Long-Standing Persistent Atrial Fibrillation:
Can We Distinguish Ectopic Activity From Reentry by Epicardial Mapping?

Running title: de Bakker et al.; Can epicardial mapping reveal the AF mechanism?

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Both abnormal impulse initiation and reentry have been proposed as mechanism for the initiation and maintenance of atrial fibrillation (AF). Ectopic activity of the pulmonary veins often is the electrical trigger for AF in patients with paroxysmal AF. A high impulse frequency of the ectopic focus may give rise to irregular, fibrillatory conduction, which leads to the freakish electrical pattern of AF. It is, however, often unclear whether the ectopic activity is based on abnormal impulse formation or abnormal conduction (reentry).

Experimental and clinical data provide evidence for both mechanisms. Other data show that multiple wavelet reentry may be present in the early phase of atrial remodelling as well. Remodelling of the atrium may be progressive due to an underlying cardiac disease and/or the arrhythmia itself (AF begets AF). Remodelling involves changes of structural, electrical and neural parameters. This will change the mechanism of AF and finally result in persistent AF, in which the substrate becomes more complex and AF is more difficult to treat.

Knowledge about the mechanism of the arrhythmia is important for treatment strategies, but there is still discussion about the mechanism of AF. Although evidence has been provided for both reentry and abnormal impulse initiation, one should realize that the mechanism may change if remodelling progresses. In addition, the mechanism of AF will depend on the underlying cardiac disease. Heart failure, hypertension, valvular heart disease, Wolff–Parkinson-White syndrome and hyperthyroidism are all triggers for AF and may give rise to different mechanisms of the arrhythmia.

In this issue of Circulation, the Waldo group carried out high density epicardial mapping of the atria in patients with persistent AF. Patients had multiple comorbidities and virtually all had valvular heart disease, hypertension and heart failure, which means that the group of patients is rather uniform. The investigators observed that epicardial wave fronts originated from foci or
breakthrough sites and that reentry in this group of patients did not occur. Both, mapping of the epicardial electrical activity and waveform analysis have been used to support these conclusions. Recordings were carried out carefully and results are interesting and important in delineating treatment strategies, but the question arises how solid the mapping data are to distinguish reentrant from focal mechanisms.

**Mapping of atrial electrical activity**

Mapping of the electrical activity during an arrhythmia is often the method of choice to delineate its mechanism. However, this method is not without pitfalls. To proof reentry, the presence of an activation map that shows continuity of activation in a (reentrant) circuit is not sufficient. Continuity may be apparent, for instance in case focal activation exits unidirectionally and activation arrives via the presumed reentry path at the exit site just before a next ectopic activation is issued. Similarly, a site from which electrical activation spreads centrifugally does not necessarily mean that myocardial cells at that site generate activation by abnormal impulse initiation. If a reentrant circuit is small compared to the inter-electrode distance of the recording grid, the activation pattern may also be centrifugally.

Another interfering factor is the fact that recordings are often made in two dimensions (2D), whereas the heart, including the atria, has 3 dimensions (3D). The role of the third dimension of the atria has been investigated in detail by the group of Allessie. The reason for a 2D choice in the clinical setting is clear because 3D mapping requires needle electrodes to be impaled in the myocardium, an undesirable procedure in patients. Thus, epicardial activation maps should be considered with care and spatial resolution of electrode terminals must be sufficient. In the study of Waldo et al. spatial resolution of the mapping electrodes was 5.2 – 7.0 mm, which means that reentry circuits with a smaller diameter might have been missed.
Experimental studies have shown that the diameter of reentrant circuits can be much smaller, at least in the experimental setting.\textsuperscript{6}

The distance between isochronal lines on the epicardium could also be helpful to discriminate an epicardial origin from epicardial breakthrough. If the epicardial activation pattern is generated by an epicardial focus, the isochronal lines are closer together then in the case there is epicardial breakthrough. To use this tool, the magnitude of the conduction velocity at the epicardium should be known. However, as shown in figure 5 of the study of Waldo et al., the epicardial activation pattern can be rather complex.\textsuperscript{4} Multiple areas of conduction block and breakthrough or focal sites are present. The involved anatomical structure of the atrium will certainly contribute to this complexity, which is further increased by the remodelling process. All these factors make the interpretation of epicardial maps challenging.

**Electrogram morphology to distinguish focal activity from reentry**

Electrogram morphology might also be helpful to distinguish focal activity from reentry, but also here different pitfalls are present. The morphology of the unipolar electrogram provides information about the behaviour of the wave front at the recording site. If the activation front passes the electrode terminal, the unipolar electrogram is biphasic, consisting of a positive deflection followed by a negative one. The positive deflection is caused by the approaching wave front, whereas the negative deflection is generated by the receding front. If activation is blocked, the electrogram is only positive, whereas the signal is negative only at a site where activation arises.\textsuperscript{7} Although these rules are in general correct, there are exceptions. The initially negative deflection in the unipolar electrogram is frequently used to trace an origin of activation, i.e. ectopic activity. However, the same shape of the unipolar electrogram may arise at a tissue discontinuity, for instance a site where a small bundle inserts in a broad one. A wave front
traveling via the small bundle toward the wide one will generate a tiny R-wave at the interface between the bundles. In contrast, the activation front in the wide bundle that recedes from the interface will generate a large negative deflection (Q) because the tissue mass and therefore the extracellular current that generates the electrogram, is large.

Anisotropy of cardiac tissue can also disturb the simple concept of signal morphology. Spach et al. have shown that by stimulating an epicardial sheet of cardiac tissue, recordings made at sites where activation moves perpendicular to the fiber direction may reveal initially negative deflections. These negative deflections are, however, remote and caused by the strong activation fronts that run in the fiber direction, away from the recording site. Similar effects may arise at sites of epicardial breakthrough in the atrium. The general idea is that focal epicardial activity generates a Q-wave in the unipolar electrogram at the epicardial origin and that in case of an epicardial breakthrough an R-wave (due to the approaching wave front from the endocardium) precedes the Q-wave. However, at sites where the wall thickness is small, the approaching wave front from the endocardium may be tiny and hardly generates an R-wave at the epicardial site that faces the endocardial origin. It is true that in the majority of the cases an R-wave is present, but its amplitude is small and can easily be missed. In addition, a breakthrough site is not very informative regarding the mechanism of the arrhythmia, because it can be caused by epi/endo reentry as well or by a focus that is located at the endocardium or intramurally.

Which mechanisms does high resolution mapping of persistent AF in man reveal?

Studies with high resolution mapping of persistent AF have been performed in patients during cardiac surgery by several groups. De Groot et al. observed that fibrillation waves were frequently of focal origin, but these waves were not repetitive and were found over the entire epicardial surface. Unipolar electrograms at the earliest activated epicardial sites exhibited R-
waves, suggesting that they were caused by epicardial breakthrough. Similar observations with 
eticardial exit sites, but without sustained activity were made by Lee et al. According to 
llissie, these high resolution mapping studies point to epicardial-endocardial dissociation as 
mechanism for persistent AF. These data differ from the observations made by Waldo et al., 
but as outlined before it is often difficult to distinguish a real focus from breakthrough on the 
base of electrogram morphology or an epicardial activation map.

Narayan et al. claimed that human AF might also be due to rotors, driving sustained 
AF. Mapping of the electrical activity was, however, carried out with basket catheters, which 
have a much lower spatial resolution than the electrodes used during intraoperative mapping. 
Next to the reduced spatial resolution, basket recordings suffer from contact problems, which 
results in artefacts and further reduces the number of electrodes that can be used for analysis. In 
addition, special analyzing techniques were used to produce videos of activation from which the 
mechanism was inferred. The quality of the electrograms and the analysis technique used 
question whether rotors are indeed present in man.

There is still uncertainty about the mechanism of persistent AF in man. Jalife et al. 
observed spiral wave reentry in animal models. Transient rotational activity around a core of 
high frequency activity suggesting the presence of a rotor has been described in man, but data 
about sustained rotors are missing. The high resolution mapping of Waldo et al. indicates that 
macro reentry at the epicardium does not occur. Their data do, however, not exclude the 
possibility that micro-reentry, transmural reentry and/or endo-epicardial dissociation are 
involved.

**Conflict of Interest Disclosures:** None.
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