Individualised Ablation Strategy Guided by Live Simultaneous Global Mapping to Treat Persistent Atrial Fibrillation

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Title:

Individualised Ablation Strategy Guided by Live Simultaneous Global Mapping to Treat Persistent Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is the most common clinical arrhythmia encountered. Catheter ablation has become the first-line therapy for symptomatic drug-refractory paroxysmal and persistent AF. Although pulmonary vein (PV) electrical isolation is still the cornerstone of the ablation strategy, the clinical outcome particularly in treating persistent AF is suboptimal. Significant efforts have been applied with live global chamber mapping of AF aimed to identify patient-specific drivers and/or maintainers located outside of the PVs to further improve the outcome of catheter ablation. Within this review, we present an overview of contemporary global chamber AF mapping technologies and characteristics, with a particular focus on global, non-contact, dipole density mapping illustrated with a clinical case of persistent AF ablation using this novel methodology.

Key Words

Atrial fibrillation, catheter ablation, non-contact mapping
Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, affecting approximately 1.5-2% of the general population [1, 2]. The prevalence of AF will continue to increase as the population ages [3-6]. The persistent and permanent forms of AF are the most frequent, representing 68-80% of patients identified of the general population or in patients hospitalised for AF, and with approximately 20% having suffered at least two recurrences during the previous year of observation [7-11]. Moreover, AF is far from benign, it incurs a 5-fold increased risk of stroke [12, 13], 3-fold increased risk of heart failure [14], 2-fold increased risk of mortality [15], 2.4-fold increased risk of development of dementia [16, 17], and even sudden death [18, 19]. Technical advancements in catheter-based intervention over the past decades has increased the application of catheter ablation of AF, with ablation often chosen as the first-line treatment for symptomatic drug-refractory paroxysmal and persistent AF [20-22] over an exclusively pharmacological treatment [23-26].

Evolution of AF ablation and the challenges in ablation of persistent AF

The mechanisms of AF are not well understood despite intense investigations at least over the past century. Three main hypotheses concerning the mechanisms of AF include multiple re-entrant wavelets, rapidly discharging automatic foci and a single re-entrant circuit with fibrillatory conduction [27-29]. A key breakthrough was the
recognition of rapidly firing foci which triggered AF [30, 31]. This discovery ushered in the modern era of performing pulmonary vein electrical isolation (PVI) for primarily treating paroxysmal AF [31, 32] with its application subsequently extended to persistent AF as well [32-34].

Currently, PVI is the cornerstone of ablation for both paroxysmal and persistent AF, although the clinical outcome of PVI alone to treat persistent AF is not satisfactory [34-36]. Consequently, adjunctive ablation strategies in addition to PVI have been investigated, which included targeting the Complex Fractionated Atrial Electrograms (CFAE) [37, 38], linear ablation [39-42], ganglionated plexi ablation [43-45], non-PV triggers [46-48], left atrial appendage electrical isolation [49, 50] and so on. Despite encouraging acute outcomes of ablating persistent AF in some studies, the medium to longer term follow-up clinical outcomes were less impressive [39, 51-53].

The challenges to the success in ablating persistent AF [54] include: 1) the lack of full understanding of the mechanisms of AF specific to the individual patient being treated, although there is a broad acceptance of the concept that triggers and substrate are essential to the initiation and the maintenance of AF [55-57]; 2) the limited ability to identify non-PV atrial triggers [58] (identified in only 10%-33% of unselected AF patients referred for catheter ablation) on the posterior left atrial (LA) wall, the superior vena cava, the crista terminalis, the coronary sinus, the ligament of Marshall and the left atrial appendage [49, 59-62]; 3) difficult to achieve complete transmural
and durable lesion from endocardial ablative approach, although the use of contact force-sensing technology [63-67], adenosine testing after ablation [68-70], and pace capture-guided ablation [71] may be of help.

Global mapping of AF using current technologies

Non-contact endocardial mapping with EnSite® Array

Due to the complex mechanisms and irregular activation of AF, conventional point-by-point mapping may be difficult or even not feasible. Thus, the first non-contact, global chamber mapping technology (EnSite Array, Abbott/St. Jude Medical Inc., St Paul, MN, US) emerged early-on in the history of 3D mapping, both in terms of technology and concept in mapping AF [72]. The multipolar non-contact catheter has 64 unipolar electrodes, which record cavitary unipolar electrograms and calculate endocardial unipolar electrograms using a mathematical inverse algorithm, which is a solution to Laplace’s equation. The calculated electrograms are displayed on a surface mesh with 2592 rectangular facets. The mesh represents the geometry of the endocardial surface that is physically traced by a conventional catheter [73].

There are limitations of using this technology in mapping AF, which include 1) the precision of the inversely calculated EGMs depended on the distance from the centre of the array to the endocardial surface, and the method was validated only for distances <40 mm [73, 74]; 2) it is not consistently used for catheter ablation of AF,
although it may facilitate recognition of gaps in ablation lines and for localisation of arrhythmogenic non-PV foci [72]; 3) the difficulties of manipulating ablation catheter with the balloon mapping catheter in LA, may have restricted the widespread use of this technology.

Contact FIRM Phase mapping

The Topera RhythmView™ 3D Mapping System (Abbott/Topera Medical, Palo Alto, CA, USA) utilises the FIRMap™ Catheter, a 64-electrode, contact mapping basket catheter, which collects electrophysiologic activity, and translates this to an existing geometry, that is created on a non-Topera 3-D mapping system of the atrial chamber [75]. Proprietary software processes electrograms through a phase mapping algorithm with analysis of repolarisation and conduction dynamics to identify electrical sources of AF rotors and foci, and thereby guide FIRM (Focal Impulse and Rotor Modulation) ablation [76]. The technology identified sites of spiral rotors and focal drivers of AF in humans for the first time without the need for incorporating surgically placed electrodes. In individual FIRM guided ablation studies, a wide variation in mid-term and long-term freedom from AF has been reported 17-80% [76-82].

Within the variation of results from the various case series of FIRM mapping, it has been postulated that perhaps some of the differences are due to the catheter shape resulting in unequal topographical coverage of the atria and in some cases electrodes either not being in contact (46%) [80], catheter protruding through the mitral valve, or
electrogram quality was unusable. From groups with both high and low result success in terms of outcome, the conclusion was that a multicentre trial of FIRM mapping would be useful. In the first small multicentre trial of FIRM mapping involving 78 patients at 10 experienced centres, freedom from AF at 1 year was reported as 80% [83].

Although cardiac electrophysiologic activity of the chamber could be acquired simultaneously, limitations remain with this methodology [84]. First, the electrode contact on the atrial wall is not consistent, leading to inadequate electrogram resolution required for rotor site identification. Secondly, localisation of contact catheters to guide an ablation catheter to the FIRM map target is absent.

Non-contact body surface mapping

The ECVUE™ Mapping System (CardioInsight, Medtronic, Minneapolis, MN, USA), is a non-invasive body surface mapping system that uses 252 external electrodes in combination with computed tomography to record bi-atrial unipolar electrograms and create simultaneous bi-atrial three-dimensional maps [85-87]. Proprietary body-surface phase mapping algorithms are applied to the selected AF segment to identify active AF driver regions (classified as focal or re-entrant) [88, 89]. Clinical studies have shown a high AF-termination rate with reduced RF-time compared with the stepwise approach and favourable follow-up results of driver-based ablation of persistent AF [88, 90].
The system utilises the maximum dv/dt [91] and therefore was originally used for study of ventricular activation [92]. Evolution of the technology has allowed mapping of AT [93], paroxysmal and persistent AF [85, 94-96]. Studies of persistent AF using this technology are limited to a single centre experience in Bordeaux, and one multi-centre (AFACART study) [90]. In the multicentre AFACART study, driver only ablation resulted in termination of AF in 64% of those studied, and at 1-year follow-up, 78% were off anti-arrhythmic drugs and 77% were free of AF recurrence. However, of those with no AF recurrence, 49% experienced at least one episode of AT [90].

Limitations noted of the Cardio-Insight system are the detection of false rotors due to the phase-based analysis; some of the AF circuits may not be displayed due to the subtraction of long R-R interval sequences only; and small signals <0.15mv can be difficult to resolve from far-field signals [88, 97]. Secondly, the assessment of the drivers within the inter-atrial septum may be difficult to map by the technology. Thirdly, the processed phased data (identified driver areas) is projected on a 3D shell acquired by CT rather than the atrial geometry constructed by a separate 3D mapping system. This may influence the ability of the operator to accurately navigate the ablation catheter to the identified sites.

**Novel non-contact dipole density mapping**
The AcQMap® High Resolution Imaging and Mapping System (Acutus Medical, Carlsbad, CA) provides a suite of static and dynamic, 3D maps of electrical activation across an ultrasound-acquired cardiac chamber surface and localises auxiliary electrode catheters within and around the surface. The system is comprised of an invasive diagnostic recording catheter that is inserted transvenously into either the left or right atrial chambers [98]. The catheter is attached to the AcQMap Console, which contains electronic instrumentation that drives transmission and acquisition of the ultrasound, localisation, and cardiac electrical data. Body-surface electrocardiogram (ECG) and patch electrodes are placed on the patient to provide ECG signals and localisation data to the system, respectively. A separate quadripolar catheter is transvenously placed below the diaphragm and serves as a universal electrical reference.

The AcQMap catheter is a 10F, non-deflectable catheter that is introduced into the chamber of interest over a 0.032-inch guidewire. The distal end of the catheter is deployed into a 25mm diameter spheroid, formed by six splines. Each spline has eight ultrasound transducers interspersed between eight biopotential electrodes, resulting in a total of 48 sensors of each type (Figure 1). The catheter and system are designed to acquire data without the need to contact the chamber surface, which is referred to as “non-contact” mapping.
Ultrasound is used to image the endocardial surface by acquiring points that reconstruct the 3D chamber anatomy. When ultrasound is activated, acoustic waves travel through the blood until they reach the tissue surface. A portion of the wave continues travelling through the cardiac tissue while a portion is reflected and detected by the transducer. The duration of time for the acoustic wave to travel from the transducer to the cardiac surface and return to the transducer is proportional to the distance travelled. Accordingly, the system places points along the chamber wall at the calculated distance corresponding to the location of each point of reflection (Figure 2). During ultrasound point acquisition the user continuously rotates the catheter approximately 60 degrees in both directions to ensure the entire endocardial surface is sampled. The system samples up to 115,000 surface points per minute. The entire set of surface points are usually collected in 2-3 minutes. The 3D surface is algorithmically reconstructed from the ultrasound point-set, comprising a mesh of more than 7,000 triangles. Minimal post-processing is performed to remove unneeded points and add definition to anatomical structures. The resulting chamber anatomy corresponds to the end-diastolic size and shape. The final post-processed anatomy is a key input into the inverse solution used to derive the location of charge sources on the endocardial surface (see Supplement video 1 of anatomy construction).

The intracardiac potential-field is measured by the 48 biopotential electrodes, which are engineered to provide low-noise and high-fidelity input into an inverse solution. Raw, non-contact, unipolar intracardiac potentials are measured across the
endocardial surface by placing the catheter into the centre of the chamber and recording data for any selected duration of time, as appropriate for the rhythm to be mapped. The system samples the whole potential field at a rate of 150,000 samples/second. After data is recorded, the traces from the 48 electrodes are reviewed all at once and outliers are excluded. In the case of irregular rhythms, particularly atrial fibrillation, an algorithm is applied to remove the QRS complex and enable continuous display of the activation wave front. Maps can be displayed as either dipole density- or voltage-based representations of the activation wave front (see Supplement video 2 of the work flow of dipole density mapping).

Dipole density principle

Voltage has served as the gold standard in electrical analysis of cardiac signals for the past 120 years [99]. In contrast, dipole density represents the actual biophysics of cardiac activity and is a more localised entity that provides a more focused view into the details of cardiac activation. Dipole density mapping, expressed in units of µCoulombs/cm, represents the magnitude of these sources on the endocardial surface of the chamber with a view of cardiac activity that is at least four times sharper and narrower than voltage [100, 101].

Dipole density is the distribution of actual charge-sources that embody the native resolution of electrical activity at the cellular level. A dipole consists of two oppositely charged particles separated by a very small distance. Each time a cell is
stimulated, ions move across the cellular membrane through ion-selective channels. During ionic movement, a small dipolar imbalance in charge emerges in the adjoining extracellular medium. After the first cell is stimulated, ion channels in adjacent cells are “recruited” and a wave of “activation” spreads outward. The combined activation of these cells forms a macroscopic double-layer of dipoles that directly represents the wave front and, in turn, generates the cardiac potential field, measured in units of Volts.

The fundamental difference between voltage and dipole density lies in both the averaging effect of “spatial summation” and in the volume of space occupied by each. Spatial averaging causes the distribution of voltage to surround the charges and extend far beyond the compact, physical boundary of the charges. It also smooths out some of the localised details of the geometric shape of the wave front [102-103]. This explains why it is possible to measure the body surface ECG, although with significantly less spatial detail than intracardiac electrograms.

The AcQMap System applies an inverse solution to derive the dipolar charge sources (the cause of the field, measured as dipole density) that exist on the endocardium. The causal relationship between charge and potential are based on Poisson’s equation, published in 1813, which defines how the potential-field at any point (measured as voltage) is equal to the local sources plus the sum of distant sources[103]. Thus, dipolar charge sources solved for by the AcQMap System are intrinsically linked to
the intracavitary potentials measured.

To solve the inverse solution for dipole density, the AcQMap system leverages the fundamental constraints of cardiac activation for which charge sources exist only on and within the excitable cardiac tissue. This constraint minimises the mathematical complexity of the inverse solution. Solving the inverse solution therefore requires 3 key inputs: 1) multiple simultaneous measurements of the potential field in the chamber, which can be collected by the 48 electrodes on the AcQMap Catheter; 2) an accurate anatomic surface (ultrasound anatomy construction) used to define the location of the charge sources; 3) a common coordinate system in which the AcQMap catheter is localised with 3D coordinates that correspond with the 3D coordinates of the reconstructed anatomical mesh. Provision of the inputs listed above enables spatially-localised and temporally-animated derivation of the dipolar charge-sources on the endocardial surface. The corresponding waves of activation are displayed across the reconstructed 3D surface through time.

The activation wave front can be displayed in its rawest form as either a dipole- or voltage-based map of depolarisation, with voltage forward-calculated from the derived dipole density. Additional post-processing of the data can be applied to extract specific information from the map. A propagation-history map uses bands of colour to show the location and velocity of the leading edge of the wave front over a set duration of time. The colour red is used to indicate the leading edge of the wave front
with the trailing colour-bands showing earlier locations of the wave front. The width
of the colour bands conveys the conduction velocity of the wave front, with wider
bands indicative of fast conduction and narrow bands of slow conduction. Conduction.

Figure 3 shows the relationship between raw voltage-based maps, raw dipole-density
based maps, and propagation history maps (Supplement video 3).

AF propagation map guided by AcQMap
The propagation history map identifies and locates the discrete and coupled
mechanisms responsible for initiating and maintaining the arrhythmia. Interpretation
of propagation history maps derived from recordings of AF has revealed three atrial
activation patterns of interest (API), including focal, localised rotational activation
(LRA, spiralling around a small confined zone ≥ 270°) and localised irregular
activation (LIA, entry/exit through, and pivoting around a confined zone), Figure 4
and Supplement video 4. The areas of API are considered to be the “driver” and/or
“maintainer” of AF. Such confined areas have dimensions ranging from 5 to 15 mm
in diameter [104].

The ablation strategies guided by AcQMap mapping system consist PVI followed by
ablation targeting these APIs (drivers and maintainers of AF) separately at each
remapped stage, connecting the API guided lesion sets to near PVI circumferential
lesions and/or anatomical barriers. During the procedure, a circular catheter was used
to confirm the exit/entrance block as conventional PVI ablation procedure. When
sinus rhythm could not be restored by ablation targeting APIs in left atrium (LA), the AcQMap catheter can be deployed in the right atrium (RA), trying to look for APIs in RA. The procedural endpoint is AF termination by ablation [105].

The clinical experience of this combined imaging and mapping technology is still early and limited to few centres. Its limitations therefore will perhaps have to be better explored over time. In the meantime, as this platform is novel, the validation and the efficacy to guide ablation data in human is not yet available although currently being collected. The utility of the basket catheter is confined to the atrial chambers. To our knowledge, to date attempt has not been made to use this technology to map human ventricles.

**Live Dipole density mapping of persistent AF to guide ablation - a case study**

A 54-year-old male with a 2-year history of symptomatic *de novo* non-valvular persistent AF and one previous failed cardioversion underwent catheter ablation utilising the AcQMap system. The echocardiography showed normal heart structure with mild enlargement of LA (diameter of 45mm) and normal left ventricular size and ejection fraction.

After informed and consented, the patient underwent AF ablation with a strategy to achieve PVI first, followed by API targeted, non-PV drivers and maintainers ablation. A decapolar catheter was placed in the coronary sinus and a quadripolar catheter (as
the unipolar reference) was placed in the inferior vena cava. Through transeptal puncture, the AcQMap catheter was introduced into the LA over a 0.032-inch guidewire. The basket of the AcQMap catheter was fully opened and placed in the middle of the chamber. By rotating the catheter, the ultrasound crystals collect points to reconstruct the chamber anatomy. The final post-processed anatomy was used for navigation and mapping to guide catheter ablation.

The propagation map showed two predominant APIs consisting of LRA and LIA patterns located at the mid-anterior wall and lower posterior wall near the left inferior PV (Figure 5 panel A). Remap after PVI showed that the API at the anterior wall of the LA shifted slightly towards the right-sided PVs (Figure 5 panel B).

The API on the anterior wall was ablated first. This cluster of ablation was then connected to the nearest electrical barrier (circumferential lesion near the right PVs) and anatomical barrier (anterior aspect of the mitral valve annulus). The re-map after this lesion set revealed a significant conduction modification of the anterior API. The posterior API persisted. This was targeted with ablation next and the focal lesion set was joined to the electrical barriers (circumferential lesions near the left/right inferior PVs), see Figure 6. On completion of the lower posterior line, AF terminated with conversion to left atrial tachycardia (cycle length of 215ms with the coronary sinus sequence from distal to proximal). The re-map of this left atrial tachycardia showed that it was a macro-reentrant tachycardia conducting through an isthmus in the middle
of the previously ablated anterior line (Figure 7). Further ablation at this site terminated the atrial tachycardia to sinus rhythm (Supplement video 5).

**On-going studies in dipole density mapping guided ablation**

The novel non-contact AcQMap mapping system may represent a significant advance in treating persistent AF when compared to conventional 3D mapping systems, but clinical data of AF ablation in assessing this technology is at a preliminary stage. The prospective, single-arm, international multi-centre, nonrandomised UNCOVER-AF clinical study (NCT02825992) being conducted at the moment aimed to address both procedural and long-term outcomes of catheter ablation in 125 persistent AF patients guided by this novel mapping system. Large multicentre randomised control trial is required to assess the efficacy of dipole density mapping guided ablation to treat AF.

**Future perspective**

In the last decade, significant efforts and intense research have been incorporated into newer mapping systems, to improve procedural efficiency and outcomes for AF ablation. Accurate panoramic live mapping of AF is a novel approach that may lead to an increasingly successful outcome of ablation. There are several fundamental and important requisite in understanding the complexity of persistent AF, so clinicians can target optimal ablation sites to treat persistent AF. They include an accurate anatomic surface-mesh and an accurate live mapping of the dynamic rapidly changing wave fronts. Identification and understanding of fibrillary circuits is a formidable challenge.
but durable success for ablation also requires effective ablation lesion delivery to achieve transmural and durable lesions in the targeted location.

The next phase in AF mapping will depend heavily on advancing fundamental knowledge of arrhythmia mechanisms in humans. Increasing success will depend upon the ability to simultaneously accurately map temporal, spatial, and high-resolution electrogram data to offer bespoke lesions to target both non-PV triggered and complex persistent AF.

Conclusion

Persistent AF is a complex, patient-specific arrhythmia. The result of catheter ablation to treat this arrhythmia is currently suboptimal, although PVI remains the cornerstone of the ablation strategy. Conventional contact and non-contact voltage-based mapping may not adequately identify patient-specific drivers and/or maintainers of AF due to their spatially averaged representation of the actual complex and irregular spatiotemporal characteristics of cardiac conduction. The emergence of simultaneous global chamber, live mapping systems may help us to accurately identify clinically-critical non-PV targets for ablation with an aim to improve clinical outcome. Future clinical studies are required to investigate if these novel mapping technologies such as non-contact dipole density mapping can provide a better understanding of the mechanistic characterisation of AF and individualised ablation strategies that relate to an improved clinical outcome.
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Figure 1. The AcQMap mapping catheter

![AcQMap Catheter Diagram]

- 48 Ultrasound Transducers
- 48 Engineered Electrodes
- 25mm diameter
- Up to 115,000 ultrasound points/minute
- 150,000 intra-cardiac unipolar voltage samples/second
Figure 2. The process to illustrate how ultrasound transducer collects acoustic wave data.

Panel A shows an acoustic pressure wave transmitted from the ultrasound transducer. Panel B demonstrates the wave propagates through the blood until it contacts the tissue. A portion of the wave continues through the tissue and a portion is reflected. Panel C shows the reflected wave detected by the ultrasound transducer. The time interval between transmission and reception of the reflection is proportional to the range of the target.
Figure 3. Voltage map, dipole density map and propagation-history map.
Figure 4. Three atrial activation patterns of interest (API) identified by dipole density mapping

- **Driver**
- **Maintainer**
- **Maintainer**

Localised Rotational Activation, LRA (spirals around a confined zone)

Localised Irregular Activation, LIA (enters and exits a confined zone)

(both with multiple directions from collision and block)
**Figure 5.** Initial pre- and post-PVI propagation history map in persistent AF

Two spatial and temporal consistent API located on middle anterior wall (AP View) and on the lower posterior wall (PA view) pre-PVI (Panel A) and post-PVI (Panel B), respectively. API=atrial activation patterns of interest; LIPV=left inferior pulmonary vein.
Figure 6. The ablation strategies guided by dipole density mapping.

After PVI, the API at the anterior LA wall was ablated first, connecting the lesion sets to the circumferential lesion near right PV and anterior mitral valve annulus (AP view). The API at the low posterior wall was targeted next, followed by connecting that to left and right circumferential lesions posteriorly (PA view).
**Figure 7.** Atrial tachycardia (AT) dipole density map of the left atrium

A gap (blue arrow) in the middle of anterior ablation lesion was detected by the dipole density mapping during AT (cycle length of 215 ms). Ablation at the gap terminated the AT to sinus rhythm.
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In the original FIRM ablation study, 92 patients were enrolled to undergo ablation for AF in 107 consecutive ablation procedures. In 73 patients, a second constellation catheter was used to map the right atrium (RA). Success rate was reportedly high -77.8% freedom from AF after a median follow-up of 890 days [76].

Other studies using FIRM mapping have shown variable success rates. In a comprehensive study by Mandapati et al [79], an average of 1.6 +/- 0.8 rotors for the LA, and 0.6 +/- 0.8 rotors for the RA were identified. In this study, changes in Chirality were often noted around the same site. AF termination only occurred in 1/24 of cases, conversion from AF to atrial tachycardia in 3/24, slowing of the atrial cycle
length in 8/24. Ablation at rotor sites even when accompanied by PVI did not result in AF termination in 83% of patients and at 500 days follow-up, only 46% had freedom from AF.

In 2016, Shivkumar et al [80] published data from a period covering 2012-2013 based upon FIRM mapping, which found 2.6 +/- 1.2 rotors in 43 patients with AF (56% PAF). Results differed from the original FIRM studies at about the same time period, with AF termination in 4, organisation in 7, and >10% slowing of AF in 9. At 18+/7 months follow-up, freedom from AF of was only 37%. Natale et al [81] studied 29 patients with persistent AF, with an acute success rate of 41%, but with zero AF terminations, 2 with AF slowing and 10 with AF organisation. At a mean 5.7 months of follow-up, freedom from AF was 17%.

Of 170 consecutive patients (Paroxysmal AF 37%, Persistent AF 31%, Longstanding persistent AF 19%) published in 2017, Dandamudi et al [82] in the Indiana FIRM registry found focal sources in the RA in 85% (1.8+/1.3) of patients, and 90% (2.0 +/-1.3) in the LA. One year freedom from AF was 77% (PAF), 75% for persistent AF and 57% Longstanding persistent AF.

Within the variation of results from the various case series of FIRM mapping, it has been postulated that perhaps some of the differences are due to the catheter shape resulting in unequal topographical coverage of the atria and in some cases electrodes
either not being in contact (46%) [80], catheter protruding through the mitral valve, or electrogram quality was unusable. From groups with both high and low result success in terms of outcome, the conclusion was that a multicentre trial of FIRM mapping would be useful. In the first small multicentre trial of FIRM mapping involving 78 patients at 10 experienced centres, freedom from AF at 1 year was reported as 80% [83].

Although cardiac electrophysiologic activity of the chamber could be acquired simultaneously, limitations remain with this methodology [84]. First, the electrode contact on the atrial wall is not consistent, leading to inadequate electrogram resolution required for rotor site identification. Secondly, localisation of contact catheters to guide an ablation catheter to the FIRM map target is absent.

**Non-contact body surface mapping**

The ECVUE™ Mapping System (CardioInsight, Medtronic, Minneapolis, MN, USA), is a non-invasive body surface mapping system that uses 252 external electrodes in combination with computed tomography to record bi-atrial unipolar electrograms and create simultaneous bi-atrial three-dimensional maps [85-87]. Proprietary body-surface phase mapping algorithms are applied to the selected AF segment to identify active AF driver regions (classified as focal or re-entrant) [88, 89]. Clinical studies have shown a high AF-termination rate with reduced RF-time compared with the stepwise approach and favourable follow-up results of driver-based ablation of
persistent AF [88, 90].

The system utilises the maximum dv/dt [91], and therefore was originally used for study of ventricular activation [92], evolution of the technology has allowed mapping of AT [93], paroxysmal and persistent AF [85, 94, 95]. However, the accuracy of AT mapping is 92% in one study [96] due to the complex signal to noise ratios, and sometimes circuits within the inter-atrial septum, a site which cannot be mapped by the technology. In patients in whom previous AF ablation had a resultant AT, the success rate was lower at 83% [96]. The accuracy of the system has been calculated by the inventor to be 6mm [89], and therefore is unable to differentiate micro-re-entrant AT from focal AT.

In AF where the complexity of the arrhythmia is visualised by the system, the success rate is variable, and studies have been limited. The subtraction analysis requires relatively long R-R intervals to subtract the electrical vector from the ST segment, and in the study of Haissaguerre et al [88] spontaneous or diltiazem provoked prolonged R-R intervals were used. Of 111 patients with persistent AF, 103 were eligible for study, including 26 persistent AF in sinus rhythm following cardioversion 4 weeks pre-procedure, 57 persistent AF<12 months, and 20 AF patients for more than 12 months. It was noted that repetitive re-entry represented 73% and focal single rotations 27%. The meandering of a core was 7±2cm. A median of 4 drivers per patient was noted. In 21 patients, endocardial mapping was performed with 62%
having prolonged fractionated electrograms at these sites. There was an increase in the number of drivers with the duration of AF. However, the effect of diver ablation, in terms of elimination of detected AF drivers, and emergence of new drivers or multiple wavelets was not assessed due to the absence of remapping during the procedure [88]. At 12 months follow-up, 64% were in SR, 22% in AT, and 20% in AF. Of interest at 1-year, 85% of patients with termination of AF at ablation were free from AF [88].

In the AFACART study [90], 118 patients with persistent AF were studied. Driver only ablation resulted in termination of AF in 64% of those studied, and at 1-year follow-up, 78% were off anti-arrhythmic drugs and 77% were free of AF recurrence. However, of those with no AF recurrence, 49% experienced at least one episode of AT. In some examples of simple AF, targets for ablation manifesting as a single spiral wave with a broad sweeping wave-front have been identified. In more complex forms, multifocal wavelets with a high degree of curvature are seen, with a rapidly changing and dynamic activation pattern making targets for ablation more challenging to understand. The commonest pattern described by Haissaguerre et al [88] consists of multiple wavelets and focal activity around the PVs. In an atrium with scar fractionation of multicomponent signals with similar amplitude and steepness can be difficult to interpret and careful editing is required to display isochrones of activation. Ablation was performed in a hierarchical approach, with regions of the atrium displaying the highest driver density until AF terminated.
Limitations noted of the Cardio-Insight system are detection of false rotors due to the phase-based analysis, some of the AF circuits may not be displayed due to the subtraction of long R-R interval sequences only, small signals <0.15mv can be difficult to resolve from far-field signals [88, 97]. Studies of persistent AF using this technology are limited to a single centre experience in Bordeaux, and one multi-centre (AFACART study).

Although this body surface mapping system allows for pre-procedural, non-invasive AF mapping and preparation of an individualised ablation strategy, assessment of the drivers in the septal area may be difficult to identify from body surface signals. The processed phased data is projected on a 3D shell acquired by CT leaving the identified driver areas to be mentally interpreted and translated onto either the 2D fluoroscopic view of the atrial chamber or reconstructed atrial geometry of a separate 3-D mapping system. This may influence the ability of the operator to accurately navigate the ablation catheter to the identified sites.

**Novel non-contact dipole density mapping**

The AcQMap® High Resolution Imaging and Mapping System (Acutus Medical, Carlsbad, CA) provides a suite of static and dynamic, 3D maps of electrical activation across an ultrasound-acquired cardiac chamber surface and localises auxiliary electrode catheters within and around the surface. The system is comprised of an
invasive diagnostic recording catheter that is inserted transvenously into either the left or right atrial chambers [98]. The catheter is attached to the AcQMap Console, which contains electronic instrumentation that drives transmission and acquisition of the ultrasound, localisation, and cardiac electrical data. The data is passed from the AcQMap Console to the AcQMap Workstation on which the AcQMap software is installed and operated to process and display the collected cardiac data. Body-surface electrocardiogram (ECG) and patch electrodes are placed on the patient to provide ECG signals and localisation data to the system, respectively. A separate quadripolar catheter is transvenously placed below the diaphragm and serves as a universal electrical reference.

The AcQMap catheter is a 10F, non-deflectable catheter that is introduced into the chamber of interest over a 0.032-inch guidewire. The distal end of the catheter is deployed into a 25mm diameter spheroid, formed by six splines. Each spline has eight ultrasound transducers interspersed between eight biopotential electrodes, resulting in a total of 48 sensors of each type (Figure 1). The catheter and system are designed to acquire data without the need to contact the chamber surface, which is referred to as “non-contact” mapping.

Ultrasound is used to image the endocardial surface by acquiring points that reconstruct the 3D chamber anatomy. When ultrasound is activated, acoustic waves travel through the blood until they reach the tissue surface. A portion of the wave
continues travelling through the cardiac tissue while a portion is reflected and detected by the transducer. The duration of time for the acoustic wave to travel from the transducer to the cardiac surface and return to the transducer is proportional to the distance travelled. Accordingly, the system places points along the chamber wall at the calculated distance corresponding to the location of each point of reflection (Figure 2). During ultrasound point acquisition the user continuously rotates the catheter approximately 60 degrees in both directions to ensure the entire endocardial surface is sampled. The system samples up to 115,000 surface points per minute. The entire set of surface points are usually collected in 2-3 minutes. The 3D surface is algorithmically reconstructed from the ultrasound point-set, comprising a mesh of more than 7,000 triangles. Minimal post-processing is performed to remove unneeded points and add definition to anatomical structures. The resulting chamber anatomy corresponds to the end-diastolic size and shape. The final post-processed anatomy is a key input into the inverse solution used to derive the location of charge sources on the endocardial surface (see Supplement video 1 of anatomy construction).

The intracardiac potential-field is measured by the 48 biopotential electrodes, which are engineered aimed to provide low-noise and high-fidelity input into an inverse solution. Raw, non-contact, unipolar intracardiac potentials are measured across the endocardial surface by placing the catheter into the centre of the chamber and recording data for any selected duration of time, as appropriate for the rhythm to be mapped. The system samples the whole potential field at a rate of 150,000
samples/second. After data is recorded, the traces from the 48 electrodes are reviewed all at once and outliers are excluded. In the case of irregular rhythms, particularly atrial fibrillation, an algorithm is applied to remove the QRS complex and enable continuous display of the activation wave front. Maps can be displayed as either dipole density- or voltage-based representations of the activation wave front (see Supplement video 2 of the work flow of dipole density mapping). While voltage has served as the gold standard in cardiac mapping for the past 120 years [99], physiologically dipole density is more localised and it provides a sharper and narrower view into the details of cardiac activation.

**Dipole density principle**

Cardiac voltage arises as a spatially broad summation of local, dipolar charge sources generated by the action of cellular ion channels throughout the myocardium. Dipole density mapping (µCoulombs/cm) represents the magnitude of these sources on the endocardial surface of the chamber with a view of cardiac activity, which is at least four times sharper and narrower than voltage [100, 101].

Dipole density is the distribution of actual charge-sources that embody the native resolution of electrical activity at the cellular level. A dipole consists of two oppositely charged particles separated by a very small distance. Each time a cell is stimulated, ions move across the cellular membrane through ion-selective channels. During ionic movement, a small dipolar imbalance in charge emerges in the adjoining
extracellular medium. After the first cell is stimulated, ion channels in adjacent cells are “recruited” and a wave of “activation” spreads outward. The combined activation of these cells forms a macroscopic double-layer of dipoles that, in turn, generates the cardiac potential field, measured in units of Volts. Dipole density cannot be directly measured, but it can be accurately derived from the potential field by using an inverse solution.

An inverse problem in science is the process of calculating from a set of observations the causal factors that produced them. The problem starts with the results and then calculates the causes. Inverse solutions commonly leverage foundational relationships between the causes and the results to simplify the calculation. Inverse problems are frequently used in science and mathematics to solve for phenomena that cannot be directly observed or measured. Inverse solutions are broadly used in fields such as astrophysics, acoustics, astronomy, geophysics, oceanography, optics and medical imaging. Image calculations in computed tomography and magnetic resonance imaging are familiar examples where inverse solutions have been applied [102].

The inverse solution used by the AcQMap System for intracardiac mapping measures the potential field (the result, measured as voltage) within the chamber to derive the dipolar charge sources (the cause of the field, measured as dipole density) that exist on the endocardium. The foundational relationship between charge and potential are based on the general wave equations first published by Maxwell in 1865 [103].
Maxwell’s equations describe how electric fields are created by electric charges and currents. More specifically, Poisson’s equation, a precursor to Maxwell’s equations published in 1813 describes how the potential field (measured as voltage) at any point is equal to the local sources plus the sum of the distant sources [104]. Thus, dipolar charge sources solved for by the AcQMap System are intrinsically linked to the intracavitary potentials measured.

To solve the inverse solution for dipole density, the AcQMap system leverages the fundamental constraints of cardiac activation for which charge sources exist only on and within the excitable cardiac tissue. This constraint minimises the mathematical complexity of the inverse solution. Solving the inverse solution therefore requires 3 key inputs: 1) multiple simultaneous measurements of the potential field in the chamber, which can be collected by the 48 electrodes on the AcQMap Catheter; 2) an accurate anatomic surface (ultrasound anatomy construction) used to define the location of the charge sources; 3) a common coordinate system in which the AcQMap catheter is localised with 3D coordinates that correspond with the 3D coordinates of the reconstructed anatomical mesh. Provision of the inputs listed above enables spatially-localised and temporally-animated derivation of the dipolar charge-sources on the endocardial surface. The corresponding waves of activation are displayed across the reconstructed 3D surface through time.

The activation wave front can be displayed in its rawest form as either a dipole- or
voltage-based map of depolarisation. Additional post-processing of the data can be applied to extract specific information from the map. A propagation-history map uses bands of colour to show the location and velocity of the leading edge of the wave front over a set duration of time. The colour red is used to indicate the leading edge of the wave front with the trailing colour-bands showing earlier locations of the wave front. The width of the colour bands conveys the conduction velocity of the wave front, with wider bands indicative of fast conduction and narrow bands of slow conduction. Figure 3 shows the relationship of voltage map, dipole density map and propagation-history map (Supplement video 3).

**AF propagation map guided by AcQMap**

The propagation history map identifies and locates the discrete and coupled mechanisms responsible for initiating and maintaining the arrhythmia. Interpretation of propagation history maps derived from recordings of AF has revealed three atrial activation patterns of interest (API), including focal, localised rotational activation (LRA, spiralling around a small confined zone ≥ 270°) and localised irregular activation (LIA, entry/exit through, and pivoting around a confined zone), Figure 4 and Supplement video 4. The areas of API are considered to be the “driver” and/or “maintainer” of AF. Such confined areas have dimensions ranging from 5 to 15 mm in diameter [105].

The ablation strategies guided by AcQMap mapping system consist PVI followed by
ablation targeting these APIs (drivers and maintainers of AF) separately at each remapped stage, connecting the API guided lesion sets to near PVI circumferential lesions and/or anatomical barriers. The procedural endpoint is AF termination by ablation [106].

**Live Dipole density mapping of persistent AF to guide ablation - a case study**

A 54-year-old male with a 2-year history of symptomatic *de novo* non-valvular persistent AF and one previous failed cardioversion underwent catheter ablation utilising the AcQMap system. The echocardiography showed normal heart structure with mild enlargement of LA (diameter of 45mm) and normal left ventricular size and ejection fraction.

After informed and consented, the patient underwent AF ablation with a strategy to achieve PVI first, followed by API targeted, non-PV drivers and maintainers ablation. The AcQMap catheter was deployed in the LA and ultrasound was activated to collect points and reconstruct chamber anatomy. The final post-processed anatomy was used for navigation, mapping to guide catheter ablation.

The propagation map showed two predominant APIs, consist of LRA and LIA patterns, located at the mid-anterior wall and lower posterior wall near left lower PV respectively (Figure 5 panel A). Remap after PVI, the API at the anterior wall of the LA shifted slightly towards the right-sided PVs (Figure 5 panel B)
The API on the anterior wall was ablated first, this cluster of ablation was then connected to the nearest electrical barrier (circumferential lesion near the right PV) and anatomical barrier (anterior aspect of the mitral valve annulus). The remap after this lesion revealed a significant conduction modification of anterior API. The API at the posteriorly of the LA persistent, therefore was ablated followed. Again, the posterior cluster of lesion in targeting the posterior API by joined to the electrical barriers (circumferential lesion near the left lower PV and that near the right lower PV), Figure 6. Near the completion of the lower posterior line, AF terminated with conversion to left atrial tachycardia (cycle length of 215ms with the coronary sinus sequence from distal to proximal). The remap of this left atrial tachycardia showed that it was a macroreentrant tachycardia conducting through a gap in the middle of the anterior LA along the previous ablated anterior line (Figure 7). A further ablation at the gap converted atrial tachycardia to sinus rhythm (Supplement video 5).

**On-going studies in dipole density mapping guided ablation**

The novel non-contact AcQMap mapping system may represent a significant advance in treating persistent AF when compared to conventional 3D mapping system, but clinical data of AF ablation in assessing this technology is at a preliminary stage. The prospective, single-arm, international multi-centre, nonrandomised UNCOVER-AF clinical study (NCT02825992) being conducted at the moment aimed to address both procedural and long-term outcomes of catheter ablation in 125 persistent AF patients.
guided by this novel mapping system. Large multicentre randomised control trial is required to assess the efficacy of dipole density mapping guided ablation to treat AF.

**Future perspective**

In the last decade, significant efforts and intense research are been incorporated into newer mapping systems, to improve procedural efficiency and outcomes for AF ablation. Accurate panoramic live mapping of AF is a novel method that may lead to an increasingly successful outcome of ablation. In understanding the complexity of persistent AF, there are several fundamental and important factors, which include an accurate anatomic surface-mesh, an accurate line mapping of the dynamic rapidly changing wave fronts to target optimal ablation sites responsible for persistent AF. Identification and understanding of circuits is a formidable challenge but durable success for ablation requires effective ablation lesion delivery to achieve transmural and durable lesions in the targeted location.

The next phase in AF mapping will depend heavily on advancing fundamental knowledge of mechanisms in humans. Increasing success will depend upon the ability to simultaneously accurately map, temporal, spatial, and high-resolution electrogram data to offer bespoke lesions to target both non-PV triggered and complex persistent AF.

**Conclusion**
Persistent AF is a complex, patient-specific arrhythmia. The result of catheter ablation to treat this arrhythmia is currently suboptimal, although PVI remains the cornerstone of the ablation strategy. Conventional contact and perhaps non-contact mapping may not adequately identify patient-specific drivers and/or maintainers of AF due to their complex and irregular spatiotemporal characteristics. The emergence of simultaneous global chamber, live mapping systems may help us to accurately identify clinically-critical non-PV targets for ablation and may lead to an improved clinical outcome. Future clinical studies are required to investigate if these novel mapping technologies such as non-contact dipole density mapping will provide better understanding of the mechanistic characterisation of AF and individualised ablation strategies that relate to an improved clinical outcome.

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Supplement Video 1. LA anatomy construction by Dipole density mapping system
Supplement video 2. The workflow of dipole density mapping
Supplement video 3. The relationship of voltage map, dipole density map and propagation-history map.
Supplement video 4. The three atrial activation patterns of atrial fibrillation.

Driver

Maintainer

Maintainer

Focal

Localised Rotational Activation, LRA (spirals around a confined zone)

Localised Irregular Activation, LIA (enters and exits a confined zone)

(both with multiple directions from collision and block)

https://mc04.manuscriptcentral.com/fm-fca
Supplement video 5. A case study of persistent AF ablation by dipole density mapping