Personalized ablation vs. conventional ablation strategies to terminate atrial fibrillation and prevent recurrence

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Aims	The long-term success rate of ablation therapy is still sub-optimal in patients with persistent atrial fibrillation (AF), mostly due to arrhythmia recurrence originating from arrhythmogenic sites outside the pulmonary veins. Computational modelling provides a framework to integrate and augment clinical data, potentially enabling the patient-specific identification of AF mechanisms and of the optimal ablation sites. We developed a technology to tailor ablations in anatomical and functional digital atrial twins of patients with persistent AF aiming to identify the most successful ablation strategy.
Methods and results	Twenty-nine patient-specific computational models integrating clinical information from tomographic imaging and electro-anatomical activation time and voltage maps were generated. Areas sustaining AF were identified by a personalized induction protocol at multiple locations. State-of-the-art anatomical and substrate ablation strategies were compared with our proposed Personalized Ablation Lines (PersonAL) plan, which consists of iteratively targeting emergent high dominant frequency (HDF) regions, to identify the optimal ablation strategy. Localized ablations were connected to the closest non-conductive barrier to prevent recurrence of AF or atrial tachycardia. The first application of the HDF strategy had a success of >98% and isolated only 5–6% of the left atrial myocardium. In contrast, conventional ablation strategies targeting anatomical or structural substrate resulted in isolation of up to 20% of left atrial myocardium. After a second iteration of the HDF strategy, no further arrhythmia episode could be induced in any of the patient-specific models.
Conclusion	The novel PersonAL *in silico* technology allows to unveil all AF-perpetuating areas and personalize ablation by leveraging atrial digital twins.
Keywords	Atrial fibrillation • Digital twin • Electro-anatomical mapping • MRI • Personalized ablation • Computational model

Introduction

Atrial fibrillation (AF) is the most common supraventricular arrhythmia in humans with both increasing prevalence and incidence globally. The pulmonary veins are the main arrhythmia sources in paroxysmal AF and pulmonary vein isolation (PVI) is associated with high (80–85%) 12-month arrhythmia-freedom rates in patients with paroxysmal AF.[1] In contrast, 1-year success rates after AF ablation in patients with persistent AF are reduced with 50% of patients experiencing AF or atrial tachycardia (AT) recurrences.[2] This unsatisfactory success rate is associated with the higher incidence of fibrosis-related atrial conduction slowing in these patients, which constitutes the arrhythmogenic substrate for AF.

Currently, two diagnostic methods are used to identify atrial fibrotic substrate. During electrophysiological mapping studies, atrial fibrotic areas can be detected as areas displaying low-voltage and fractionated late potentials during sinus rhythm. An alternative magnetic resonance imaging (MRI)-based method to diagnose atrial fibrosis is the use of late

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What's new?

- Ablation of the fibrotic substrate leads to high success (>90%) but crucially depends on accurate localization of these areas.
- A reliable way of identifying the arrhythmogenic substrate is the dominant frequency (DF) in computational digital twin models.
- Iteratively ablation of high DF regions results in termination of atrial fibrillation (AF) and prevents recurrence in AF personalized models.
- Connecting localized ablation points to the nearest non-conductive barrier prevents recurrence and increases ablation success.
- Atrial digital twins in combination with personalized induction protocols from multiple sites pre- and post-ablation unveils all emergent AF drivers.

gadolinium-enhancement (LGE). Recent studies revealed that the presence of atrial fibrosis as assessed during electrophysiological mapping or MRI is associated with onset of AF, AF persistency, and increased arrhythmia recurrences after PVI underlining the clinical relevance of atrial fibrotic remodelling.[3–5]

Over the last years, catheter-based ablation of atrial fibrillation (AF) has become the first-line therapeutic option in case of symptomatic episodes. Catheter ablation (CA) of AF relies on PVI as the cornerstone of any ablation procedure.[1] However, extra-PV regions become more relevant in AF initiation and maintenance as atrial remodelling evolves and the underlying substrate gains complexity in persistent and long-standing persistent types of AF.[2] A common strategy to treat symptomatic AF episodes after permanent PVI is to ablate other atrial anatomical structures (e.g. mitral isthmus, roof, vein of Marshall) potentially associated with AF onset and perpetuation. However, many of these atrial regions are empirically targeted for ablation without robust underlying supportive mechanistic insights.

Recent advances in mapping technologies have enabled the development of more patient-specific ablation strategies that complement standard approaches in persistent AF. These can directly target either AF sources [ectopic triggers or rotational drivers (RDs)] identified invasively using basket catheters or non-invasively using body surface electrodes, or regions where the atrial substrate is expected to be arrhythmogenic, currently estimated as low-voltage areas (LVA)[4] or high LGE areas.[6] However, no correlation has been shown between LVA and LGE regions.[7–10] The role of RDs as drivers for AF has been long recognized. However, RD-guided ablation is limited by the challenges of mapping and visualizing electrical activity on the endocardial surface with sufficiently high resolution. This can explain contradictory outcomes of multicentre trials, some of which have shown favourable outcomes of RD-guided ablation,[11] while others have failed to demonstrate advantages of this approach compared with PVI.[12] In addition, rotor lifetime, inter-formation times, and renewal rate were lately shown to be important factors when analysing AF dynamics.[13] Recent studies demonstrated that low-voltage guided ablation was associated with a significantly higher arrhythmia-free survival compared with a conventional CA approach.[3–5] However, a large-scale multicentre study is lacking. A recent study by Bisbal *et al.*[14] and the lately presented DECAAF-II trial by Marrouche *et al.*[15] reported no additional benefit of MRI-guided ablation compared with a conventional PVI-only ablation approach.

Novel frameworks enabled the assessment of initiation, maintenance, and progression of AF via patient-specific computational modelling.[16–20] Nowadays, virtual replicas of human atria can be generated integrating information from multiple clinical data in an automated manner,[17] becoming a useful tool for clinicians in therapy planning.[20,21]

We sought to develop a technology for tailored ablations in atrial digital twins of patients with persistent AF. We aimed at unveiling all areas vulnerable to sustain AF applying personalized inducing protocols at multiple sites on anatomical and functional atrial digital twins. We designed a platform to comprehensively compare state-of-the-art ablation strategies targeting anatomical structures and substrate with our proposed Personalized Ablation Lines (PersonAL) approach. The PersonAL plan consists of an iterative process to identify and terminate all possible latent AF drivers that could manifest post-ablation. We pursued a unique personalization of anatomy, fibrosis, and electrophysiology of the digital twin models, which enables to uncover potential arrhythmogenic substrates and predict the optimal minimal set of ablation targets to eliminate AF and prevent recurrence. We eventually sought to demonstrate the clinical feasibility in guiding ablation integrating the final PersonAL plan into the original clinical map.

Methods

An overview of the automatic pipeline to assess AF vulnerability in personalized atrial computational models and provide PersonAL is illustrated in *Figure 1* and briefly described here before providing details for each step in the following sections. The only user interaction needed for the whole pipeline is the choice of one reference point per atrium.[17] The input can be atrial surfaces obtained from an electro-anatomical mapping system or derived from tomographic segmentation (e.g. MRI or CT). In this study, both input modalities were available. Input geometries are pre-processed and patient-specific Augmented Atria (AugmentA)[17] models are generated by fitting a statistical shape model (SSM)[22] and adding anatomical structures annotation and fibre orientation along with the electrophysiological information present in the original clinical data. Fibrotic distribution can be retrieved from substrate data, e.g. either using image intensity ratio (IIR) of LGE-MRI or LVA derived from electro-anatomical maps. For the IIR method, the left atrial mean blood pool intensity was automatically identified and IIR was calculated as the ratio between signal intensity of each voxel of the mid-myocardial LA layer normalized by the mean blood pool intensity. Following the methodology described in Benito *et al.*,[23] voxels with an IIR of >1.2 were considered as interstitial fibrosis and an IIR of >1.32 as dense scar. Conduction velocity is locally adapted to reproduce the clinical local activation time (LAT) from the patient's electrophysiological mapping data.[17] Each element conductivity was iteratively tuned to minimize the root mean squared error between the clinical and the simulated LAT. Patient-specific inducibility is assessed by applying Pacing at the End of the Effective Refractory Period (PEERP)[16] at variable pacing locations. We decided to apply the PEERP protocol due to its ability to initiate different degrees of arrhythmic complexity requiring a low number of stimuli.[16] Then, the optimal ablation targets are automatically identified. Inducible models are iteratively treated with PersonAL until free from current and emergent AF episodes. Reinducibility is tested by re-applying the PEERP protocol. Finally, the PersonAL plan is provided to the cardiologist.
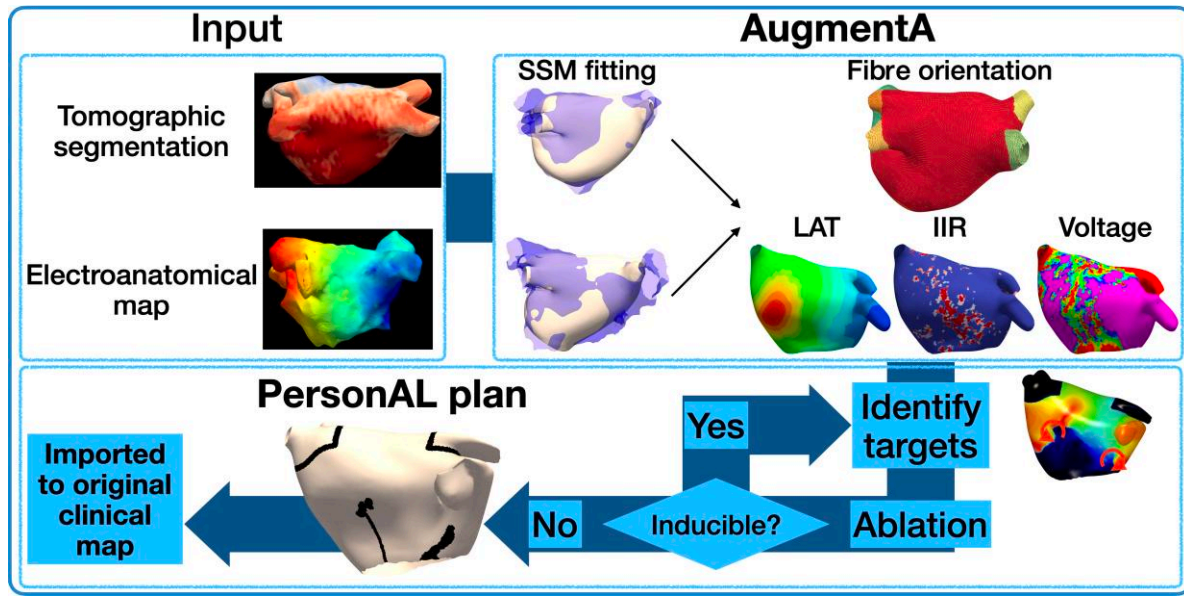
Figure 1 Workflow to identify Personalized Ablation Lines (PersonAL) using atrial digital twins. Tomographic segmentations (CT or LGE-MRI) and/or electro-anatomical maps (EAM) are processed by a highly automated pipeline to generate a patient-specific Augmented Atria (AugmentA)[17] computational model. In case both LGE-MRI and EAM are given, an augmented anatomical and functional digital twin integrating both non-invasive and invasive electrophysiological data is provided. Tailored simulations are performed to assess atrial fibrillation (AF) inducibility using the Pacing at the End of the Effective Refractory Period (PEERP) protocol[16] and regions vulnerable to sustain AF are identified. Then, AF drivers are targeted for ablation and connecting lines to the closest non-conductive barrier (anatomical orifice or previous ablation) are included. The PEERP protocol is then repeated to localize post-ablation emergent AF episodes. If new drivers are identified, they are targeted for ablation. The latter two processes are repeated until no AF episode can be induced in the patient's model. The PersonAL plan is finally exported to the clinical mapping system data format. SSM, statistical shape model; LAT, local activation time; IIR, image intensity ratio.

Table 1 Tested ablation strategies

Ablation strategies

i) PVI	viii) PVI + HDF$_{conn}$
ii) PVI + RL + ML	ix) PersonAL
iii) PVI + IIR > 1.32$_{conn}$	x) PVI + IIR > 1.32
iv) PVI + IIR > 1.2$_{conn}$	xi) PVI + IIR > 1.2
v) PVI + LVA$_{conn}$	xii) PVI + LVA
vi) PVI + CV0.3$_{conn}$	xiii) PVI + HDF
vii) PVI + CV04$_{conn}$	

Ablation approaches targeting anatomical structures, coloured in green, consist in PVI and PVI + RL + ML. Substrate ablations, shown in blue, include approaches targeting regions with IIR > 1.32, IIR > 1.2, LVAs, CV < 0.3 m/s, or CV < 0.4 m/s. Functional ablation strategies, in red, subdivided in a single procedure targeting HDF areas or multiple procedures iteratively targeting emergent driver locations identified as HDF areas (PersonAL). PVI+( )$_{conn}$, PVI plus ablation targeting anatomical/structural/functional substrates and connecting localized ablation lesions to the closest non-conductive barrier (anatomical orifice or previous ablation); PVI, pulmonary vein isolation; RL, roof line; ML, mitral isthmus line; IIR, image intensity ratio; LVA, low-voltage areas; CV, conduction velocity; HDF, high dominant frequency.

Dataset

A cohort of 29 patients with persistent AF (65 ± 9 years, 86% male) including both electro-anatomical maps and MRI segmentations of the LA were included in this study. A high-density electro-anatomical bi-atrial map (2129 ± 484 sites) was acquired in sinus rhythm before PVI using a 20-pole mapping catheter and the CARTO 3 system (Biosense Webster Inc., Diamond Bar, CA, USA). The post-processing of the LA LGE-MRI (Siemens 3 T) was performed by a blinded expert laboratory (Adas3D Medical SL, Barcelona, Spain). Patients' characteristics are available in Supplementary material online, Table 1. The study was approved by the institutional review board, registered in the German WHO primary registry DRKS (unique identifier: DRKS00014687), all patients provided written informed consent before enrolment and the investigation conformed to the principles outlined in the Declaration of Helsinki.

Personalized atrial model generation

For each patient, our recently proposed AugmentA generation pipeline[17] was applied to each electro-anatomical map and LGE-MRI segmentation. An automated algorithm manually selecting only one reference point (left atrial appendage apex) was applied to open atrial orifices. The mitral valve and the pulmonary veins were automatically identified and labelled. Each target geometry was at first rigidly aligned with the mean shape of a previously built bi-atrial SSM.[22] Subsequently, 36 landmarks were automatically computed and a fitting procedure was applied. In this regard, non-rigid shape model fitting using Iterative Closest Points and Gaussian Process regression[24] was performed to establish dense point-by-point correspondence between the bi-atrial SSM and each target geometry. Then, each data vector (e.g. LAT, voltage) was mapped from the original mesh to the fitted SSM using a nearest neighbour approach. Since the resulting instance is a deformed version of the mean

shape, all models had the same number of nodes and vertices and the nodes always represented the same anatomical structures. Therefore, the electrophysiological data mapped from one patient's electro-anatomical map to the resulting SSM instance could be easily transferred to the SSM instance derived from the respective MRI segmentation. Since we assumed that the MRI segmentation was a better representation of the patient's real atrial anatomy compared with the electro-anatomical map, we decided to register LAT as well as uni- and bipolar voltage maps to the SSM instance derived from the MRI data. Finally, AugmentA automatically annotated the various anatomical structures and computed the fibre orientation using a Laplace-Dirichlet rule-based method. The resulting bilayer atrial model[25] was ready-to-use for electrophysiological simulations. Fibrosis distribution was included in the model either using LVA or high LGE-MRI. In this way, we generated two atrial models for each of the 29 patients. Details about the modelling of atrial electrophysiology in fibrotic and non-fibrotic tissue can be found in the Supplementary material online.

Induction protocol and arrhythmia analysis

Arrhythmia initiation vulnerability was assessed by applying the PEERP protocol.[16] We tested inducibility of arrhythmic episodes by pacing from stimulus locations placed on the endocardial surface with inter-point distance of 2 cm. This pacing site distribution allowed capturing all possible arrhythmias that could arise in the given patient-specific model as shown in Azzolin *et al.*[16] At each stimulus location, a transmembrane current of 30 μA/cm^2 was injected in an area of 2 mm × 2 mm.

We considered a point to be 'inducing' if the application of the PEERP protocol at that location induced an arrhythmia that was sustained for at least 5 s. Dominant frequency (DF) maps were computed based on the last 1.5 s of each reentrant episode's transmembrane potential. All pacing-induced arrhythmias were analysed to determine an initial set of ablation lesions.

To identify regions of high DF (HDF), a threshold was applied at 1 SD above the mean and HDF points were clustered into connected regions.[19] The RDs lifetime was calculated by detecting the phase singularities (PSs)[26] and tracking their spatio-temporal behaviour. Phase singularities with a lifetime of at least 500 ms were considered.

Modelling ablation scars

We tested 13 different ablation approaches, as presented in *Table 1*: (i) PVI alone, modelled as circumferential isolation of the ipsilateral pulmonary veins; PVI together with: (ii) roof and mitral isthmus lines; (iii) isolating all regions with IIR > 1.32; (iv) isolating all regions with IIR >1.2; (v) isolating all LVAs (bipolar voltage <0.5 mV); (vi) isolating all low conduction velocity regions (CV < 0.4 m/s); (vii) isolating all low conduction velocity regions (CV < 0.3 m/s); and (viii) isolating all HDF regions. The PersonAL plan (ix) consists in iteratively targeting emergent drivers, identified as HDF. All previously described ablation strategies included connecting lines to the closest non-conductive barrier. Finally, we also assessed how omitting these connecting lines isolating affects (x) ablation targeting regions with IIR > 1.32, (xi) ablation targeting regions with IIR > 1.2, (xii) LVAs ablation, and (xiii) HDF ablation. *Figure 2* shows exemplary anatomical, substrate, and functional ablation strategies for Patient #18.

The ablation lesions were automatically applied and produced consistent lesions across patients. The technical details regarding the ablation strategies are described in the Supplementary material online. Virtual ablation lesions consisted of the myocardial tissue within 2 mm of the direct line (ablation lesion radius for standard irrigated-tip catheters)[27] and were modelled as non-conductive. Ablation targeting substrate regions were limited to the boundary of the regions instead of the whole region to minimize procedural time.

Ablation success was automatically classified as either ongoing AF, termination, or AT. Atrial tachycardia was defined as cases with DF < 4.7 Hz or with more than 50% of the atrial surface having a DF ≥ the 95th DF percentile.[19]

Reinducibility assessment after ablation

Catheter ablation therapies for atrial arrhythmias often take the suppression of inducibility as treatment endpoint.

Therefore, in the atrial models in which a specific ablation strategy was able to terminate all AF episodes, we assessed reinducibility by applying the PEERP protocol again from all initial stimulation points located in non-isolated tissue.

Importing personalized targets into the clinical electro-anatomic navigation system

To facilitate clinical translation, optimal ablation targets identified by PersonAL were transferred to the electro-anatomical map. The point correspondence between the SSM instances derived from the MRI and electro-anatomical map allowed for a trivial mapping of the ablation locations from the MRI-fitted digital twin to the respective electro-anatomical map. Merging patient-specific imaging with electro-anatomic mapping data to display ablation targets in the mapping system together with the current position of the catheter increases usability.

Results

Inducibility and identification of atrial fibrillation drivers

The PEERP protocol-initiated AF episodes in 17/29 and 20/29 patient digital twins when fibrotic tissue was modelled where the voltage was <0.5 mV or IIR > 1.2 in the clinical maps, respectively. Finally, 99 and 88 episodes were induced, respectively. Different degrees of AF complexity were initiated, from localized RDs to chaotic wave collisions, as shown in the videos attached as Supplementary material online. Atrial fibrillation drivers were correctly identified by HDF regions and verified via visual inspection as shown for Patient #20 with fibrosis distributed according to LVA in *Figure 3*. The RDs lifetime was 1334 ± 298 ms, with a minimum of 512 ms.

Acute atrial fibrillation termination success for different ablation strategies

Ablation outcomes of the strategies including connection lines to the closest non-conductive obstacles, classified as AT or termination, varied considerably across the cohorts of patients with fibrosis modelled according to either voltage <0.5 mV or IIR >1.2 depending on the ablation approach, as shown in *Figure 4*. 18.9% of the LA surface area was identified as low-voltage (<0.5 mV) in this cohort of inducible ablation-naive persistent AF patients (*Figure 4B*) and 14.8% were identified as IIR > 1.2 in LGE-MRI (*Figure 4E*). Pulmonary vein isolation-only was the ablation strategy with the lowest acute success rate in our persistent AF patient cohort with the comprehensive PEERP protocol. Anatomical ablation approaches led to the smallest
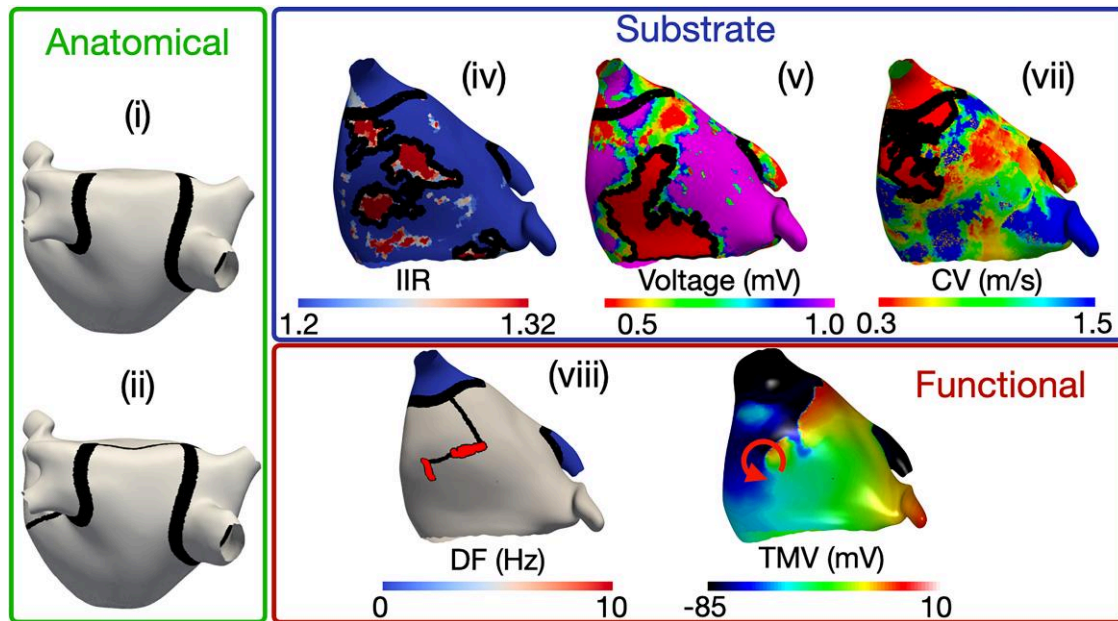
Figure 2 Anatomical, substrate, and functional ablation strategies. The ablation lesions are indicated by the black ablation lines. Ablation approaches targeting anatomical structures, shown in the green box, consist in PVI (i) and PVI + RL + ML (ii). Substrate ablations, shown in the blue box, include, e.g. approaches targeting regions with IIR > 1.2 (iv), LVAs (v), and regions with CV < 0.3 m/s (vii). Functional ablation strategies, shown in the red box, targeted HDF areas (viii).

share of atrial tissue being ablated (3.1–4.2%). Targeting the regions modelled as fibrotic tissue successfully terminated or converted AF to AT in 88.9% and 90.9% of the AF episodes when fibrosis distribution patterns were modelled according to voltage <0.5 mV and IIR >1.2, respectively. When the fibrosis could not be exactly localized (i.e. when it was modelled where IIR > 1.2 but ablated according to LVA or vice versa), the success rates dropped to 49.5% and 53.4%, respectively. Inactive tissue after ablation strategies targeting atrial substrate varied between 21% and 28% of the atrial myocardium. The first application of the ablation strategy aiming at HDF areas led in both cases to termination or conversion to AT of more than 98% of all AF episodes. However, following the same ablation strategies without connecting the targeted areas to the closest non-conductive barriers resulted in a decrease of the success rate by 15–35%, as shown in *Figure 5*. An example of the ablation plan targeting HDF areas applied to Patient #18 is presented in *Figure 6*. The amount of inactive tissue post-ablation isolating the HDF areas including connection lines was 5–6% of the atrial tissue. Exemplary videos demonstrating the efficacy of the HDF ablation strategy to convert AF to AT are included as Supplementary material online.

Ablation of emergent atrial fibrillation drivers and reinducibility

The PersonAL plan consists of iteratively identifying and targeting AF-perpetuating areas, defined as HDF regions, until a patient-specific digital twin model is rendered completely non-inducible. Therefore, in the models in which the first application of HDF areas ablation did not terminate all AF episodes or converted into AT (two and one episodes in atrial models with fibrosis modelled according to

voltage <0.5 mV or IIR > 1.2, respectively), the emergent AF drivers were detected and new ablations were added. A second application resulted in 100% success rate and no further AF episode could be induced in any of the models.

Discussion

Ablation of fibrotic substrate is linked to high acute success

Our study showed that a clear identification of the arrhythmogenic substrate (fibrotic or slow conducting areas) is needed to obtain high ablation success. When there was mismatch between where fibrosis was modelled in the digital twin and where it was assumed to be for identifying ablation sites, e.g. when fibrosis was distributed in the model as IIR > 1.2 but it was assumed to be identified as LVA when performing ablation, and vice versa, the success rate dropped by around 40% (Columns 4 and 5 in *Figure 4A* and *D*). The limited accuracy of current technology in detection of the fibrotic substrate can therefore explain the sub-optimal results of previous clinical trials targeting substrate.[2,14]

Clinical studies ablating fibrotic tissue distribution determined using LGE-MRI had no evident improvement in respect to the standard-in-practice PVI. This may be explained by the lack of reproducible and standardized characterization of the substrate by atrial LGE-MRI.[9,14] The choice of the LGE-detection protocol (e.g. IIR or Utah) and the respective cut-off values are influencing the estimated fibrotic distribution.[8,10] Moreover, current LGE-MRI technology does not have the required resolution to well distinguish fibrosis within the thin atrial myocardial wall. Accuracy is essential in this
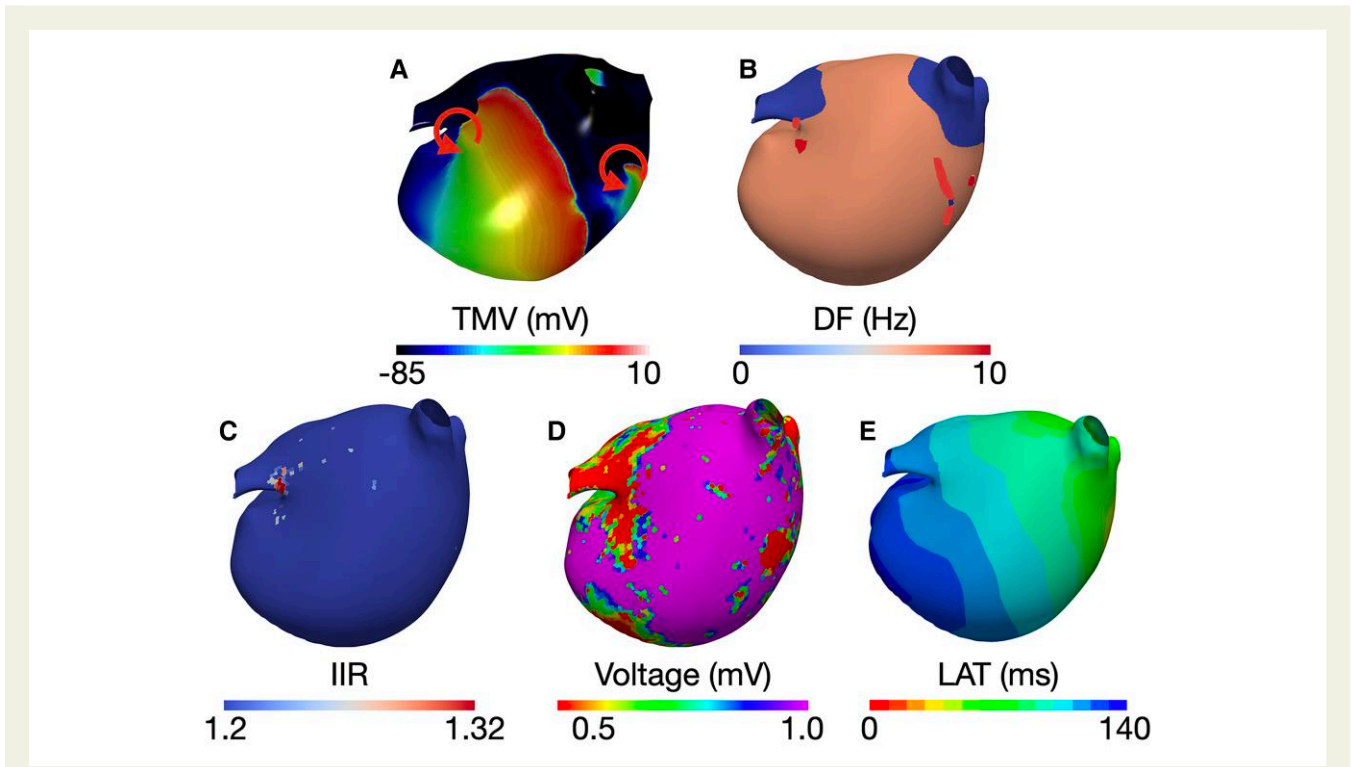
Figure 3 Identification of HDF areas in Patient #20 with fibrotic tissue modelled according to low-voltage area <0.5 mV (LVA) in the clinical voltage map. (*A*) Atrial fibrillation episode perpetuated in LVAs close to the inferior left pulmonary vein and at the posterior septum; (*B*) DF map; (*C*) IIR map; (*D*) bipolar voltage map; (*E*) simulated activation (LAT) map.

case, as inclusion of external structures in the segmented myocardium can lead to a consideration of fat or outer tissue as scar or fibrosis, and omitting parts of the myocardium in the segmentation may hinder detection of fibrotic areas.[28] The presence of multiple devices and algorithms from different manufacturers makes reproducibility of results difficult. Moreover, evidence of the relationship between MRI-characterized scar and histological fibrosis has not been proven on atrial myocardium but for the thick-walled ventricular myocardium in ischaemic and dilatative cardiomyopathy. Clinical trials based on LGE-MRI-guided ablation[14,15,29] failure in showing higher success compared with conventional CA might be also due to the lack of connecting lines to prevent emergent AF drivers. Our *in silico* experiments clearly showed that the ablation outcome of IIR-based strategies dropped when these connecting lines were not included (*Figure 4B*).

Low-voltage areas ablation presented promising results in various clinical trials in persistent AF patients.[3–5] However, ablation strategies guided by LVA also have their limitations, due to the challenges in classifying AF-perpetuating atrial tissue. Bipolar voltage is affected by the bipole orientation with respect to the direction of the electrical propagation wavefront. Approaches using high-density mapping or omnipolar electrograms hold promise to overcome the dependence on directionality. Nevertheless, no clear voltage threshold has been determined to clearly identify arrhythmogenic substrate. Recently, a region-specific bipolar voltage thresholding method was proposed as a possible solution.[30]

Our current work also reveals that reentrant AF driver sites localize to slow conduction areas in electro-anatomical LAT maps.

However, methodologies to accurately and robustly elucidate slow conduction regions from clinical data are needed.[31]

Connecting ablated areas to non-conductive barriers increase the success

Our work highlights the beneficial effect of including ablation lines connecting the targeted area to the closest anatomical orifice or previous ablation. The ablation success of the same ablation strategy decreased by 15–35% when no connecting lines were added. The idea behind this approach is to prevent the formation of macroreentries around the isolated tissue, to prevent anchoring of reentrant drivers and to prevent AT. This could explain the not consistent success rate of focal impulse and rotor modulation clinical trials.[27,32]

Highest success applying the PersonAL strategy

The identification and consequent ablation of fibrotic tissue had in general high success (≈80–90%) but still lower than a first application of the strategy targeting AF-perpetuating areas (≈98–99%), characterized as HDF areas. This means that even if a clear determination of fibrotic tissue and/or slow conduction regions will be possible with high-resolution mapping technologies and imaging data in combination with advanced analysis algorithms, we would nevertheless miss possible AF-perpetuation areas. Moreover, substrate-driven ablation strategies led to >20% of inactive/dead tissue, compared with only ≈5–6% of electrically isolated tissue with tailored ablation lines
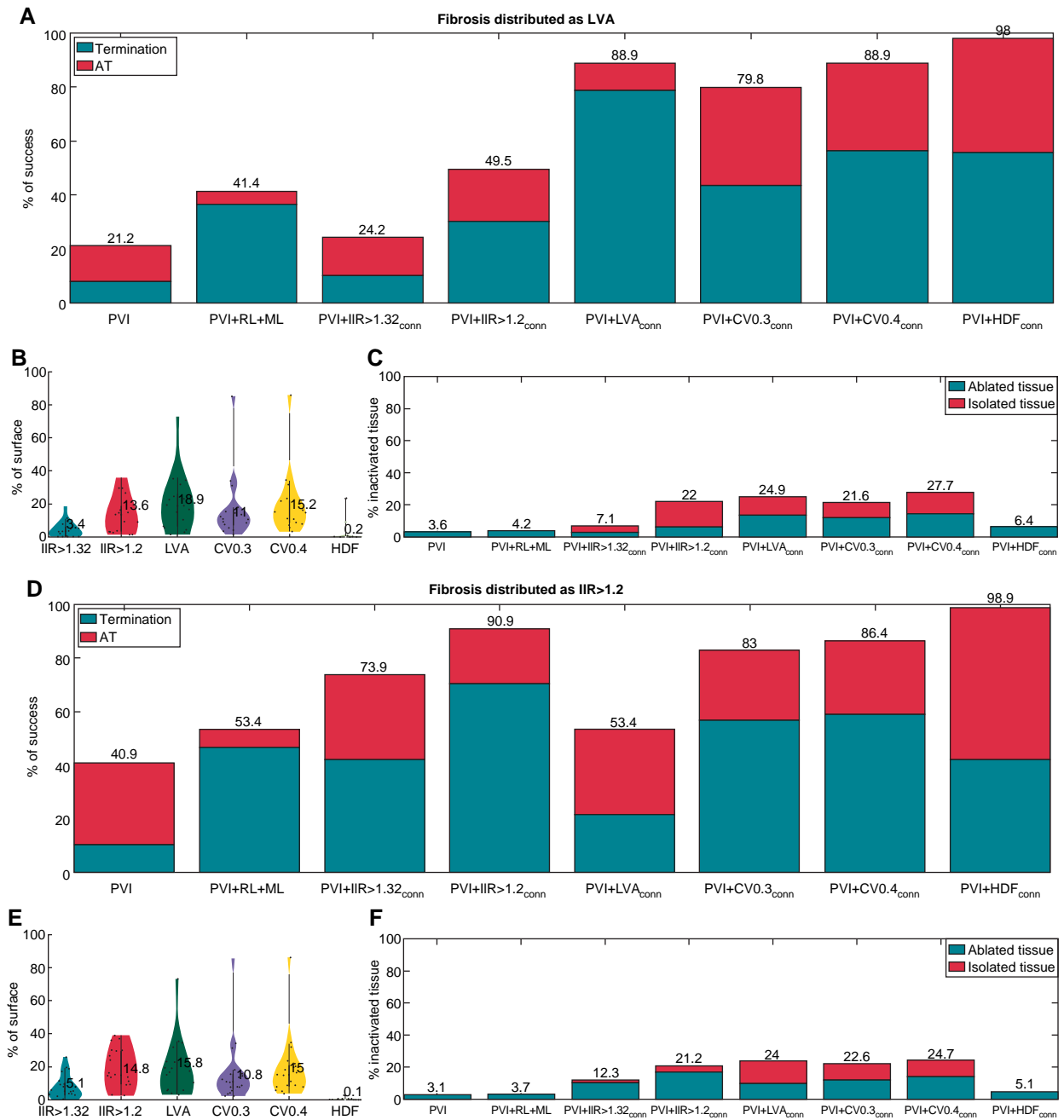
Figure 4 Success rate of each ablation strategy including connection lines to the closest non-conductive obstacle applied to the patient models cohort in which distribution of fibrotic tissue was modelled according to either voltage <0.5 mV (LVA) in clinical electrophysiological voltage maps (*A*) or LGE-MRI areas as identified by image intensity ratio (IIR) >1.2 (*D*). Ablation strategies that resulted in AF termination are shown in blue and conversion to atrial tachycardia (AT) in red. Percentage of atrial surface identified as substrate by the different substrate mapping methods before ablation in inducible patients with fibrosis adapted according to either LVA (*B*) or IIR >1.2 (*E*). Percentage of inactivated myocardium following each ablation strategy categorized in ablated tissue and isolated tissue in atrial models with fibrosis applied according to either LVA (*C*) or IIR >1.2 (*F*). IIR > 1.32, atrial regions with image intensity ratio (IIR) >1.32; IIR > 1.2, atrial regions with image intensity ratio (IIR) >1.2; LVA, low-voltage areas (bipolar voltage <0.5 mV); CV0.3, atrial regions with conduction velocity (CV) <0.3 m/s; CV0.4, atrial regions with CV <0.4 m/s; HDF, high dominant frequency areas; PVI, pulmonary vein isolation; PVI + ( )conn, PVI plus ablation targeting anatomical/structural/functional substrates and connecting localized ablation lesions to the closest non-conductive barrier (anatomical orifice or previous ablation). PVI + RL + ML, PVI plus roof line (RL) plus mitral isthmus line (ML).
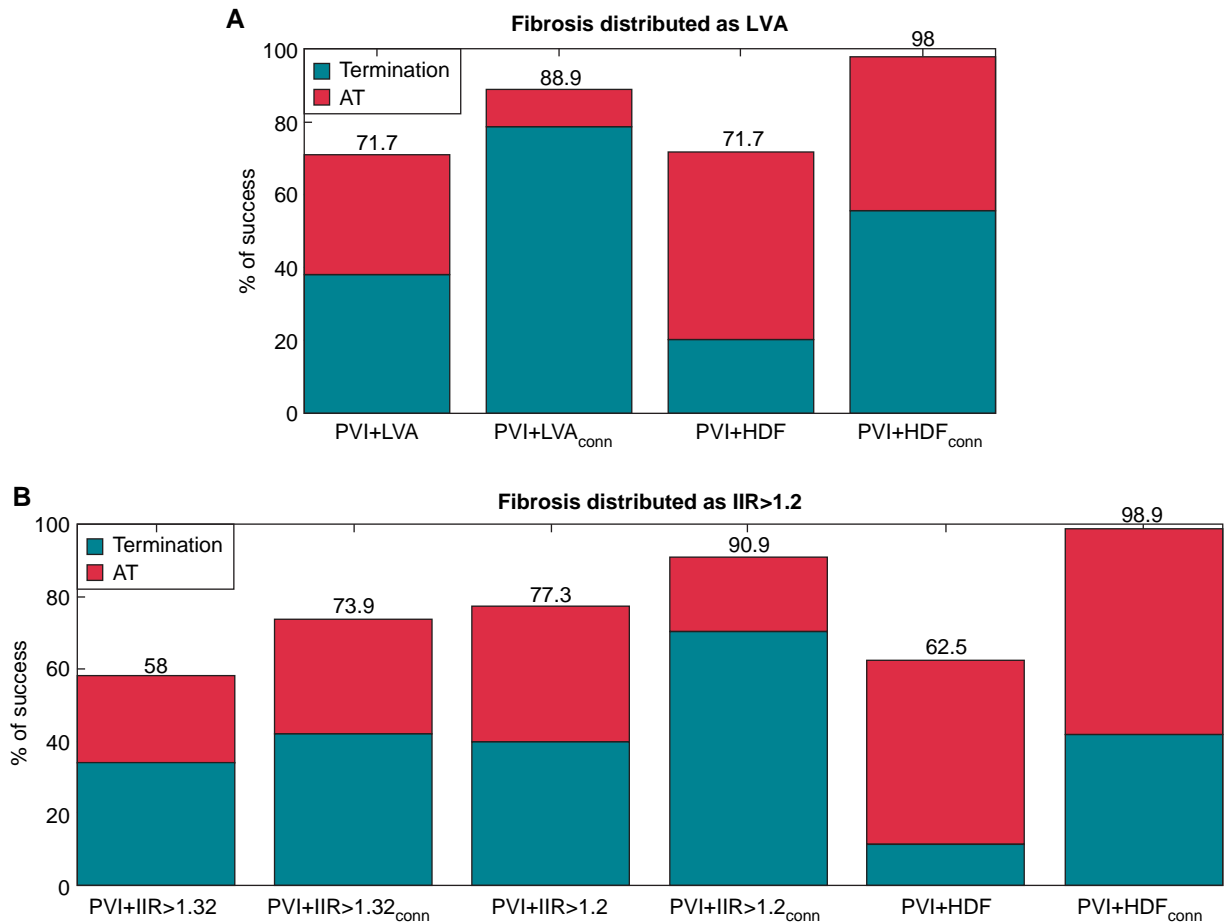
A Fibrosis distributed as LVA

B Fibrosis distributed as IIR>1.2

Figure 5 Influence of inclusion of connecting lines to the closest non-conductive obstacle on the success rate for each ablation strategy applied to the patient models cohort in which distribution of fibrotic tissue was modelled according to either voltage <0.5 mV (LVA) in clinical electrophysiological voltage maps (*A*) or LGE-MRI areas as identified by image intensity ratio (IIR) >1.2 (*B*). Ablation strategies that resulted in AF termination are shown in blue and conversion to atrial tachycardia (AT) in red. IIR > 1.32, atrial regions with image intensity ratio (IIR) >1.32; IIR > 1.2, atrial regions with image intensity ratio (IIR) >1.2; LVA, low-voltage areas (bipolar voltage <0.5 mV); HDF, high dominant frequency (HDF) areas; PVI, pulmonary vein isolation; PVI + ( ), PVI plus ablation targeting anatomical/structural/functional substrates; PVI + ( )$_{conn}$, PVI plus ablation targeting anatomical/structural/functional substrates and connecting localized ablation lesions to the closest non-conductive barrier (anatomical orifice or previous ablation).

targeting AF drivers. Fewer lesions have the advantage of shorter ablation procedures, more remaining viable cardiac tissue, which is beneficial for haemodynamic performance and fewer possible complications for the patient. The PersonAL strategy consists of iterative personalized simulations and AF assessment, locating resulting HDF areas, and targeting them with ablation connected to existing non-conducting structures. Previous studies showed that HDF regions are prone to develop at slow conduction sites identified during sinus rhythm mapping.[33] However, clinical studies targeting HDF or RD regions failed to show an increased success.[12,27] The advantages of our approach are that we integrated connecting lines and that we leveraged digital twins to integrate and augment clinical data. Our patient-specific models were exposed to aggressive and comprehensive inducibility tests pre- and post-ablation from various locations unveiling all areas vulnerable to sustain AF, which is not feasible *in vivo*. Moreover, the *in silico* DF maps were computed considering multiple episodes and finally merged to determine all HDF regions.

Conversely, clinical DF mapping is able to identify only ongoing AF episodes. For PersonAL, DF was computed based on the localized transmembrane voltage information and not on extracellular potentials as measured by clinical electrograms, which are impaired by different kinds of artefacts including far field and noise. Lately, promising studies proposed methodologies to identify AF drivers location during AF mapping in clinics using DF or AF cycle length statistics.[34,35] However, a more accurate identification required longer recordings. Our strategy could be further extended to address also AT episodes and prevent AT recurrence by integrating computational methods to reveal latent macroreentrant pathways in the workflow.[36] Tailored ablation lines targeting these pathways could finally prevent recurrence of both AF and AT. The study is not based on the assumption that AF is sustained by stable high-frequency driver locations. Indeed, high-frequency drivers locations were only used for one of the evaluated ablation strategies and could likely be replaced by other means to identify them (e.g. PSs analysis).
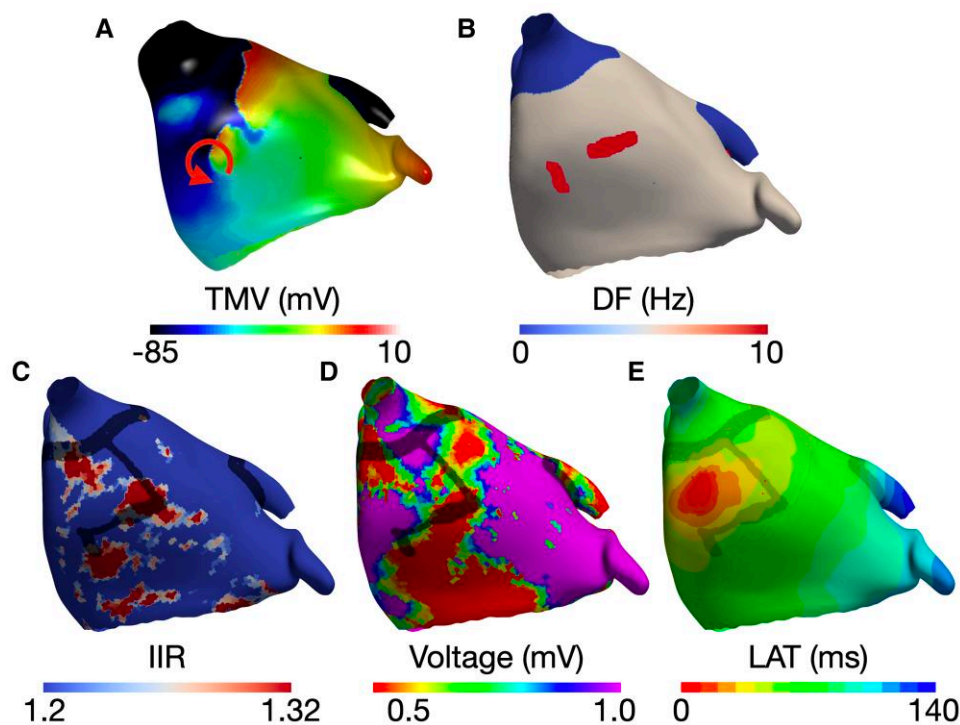
Figure 6 First application of HDF ablation for Patient #18 with fibrosis modelled according to IIR > 1.2 from LGE-MRI. (*A*) Sustained AF episode in slow conduction area located on the anterior wall in proximity to the border zone of a low-voltage/IIR > 1.2 area; (*B*) DF map; (*C*) IIR map; (*D*) bipolar voltage map; (*E*) adapted electrophysiological LAT map.

Assessing inducibility pre- and post-ablation from multiple sites to unveil all atrial fibrillation episodes

All current AF mapping techniques are only able to identify drivers that manifest in a patient in that specific moment or induced AF episodes. New possible AF drivers, which could spontaneously arise before or after an initial set of ablation lesions modifies the atrial substrate and can lead to AF recurrence are not considered. Moreover, assessing inducibility pre- and post-ablation from multiple locations in clinical practice will considerably prolong the procedure.

However, in our computer models, AF inducibility was assessed by applying the exhaustive and aggressive PEERP protocol from multiple locations in the same patient. In this way, all possible arrhythmic episodes which could sustain in that specific atrial digital twin could be unveiled. After testing AF reinducibility in all patients treated with the PersonAL plan, only AT episodes could be initiated. Therefore, the proposed PersonAL strategy was not only able to terminate all AF episodes or convert them to AT, but the treated models were unsusceptible to future AF.

Proof-of-concept clinical feasibility study

The final step of our pipeline consists in importing the PersonAL plan into the original clinical maps. The integration of computer model predicted ablation targets and consequent proposed ablation lines into the clinical procedure as shown in *Figure 7* for
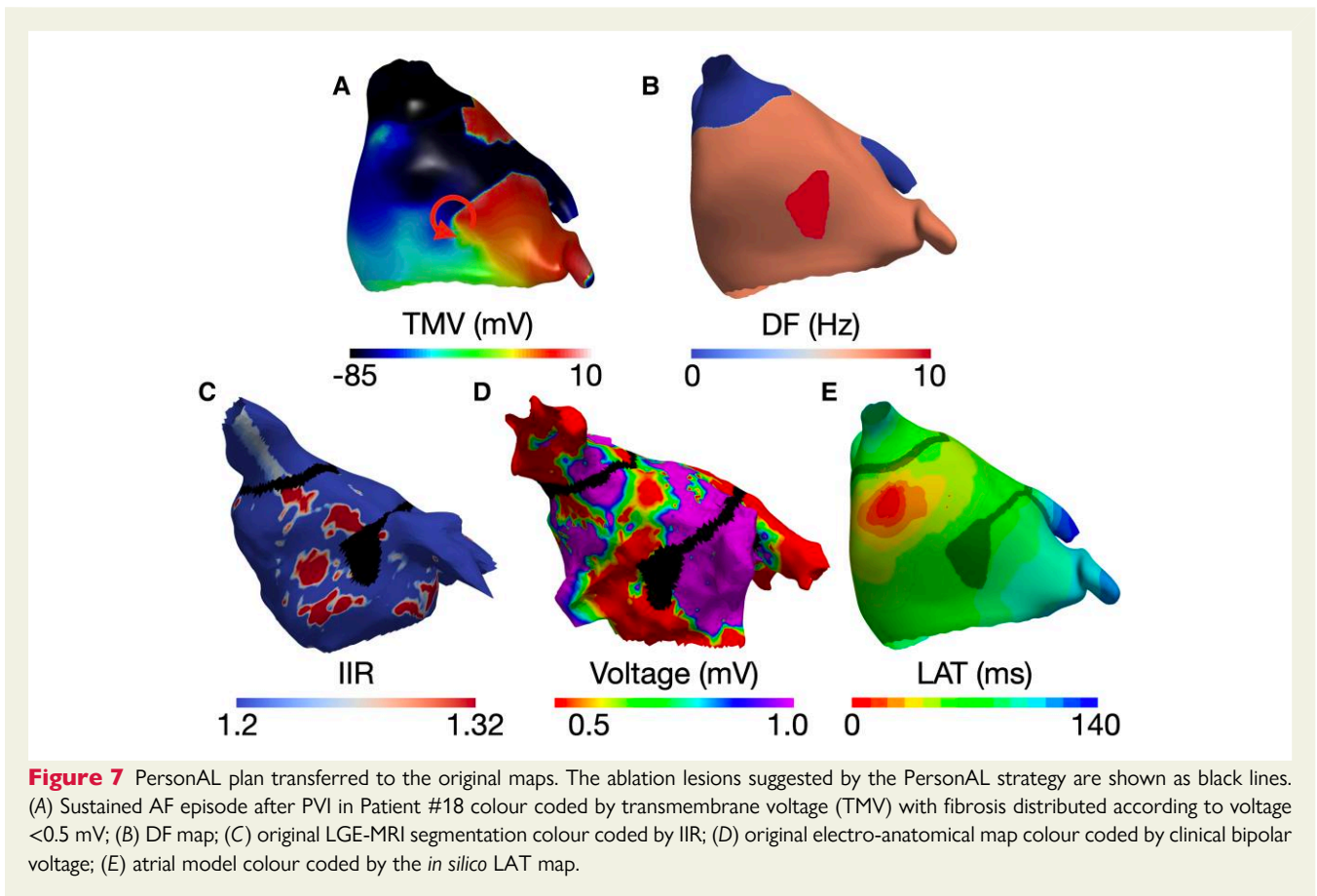
Patient #18 facilitates future clinical translation. Importing the PersonAL strategy into the clinical mapping system could provide not only a reliable and accurate prediction of AF ablation targets but could also avoid time-consuming and difficult mapping of AF drivers.

Comparison to previous studies providing computer-guided ablation strategies

Previous works attempted to use personalized computational simulations to guide clinical ablation of AF in patients.[18,20,21]

In Shim *et al.*,[21] atrial models consisted of endocardial CT-based LA shells only and AF was induced using a non-personalized pacing protocol (rapid pacing) applied only at the Bachmann's bundle location. The fibre orientation was not considered in the atrial models. A fixed isotropic conduction velocity of 0.4 m/s and no regional differences in myocyte action potentials were considered to represent patient electrophysiology. Four different anatomical ablation strategies (PVI only, PVI + lines), manually applied point-by-point on a user interface, and a CFAE-guided ablation were tested and the best-performing in the simulations was empirically selected as the one to be executed clinically. No AF reinducibility was assessed post-ablation.

The OPTIMA approach presented by Boyle *et al.*[20] targeted, in personalized bi-atrial models, the RD-perpetuating areas within the fibrotic substrate derived from LGE-MRI, including those that

Figure 7 PersonAL plan transferred to the original maps. The ablation lesions suggested by the PersonAL strategy are shown as black lines. (*A*) Sustained AF episode after PVI in Patient #18 colour coded by transmembrane voltage (TMV) with fibrosis distributed according to voltage <0.5 mV; (*B*) DF map; (*C*) original LGE-MRI segmentation colour coded by IIR; (*D*) original electro-anatomical map colour coded by clinical bipolar voltage; (*E*) atrial model colour coded by the *in silico* LAT map.

appeared after a first application of virtual ablation. Atrial fibrillation was induced using the same train of pulses for each patient. Conduction velocity in non-fibrotic tissue was set to 0.43 m/s. The final plan was imported, via co-registration, on the electro-anatomical mapping system. Nonetheless, the lack of full patient-specific electrophysiological properties could bring a level of uncertainty in identifying the OPTIMA targets. While RD dynamics are influenced by fibrosis distribution, other factors play important roles as well.[37] In Deng *et al.*,[37] fibrotic tissue was included in the models based on the IIR and the conduction velocity was modified within the fibrotic regions. Therefore, slow conduction areas were set to be the same as fibrotic tissue. Even in that case, changes in APD/CV enhanced or decreased the probability that an RD anchored to a specific location.[37] Even if using non-invasive clinical data only can be seen as an advantage due to the extended time frame to generate computational models, the level of uncertainty present in patient-specific atrial models reconstructed without any invasive measurements (i.e. incorporating each individual's unique distribution of fibrotic tissue from medical imaging alongside an average representation of AF-remodelled electrophysiology) is sufficiently high that a personalized ablation strategy based on targeting simulation-predicted RD trajectories alone may not be related to the real arrhythmogenic substrate in the patient.[37] Therefore, having insights on electrophysiological properties are important since they could result in RDs sometimes relocating to or appearing in other portions of the atria.

In Lim *et al.*,[18] the generation of atrial models requires multiple manual steps, from the pre-processing of the clinical geometries to the registration of the electro-anatomical map onto the imaging segmentation. Even if the registration between the electro-anatomical map and the CT model was performed by an experienced technician, any registration error due to the manual procedure during the clinical mapping process that may have had an impact on the accuracy of the model cannot be excluded. Computer simulations are performed on a monolayer surface mesh, neglecting the myocardial thickness and the different fibre arrangement between endocardium and epicardium. Inducibility was assessed stimulating from one point close to the Bachmann bundle only. Reducing drastically the chances of unveiling all possible regions vulnerable to sustain arrhythmia. No virtual ablation is performed and, therefore, no ablation success rate is delivered.

In Roney *et al.*,[19] atrial geometries derived from tomographic segmentations were manually processed and labelled. The endocardial and epicardial fibres were not calculated on the respective anatomical mesh but were mapped from an atlas and integrated in the model using the universal atrial co-ordinates. Fixed conductivity values were initially globally assigned to the models and then regionally scaled according to the normalized LGE-MRI intensity values. However, electrophysiological remodelling was modified regionally according to the IIR values. A single and equivalent phase distribution map consisting of four PSs was used as initial state to induce AF in all atrial models. The substrate ablation strategies were limited to target fibrotic tissue identified using LGE-MRI maps. No reinducibility was tested.

We proposed a highly automated framework to generate atrial digital twins with the selection of only one reference point per atrium.[17] In the case both non-invasive imaging data and intra-cardiac maps are available, all electrophysiological information was automatically integrated in the resulting bilayer atrial models augmented by using a SSM and rule-based fibre orientation.

Information from different clinical modalities (e.g. IIR or LVA) can be used to inform the spatial distribution of fibrosis in the model and conduction velocity is locally tuned to match the clinical LAT map. Atrial fibrillation vulnerability is assessed on the patient-specific atrial models using our personalized inducing protocol[16] in multiple pacing locations, unveiling all possible AF-sustaining regions. Drivers are automatically identified and targeted for ablation. The process is repeated until no AF episode can be initiated. Finally, the final PersonAL plan is transferred to the original clinical system (tomographic imaging or electro-anatomical mapping system). Moreover, numerous different ablation strategies were exhaustively compared in a rather large patient cohort and the ablation success was evaluated in almost 200 induced AF episodes.

Heterogeneous anatomical thickness was shown to have an influence on RD dynamics.[38] However, this was mostly presented in the right atrium, in the proximity of the pectinate muscles and crista terminalis.[38] Even if no volumetric meshes were used in the current atrial models, the bilayer models demonstrated to be able to simulate endo-epicardial wave propagation delay and integrated different fibre arrangements in the endocardium and epicardium.[25]

Although right atrial driver sites in patients with AF are less frequent than triggers in the LA, the current LA-only models would not be able to detect RA trigger sites. However, the pipeline was shown to be able to generate bi-atrial personalized models when both LA and RA were provided.[17] In case no RA information is present, the closest instance of a bi-atrial SSM could be used to infer the RA anatomy.[24] Atrial fibrillation vulnerability assessment and ablation of AF drivers could be conducted following the same methodology in a bi-atrial model.

Future studies could include the simulation of ectopic foci as the cause of arrhythmic episodes.

Different modelling strategies of fibrotic tissue were shown to influence the dynamics of arrhythmic episodes. We decided to include both the zig–zag propagation effect due to myocites' electrical decoupling and the presence of cytokines.

Translational perspective

Our pipeline offers a reproducible and comprehensive platform to assess AF vulnerability and provide patient-specific treatments using highly detailed anatomical and functional atrial digital twins. We have presented a new technology for tailored ablation guided by computer simulations which outperformed conventional approaches and demonstrated its feasibility in an *in silico* study in a cohort of 29 patients. Our study highlighted that a clear characterization and ablation of the fibrotic substrate leads to high success (>90%). Iteratively identifying and targeting for ablation high dominant frequency regions with our PersonAL plan resulted in AF termination and prevented recurrence in the whole patients' cohort. Connecting lines to the nearest non-conductive barrier prevented recurrence and increased ablation success. This work is a step

forward in the direction of personalized medicine using digital twins to guide patient-specific catheter ablation therapy for the most common human arrhythmias as atrial fibrillation and atrial tachycardia.

Supplementary material

Supplementary material is available at *Europace* online.

Data availability
The anatomical models underlying this article are publicly available on Zenodo: https://doi.org/10.5281/zenodo.5589289. Simulations were performed using the open electrophysiology simulator openCARP.[39] The source code of the AugmentA algorithm can be found online at https://github.com/KIT-IBT/AugmentA.

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