Quantitative Assessment of Left Atrial Substrate of PsAF patients Using Functional Mapping, An Area-Based Observational Study

Saman Golmaryami[1], Etel Silvia García[2], Juan Fernández Armenta[3]

[1,2,3] Fundación de investigación y innovación biomédica de Cádiz, Cádiz, Spain.
[1,2,3] Hospital Universitario Puerta del Mar, Cádiz, Spain

Abstract

Persistent atrial fibrillation (PsAF) is associated with complex structural and functional remodeling of the left atrium (LA). Conventional substrate assessment during sinus rhythm (SR) or atrial fibrillation may not fully characterize dynamic electrophysiological abnormalities that become apparent under functional stress. Programmed atrial stimulation using extra-stimuli can unmask latent conduction slowing, electrogram (EGM) prolongation, and voltage reduction associated with an arrhythmogenic atrial substrate.

This study aims to quantitatively characterize dynamic changes in atrial voltage and conduction during functional mapping using triple extra-stimulation and to determine their relationship with the proportion of sites exhibiting a positive functional response.

Twenty-four patients with PsAF undergoing high-density LA functional mapping were analyzed. Local bipolar EGMs were processed using a threshold-based delineation algorithm to identify activation onset and derive local activation times (LATs). LAT values were interpolated across a triangulated LA surface using a minimum Dirichlet energy formulation. Local conduction velocity (CV) was subsequently estimated from the spatial gradients of the interpolated LAT field.

Low-voltage area (LVA%; bipolar voltage <0.5 mV), slow-conduction area (LowCV%; CV <0.5 mm/ms), and positive response area (POS%) were expressed as percentages of the total mapped atrial surface. POS% represented the proportion of sites demonstrating a positive functional response to extra-stimulation, characterized by EGM prolongation and voltage reduction relative to SR. Changes in functional substrate between successive stimulation stages were additionally quantified, including changes in LVA%.

POS% showed a progressively stronger correlation with LVA% across successive stimulation stages: first stimulation, $\rho=0.37$ ($p=0.07$); second stimulation, $\rho=0.50$ ($p=0.013$); and third stimulation, $\rho=0.60$ ($p=0.002$).

Stronger associations were observed between POS% and LowCV% at all stimulation stages: first, $\rho=0.73$ ($p<0.001$); second, $\rho=0.80$ ($p<0.001$); and third, $\rho=0.76$ ($p<0.001$).

The early functional response from the first to second stimulation was associated with POS% for both LVA change ($\rho=0.45$, $p=0.027$) and LowCV change ($\rho=0.57$, $p=0.003$), whereas changes occurring between the second and third stimulation were not significantly associated with POS%. Mean CV was inversely correlated with POS% throughout functional stimulation (ρ approximately -0.72 to -0.78, all $p<0.001$).

Functional substrate mapping using extra-stimulation reveals graded electrophysiological remodeling in patients with PsAF. The proportion of sites exhibiting a positive functional response is strongly associated with the spatial extent of conduction slowing and, increasingly, with low-voltage substrate during progressive stimulation. The greatest dynamic changes occur early in the stimulation sequence, suggesting that functional stress may identify clinically relevant abnormalities not apparent during conventional mapping alone.

Keywords: persistent atrial fibrillation; functional mapping; conduction velocity; low-voltage area; electrogram; extra-stimulation; atrial substrate

1. Introduction

Persistent atrial fibrillation is associated with progressive structural and electrophysiological remodeling of the left atrium. These changes include fibrosis, altered cellular coupling, conduction heterogeneity, regions of reduced electrogram voltage, and localized conduction slowing, all of which may contribute to the maintenance of atrial fibrillation and to recurrence following catheter ablation [1,2].

Electro-anatomical substrate mapping has traditionally relied on voltage measurements acquired during sinus rhythm or on activation characteristics recorded during atrial fibrillation. Low-voltage regions identified during sinus rhythm are frequently interpreted as markers of atrial structural remodeling. However, voltage alone provides an incomplete representation of the underlying arrhythmogenic substrate. Atrial tissue that appears

relatively preserved under baseline conditions may demonstrate marked conduction abnormalities when exposed to premature activation.

Functional substrate mapping has therefore emerged as a complementary strategy for assessing the dynamic electrophysiological properties of atrial myocardium. Programmed stimulation using progressively premature extra-stimuli can reveal abnormalities that are not apparent during baseline rhythm, including slowing of conduction, electrogram prolongation, fractionation, and reduction in bipolar voltage [3–5]. These responses may reflect impaired conduction reserve within diseased atrial myocardium.

Previous functional mapping studies have demonstrated that specific atrial regions exhibit exaggerated electrophysiological responses to premature stimulation. However, the relationship between these local functional responses and the overall spatial burden of voltage and conduction abnormalities across the LA has not been fully quantified.

According to the PERSUADE functional-mapping protocol, EGMs recorded during sinus rhythm are classified as negative (normal) or positive based on morphology in response to triple extra functional pacing. Normal EGMs are defined as sharp electrograms with ≤3 distinct positive or negative deflections or an EGM duration <40 ms, whereas fractionated EGMs show >4 deflections and a duration ≥40 ms; highly fragmented EGMs are characterized by ≥5 deflections and prolonged duration.

A particularly relevant question is whether patients with a greater proportion of positively responding sites also demonstrate more extensive low-voltage and slow-conduction substrate. Furthermore, it remains uncertain whether these relationships evolve progressively with increasingly premature stimulation or whether the most important changes occur during the earlier stages of functional stress.

The present study therefore aimed to quantitatively characterize changes in LA voltage and conduction during sequential triple extra-stimulation in patients with PsAF. Area-based measures of low voltage and slow conduction were derived from high-density electro-anatomical maps and compared with the proportion of sites exhibiting a positive functional response.

We hypothesized that a greater positive functional response would be associated with a larger burden of low-voltage and slow-conduction substrate and with lower overall conduction velocity, and that these relationships would become more apparent under progressively premature stimulation.

2. Methods

The study included 24 patients with persistent atrial fibrillation undergoing high-density LA functional mapping as part of their electrophysiological evaluation.

High-density electro-anatomical mapping of the LA was performed using the Carto3 system and PentraRay catheter. Mapping was performed during sinus rhythm while applying the triple extra protocol. Functional assessment consisted of three sequential stimulation stages, referred to throughout this study as the first, second, and third stimulation conditions.

The atrial effective refractory period (AERP) was calculated as the maximum interval between two consecutive stimuli in which the whole atrial activation fails to occur. Following the determination of AERP, the first extra stimulus (S1) was delivered at an interval of AERP + 60 ms after the onset of sinus rhythm. The second (S2) and third (S3) extra stimuli were then applied at AERP + [40–20] ms and AERP + [30–20] ms after S1 and S2, respectively.

High-density bipolar EGMs and their corresponding spatial coordinates were recorded at each stimulation stage. Local bipolar EGMs were analyzed using a threshold-based delineation algorithm developed to identify the onset of local atrial activation. For each EGM, the detected activation onset was used to assign a local activation time. LAT measurements were subsequently associated with their corresponding three-dimensional electro-anatomical coordinates.

Because electro-anatomical recordings provide activation measurements at discrete spatial locations, LAT values were interpolated across the reconstructed LA surface. The atrial geometry was represented as a triangulated surface mesh. A continuous LAT field was estimated using a minimum Dirichlet energy solution, producing a spatially smooth activation-time distribution while respecting the measured LAT values.

The interpolated LAT field was obtained by minimizing the Dirichlet energy over the atrial surface:

$$Eq1 \qquad min_u\, E(u) = \frac{1}{2}\int_{\Omega} \|\nabla u(x)\|^2 dx$$

Equation 1. Minimum Dirichlet energy formulation for LAT interpolation. This approach generated continuous activation maps from the spatially distributed LAT measurements and enabled estimation of local spatial activation gradients (Figure 1.II).

Local conduction velocity was derived from the spatial gradient of the interpolated LAT field. Conceptually, the magnitude of conduction velocity was calculated as the inverse of the local LAT gradient:

$$Eq2 \qquad CV = \frac{1}{||\nabla T||}$$

where (T) represents the interpolated LAT field and ($||\nabla T||$) represents the magnitude of its spatial gradient over the atrial surface. Local CV vectors were calculated

across the triangulated LA surface, providing both the magnitude and direction of propagation. Representative voltage and CV maps are illustrated in Figure 1. II.

Local bipolar voltage was evaluated across the mapped LA surface. Low-voltage tissue was defined using a bipolar voltage threshold of $V < 0.5$ mV. The low-voltage area was expressed relative to the total mapped LA surface (LVA%). This area-based approach allowed comparison of the overall low-voltage burden between patients and stimulation stages.

Regions exhibiting a local conduction velocity below 0.5 mm/ms were classified as slow-conduction regions. The slow-conduction area was expressed relative to the total mapped LA surface (LowCV%). Mean CV across the mapped atrial surface was additionally calculated for each stimulation stage.

The functional response of individual EGMs to premature stimulation was evaluated relative to their corresponding baseline behavior. A site was considered to demonstrate a positive functional response when extra-stimulation resulted in electrophysiological changes characterized by increased EGM duration together with reduced EGM voltage relative to SR/baseline conditions.

POS% was calculated as the proportion of evaluated sites demonstrating a positive functional response relative to the total mapped LA surface. Thus, POS% represented a patient-level measure of the overall burden of functionally abnormal atrial tissue.

To characterize the response to progressively premature stimulation, changes in substrate measures were evaluated between consecutive stimulation stages. The early functional response was defined as the change between the first and second stimulation. The late functional response was defined as the change between the second and third stimulation. For low-voltage substrate, the change in LVA was quantified as ΔLVA%. Equivalent changes in LowCV% were evaluated to characterize the dynamic progression of conduction slowing.

Associations between POS% and electrophysiological substrate parameters were evaluated using Spearman rank correlation coefficients (ρ). The relationship between POS% and LVA%, LowCV%, and mean CV was evaluated independently at the first, second, and third stimulation stages. Associations between POS% and dynamic changes occurring from first to second stimulation and from second to third stimulation were also assessed.

3. Results

POS% showed a progressively stronger association with the extent of low-voltage substrate across successive extra-stimulation stages. The correlation between POS% and LVA% increased from the first stimulation ($\rho = 0.37$, $p = 0.07$) to the second ($\rho = 0.50$, $p = 0.013$) and was strongest during the third stimulation ($\rho = 0.60$, $p = 0.002$). These findings indicate that patients with a greater proportion of positively responding sites developed a more extensive low-voltage substrate as stimulation became progressively premature.

The association between POS% and slow-conduction area was stronger than that observed for low-voltage area. POS% correlated strongly with LowCV% at the first stimulation ($\rho = 0.73$, $p < 0.001$), reached its maximum correlation at the second stimulation ($\rho = 0.80$, $p < 0.001$), and remained strongly associated at the third stimulation ($\rho = 0.76$, $p < 0.001$). Therefore, patients with a greater positive functional response exhibited a larger proportion of atrial surface characterized by slow conduction.

Mean conduction velocity was also strongly and inversely associated with POS% across all stimulation stages (ρ approximately -0.72 to -0.78, all $p < 0.001$), indicating that a greater functional response was associated with slower overall atrial conduction.

Dynamic changes between consecutive stimulation stages were subsequently evaluated. The early functional response, from the first to the second stimulation, was significantly associated with POS% for both the change in low-voltage area ($\rho = 0.45$, $p = 0.027$) and the change in slow-conduction area ($\rho = 0.57$, $p = 0.003$). In contrast, changes occurring between the second and third stimulation were not significantly associated with POS%.

Overall, the strongest relationship between POS% and LVA% was observed during the third stimulation, whereas the strongest association between POS% and LowCV% occurred during the second stimulation (Figure 1.I). These findings suggest that conduction abnormalities are strongly related to the functional response and may become apparent earlier than the maximal low-voltage response during progressive extra-stimulation.

4. Conclusion

Functional substrate mapping using sequential extra-stimulation reveals graded electrophysiological abnormalities in patients with persistent atrial fibrillation. A greater positive functional response was associated with a larger slow-conduction area, lower mean conduction velocity, and progressively greater low-voltage substrate.

Importantly, the principal dynamic changes in low-voltage and slow-conduction areas occurred between the first and second stimulation stages, whereas additional changes between the second and third stimulation were not significantly related to POS%. These findings suggest that early functional stimulation captures a substantial component of the abnormal atrial response and may reveal impaired conduction reserve that is not fully identified by conventional static mapping.

5. Limitations

Several limitations should be considered.

First, this was a relatively small study including 24 patients with PsAF. The observed associations should therefore be validated in larger independent populations.

Second, electro-anatomical measurements depend on

mapping density, catheter orientation, electrode-tissue contact, activation direction, filtering, and signal-processing methodology. Although area-based measurements reduce some dependence on point density, these factors may still influence voltage and LAT measurements.

Third, conduction velocity was derived computationally from spatial gradients of an interpolated LAT field rather than measured directly. CV estimates are therefore dependent on the accuracy of LAT annotation and the assumptions underlying the interpolation methodology.

Fourth, the voltage threshold of 0.5 mV and CV threshold of 0.5 mm/ms represent operational definitions of abnormal substrate and may not capture the full continuous spectrum of atrial remodeling.

Fifth, the present analysis primarily establishes associations between functional EGM response, voltage abnormalities, and conduction abnormalities. It does not establish a causal relationship between these parameters.

Finally, the clinical relevance of the identified functional substrate with respect to ablation outcome and long-term AF recurrence remains to be established prospectively.

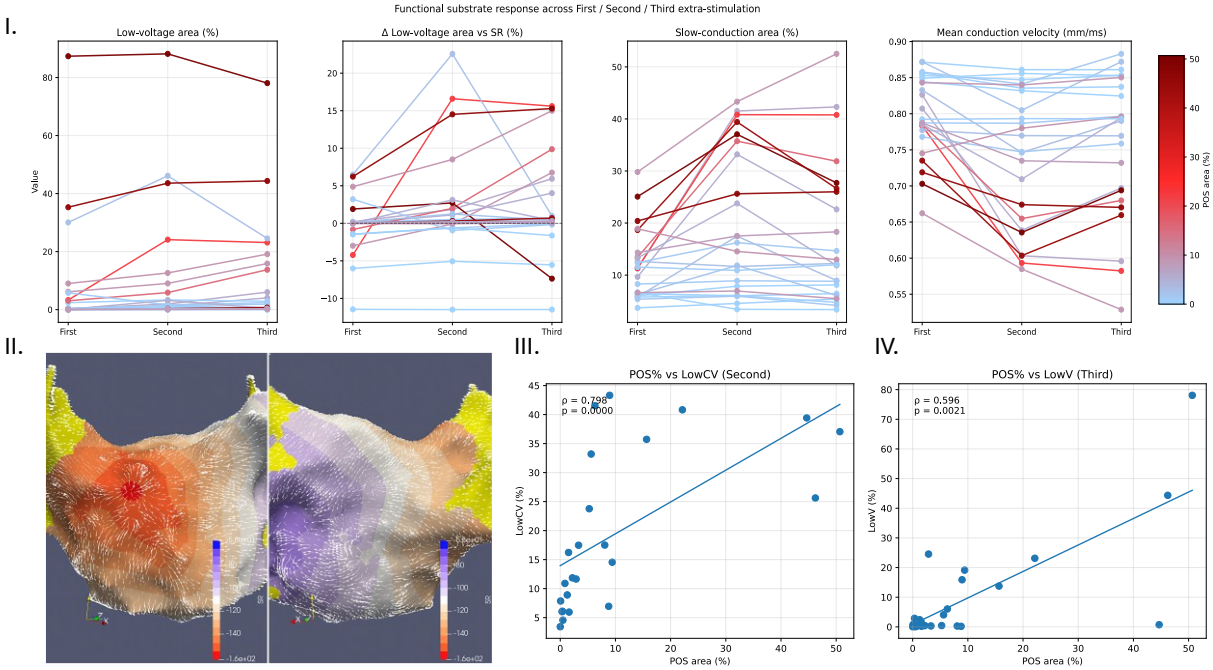

Figure 1 Figure 2. Functional substrate response across extra-stimulation. (I) Patient-wise changes in low-voltage area (LVA%), ΔLVA%, slow-conduction area (LowCV%), and mean conduction velocity from First to Third stimulation, color-coded by POS%. (II) Representative LA maps showing the voltage map and conduction velocity vectors. (III–IV) POS% correlates with LVA% at Third and LowCV% at Second stimulation, indicating the greatest Spearman coefficient and lowest p-values.

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Hospital Universitario Puerta del Mar, 9th Floor, Research Unit, Avenida Ana de Viya, 21, 11009 Cádiz, Spain:
SeyedSaman Golmaryami.
Saman.golmaryamii@gmail.com