General Discussion

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GENERAL DISCUSSION

Controversy in mechanisms underlying atrial fibrillation

For most atrial tachyarrhythmias the mechanism, i.e., pathological electrical pathway is known and therefore ablative procedures for these tachyarrhythmias are very effective. On the other hand, the mechanism underlying atrial fibrillation (AF) remains uncertain and controversy exists between researchers studying AF. What *is* known is that paroxysmal AF is in most cases triggered by electrical activity from the pulmonary veins.[1] Many theories have been proposed for persistence of AF and the two main positions taken over the last years were researchers supporting the concept of rotors or focal activity driving AF vs researchers supporting the multiple wavelet theory.[2-5] Evidence for both sides has been published and this raises the question: why do results between AF studies differ so significantly?[2-4, 6, 7] In 2014, both positions were argued in a crosstalk and the important argument was made that the mapping resolution and signal processing technologies are fundamentally different.[8-11] Mapping, i.e., the representation of electrical activity pathways is based on, first, recording of local electrical activity on electrograms, and then determining the local activation time of each signal recorded on the electrogram. Mapping outcomes are determined by recording modus, quality of electrograms, density and surface area of electrogram recordings. The next paragraphs will discuss which previous mapping studies and mapping approaches have been performed and which mechanism they supported, which resolution is required for AF mapping, the effect of recording modus, and will argue the added complexity in AF mapping caused by endo-epicardial asynchrony.

Mapping studies of atrial fibrillation

Studies that have mapped AF activation patterns in patients with persistent AF to find the underlying mechanism, and have used direct contact mapping with different resolution or recording mode have been summarized in Table 1. In the last column the dominant supporting theory is shown, meaning which pattern of activation is seen in most patients/most of the recording time. Table 2 specifies also the other activation patterns that were observed in these studies. Rotors have been mostly detected during mapping with a very low resolution (0.6-1/cm^2) and in these studies rotors were present in >88% of patients.[5, 12-14] There was one high-resolution mapping that showed (mostly) transient rotors during only 12% of the recording time with a median of 3 rotations. In one case, a relatively stable rotor (presence >95% of the time) was seen.[7] The studies with the highest resolution of 19 and 21-24/cm^2 mainly supported the multiple wavelets theory because drivers were not or only sparsely observed.[2-4, 7] Earlier studies with a low to medium resolution (0.8-8.5/cm^2) often attributed their findings to micro- or macro-re-entry, however, often it was based on a theoretical explanation of either a focal pattern of activation or regular repetitive activation pattern without demonstration of a re-entry pathway (Table 2).[15-18] Important is to not

Table 1. Human mapping studies of atrial fibrillation

Study	Electrode size (mm)	Resolution (electrodes/ cm^2)*	Total area (cm^2)	Recording modus (IES,mm)	Location	Side	AF type	Dominant supporting theory
Harada et al. 1996[15]	2	0.8	71.6	Unipolar	RA + LA	Epicardium	PsAF/ LsPAF	Micro-reentry or ectopic focus (LA)
Holm et al. 1997[16]	1	7 / 14	17	Bipolar (3)	RA	Epicardium	LsPAF (+PsAF)	Micro or macro-reentry
Wu et al. 2002[17]	-	8.5 / 17	26.4	Bipolar (3)	RA + LA (s)	Epicardium	LsPAF (+PsAF)	Ectopic focus (PV) or micro-reentry (LA)
Yamauchi et al. 2002[18]	2	1.7	71.5	Unipolar	RA + LA	Epicardium	LsPAF	Ectopic focus or micro-reentry (LA)
Nitta et al. 2004[27]	-	3	91.1	Unipolar	RA + LA (s)	Epicardium	LsPAF	Ectopic focus (PV/LA)
Takahashi et al. 2006[6]	1	1.0 / 2.1	96	Bipolar (2)	RA + LA	Endocardium	PAF (+ LsPAF + PsAF)	Multiple wavelets
De Groot/ Allessie et al. 2010[2, 3]	0.3	24 + 21	23.4	Unipolar	RA + LA	Epicardium	LsPAF	Multiple wavelets
Narayan et al. 2012-2019[5, 13, 14]	1	1 + 0.6	128-226†	Unipolar/ Bipolar (4-5) → MAP	RA + LA (s)	Endocardium	PsAF (+PAF)	Rotors
Lee/ Walters et al. 2014[4, 7]	0.7	19	27	Bipolar (2.5)	RA + LA	Epicardium	PsAF	Multiple wavelets
Lee et al. 2015/2017[28, 29]	-	2.2 / 5.5	92.9	Bipolar (1.2)	RA + LA + BB (s)	Epicardium	LsPAF (+PsAF)	Ectopic foci
Honarbakhsh et al. 2018[12]	1	0.8 + 0.6	78.5†	Unipolar	LA	Endocardium	PsAF/ LsPAF	Rotors

* For bipolar recording the number of recording sites (electrode pairs) and / total electrodes are shown. † Calculated from the diameter of the balloon, real surface area is smaller due to absence of electrically active tissue at the location of the atrioventricular valve. IES = interelectrode spacing; MAP = monophasic action potentials; s = simultaneous recordings; RA = right atrium; LA = left atrium; AF = atrial fibrillation; PAF = paroxysmal AF; PsAF = persistent AF; LsPAF = longstanding persistent AF; PV = pulmonary veins.

Table 2. Observed activation patterns during atrial fibrillation

Study	Regular repetitive activation	Stable repetitive focal waves	Transient repetitive focal waves	Random focal waves	Reentry	Stable rotor	Transient rotor	Multiple wavelets
Harada et al. 1996[15]	x		x					x
Holm et al. 1997[16]			x		x			x
Wu et al. 2002[17]	x							x
Yamauchi et al. 2002[18]	x				x			x
Nitta et al. 2004[27]	x	x		x	x			x
Takahashi et al. 2006[6]			x					x
De Groot/ Allessie et al. 2010[2, 3]				x				x
Narayan et al. 2012-2019[5, 13, 14]		x				x	x	
Lee/ Walters et al. 2014[4, 7]			x				x	x
Lee et al. 2015/2017[28, 29]		x	x					
Honarbakhsh et al. 2018[12]			x				x	

exclude the multiple wavelets theory only based on transient regular repetitive activities or activation patterns at certain atrial parts. This theory does not imply that all waves have to be random at all time, based on local functional or anatomical features, predilection for certain activation patterns may exist.

Moreover, the definition used for a rotor in human mapping studies is very debatable. On a basic level, the difference between normal re-entry and a rotor is the electrically active core (phase singularity) of a rotor in comparison to the electrically inactive center of re-entry around an obstacle.[19] However, human mapping studies define rotors only as rotational activity around a center which was, in the beginning, required to remain sustained for >50 or >1000 cycles, but later also >10 cycles or >2-3 cycles was defined as a rotor.[4, 5, 7, 12, 14, 20] Core electrical activity of rotational activation patterns in these studies cannot be determined due to the low resolution. Currently, due to technological limitations, *endo*cardial mapping is of low resolution and high-resolution mapping with multi-electrode arrays can only be performed *epi*cardially. Therefore, it is unknown if there is an association between the atrial side of mapping (endocardium vs epicardium) and the fact that rotors are mainly found in endocardial mapping studies. One advantage of low-resolution mapping is that a large area can be mapped simultaneously providing a total overview of the atrial activation pattern.

Chapters 4 and 5 introduced a new epicardial mapping approach covering both atria and Bachmann's bundle with a resolution higher than in the studies of Table 1. At 9 atrial areas, 192 electrograms were recorded simultaneously with a density of 30/cm^2 (total surface 58 cm^2) in order to identify small conduction disturbances and to create a detailed map of activation patterns during sinus rhythm, pacing and AF. This technique can also be applied during minimally invasive surgery, although for complete left atrial mapping additional incision sites would then be required. Also, in Chapter 9 another new mapping technique was introduced of simultaneous epicardial and endocardial high-resolution mapping that provided a new possible mechanism expanding on the multiple wavelets theory.

The resolution required for atrial fibrillation

To determine the required resolution for mapping of AF, it is necessary to have an understanding of the resolution of AF itself. Sizes of waves in human AF have been described in two previous studies that performed high-resolution mapping. Lee et al. defined narrow AF wavelets as waves between 5-15 mm and observed a mean wave size of 20.9±15 mm and median wave size of 15 mm (interquartile range: 15-35 mm).[4] AF waves in the figures of studies by Allessie et al. and De Groot et al.[2, 3] were as narrow as a single electrode row translating to a wave diameter of ±2.5 mm. In patients with longstanding persistent AF the number of waves per cm^2 was 4.5 (4.1-5.1) compared to the 2.3 (1.7-2.9) waves/cm^2 in

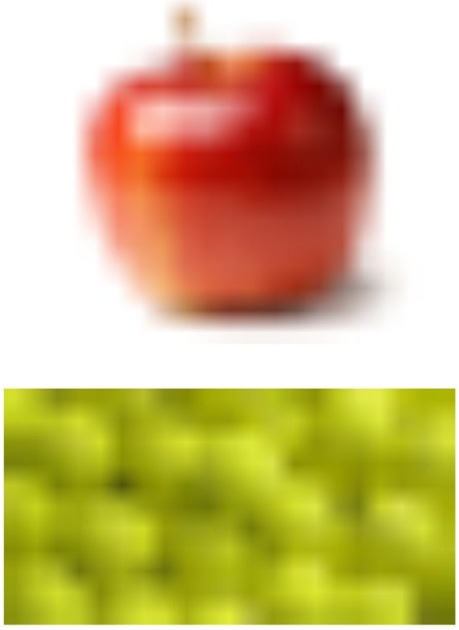

Figure 1. Low-resolution pictures.

patients without AF in whom AF was induced.[2] The focal waves observed in Chapter 9, were defined to have a minimal size of 4 electrodes. Smallest focal waves with sizes of 4, 5 and 6 electrodes comprised, respectively, 5.3%, 4.9% and 4.2% of all focal waves. Sizes of focal waves therefore range in 15% between 16-24 mm^2. Mapping approaches with a low resolution will not be able to detect these small AF wavelets because it would require a minimum resolution of unipolar electrodes or bipolar electrode pairs of 7 per cm^2 to be able to register these AF waves on one electrode alone. From the 11 mapping studies presented in Table 1, 4 studies meet these requirements. When comparing the resolution of high-resolution electrode arrays to the resolution of the basket catheter used in the studies of Narayan et al[5, 13, 14] and Honarbakhsh et al[12], the resolution of the latter is 30 to 50 times lower (0.6 or 1 electrode/cm^2 vs 30 electrodes/cm^2). A high-resolution during mapping of AF will decrease the chance of under-detection of AF waves and of incorrect interpretation of atrial activation patterns.

Why are current mapping technologies sufficient for most atrial arrhythmias, but not AF? The required resolution of mapping depends on the level of complexity of the arrhythmia. For example, in Figure 1 two pictures with the same low resolution are shown. The top picture is simple and even with a very low resolution you will be able to determine its

content. However, the bottom picture is much more complex and the low resolution here can easily result in a false interpretation of the actual picture (the high-resolution versions are shown in Figure 2). Similar with regular tachyarrhythmias and AF; regular tachyarrhythmias are mostly easy to identify even with a low resolution, however, the chaotic patterns of activation and small wavelets during AF require a high resolution. The challenge with current high-resolution mapping is that due to the relatively small size of the arrays, atrial areas need to be mapped sequentially. This can be explained as having to take several small pictures of one large picture in order to cover the entire object (black square in Figure 2). You will still be able to correctly deduce the object, but if the situation changes between pictures, for example a few balls are taken away or moved, this may not be noticed. Although studies have shown that patterns of activation remain stable in areas during 10 minutes of AF[7], a more panoramic high-resolution view will help to identify and understand the mechanisms underlying AF even better.

Endo-epicardial asynchrony: a new mechanism during atrial fibrillation

Focal waves observed in the study of De Groot et al. in 2010 led to the concept of asynchrony between epicardial and endocardial activation being the origin of focal waves.[3] The evidence for this theory was provided in the study presented in Chapter 9. This was the first study to perform simultaneous epicardial *and* endocardial mapping in living human subjects to investigate differences in electrical activation. Because mapping on both sides simultaneously is technically very challenging, it can only be consistently performed at the right atrial free wall. The right atrial appendage is the only location where an incision in the atrium is standardly made during cardiac surgery *before* induced cardiac arrest. Endo-epicardial asynchrony (EEA) occurred in patients at 0.9-55.9% of the sites during 10 seconds of AF. EEA was especially observed in patients with longstanding persistent AF; all patients with longstanding AF demonstrated EEA in over 20% of the sites. Focal waves were preceded by a wave of activation on the opposite side in 65% which means that the majority of focal waves could be attributed to transmural electrical conduction. These findings constitute an important new mechanism during AF. The electrical dissociation between the layers provides an opportunity for waves to travel from one side to the other and create new (focal) waves by conducting through the atrial wall. The possibilities for waves to encounter excitable tissue thereby increase substantially. Focal activation observed in previous studies may actually represent transmural conduction of AF waves.

Significance of EEA is not limited to AF alone, EEA also increases in atrial extrasystoles which can act as triggers for AF (Chapter 15) and EEA has also been significant in some cases of atrial flutter.[21] The presence and likely important role of EEA during arrhythmia further complicates mapping of AF. Current technologies can only record electrograms from one side of the atrial wall and therefore lack information about electrical activation

on the other side. This presents a great challenge as the incidence of EEA is high and there are no simple technical solutions to record the entire atria on both sides simultaneously. However, in Chapter 12 the morphology of epicardial and endocardial electrograms was compared during sinus rhythm. A possible solution was provided by the discovery that EEA can be reflected on the electrogram by fractionation. Analyzing fractionation of the electrogram could be the key to indirectly detect EEA. This possibility was explored further in Chapter 14. Areas at the right atrial free wall demonstrating EEA in patients during sinus rhythm, pacing or atrial extrasystoles were analyzed to determine how sensitive fractionation is in identifying EEA. In 86% of patients, EEA was visible on the epicardial or endocardial electrogram at a median of 75% and 72% electrode sites with EEA, respectively. EEA was easier to identify on unipolar electrograms than on bipolar electrograms.

Electrograms: unipolar vs bipolar and functionality of fractionation

As explained, bipolar electrograms are the difference between two unipolar electrograms and therefore farfield electrical activity is mostly cancelled. The disadvantage of bipolar electrograms is that they are affected by wave orientation.[22, 23] When the activation direction is parallel to the two poles or in case of simultaneous activation, timing of the signals are similar and electrogram voltage can decrease to very low values making it more difficult to determine the local activation time. Especially during AF, where AF waves travel in chaotic patterns constantly changing direction, bipolar electrograms are likely much more often affected than during other atrial tachyarrhythmias. Furthermore, technical properties such as a larger electrode size and larger electrode spacing increase the amount of electrogram fractionation on the bipolar electrogram.[24] The foundation for unipolar fractionation was elegantly demonstrated a long time ago by Spach and co-workers. On a microscopic level it was seen that each component of a fractionated electrogram could be traced to activation of a specific muscle bundle.[25] Although in Chapter 11 other possible factors contributing to fractionation were discussed, the conclusion in Chapter 12 was that 95% of fractionation on unipolar high-resolution electrograms could be attributed to remote atrial activation. It was also demonstrated that EEA causes fractionation of unipolar electrograms. It was then theorized that EEA based electrogram fractionation would be largely removed from bipolar electrograms as farfield electrical activity is substracted. In actuality, EEA remote electrical activity proved to be local enough to appear on bipolar electrograms as well. However, fractionation corresponding to EEA was less distinguishable from the noise on bipolar electrograms and more additional fractionation will make it more difficult to identify fractionated deflections based on EEA (Chapter 14). These observations indicate that unipolar electrograms are better suited for mapping of AF than bipolar electrograms.

Figure 2. High-resolution pictures.

In some AF mapping studies of Table 1, a different type of electrogram analysis was performed to map AF. In the endocardial electrophysiology studies by Narayan et al. unipolar or bipolar electrograms are converted to monophasic action potentials from which activation maps are created.[5, 14] Recently, the effects of mapping using monophasic action potentials (phase mapping) were demonstrated by direct comparison of activation mapping from unipolar electrograms to mapping based on phase analysis of unipolar electrograms.[26] Mapping in this study was performed with a very high resolution of 50 electrodes/cm^2. The specificity of rotor waves by phase mapping was only 10%, and false-positive cases were mostly localized at lines of conduction block with waves traveling opposite to each other in unipolar activation maps.[26]

Limitations of high-resolution mapping

Currently, there are still several limitations of high-resolution mapping. First, high-resolution arrays can only be placed on the epicardium due to their size, thereby certain atrial areas such as the septum cannot be mapped. Secondly, the arrays can, due to its epicardial application, only be used during cardiac surgery. Endovascular electrophysiological procedures are much less invasive and therefore available to a larger AF population. Finally, to cover the entire atrial surface, mapping is performed sequentially in high-resolution

mapping, whereas low-resolution mapping studies can map the entire surface simultaneously. As mentioned, the entire activation pattern of both atria cannot yet be visualized by high-resolution mapping. Both low-resolution and high-resolution mapping have certain advantages and disadvantages; however, these differences also lead to differences in study outcomes of AF mechanisms. It is plausible that different mechanisms of AF are involved in different patients. Because of the complexity of AF, high-resolution mapping is necessary in order to find the individual arrhythmogenic substrates and to not make false assumptions based on an undetailed map. This way, the optimal treatment course can be determined for each AF patient. To this end, technical advancements need to follow in order to further unravel mechanisms underlying AF.

CONCLUSIONS AND FUTURE PERSPECTIVES: BACK TO THE DRAWING BOARD

Mapping of AF requires a high resolution of electrogram recording sites that is able to spot detailed conduction disorders and thereby identify the arrhythmogenic substrate in individual patients. Asynchrony in activation between the epicardial and endocardial layers is a potential substrate for AF and a new mechanism explaining perpetuation of AF. Although current mapping tools are unable to identify EEA, it was discovered here that EEA is reflected on the electrogram as fractionation in most patients. To detect EEA on the electrogram, unipolar electrograms are superior to bipolar electrograms due to less disturbances and a better signal-to-noise ratio of EEA based fractionation. As the frequent occurrence of EEA demonstrated, AF is even more complex than previously thought and current technologies for AF mapping are insufficient. To actually understand mechanisms involved in AF, we need to go back to the drawing board and start to critically review mapping techniques that may lead to false interpretation of AF and develop new high-resolution tools and software.

The most optimal AF mapping tool will require the following features:

1. A high resolution/ electrode density
2. Cover the entire surface of both atria
3. Simultaneous recordings of all electrograms
4. Use unipolar electrograms
5. Be able to detect asynchrony between epicardium and endocardium
6. A high sample rate (to increase accuracy of fractionation)
7. Preferably record from the endocardium

The technical side of developing a system of high-resolution than can be placed within small catheters but still cover the entire atrium will be extremely challenging. It will require experts in electrical engineering to design and develop such an advanced mapping system. Development of feature 5 can be continued based on findings in this thesis. It would require software that is able to relate fractionation to activation patterns and identify fractionation caused by EEA. Therefore, future studies will need to characterize fractionated unipolar deflections which identify EEA and determine features that provide the best sensitivity and specificity for EEA.

Finally, to overcome current controversies in AF mechanisms, besides upgrading mapping tools, research into AF would greatly benefit from exchanging electrogram data between research groups to discover the differences in annotation and analysis of electrograms resulting in activation maps. If a consensus is made over how to analyze and interpret electrograms based on (previous) experimental data, study outcomes will likely become more in agreement.

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