frontiers
in Physiology

Linking Electrical Drivers With Atrial Cardiomyopathy for the Targeted Treatment of Atrial Fibrillation

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The relationship between atrial fibrillation (AF) and underlying functional and structural abnormalities has received substantial attention in the research literature over the past decade. Significant progress has been made in identifying these changes using non-invasive imaging, voltage mapping, and electrical recordings. Advances in computed tomography and cardiac magnetic resonance imaging can now provide insight regarding the presence and extent of cardiac fibrosis. Additionally, multiple technologies able to identify electrical targets during AF have emerged. However, an organized strategy to employ these resources in the targeted treatment of AF remains elusive. In this work, we will discuss the basis for mechanistic importance of atrial fibrosis and scar as potential sites promoting AF and emerging technologies to identify and target these structural and functional substrates in the electrophysiology laboratory. We also propose an approach to the use of such technologies to serve as a basis for ongoing work in the field.

Keywords: atrial fibillation, fibrosis, cardiac imaging, electrophysiologic mapping, electrical rotors, focal sources

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the United States (Chugh et al., 2014). Catheter ablation is offered for patients with symptomatic AF despite medical therapy (January et al., 2014, 2019; Calkins et al., 2017), but success rates for ablation of persistent AF continues to be suboptimal with recurrent AF occurring in around 40–60% of patients in the landmark CABANA (Packer et al., 2019) and STAR-AF2 (Verma et al., 2015) trials. Potential contributing factors to the suboptimal success rates are the diverse phenotypes of atrial structural and functional abnormalities seen in patients with AF (Kottkamp, 2013; Krummen et al., 2015). While emerging technologies are now able to detect, classify, and target abnormal atrial substrate, their use is not well guided by existing guidelines or supported by randomized clinical trials (Quintanilla et al., 2016; Calkins et al., 2017). The purpose of this review is to propose a personalized AF ablation strategy utilizing emerging mapping and imaging techniques to target electrical drivers with or without associated atrial fibrosis. First, electrical and structural mechanisms of AF are summarized, followed by a review of the evidence linking fibrosis with electrical drivers of AF. Second, contemporary electrical invasive and non-invasive mapping and imaging techniques are discussed to localize electrical drivers and fibrosis. Finally, a proposed algorithm is proposed to help

guide personalized clinical treatment using these technologies and guide further clinical research.

DIVERSE ATRIAL SUBSTRATES UNDERLYING AF

In clinical practice, AF patients present with a spectrum of atrial electrical and structural substrates (Everett and Olgin, 2007; Kottkamp, 2013; Goette et al., 2016). **Figure 1** compares two patients from our electrophysiology laboratory with contrasting degrees of atrial cardiomyopathy. Patient 1 presented with persistent AF who remained symptomatic despite medical management and was referred for ablation. Voltage and activation mapping revealed relatively preserved bi-atrial voltages (**Figure 1A**) and a rapid left upper pulmonary vein electrical driver perpetuating AF (**Figure 1B**). Localized ablation terminated AF, which was subsequently non-inducible. In this patient with normal structural substrate, the AF was likely driven by an electrical driver from the pulmonary veins, as classically described (Haïssaguerre et al., 1998).

Patient 2 presented with recurrent persistent AF despite prior pulmonary vein isolation ablation. Voltage mapping revealed diffuse low voltage in the left atrium (**Figure 1C**), while panoramic multielectrode catheter mapping identified a rotational AF driver at the LA roof (**Figure 1D**). Limited ablation in the region of this driver terminated AF (**Figure 2C**), and the patient has remained in sinus rhythm during follow-up. In this patient with significant atrial fibrosis, extra-pulmonary vein drivers arising from the fibrotic substrate likely contributed to AF maintenance. These two examples demonstrate a broad spectrum of the structural and electrical substrate that may underly AF. While increasing atrial fibrosis typically correlates with a greater prevalence of extra-pulmonary vein sources (Angel et al., 2015; Cochet et al., 2018), counterintuitively, patients without fibrosis may have persistent AF while patients with extensive atrial fibrosis due to atrial cardiomyopathy may only have brief paroxysms of AF (Kottkamp, 2013). In a study by Kircher et al. (2018) in which invasive substrate mapping was performed in 119 patients, only 40% of persistent AF patients had low voltage zones, yet low voltage zones were still found in 18% of paroxysmal AF patients. While the AF source in the first patient would have been accounted for with guideline-directed pulmonary vein isolation (Haïssaguerre et al., 1998; Narayan et al., 2008), the driver located at the left atrial roof in patient 2 would not. Such examples, prevalent in the literature (Narayan et al., 2012a; Shivkumar et al., 2012) demonstrate the need for additional guidance regarding the use of patient-specific mapping and targeting strategies to treat AF.
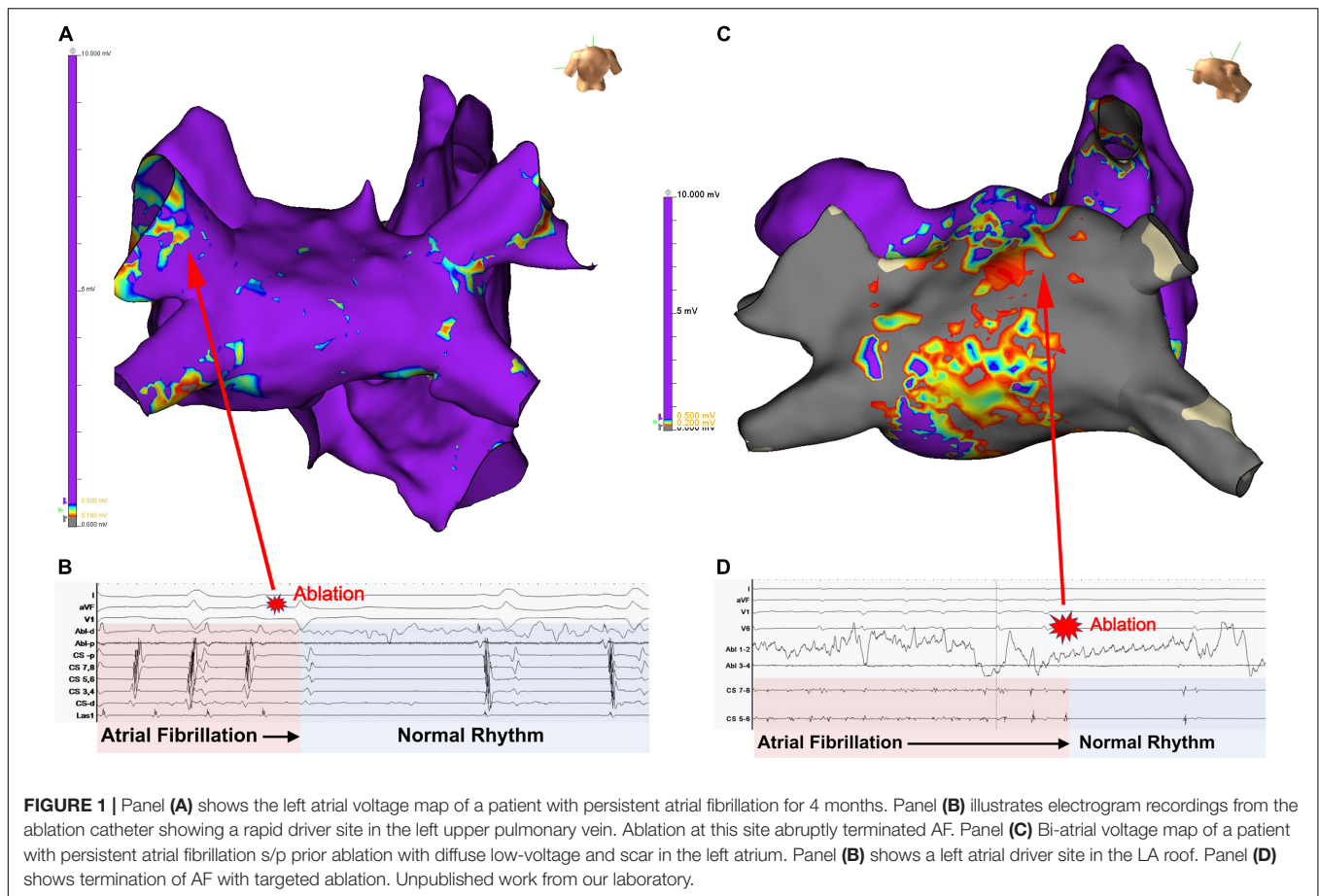
MECHANISMS OF ATRIAL FIBRILLATION

There remains controversy surrounding the exact mechanisms of AF. This is likely due to multiple phenotypes of the arrhythmia and reflects a heterogeneous substrate (Krummen et al., 2015; Quintanilla et al., 2016; Calkins et al., 2017). Both abnormal

electrical (Krummen et al., 2012; Baykaner et al., 2014, 2018; Haissaguerre et al., 2014; Schricker et al., 2014; Quintanilla et al., 2016) and structural/fibrotic abnormalities (Everett and Olgin, 2007; McDowell et al., 2013, 2015; Gonzales et al., 2014; Hansen et al., 2015, 2018; Sohns and Marrouche, 2020) have been implicated as mechanisms of AF, and may be different for each patient.

Electrical Substrate

Abnormal electrical substrate underlying AF may exist with or without the presence of fibrosis, and can be divided into 3 phases: initiation, transition and maintenance (Heijman et al., 2014; Krummen et al., 2015).

1. Initiation: The initiation of AF is thought to arise from rapid activation from a source, including the pulmonary veins (Haïssaguerre et al., 1998), superior vena cava, or other rapid foci (Gerstenfeld et al., 2003; Lin et al., 2003; Chen and Tai, 2005; Van Campenhout et al., 2013; Hayashi et al., 2015). This rapid ectopic activity can be caused by triggered activity [abnormalities in calcium handling leading to delayed afterdepolarizations (Dobrev et al., 2011) or loss of K + currents and delayed repolarization leading to early afterdepolarizations (Zellerhoff et al., 2009)] and abnormal automaticity, which have all been described around the LA/PV junction (Chou et al., 2005; Numata et al., 2012). At present, the standard of care for AF ablation is directed primarily at targeting triggers of AF from the pulmonary veins only. While reasonably effective, long-term elimination of AF triggers may be difficult or impossible, depending upon the rate of trigger formation, the dispersal of AF sources, and their frequency during invasive mapping and ablation procedures.

2. Transition: The transition period is the time during which the rapid activations from a focal source interact with regions with heterogeneous repolarization properties resulting in regional wavefront block, wavefront slowing, and the initiation of reentry (Krummen et al., 2012; Lalani et al., 2012; Schricker et al., 2014). This tissue heterogeneity can be manifested by both spatial dispersion of atrial fibrosis (Li et al., 1999; Chang et al., 2007) and ion currents [such as density of the rapid delayed rectifier current IKr (Li et al., 2001)], causing differences in conduction slowing, tissue refractoriness, and steep APD restitution (Krummen et al., 2012) to favor reentry.

3. Maintenance: Although the precise mechanisms of AF maintenance are incompletely understood, there is increasing evidence that AF is maintained by organized mechanisms. The exact type of organization is a topic of controversy, as some groups have proposed that AF is maintained via dissociated endo-epicardial breakthroughs (de Groot et al., 2010) or focal or rotational drivers (Jalife, 2003; Baykaner et al., 2014; Haissaguerre et al., 2014; Lalani et al., 2014; Schricker et al., 2014; Hansen et al., 2015, 2017, 2018; Quintanilla et al., 2016; Zahid et al., 2016; Csepe et al., 2017; Nattel et al., 2017; Zhao et al., 2017). Recent seminal work has demonstrated that rotational and

FIGURE 1 | Panel **(A)** shows the left atrial voltage map of a patient with persistent atrial fibrillation for 4 months. Panel **(B)** illustrates electrogram recordings from the ablation catheter showing a rapid driver site in the left upper pulmonary vein. Ablation at this site abruptly terminated AF. Panel **(C)** Bi-atrial voltage map of a patient with persistent atrial fibrillation s/p prior ablation with diffuse low-voltage and scar in the left atrium. Panel **(B)** shows a left atrial driver site in the LA roof. Panel **(D)** shows termination of AF with targeted ablation. Unpublished work from our laboratory.

focal drivers exist at sites that terminate AF when ablated, reinforcing the role of organized drivers maintain (Zhao et al., 2017; Kowalewski et al., 2018; Zaman et al., 2018; Leef et al., 2019).
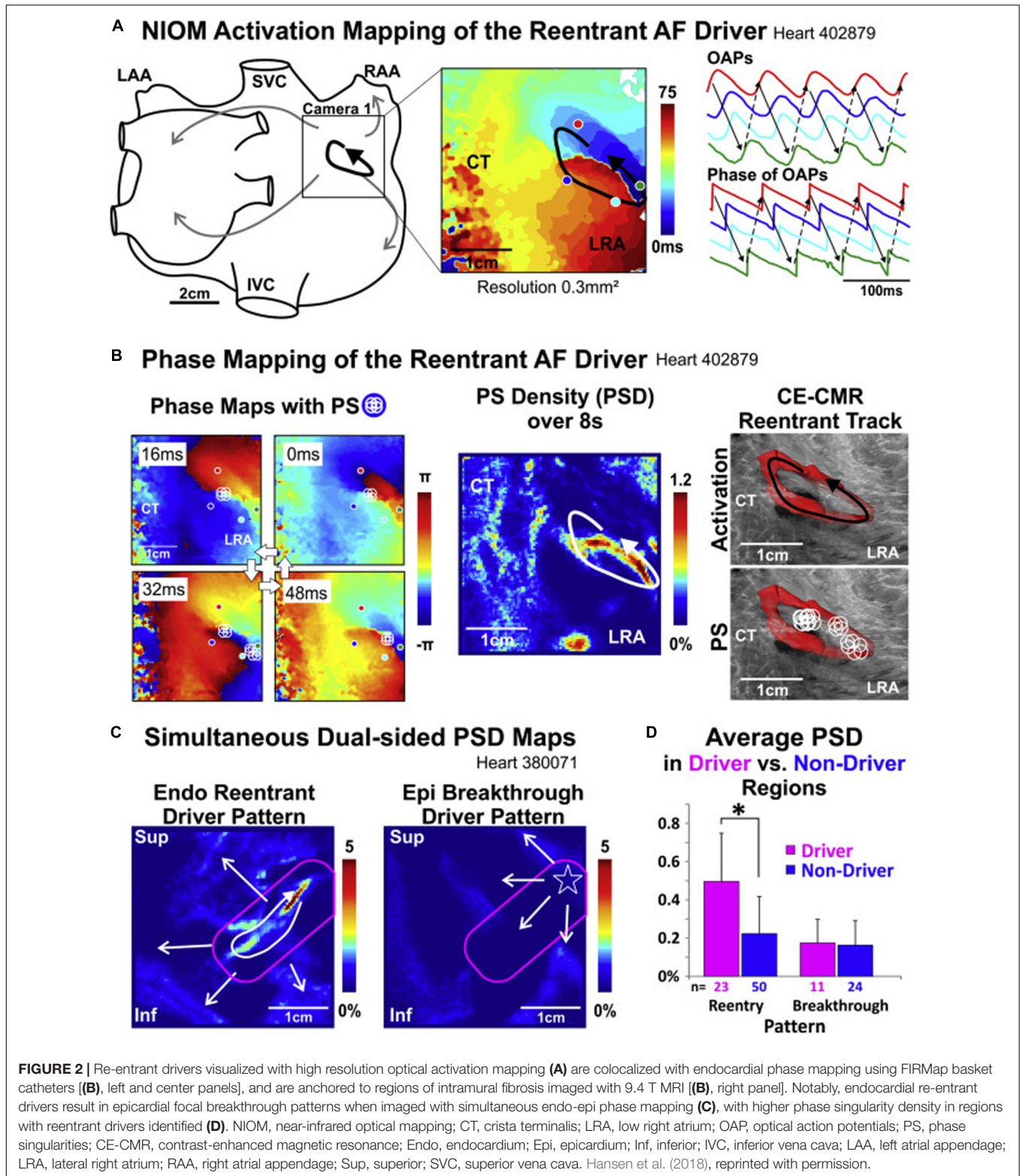
Contribution of Fibrosis to Tissue Electrical Remodeling

Fibrotic atrial myopathy is associated with alterations in ionic currents, calcium cycling, and gap junctions leading to electrophysiologic remodeling and increased atrial susceptibility to triggered activity, automaticity, and reentry (Nattel et al., 2008; Shen et al., 2019). First, triggered activity may result from direct myofibroblast-cardiomyocyte interactions via gap junction coupling and diastolic depolarization of atrial myocytes by fibroblasts (Yue et al., 2011; Heijman et al., 2014). Secondly, fibroblast ion channel remodeling may also promote AF, with increased expression of $Ca + +$ permeable TRPC3 channels and direct myofibroblast-cardiomyocyte interactions which cause conduction slowing due to $Na +$ channel inactivation and impaired cell-cell coupling (Heijman et al., 2014). Changes in ionic channel properties occur with significant heterogeneity between the left and right atria, which may explain the propensity of AF to originate from the left atrium (Caballero et al., 2010). Remodeling of gap junctions such as connexin 40 and 43 and their expression, distribution, and intercellular orientation

in atrial myopathy causing anisotropic conduction leading to reentry has been attributed to sustained AF (Shin et al., 2015). Finally, fibrosis and collagen deposition directly causes conduction slowing and heterogeneity.

Linking Fibrosis to Electrical AF Drivers

Advances in understanding the effects of fibrosis on electrical remodeling described above has provided a cellular basis that support recent observations correlating regions of fibrosis with focal and reentrant AF drivers. Prior work has demonstrated the relationship between functional electrical reentry and atrial structural heterogeneities such as fibrosis (Morgan et al., 2016) and fiber-angle discontinuities (Gonzales et al., 2014). Elegant *ex vivo* studies by Fedorov and colleagues reveal that AF re-entrant drivers are anchored to micro-anatomic regions of interstitial fibrosis (Hansen et al., 2015, 2016, 2017, 2018; Csepe et al., 2017; Zhao et al., 2017). In explanted human bi-atrial tissue sections shown in **Figure 2**, reentrant drivers were identified with high resolution optical activation mapping (**Figure 2A**) and colocalized using endocardial basket catheters (**Figure 2B**, left and center panels) with a clinical phase mapping system (FIRM, Abbott, Illinois) (Hansen et al., 2018). These drivers were anchored in regions of interstitial fibrosis imaged using high resolution 9T MRI (**Figure 2B**, right panel). Notably, epicardial electrodes revealed

FIGURE 2 | Re-entrant drivers visualized with high resolution optical activation mapping **(A)** are colocalized with endocardial phase mapping using FIRMap basket catheters [**(B)**, left and center panels], and are anchored to regions of intramural fibrosis imaged with 9.4 T MRI [**(B)**, right panel]. Notably, endocardial re-entrant drivers result in epicardial focal breakthrough patterns when imaged with simultaneous endo-epi phase mapping **(C)**, with higher phase singularity density in regions with reentrant drivers identified **(D)**. NIOM, near-infrared optical mapping; CT, crista terminalis; LRA, low right atrium; OAP, optical action potentials; PS, phase singularities; CE-CMR, contrast-enhanced magnetic resonance; Endo, endocardium; Epi, epicardium; Inf, inferior; IVC, inferior vena cava; LAA, left atrial appendage; LRA, lateral right atrium; RAA, right atrial appendage; Sup, superior; SVC, superior vena cava. Hansen et al. (2018), reprinted with permission.

epicardial breakthroughs at sites of the endocardial reentrant drivers (**Figure 2C**). Ablation of these re-entrant drivers terminated AF, verifying their dominant role in AF (Hansen et al., 2015; Zhao et al., 2017). These findings confirm

that the rotational drivers identified with phase mapping truly exist with high resolution optical activation mapping and reconcile how intramural rotational drivers may result in epicardial breakthroughs. Furthermore, these findings link

TABLE 1 | Clinical technologies to localize areas of fibrosis.

Technique	Advantages	Disadvantages	Landmark clinical studies
Cardiac MRI	Non-invasive, high signal-to-noise ratio	Artifact from cardiac devices, reproducibility of segmentation/windowing	DECAAF, Marrouche et al., 2014
Perfusion CT	High resolution, quick	Radiation, contrast	Ling et al., 2015
MRI-based computer modeling	Non-invasive, functional data in addition to structural data	Assumptions in computational model, variabilities with segmentation	Boyle et al., 2019
Electro-anatomic voltage mapping	High resolution, real-time	Invasive, time-intensive, assumptions of electrode recordings	Jadidi et al., 2016; Kottkamp et al., 2016; Yagishita et al., 2017

these electrical drivers with regions of fibrosis identified with high resolution MRI.

Likewise, clinical studies using non-invasive electrocardiographic imaging (ECGi) (Cochet et al., 2018) also correlated re-entrant drivers to late gadolinium-enhanced (LGE) areas on MRI. However, other clinical studies failed to correlate rotational drivers identified using invasive phase mapping with LGE on MRI (Chrispin et al., 2016) and electroanatomic voltage mapping (Schade et al., 2016). This discrepancy may reflect differences in mapping and imaging technologies, but may also highlight the possibility that electrical drivers can arise from (1) a purely electrical substrate [electrical remodeling altering cellular gap junction distribution (Fry et al., 2014; Shin et al., 2015) without fibrosis or shortened atrial refractory period (Wijffels et al., 1995)] or (2) structural heterogeneities such as fiber angle discontinuities found in the pulmonary vein antra (Narayan et al., 2008; Pashakhanloo et al., 2016) or crista terminalis (Gonzales et al., 2014), creating anisotropic conduction which may lead to reentry.

STRATEGIES TO ATTENUATE AND RISK-STRATIFY ATRIAL FIBRILLATION PRIOR TO ABLATION

Risk Factor Modification

Recent studies have shown that risk factor modification can reduce or suppress AF (Pathak et al., 2014, 2015; Lau et al., 2017). Obstructive sleep apnea (OSA) may lead to atrial electrophysiologic remodeling with increased atrial fibrosis and downregulation of connexin-43 due to repeated apneic episodes (Iwasaki et al., 2014). In a rat model, this resulted in substantial atrial conduction slowing and increased inducibility and duration of AF. Patients with OSA undergoing clinical AF ablation were found to have a reduction in bi-atrial voltage, widespread conduction abnormalities and longer sinus node recovery times (Dimitri et al., 2012).

Multiple studies have demonstrated the strong link between obesity and risk of developing AF. In sheep models, those with more significant obesity were found to have increased cytoplasmic transforming growth factor β1, platelet-derived growth factor, and larger left atrial size (Mahajan et al., 2015). Furthermore, there was also increased atrial fibrosis, infiltration of the epicardial fat into the posterior left atrial wall, heterogenous and slowed atrial conduction velocity, and higher rates of

inducible and spontaneous AF in the obese group in both sheep and humans (Munger et al., 2012; Abed et al., 2013). Weight reduction is associated with improved AF control. In the LEGACY study, weight loss of ≥10% resulted in a 6-fold increased probability of arrhythmia-free survival (Pathak et al., 2015). Similarly, the ARREST-AF study showed that weight reduction with other risk factor modifications resulted in longer arrhythmia-free survival after AF ablation (Pathak et al., 2014). These studies suggest that atrial remodeling associated with obesity may be reversible with weight reduction (Aldaas et al., 2019).
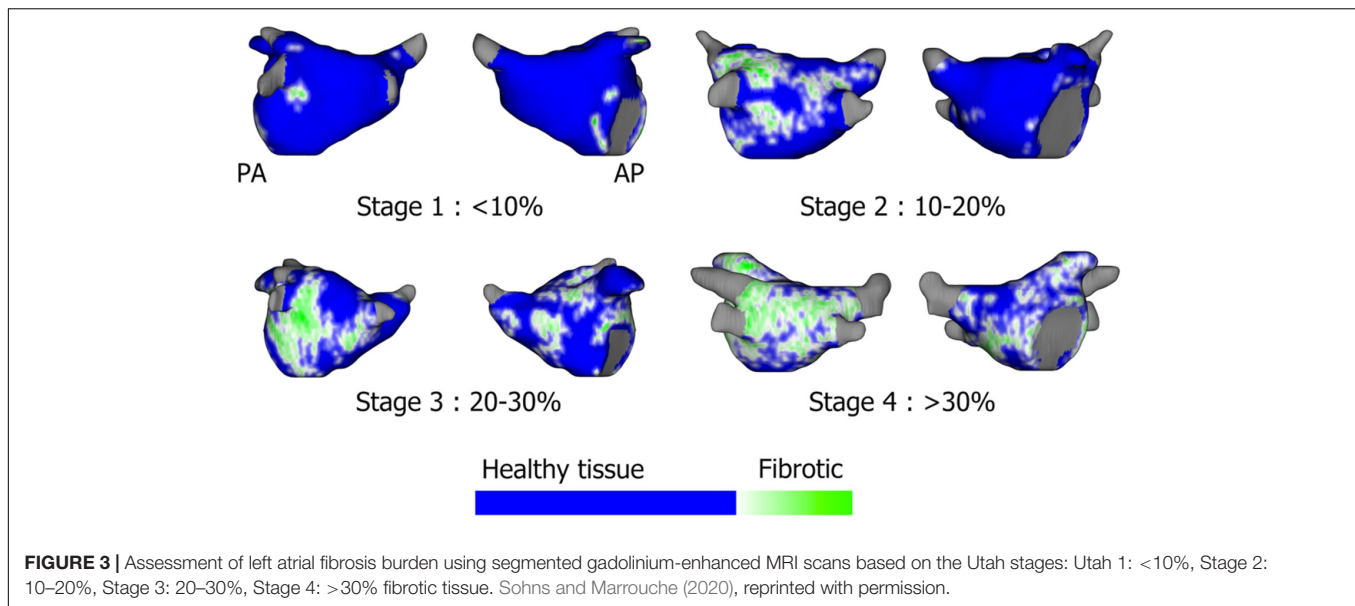
Varying degrees of alcohol consumption has been associated with risk of incident AF and recurrence of AF after catheter ablation. This may be partly contributed by alcohol's association with other known risk factors for AF such as obesity, hypertension, and disordered sleep pattern. However, prior work has shown acute changes in atrial electrophysiology as a direct result of alcohol consumption and binge drinking, including shortening of the effective refractory period, slowed intra-atrial conduction, and prolonged p wave duration (Voskoboinik et al., 2016). Additionally, chronic drinking is an independent multivariate predictor of discrete atrial fibrosis (Qiao et al., 2015). Regarding the effect of alcohol cessation on burden of AF, the ARREST-AF study demonstrated decreased AF recurrence and symptom severity in patients with risk factor management including decreased alcohol consumption (Pathak et al., 2014).

Identify Fibrosis

Atrial fibrosis can be identified with a range of imaging and mapping technologies, of which some are detailed in a 2016 EHRA consensus statement (Donal et al., 2016). **Table 1** lists techniques that have been developed to characterize atrial substrate. However, it is important to note that all modalities identify indirect surrogates for atrial fibrosis, and use of fibrosis to guide ablation may be non-specific and as fibrosis is not synonymous with arrhythmogenicity.

Cardiac MRI

In some centers, cardiac MRI is used pre-procedurally to characterize atrial anatomy and burden of fibrosis in preparation for catheter ablation (Mahnkopf et al., 2010; Daccarett et al., 2011; Malcolme-Lawes et al., 2013; McGann et al., 2014; Calkins et al., 2017; Sohns and Marrouche, 2020). The multicenter prospective DECAAF trial (Marrouche et al., 2014) has established the role of MRI as a prognostic tool to predict success of PVI ablation based on the degree of atrial fibrosis (**Figure 3**). Additionally, other

FIGURE 3 | Assessment of left atrial fibrosis burden using segmented gadolinium-enhanced MRI scans based on the Utah stages: Utah 1: <10%, Stage 2: 10–20%, Stage 3: 20–30%, Stage 4: >30% fibrotic tissue. Sohns and Marrouche (2020), reprinted with permission.

studies have evaluated the ability of MRI to detect gaps in PVI lesions in order to identify PV reconnections (Bisbal et al., 2014). However, the utility of MRI to localize fibrotic areas as potential targets for ablation is still unknown and is under investigation with the DECAAF-2 trial (NCT 02529319). A limitation of current cardiac MRI technology is artifact from cardiac devices and variability in acquisition sequences and thresholding (Karim et al., 2013; Calkins et al., 2017). A second challenge is that fibrotic areas may not always correlate with arrhythmogenicity. Additional work is required to determine the optimal role of MRI in AF procedural planning.

MRI based computer simulations

One proposed method to identify areas of fibrosis with potential arrhythmogenicity is building computer simulations using fibrotic areas derived from MRI combined with electroanatomic computer simulations to identify re-entrant drivers. This technique was described in a proof-of-concept clinical study showing feasibility of this non-invasive method (Zahid et al., 2016; Boyle et al., 2019). Prospective studies are needed to see whether this technique may improve AF ablation outcomes.

Cardiac CT

A proposed technique using perfusion cardiac computed tomography (CT) to identify surrogate regions of fibrosis was described by Ling and colleagues (Ling et al., 2015). In this technique, contrast-enhanced gated cardiac CT were segmented by degree of contrast attenuation, and areas of low attenuation correlated with low voltage points obtained from invasive electroanatomic bipolar voltage maps ($p = 0.04$) and qualitative agreement in about 80% of patients. Contemporary cardiac CT provides improved resolution (∼0.5 mm) as compared to MRI (∼1.5–2.0 mm) (Saeed et al., 2015), but has a lower signal-to-noise ratio. Although cardiac CT imaging is routinely obtained for evaluation of gross atrial anatomy prior to AF ablation, additional work is needed to both improve the ability of CT

perfusion imaging to detect fibrosis and define its role in targeting AF-sustaining substrate.

Electro-Anatomic mapping

Invasive electroanatomic mapping is an established method of characterizing electrical substrate to identify regions as a surrogate for fibrosis. Improvements in electroanatomic mapping systems and multi-electrode mapping catheters have enabled spatial resolution down to 2–3 mm and higher density maps. Similar to substrate homogenization-based strategies to ablate ventricular tachycardia, individually tailored substrate ablation has been proposed and studied for AF. However, unlike ventricular tachycardia in which substrate mapping can be used to define the critical isthmus of a scar-based monomorphic VT circuit, the precise fibrotic microstructure underlying AF is less well characterized.

The efficacy of a substrate modification approach utilizing box isolation of fibrotic areas (BIFA) was tested in 28 patients with both paroxysmal and persistent AF who had low voltage areas <0.5 mV identified using a contact force ablation catheter (Kottkamp et al., 2016). The BIFA approach entails surrounding low voltage areas with linear ablation lines anchored to non-conducting regions such as wide area circumferential (WACA) ablation circles. This resulted in a 90% 1 year freedom in 10 paroxysmal AF patients and 72% 1 year freedom in 18 persistent AF patients. In another study by Kircher et al. (2018), 124 patients with either paroxysmal or persistent AF undergoing PVI were randomized to additional standard linear ablation versus an individually tailored approach to target low voltage areas. Voltage mapping was performed using a circular mapping catheter (1 mm electrode spacing) with low voltage cut-offs of <0.5 mV. Ablation of these voltage areas either in a cluster, linear ablation anchored to non-excitable regions or box isolation resulted in a significant improvement in freedom from atrial arrhythmia (68 vs 42%) after a single procedure. Although there was an improvement in this technique over empiric linear ablation, the recurrence in almost a

third of patients suggests that the underlying etiology of AF in these patients still has not been fully addressed. Disadvantages to substrate homogenization include the non-specificity of low voltage zones without integrated functional data and limitations of invasive voltage mapping described below.

Several clinical studies have attempted to characterize voltage cut-offs to represent the spectrum of atrial fibrosis (**Table 2**). In general, these studies used either ablation catheters with 4 mm electrodes (Oakes et al., 2009; Spragg et al., 2012) or multi-electrode catheters (Verma et al., 2005; Kapa et al., 2014; Rolf et al., 2014; Anter et al., 2015; Kottkamp et al., 2016) with 1 mm electrodes and 2–6 mm electrode spacing to define: dense scar at <0.2 mV, borderzone fibrosis at <0.5 mV and normal tissue >0.5 mV when compared in AF patients with healthy or abnormal atria, by the presence of LGE on MRI in 4 studies (Oakes et al., 2009; Spragg et al., 2012; Kapa et al., 2014; Anter et al., 2015). However, some investigators have argued abnormal tissue can exist with voltages <1.5 mV and viable tissue exists at >0.05 mV. This discrepancy could be contributed by several limitations and misconceptions of interpreting low voltage as a surrogate for fibrosis as described by Josephson and Anter (2015). Electrogram voltage may be affected by conduction velocity, fiber orientation and curvature, relationship of fiber orientation to the propagating wavefront, tissue contact, edema, fat and characteristics of the recording catheter such as electrode size, interelectrode spacing. Newer multielectrode catheters have been developed which could potentially address some of these issues, such as the orthogonal grid catheters and high-density baskets with 0.4 mm electrodes; however, these have not been systematically studied in this regard.

Identifying AF Triggers

Patients who have a high burden of atrial flutter or supraventricular tachycardias (SVT) may undergo atrial remodeling and develop both electrical and fibrotic substrate for AF (Franz et al., 1997). Thus, identifying a defined, consistent trigger is an important component of an AF ablation strategy (Calkins et al., 2017).

Supraventricular Tachycardias and Atrial Tachycardia/Flutters

Prior studies have shown an association between AF and supraventricular tachycardia (SVT) (Sauer et al., 2006) and cavo-tricuspid isthmus dependent atrial flutters (TAFL) (Pérez et al., 2009). Based upon these studies, it is recommended to evaluate for co-existing SVT or atrial tachycardia/flutter mechanisms either before or after AF ablation.

Pulmonary Vein Triggers

Foundational work in AF ablation demonstrated the importance of pulmonary vein (PV) triggers to AF (Haïssaguerre et al., 1998). The initial approach to PV trigger ablation was to perform segmental pulmonary vein isolation. A subsequent randomized study by Arentz et al. (2007) demonstrated improved outcomes with wide area circumferential ablation (WACA) compared to segmental ablation, potentially by disrupting other sustaining AF mechanisms at the PV antra characterized by fiber angle discontinuities (Pashakhanloo et al., 2016) and increased repolarization restitution (Narayan et al., 2008).

Non-PV Triggers

Ongoing work has revealed that non-PV ectopic beats and PACs may be present in 10–33% of patients with AF (Chen and Tai, 2005; Takigawa et al., 2015; Santangeli et al., 2016; Hojo et al., 2017), and suggested the potential utility of aggressive trigger induction with high dose isoproterenol. These triggers may originate from the posterior LA wall, superior vena cava (SVC), crista terminalis, coronary sinus (CS), Eustachian ridge, Ligament of Marshall, and left atrial appendage (Lin et al., 2003; Chen and Tai, 2005; Calkins et al., 2017). Additional work is required to determine the significance of these triggers to perpetuation of AF and whether this approach yield long-term improvement in AF-free survival after ablation.

Identify Drivers

A challenge in mapping drivers of AF is that standard activation mapping techniques using point by point mapping are unable to fully resolve the evolving wavefront propagation patterns during

TABLE 2 | Studies of bipolar voltage cutoffs.

Voltage cut-off (mV)	Study	Mapping catheter used	Gold standard for fibrosis	Patients	Rhythm
<0.2: dense scar <0.5: diseased	Verma et al., 2005	Circular (2-6-2 mm spacing)	Clinical history	700	NSR
<0.1: dense scar >0.5: normal	Oakes et al., 2009	Linear (4 mm tip, 1-7-4 mm)	LGE-MRI	54	60% NSR
>0.5 mV: normal	Spragg et al., 2012	Linear (3.5 mm tip, 2 mm)	LGE-MRI	10	?
<0.27: scar >0.45: normal	Kapa et al., 2014	Circular (2-6-2 mm)	LGE-MRI	20	NSR
<0.2: scar >0.5: normal	Rolf et al., 2014	Circular (2-6-2 mm or 2-4-2 mm)	Clinical history	178	NSR
<0.25: dense scar >0.48: normal	Anter et al., 2015	Multi-spline (2-6-2 mm)	LGE-MRI	30	NSR
<0.5: scar >1.5: normal	Kottkamp et al., 2016	Circular (2-6-2 mm)	Clinical history	41	NSR

NSR, normal sinus rhythm; AF, atrial fibrillation.

AF due to lack of having a standard reference. A second challenge is that AF drivers potentially utilize several sites of abnormal substrate during ongoing AF.

To address these challenges, an increasing number of specialized electrogram processing techniques and panoramic mapping methods have been developed. The variety of technologies, their requirements, risks and available data are illustrated in **Table 3**.

Focal Impulse and Rotor Modulation

One of the first technologies developed to specifically target the sustaining mechanisms of AF was focal impulse and rotor modulation (FIRM) mapping (Narayan et al., 2012a,b,c, 2013). This technique utilizes 64-electrode basket catheter recordings during AF analyzed by computational activation and phase analysis to identify semi-stable focal (centripetal activation) and rotational activation patterns. The results from the initial trial of this approach were reported in the CONFIRM trial (Narayan et al., 2012d), in which 92 patients undergoing AF ablation underwent pulmonary vein isolation alone versus PVI plus rotor ablation. Patients undergoing PVI + FIRM ablation experienced a greater number of AF terminations during ablation and had a greater AF-free survival at a median of 273 days after ablation. Subsequent work demonstrated that these results were durable, improving AF-free survival over a median follow-up of 870 days (Narayan et al., 2014). These outcomes were reproduced in independent studies from more than 10 sites (Miller et al., 2014) including Miller et al. (2017) who reported their results for 170 consecutive patients undergoing AF ablation employing PVI plus AF rotor ablation. Freedom from all atrial arrhythmias was 75% in patients with persistent AF and 57% in longstanding persistent AF at 1 year, off antiarrhythmic drug therapy. A meta-analysis by Baykaner et al. (2018) analyzed all published studies of FIRM mapping and ablation found a significant improvement in freedom from atrial arrhythmia recurrence in patients undergoing pulmonary vein isolation plus FIRM ablation. Ongoing work is required to determine the precise population who maximally benefit from this approach.

Electrocardiographic Imaging

Electrocardiographic imaging (ECGVue, Medtronic, Minneapolis, MN) is a non-invasive technique utilizing a 252-electrode vest integrated with a non-contrast CT has been used to record unipolar epicardial potentials during AF using inverse solution modeling (Ramanathan et al., 2004). Similarly, phase mapping has been applied to these potentials (Haissaguerre et al., 2014), and in a study of 103 patients with persistent AF, identified rotational and focal drivers (**Figure 4**).

Although changing wavefronts and transient reentrant activity were observed, AF drivers occurred repetitively in the defined regions. Ablation of such regions terminated persistent AF in 75% of patients and resulted in 1 year freedom from AF in 85% of patients. In the AFACART study (Knecht et al., 2017) of 118 patients with persistent AF, a step-wise ablation approach (driver only then PVI then linear ablation) showed that driver-only ablation terminated AF in 64% of patients, and this step-wise approach resulted in single procedure 1 year freedom from AF in 78% of patients, though 49% experienced atrial tachycardia.
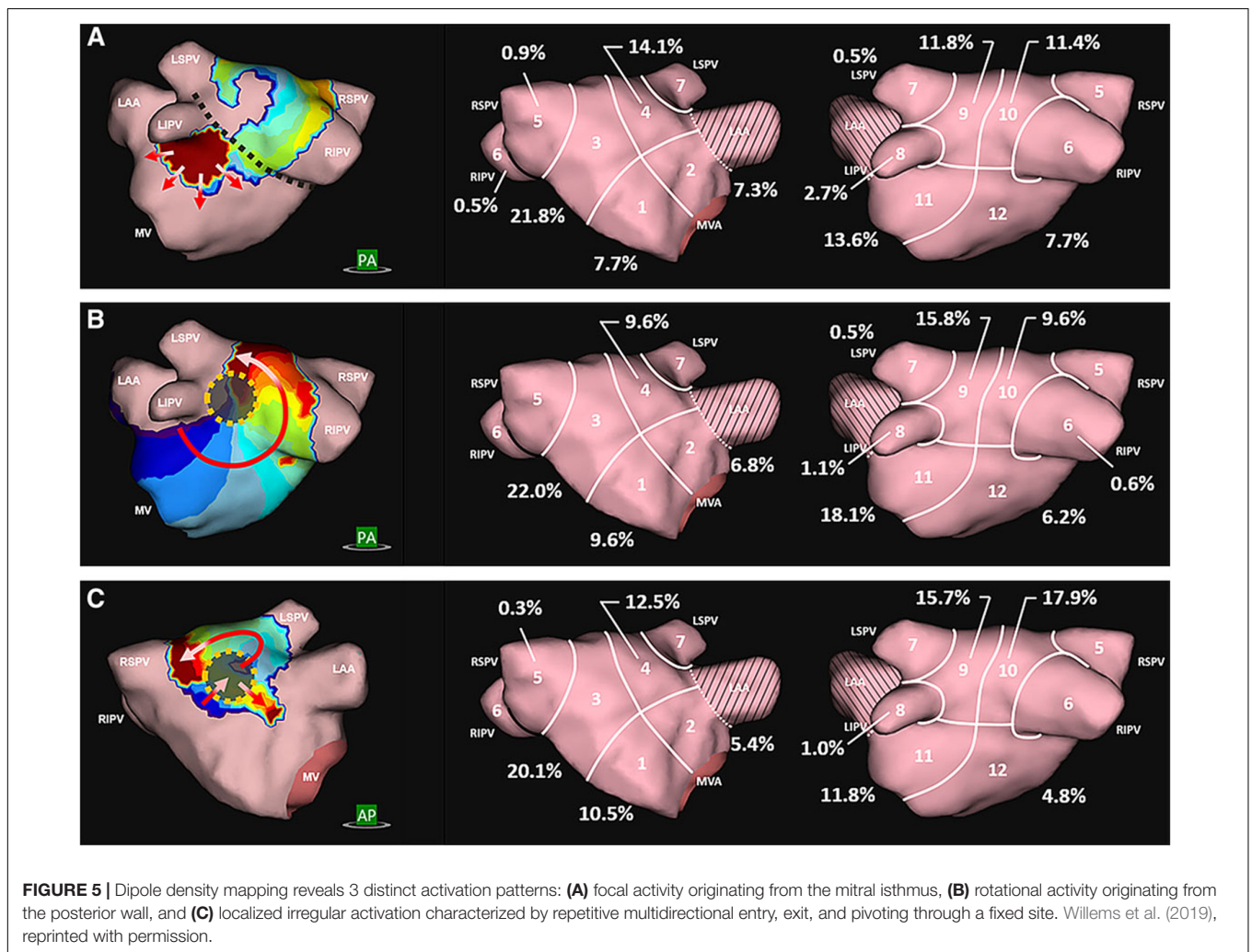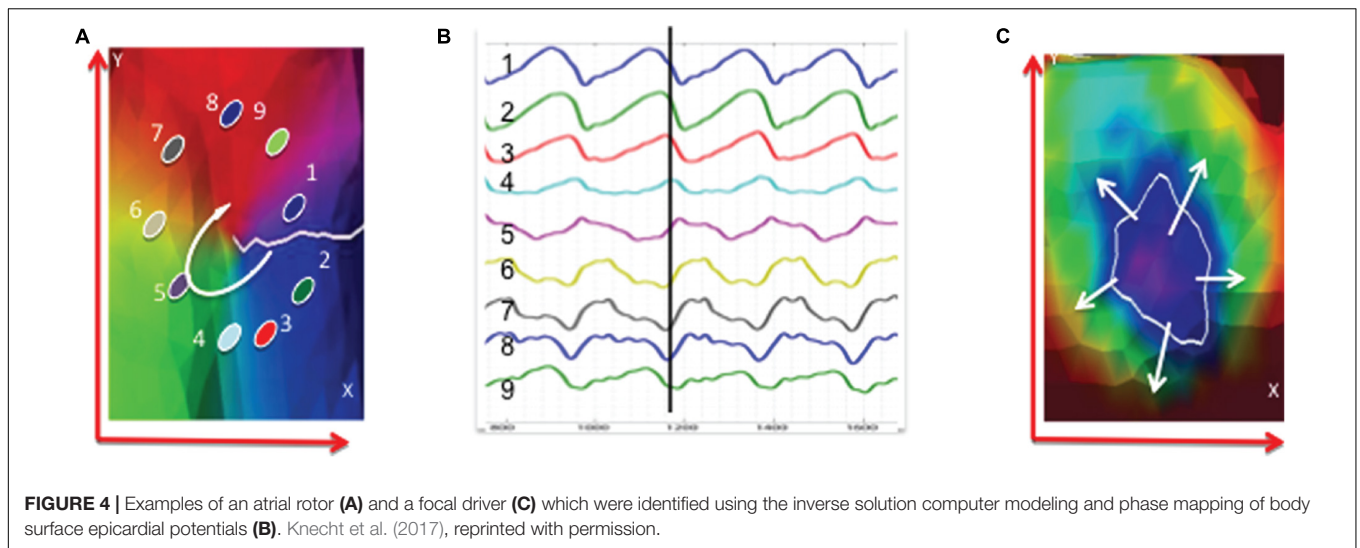
Dipole Density Mapping

A system using dipole density mapping combined with ultrasound (Grace et al., 2017; Shi et al., 2020) (AcQMap, Acutus Medical Inc., Carlsbad, CA, United States) has been developed to create high resolution endocardial activation maps (150,000 points per second). AcQMap consists of a basket catheter with 48 ultrasound transducers and electrodes to sample the intracardiac potential field to create an instantaneous activation map using a non-contact, inverse solution algorithm (**Figure 5**). This basket is placed via a 16 French steerable sheath.

The AcQMap system was validated with contact mapping in 20 patients (Shi et al., 2020) showing good agreement for points up to 4 cm away from the center of the catheter. It was prospectively studied in 127 patients with persistent AF in the multicenter UNCOVER-AF trial (Willems et al., 2019) and identified organized sources including localized irregular activation (repetitive conduction through a confined zone, **Figure 5C**), focal sources and rotational

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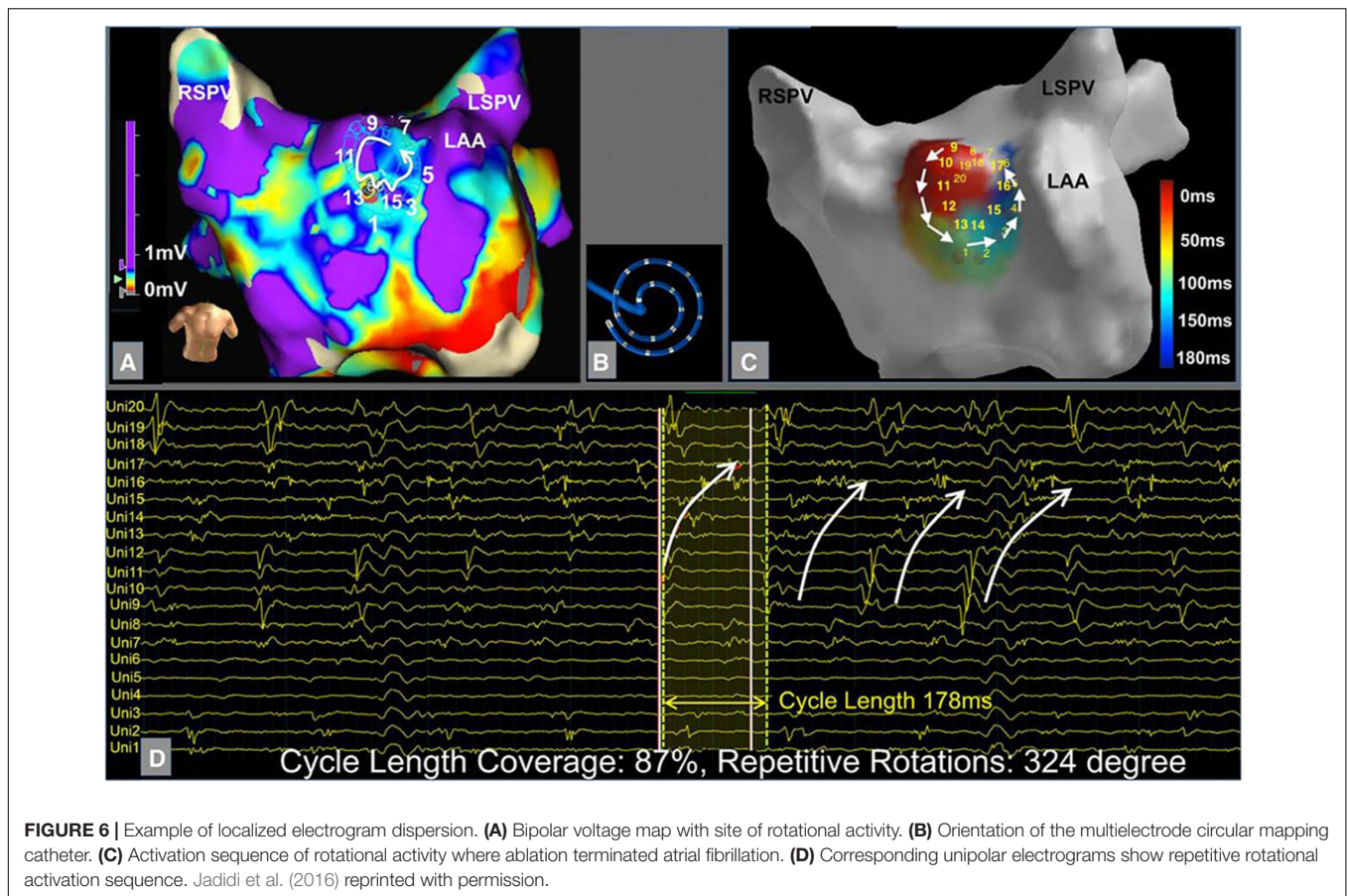**TABLE 3 |** Clinical technologies to Localize AF drivers.

Technique	First clinical study	Methodology	Equipment needed	Access	Disadvantages
FIRM	2012	Phase mapping	64-electrode basket	8.5 Fr sheath	Basket catheter tissue contact, false-positive rotors
ECGi	2014	Activation and phase mapping	252-electrode disposable vest	Non-invasive	Epicardial potentials only/misses septal sites
Localized Electrogram Organization	2016	Activation, voltage & EGM characteristics	Multi-electrode catheter	8.5 Fr sheath	Subjective qualititative EGM assessment, non-panoramic
CARTOFINDER	2018	Activation mapping	64-electrode basket	8.5 Fr sheath	Basket catheter tissue contact, activation mapping limited by low temporo-spatial resolution
Acutus	2019	Activation mapping	48 electrode basket	16 Fr sheath	Large 16 Fr trans-septal sheath risks
Wavefront Mapping	2019	Propagation vector mapping	64-electrode basket	8.5 Fr sheath	Basket catheter tissue contact
FAST	2020	Spectral and unipolar EGM	Multi-electrode catheter	8.5 Fr sheath	Non-panoramic method, time consuming

FIGURE 4 | Examples of an atrial rotor **(A)** and a focal driver **(C)** which were identified using the inverse solution computer modeling and phase mapping of body surface epicardial potentials **(B)**. Knecht et al. (2017), reprinted with permission.

FIGURE 5 | Dipole density mapping reveals 3 distinct activation patterns: **(A)** focal activity originating from the mitral isthmus, **(B)** rotational activity originating from the posterior wall, and **(C)** localized irregular activation characterized by repetitive multidirectional entry, exit, and pivoting through a fixed site. Willems et al. (2019), reprinted with permission.

activation were found with an average of 5 sources per patient. Ablation of these sources resulted in termination in 32% of patients and 1-year freedom from AF in 73% with a single procedure and 93% with a second procedure. Randomized studies are still needed to establish a clear benefit using this strategy.

FIGURE 6 | Example of localized electrogram dispersion. **(A)** Bipolar voltage map with site of rotational activity. **(B)** Orientation of the multielectrode circular mapping catheter. **(C)** Activation sequence of rotational activity where ablation terminated atrial fibrillation. **(D)** Corresponding unipolar electrograms show repetitive rotational activation sequence. Jadidi et al. (2016) reprinted with permission.

Localized Electrogram Dispersion

A few methods have been proposed using qualitative analysis of electrogram temporospatial organization obtained from standard circular or multi-spline catheters. These methods expand upon complex fractionated atrial electrogram (CFAE) mapping by further evaluating propagation of electrograms on neighboring electrodes in an organized fashion to determine the presence of an active driver. Jadidi et al. (2016) proposed a method to identify regions with low voltage (<0.5 mV, **Figure 6A**) and electrograms spanning >70% of the AF cycle length over neighboring electrodes (**Figures 6B,C**) to identify a surrogate of an AF driver.

In a prospective study of 62 patients with persistent AF, ablation of these low voltage areas in addition to PVI led to acute AF termination in 73% and single procedure 1 year freedom from AF in 69%, compared to 47% in a matched PVI only control group ($p < 0.001$).

Another method described by Seitz et al. (2017) involves localization of regions of temporal and spatial dispersion of electrograms (minimum of 3 adjacent bipoles with activation spanning the entire AF cycle length) using a multi-spline catheter (Pentaray, Biosense-Webster, CA, United States). In the SUBSTRATE HD study (Seitz et al., 2017) of 105 patients (77% persistent AF), ablation of only driver regions terminated AF in 95% of patients, and 1.5-year freedom from atrial arrhythmias (median 1.4 procedures) was 85% compared to 59% of a

validation control group who underwent step-wise PVI and linear ablation approach. Further randomized and multicenter centers with inexperienced operators are needed to confirm these promising results for localized driver ablation.
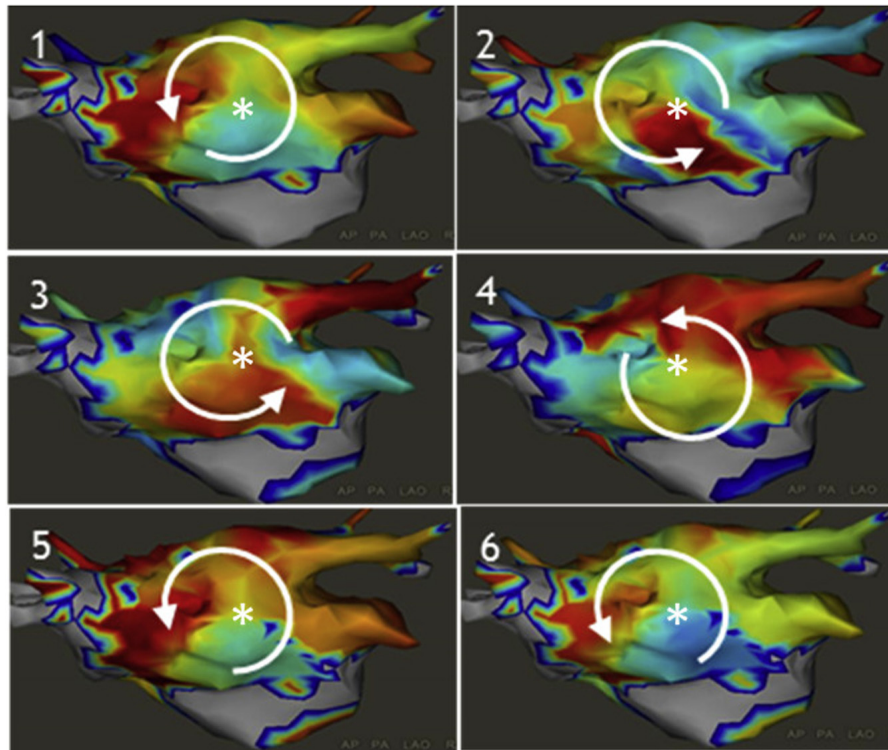
CARTOFINDER^{TM}

The CARTOFINDER^{TM} system (Daoud et al., 2017) is an activation mapping based algorithm that records unipolar endocardial electrograms from 64-electrode basket catheters (**Figure 7**, left panel). The system calculates the percentage of the atrial surface geometry that is covered by the basket to guide repositioning. Activation patterns are then analyzed on the CARTO system to identify focal or reentrant drivers (**Figures 7A–D**).

In a study of 20 patients with persistent AF, CARTOFINDER identified rotational or focal drivers in all patients and AF terminated in half of the patients with driver ablation (Honarbakhsh et al., 2018). Randomized, longer-term outcome studies are needed to determine whether this method may effectively identify drivers to improve freedom from AF.

Focal Source and Trigger Mapping (FaST)

A novel quantitative algorithm (Gizurarson et al., 2016; Daoud et al., 2017) identifying sites with periodicity

FIGURE 7 | Example of CARTOFINDER showing a counter clockwise rotational repetitive activation pattern through time (panels 1–6). Daoud et al. (2017) reprinted with permission.

and QS unipolar electrogram morphology was described by Chauhan et al. (2020). From bipolar and unipolar electrograms collected from a circular mapping electrode (Lasso, Biosense-Webster), the electrograms are analyzed by an algorithm (**Figure 8A**) that assesses bipolar EGM periodicity (segments with a spectral peak >10% of the total spectral power) and assesses the presence of QS morphology on the unipolar EGMs as a surrogate for organized focal drivers (**Figure 8B**).

This algorithm was tested in a randomized study of 80 patients (Chauhan et al., 2020) (48% persistent AF) to PVI + FAST versus PVI only, and resulted in a trend toward improved 1-year freedom from AF (74% with PVI + FAST compared to 51% with PVI-only, $p = 0.06$). Larger multicenter trials are needed to see if this method may significantly improve AF ablation success.
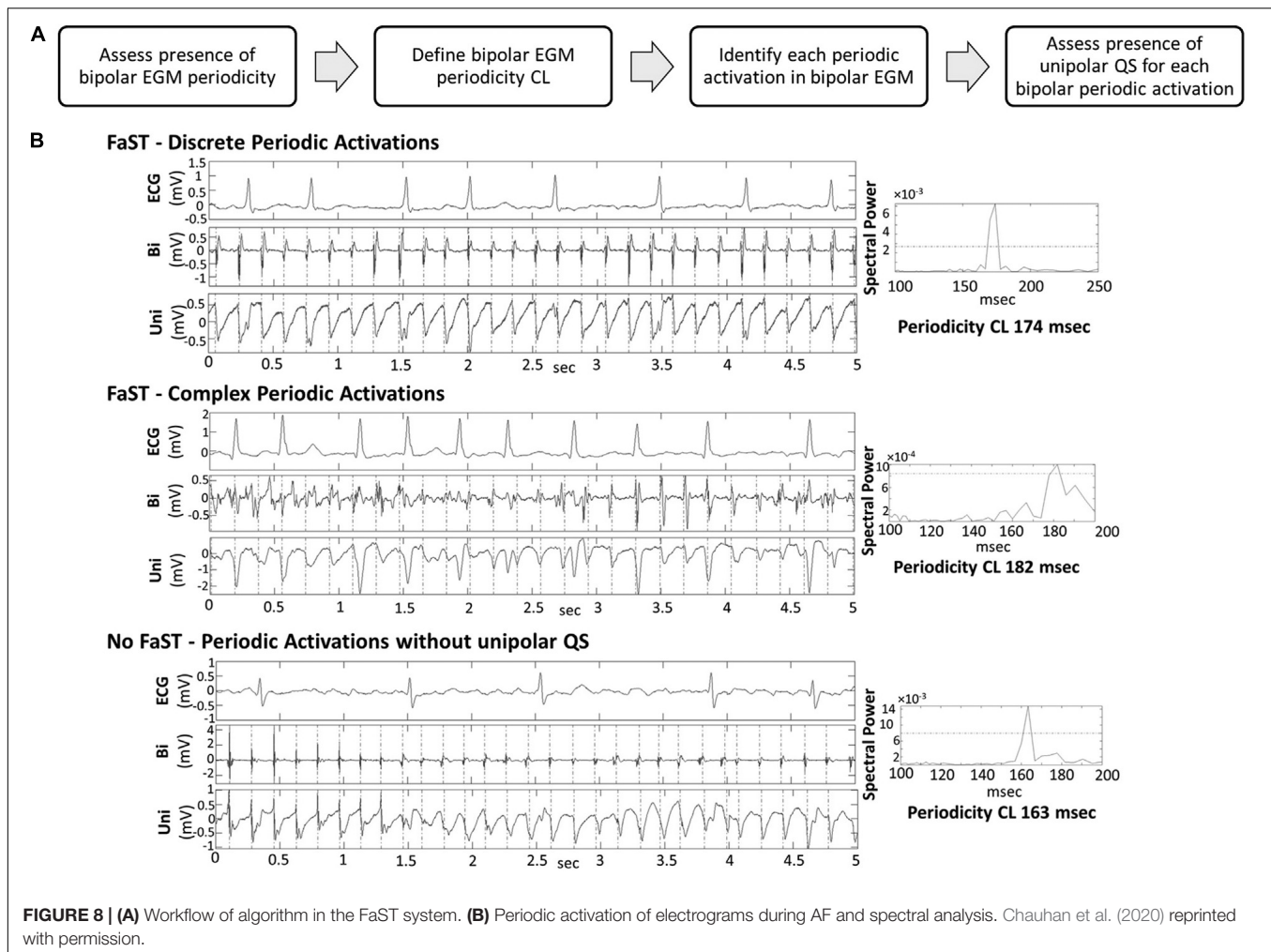
Wavefront Field Mapping

A promising technique was recently proposed using wavefront field mapping (Leef et al., 2019) to reveal organized areas of control during AF (**Figures 9A,B**). This novel vector mapping method computes activation times to calculate phase (**Figure 9C**), activation fronts, and gradient matching to display the vector fields (**Figures 9D–F**) to describe propagation of these fronts.

An advantage of this method is the ability to identify regions that control larger areas of the atria during AF,

and thus distinguish true driver of AF compared to passive organized areas. This concept was studied retrospectively in 54 patients (Leef et al., 2019) in whom ablation of proposed drivers (from phase mapping) terminated AF, and all sites that were found to control larger atrial areas terminated AF with ablation. Prospective studies are ongoing to evaluate the ability of this method to identify critical drivers of AF to improve the targeted therapy of AF.

WHAT IS THE OPTIMAL ABLATION STRATEGY TO TARGET MECHANISMS OF AF?

The plethora of new imaging and mapping technologies reviewed above attempt to provide a personalized approach to improve the treatment of AF. Although there is a strong link between atrial fibrosis and electrical drivers (Cochet et al., 2018; Hansen et al., 2018), they do not always co-exist (Chrispin et al., 2016; Schade et al., 2016), suggesting electrical remodeling and structural heterogeneities other than fibrosis are also important AF mechanisms (Stiles et al., 2009; Lalani et al., 2012; Schricker et al., 2014; Zaman and Narayan, 2015). There are some patients who may have only an electrical substrate without fibrosis (such as lone AF due to a pulmonary vein driver), and there are other patients who have extensive atrial fibrosis with multiple AF

FIGURE 8 | (A) Workflow of algorithm in the FaST system. **(B)** Periodic activation of electrograms during AF and spectral analysis. Chauhan et al. (2020) reprinted with permission.
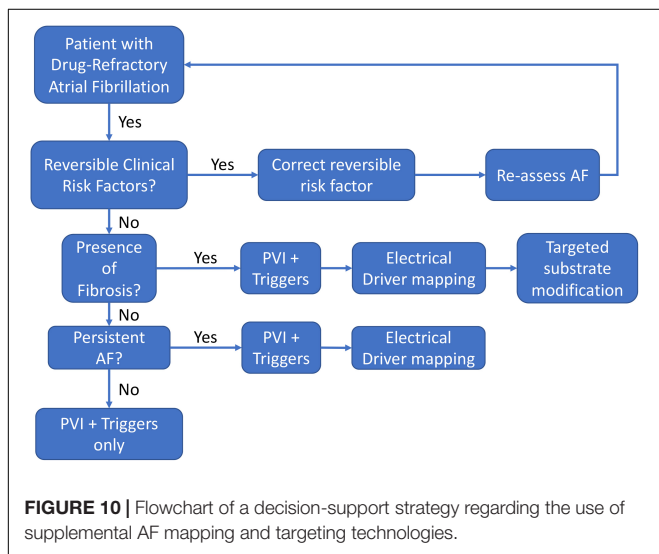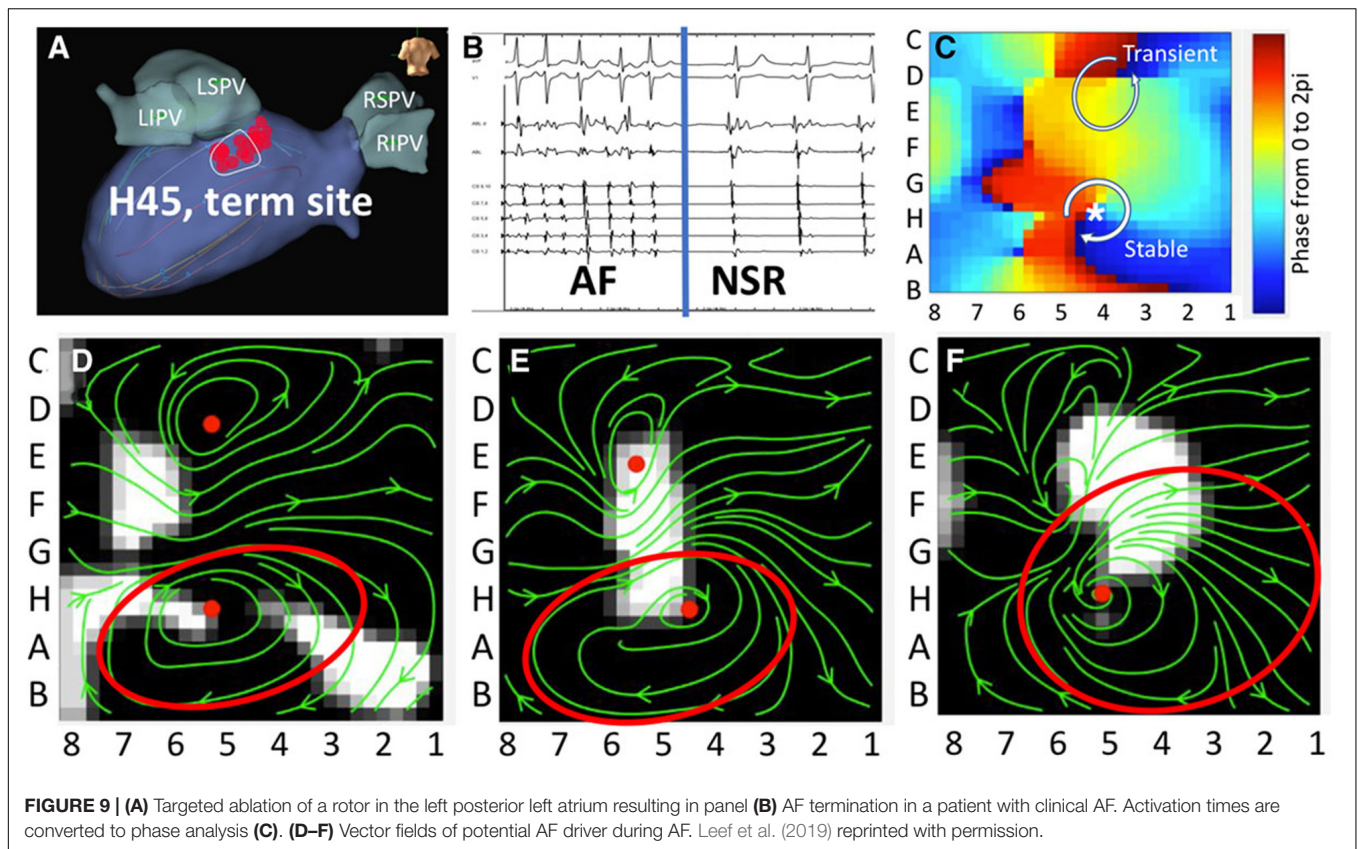
drivers (such as a patient with familial atrial cardiomyopathy). In the first case, PVI alone or driver mapping-guided ablation may be enough to eliminate the AF mechanism, but may not be enough in the second case. While meta-analysis of driver ablation studies show a benefit toward driver ablation (Baykaner et al., 2018), AF recurrence still recurs in ∼30%. This may be partly due to technological shortcomings and operator inexperience, but a possibility is that new drivers may recur in certain patients with progressive primary atrial cardiomyopathies.

More work is needed to determine how to identify patients with progressive underlying atrial cardiomyopathies and how to incorporate a substrate modification strategies in addition to AF drivers. However, importantly, more ablation is not necessarily better particularly with empiric atrial debulking strategies, as STAR-AF2 showed a proarrhythmic effect of empiric linear ablation primarily due to creation of substrate for atypical atrial flutters (Verma et al., 2015) and development of stiff atrial syndrome (Gibson et al., 2011).

Based upon the above discussion, we propose the following strategy for the management of drug-refractory AF (**Figure 10**), incorporating an organized approach to manage and reduce risk

factors, and to use imaging to reveal the diverse types of AF. First, reversible clinical risk factors, such as obesity, hypertension, obstructive sleep apnea, and excessive alcohol use should be optimized in all patients to help reverse atrial remodeling (Lau et al., 2017). Second, PVI should usually be performed in all patients as an initial strategy. In the most recent 2017 expert consensus document for AF ablation, pulmonary vein isolation is the only ablation strategy given a Class 1 indication (Calkins et al., 2017). Third, elimination of AF triggers such as frequent PACs/atrial tachycardias should also be strongly considered, which is given a Class 2A indication. Fourth, in patients in whom AF sustains or remains inducible, adjunctive strategies addressing patient-specific AF mechanisms may be needed to improve the success of ablation. To address the potential for fibrotic mechanisms discussed previously, pre-procedural imaging or comprehensive invasive voltage mapping should be considered to determine the presence of significant atrial fibrosis which may prognosticate a need to perform electrical driver ablation and/or substrate modification to eliminate extra-PV AF mechanisms. Finally, in patients with persistent AF in whom AF is more likely to recur after PVI alone, electrical driver mapping should be considered to eliminate extra pulmonary

FIGURE 9 | (A) Targeted ablation of a rotor in the left posterior left atrium resulting in panel **(B)** AF termination in a patient with clinical AF. Activation times are converted to phase analysis **(C)**. **(D–F)** Vector fields of potential AF driver during AF. Leef et al. (2019) reprinted with permission.

FIGURE 10 | Flowchart of a decision-support strategy regarding the use of supplemental AF mapping and targeting technologies.

vein AF mechanisms in a targeted, patient-specific approach. At present, the choice of adjunction functional mapping should in part be determined by operator experience and electrophysiology laboratory factors in the absence of definitive clinical trial data evaluating the new adjunctive technologies. While the current AF ablation consensus guidelines do discuss some of the earlier imaging and driver technologies, they are given

a Class IIb indication due to lack of good quality clinical data. With improvements in mapping and imaging technologies discussed above, we await clinical trials to confirm the optimistic preliminary clinical studies supporting these mechanistic AF treatment strategies.

CONCLUSION

This review summarizes data linking fibrotic atrial cardiomyopathy with AF drivers and summarizes current clinical approaches for the targeted therapy of substrate and electrical mechanisms underlying atrial fibrillation. As the two patients presented at the beginning demonstrate, causes of AF may be heterogeneous; it is possible that AF in patient 1 may have been caused by electrical substrate only (triggered activity from an ectopic pulmonary vein source). In contrast, patient 2 may have an underlying primary atrial cardiomyopathy, compounded by the presence of scar from prior ablation, and although driver ablation terminated AF, he may have recurrence of AF with new driver sites. Similar to scar-based VT, a combination of substrate modification guided by electrical driver mapping may be needed in certain patients.

We believe that current data support an approach in which risk factor modification is addressed in all patients, and a patient specific strategy incorporating targeted therapy of structural and electrical substrate is considered in particular for

patients with anatomic and functional remodeling suggestive of advanced atrial remodeling and AF drivers outside the pulmonary vein anatomy. Ongoing work is required to determine the optimal combination of imaging and AF functional mapping to optimize procedural results in the management of patients with refractory arrhythmias.

DISCLOSURES

Dr. Ho receives grant support from the American Heart Association (AHA 19CDA34760021), National Institutes of Health (NIH 1KL2TR001444-06), and reports equity in Vektor Medical Inc. unrelated to this work. Dr. Krummen receives grant support from the UCSD Galvanizing Engineering in Medicine Foundation. He also reports equity in Vektor Medical unrelated to this work.

AUTHOR CONTRIBUTIONS

GH reviewed the current literature for the present manuscript, wrote the outline, identified important figures, composed the manuscript, and provided critical editing of the manuscript. AL performed background research for the manuscript and provided critical editing of the manuscript. DK reviewed the literature, composed the manuscript, and provided critical editing of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

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