Voltage-Guided Ablation for Atrial Fibrillation – Current Insights and Future Directions

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Abstract

The prevalence of atrial fibrillation (AF) is forecasted to increase manifold, emphasizing the need for efficacious treatments. Pulmonary vein isolation (PVI) to eliminate ectopic triggers is now established as a fundamental component of the invasive treatment of AF, however its efficacy in persistent AF remains suboptimal. The atrial myocardium undergoes adverse fibrotic remodeling as AF progresses, favoring arrhythmia initiation and maintenance. Reductions in left atrial bipolar voltage have been suggested to identify regions of such pathological remodeling, and represent novel targets for ablation to target the arrhythmogenic substrate. Early observational studies targeting these low voltage areas (LVA) have been encouraging, however results from more recent randomized trials are more mixed. Importantly, there is significant heterogeneity in the techniques for identifying LVAs and the strategies for ablation. In reality, the atrial arrhythmogenic substrate is multi-faceted rather than being limited to fibrosis and there remains uncertainty as to how accurately LVAs represent regions of fibrosis. Additionally, bipolar voltage is influenced by numerous physiological and biophysical factors. The present review summarizes the current evidence for LVA ablation in AF. We then analyze the components of the atrial arrhythmic substrate, its relationship to LVAs and the limitations in LVA assessment. Finally we discuss novel techniques for delineating the atrial substrate.

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Short Title: Voltage-Guided Ablation for AF

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The present review summarizes the current evidence for LVA ablation in AF. We then analyze the components of the atrial arrhythmic substrate, its relationship to LVAs and the limitations in LVA assessment. Finally we discuss novel techniques for delineating the atrial substrate.

Keywords: Atrial fibrillation, substrate, ablation, voltage, fibrosis

Abbreviations

AF – Atrial fibrillation

DeEP - Decremental evoked potential

EAM – Electro-anatomical mapping

FAM – Fast anatomical mapping

LA – Left atrium

LVA – Low voltage area

PAF – Paroxysmal atrial fibrillation

PBP – Point-by-point

PsAF – Persistent atrial fibrillation

PVI – Pulmonary vein isolation

SR – Sinus rhythm

VGA – Voltage guided ablation

Introduction

The worldwide prevalence of atrial fibrillation (AF) continues to follow an upward trajectory, mirroring evolving population demographics and the growing burden of comorbidities known to increase the risk of developing AF. Epidemiological studies indicate that between 20-30% of individuals with AF have the paroxysmal form; in most cases it is either persistent or permanent (1). Single procedure success rates following pulmonary vein isolation (PVI) utilizing contemporary techniques for catheter ablation in paroxysmal AF (PAF) approach 80% at 12 months (2). Outcomes following PVI in persistent AF (PsAF) are far more modest, with often more than 50% of patients experiencing recurrence within a year (3).

The trigger-substrate model of arrhythmogenesis consists of an initiating arrhythmogenic trigger, often an ectopic beat, encountering a tissue substrate with electrophysiological properties conducive to sustaining the arrhythmia (4). PVI, aimed at eliminating such ectopic triggers, is now established as a fundamental component of invasive therapies for rhythm control (5). However targeting pulmonary vein triggers has not proven to be effective in PsAF and shifted focus to adjunctive targets aimed at altering the arrhythmogenic substrate. To date, substrate modification approaches have included linear ablation lesions, aimed at compartmentalizing and debulking the atrial tissue, rendering it less able to accommodate re-entry (6–8). Attempts have also been made to target critical areas involved in promoting re-entry and/or harboring potential drivers for AF. Such an approach has included the ablation of complex fractionated atrial electrograms (CFAEs), presumed to be sites of slow conduction, thus providing pivot points for re-entrant waves (9). Focal impulse and rotor modulation mapping has been suggested to identify drivers for AF (10). While all of these approaches have shown encouraging results in initial trials, their early promise has never borne out when implemented on a larger scale (11,12).

There is growing interest in substrate modification targeting areas of low voltage (LVAs) identified during electro-anatomical mapping (EAM). Such LVAs represent areas of pathological fibrosis that have a pivotal role in promoting re-entry and perpetuating AF, a construct adapted from learnings through ablation of ventricular arrhythmia. Indeed progressive fibrotic infiltration of the atrial myocardium has been noted in animal models (13,14) and human studies of AF (15,16), and suggested to correlate with AF recurrence following ablation (17). However there is no consensus on methods to delineate de novo fibrotic tissue or how to differentiate electrical inert bystander tissue from that involved in maintaining AF. In the present review, we summarise the current experience in LVA-guided substrate modification, and then discuss the components of the arrhythmogenic substrate in AF and techniques for assessing this in the clinical setting.

Outcomes from LVA-guided ablation

Observational studies

Several observational studies have reported favorable outcomes when combining PVI with targeted ablation of LVAs; a summary is provided in Table 1. Rolf et al., performed voltage-guided ablation (VGA) in 178 patients with either paroxysmal or persistent AF (18). Left atrial (LA) voltage mapping was performed in sinus rhythm (SR) using a multipolar catheter, with LVAs defined as areas with peak-to-peak voltage <0.5mV. Twelve-month freedom from AF was comparable between patients with no LVAs and those with LVAs who underwent PVI plus ablation of LVAs, and significantly higher in patients with LVAs who did not undergo such substrate modification. Ziv and colleagues performed LVA assessment on the posterior wall of

the LA through point-by-point (PBP) mapping in patients with PsAF (19). Patients undergoing VGA of the posterior wall fared better than those with standard therapy, and this superiority was maintained over long-term follow-up of 5 years (20). This could highlight the role of the posterior wall as a trigger for AF, given the shared embryology with the pulmonary veins.

In keeping with these studies, Jadidi et al. also employed a peak-to-peak voltage threshold of 0.5mV, however voltage mapping was performed using a multipolar catheter with subjects in AF rather than SR (21). Only those' LVAs, or regions bordering these, harboring distinct electrogram characteristics suggestive of arrhythmogenesis, such as fractionation spanning 70% of the AF cycle length, were targeted for ablation. They observed high rates of AF termination during LVA ablation, and combining PVI with selective VGA improved freedom from AF in PsAF compared to a standalone PVI strategy. Arruda and colleagues also evaluated LA voltage in AF utilizing a threshold of 0.5mV to delineate LVAs, however voltage mapping was performed manually in a PBP fashion (22). Single procedure success rates at 12 months were comparable in patients with LVAs who underwent PVI + VGA ablation and those without LVAs treated with PVI alone, adding credence to a prognostic role of LVAs and potential therapeutic benefit in targeting these with ablation.

Yang et al. employed VGA ablation in 86 consecutive patients with a history of non-paroxysmal AF (23). LVAs were defined as areas with peak-to-peak voltage between 0.1 – 0.4mV while transitional zones had a bipolar voltage range 0.4 – 1.3mV. Within LVAs, ablation was performed to eliminate all identified electrograms, aiming to achieve an absolute bipolar voltage of <0.1mV. Further ablation was performed in transitional zones, targeting abnormal electrograms. When compared with a historical cohort that underwent stepwise ablation, maintenance of SR and rates of post-ablation atrial tachycardia were significantly improved in the study population.

Randomized controlled trials

The efficacy of substrate modification through ablation of LVAs has been more mixed when evaluated in randomized trials. Wang et al., randomized 124 patients with long-standing persistent AF to either standard ablation, consisting of PVI with further linear and CFAE ablation aiming for AF termination, or a VGA strategy (24). At 12 months VGA was associated with significantly improved rates of freedom from AF and lower rates of post-ablation atrial tachycardia. Hindricks and colleagues also reported improved arrhythmia free survival in a mixed cohort of patients with either paroxysmal or persistent AF randomized to either LVA ablation or standard therapy (25). In a recent multi-center randomized trial, VGA for patients undergoing first ablation for PsAF was superior to PVI alone (26).

In a multi-center study, Yang et al. randomized 229 patients with non-paroxysmal AF to VGA in a technique similar their earlier observational study (23), or PVI plus linear ablation (27). The authors reported no difference in outcomes between the two groups. In the study by Kumagai et al., 54 patients with non-paroxysmal AF and LVAs on EAM were randomized to either PVI, posterior wall isolation and LVA ablation or PVI plus posterior wall isolation (28). LVA ablation in addition to isolation of the posterior wall did not demonstrate an additive effect in improving freedom from atrial arrhythmias. The presence of LVAs was associated with adverse outcomes in another randomized study of PAF, however ablation targeting these did not improve freedom from AF during early (29) or extended follow-up (30).

Meta-analyses

Meta-analyses of studies employing LVA ablation in addition to PVI do demonstrate improved freedom from AF and reduced rates of post-ablation atrial tachycardia with VGA when compared to conventional ablation approaches (31,32). However, as evident in Table 1, most data are from observational studies with relatively small cohorts of patients, a mixed history of AF duration, and many utilizing historical outcomes as controls. Moreover, the strategies employed in delineating and ablating LVAs are highly heterogeneous with respect to catheter properties, mapping rhythm and voltage thresholds making detailed comparisons challenging.

The Substrate in AF

The atrial substrate has been variably defined, and represents an umbrella term encompassing the spectrum of alterations in the electrical properties of the atria associated with AF. A panoply of remodeling phenomena have been described in experimental models and clinical studies, and while it remains unclear to what extent each is a cause or consequence of AF, many possess the potential to facilitate reentry and thus perpetuate AF. Classically these maladaptive remodeling processes have been categorized as electrical changes evident at the cellular level, or structural remodeling at the tissue level. Much of the recent focus has been on the latter and in particular the deposition of fibrotic tissue within the atrial landscape, perhaps reflecting the perception of this representing a more advanced and potentially irreversible stage of the arrhythmogenic process.

Structural and Gap Junction Remodeling

Significant morphological alterations in the architecture of the heart have been observed in the context of AF, affecting the cardiomyocytes themselves and myocardial interstitium. Frustaci et al. collected biopsy samples from the atrial septum in patients with PAF and demonstrated hypertrophy, vacuolar degeneration, necrosis of myocytes and patchy fibrosis (16). Hatem and colleagues also reported evidence of apoptotic myocyte death in the right atrial appendage associated with AF (33). In both studies, these findings were absent in biopsies from control samples. Histological analyses of LA samples have similarly demonstrated significantly increased collagen deposition surrounding muscle bundles and between individual cardiomyocytes (34). Furthermore, the degree of extracellular matrix remodeling correlates with the duration of AF persistence (figure 1a-c) (35) and is a risk factor for post-operative AF in patients undergoing coronary artery bypass surgery (36,37).

These studies provide compelling evidence of increased fibrotic atrial remodeling associated with AF. However, such histological studies to date have been correlative and do not establish a causal relationship between structural remodeling and AF persistence, nor do they serve to explain how these changes provide a substrate for arrhythmia maintenance. The loss of myocytes, through either apoptosis or necrosis, may reflect a lack of reversibility in the remodeling process, potentially contributing to the progressive and increasingly intractable nature of AF. Disruption in gap junction organization and activity is also likely to be contributory. Expression levels of connexins appear to be reduced in AF and their location being less limited to the intercalated discs (38,39). Such changes are likely to impact conduction properties, favoring re-entry (40).

Beyond these proposed effects on the coupling between cardiomyocytes, fibrotic remodeling also appears to have the potential for more direct modulation of the electrical properties of the cardiac cells. Though non-excitable, fibroblasts appear to express gap junction proteins and make heterocellular contact with cardiomyocytes in vitro (41,42). The resting membrane potential of fibroblasts is less negative than that of atrial cardiomyocytes (43), thus when electrically coupled with myocytes they may act as a current source during electrical diastole and current sink during myocyte depolarization (44). Accordingly, co-culturing of fibroblasts with cardiomyocytes in vitro results in a density-dependent depolarization of the cardiomyocyte resting membrane potential (45), thereby inactivating voltage-gated sodium channels and impeding conduction (46). In keeping with this, under experimental conditions, myofibroblast interaction with cardiomyocytes is associated with reduced conduction velocity across the tissue (47). Interestingly, the experiments also suggested passive transmission of an impulse across an area of fibrosis with significant conduction delay and block. Notably, similar passive electrotonic activity in scar zone myofibroblasts has also been reported in an ex vivo whole heart model (48,49). These results highlight the potential for conduction slowing, anisotropy and block secondary to fibrotic remodeling, all of which support re-entry.

Changes in atrial refractory properties have long been considered as key aspects of arrhythmogenesis in AF and have generally been attributed to altered ion channel activity (50). Myofibroblast-cardiomyocyte coupling may act as a current sink during the myocyte action potential peak and plateau phases, thereby abbreviating the action potential duration and contributing to the dispersion of atrial refractoriness. In

laboratory preparations, myofibroblast-cardiomyocyte coupling increases the propensity for ectopic activity in a dose-dependent fashion (51). Moreover, in-silico modeling studies suggest fibrosis-induced disruption of myocyte coupling promotes automaticity and atrial ectopic activity (52). Thus, such fibrotic remodeling potentially generates non-pulmonary vein triggers for AF, in addition to the described effects of conduction and refractoriness.

Such experimental reports underline the arrhythmogenic potential of adverse structural remodeling, however there appears to be significant variability in the nature of fibrosis in AF and the precise role of these changes in its pathogenesis remains debated. For example, in a canine heart failure model, AF induced through right ventricular tachy-pacing is associated with marked atrial interstitial fibrosis and conduction heterogeneities, but no alterations in atrial refractory properties (53). In contrast, in rapid atrial pacing models, AF maintenance is primarily mediated through electrical remodeling with few structural abnormalities (54). However, structural remodeling is more evident when rapid atrial pacing is combined with mitral regurgitation. The combination confers greater vulnerability to AF (55), together suggesting that structural remodeling can contribute to AF maintenance, but that AF may also persist in its absence.

Significant variability has also been reported in the composition of fibrotic remodeling in AF. Studies evaluating the nature of gap junction remodeling have reported markedly discrepant results with increased, decreased, and unaltered expression of atrial connexin isoforms (38,56,57). Inconsistencies are also apparent in the nature of collagen deposition, further emphasizing the complex nature of fibrotic remodeling seen in AF. A two-fold increase in left atrial collagen I deposition was seen in patients with AF compared to those with sinus rhythm (34). However, patients with significant mitral valve disease also display a significant increase in collagen III deposition, which was not observed in those with 'lone' AF.

Conflicting reports from human studies further highlight the complexities of structural remodeling. Ho and colleagues performed morphometric analysis of post-mortem tissue samples, and described significantly increased fibrosis associated with AF (58). The extent of remodeling was more pronounced in those with a history of non-paroxysmal AF. Extracellular matrix remodeling also correlated with AF duration in patients with a background of dilated cardiomyopathy (35). However, in the study by Frustaci et al., fibrotic remodeling was evident in patients with PAF (16). Such early-onset of fibrosis was also demonstrated in patients with AF undergoing cardiac surgery, with no appreciable increase in fibrosis seen in patient with long-standing persistent AF compared to those with AF of more recent onset (34,59). Progressive fibro-fatty deposition has also been purported to underlie the increasing propensity to AF with ageing as well as a number of chronic conditions such as hypertension and diabetes. However, in histological analyses, the degree of fibrotic change has similarly failed to mirror the burden of comorbidities (58).

Fibrotic remodeling is often considered a convergent pathological end point of a multitude of conditions associated with a propensity to AF; the pattern of fibrosis is in itself not uniform. Indeed fibrosis is broadly categorized as either reparative or reactive, each with a differing composition of extracellular matrix constituents and deposition patterns (figure 1d). The former describes fibrotic replacement in zones of degenerating myocardial parenchyma, producing discontinuities in the cardiomyocyte network and potentially forming barriers to conduction. Reactive fibrosis is thought to be driven by cardiac inflammation, occurring within the interstitium remote from areas of focal injury. For example, substantial atrial myocyte death is observed in experimentally induced heart failure favoring reparative fibrosis (60).

Reactive fibrosis is associated with expansion of the interstitial space, forming thicker sheaths of fibrous tissue around muscle bundles, but significantly not disrupting the muscle bundle itself. Longitudinal conduction through the muscle remains intact, and may even be enhanced through insulation of individual muscle bundles. Chronic pressure overload is associated with progressive interstitial fibrosis, initially in the perivascular space and later becoming more diffuse (61). Histological analysis of left atrial appendage tissue from individuals undergoing surgical AF ablation revealed no difference in fibrotic burden between paroxysmal and persistent AF (62). Interestingly longitudinal conduction velocity was higher in samples with greater interstitial collagen content, although rate-dependent conduction slowing and zig-zag conduction were observed. It remains unclear which form predominates in AF, or it varies according to the underlying

etiology. The fibrosis patterns need not be mutually exclusive and may co-exist within a single atrium.

Deposition of fibrotic tissue thus forms an integral component of atrial structural remodeling in AF. However, while fibrosis is commonly considered a stereotyped process with predictable effects on the electrical properties of the atria, in reality the processes involved are not quite so uniform. The relationship between AF duration and fibrosis is non-linear, and it is clear that such fibrotic remodeling is not a pre-requisite for AF to persist. Importantly, given the variability in the pattern of structural remodeling, and its effects on the electrical properties of the atria, the optimal strategy for delineating arrhythmogenic tissue through electro-anatomical mapping remains debated.

Electrical Remodeling

Alterations in myocyte ion channel properties have long been known to precede fibrotic remodeling and predominate in the domestication of AF in its early stages. In early animal models, artificially maintaining AF through rapid atrial pacing enhanced AF inducibility and a tendency to sustain (13,14). Pronounced reduction in atrial refractory properties and reverse adaptation of repolarization to rate were observed to underlie these phenomenon. In the animal models, significant alterations in repolarization properties are observed early in AF, implying acute changes in ion channel function and expression. For example, in the goat model of pacing-induced AF, significant reductions in atrial ERP are seen within 24 hours, and peak at 2-3 days.

Valuable insights into the relative contribution of the various ion channels have been garnered from genetic studies. Gain of function mutations in the *KCNQ1* gene encoding the pore-forming subunit of the voltage-gated potassium channel Kv7.1 several other beta accessory subunit genes have been linked to familial or early-onset lone AF (63). Genetic mutations have similarly been reported in numerous other members of the cardiac potassium channel superfamily. Both gain and loss of function mutations have been associated with a predisposition to AF, and in some cases the pathological relevance of the mutation remains yet to be elucidated (64,65). Frequently however, these mutations seem to result in abbreviation of the action potential duration, promoting re-entry and arrhythmia maintenance. Loss of function mutations in the*SCN5A* gene encoding the alpha subunit of the voltage-gated sodium channel, NaV1.5, or in the genes encoding one of its four beta subunits would be anticipated to result in conduction slowing (66,67). Such mutations, in addition to gain of function mutations, have been linked to cases of AF, although the electrophysiological phenotype have not been characterized.

Mutations such as those described are thought to account for a small proportion of AF cases overall, however atrial electrophysiological properties observed in most cases appear phenotypically analogous. Consistent with findings in animal models, time-dependent alterations in atrial activation and repolarization characteristics have been observed in human studies. Thus pacing-induced AF was associated with early reductions in atrial effective refractory periods, which recovered to baseline levels shortly after the restoration of sinus rhythm, in keeping with reversible modulation of ion channel function (68). Such shortening of atrial refractory periods has similarly been associated with PsAF (69). Abbreviation of the action potential duration has also been noted in the context of PsAF in several studies (70–72). The shortening of atrial refractory periods, action potential duration, and its adaptation to heart rate, have been attributed to a reduction inI_{Ca}, secondary to reduced expression of L-type calcium channels (73,74), and modification in the expression and functional properties of a variety of potassium channels. The latter include reductions in the transient outward potassium current (I_{to}) (70,72) and upregulation of the constitutively active G-protein gated potassium channel,I_{KAch} (75). Reductions in the inward sodium current through the voltage-gated sodium channel,I_{Na}, would be anticipated to contribute to conduction slowing, however data evaluating this is limited, and no changes in the expression of this ion channel have been reported to date (70).

It should be noted that much of the data pertaining to the molecular correlates of electrical remodeling are conflicting and difficult to reconcile. Additionally, the functional consequences of changes in individual ion

channel expression and function often appear subtle, and in isolation insufficient to promote arrhythmogenesis. It is likely that it is the synergistic effect of a collection of alterations that supports arrhythmia initiation and maintenance (76,77). Additionally, some discrepancies in the data may reflect the patchy nature of remodeling across the atrial landscape.

Evaluating the atrial substrate

Adverse atrial remodeling is multi-faceted and likely to be driven by disease processes that increase AF risk. Consequently, remodeling phenomena are unlikely to follow a stereotyped process and the nature of the arrhythmogenic substrate will vary depending on the circumstances and clinical profile of the patient. Despite these challenges, the alterations in electrophysiological properties have been proposed to manifest as a reduction in bipolar voltage and thus be an effective means of discriminating arrhythmogenic tissue from healthy areas within the left atrium, and particularly a marker for atrial fibrosis.

Clinical significance of atrial LVAs

A growing number of studies have highlighted the prognostic significance of LVAs in AF. In a mixed cohort of AF patients undergoing ablation, areas of very low voltage (<0.05mV) were associated with a three-fold increased likelihood of recurrent AF during follow-up (78). Oshima and colleagues similarly reported a negative influence of LVAs in freedom from AF following PVI in patients with non-paroxysmal AF (79). In their study, LVAs were defined as regions with bipolar voltage <0.5mV, and determined LVAs covering more than 24% of the LA surface as a threshold for discriminating the likelihood of recurrent AF following ablation, albeit with a sensitivity of 52% and specificity of 78%. In a separate study also utilizing 0.5mV to define LVAs, the presence of LVAs was an independent predictor for AF recurrence following ablation (80). Interestingly, patients with PsAF and no LVAs had similar rates of freedom from AF as individuals with PAF. Furthermore, studies limited to subjects with PAF have similarly correlated LVAs with AF recurrence following ablation (81,82).

Mechanistic insights have further corroborated the potential role of LVAs in the pathogenesis of AF. Approximately three-quarters of high dominant-frequency sites, proposed as foci of rotational activation (83), were located within LVAs or their border zones in a cohort of 70 patients with non-paroxysmal AF (79). Left atrial bipolar voltage was also shown to correlate with conduction velocity (84). Miyamoto et al. reported conduction slowing in regions of the left atrial with bipolar voltage <0.5mV and these regions were significantly more likely to harbor CFAEs (85). Chauhan and colleagues reported co-localization of CFAEs to regions of low voltage, with the degree of fractionation inversely proportional to voltage (86). Potential left atrial non-pulmonary vein triggers for AF appear more common in PsAF and show a predilection for LVAs (87).

Temporal changes in the size of LVAs have been reported, mirroring the progressive fibrotic remodeling seen in animal models that underpin the increasing propensity for AF to sustain with time. AF type, either paroxysmal or persistent, was independently associated with LVAs on multivariable analysis in an early study of VGA (18). In the study by Hindricks' group, LVAs were twice as likely to be observed in PsAF than in PAF (25). Yagishita et al. also reported higher prevalence of LVAs in patients with non-paroxysmal forms of AF compared to those with PAF, with LVAs covering a greater overall area of the atrium and being more diffusely spread in those with PsAF (88).

However, the frequency and burden of LVAs observed in a number of studies is at odds with these reports and raises several of important issues. For example, Huang et al. measured left atrial voltage in patients with either paroxysmal or persistent AF and found no difference in the size of LVAs between the groups (89). Additionally, the extent of LVAs at baseline did not predict AF recurrence following PVI. In patients with non-paroxysmal AF, the degree of LVAs did not correlate with AF duration (90). Birnie and colleagues

used high-resolution mapping to characterize the burden of LVAs in patients with AF (91). No differences in the burden of LVAs were observed between patients with paroxysmal or persistent AF, with only age and LA size, being identified as predictors of LVAs on multivariable analysis. The study also reported significant variability in the presence of LVAs across the cohort, and such differences are also evident across the studies where left atrial voltage has been examined.

In an early study of VGA, LVAs were present in 10% of patients with PAF and 35% in those with PsAF (18). Data from the study by Kircher et al. were broadly similar with LVAs being detected in 29% overall, with 18% of patients with PAF and 41% of patients with PsAF (25). In contrast, other studies have reported substantially higher prevalence of LVAs, with nearly two-thirds of patients with PAF exhibiting LVAs (82,92) and over 80% of patients with PsAF (79,89).

Differences in study cohorts beyond AF classification may have contributed to such variation. However, reductions in atrial bipolar voltage have been purported to be a surrogate for the adverse atrial remodeling underpinning AF persistence and as such the lack of a difference in the burden of LVAs between paroxysmal and persistent AF within the same study, where the methods utilized for voltage mapping would be consistent, is intriguing. Recent analyses of AF burden using continuous ECG monitoring have highlighted that these clinical classifications of AF type only loosely associate with AF burden, with significant overlap in the time spent in AF between patients with paroxysmal and persistent AF (93,94). This variability in AF burden may be reflected in the extent of LVAs, and further endorse the need to more patient-specific approaches to ablation.

While a small proportion of studies report presence of LVAs in the majority of patients with PsAF, in most studies LVAs are recorded in less than half of the study cohort. The absence of LVAs in such cases may signify the absence of advanced remodeling where a standalone PVI strategy may suffice. However, the absence of LVAs in such a sizeable fraction of a cohort with sustained AF may conversely question the sensitivity of LVAs, and/or the techniques utilized in defining them, in characterizing the atrial substrate. Indeed, where the relationship of conduction and voltage have been studied, not all regions of low voltage were associated with conduction slowing and conversely some regions with abnormal conduction properties displayed normal bipolar voltages (84). Furthermore, approximately 30% of sites with high dominant frequency activation are found in regions of normal voltage (79).

These issues highlight the challenges in delineating the atrial substrate and perhaps representing this through voltage mapping in isolation, particularly with the approaches utilized up to now, may not do so with sufficient sensitivity and specificity. While ablation targeting LVAs as an adjunct to PVI gains traction, it is essential to note the significant paucity of data on precisely how voltage measurements relate to adverse atrial remodeling in AF. In particular, low voltage is generally considered to represent native atrial fibrosis, however at present there is no histological data to support this assertion. The myocardial fiber arrangement in the atrium is highly complex with regional heterogeneity in fiber orientation and tissue depth. Beyond this, the process of fibrosis has significant variability in the pattern of deposition and degree of transmurality, and how this affects voltage measurements is unclear. Added to this milieu is the multi-faceted nature of the atrial substrate as described above. It is unlikely that amongst the array of remodeling phenomena that have been documented in AF, none other than fibrosis alters the recorded tissue voltage. Therefore, while favorable outcomes have been reported in VGA studies, many questions remain unanswered in assessing atrial voltage.

Electro-anatomical mapping of LVAs

The variability in the prevalence of LVAs reported in the published literature, particularly among patient groups with seemingly similar clinical profiles, partly reflect differing approaches in the technical application of voltage mapping. Voltage assessment in clinical practice is almost exclusively performed using maximum peak-to-peak voltage measurements from bipolar electrograms. Bipolar electrograms represent the difference

in voltage between two unipolar electrograms recorded from separate, often closely spaced, electrodes. Thus a bipolar electrogram represents the temporal offset of unipolar electrograms intended to record the same activation wavefront. Consequently, for a given conduction velocity, the temporal offset and therefore the bipolar voltage will be a function of the inter-electrode distance. Theoretically, where the distance between the electrodes is small, or the conduction velocity is fast, one would expect a slight temporal offset and in turn a lower bipolar peak-to-peak voltage. Conversely where conduction velocity is slow, often considered a marker for diseased tissue, the temporal offset may be exaggerated and the recorded voltage being paradoxically larger (95). LA voltages measured in SR were higher with widely spaced electrodes compared with a shorter inter-electrode distance (96). In in-silico models of healthy atrial tissue, increasing electrode spacing is similarly associated with increments in bipolar voltage up to an inter-electrode distance of 4mm, after which the bipolar voltage plateaus, denoting the wavelength of the activation wavefront (97).

Several other catheter-related factors may influence bipolar voltage amplitude, including catheter orientation, tissue contact force and electrode size. The angle of the recording bipolar electrodes relative to the direction of the activation wavefront will modulate the bipolar voltage amplitude. The temporal offset between the unipolar electrograms will be most significant when they are aligned parallel to the direction of activation, thereby recording maximal bipolar voltage (97). Where the electrodes lie perpendicular to the excitation wavefront, both electrodes would be activated simultaneously, producing a misleading bipolar voltage of zero (so-called bipolar ghosting). The angle of incidence between the catheter and endocardium further alter the morphology and amplitude of the bipolar electrogram (95). Increasing the angle of incidence renders the proximal electrode farther from the tissue, reducing the nearfield contribution to the electrogram amplitude and morphology, while also increasing the sensitivity to far-field contamination (98).

Contemporary multipolar catheters utilize impedance measurements to judge tissue contact. Bipolar mapping catheters with contact force sensing capabilities have been advocated for use in voltage assessment due to the advantage of confirming adequate tissue contact. Despite the potential advantages of contact force feedback, a modest correlation being contact force and bipolar voltage has been reported with marginal increments in bipolar amplitude with increasing contact force when contact is light (up to 5g), and no correlation was observed at moderate or high degrees of contact (99,100).

Electrode size has been shown to have variable and interacting effects on the recorded voltage. Marcus et al., compared voltage measurements from 4mm and 8mm NaviStar catheters (Biosense Webster), each with 1-7-4 electrode arrangements and reported significantly higher voltages with the larger electrode in patients with PAF (101). This would be in keeping with larger electrodes producing a broader footprint over the tissue being evaluated, accentuating the nearfield signal. More recent studies have compared PBP assessment using a larger tip linear ablation catheter with fast anatomical mapping (FAM) using multipolar catheters with smaller electrodes. Such studies have alluded to a bidirectional relationship between electrode size and the nature of the underlying tissue in determining the bipolar voltage amplitude. In patients undergoing ablation for AF, the burden of LVA was perhaps surprisingly lower and mean bipolar voltage was higher when evaluated with a circular multipolar catheter with 1mm electrode size compared with a larger tipped ablation catheter (102,103). In these studies, the inter-electrode distance was larger with the multipolar catheter, possibly confounding the higher voltage measurements. However the discrepancy in the size of LVAs and bipolar voltage measurements was similarly evident when utilizing multipolar catheters with more closely spaced electrodes (96,104).

Interestingly the divergence in voltage measurements appears more pronounced in regions with low voltage generally. Anter et al., compared atrial voltage measurements from a linear ablation catheter and multipolar catheter in a group of healthy subjects, and reported no difference in bipolar voltage amplitudes (104). Zghaib et al., also reported comparable voltages measurements from the two catheter types in areas of left atria where voltages were generally preserved, whereas in regions of low voltages recordings from the multipolar catheter were left shifted (i.e. lower) compared to the linear catheter (105). In patients undergoing ablation for PsAF, Mano and colleagues paired mapping points recorded by each catheter according to location, and analyzed electrogram properties (106). Bipolar voltage amplitudes recorded using a multipolar catheter were

higher across the entire distribution of voltages, however in regions defined as healthy, voltages recorded by the large tipped linear catheter correlated well with those from the multipolar catheter. In contrast, no such relationship was observed in regions with voltages <0.5mV.

Computer modelling studies previously demonstrated degradation in spatial resolution associated with increasing electrode size (98). Increasing the electrode size can augment the near-field contribution to the electrogram, but may also render the electrogram more susceptible to far-field signals. Moreover, the larger recording footprint of the electrode also represents an electrogram over a larger span of tissue, expressing differing electrical properties from a collection of fibers in a single electrogram. In heterogeneous tissue, for example regions with patchy fibrosis or complex fiber orientation, larger electrodes may average voltages from a range of tissue types and/or complex excitation wavefronts, yielding electrograms that are comparatively smoother, longer in duration and attenuated in amplitude. Alternatively, electrodes of smaller size appear to be better able to discriminate between surviving myocardial fibers embedded within an area of general low voltage, yielding a higher resolution voltage map with smaller LVAs and higher mean bipolar voltage.

The influence of tissue properties on recorded bipolar voltage extends beyond electrode size. Mirroring the effect of electrode size, larger LVAs and lower mean voltages within low voltage zones were derived when using multipolar catheters with wider electrode spacing than equivalent catheters with more closely spaced electrodes, presumably also reflecting the summation of signals over a heterogeneous substrate. From a clinical perspective, the variability in voltage measurements seems to be most significant in precisely the regions requiring high resolution to correctly identify areas of possible pathogenic potential, while not extending targets for ablation to regions of normal activity. In this context, catheters with larger, more widely spaced electrodes appear more susceptible to far-field contamination, averaging and signal cancellation.

Aside from these catheter-related factors, the other major technical determinant of the size of LVAs is the voltage threshold employed to define low voltage. It must be borne in mind that at present there is no histological data corroborating bipolar voltage measurements with native atrial fibrosis. Initial studies of atrial voltage mapping used a value of 0.05mV to identify regions of dense scar, a value founded on the baseline noise levels in early iterations of the then available EAM systems (107). Most recent studies have adopted a threshold of 0.5mV to classify regions of abnormally low voltage, irrespective of the voltage mapping technique employed. This value was somewhat arbitrarily utilized in early investigations of potential atrial fibrosis (108,109) and has gained traction through more recent reports validating its application. Kapa et al., evaluated the distribution of left atrial voltage measurements in 10 patients with PAF and found 95% of all recordings on the posterior wall had amplitudes >0.2mV and >0.45mV throughout the rest of the left atrium (110). In a similar study, also of 10 patients with a history of PAF, Anter et al. demonstrated the fifth centile of LA voltages being 0.5mV and based upon this considered normal LA voltage to be [?]0.5mV (104).

Other studies have applied a similar approach in patients without a known history of AF or structural heart disease to derive reference values for normal voltage. Detailed left atrial voltage maps were analyzed in 9 patients with either left sided accessory pathways of focal atrial tachycardia and the fifth centile of voltages was reported as 0.5mV (111). Lin et al. also assessed left atrial voltage in 10 patients undergoing ablation for accessory pathway mediated tachycardia and demonstrated 95% of all voltage measurements being above 0.38mV, and thus advanced 0.4mV as a cut-off for low voltage (112).

In assessing LA voltage measurements in 6 control patients without a history of AF, results from a study by Arruda and colleagues challenge the 0.5mV cut-off. Overall, their findings suggest that such voltage assessment of atrial remodeling may be far more nuanced (88). The study highlighted regional differences in mean bipolar voltage within the LA and noted the inferior and septal territories displayed lower voltages in control hearts. Applying the 95% cut-off strategy to voltage measurements acquired from the septal segments where mean voltage was lowest of all, they identified a threshold of 1.17mV. In a mixed cohort of patients with AF without LVAs <0.5mV, 43% had abnormal voltage readings of 0.5-1.17mV and these patients were at significantly greater risk of recurrent atrial arrhythmias after ablation. Several studies have similarly reported significant regional variations in mean bipolar voltage, suggesting a single voltage

threshold may not be universally applicable (82,110,113). Regional variation in the distribution of LVAs also appears to differ in hearts depending on the classification of AF. Chang et al. reported lower bi-atrial voltages in PsAF compared to PAF, with limited areas of low voltage in the context PAF but becoming far more diffuse where AF was persistent (108). Differential baseline voltage measurements between atrial regions, together with reducing overall mean voltages and proliferation of LVZs with increasing duration of AF have also been reported in a number of other studies (112,114,115). However no consistent trend in the geographical distribution of such LVZs has become apparent to date.

The distribution of voltages across the atrium likely, in part, reflect regional differences in the architectural arrangement of muscle fibers and the overall tissue mass. Indeed in post-mortem analyses, left atrial wall thickness varies between regions (116,117), and wall thickness has previously been shown to modulate bipolar voltage amplitudes (118) and account for differences in the prevalence of LVAs (119). The organization of left atrial muscle fibers also shows significant regional heterogeneity with some areas displaying a high dispersion in the transmural orientation of fibers, while in other areas, fiber orientation is fairly constant through its thickness (117,120). The heterogeneity in transmural fiber orientation is therefore likely to contribute to regional variation in voltage. Importantly, while such arrangement of fibers was broadly consistent between most hearts, alternative fiber configurations were also observed. This variation together with the differing distribution of LVAs seen would advocate a bespoke approach to ablation rather than recourse to pre-defined lesion sets.

Extrinsic factors also likely to contribute to regional differences in LA voltage. Regions of high atrial wall stress appear to be associated with lower bipolar amplitudes. Such areas were commonly observed at flexures such as the appendage ridge and points of deformation due to external structures (121). The imprint of the ascending aorta on the anterior LA and vertebrae to the posterior wall correlate with LVAs in both paroxysmal and persistent AF (122,123). While atrial wall stress and stretch may induce localized fibrotic remodeling and contribute to increased risk of AF associated with conditions where these occur, other processes may also contribute to the low voltage measurements. For example acute reduction in LA size are seen following treatment for mitral stenosis, accompanied by an immediate increase in bipolar voltage across all segments, normalization conduction velocity and reduction in AF inducibility (124). Such brisk recovery in bipolar voltage underline the involvement of electrical remodeling such as a role for stretch-sensitive ion channels (125,126), emphasizing that not all LVAs are accounted for by fibrosis and in some cases the underlying atrial myocardial may ostensibly be normal.

Studies evaluating the efficacy of VGA differ in the atrial rhythm during voltage mapping and this appears to be an important source of variation in the burden of LVAs. Ndrepepa et al. reported a three-fold reduction in mean LA voltage when measured in AF compared with SR (127). Furthermore the difference in voltage between AF and SR were greatest in regions with shorter AF cycle lengths, where the tissue is likely to be partially refractory through rapid fibrillatory activation. The simultaneous recording of multiple wavefronts in AF and variation in the direction of activation relative to the catheter are also likely to have contributed to the observed disparity. Accordingly, voltage differences in organized atrial arrhythmias are more modest. Shivkumar and colleagues reported higher right atrial voltages when mapping in atrial flutter compared to SR (128).

In keeping with these studies, data from Sarkozy's group further highlight the importance of disorganized activity and variable cycle lengths on atrial voltage (129). Mean left atrial voltage was highest when assessed in SR, intermediate in atrial flutter and significantly lower when mapped in AF. SR voltage moderately correlated with voltage in AF (Kendall's tau = 0.56) with a voltage in AF of 0.31mV suggested to predict a SR voltage of 0.5mV with reasonable accuracy (sensitivity 0.82, specificity 0.95). Importantly, correlation between repeated AF voltages was modest (Kendall's tau = 0.52), highlighting the impact of disorganized activation on reproducibility. Yagishita et al., also reported higher voltages in SR than AF with a moderate correlation between the two (r = 0.707) (88). Mean LA voltage was higher in PAF than PsAF, though interestingly the correlation between SR and AF voltages was stronger in PsAF cases. Indeed in both studies, voltage measurements in AF better correlated with those in SR where bipolar amplitudes were at

the lower end of the spectrum, perhaps suggesting that where remodeling is most pronounced lower voltages are evident irrespective of the specifics of the mapping approach. Where remodeling is less extensive, bipolar voltage is sensitive to the mapping rhythm, displaying functional reductions when being activated more rapidly.

Teh et al., reported significantly higher voltages and smaller LVAs during coronary sinus pacing compared with AF (115). Other than in the anterior wall, they reported no correlation in LA voltages between AF and coronary sinus pacing. Moreover, regions of low voltage and CFAEs observed in AF appeared largely normal when assessed during the paced rhythm. Voltage mapping in SR or under conditions of regular pacing may therefore not adequately unmask functional electrophysiological properties that form part of the arrhythmogenic substrate (figure 2). Masuda et al. on the other reported good correlation between SR and AF voltages (r = 0.73) in areas where electrogram morphology was normal in both rhythms (130). However regions displaying normal electrograms in SR frequently exhibited fractionation in AF, with poor correlation in bipolar voltages at such sites. The pathological significance of low voltage and electrogram fractionation in AF therefore remains unclear, as do the validity of methods posited for voltage adjustment between rhythms (88,129,131).

The technical aspects of EAM clearly have a significant impact on LA substrate assessment The rhythm during mapping and catheter properties such as electrode spacing are important, yet perhaps under-appreciated, determinants of voltage. Indeed the variety of voltage assessment techniques utilized in the VGA studies (Table 1) highlight a lack of consensus as to the most appropriate approach for devising a substrate guided ablation strategy. Such differences in treatment strategies poses challenges in comparing study outcomes.

In the context of such caveats, there remains significant uncertainty as to what areas of low bipolar voltage represent at the tissue level and how this relates to arrhythmogenic potential. Importantly histological data corroborating atrial fibrosis with voltage measurements is exceedingly limited. In an animal study of post-myocardial infarction, ventricular scar correlated with a bipolar voltage threshold of 0.5 mV (132). Harrison et al. examined ablation induced scar in porcine right atria following ablation along the intercaval line (133). Mean bipolar voltage along the line acutely after ablation was 0.6 mV, and 0.3 mV at 8 weeks post-ablation. Such values might suggest that the commonly employed thresholds of 0.05 mV for dense scar and 0.4 - 0.5 mV for scar might underestimate the overall LA low voltage burden. Moreover the study also alludes to crucial limitations in current assessment and ablation of LVAs, and the need for a more detailed assessment. Firstly, if higher bipolar voltage thresholds were utilized to distinguish LA scar from healthy tissue, this could extend the ablation target in a VGA strategy to a large proportion of the LA, which may not be feasible or desirable due to potential risks. Secondly, ablation scar is more likely to be associated with dense and predictable fibrosis. Native atrial fibrosis is on the other hand interspersed with surviving myocardial bundles, and thus less amenable to dichotomizing as scar tissue versus normal tissue. Rather, fibrotic remodeling is progressive, and the goal is therefore to delineate arrhythmogenic tissue from tissue which activates passively.

In keeping with the paradigm of progressive fibrotic infiltration, Node and colleagues recently assessed the degree of fibrosis and compared this to global LA voltage (134). Increasing percentage of septal fibrosis negatively correlated with mean global LA voltage. Moreover a high burden of LVAs was associated with reduction in LA voltage when assessed globally, but also across all individual segments of the LA, together suggesting that fibrosis and reductions in LA voltage are progressive and diffuse. Although reductions in LA voltage and increasing burden of LVAs have been shown to increase the risk of AF recurrence, threshold values at which this risk increases significantly remains unclear. Furthermore, recent histological analysis noted no difference in fibrosis burden between control patients and those with either paroxysmal or persistent AF (135). Additionally, the study report no overlap between areas of fibrosis and low voltage, nor arrhythmogenic electrophysiological properties, questioning the role of fibrosis altogether in the pathogenesis of AF. It must be noted that analyses were limited to tissue from the right and left atrial appendages and the overall number of patients was small, however highlights important gaps in our understanding of AF persistence and issues that we need to bridge to devise more effective treatment strategies.

Novel strategies for atrial substrate assessment

Recent technological advances and a better understanding of the processes underpinning AF have spawned novel approaches to characterizing the atrial substrate and guiding ablation strategies. Being the rhythm of interest, mapping in AF would logically seem advantageous in potentially identifying sites involved in maintaining the arrhythmia, but has been challenging owing to the continually changing activation patterns and uncertainty regarding the significance of such activity. High-resolution mapping and novel signal processing algorithms has made this more feasible.

Hwang et al., performed voltage assessment during AF in a cohort of 50 patients with non-paroxysmal AF and identified LVAs as points with bipolar voltage <0.5mV (136). Patients randomized to the intervention arm underwent PVI plus adjunctive ablation of CFAEs located within LVZs. Compared to a standalone PVI strategy, PVI+CFAE ablation was associated with improved freedom from AF at 12 months, although the overall freedom from any atrial arrhythmia did not differ between the groups. Jadidi et al., similarly targeted CFAEs co-locating with LVAs during substrate assessment in AF (21). Selective ablation of CFAEs displaying prolonged activation and rapid firing was frequently associated with acute termination of AF to SR, as well as improved freedom from AF on follow-up. Further analysis of CFAEs at sites of AF termination demonstrated that all were located within or adjacent to LVAs, and had lower mean voltage than other parts of the atrium (137). Malaczynska-Rajpold et al. also employed high resolution mapping to identify consistent drivers for AF and report improved AF-free survival in patients with either persistent or long-standing persistent AF (138). Our group have also utilized non-contact charge density mapping for panoramic assessment of atrial activity in AF to identify potentials sites critical for AF maintenance (139). Targeted ablation of such drivers as an adjunct to PVI improved outcomes compared to a conventional linear ablation strategy.

Substrate assessment in AF may therefore provide mechanistic insights to guide intervention, which may be more relevant in the clinical setting. Indeed LVAs identified during mapping in AF more accurately matched late gadolinium enhancement observed on magnetic resonance imaging than LVAs identified in sinus rhythm (140). The study suggested maintaining stable catheter position for more than 4 seconds would suffice in extracting maximal voltage in AF, presumably being an adequate time to allow for the electrode pair to encounter wavefronts traversing in a parallel direction. However EAM in AF remains sensitive to technical limitations of bipolar electrograms. Furthermore, while electrogram patterns such as CFAEs may allude to drivers of AF, not all such waveforms appear to be pathological and may represent passive phenomena such as wavefront collision.

Omnipolar mapping

Omnipolar mapping has been reported to overcome technical limitations associated with conventional bipolar electrograms, obviating issues with electrode orientation and activation timing (141). Omnipolar electrograms leverage data from unipolar and bipolar electrograms applied to a mathematical model of a propagating wavefront to produce 'virtual' bipolar electrograms. By interrogating electrograms through 360°, omnipolar mapping can extract maximal voltage independent of catheter orientation as well as providing measures activation direction. Validation studies using in silico modelling, multi-electrode array recordings of cardiomyocyte monolayers, and optical mapping of uniform and re-entrant waves have demonstrated good correlation between omnipolar parameters and conventional electrophysiological techniques (142).

Whole heart studies have provided further evidence of the utility of omnipolar technology. In Langendorff-perfused rabbit and porcine hearts, omnipolar voltages measured from the interventricular septum were significantly higher than those obtained with horizontally or vertically orientated bipolar electrodes (143). Voltages in ex-vivo human hearts were similarly increased. They highlighted the potential need for adjusting thresholds for defining scar given more tissue would be characterized as healthy if current standards are used. Haldar et al. compared atrial bipolar and omnipolar voltages in canine hearts, and reported higher voltages with the latter when assessed in sinus rhythm or AF (144). Notably, omnipolar voltages demonstrated remarkable beat-to-beat consistency across rhythms in both studies, potentially reducing the influence of

rhythms with variable activation patterns such as AF. Rillo et al. reported higher atrial voltages and smaller burden of LVAs in patients undergoing AF ablation when mapped in sinus rhythm (145).

Rhythm during voltage assessment

The majority of VGA studies have undertaken substrate assessment in sinus rhythm. It remains uncertain how adequately voltage mapping in regular rhythms highlight areas involved in AF perpetuation. For example, both LVAs and regions harboring electrogram fractionation when mapped in AF, often display more normal parameters when reassessed in SR (115). This rhythm-dependent variability in electrogram size and morphology likely represents functional properties of the tissue, which may harbor arrhythmogenic potential. At lower rates of activation in regular rhythms, such diseased tissue may not be under sufficient physiological stress, and appear 'normal'. Rapid activation, such as in AF, may exceed the functional reserve of the tissue and manifest as lower bipolar voltages and/or fractionated signals. These functional properties may be exploited through pacing protocols to identify arrhythmogenic sites, when mapping is performed in sinus rhythm or coronary sinus pacing.

Insights from VT substrates

Techniques for delineating the atrial substrate requires refinement and perhaps useful insights can be gained from the evolution of ventricular tachycardia (VT) mapping strategies. While activation and entrainment mapping remain preferable in VT ablation, this is not feasible in the majority of cases due to poor hemodynamic tolerance. Thus substrate guided ablation remains the mainstay of VT ablation strategies, with voltage maps used to identify abnormal tissue. Marchlinski et al. posited 1.5 mV as a threshold to distinguish normal tissue from areas of scar based on the voltage at the 5^{th} centile of all mapping point, with a value of 0.5 mV arbitrarily used to segregate dense scar from the scar border zone (146). Cassidy et al., described electrogram characteristics within such LVZs denoting arrhythmogenic sites and with more recent refinements to better discern these electrograms (147,148).

Traditionally, post-infarct VT has been considered as a re-entrant arrhythmia through anatomically defined and somewhat static circuit. However more recent insights highlight the importance of functional properties in arrhythmia initiation and maintenance. Both animal and human studies suggest functional modulation of electrophysiological properties play a significant role in the genesis of a re-entrant circuit, and some of the footprints of the VT circuit may therefore not be apparent when mapping in sinus rhythm. Canine studies in early post-infarct VT demonstrated the participation of lines of functional block in the supporting VT. More recent studies in a porcine model of post-infarct VT also suggested arrhythmias were primarily determined by functional block (149). Cain and colleagues demonstrated development of slowed conduction and functional lines of block in the mechanism of VT in 8 patients with a history of ischemic heart disease (150). Segal et al. more recently observed formation of unidirectional block and lines of functional block at the border of LVZs at the initiation of VT using non-contact mapping in patients with post-infarct VT (151).

These observations and the potential for components of the re-entrant circuit being masked during mapping in SR have spawned novel approaches to VT substrate mapping. Indeed significant variation in late potentials is seen when pacing from different sites (152). In another study, sites showing functional conduction slowing and/or electrogram fractionation during S1S2 pacing protocols more accurately identified critical substrates for VT than conventional late potential mapping (153). The Decremental evoked potential (DeEP) mapping protocol involves imposing a drive train and extra, assessing for development of local activation delay and electrogram fractionation after the latter. Early studies have suggested improved specificity in identifying the critical isthmus than conventional late potential mapping (154). In a subsequent multicenter study, limiting ablation to only DeEP identified sites demonstrated improved acute outcomes compared to late potential ablation (153). In a variation of this dynamic mapping approach, mapping during single sensed extras was better able to identify late potential and LAVAs compared with sinus rhythm (155).

Dynamic assessment of atria substrate through pacing

Wong et al. reported significant variation in left atrial voltage, burden of LVAs and electrogram fractionation during atrial pacing, depending on the pacing site and atrial rate (156). The prognostic implication of these changes was no examined. Kim et al., previously demonstrated steeper action potential restitution curves associated with AF (157). Williams et al. evaluated electrophysiological responses to incremental atrial pacing in a cohort of patients with PAF (158). Patients displayed highly variable changes in electrogram voltage and fractionation, however greater rate-dependent activation dispersion was associated with increased AF vulnerability. Finally, Hunter and colleagues assess conduction velocity dynamics in patients undergoing ablation for PsAF (84). Most sites with early rate-dependent conduction slowing were located in regions of low voltage, many of which harbored rotational drivers for AF.

Some groups have implemented electrophysiology study-guided LA substrate modification in PsAF with favorable results. In patients without LVAs on the posterior wall of the LA, Yamaji et al. performed posterior wall isolation if regions of the LA demonstrated pro-arrhythmic repolarization properties or AF/AT was inducible during electrophysiological testing (159). Patients who underwent posterior wall isolation displayed greater freedom from AF/AT than those without LVAs who had PVI alone, suggesting that atrial voltage assessment in isolation may underestimate the risk of AF recurrence.

Finally the majority of studies in the current era of substrate modification have focused on endocardial evaluation of the LA. Recent high-resolution EAM has demonstrated significant burden of LVAs in the right atrium as well as other pro-arrhythmic markers such as conduction slowing and block (160). Comprehensive substrate modification in the future will likely involve concomitant assessment of the right atrium. A recent analysis of atrial LVAs have shown that these may be located exclusively in the epicardial layer and correspond to normal bipolar voltages when measured endocardially (161). Conventional bipolar mapping and novel omnipolar technology have a limited field of view, and thus are less sensitive to epicardial voltage when mapping endocardially, and vice versa. Unipolar measurements do seem to improve the detection of such epicardial LVAs to some degree, but a large proportion of potentially arrhythmogenic areas may still be missed (162).

In summary, novel approaches to atrial substrate assessment are moving towards a genuinely individualized ablation strategy, guided by multimodal assessment of atrial electrophysiology. Progress on this front will require a reassessment of historical definitions of low voltage, appreciating the influence of clinical and technical factors. Moreover, it is clear that low voltage in isolation is unlikely to capture the arrhythmogenic potential of the tissue fully, and further functional evaluation may be required to identify sites critical to AF maintenance correctly. Finally, efficacious treatment of AF requires not only accurate substrate characterization, but also means of delivering durable ablation lesions safely.

Conclusion

Adverse atrial remodeling plays a large part in the tendency for AF to persist with time. While the AF substrate and atrial fibrosis are commonly used interchangeably, and low voltage is often taken to represent this during electro-anatomical mapping. In reality the arrhythmogenic substrate is multi-faceted and highly complex. Reductions in atrial voltage reflect fibrosis, a process that is not uniform, but also altered electrical properties of myocardiocytes. Moreover, atrial voltage is significantly influenced by the technical approach to electro-anatomical mapping. Recent technological advances have renewed interest in substrate modification, and bridge the gap in the ablative management of paroxysmal and persistent AF. Finally, adverse atrial remodeling is a dynamic and progressive process, driven by upstream risk factors. Without adequate risk factor modification, ongoing substrate development and AF recurrence is likely, stressing the importance of a holistic approach to AF care.

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Table 1: Details of studies employing voltage guided ablation

Study
Rolf et al., 2014 (18)
Wang et al., 2014 (24)
Cutler et al., 2016 (19)
Jadidi et al., 2016 (21)
Kottkamp et al., 2016 (163)
Yamaguchi et al., 2016 (164)
Yang et al., 2016 (23)
Yagishita et al., 2016 (88)
Yang et al., 2017 (27)
Mohanty et al., 2017 (165)
Schreiber et al., 2017 (166)
Kircher et al., 2018 (25)
Yamaguchi et al., 2018 (167)
Zhou et al., 2018 (92)
Ahmed-Jushuf et al., 2019 (80)
Kumagai et al., 2019 (168)
Kumagai et al., 2019 (28)
Efremidis et al., 2019 (169)
Masuda et al., 2020 (29)
Hwang et al., 2021 (136)
Huo et al., 2022 (26)

LVA – Low voltage ablation; PAF – paroxysmal atrial fibrillation; PsAF – persistent atrial fibrillation; LSPAF – long-standi

Figure 1: Light microscopy of post-mortem myocardial specimens without a history of AF (A), paroxysmal AF (B) and persistent AF (C) (Masson's trichrome stain, magnification x 200) (adapted with permission from (58)). Burden of fibrotic tissue, stained in blue, correlates with duration of AF. D) Diagram detailing normal atrial myocyte bundles and different patterns of fibrotic deposition. In replacement (reparative) fibrosis, degenerating myocytes are replaced by fibrotic tissue within myocyte bundles. Reactive (interstitial) fibrosis involves expansion of the fibrotic tissue in between myocyte bundles. Both forms may coexist within a single atrium.

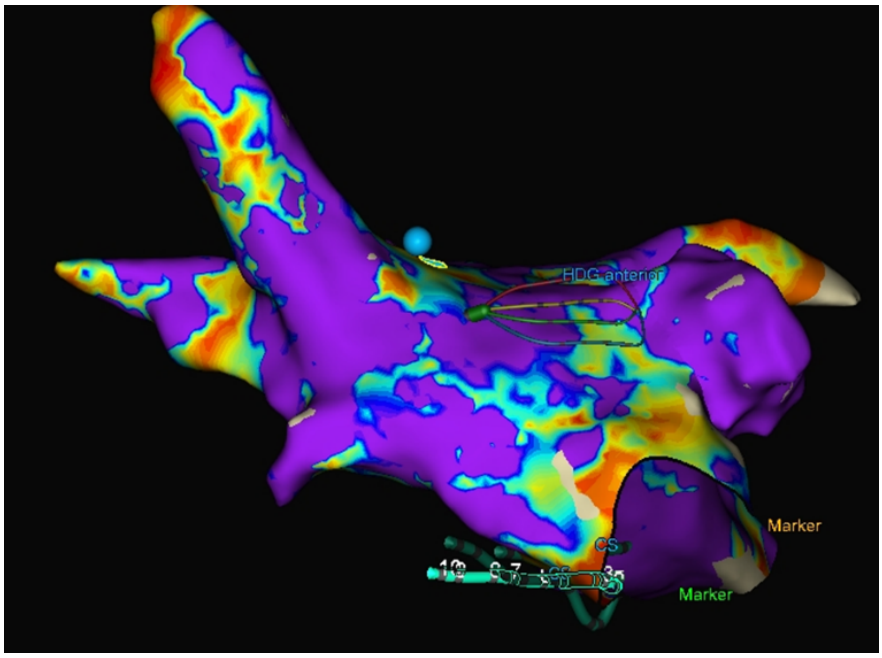

Figure 2: Bipolar voltage maps of a single left atrium collected during AF (panels A and C) and coronary sinus pacing (panels B and D) at a cycle length of 600 ms. Low voltage zones in red defined as regions with peak-to-peak voltage <0.5 mV.

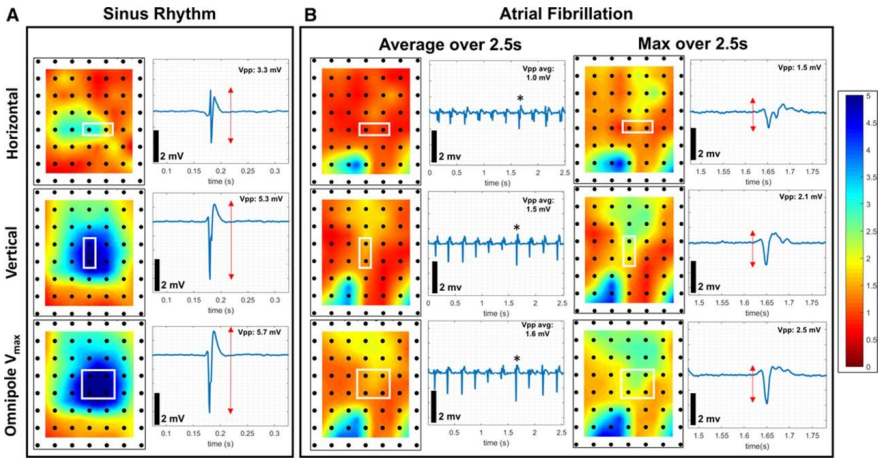

Figure 3: In vivo epicardial recordings from canine atria showing bipolar EGMs using a multielectrode atria with varying electrode pairings as depicted by box on left image. Upper panels use horizontal pairing, middle panels utilise vertical pairing and lower panels use clique of 4 electrodes to generate omnipolar direction-independent EGM. Panel A shows EGMs during sinus rhythm with marked direction dependence as evident from difference in peak-to-peak voltage (Vpp) between horizontal and vertical electrode pairings. In contrast omnipolar Vpp is larger and more similar to the maximal measured voltage. Panel B shows similar measurements in AF averaged over 2.5 seconds with maximal Vpp using omnipolar EGMs higher than either horizontally or vertically paired electrodes. (Adapted with permission from (144)).

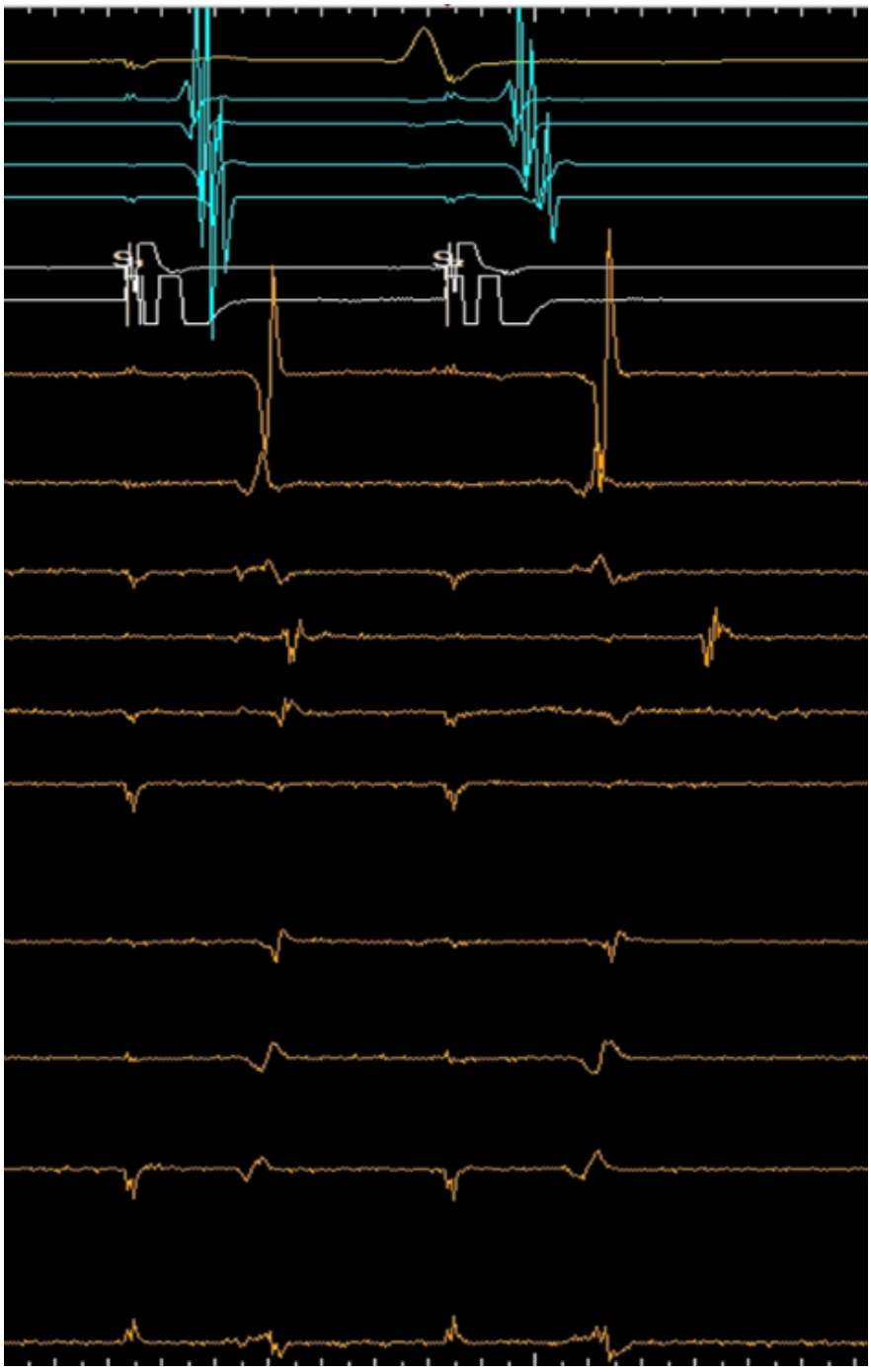

Figure 4: Examples of atrial decremental evoked potentials (DeEP) in response to extraistimulus testing with a drive train (S1) at 600 ms and extrastimulus (S2) at 20 ms above the refractory period, with a multipolar catheter placed at multiple regions with the atrium. DeEP positive sites may showed marked latency of activation (A), EGM fractionation (B) or a combination of the two (C).