions led to the development of a strategy to predict, preprocedure before PVI, which patients are most likely to experience AF recurrence after PVI. To achieve that, Shade et al[42] combined LGE-based atrial digital twinning with machine learning in a proof-of-concept study of 32 patients. The algorithm used as input results of rotor induction simulations in the fibrotic substrate with imaging features derived from pre-PVI LGE scans (Figure 4). The machine learning classifier to predict the probability of AF recurrence post-PVI achieved an average validation sensitivity and specificity of 82% and 89%, respectively, and a validation area under the curve of 0.82. The study presented a highly generalizable AF recurrence predictor, despite the small training data set.

With the further development of the DT technology, the hope is that outstanding questions pertaining to AF

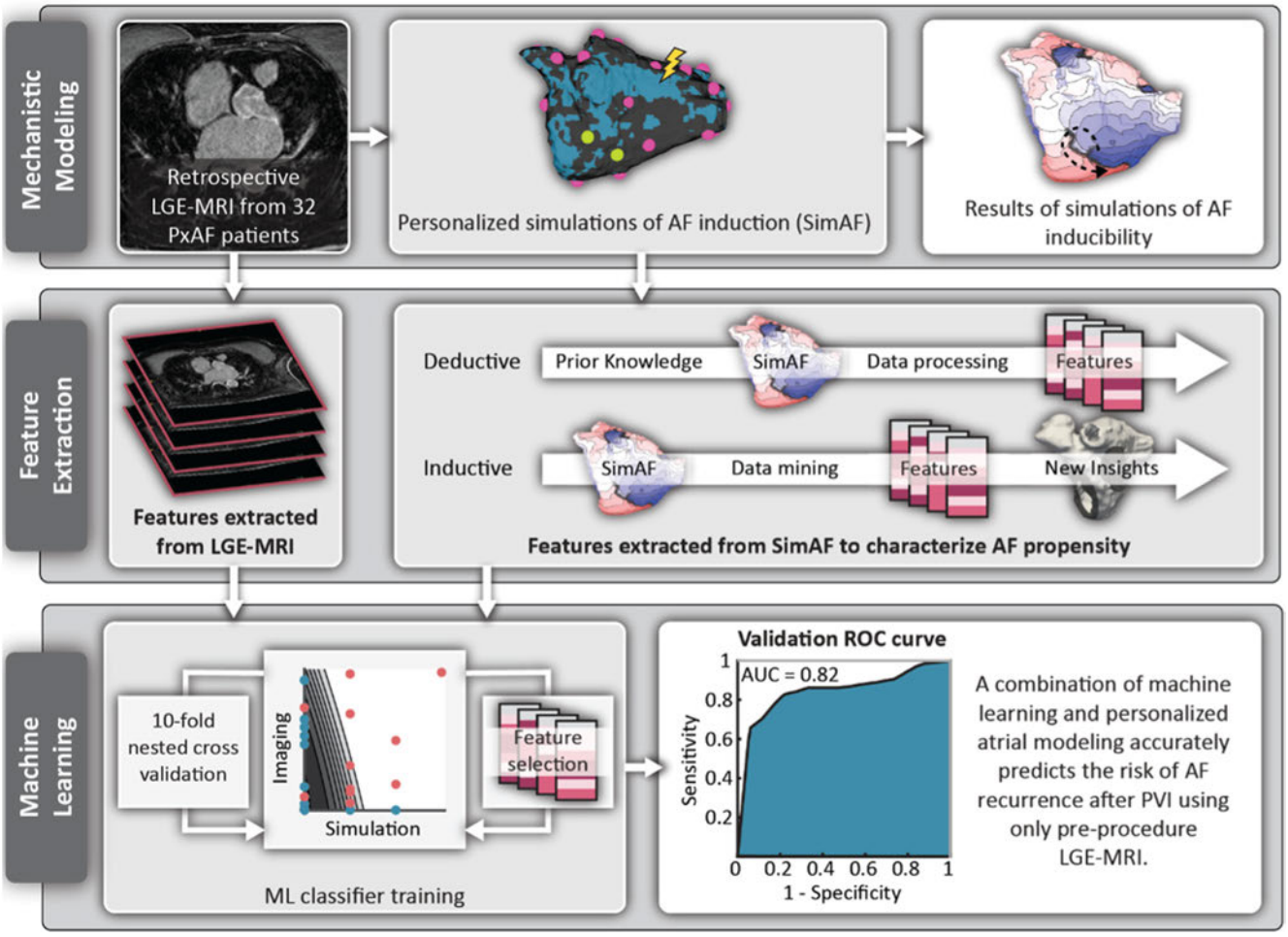

Figure 4
Predicting atrial fibrillation (AF) recurrence post–pulmonary vein isolation (PVI) by using the results of simulations with atrial digital twins (DTs), and training a machine learning (ML) classifier to predict, preprocedurally, clinical outcome. Features in DT simulation results can be extracted in 2 ways: deductively and inductively. AUC = area under the curve; LGE-MRI = late gadolinium enhancement–magnetic resonance imaging; PxAF = paroxysmal atrial fibrillation; ROC = receiver operating characteristic. Modified with permission from Shade et al.[42]

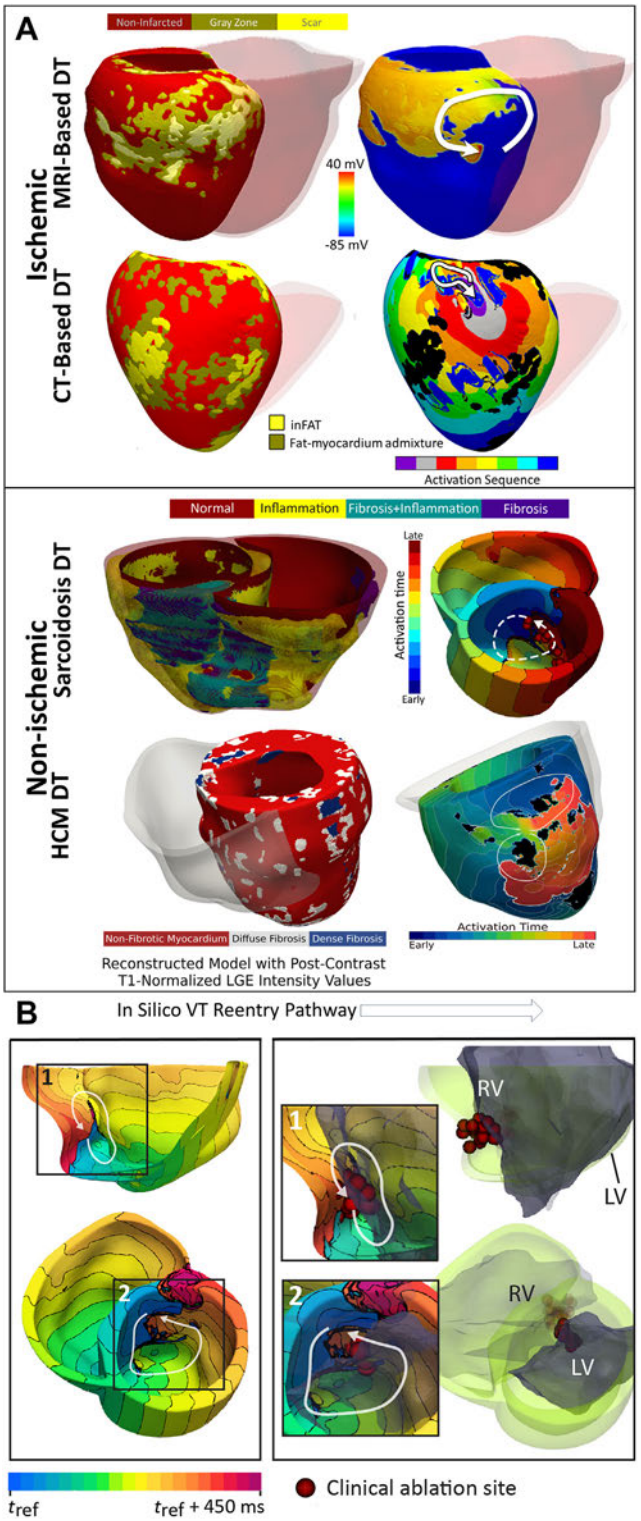

Figure 5

A: Personalized ventricular digital twins (DTs) with the corresponding predicted ventricular tachycardias (VTs). Shown here are the DTs of patients with ischemic cardiomyopathy (**upper box**) reconstructed from late gadolinium enhancement–magnetic resonance imaging (LGE-MRI) (**top**)[43] and computed tomography (CT) (**bottom**)[44] scans. The **lower box** shows the DT of a patient with sarcoidosis, which incorporates the region with inflammation detected from the positron emission tomography scan (**top**). Modified with permission from Shade et al.[45] Post-contrast T1 mapping scans were used to personalize the detection of diffuse and dense fibrosis in the DT reconstruction of a patient with hypertrophic cardiomyopathy (HCM; **bottom of the lower box**). Modified from O'Hara et al[46] (permission exempt per https://elifesciences.org/terms). **B:** Validation of the personalized DT of a patient with sarcoidosis with clinical ablation data. Two in silico VTs were induced in the DT (*white arrows*). The *red spheres* show the location of the clinical ablation lesions recorded in the patient electroanatomic mapping (EAM) data during the procedure. The EAM data co-registered to the DT show the correspondence between the predicted VTs and the clinical ablation lesions. inFAT = penetrating adipose tissue; LV = left ventricle; RV = right ventricle; t_{ref} = reference time point. Modified from Shade et al[47] (permission exempt per https://creativecommons.org/licenses/by-nc/4.0/).

management will also be addressed. These include why some patients with fibrosis never develop AF, whether PVI will be the required strategy if ablation lesions in the fibrotic substrate eliminate its ability to sustain reentrant activity, or what are the important characteristics of the substrate that render it arrhythmogenic in patients with AF.

DTs for VA management

Personalized ventricular DTs have also made significant contributions toward being part of the clinical management of VAs. Such DTs have been constructed and used for a number of cardiomyopathies, both ischemic and nonischemic. Construction of ventricular DTs follows the general steps as outlined for atrial DTs, with the difference that in addition to using LGE-MRI for model construction, other imaging modalities have been used, often developing a personalized DT by fusing the different clinical images to represent different types of structural remodeling and functional remodeling (eg, inflammation). Figure 5A shows ventricular DTs reconstructed from various imaging modalities.[43–46] Frequently, before being used to suggest clinically relevant decisions, personalized DTs have been validated with clinical data (Figure 5B). Below we review 2 major clinical applications of computational modeling: the prediction of sudden cardiac death (SCD) due to arrhythmias in various diseases and the use of computational modeling to advance and ultimately provide guidance in arrhythmia treatment by catheter ablation.

Personalized ventricular DT studies have been compelled to address the issue of predicting the risk of SCD. It is an important clinical issue, as worldwide the prevalence of SCD, already high, is on the rise; it results predominantly from VAs, particularly in patients with prior heart disease. Accurate SCD risk assessment is thus crucial to enable primary prevention of SCD via the deployment of implantable cardioverter-defibrillators (ICDs).[48] Currently, the decision is based on a single clinical metric, which is not sensitive.[49] Thus, many patients receive ICDs without deriving any health benefit[50] (90%–95% of implanted ICDs are never used), whereas others are not protected, dying suddenly in the prime of their life. The conventional approach to SCD risk stratification has been to search for biomarkers that correlate with increased SCD risk. However, thus far, no biomarkers have enabled an accurate SCD risk assessment. Thus, inadequate SCD risk assessment poses a large public health and socioeconomic burden and remains a major unmet clinical need.

The study by Arevalo et al[51] demonstrated the first use of DTs of a cohort of patients with ischemic cardiomyopathy (n =

41) to determine the patients' propensity to develop infarct-related VAs and SCD. All patients were with reduced left ventricular (LV) ejection fraction (<35%), thus deemed of high SCD risk, and all underwent ICD deployment. The patient's risk was assessed on the basis of whether arrhythmia was inducible from any of the numerous pacing sites tested in the DT; if it did, the patient was deemed at high risk. The comparison of the predictive capabilities of this DT approach with those of other clinical risk assessment metrics, including left ventricular ejection fraction and other imaging variables, revealed that only the outcome of the heart DT was significantly associated with arrhythmic risk in this patient cohort. The study demonstrated that DTs of patients with prior infarction can be used to determine which patients should have prophylactic ICD implantation for primary prevention. In addition, in a small proof-of-concept study, SCD risk was investigated in a small cohort of patients with myocardial infarction and preserved ejection fraction with the DT results matching clinical outcome.[52] A more complex approach to the development of DTs of patients with prior infarcts was recently presented,[53] where the patient heart DT also incorporated the distribution of penetrating adipose tissue (inFAT), which develops in infarcts >3 years old. This was a 2-center prospective clinical computational study, where enrolled patients underwent both LGE-MRI and CT (n = 24). inFAT was reconstructed in the DT from the patient computed tomography (CT) scans. The hybrid CT-MRI heart DTs, combined with electroanatomic map (EAM) data, revealed that for these infarcts inFAT exhibits greater proarrhythmic EP abnormalities than does scar and that it is the primary driver of substrate arrhythmogenic propensity. Subsequent clinical studies confirmed these DT predictions.[54–56] Finally, in addition to further developing heart DTs that are based on mechanistic considerations, recently new deep learning on different types (multimodality) of data has been proposed.[57] The deep learning analysis (termed survival study of cardiac arrhythmia risk) combined learning unprocessed (raw) patient LGE-MRI scans and clinical covariates of patients with ischemic cardiomyopathy and was imbedded in survival analysis to predict time to SCD over a period of 10 years; it performed well on the external validation data set, demonstrating generalizability. Algorithms such as survival study of cardiac arrhythmia risk are paving the way for multimodal prediction of patient outcome, but they will become particularly powerful when combined with DT for interpretability and mechanistic insight.

For SCD risk prediction in patients with nonischemic cardiomyopathies, several heart DT studies have demonstrated the clinical utility of the approach. The first 2 applications of personalized DTs in nonischemic cardiomyopathy were in pediatric patients. The first assessed VA risk in acute pediatric myocarditis.[58] In the second study, DTs were constructed from patients with repaired tetralogy of Fallot[59]; the childhood surgical intervention in these patients led to potential arrhythmogenic scarring in the heart. DT risk assessments in repaired tetralogy of Fallot predicted high risk, later validated by clinical outcome, in those patients in whom an ECG-based clinical algorithm predicted low risk. In hypertrophic cardiomyopathy, a common genetic disease characterized by thickening of heart muscle, high SCD risk arises from the proliferation of fibrosis in the heart. The study by O'Hara et al[46] used DT technology to analyze how disease-specific remodeling promotes arrhythmogenesis and to develop a personalized strategy to forecast the risk of arrhythmias in these patients (n = 26). The authors combined LGE-MRI and T1 mapping data to construct fusion DTs that represented the patient-specific distribution not only of dense scar but also of diffuse fibrosis; the latter was reconstructed from T1 maps.[60] The analysis demonstrated that the presence of diffuse fibrosis, which is rarely assessed in these patients, increases VA propensity. In forecasting future arrhythmic events in these patients, the DT approach significantly outperformed current clinical risk predictors; both the American College of Cardiology Foundation/American Heart Association and the European Society of Cardiology risk models offered prognoses that were inferior in accuracy, sensitivity, and specificity than the LGE-T1 DT prognosis. Another nonischemic cardiomyopathy associated with high SCD risk and difficult risk prediction is cardiac sarcoidosis. Shade et al[47] developed a 2-step prediction approach, combining digital twinning with machine learning in a study of 45 patients. The patient's arrhythmogenic propensity was assessed using a novel hybrid DT, reconstructed from the fusion of LGE-MRI and positron emission tomography scans. The results of DT simulation were fed, together with a set of clinical biomarkers, into a supervised classifier—and the technology outperformed current clinical decision making.

Finally, a genotype-specific heart DT (Geno-DT) approach was recently developed to investigate the role of pathophysiological remodeling in sustaining arrhythmia and to predict the arrhythmia circuits in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) and different genotypes.[61] This approach integrated the patient's disease-induced structural remodeling and genotype-specific cellular EP properties and revealed that the underlying arrhythmia mechanisms differ among ARVC genotypes. In a retrospective study of 16 patients with ARVC and 2 genotypes—plakophilin-2 (*PKP2*; *n* = 8) and gene-elusive (GE; *n* = 8)—Zhang et al[61] found that Geno-DT accurately and noninvasively predicted the ventricular tachycardia (VT) circuit locations for both genotypes with very high accuracy, sensitivity, and specificity in both the GE and *PKP2* patient groups when compared with VT circuit locations identified during clinical EP studies. Importantly, the results revealed that the underlying VT mechanisms differ among ARVC genotypes: in GE patients, fibrotic remodeling is the primary contributor to VT circuits, while in *PKP2* patients, slowed conduction velocity and altered restitution properties of cardiac tissue, in addition to the structural substrate, are directly responsible for the formation of VT circuits. Figure 6 shows an interesting result: when the genotype in DTs was mismatched, VT circuits could no longer be predicted correctly. With its incorporation of genetic EP information, Geno-DT is the latest development in heart DT applications. The Geno-DT approach demonstrated the potential to augment therapeutic precision in the clinical setting and lead to more personalized treatment strategies in ARVC.

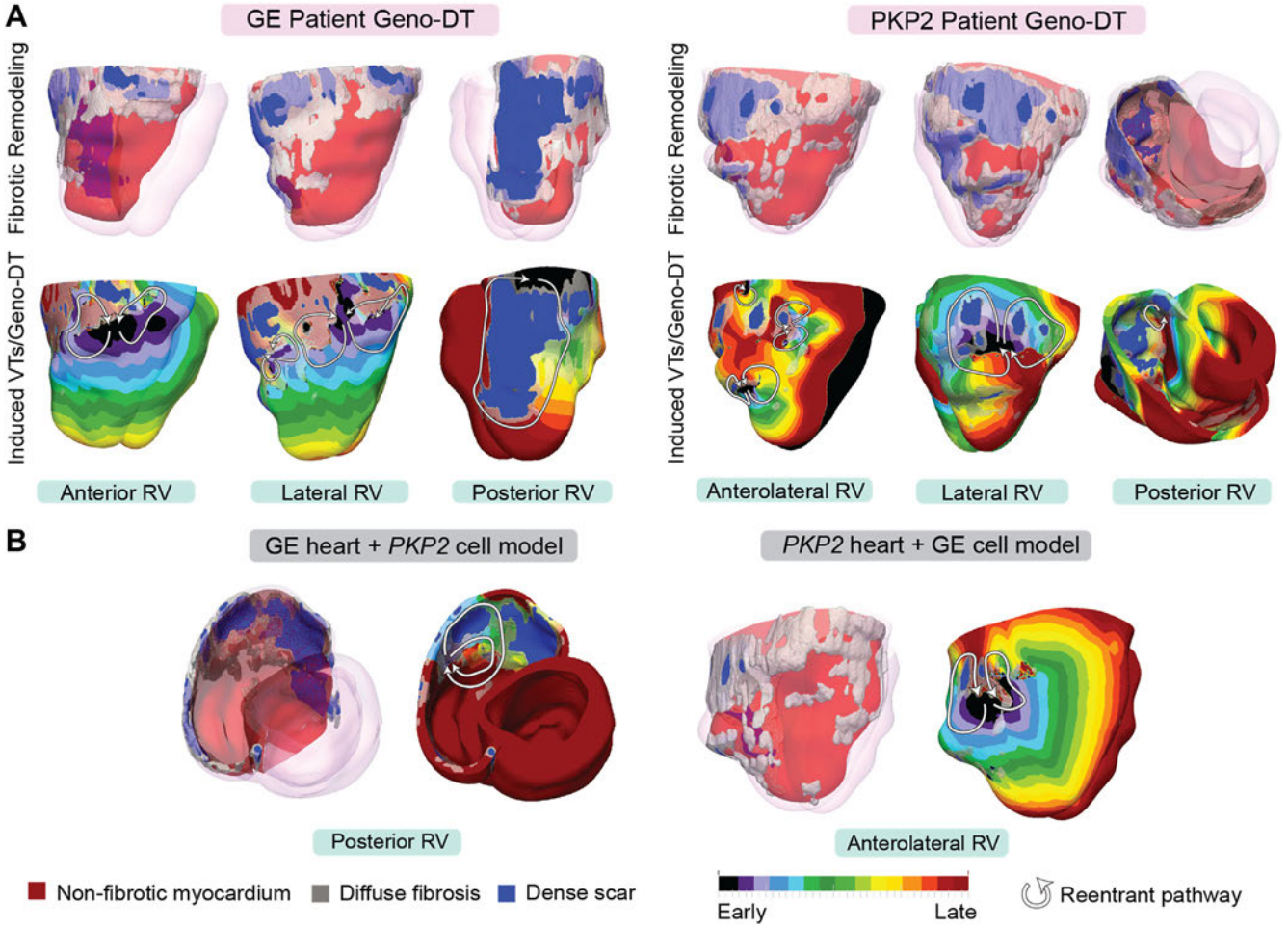

Figure 6
Ventricular tachycardia (VT) prediction using genotype-specific heart digital twin (DT; Geno-DT) of patients with arrhythmogenic right ventricular cardiomyopathy. Reconstructed DTs from 2 patients of gene-elusive (GE) and plakophilin-2 (*PKP2*) genotypes along with the simulated VTs with (**A**) genotype-matched condition and (**B**) genotype-mismatched condition. The mismatched condition led to an incorrect prediction of VT circuits. RV = right ventricle. Modified from Zhang et al[61] (permission exempt per https://elifesciences.org/terms).

Like the management of AF, catheter ablation plays a major role in the contemporary management of VAs. Eliminating VAs with ablation has achieved, however, modest success, 50%–88%.[62,63] Similar to AF ablation, a number of patients, for whom the initial procedure fails, are repeatedly ablated, further extending adverse structural remodeling in the ventricles. Discovering new strategies that result in accurate identification of the optimal ablation targets for VAs in patients with different heart diseases, and which also deliver long-term freedom from VAs, is a quest of paramount clinical significance. Personalized DT technology has made major strides in improving ablation precision by providing noninvasive localization of ablation targets. A study using DTs from 13 postinfarct patients who underwent ablation showed that ablation targets from DTs were consistent with the targets executed in the clinic.[64] The landmark study by Prakosa et al[43] was demonstrated for the first time the clinical utility of personalized DTs in determining noninvasively the optimal (ie, minimum lesion size) VT ablation targets and guiding the clinical procedure of VT ablation. The capability of the approach was first assessed in a retrospective study (n = 21), where predicted targets were compared with clinical data. This included patients in whom image construction was done from clinical images with device artifacts. Furthermore, the feasibility of using DTs to guide clinical VT ablation was demonstrated in a proof-of-concept prospective study (n = 5) in 2 clinical centers (Figure 7A). This work highlighted the potential of DT technology to impact the clinical management of VAs. The sensitivity of DT ablation targets to EP parameter variability has also been assessed.[65] Using DTs based on the CT scans of patients has also been shown, in a retrospective cohort of 29 postinfarct patients, to be able to provide guidance in ventricular ablation.[44] DTs predicted not only the targets on index ablation but also the ablation targets on a redo procedure several years later (Figure 7B). Overall, the ablation targets predicted by the heart DTs consistently encompassed much less lesion volumes. Since CT is accessible across a broad range of clinical centers, DTs could be readily deployed prospectively to improve ventricular ablation.

DTs have also been used to improve ablation by better understanding VT circuit morphology. Sung et al[66] demonstrated that inclusion of repolarization gradients, both

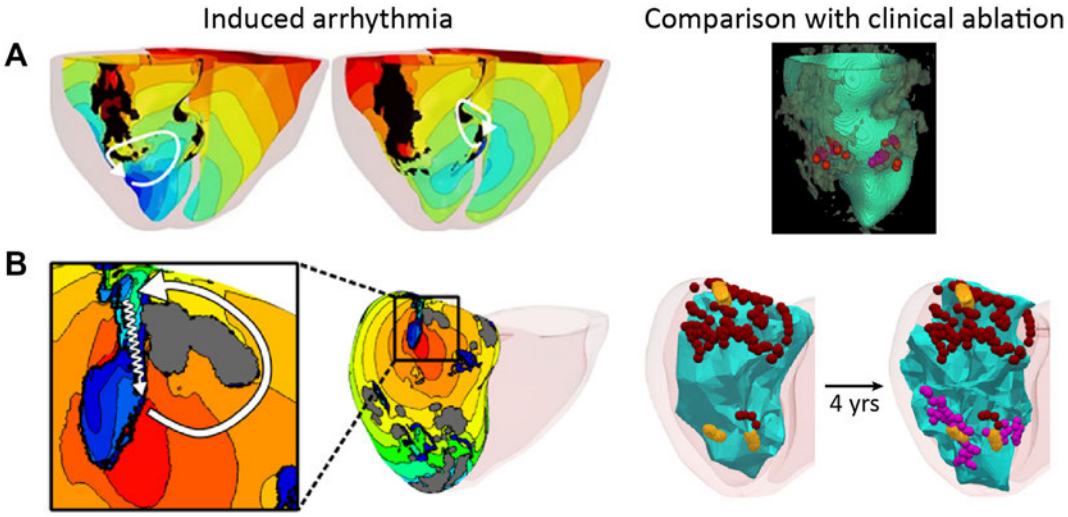

Figure 7
Digital twins (DTs) guiding ventricular ablation. **A:** Ablation in a prospective patient with ischemic cardiomyopathy guided by magnetic resonance imaging–based DT. Shown are the 2 predicted VT circuits, and intraprocedural electroanatomic mapping (CARTO) with the predicted (*purple*) and actual (*red*) lesions. Modified from Prakosa et al[43] (permission exempt per https://www.nature.com/nature-research/reprints-and-permissions/permissions-requests). **B:** Using a computed tomography–based DT in a postinfarction patient with infiltrating fat to predict VT circuits (**left**; the *inset* presents the detail of activation; *white arrows* denote the reentrant pathway; *zigzag arrows* denote the conduction channels) and ablation targets retrospectively, where predicted ablation targets and clinical ablation lesions colocalize in a patient who underwent redo ablation ≈4 years after the index procedure. Modified with permission from Sung et al.[44]

transmural and apicobasal, altered VT circuit morphologies, with minimal change in ablation targets. DT simulations of VT circuits have also been combined with automated ECG-based localization algorithm to predict VT exit sites,[67] highlighting a potential synergy between the 2 methodologies. A recent study further developed and validated a technique called reentry vulnerability index, demonstrating that the technique allows localization of ablation targets.[68] In the clinic, multiple wavefront pacing (MWP) and decremental pacing are 2 EAM strategies that have emerged to characterize[62,63] the VT substrate and determine ablation targets. A recent DT study in 48 patients assessed how well MWP, decremental pacing, as well as other techniques used in clinical studies improve identification of EP abnormalities at critical VT sites.[69] The study found that EAM with MWP is more advantageous for the characterization of substrate for ablation in hearts with less remodeling.

Concluding remarks

The development and examples of applications of heart DTs in arrhythmia management by our team presented in this review highlight the significant advancements that cardiac computational modeling has made in bringing such tools closer to the patient point of care. Heart DTs could potentially become a disruptive approach, fully embodying the expectations of precision medicine in cardiology, as these virtual tools leverage robust physics and physiology-based mechanistic insights, are capable of encoding pathophysiological complexity across multiple spatial scales, and can be continuously updated with the individual patient's clinical and lifestyle data.

The pathway to accelerate the clinical impact of heart DTs is to continuously work on increasing the trust in the technology among researchers, clinicians, and health care professionals; to emphasize its benefits to patients; and to educate the society at large. An important aspect in this endeavor is to always recognize and account for the limitations of the technology. DTs of organs and patients will likely never represent all aspects of physiological reality. Thus, focus should be steadily on DT performance and the resulting patient outcome, both becoming increasingly important. To cite George Box, "all models are wrong, some are useful"—it is this usefulness that we will strive to enhance in the years to come.

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