Drifting Rotor Prevalence is associated with Dominant Frequency Reduction after Persistent Atrial Fibrillation Ablation

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Abstract

Identification and targeting of arrhythmogenic atrial regions remains an evident challenge in persistent atrial fibrillation patients. Frequency and phase analysis have shown their usefulness for better understanding the arrhythmia. This study aimed to investigate the spatio-temporal association between dominant frequency (DF) and re-entrant phase activation areas. For this, eight persistent AF patients were enrolled and 2048 left atrial AF electrograms (AEG) were acquired from each for up to 15 seconds following ventricular far-field cancellation. DF and phase singularity (PS) points were automatically identified and tracked over consecutive frames for spatio-temporal analysis. As result, simultaneous not spatio-temporally stable PS points were identified drifting throughout the left atrium. After pulmonary vein isolation PS incidence reduced (90.8±59.8 vs. 23.8±31.6, $p<0.05$), concomitantly, DF decreased (DF_{max} from 7.3±0.4 Hz to 7.1±0.8 Hz, $p=0.26$ and DF_{min} from 5.1±1.2 Hz to 4.2±1.1 Hz, $p<0.05$). Higher concentrations of PS areas seem to have a certain degree of co-localisation with HDF regions. Both frequency and phase analyses seem to have a role in identifying atrial regions that might be perpetuating persistent AF. Concatenated DF/PS mapping may contribute as an auxiliary tool for AF ablation.

1. Introduction

The theory of atrial fibrillation (AF) in humans suggests the existence of multiple mechanisms involved in the initiation and perpetuation of AF, including re-entrant circuits, rapidly firing foci and high frequency sites [1-3] These mechanisms are believed to be more pronounced in patients whose AF persists for long-term periods (persAF) or in which noticeable electrical and structural atrial substrate remodelling are observed [4,5]. However, the characterisation of arrhythmogenic atrial regions for successful ablation in the presence of concurrent fibrillatory mechanisms remains an evident challenge, usually requiring multiple procedures [5].

Dominant frequency (DF) ablation resulted in interatrial DF gradient reduction, prolonging patient's sinus rhythm [6]. In addition, high-density DF mapping of persistent AF allowed recognition of dynamic spatio-temporal patterns [7], suggesting that ablation therapy is unlikely to be favoured by observing a single time frame. Investigators identified AF re-entry sources using phase analysis techniques in invasive [8] and non-invasive [9] electrophysiology (EP) systems. They also showed that targeting these sources appears to favour treatment success. The relationship between the two analyses – DF and phase – has been previously assessed on intracardiac contact recordings [10,11]. These studies have shown that highest DF boundary areas were circumscribed by rotors, suggesting the occurrence of wavebreak close to these boundary areas. However, the relationship between frequency and phase analyses on non-contact mapping have not been clarified and is of interest to the investigation of spatio-temporal associations between DF and phase singularity (PS) re-entrant activity.

The aims of this study were (1) to investigate the feasibility of high-density phase mapping of the left atrium (LA) substrate to identify arrhythmogenic sites and circuits during persistent AF and, (2) to study the association between atrial regions PS and high DF activity (HDF) in the LA substrate during persAF.

2. Methods

2.1. Electrophysiological Study

A non-contact multi-electrode array (MEA) catheter (EnSite 3000, St Jude Medical, USA) was introduced trans-septally into the LA of eight patients (age: 47±10 years; AF duration: 34±25 months) undergoing catheter ablation of persAF for the first time and with no previous history of heart diseases. Without contact between the endocardium wall and electrodes from the MEA, the system generates reconstructed unipolar virtual electrograms (AEGs) using inverse solution mathematics [12] projected to the endocardial 3D geometry of the LA. Anatomical landmarks were identified and annotated on the detailed endocardial 3D LA surface. After AEGs acquisition in AF steady state, the MEA was removed and AF ablation proceeded as per standard practice. This study had informed consent from the patients undergoing persAF ablation for the use of electrical data acquired.

2.2. Signal processing

AEGs were sampled at 1200 Hz and 15-second long segments of non-induced persistent AF were exported for off-line analysis. The AEGs were band-pass filtered between 3 Hz to 30 Hz following ventricular far-field influence cancellation [13].

Phase analysis

The phase representation of each AEG was obtained and NCM phase maps were created to obtain subsequent maps with automatic identification of PS points. Firstly, a Hilbert transform was applied to the AEG to produce an analytic signal, followed by the inverse tangent calculation of the imaginary and real part of the analytic signal [11]. Thus, for each sample, the calculated phase was limited between $-\pi$ and $+\pi$. Once phase analysis was applied to all 2048 AEGs, sequential 2D and 3D phase maps were developed. The spatial phase distributions were analysed to locate phase singularity (PS) points. PSs were automatically identified by looking at locations where the phase progresses through a complete cycle around them from $-\pi$ to $+\pi$ [11]. Only PS points lasting over consecutive frames for at least 100 ms were considered [14].

Frequency analysis

Spectral analysis consisted of identifying the DF – defined as the frequency with the highest power within 4 Hz to 10 Hz – to produce sequential 2D and 3D DF density maps of the LA [7]. Fast Fourier Transform (FFT) with a Hamming window was applied to the 2048 simultaneous AEGs on sequential segments of 4 s windows with 50% overlap (by shifting forward by 2 s) to produce consecutive 3D DF maps. The spectral resolution was 0.25 Hz and zero padding was applied to produce frequency steps of 0.05 Hz. After generation of the sequential DF maps, a representative DF mean map corresponding to the average frequency spectrum was plotted. The average spectrum of each 2048 AEG was calculated by averaging the window segments spectrum within the AF physiological range (4-10 Hz), followed by identifying the DF for each AEG and then plotting the respective 3D DF mean map.

Phase and frequency spatio-temporal analysis

The DF maps behaviour was investigated with both highest DF (HDF) and lowest DF (LDF) automatically identified which contain the values within 0.25 Hz of the highest and lowest DF respectively. This would present an area that reflects the average local activity minimising the effect of isolated DF sites.
The spatio-temporal correlation between DF and PS regions was studied by observing the geometric relationship between LA areas containing high frequency activation and high incidence of singularities. Higher PS appearance presented within the boundaries of the HDF areas and/or located nearby (up to 5 adjacent nodes) were considered to both DF and PS regions be co-localised.

3. Results

3.1. Spatio-temporal phase analysis

The PS identification was systematically tracked over consecutive time frames. It was observed that although PS points are commonly present on AEG recordings from persistent AF patients, their spatial locations are not anchored to particular areas. The PS points drift within regions of the LA suggesting a lack of spatial stability.

Phase singularities

The impact on the PS occurrences after anatomic based strategy ablation showed that pulmonary vein isolation (PVI) decreased significantly the PS incidence in the LA from 2872.8±743.8 to 1770.2±635.7 (-36.7±22.6%, $p<0.05$). Figure 1A depicts the number of PS occurrences obtained successively from a 15 s segment, from one patient, prior to ablation. Areas such roof, posterior and anterior wall presented higher concentration of singularities compared with other LA locations. The impact of AF ablation strategy can be observed in Figure 1B. Both the number of occurrences and the LA area covered have reduced significantly, highlighting the passive nature of PS on the LA during persistent AF.

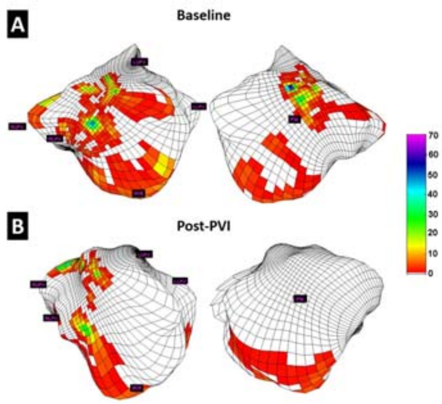

Figure 1. Comparison of PS histograms between baseline (A) and post-ablation (B) from a 15-sec segment.

3.3. Frequency mapping

DF analysis presented a similar trend as observed previously with the reduction of the PS concentration after PVI. DF_{max} decreased from 7.3±0.4 Hz to 7.1±0.8 Hz ($p=0.26$) and DF_{min} from 5.1±1.2 Hz to 4.2±1.1 Hz ($p<0.05$). DF_{grad} (DF_{max} - DF_{min}) had increased from 2.2±0.8 Hz to 3.0±1.2 Hz ($p=0.1$). The average spectrum of the entire LA showed the global effect of PVI on the AEGs, with a DF reduction of the population LA from 6.8±0.5 Hz to 6.0±1.4 Hz ($p=0.08$). Figure 2 illustrates the influence of AF ablation on DF in the LA. On Figure 2A, the LA presents a large 6.1 Hz area with the highest DF centred at 6.9 Hz. After ablation, both frequency areas and frequency values were reduced. The former highest DF area decreased to a frequency value of 3.45 Hz.

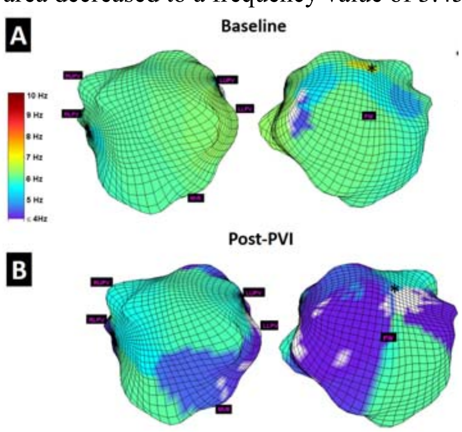

Figure 2 – The DF mapping (A) prior and (B) after PVI.

3.4. Phase vs. frequency mapping

Although reduction prevalence has been seen in both phase and frequency indices after ablation, it is not known whether a spatiotemporal agreement between high DF areas and regions of the LA harbouring high incidence of PSs exists. In total 156 3D maps were investigated (96 on baseline and 60 post PVI) and 87.2% of the maps showed a spatio-temporal a relationship between DF and PS regions. From these cases, the majority (98.5%) showed a pattern where the PS points were concentrated on areas that are neighbours of the HDF and then spreading to the remaining LA areas (Figure 3A). From those cases, 37.3% had some PSs at the same spatiotemporal regions of the HDF areas, by their border (Figure 3B).

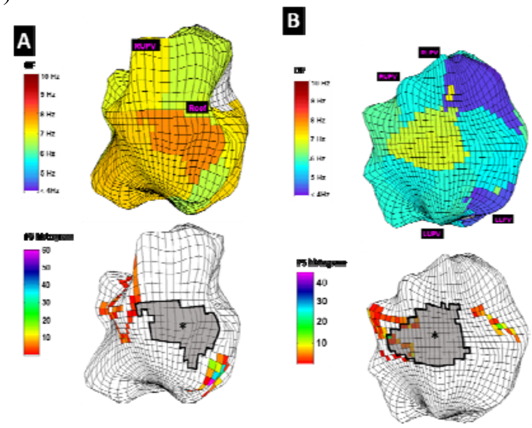

Figure 3 - Spatiotemporal correlation between PS points and HDF areas. (A) surrounding the HDF areas (A); and either surrounding or just inside of the HDF areas (B).

4. Discussion and conclusions

PSs during cardiac fibrillation have been demonstrated to be a pivot of functional re-entrant circuits [11] and essential for mapping fibrillatory patterns [15] in both animal and human studies. Advanced stages of AF such as observed at the atria of persistent AF patients would have episodes of re-entry activity and, consequently, presence of PSs. Our findings showed multiple simultaneous paired PS points that are not anchored but drift throughout large areas of the LA even in short time durations. Moreover, the degree of PS appearance after ablation seemed to be influenced by the strategic therapy performed (Figure 1) suggesting that in persistent AF relevant AF subtract can be identified by phase mapping.

Our data show that the DF value from high and low DF areas decreased after ablation with extended reduction to the overall LA frequency (Figure 2). These results are in agreement with the decrement of the PS incidence after PVI, which suggests that both DF and PS might have a role at identifying key arrhythmic areas.

From our observations, we identified that regions showing high concentration of singularities somehow seemed to be neighbouring or even invading the borders of areas harbouring HDFs.

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References

[1] Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. The New England Journal of Medicine Sep 3 1998;339:659-666.

[2] Jalife J, Berenfeld O, Mansour M. Mother rotors and fibrillatory conduction: a mechanism of atrial fibrillation. Cardiovascular Research 2002;54:204-216.

[3] Moe GK, Rheinboldt WC, Abildskov JA. A Computer Model of Atrial Fibrillation. American Heart Journal Feb 1964;67:200-220.

[4] Brooks AG, Stiles MK, Laborderie J, Lau DH, Kuklik P, Shipp NJ, Hsu LF, Sanders P. Outcomes of long-standing persistent atrial fibrillation ablation: a systematic review. Heart Rhythm 2010;7:835-846.

[5] Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. Physiological Reviews 2011;91:265-325.

[6] Atienza F, Almendral J, Jalife J, Zlochiver S, Ploutz-Snyder R, Torrecilla EG, Arenal A, Kalifa J, Fernandez-Aviles F, Berenfeld O. Real-time DF mapping and ablation of dominant frequency sites in atrial fibrillation with left-to-right frequency gradients predicts long-term maintenance of sinus rhythm. Heart Rhythm 2009;6:33-40.

[7] Salinet JL, Tuan JH, Sandilands AJ, Stafford PJ, Schlindwein FS, Ng GA. Distinctive patterns of dominant frequency trajectory behavior in drug-refractory persistent atrial fibrillation: preliminary characterization of spatiotemporal instability. Journal of Cardiovascular Electrophysiology 2014;25:371-379.

[8] Narayan SM, Patel J, Mulpuru S, Krummen DE. Focal impulse and rotor modulation ablation of sustaining rotors abruptly terminates persistent AF to sinus rhythm with elimination on follow-up: a video case study. Heart Rhythm 2012;9:1436-1439.

[9] Haissaguerre M, Hocini M, Denis A, et al. Driver domains in persistent atrial fibrillation. Circulation 2014;130:530-538.

[10] Samie FH, Berenfeld O, Anumonwo J, Mironov SF, Udassi S, Beaumont J, Taffet S, Pertsov AM, Jalife J. Rectification of the background potassium current: a determinant of rotor dynamics in ventricular fibrillation. Circulation Research 2001;89:1216-1223.

[11] Umapathy K, Nair K, Masse S, Krishnan S, Rogers J, Nash MP, Nanthakumar K. Phase mapping of cardiac fibrillation. Circulation 2010;3:105-114.

[12] Schilling RJ, Peters NS, Davies W. Simultaneous endocardial mapping in the human left ventricle using a noncontact catheter - Comparison of contact and reconstructed electrograms during sinus rhythm. Circulation 1998;98(9):887-898.

[13] Salinet JL, Jr., Madeiro JP, Cortez PC, Stafford PJ, Ng GA, Schlindwein FS. Analysis of QRS-T subtraction in unipolar atrial fibrillation electrograms. Medical & Biological Engineering & Computing 2013;51:1381-1391.

[14] Samie FH, Berenfeld O, Anumonwo J, Mironov SF, Udassi S, Beaumont J, Taffet S, Pertsov AM, Jalife J. Rectification of the background potassium current: a determinant of rotor dynamics in ventricular fibrillation. Circulation Research 2001;89:1216-1223.

[15] Pandit SV, Jalife J. Rotors and the dynamics of cardiac fibrillation. Circulation Research 2013;112:849-862.

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