The Inhomogeneity and Complexity in defining Fractionated Electrograms

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ABSTRACT

Background: Ablation strategies targeting areas of complex fractionated atrial electrograms (CFAE) are not successful in the treatment of atrial fibrillation. Fractionation of atrial electrograms may have multiple causes of both pathological and non-pathological origin. In order to get insight in the definitions used for determining areas of fractionation a literature search was performed using a systematic approach.

Methods and Results: A Pubmed search for studies describing fractionation during human atrial electrophysiological measurements resulted in 348 articles that were screened for new definitions of fractionation. The 24 studies remaining after screening described 11 different visual definitions for fractionation, 3 automated CFAE detection programs and 7 new parameters for measuring fractionation. Five different definitions for continuous electrical activity were presented. Electrode properties were often not described and endocardial bipolar recordings in recent studies used electrode diameters ranging from 1-8 mm with a 2-5 mm interelectrode distance.

Conclusions: No uniform definition or recording method is used for measuring fractionation of cardiac atrial electrograms. The different electrophysiological causes for fractionation and the influence of recording device properties on fractionation complicate identification of true pathological inhomogeneous conduction. The first step in discrimination between origins for fractionation may be accomplished by relating electrogram morphology to the spatial patterns of activation. Before revisiting ablation of areas with fractionated electrograms, we need to determine the correct method for identifying pathological fractionation.

INTRODUCTION

To this day, atrial fibrillation (AF) is a major concern complicating worldwide healthcare and novel strategies are continuously being developed in an attempt to effectively treat this arrhythmia. One invasive modality developed in the previous decade is ablation of complex fractionated atrial electrograms (CFAE). It was first performed by Nademanee et al[1] and many studies have investigated the value of CFAE ablation.[2-6] In recent perspective, there seems no clinical beneficial effect of CFAE ablation in addition to pulmonary vein isolation for both paroxysmal and persistent AF.[4-6] There might even be an increased risk of organized atrial tachycardias after CFAE ablation.[3] Notably, the electrophysiological origin for CFAEs that are targeted during these ablation procedures is actually not exactly known, and different methods are used for identifying fractionated electrograms (EGMs). Therefore, we reviewed the electrophysiological basis of fractionation and investigated the measurement methods and definitions of atrial EGM fractionation using a systematic approach.

Pathophysiology

A unipolar recording of extracellular cardiac EGMs in homogenous tissue consists of a positive spike followed by a negative deflection, representing a depolarizing wave front approaching and moving away from the electrode, respectively. If the wave front originates or ends at the electrode site, the unipolar EGM morphology can also consist of only a negative or positive deflection.[7] The steepest point of deflection coincides with the rapid depolarization phase (phase 0) of the membrane potential and therefore local depolarization. Bipolar recordings subtract the potential at one recording site from an adjacent recording site, resulting in clearance of most farfield signals. Here, the initial peak is the local depolarization time.[7] However, bipolar EGM morphology is also affected by other factors that do not affect unipolar EGMs. For instance, the amplitude of the signal depends on the direction of the wavefront. A small spacing between the electrodes is important to diminish the impact of wave orientation. Furthermore, a bipolar EGM is the sum of two unipolar EGMs with a time delay due to the interelectrode distance. A significant time delay between two simple unipolar EGMs will result in a fractionated EGM when converted to a bipolar EGM as illustrated by Figure 1.

Fractionated electrograms consist of multiple deflections and are often prolonged. Several sources have been demonstrated to result in EGM fractionation. The causes for fractionation can be divided into three categories[8]: 1) artifacts, 2) remote activation, 3) inhomogeneous conduction of the tissue beneath the electrode. First, artifacts due to movement, signals from other muscles or filter settings can mimic fragmentation of the EGM.[9] Second, activation of remote regions may be recorded due to their proximity to

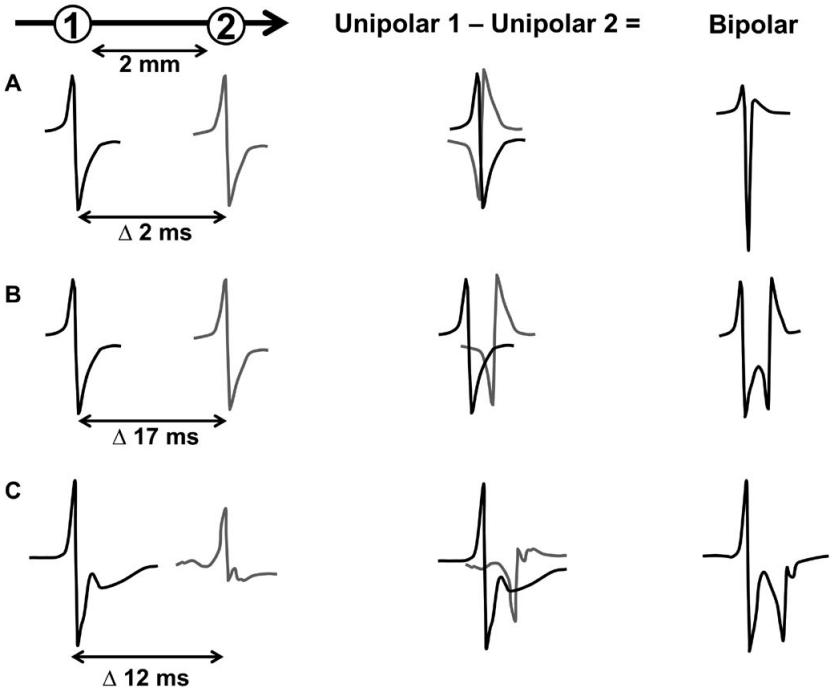

Figure 1. Fractionation in bipolar electrograms.
A depolarizing wavefront travels from electrode 1 to electrode 2 that are separated by an interelectrode distance of 2 mm. In situation A, the wavefront passes the electrodes with a time delay of 2 ms which results in a simple bipolar EGM. In situation B, the time delay is increased to 17 ms either due to increased electrode spacing or decreased velocity of the wavefront. This will result in an extra negative and increased positive bipolar deflections. C is an example of two real unipolar electrograms recorded during AF by electrodes with a diameter of 0.45 mm and 2 mm interelectrode spacing and filtered from 0.5-400 Hz. The time delay is 12 ms and conversion to a bipolar electrogram gives rise to a fractionated EGM.

the recording area. For example, excitation of adjacent macroscopic structures such as the coronary sinus or pulmonary veins, which may occur later in time than the recording site itself, can be recorded simultaneously. Besides recording artifacts or the activation of neighboring structures, fractionation can also originate from inhomogeneous conduction within the recording area. A single 1-mm electrode translates excitation of approximately 10,000 to 100,000 cardiac muscle cells into one signal. In case of a nonuniform pattern of myocyte excitation, EGM fractionation occurs (Figure 2).

Microscopic electrophysiological measurements have shown that even in normal cardiac tissue conduction velocity decreases and fractionation occurs with a transverse direction of propagation (anisotropy). Propagation in the transverse direction occurs more inhomogeneously with age, probably due to electric uncoupling caused by an increased presence

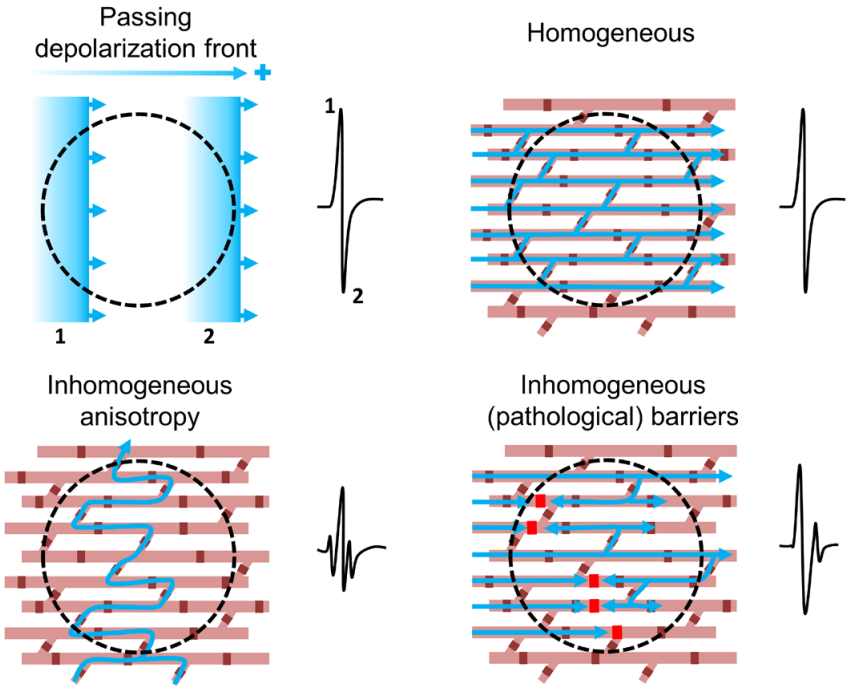

Figure 2. Myocardial activation patterns of simple and fractionated electrograms.
A homogeneous activation front across myocardial cells results in a simple electrogram (top panels). An inhomogeneous activation front, where the direction of the activation front changes, either due to the direction of propagation and coupling structure of myocardial fibers (anisotropy) or due to functional or pathological barriers between myocardial fibers, will result in a complex electrogram with multiple deflections (bottom panels).

of nonmuscular fibrous tissue.[10, 11] These structural barriers may lead to the circuitous path of conduction as proposed by Gardner et al.[11] Furthermore, high resistant gap junctions between myocytes or disrupted ion channel function due to antiarrhythmic drugs or genetic mutations can result in intracellular and/or intercellular barriers for conduction.[11] In normal functioning cardiomyocytes, premature or high-frequency stimulation within the refractory period creates an opportunity for dispersion of excitability and fractionation. In addition, it has recently been demonstrated that the right atrial endo- and epicardial myocardium is asynchronously activated during AF, which translates to a transmural inhomogeneity in conduction as well.[12, 13] Therefore, inhomogeneous conduction can occur in the presence of normal functionality and anatomy or occur due to pathological processes that cause structural or cellular barriers for homogeneous conduction. Figure 3 shows an overview of causes for fractionation. The methods and definitions used for identifying EGM fractionation need careful consideration because significant methodological differences can lead to a disparity in study results.

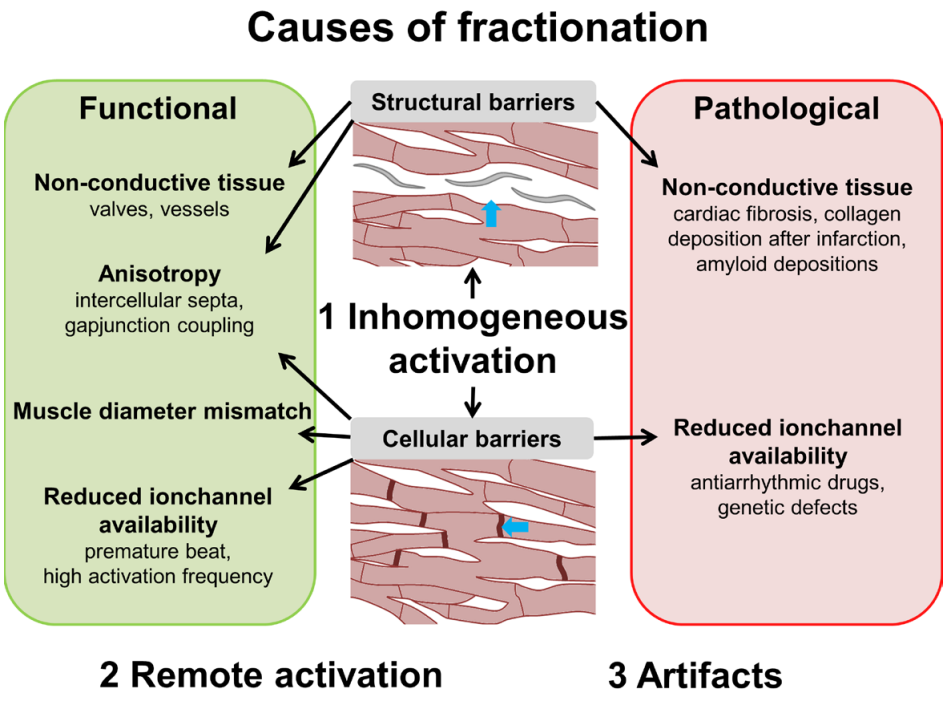

Figure 3. Schematic overview of the causes of fractionation.

METHODS

A PubMed database search was performed with the following MeSH terms: atrial fibrillation or heart atria, and humans, and cardiac electrophysiologic techniques or body surface potential mapping or electrocardiography or electrophysiology, and also containing in any of the fields: fractionated or fractionation or fragmented or AF nests. Editorials, comments, reviews and case reports were excluded from the search. The search resulted in 345 articles. To also include the most recent articles not yet indexed, an additional search without MeSH terms was performed within all fields containing the following words: atrial fibrillation or atria, and electrophysiology or epicardial mapping, and fractionated or fractionation or fragmented or AF nest. The results published in the past two years were screened for inclusion and three more articles were added. All 348 articles were screened for inclusion and exclusion criteria. A flowchart of inclusion and exclusion with criteria is shown in Figure 4. The definitions of these articles were compared and only the articles first describing a (different) definition were included. Dominant frequency was not considered a definition for fractionation, and these articles were excluded. A total of 24 articles remained after selection. Thereafter, definitions were checked for references to a previous article and, if so provided, the references were included instead.

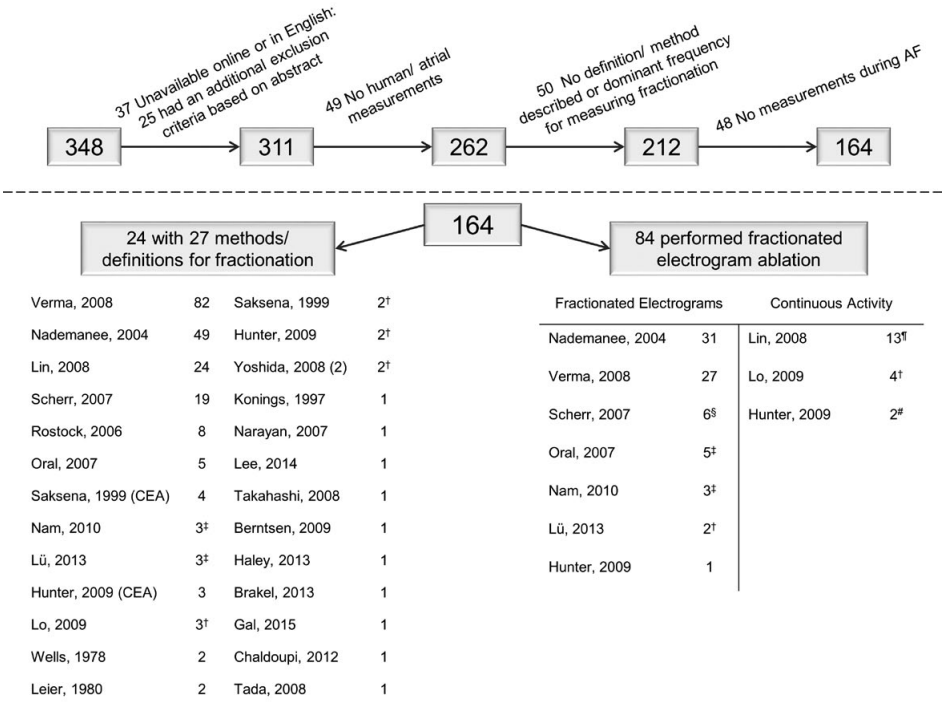

Figure 4. Flowchart of article in- and exclusion and definitions.
After the initial screening, 164 articles remained of which 24 described 27 methods/ definitions for fractionation. Of the 164 studies, 56 used multiple or a combination of these methods/ definitions. Fractionated electrogram ablation was performed by 84 studies, 10 used multiple or a combination of methods/ definitions. †/ ‡ all/ all but one article(s) of same research group, § ICL cut-offs described of >5 and >7 during 2.5 sec and ≥26 during 5 sec, ¶ Mean interval upper limit between 50-80 ms. # 70 or 75% of the recording time absence of isoelectric intervals of 70 or 50 ms. CEA, continuous electrical activity.

RESULTS

Definitions

The descriptions of fractionation that were found are given in Table 1. Eleven definitions were described in the articles found.[1, 14-24] Six studies that investigated characteristics of CFAE or aimed to find new manners to quantify CFAE introduced new parameters to describe CFAE.[25-30] In addition, 3 different automated software algorithms to detect CFAE were described: interval confidence level (ICL)[31, 32], CFE mean[32, 33] and an automated program calculating a CFAE percentage[34]. Figure 5 illustrates the manner in which these programs detected CFAE. Ablation of CFAE or continuous electrical activity was performed in 5 studies.[1, 18, 22, 33, 35] The definition of Nademanee et al.[1] is most often used, combined with the derived automated detection analysis algorithm CFE mean (Figure 4). Rostock et al.[36] made a minor change to the definition from ≥2 to ≥3 deflections. When continuous

Table 1. Definitions of fractionation

Study	Year	Electrogram Definition of Fractionation
Wells[14]	1978	Beat-to-beat complexes of variable morphology with an isoelectric baseline having perturbations of varying degrees.
Leier[15]	1980	Duration ≥80 ms
Konings[16]	1997	>2 deflections within 50 ms
Saksena[17]	1999	Prolongation of the duration of the local EGMs >50 ms with or without appearance of double or multiple potentials.
Nademanee[1]	2004	1) ≥2† deflections and/or perturbation of the baseline with continuous deflection of a prolonged activity complex over 10 sec recording, 2) very short cycle length ≤120 ms averaged over 10 sec.
Oral[18]	2007	Cycle length ≤120 ms or shorter than in the coronary sinus or that were fractionated or displayed continuous electric activity
Narayan[19]	2007	High-frequency with duration ≥60 ms
Hunter[20]	2009	Discrete, <70 ms and complex ≥5 direction changes
Nam[21]	2010	Highly fractionated, nearly continuous
Lü[22]/ Rostock[23]	2013/ 2008	Fractionated or continuous electrical activity, or locally short AF cycle length (<120 ms) or intermittent local burst activity
Lee[24]	2014	≥3 deflections over >50 ms duration separated by a discrete iso-electric baseline
Fractionation in parameters		
Yoshida[25]	2008	1. Complexity index: how often depolarizations changed polarity (+/-) per sec 2. Fractionation index: how often the direction (polarity) of the depolarization slope (dV/dt) changed per second
Takahashi[26]	2008	Number of deflections with an absolute value of >0.05 mV from the baseline
Berntsen[27]	2009	Number of deflections >50 μV/s
Haley[28]	2013	Percentage of time, deflections above baseline occurred, <120 ms apart
Brakel[29]	2013	Number of subsequent negative deflections within one EGM with a defined cycle length between two deflections of <120 ms expressed as median over a 10-s AF file
Gal[30]	2015	Number of deflections >0.015 mV/ms, >0.05 mV, per 1 sec, reduced by the number of main deflections
Automated fractionation detection		
Scherr[31]/ Nademanee[32]	2007/ 2006	During 2.5 sec recording, deflection peaks within 0.05-0.15 mV tagged, all interval measured between 2 peaks, number of intervals between 70-120 ms determined = ICL. CFAE site: >1 ICL.
Verma[33]/ Nademanee[32]	2008/ 2006	During 8 sec recording, CFE mean interval is determined of consecutive deflections exceeding a sensitivity threshold and down stroke morphology with maximum and minimum within a set time duration, and exceed a refractory period. CFAE site: CFE mean <120 ms
Chaldoupi[34]	2012	CFAEs: periods of successive atrial deflections with (a) dV/dt < –0.04 V/s, (b) amplitude >2% of the highest unipolar electrogram recorded in every tracing, (c) continuous atrial activation or deflections separated by an interval ≤104 ms
Electrogram definitions of continuous electrical activity		
Saksena[17]	1999	Variable morphology and cycle length, but indistinct/ absent isoelectric interval
Lin[37]	2008	Mean interval <50 ms
Tada[38]	2008	No isoelectric segments for ≥1 sec
Hunter[20]	2009	Continuous deflections without pause at the isoelectric line for ≥70 ms, occupying ≥70% of sample, with an uninterrupted segment of 1 sec
Lo[35]	2009	Fractionation or repetitive rapid activity lasting for >8 seconds

† Rostock et al. (2006)[36]: ≥3 deflections. AF = atrial fibrillation; CF(A)E = complex fractionated (atrial) electrograms; EGM = electrogram; ICL = interval confidence level.

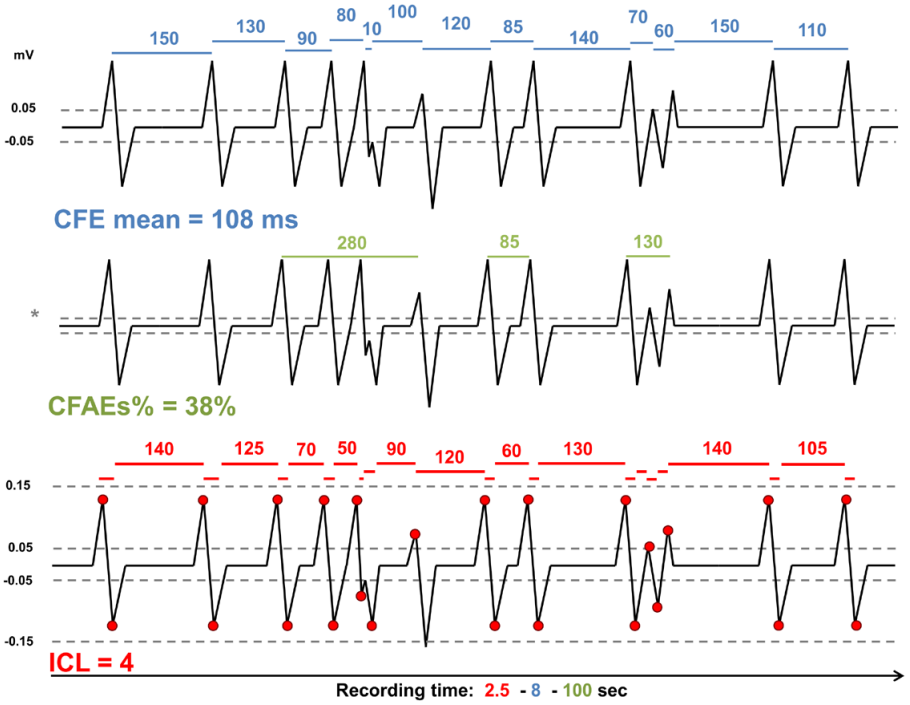

Figure 5. Algorithms for automated fractionation detection.
Schematic electrogram example illustrates the methods for determining CFE mean (blue), CFAE% (green), ICL (red). * >2% of highest amplitude. CF(A)E complex fractionated (atrial) electrograms; ICL interval confidence level.
Example calculations: CFE mean = (150+130+90+80+110+120+85+140+70+60+150+110)/12; CFAE% = % time periods intervals ≤104 ms = (280+85+130)/1295; ICL = number of intervals 70-120 ms = 4.

activity is defined apart from fractionation almost all studies define the absence of an isoelectric interval. However, different durations of continuous electrogram (EGM) deflections are described for the definition of continuous activity. The automated detection for continuous activity is set as a mean interval between deflections <50 ms.[17, 20, 35, 37, 38]

EGM parameters used to define fractionation are 1) number of deflections, 2) EGM duration, 3) interval duration between deflections, 4) number of short duration intervals between deflections, 5) amplitude of deflections, 6) slope of deflection, 7) number of polarity changes of deflections or slope of deflections (Figure 6), and 8) baseline. Three definitions use descriptive terms to define fractionation.[19, 21, 22] Nademanee et al.[1] use the most properties to define fractionation: number of deflections, EGM complex duration, baseline and interval duration between deflections. The automated CFE mean derived from this definition sets boundaries for the sensitivity of deflection detection with also a selectable amplitude level, refractory period and EGM width.

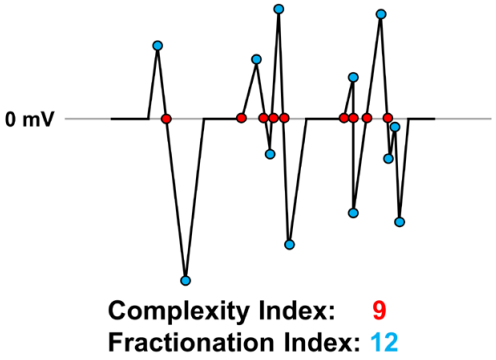

Figure 6. Fractionation parameters complexity index and fractionation index.
The complexity index (red) counts the number of polarity changes. The fractionation index (blue) counts the number of polarity changes of the derivative.

Table 2. Measuring method and device properties

Study	Endo-/ epicardial	Bi-/ unipolar	Electrode surface (mm)	Interelectrode spacing (mm)	Filter settings (Hz)
Wells, 1978	epi	bi	-	5-10	12-500
Leier, 1980	endo	bi	-	10	30-500
Konings, 1997	epi	uni	0.3	2.25	1-500
Saksena, 1999	endo	bi	-	2-5/8-2 + 5-10-5	-
Nademannee, 2004	endo	bi	-	-	30-500
Rostock, 2006	endo	bi	1	4-4-4	30-500
Oral, 2007	endo	bi	8	-	30-500
Narayan, 2007	endo	bi	-	-	30-500
Hunter, 2009	endo	bi	3.5	2-5-2	30-250
Nam, 2010	endo	bi	-	-	30-500
Lü, 2013	endo	bi	3.5	2-5-2	30-500
Lee, 2014	epi	bi	-	2.5	0.05-400
Yoshida, 2008	endo	bi	-	2.5	-
Takahashi, 2008	endo	bi	-	-	30-250
Berntsen, 2009	endo	bi	8 + 1	- + 2-5-2	30-400
Haley, 2013	endo	bi	3.5	2	0.5-250
Brakel, 2013	epi	bi	-	5	-
Gal, 2015	endo	bi	1	4-4-4	30-500
Scherr, 2007	endo	bi	3.5	-	30-400
Verma, 2008	endo	bi	3.5	2	30-500
Chaldoupi, 2012	endo	uni	-	5	0.05-500
Lin, 2008	endo	bi	4	-	-
Tada, 2008	endo	bi	3.5	2-5-2	30-500
Lo, 2009	endo	bi	4	-	-

Measuring methods

Table 2 lists the device properties and measuring methods that were used in these studies. Twenty studies used endocardial and 4 used epicardial mapping approaches. Two studies used unipolar recordings. In 11 studies electrode size was not described and in 8 the electrode spacing was not reported or could not be derived from the catheters that were used. Minimal electrode size for endocardial recordings was 1 mm, used in 3 studies, while the other 9 studies used electrode sizes of 3.5, 4 or 8 mm, substantially larger than the 0.3-mm electrode of the epicardial mapping study of Konings et al.[16] Interelectrode spacing mostly ranged between 2-5 mm and was only larger in the studies before the year 2000.

DISCUSSION

Clinical practice

Pathophysiological studies have shown that inhomogeneous conduction can give rise to both initiation and maintenance of AF.[39, 40] Therefore, Nademanee et al. proposed the ablation of areas with fractionated EGMs in order to terminate AF. At first, fractionated areas were identified visually; today automated detection software has been implemented in the CARTO (Biosense Webster, Diamond Bar, CA) and NavX (St. Jude Medical, Minneapolis, MN) 3-dimensional mapping systems and is most often used for the identification of CFAE areas. However, functional areas of fractionation could also be targeted during ablation. Limiting the number of unnecessary scars is important to decrease the risk of postablative iatrogenic atrial tachycardias. The first step towards delineating pathological from normal areas of fractionation or artefacts is to optimize the method in which fractionation is measured and to use a uniform definition for fractionation. This review has shown that definitions to date have widely varied, including definitions applied for ablation purposes.

Relation between definitions and the electrophysiological basis

Over 35 years, at least 11 definitions and 7 fractionation parameters have been used to define fractionation using 8 different EGM parameters. The studies that defined fractionation only by prolonged EGM duration, could have included areas where slow but homogeneous conduction occurs. Descriptive terms, mainly used in early studies, such as high-frequency, highly fractionated, or burst activity, provide insufficient information to distinguish the intended EGM morphology. Therefore, automated techniques for CFAE detection were developed including CFE mean, ICL and CFAE%, which utilize the AF cycle length to determine areas with highly frequent or short coupled activations. These methods are most often used in recent studies. However, the morphology of the EGM is not included with these methods. In addition, the refractory period that is set can overlook ‘true’ fractionated deflections caused by inhomogeneous conduction of myocytes

within the recording area. The close intervals that are detected are actually a measure of high-frequency activations, not inhomogeneous conduction per se. These CFAE could, for example, also represent a rotor or an ectopic focus (driver). In fact, these automated methods have shown to correlate poorly with each other and also corresponded poorly to inhomogeneous conduction patterns.[41]

Fractionated EGMs have been found both at the center and periphery of AF drivers.[42, 43] Narayan et al. found that electrograms with ≥7 short intervals in 4 sec mainly presented peripheral to driver sources.[42] Lin et al. reported fractionated electrograms defined as Nademanee et al.[1] at the center in 70% of rotors.[43] At high frequencies of activation, intermittent conduction block and interrupted patterns of activation occur, characterizing inhomogeneous or fibrillatory conduction. Anatomical transition sites demonstrated to be preferential sites for frequency-dependent conduction block[44] and could also exhibit significant conduction disturbances at an earlier stage in response to remodeling. The nature of conduction disorders during fibrillatory conduction can be physiological because of activation frequencies close to the refractory periods of surrounding myocytes or frequency-depended source to sink mismatch, or pathological because of structural/electrical remodeling of surrounding myocytes causing frequency-dependent conduction disorders. Fractionation at the center of rotors may be due to the sharp angle of the activation front representing as close-interval or continuous activity on the EGM, or the electrical remodeling is not homogeneously in the entire center causing conduction disturbances as well. In a recent report, rotors were accompanied by functional conduction disorders at the center that demonstrated “core” fractionation.[45]

EGMs in which atrial deflections comprise the entire recording time without an apparent baseline are referred to as continuous activity. Although definitions of continuous activity are more uniform, the length of the electrical activity before defining the EGM as continuous activity differed among studies. Continuous activity during AF is associated with multiple wavelets entering and exiting the recording area causing frequent wave collision and wave break.[46] Consequently, conduction is more inhomogeneous in areas with continuous activity and this explains the appearance of non-stop activity on the EGM. It features a high degree of inhomogeneous conduction of the multiple fibers representing the recording area. Therefore, continuous activity is likely the result from a low spatial resolution of the recording area and accordingly is related to the electrode diameter and recording modus.

Electrode size and spacing

The atrial EGM is the sum of the activation pattern of all muscle fibers underneath and closely surrounding the electrode. Therefore, a larger electrode size should increase the chance of the occurrence of fractionation. High-resolution epicardial mapping studies

recording with 0.3-mm electrodes have shown that delays in activation of >12 ms occur between sites at 2.25 mm distance.[47] Endocardial mapping studies often use electrode diameters of 3.5-4 mm covering an area of more than two high-density electrodes. Consequently, activation of an area with conduction block below the endocardial electrodes will exist of multiple activations leading to fractionation of the recorded signal. A computational model has shown that increasing the inhomogeneity of wavefronts increases the degree of fractionation more with a larger electrode size.[48] However, if a wavefront propagates homogeneous, the electrode size does not influence EGM morphology because there is no cause for fractionation to occur. The advantage of a smaller electrode size would thus be the ability to locate the inhomogeneous site more accurately. In addition, the required ratio of the area of inhomogeneity to the electrode size before the EGM becomes fractionated remains unclear and a smaller electrode also might be able to identify small areas of inhomogeneous conduction. On the other hand, a larger recording area may have the advantage of a zoomed-out perspective of the myocardial area creating a distant view for inhomogeneous conduction. However, a larger electrode will also increase the chance of recording remote activation. Nevertheless, this has not been validated in vivo yet, so the clinical relevance of electrode diameter can only be speculative. Increased electrode spacing in bipolar recordings has been shown to increase the degree of fractionation in vivo.[9, 41, 48] It is probably the consequence of the bipolar EGM being formed by the area of two, often, large electrodes of 3.5 or 4 mm. Increasing the interelectrode distance is followed by an increase of the recording area and of the differences between the EGMs recorded from the two poles. Because of the high level of inhomogeneity in AF, recordings of two poles can differ significantly during AF, making bipolar recordings less suitable, or should be recorded with an interelectrode distance <1 mm.[46] The multidirectional waves during AF can also cause a variation in bipolar EGM amplitudes. The study of Lau et al. demonstrated that unipolar fractionation is a better measure for inhomogeneity in conduction.[41] In the present study, electrode properties were often not described and the bipolar interelectrode distance was 2 mm or more.

Future directions

In future investigations, both the technical aspects and physiological causes of fractionation need to be determined in order to identify pathological areas of fractionation. We propose the following steps. First, device properties such as electrode diameter, interelectrode distance and filter settings will need to be investigated by using different device properties in areas with inhomogeneous conduction of different complexities. The next step is to relate spatial patterns of activation to EGM morphology. The complex patterns of high frequency, inhomogeneous activations during AF make it difficult to distinguish inhomogeneous conduction from “new” or remote activations. High-resolution electrophysiological mapping and optical mapping can provide more detailed answers in this

matter and could help discriminate between fractionation due to the presence of multiple wavefronts within the recording area and “true” fractionation due to discontinuity in propagation between cardiac myocytes. Finally, the functional and anatomical causes for fractionation should be identified. The significant role of the underlying atrial structure in physiological causes for fractionation means an approach will be required in which the anatomical structure of the recording site can be visualized. To this end, both in-vivo and ex-vivo human studies are necessary because the current, clinically applicable techniques have certain limitations that can be overcome by ex-vivo studies. In vivo local anisotropy in conduction determined by previously described methods[49] can be correlated to the degree of EGM fractionation and imaging techniques, such as magnetic resonance imaging, can be combined with EGM recordings to help identify fibrotic-related fractionation.[50] However, ex-vivo human studies that combine high-resolution endo-epicardial mapping with imaging or histology are essential to determine the specific anatomical structural causes of fractionation.[10, 51]

When these technical and pathophysiological issues in identifying pathological fractionation have been resolved, the clinical benefits of ablation of (pathological) fractionated EGMs can be reevaluated. Although research would benefit from a universal definition of fractionation, it does not seem possible at this time because of multiple factors complicating the interpretation of fractionation. In our opinion, fractionation during AF should be defined based on an EGM morphology with multiple deflections (>1 in unipolar and >2 in bipolar recordings) within the refractory period indicating “true” inhomogeneous conduction.

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