Critical Appraisal of Technologies to Assess Electrical Activity during Atrial Fibrillation

A Position Paper from the European Society of Cardiology Working Group on eCardiology in collaboration with the European Heart Rhythm Association, Heart Rhythm Society, Asia Pacific Heart Rhythm Society, Latin American Heart Rhythm Society and Computing in Cardiology

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Abstract

Aims: We aim to provide a critical appraisal of basic concepts underlying signal recording and processing technologies applied for 1) AF mapping to unravel AF mechanisms and/or identifying target sites for AF therapy and 2) AF detection, to optimize usage of technologies, stimulate research aimed at closing knowledge gaps and developing ideal AF recording and processing technologies.

Methods: Recording and processing techniques for assessment of electrical activity during AF essential for diagnosis and guiding ablative therapy including body surface electrocardiograms and endo- or epicardial electrograms (EGM) are evaluated.

Results: Discussion of 1) differences in uni-, bi- and multipolar (omnipolar/Laplacian) recording modes, 2)impact of recording technologies on EGM morphology, 3)global or local mapping using various types of EGM involving signal processing techniques including isochronal-, voltage- fractionation-, dipole density-and rotor mapping, enabling derivation of parameters like atrial rate, entropy, conduction velocity/direction, 4) value of epicardial and optical mapping, 5) AF detection by cardiac implantable electronic devices containing various detection algorithms applicable to stored EGMs, 6) contribution of machine learning to further improvement of signals processing technologies.

Conclusion: Recording and processing of EGM are the cornerstones of (body surface) mapping of AF. Currently available AF recording and processing technologies are mainly restricted to specific applications or have technological limitations. Improvements in AF mapping by obtaining highest fidelity source signals (e.g. catheter-electrode combinations) for signal processing (e.g. filtering, digitization and noise elimination) is of utmost importance. Novel acquisition instruments (multipolar catheters combined with improved physical modelling and machine learning techniques) will enable enhanced and automated interpretation of EGM recordings in the near future.

Keywords: atrial fibrillation, signal recording, signal processing, mapping, machine learning, cardiac implantable electronic devices.

1. Introduction

Recording, processing and subsequently interpretation of electrical activity of the atria is essential for diagnosis and guiding (ablation) therapy of atrial fibrillation (AF). Atrial electrical activity in clinical practice can be measured using body surface electrocardiograms (ECG) or endo- and epicardial electrograms (EGM); optical action potentials are also used in research settings. ECGs recorded by implantable loop recorders or EGMs by pacemaker and ICDs can be used for AF detection.

In the electrophysiology laboratory, analysis of EGMs recorded by catheters plays an important role in adjunctive ablation strategies performed in addition to pulmonary vein isolation, particularly in patients with (longstanding) persistent AF. However, electrical activity during AF is highly complex requiring advanced mapping systems equipped with sophisticated processing technologies for identification of suitable target sites for ablation. As standard approaches for recording and processing electrical activity during AF do not exist a lot of effort has been put in clinically evaluating a variety of mapping systems yet with mixed outcomes. Many of the currently available recording and processing technologies are also restricted to specific applications or have technological limitations hampering wide-spread applicability. Importantly, guidelines or recommendations in this area currently do not exist.

Aims and Scope

The objectives of this document are to 1) provide a critical appraisal of basic concepts underlying signal recording and processing technologies applied for AF mapping to unravel AF mechanisms and/or identifying target sites for AF therapy and AF detection, 2) discuss clinical values and limitations based on unique features of these technologies, 3) advise on their applications and 4) to identify unmet needs in context of signal recording and processing. This position paper provides up-to-date knowledge for clinicians, engineers and researchers to

optimize usage of signal recording and processing methodologies, stimulate research aimed at closing knowledge gaps and developing ideal AF recording and processing technologies. As novel signal recording and processing technologies are continuously being developed, we do not aim to review all features offered by currently existing mapping systems.

Invasive Mapping of Atrial Fibrillation

2.1 Unipolar and bipolar EGMs

An EGM is the extracellular potential difference between two adjacent electrodes (bipolar, Bi-EGM) or the potential difference between one single electrode in tissue contact relative to an indifferent electrode at zero potential or Wilson Central Terminal (unipolar, U-EGM). Figure 1 shows examples of U-EGM and corresponding Bi-EGM recorded during AF.[1, 2] Though AF mapping is most frequently performed with Bi-EGM, U-EGM are nowadays also increasingly being used. Sofar, differences between U-EGM and B-EGM for AF mapping have only been examined for identification of low voltage areas in single centre clinical studies and experimental studies (section 4.2) and of endo-epicardial asynchronously activated areas in experimental studies (section 6.2). The advantage of U-EGMs is that determination of local activation time (LAT) is straightforward (section 4.1). The main disadvantage of U-EGMs is that local fibrillation potentials may be masked by far-field potentials or distant atrial activity caused by respectively the ventricles and multiple fibrillation waves, as U-EGMs are sensitive to remote electrical activity. Sofar, in only one report, U-EGM features (dV/dT_{max}< 0.05V/s, amplitudes < 0.2mV and durations>35ms) used to discriminate local from far field fibrillation potentials have been described. [3] The major advantage of Bi-EGM is its relative insensitivity to remote electrical activity and electrical noise (due to common mode rejection) and it is therefore often the preferred recording mode used for AF mapping[1, 2]. However, a disadvantage of Bi-EGM is that its amplitude depends on wavefront direction; when a fibrillation wave

passes both electrodes at the same time, subtraction of virtually equal U-EGMs results in no residual Bi-EGM. Annotation of LAT is also more ambiguous (section 4.1). In addition, Bi-EGM morphology not only depends on interelectrode spacings,[4] but also on conduction velocity (CV) and direction of the fibrillation waves which both vary from beat-to-beat during AF.

Thus, Bi- and U-EGM have their own (dis) advantages (Table 1) for AF mapping and their morphology is affected by various variables (supplemental Table 1). At present, there are no clinical studies demonstrating that either U- or Bi-EGM are more suitable for AF mapping. As they provide complimentary information, combined usage for AF mapping could be beneficial.

2.2 Multipolar EGMSs

Multipolar EGM include Laplacian and omnipolar EGMs (Figure 2). Laplacian EGMs are calculated by subtracting the centre electrode U-EGM from the U-EGM of either evenly distributed surrounding close-by electrodes, (fixed electrode-array), or sequentially obtained EGMs weighted for distance utilizing an electro-anatomical mapping system. [5] If electrodes are close together, Laplacian EGMs approximate the second-order spatial derivative of the U-EGM. Omnipolar EGMs yield EGMs independent from the orientation of the recording electrodes, and hence wavefront direction. They are calculated within a clique, which is defined as a square of 4 electrodes from which the Bi-EGM with the largest amplitude is extracted.

Experiences with multipolar EGMs such as Laplacian and omnidirectional EGMs during AF are limited to voltage mapping in experimental settings in canine and human atria. [5, 6] Table 1 summarizes (dis)advantages of omnipolar and Laplacian EGMs. Sofar, there are no clinical studies demonstrating advantages of multipolar EGM over U- and Bi-EGM for AF mapping.

2.3 Impact of recording technology on EGM morphology

EGM morphology is affected by the size of recording electrodes, shapes of electrodes (printed on splines or integrated in catheter shaft), inter-electrode distances, filtering and the sampling rate of digitization (supplemental Table 1). Smaller diameter electrodes result in higher frequency and amplitude potentials of both U- and Bi-EGM [7] but also higher noise levels caused by higher input impedances. [8, 9] A decrease in interelectrode distances is associated with a decrease in voltages and fractionation.[10, 11] Filtering and the sampling frequency also influence EGM characteristics. [12] According to the Nyquist principle, the sampling rate should be at least twice the highest intended frequency content to be measured. Filtering may attenuate respiration or movement artifacts, interference and far-field components, but it also affects EGM morphology.[1, 2, 9] Especially high-order filters that attenuate certain frequencies more steeply, may disturb EGM morphology significantly. [9, 12] Such filters are prone to ringing and may generate artificial deflections. Low- and high pass filtering may respectively increase and decrease amplitudes of U-EGM; both low- and high pass filtering decreases fractionation of U-EGM recorded during AF. [1, 9] Notch filtering increases fractionation of U-EGM during AF and reduces amplitudes.[9] Hence, filtering significantly affects the already complex morphology of EGM recorded during AF and should therefore be avoided as much as possible.

3. Local versus Global Mapping Modes

Cardiac mapping is defined as a methodology by which electrical potentials record from the heart are spatially depicted in an integrated manner, usually as a function of time.[13] Identification of underlying mechanism(s) and arrhythmogenic substrates by mapping of AF is slowly progressing. In contrast to mapping uniform arrhythmias with a stable and defined focal or re-entrant mechanisms, AF mapping is challenging, as AF is neither purely focal nor stable re-entry in nature. [14, 15] Thus, conventional mapping catheters and algorithms assuming spatiotemporal EGM stability are not applicable to AF mapping. There is no consensus on how

long AF episodes should be recorded to obtain a representative value of a specific parameter and how to determine the electropathological variable which most accurately represents arrhythmogenic tissue (e.g. mean, median, or ranges). Two concepts for recording of electrical activity during AF are 'global' and 'local mapping'.

3.1 Global AF mapping

Global mapping ('panoramic view') refers to simultaneous recording of EGMs of the entire atria using large intracardiac basket catheter(s) (supplemental Figure 1) or body surface electrodes (section 5). Endocardial, multielectrode basket catheters record up to 128 U-EGMs simultaneously from multiple locations and can be used for e.g. activation or phase mapping. Bi-atrial activity is recorded during a single interval which avoids interpolation associated with combining sequential data from multiple intervals.

Non-randomised clinical studies demonstrated that ablation targeted at stable rotational activity and focal sources could eliminate AF.[16, 17]Algorithms using data recorded by these basket catheters are often biased toward detection of rotational activities even when these do not exist; focal activation might be displayed as rotational activity if the wavefront reaches surrounding electrodes sequentially. [18, 19] Advantages of these catheters are that they measure contact EGMs and allow real-time evaluation of propagation for guiding ablation. However, they also have significant limitations: 1) suboptimal electrode-tissue contact at many poles; 2) splines are not equidistantly separated, 3) low spatial resolution, 4) lack of reproducible positioning, 5) recordings contain spline touch artefact's, 6) higher pro-coagulative tendency, 7) septum and coronary sinus are not included. Additionally, the amount of extrapolation used for construction of e.g. activation time maps is difficult to determine. Though initial, non-randomised studies in patients with AF were promising, a randomised, controlled, multicentre

clinical trial failed to demonstrated successful outcomes of ablative therapy guided by global mapping. [20]

3.2. Local AF mapping

Local mapping refers to high density mapping of smaller regions using contact multipolar catheters; the catheter moves consecutively through the atria to obtain local electrical activity. During local mapping, contact catheters directly record, rather than estimate, EGMs. This can be achieved epicardially with high-density electrode grids placed during surgery [21] or endocardially with multielectrode mapping catheters introduced percutaneously (supplemental Figure 1). [22] The resulting maps have a high local resolution but however, limited global resolution. Maps created with roving catheters often utilize Bi-EGM rather than U-EGM. A benefit of multielectrode mapping catheters over linear ablation catheters is the higher likelihood that electrodes are in contact with tissue, reducing the effect of catheter angle on EGM morphology.[23-25] Also, multi-electrode grids allow fixed uniform and reproducible interpolation unlike spline or basket multi-electrode catheters.

Multielectrode mapping catheters with smaller electrodes and closer interelectrode spacing increase the mapping resolution.[22, 26] However, the optimal mapping resolution during AF is yet to be defined. Also, the larger number of data points recorded by multielectrode mapping catheters precludes real-time manual annotation of individual signals, thus, creating dependency on automated algorithms and their accuracy. Simultaneous construction of endocardial and epicardial contact maps accounting for transmural activation sequences may be warranted in AF but has not yet been clinically implemented.[3]

4. Signal Processing Technologies

Signal processing refers to analysis, usually automated, of EGMs. Analysis is focused on identifying specific parameters defining individual EGM characteristics with the principal aim of rapidly interrogating the arrhythmogenic substrate and targeting sites critical to AF maintenance. Various signal processing techniques applicable for AF mapping discussed below are summarized in Table 2.

4.1 Local Activation Time Mapping

A LAT map depicts the activation time at every recording site relative to a reference point.[27, 28] LAT mapping is used to visualize patterns of activation to e.g. discriminate between re-entry and focal activity or to identify slow, crucial zones of slow conduction by superimposing isochrones. Figure 3 illustrates examples of difficulties encountered in annotation LAT of U- and Bi-EGM. LAT maps using U-EGM are based on the principle that the timing of $-dV/dT_{max}$ coincides with the time of maximum rate of rise of the transmembrane potential (time differences less than 50 us [29]) corresponding to the maximum increase in sodium current and its conductance. LAT determination using Bi-EGM is more complex; bipolar LAT maps are constructed by annotating the onset, peak or $-dV/dT_{max}$ of Bi-EGM. An accurate algorithm for LAT annotation utilizes the $-dV/dT_{max}$ of the first-order spatial derivative of the underlying U-EGM. This assumes that shape and velocity of the propagating wavefront remains constant, which is usually not the case during AF. Activation time mapping is an effective approach if EGMs consist of a single negative deflection but is challenging if EGMs are fractionated or contain continuous electrical activities. Several advanced signal processing technologies have been proposed to improve automated analysis of complex EGMs, including investigation of signal morphology, wavelet decomposition, deconvolution and wavefront tracking, yet clinical benefit of these technologies have not yet been demonstrated.[28, 30-33]

4.2. Voltage Mapping

A voltage (V) map depicts the peak-to-peak amplitudes of EGMs at multiple sites (supplemental Figure 1). However, both unipolar (UV) and bi-polar voltage (Bi-V) are influenced by numerous variables (supplemental Table 1). UVs are larger than Bi-V; only when the maximum V at one electrode nearly coincides with the minimum V at the other electrode, then the V of the negative deflection of Bi-EGM equals the peak-to-peak V of U-EGM (left panel Figure 1). Another determinant of EGM-V is rate and hence cardiac rhythm. [34] There is a modest correlation between Bi-V measured during AF and sinus rhythm, which becomes weaker in patients with more persistent types of AF. [35] Bi-V are higher during sinus rhythm compared to AF. During atrial extra stimuli with decreasing coupling intervals, Bi-V were more attenuated than UV.[34] Despite numerous variables affecting EGM-V, low endocardial Bi-V are regarded as surrogate markers of fibrotic tissue and low voltage areas have therefore become targets for ablative therapy in patients with AF[36]. It is important, however, to emphasize that there is limited data correlating low voltage areas to mechanisms initiating or perpetuating AF. [36] Several definitions of voltage thresholds related to 'scar tissue' have been introduced e.g. 0.5 mV (most often used, 5th percentile obtained during supraventricular tachycardia), 0.05mV (noise level electro-anatomical mapping system), 0.2 mV for the posterior left atrial wall (5th percentile of V histograms of patients with paroxysmal AF) or <0.1mV ('dense scar', patients with persistent AF). [37-39] However, none of these thresholds have been validated pathologically and outcomes of ablation targeting bipolar low voltage areas -either during sinus rhythm or AF- show conflicting results.[40] Possible explanations for these discrepancies include mapping and/or ablation strategies and patient selection. Also, since voltage depends on size and distances of electrodes, voltage maps acquired with different catheters should not be compared.

4.3. Complex Fractionated Atrial Electrograms Mapping

Complex fractionated atrial electrograms (CFAE) maps depict the location of CFAEs (supplemental Figure 1). CFAE are most often defined as potentials with 3 or more negative deflections. However, in literature, at least 27 different definitions and/or methodologies for identification of CFAE have been introduced (Table 3). [41] A review of 84 studies targeting CFAE, reported on absence of CFAE predilection sites in the right or left atrium and also no differences in degree of fractionation between patients with paroxysmal or persistent AF. [41, 42] These findings are, however, not surprising, giving the variable methodologies applied. Also, how fractionated bi-EGM should be corrected annotated is unknown. The mechanistic role of CFAEs in AF stems from the earlier work by Konings et al. who performed unipolar epicardial mapping of induced AF in patients with Wolff-Parkinson-White syndrome undergoing cardiac surgery.[43] By comparing U-EGM morphology and underlying activation patterns, they demonstrated that CFAEs during AF correlated to sites of pivot points and slow conduction. This led to the conclusion that CFAE areas during AF represent either continuous re-entry of fibrillation waves into the same area or overlap of different wavelets entering the same area at different times. This observation supports the hypothesis that AF is driven and maintained by multiple wavelets. Kalifa et al. proposed that fractionation occurs due to interruption of an activation wavefront as it crosses from one tissue boundary into another. [44] This hypothesis supported the observation that fractionation was highest at boundaries of dominant frequency (DF) domains (i.e. sites of highest DF and lowest frequencies) caused by differences in electrophysiological properties (refractory periods, CV etc.) of adjacent myocardial tissue. These findings not only dispute the multiple wavelet hypotheses but also propose that 1) AF is driven and maintained by rotors and CFAE are located adjacent to sources, 2) these sources correlate to sites of highest DF and highest regularity index (RI) i.e. sites of fastest and most organized activity and 3) that creation of borders at CFAE sites results in AF termination.

However, others argued that there is only a modest spatial correlation between CFAE sites and highest DF and with the different responses to ablation at these sites respectively this may indicate that CFAE and DF domains are separate entities.[45] A multicentre, randomized trial indeed demonstrated that CFAE ablation did not reduce AF recurrences on the long-term. [46, 47]

4.4 Dipole Density Mapping

Dipole density mapping refers to utilization of dipole density -defined as 'cellular charge sources'- to resolve local electrical activation. [48, 49] Data from an ultrasound array is used for reconstruction of the anatomy [49]. Non-contact electrodes sense intracavitary U-EGMs from which dipole densities are derived based on the precise ultrasound measured distance and reconstructed endocardial surface area. From these dipole densities, forward-calculated EGMs are reconstructed. A prediction model instead of data interpolation is used between the measuring points. Fundamental differences between voltage and dipole density lie in the averaging effect of "spatial summation" and in the volume of space occupied by each. Theoretically, dipole density–based mapping provides a more localized portrayal of activation patterns than voltage-based mapping does, and with less far-field interference.

The accuracy of non-contact dipole density map was compared to contact voltage mapping during sinus rhythm and AF and correlated well when the recorded sites were ≤40 mm from the endocardial surface, comparable to previously published for non-contact mapping systems.[50] The theoretical benefits of dipole density mapping and initial clinical outcomes from single center studies require further validation in randomized controlled trials. [50, 51]

4.5 Rotational Activity Mapping

Rotational activity is caused by functional reentry circuits (supplemental movie 1) with an excitable but non-excited core and a curved wavefront subject to source-sink mismatch driving

spiral waves. [52]Phase analysis is used to identify rotors based on identification of the phase singularity point and thereby the core of rotational activity driving AF. In phase mapping, the converted EGM is mathematically transformed to capture wavefront dynamics through the activation-recovery cycle of the underlying tissue, effectively functioning as a low-pass filter implemented on fractionated EGMs. [53]Phase analysis is particularly suited to optical mapping of action potentials with their characteristic depolarisation upstroke, intervening plateau and repolarisation downslope and has been used effectively for AF analysis in experimental models. [54] However, as the type of signals recorded, and the technique employed influences phase analysis it remains unclear whether rotational activity seen during mapping of AF in humans are representative of the same re-entry mechanism demonstrated with optical mapping [55]. In computational and experimental models, rotational activities maintain AF and therefore have been considered ablation targets. Limitations of mapping in humans that may influence the phase analysis and thereby interpretation of phase maps includes: (1) artefact due to noise, (2) far field ventricular signals and (3) limited resolution with mapping catheters particularly basket catheters resulting in data interpolation. Interpolation of phases may result in representation of non-existent rotors as the interpolation algorithm is devised to detect rotational activity. [18, 19, 56] Therefore, it remains unclear whether the current mapping modalities available in humans are able to effectively identify source mechanisms that have so elegantly been demonstrated in animal models with optical mapping. Furthermore, characteristics of these localised sources remain unclear. Spatiotemporal stability of rotational activities has been demonstrated in optical mapping studies in animal models, however, mapping of rotational activity in humans has shown inconsistent results. [16, 17, 57, 58] Whilst some studies conclude that these drivers are spatiotemporally stable [16] others have shown that even though spatially stable the drivers elicit temporal periodicity.[57] It remains unclear which of these characteristics are

the correct description of these drivers and if both are, does the temporal stability have an impact on the mechanistic importance of these drivers? These questions remain to be answered.

4.6 Atrial rate analysis

The activation rate of a recording site can be estimated in the time domain in terms of average cycle length, while several indices related to activation organization can be obtained from the dispersion of the cycle length histogram. However, this approach requires the use of automatic algorithms to estimate LATs or cycle lengths, which can be challenging in case of CFAE.[59] Atrial rate can also be computed in the frequency domain, avoiding the need of LAT detection. In order to ensure that the maximum spectral amplitude corresponds to the atrial rate and not to one of its harmonics, Botteron's preprocessing [60, 61] is applied to the raw signal before computing the spectrum. This preprocessing (supplemental Figure 2) consists of three steps: band-pass filtering, rectification and low pass filter removing details of the individual activations and converting the raw signal in a train of smooth pulses. The dominant frequency is defined as the highest spectral peak of this preprocessed signal. The organization index has been defined as the ratio of the spectral power around the dominant frequency and its harmonics to the total spectral power.[62] This index measures the periodicity of the preprocessed signal, which is a sign of periodic and organized activations. Spatial distribution of activation rate and activation organization have been studied to find AF critical sources, and therefore, candidate sites for ablation, based on the hypothesis that high activation rates and organization allows identification of sources driving AF. [63] While reduction of dominant frequency has been shown to be a marker of ablation outcome, [64] direct ablation of sites with maximum dominant frequency have shown mixed results. [65-67]

4.7 Conduction velocity and activation direction analysis

Conduction velocity (CV) along a given activation direction (AD) can be measured from differences of LATs at electrodes with known 2-dimensional interelectrode distances (Figure 4). [28, 68, 69] However, CV can only be estimated as the true 3-dimenional pathway is unknown. CV can be semi quantitively visualised by construction of ischronal maps. Model-based approaches have been used to estimate both CV and AD, using LAT from EGMs recorded by circular catheters or multielectrode arrays [68]. In general, CV and AD maps can be obtained by postprocessing activation maps if they have enough spatial resolution, [70] but they may be very sensitive to errors and inconsistencies in LAT estimates. To cope with this problem, Anter et al[69]. proposed a method which estimates a consistent global pattern of activation in the whole chamber, taking into account all candidate LATs in a single electrogram, and then locally estimated CV and AD. Uncertainties in LAT estimation have been quantified and used for LAT interpolation.[71] Recently, van Schie et al. introduced a novel, modified discrete velocity vectors methodology to calculate CV. [72] CV during AF is calculated to identify areas with low CV associated with structural remodeling. However, as the true pathlength is unknown, particularly in complex patterns of activations during AF, the calculated 'effective' CV may only be roughly estimated.

4.8 Entropy

Entropy is a dimensionless parameter of randomness, used in information theory to measure information content, estimate signal variability or randomness in time series data and can therefore be used to evaluate EGM complexity objectively. [73] When applied to EGMs, low values indicate high regularity and predictability whereas high values increase progressively with irregularity and are highest for random noise. The amplitude histogram based shannon entropy measure was only moderately inversely correlated with CFAE [73]. A recent single center

study demonstrated that sample entropy, which uses EGM segment vector comparisons, is correlated with outcomes of ablation therapy in persistent AF patients undergoing CFAE ablation.

5. Non-Invasive Mapping of AF

ECG Imaging (ECGI) is a non-invasive, body surface mapping technique (Figure 5) for reconstruction of cardiac excitation patterns using 80-250 electrodes applied to the upper torso.[74, 75] Prior to this, the cardiac anatomy and electrode positions are determined either via medical imaging (CT or MRI scans) or with 3D localization technology. [74, 76] Numerical inversion provides real-time estimates of epi- and endocardial U-EGMs, excitation wavefronts, or transmembrane voltages. From these, atrial maps of various quantities (e.g., activation time, voltage, phase, conduction velocity, and dominant frequency) can be derived and specific phenomena can be localized (e.g., ectopic foci, phase singularities, and rotors/rotor densities). Because of severe numerical problems, only a few investigators attempted to estimate transmural potentials. Inversion requires an accurate forward model including a source and an observation model. The observation model is a volume conductor model of the torso relating cardiac sources to body surface potentials. Relatively large distances between sources and electrodes translate into spatial blurring which the inversion tries to correct, but this is complicated as there are far fewer electrodes than source locations. The source model describes generation and spatiotemporal propagation of excitation, and depends on many hidden parameters—this serves as a prior to the solution. In practice, this is replaced by patient-independent assumptions and constraints on spatiotemporal smoothness. Priors are needed for regularization, because inversion is inherently an ill-posed problem with ambiguous solutions. Current systems reach resolutions of 10-20 mm, with wide standard deviations. [77] Temporal fidelity is often limited; estimated activation times have errors of 10-20ms. Also, artefacts like

447 spurious lines of block are reported.[78] Due to their lower amplitude, atrial signals are harder
448 to reconstruct than ventricular signals.

449 The promise of ECGI is that it will provide clinicians with non-invasive panoramic maps before
450 the patient moves into the EP-lab, allowing anatomic characterization and localization of AF
451 drivers, and therefore targets for ablation prior to procedures.[57] ECGI could also help verify
452 permanent post-ablation conduction block or identify gaps in ablation lines before re-do
453 procedures. [79] As a research tool, ECGI provides a means of studying AF and poorly-
454 understood mechanisms like reentry circuits, rotors and rotor densities, areas of slow
455 conduction, focal sources, CFAEs and dominant frequency heterogeneities.[80] Combined with
456 LGE-MRI, it can identify locati ons where rotors anchor to fibrotic substrates—potential
457 ablation targets. [81]

458 However, validation of ECGI remains a significant challenge. Comparison of ECGI to EGMs
459 using an intracardiac catheter mapping showed general agreement with several important
460 limitations, [53, 82, 83] primarily related to numerical challenges in the inversion. The technique is
461 sensitive to ECG noise and motion (cardiac cycle, breathing), sometimes resulting in artefacts
462 or outliers. Regularization techniques make generic assumptions on source parameters and it
463 is unclear how that impacts accuracy. Detection of small amplitude EGMs or drivers with short
464 cycle lengths using ECGI may not be reliable, in particular the assessment of drivers in the
465 septal area is challenging. Moreover, the clinical workflow is complex, requiring application
466 of an electrode vest, its anatomical registration and subsequent image processing that has not
467 yet been fully automated and may be hampered by patient-specific factors. This has limited its
468 clinical adoption. Hence, translation of ECGI maps into reliable disease markers requires
469 additional studies. [84]

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6. Research tools for AF Mapping

6.1 Optical Mapping of AF

Optical mapping involves use of voltage-sensitive dyes to examine spatiotemporal excitation patterns in cardiac tissue (Figure 6). [85] This technique has been used in animal models to elucidate tissue-scale or organ-scale atrial electrophysiology, including characterization of anti-arrhythmic drug effects, understanding cellular and molecular AF mechanisms, and exploring the prospect of light-based optogenetic cardioversion [85-87]. In contrast to isolated cell models, optical mapping enables analysis of non-disrupted myocardium in its native electrophysiological milieu. Recent advances have evaluated interplays between 3-dimensional tissue fibrosis and AF mechanisms.[88] These data have been used to calibrate computational models that realistically reproduced reentrant arrhythmia drivers seen in-vitro. Insights obtained from such studies may be useful to improve calibration of image-based computational models in contemporary studies.[89, 90] Disadvantages of optical mapping include applicability to only ex vivo cardiac tissue construction of solely 2-dimensional images. As a research tool, modern mapping technologies may integrate essential findings from optical mapping data specifically on large-scale tissue activation. Progress in this area will likely be hastened by the recent publication of open experimental protocols for relatively inexpensive construction of panoramic optical mapping systems.[91, 92] Notably, interpretation of data from optical mapping could account for limitations of experimental systems, such as the absence of extracardiac sympathetic or parasympathetic regulation of Langendorff-perfused hearts. Moreover, recent findings show that usage of Blebbistatin to reduce motion artifacts in optically mapped hearts via blocking excitation-contraction leads to non-physiological action potential duration prolongation. [93]

6.2 Epicardial Mapping of AF

Cardiac surgery offers the opportunity to perform mapping (Figure 4) of the atrial epicardium. Epicardial mapping can be performed with arrays containing a high number of electrodes (>100) with small diameters (0.4-0.6mm) and interelectrode distances (2-2.5 mm).[21, 94] As these arrays are manually positioned on the epicardium, stable contact between electrodes and atrial tissue is ensured. Also, exact locations of the electrode array in relation to anatomical structures is visualized. Another advantage of this mapping approach is access to regions which cannot be reached from the endocardium such as Bachmann's Bundle. [95] Electrode arrays used during cardiac surgery records EGM at multiple sites simultaneously, which is essential for understanding AF mechanisms. Simultaneous mapping of the endo-epicardium during surgery has indeed unravelled endo-epicardial electrical asynchrony as potential novel mechanism underlying AF persistence. [3] A disadvantage is the sequential mapping approach and the electrode arrays are custom-made and therefore not clinical available. At present, there are no clinical studies demonstrating the value of epicardial mapping guiding (surgical) ablation procedures.

7. Detection of Atrial Fibrillation

7.1 ICD/Pacemakers

In recent years, an increasing number of cardiac implantable electronic devices (CIEDs) have been implanted in patients with cardiovascular diseases. CIEDs enable AF detection with storage of intracardiac EGM for evaluation at any time. As a result of continuous monitoring of a growing number of patients, AF detection has increased dramatically, potentially impacting therapeutic strategies. [96] Atrial high rate EGM (AHREs) are commonly used to detect AF. AF detection algorithms vary between different CIEDs. Generally, in all CIEDs, the PP intervals are continuously monitored. Different models of associating the detected PP

intervals to the programmed PP values are used to identify AF (Table 4). Moreover, it should be noted that AF detection by CIEDs is not always correct, particularly when repetitive non-reentrant ventriculo-atrial synchrony ensues.[97]

7.2 Implantabele Loop recorders

Implantable loop recorders (ILRs) with dedicated AF algorithms are used for diagnosis and monitoring of AF after surgical or catheter AF ablation, and cryptogenic stroke [98-103]. ILRs have high accuracy in detecting AF burdens using incoherence of R-R intervals over a period of time.[104-107] Lorenz plots have extensively been used to demonstrate RR interval irregularity during AF and to discriminate between AF and sinus rhythm. Different ILR models equipped with algorithms for AF detection can accurately quantify AF burden (98.5 %) and are very sensitive (96.4 %) to identify asymptomatic patients with AF [105, 106]. In order to reduce the rate of false positive AF episodes, an ILR with a long sensing vector has been utilized.[108] Moreover, ILR algorithms were improved to detect visible P waves in the absence of noisy baseline or flutter waves and were enhanced with artificial intelligence tools that learn if a patient has P-waves during periods of RR irregularity. Performance of AF detection algorithms in ILRs depends significantly on the patient population, incidence rate of AF, duration of monitoring and type of AF. For example, diagnostic sensitivity will get closer to 100% for longer monitoring duration or in patients with persistent AF [107, 109, 110]. Therefore, prolonged monitoring periods (> 3 years) are a prerequisite for the improvement of the ILR's diagnostic yield.

8. Post-processing of electrical signals

Advances in the field of Artificial Intelligence (AI) and in particular Machine Learning (ML), offer new opportunities to improve analysis of electrical signals.[111, 112] Rapid progression in computational power, data storage and remote data acquisition have enabled the application of ML to ECGs and EGMs. [111] Table 5 provides a non-exhaustive list of potential applications of

548 ML in AF [112, 113]. For the discussion of the application of Artificial Intelligence (AI) for
549 detection of AF we refer to recent scientific documents. [114, 115]
550 ML has several limitations and challenges. First, external validity and generalizability remain
551 to be determined. The real value of this new approach in addition to clinical risk factors and
552 risk scores requires further investigation and validation. Second, while large amounts of data
553 can increase effectiveness of ML models, it is more difficult to critically assess their quality.
554 Third, black box ML methodologies inhibit interpretation and makes it impossible to involve
555 stakeholders in meaningful shared decisions. Fourth, as we move away from intuition and
556 physiologically-reasoned model-based approaches towards large (and deep) multivariate ML
557 models, we lose interpretability and potentially increase the likelihood of catastrophic outputs,
558 resulting in non-causal associations.
559

560 ## 9. Conclusion

561 Recording and processing of EGMs are the cornerstones of mapping of AF. Yet, at present, it
562 is unknown what the most ideal EGM recording type (e.g. uni-, bi- or omnipolar) is and thus
563 which technology should be used for recording and processing. The combination of a lack of
564 golden standard of EGM recording and processing technology during AF and of a
565 comprehensive understanding of mechanism(s) underlying AF, does not give significant
566 confidence in comparative evaluation of current technologies. AI has opened an new era for
567 signal processing, yet the clinical value still has to be further explored. CIEDS are increasingly
568 used to detect AF episodes, yet diagnostic yields need further improvement.
569 Recommendations are summarized in Table 6.
570
571
572

Future Perspectives

Improvements in AF mapping by obtaining highest fidelity source signals – including catheter-electrode combinations, to signal processing including filtering, digitization and noise elimination is of utmost importance. The cleanest source signal, with minimal and/or clearly understood processing and a well-defined protocol facilitates evaluation and clinical application. A critical evaluation of signal recording and processing techniques takes into account all assumptions and mathematical transformations. Rigorous evaluation and validation of novel technologies involves e.g. large animal arrhythmia models and organized tachyarrhythmias before extending application to AF. Algorithms integrated in signal processing software should be provided in manuals and provided as supplements in scientific publications. Simultaneous multi-electrode activation time mapping, optimized for signal quality, electrode size, density, spacing and coverage resolved to continuous high-fidelity propagation sequences with extraction of the arrhythmogenic substrate by automated software in near real-time enables minimally manipulated extraction of electrophysiological mechanisms underlying AF.

The ideal mapping system for AF should be able to automatically 1) detect noise sources and have an optimised noise removal thereby improving the signal-to-noise ratio. 2) remove farfield QRS signal from the atrial EGM 3) annotate fibrillation potentials, 4) identify specific electrogram features related to arrhythmia development or maintenance. The arrhythmogenic substrate underlying AF can be detected by AI and there is an integration of multiparametric generated maps and images (e.g. MRI) with algorithms identifying sites of driver activity or specific substrate parameters related to AF and a validated support for identification of ablation targets. Finally, there is a real-time EGM monitoring to detect variations in AF maintaining mechanisms and display of multiparametric maps.

The AF diagnostic yield of pacemaker/ICDs may be improved by enhancement of existing algorithms by use of RR interval irregularity detection algorithms. Furthermore, adequate atrial lead selection and positioning and optimal programming of atrial sensitivity may eliminate the effects of near-field P-wave or far-field R-wave oversensing by the atrial lead, runs of premature atrial complexes, electrical interference, myopotentials, or repetitive nonreentrant ventriculo-atrial synchrony on accurate AF detection.

For ILRs, further improvement in the AF detection algorithm should integrate rejection of ventricular extrasystoles in order to enhance the accuracy of AF diagnosis in patients presenting significant RR interval irregularities. Developments in multimodal ML could be used for predicting and prognosing from multimodal data (e.g., ECG, EGM, LGE-MRI), improving understanding of the AF substrate, differentiating between paroxysmal AF and persistent AF, and predicting the outcome of ablation therapies. Recent developments in Generative Adversarial Network provide the potential to develop personalized models. Also, initial experiences with ML guiding substrate-based ablation therapy of AF have been published.[116-122]

Legends

Figure 1.

Left panel: U-EGMs and corresponding Bi-EGM demonstrating the relation between the peak-to-peak amplitudes. Right panel: U-EGMs and corresponding Bi-EGMs, demonstrating that U-EGM not always result in "simple" non-fractionated Bi-EGM. On the other hand, fractionated U-EGM may give rise to non-fractionated Bi-EGM. However, an increase in fractionation complexity of U-EGM is associated with an increase in complexity of Bi-EGM. *By courtesy of Mathijs van Schie.*

Figure 2.

Panel A: cliques enclosed by four electrodes are used to record 3 U-EGM (filter: 5-400 Hz) visualized in the top of panel C. U-EGMs of three adjacent electrodes (1,2 and 3) are used to derive Bi-EGM by subtracting one U-EGM from the other U-EGM such that two pairs of Bi-EGMs (1-2 and 2-3) are constructed along the horizontal (red) and vertical (green) directions. Bi-EGMs are filtered (30-400 Hz) and visualized in the centre of panel C. Both Bi-EGMs are used to describe a depolarization wavefront as an electrical field which is electrode orientation-independent. Panel B illustrates the projections along the time-axis of the electrical field derived from both Bi-EGMs. This enables to mathematically obtain Bi-EGMs in any direction without physically rotating a sensing electrode. The E-field is subsequently scaled to analogous 2D voltage signals from which the maximal extent over the interval (T) is calculated and corresponds to the peak-to-peak amplitude of a Bi-EGM obtained along a unit vector direction. Panel C: resulting omnipolar EGM, Panel D: corresponding Laplacian EGM. *By courtesy of Mathijs van Schie.*

Figure 3.

Challenges encountered with annotation of potentials recorded during AF. Panel A: red dots indicate the different time samples. Annotation of the steepest deflection can be calculated by e.g. averaging the steepest deflection of all time samples, selecting time samples with the maximum steepest deflection, or averaging between maximum and minimum values. This information is usually not provided in manuals or in methodology sections of scientific reports Panel B: In case of multiple deflection with comparable slopes and amplitudes, additional criteria have to be developed to determine local activation times (LAT). Panel C: As a result of endo-epicardial asynchrony, endocardial LATs may be different from epicardial LATs. Panel D: Determination of LAT is affected by the filter settings which has a considerable impact on U-EGM morphology.

Figure 4.

High resolution maps of the left atrial wall (N=192, interelectrode distance 2mm) constructed during AF obtained from a patient during cardiac surgery. These maps demonstrate from the left to the right: activation times combined with isochrones, local conduction directions, conduction directions and magnitude of conduction velocities, peak-to-peak voltages. *By courtesy of Mathijs van Schie.*

Figure 5.

Upper panel: simulation of excitation of the right and left atrium. Lower panel:

Body surface maps of the right and left atrium based on simulated - and measured activation times constructed during sinus rhythm with an eighty-channel active electrode system (ActiveTwo, BioSemi, Amsterdam, The Netherlands).

Figure 6.

Schematic illustration of the use of an open source imaging toolkit for panoramic optical mapping, as described by Gloschat et al. A: Experimental optical mapping setup, including Langendorff-perfused heart. B: Heart image with superimposed silhouette (yellow) derived via an automated thresholding process. C: Data projection points for reconstruction of panoramic maps of optically-mapped data. D: Examples of optically-mapped action potentials recorded from the epicardial surface of a rat heart, including annotations for activation and 80% repolarization times. E-F: Spatial reconstructions of activation time (E) and 80% action potential duration (F) from representative rat panoramic optical data. Images reproduced from Fig. 1 (panels A-C) and Fig. 7 (panels D-F) of Gloschat et al. under the terms of the Creative Commons Attribution 4.0 International License. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/. [92]

Supplemental Data

Supplemental Figure 1.

A) Composite image of a 64-electrode basket catheter in different positions within the anatomic shell of the left atrium. Note the large LA surface (yellow dashed line) without contact with the basket electrodes-splines as well as the prolapsing splines through the mitral valve, B) multi-electrode grid for the endocardial approach, C) high density, electrode mapping array for the epicardial approach, D) LAT map of the right atrium (RA) demonstrating a reentrant circuit around an area of scar tissue (grey area) E) RA voltage map, F) RA fractionation map; CFAE sites, indicated by the red markers are superimposed on a bipolar voltage map.

Supplemental Figure 2.

The upper plot demonstrates a 2-second bipolar EGM recorded during AF without any filtering. Right panel: power spectra containing frequency distributions of corresponding signals indicated by the arrows. For the Botteron's Approach, first a 40-250 Hz band-pass filter is applied to the original signal to remove the spectral content below 40 Hz and 250 Hz in order to remove any noise (as indicated in the power spectrum in the right panel). The dominant frequency in this signal is 99 Hz. Step 2 is a nonlinear time-domain rectification process that results in the absolute value of the filtered signal. The power spectrum of this rectified signal demonstrates a fundamental frequency peak follow by harmonics with decreasing amplitude. The third step preserves only the low frequencies by applying a low-pass filter set at 20 Hz. In the time domain, the result is a smoothed pulse shape without high-frequency oscillations. In the frequency domain, this step does not have a large effect for detection of the fundamental frequency, which is 5 Hz in this example**.** *By courtesy of Mathijs van Schie.*

Supplemental Movie 1.

Video excerpt of activation mapping during AF with a 64 electrode basket catheter in the left atrium and the left superior pulmonary vein ostium. The clip shows a clockwise rotational activation (with a period of 180ms) cantered around the orange point on the roof of the LA near the left superior pulmonary vein ostium; this pattern of activation recurred without a significant change for 7 consecutive cycles.

Tables

(see attachments)

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