Revealing hidden information from unipolar extracellular potentials

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Introduction

Electrical waves exciting adjacent cardiomyocytes asynchronously give rise to extracellular potentials consisting of multiple low-amplitude deflections instead of 1 single deflection. Areas of myocardial tissue from which these fractionated extracellular potentials are recorded may play a role in the pathophysiology of cardiac arrhythmias and may therefore serve as target sites for ablative therapy.

During cardiac mapping procedures, the most frequently used technique to reconstruct the pathway of wavefront propagation is local activation time mapping. Activation maps are created by annotating the steepest negative deflection of extracellular potentials. However, in case of fractionated potentials, it may be difficult to distinguish deflections caused by local activity from deflections originating from remote activity. This may complicate construction of activation maps during atrial fibrillation (AF). Alternatively, voltage mapping displaying peak-to-peak amplitudes of extracellular potentials can be used to identify target sites for ablative therapy, but voltage measurements depend on selection of the "correct" deflection as well. Fractionated extracellular potentials thus hamper signal processing during cardiac mapping.

In this report, we introduce a novel signal processing technique in which information of all deflections of fractionated extracellular potentials is taken into account to construct activation maps instead of 1 single component, thus visualizing both local and remote electrical activity. In 1 patient with sinus rhythm (SR) and 1 patient with AF, electrical wavefronts propagating in deeper layers of myocardial tissue are revealed and a more elaborate impression of transmural asynchrony in electrical propagation is obtained. This approach is critical for

KEY TEACHING POINTS

- Fractionated extracellular potentials contain more information than was previously acknowledged.
- Omitting a blanking period during unipolar signal processing leads to more appropriate interpretation of atrial patterns of activation.
- This new methodology improves assessment of the 3-dimensional nature of electrical wave propagation.

further unraveling AF pathophysiology, as using 2-dimensional models of electrical waves is by definition simplification of the complex 3-dimensional cardiac structure.

Case report

Data selected for these cases were derived from mapping procedures acquired during a prospective observational study aimed at revealing AF-related electropathology in patients undergoing elective cardiac surgery (MEC 2014-393). Both patients provided written informed consent. The 2 signal processing techniques—the conventional and novel approach—are compared using unipolar extracellular potentials recorded during SR and persistent AF.

Mapping procedure

After sternotomy, the surgeon attached a bipolar pacemaker wire to the terminal crest and a steel wire to the substernal fat for reference and calibration, respectively. Prior to induced cardiac arrest, an array containing 8 rows of 24 unipolar electrodes (diameter: 14×46 mm, interelectrode distances: 2 mm) was placed at the atrial wall to record SR and AF. Extracellular potentials were obtained during 5 (SR) or 10 (AF) seconds at a sampling rate of 1000 Hz, a calibration signal of 2 mV, and a filter with bandwidth of 0.5–400 Hz. The full mapping procedure was previously described in more detail.[1]

Signal processing

Extracellular potentials were used for construction of color-coded wavemaps visualizing propagation of every individual
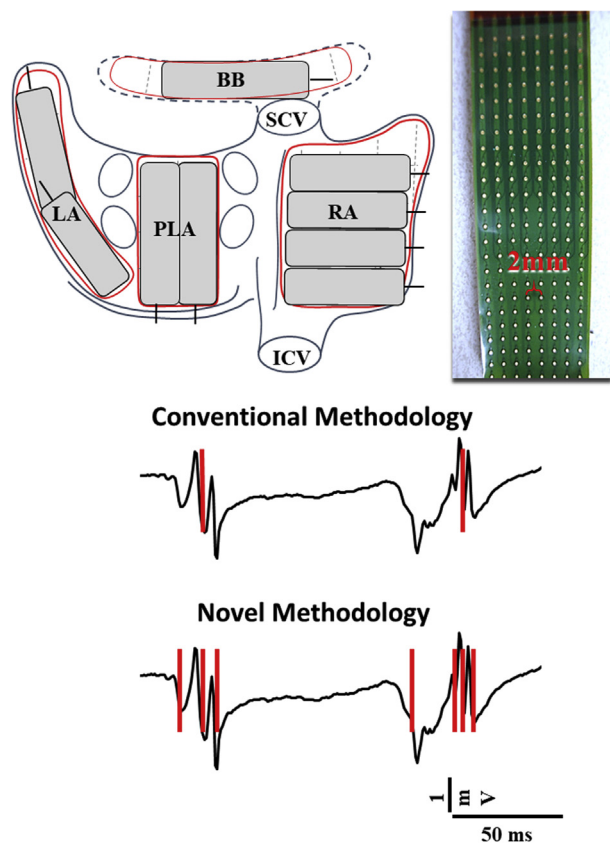
Figure 1   **Upper:** Schematic overview of the epicardial mapping scheme including the electrode array. The surgeon places the mapping array (shown at right) upon the epicardium of the right atrium (RA), left atrium (LA), posterior LA (PLA), and Bachmann bundle (BB) to record 5 seconds of sinus rhythm and/or 10 seconds of atrial fibrillation. **Lower:** Comparison of conventional and novel signal processing methodologies of unipolar extracellular potentials. Local activation, annotated by red markers, is defined as any steep deflection in the novel methodology (bottom image) instead of only the steepest deflection within a range of 50ms (conventional methodology, top image). ICV = inferior caval vein; SCV = superior caval vein.

SR or fibrillation wave. The upper panel of Figure 1 shows annotations of the steepest negative deflection of every fractionated extracellular potential, which, according to current consensus, cannot occur more often than once every 50 ms,[2] owing to tissue refractoriness (*conventional methodology*). In the lower panel, annotations of *every* component of the fractionated extracellular potentials with a slope of >0.05 mV/ms and amplitude >0.03 mV were processed regardless of time passed since preceding deflection (*novel methodology*).

To illustrate the impact of either methodology on wavefront propagation and subsequent identification of intra-atrial conduction disorders, real-time maps of local activation times (decelerated by factor 160) were constructed during 50 ms SR and AF. In addition, the same patterns of activation were demonstrated in figures of activation maps during SR and wavemaps during AF.

Case 1: SR
An 80-year-old woman underwent combined mitral valve replacement and coronary artery bypass surgery for mitral valve insufficiency and coronary artery stenosis. She had no history of tachyarrhythmias and presented in SR. The first movie (Supplemental Movie 1) shows parts of the SR wave propagating across the posterior left atrium.

When using the conventional methodology (left panel of Supplemental Movie 1 and upper panel of Figure 2), an electrical wave smoothly propagates from both the upper and lower right corner of the mapping array towards the left mid border but leaves an "island" of delayed activation at the upper border of the mapping array. This delay can be interpreted as either very slow conduction or even conduction block, eventually followed by a wave approaching from deeper tissue layers, which activates the electrodes inside the secluded area.

However, the novel methodology (right panel of Supplemental Movie 1 and lower panel of Figure 2) unravels the real pattern of activation and shows there is no slowing of conduction. Instead, this area of "slow conduction" is actually activated by a smooth wave, initially propagating downwards from right to left, but is reactivated as the wave pivots near the left edge of the array and passes the previously secluded electrodes for the second time. This second activation occurs within 50 ms; therefore only 1 of the passing waves was visible when using the conventional methodology. Multiple layers of atrial tissue must be present that are activated asynchronously by individual, subsequent SR wavelets, causing fractionated extracellular potentials when each one passes the electrode. Multiple layers, or electrical separation of atrial layers, may result from some type of conduction barrier, innate or acquired. For example, 2 parallel aligned layers may function independently when, for example, a fibrous sheath prevents conduction from 1 layer to another. This may result in isolated conduction corridors with potentially different conduction velocities.

Case 2: AF
A 66-year-old woman with a history of persistent AF (>1.5 years) was admitted to the hospital for mitral valve replacement and tricuspid valve repair. Besides mitral and tricuspid valve insufficiency, her medical history included hypertension, type 2 diabetes, and a cerebrovascular accident. She presented in AF upon the day of surgery.

AF recorded at the posterior left atrial wall is illustrated in the left panel of Supplemental Movie 2 and the upper panel of Figure 3, where patterns of activation were constructed using the conventional methodology. The pattern of activation is very complex, with multiple, small fibrillation waves arising scattered throughout the electrode array. Throughout the remainder of the 10-second recording, patterns of activation were constantly changing. On the lower left border, a wave enters the mapping area and propagates upwards along the left border, then extinguishes halfway through the array. Hereupon, 3 new, separate waves arise at a short distance from where the first wave ended. These newly generated waves can be explained by (1) electrical waves propagating from inner to outer layers of the atrial wall across endo-epicardial connections (breakthrough waves) or (2)
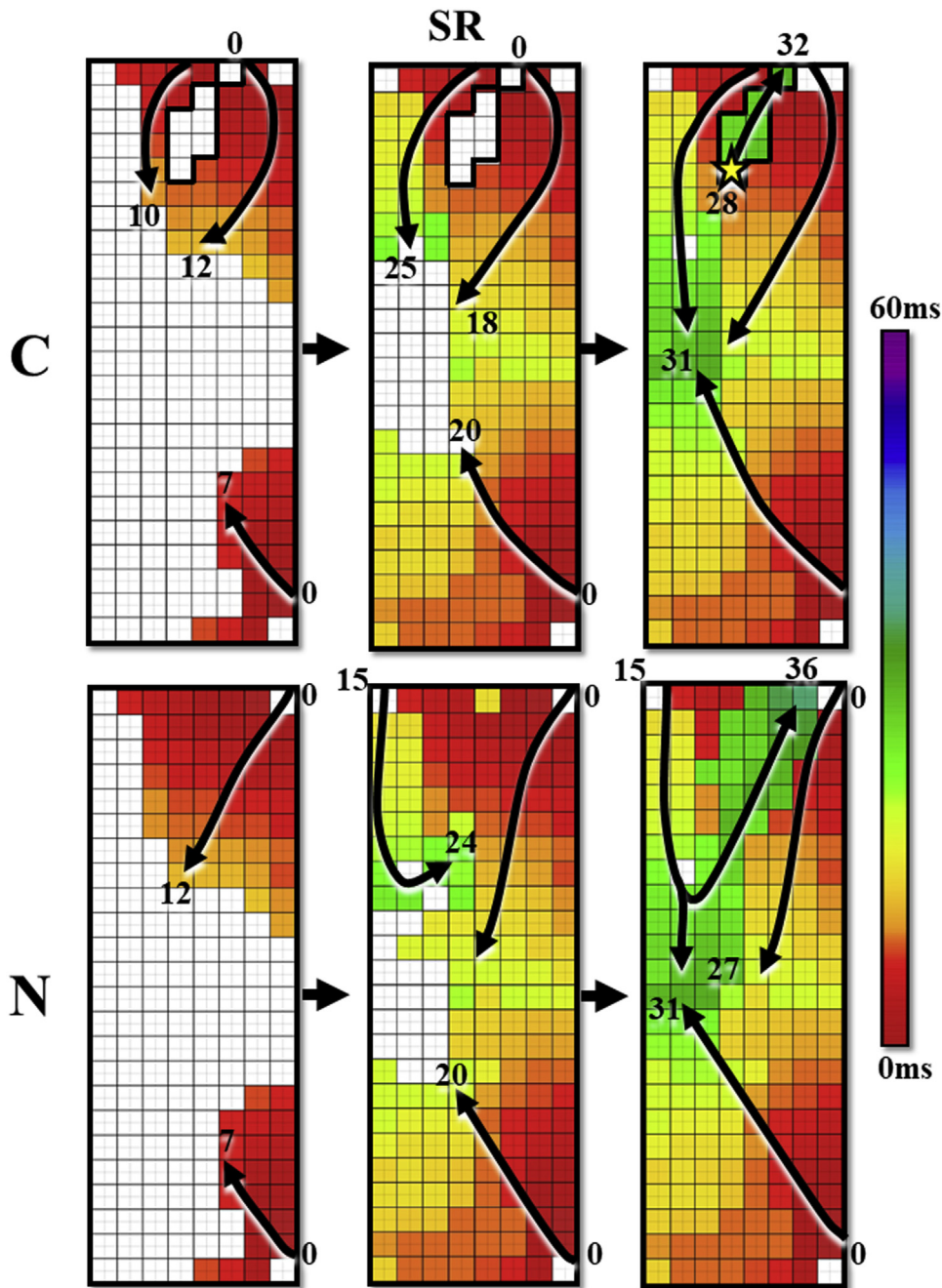
Figure 2 Conventional vs new methodology in sinus rhythm (SR). In activation maps in the upper panel, the main trajectory of a sinus beat at the posterior left atrium is reconstructed, using the conventional mapping approach (C). Three activation maps show the SR wavefront throughout different stages of excitation. The SR wavefront starts at the right side of the array and propagates to the left side, leaving out an island of electrodes in which conduction is delayed. A wave approaching from deeper tissue layers eventually activates the electrodes inside the secluded area. The lower panel shows activation maps resulting from the new mapping methodology (N). Here, it is clear that the previously secluded area of electrodes is actually activated twice with only a short (<50 ms) mutual time difference. There is no secluded area of delayed conduction, although this 3-dimensional, electrical separation of layers indicates impaired transmural conduction between superficial and more remote atrial layers. Thick black lines indicate lines of conduction block (interelectrode difference in conduction time >11 ms); black arrows indicate the main trajectory of wavefronts.

"spontaneous" generation of new electrical activity, for example by enhanced automaticity or triggered activity. When using the novel methodology (right panel of Supplemental Movie 2 and lower panel of Figure 3), however, the initial wave propagating along the left edge does not end halfway the mapping area. Instead, its main trajectory continues upward, then pivots and activates a large part of the mapping area, partly reactivating its initial trajectory. In this instance, no newly originated waves emerged, indicating that use of the conventional methodology resulted in
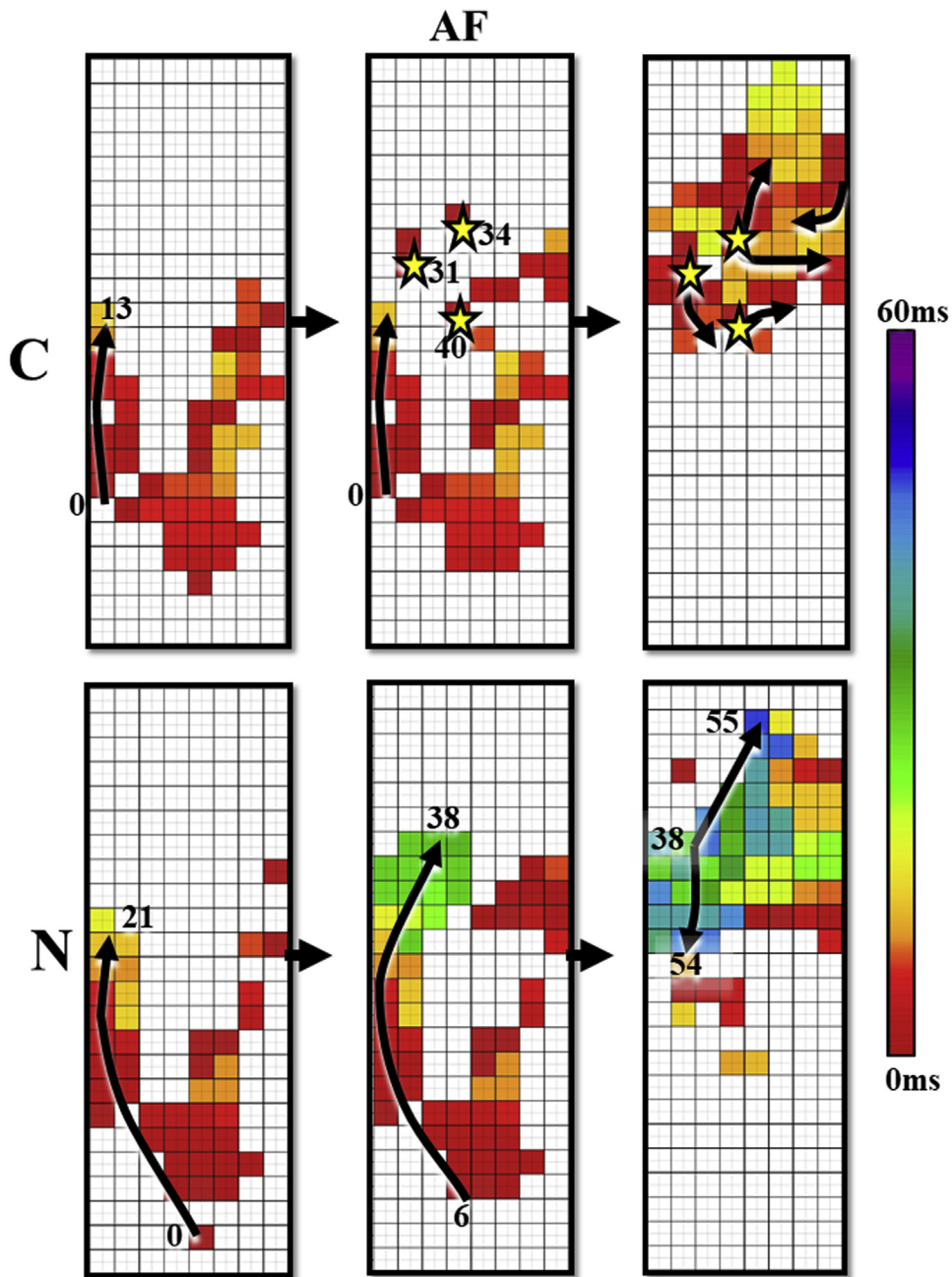
Figure 3   Conventional versus new methodology in atrial fibrillation (AF). Wavemaps in the upper panel show the main trajectory of waves during AF at the posterior left atrium, using the conventional mapping approach (C). Three wavemaps show multiple, consecutive AF wavefronts. In the first wavemap, a wave propagates upward along the border, then stops. In the second wavemap, at a short distance, 3 newly generated waves arise from deeper tissue layers and excite surrounding tissue (third wavemap). Wavemaps in the lower panel illustrate wavemaps derived from the new mapping approach (N). The first wavefront again propagates along the left border; however, this time it continues upward and excites upper regions of the mapping array. In addition, a shoot-off wavelet pivots downward and re-excites electrodes that were also activated on the way up. This quick reactivation (<50 ms) causes distortion in wavemaps generated by the conventional methodology. In the new methodology, these waves would not be classified as breakthrough waves. Black arrows indicate the main trajectory of wavefronts.

misinterpretation of the pattern of activation. Implementing the novel methodology led to an increased coherence in the observed wavefronts and a reduced amount of random, irreducible excitations. The specific, conflicting patterns of activation as illustrated in the movie were chosen for this case report, as they distinctly reflect how distortion of patterns

of activation may lead to overestimation of pathological phenomena.

Discussion

Blind spots are created in the activation maps when a blanking period is implemented during annotation of extracellular

potentials, distorting our view upon the true nature of "conduction disorders." During AF this is particularly relevant, as fractionated extracellular potentials are abundant and multiple, consecutive fibrillation waves appear continuously. Asynchronous activation of layers separating the atrial wall (epi-endocardial asynchrony) is especially observed in patients with a history of AF,[3] indicating that correct interpretation of patterns of activations is crucial for understanding mechanisms that enhance onset and perpetuation of the arrhythmia. During SR, fractionation of unipolar potentials was previously related to electrical waves propagating across the opposite tissue layers of the atrial wall.[4]

As electrical waves during AF pass more frequently and more irregularly than during SR, discrimination between different origins of sequential deflections is even more complex and increasing data resolution may be essential to unravel patterns of activation.

Our presented method shows some similarities to bipolar "ripple mapping," displaying changes in voltage over time.[5] However, any changes in voltage as caused by baseline drift or artefacts are also visualized, hampering data interpretation. In contrast, local activation times as presented in this paper can also be determined in the presence of these baseline aberrancies.

Interestingly, previous studies showed that in patients without structural heart disease, fractionated potentials are more often recorded from thicker parts of the left atrium and atrial septum than thinner parts,[6,7] supporting the assumption that asynchronous local activation is enhanced as the number of underlying cardiomyocytes increases. In addition, fractionation may frequently be functional in nature.[8] Therefore, exploring the phenomenon of fractionation in more detail may be even important to detecting "true" ablation targets.

Conclusions
Unipolar recordings of extracellular potentials contain more information than was previously recognized and could prove

very useful in identifying the arrhythmogenic substrate of tachyarrhythmias. Importantly, this newly proposed signal processing methodology of fractionated extracellular potentials unravels the 3-dimensional nature of propagation, which is not visualized when using conventional mapping technologies.

Appendix
Supplementary data
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrcr.2020.09.013.

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