Document downloaded from:

http://hdl.handle.net/10251/152482

This paper must be cited as:

Rodrigo Bort, M.; Climent, AM.; Liberos Mascarell, A.; Fernandez-Aviles, F.; Berenfeld, O.; Atienza, F.; Guillem Sánchez, MS. (2017). Highest dominant frequency and rotor positions are robust markers of driver location during noninvasive mapping of atrial fibrillation: A computational study. Heart Rhythm. 14(8):1224-1233. https://doi.org/10.1016/j.hrthm.2017.04.017

The final publication is available at

https://doi.org/10.1016/j.hrthm.2017.04.017

Copyright Elsevier

Additional Information

Highest dominant frequency and rotor positions are robust markers of driver location during non-invasive mapping of atrial fibrillation: a computational study

Short title: **Stable ECGI markers for atrial driver location**

Miguel Rodrigo, PhD[a], Andreu M. Climent, PhD[a,b,c], Alejandro Liberos, PhD[a,b,c], Francisco Fernández-Avilés, MD, PhD[b,c,d], Omer Berenfeld, PhD, FHRS[e], Felipe Atienza, MD, PhD[b,c,d], Maria S. Guillem, PhD[a]

[a] ITACA, Universitat Politécnica de Valencia, Valencia, Spain.
[b] Cardiology Department, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain.
[c] CIBERCV, Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares, Spain.
[d] Facultad de Medicina. Universidad Complutense de Madrid, Spain
[e] Center for Arrhythmia Research, University of Michigan, Ann Arbor, USA.

Address for correspondence:

Maria S. Guillem: ITACA, 1ªplanta, Edificio 8G, Universitat Politécnica de València, Camino de Vera sn, 46022 Valencia (Spain), Tel. +34963877968, email: mguisan@eln.upv.es

or **Felipe Atienza**: Cardiology Department, Hospital General Universitario Gregorio Marañón, C/ Dr Esquerdo 46, 28007, Madrid (Spain), Tel. +34915868687, email: fatienzaf@secardiologia.es

Conflicts of interest

FA served on the advisory board of Medtronic and Sorin. OB received research support from Medtronic and St. Jude Medical. He is a cofounder and Scientific Officer of Rhythm Solutions, Inc., Research and Development Director for S.A.S. Volta Medical and consultant to Acutus Medical. The other authors have no conflict of interest. None of the companies disclosed here financed the research described in this manuscript.

Number of words : 4999/5000

Código de campo cambiado

Con formato: Español (España)

ABSTRACT

Background: Dominant Frequency (DF) and rotor mapping have been proposed as non-invasive techniques to guide localization of drivers maintaining atrial fibrillation (AF).

Objective: To evaluate the robustness of both techniques in identifying atrial drivers non-invasively under the effect of electrical noise or model uncertainties.

Methods: Inverse-computed DFs and phase maps were obtained on 30 different mathematical AF simulations. Epicardial Highest DF (HDF) regions and rotor location were compared with the same inverse-computed measurements after addition of noise to the ECG, size variations of the atria and linear or angular deviations in the atrial location inside the thorax.

Results: Inverse-computed EGMs individually correlated poorly with the original EGMs in the absence of induced uncertainties (0.45±0.12) and worse with 10dB noise (0.22±0.11), 3 cm displacement (0.01±0.02) or 36º rotation (0.02±0.03). However, inverse-computed HDF regions showed robustness against induced uncertainties: from 82±18% match for the best conditions, down to 73±23% for 10 dB noise, 77±21% for 5 cm displacement and 60±22% for 36º rotation. The distance from the inverse-computed rotor to the original rotor was also affected by uncertainties: 0.8±1.61cm for the best conditions, 2.4±3.6cm for 10dB noise, 4.3±3.2cm for 4 cm displacement and 4.0±2.1cm for 36º. Restriction of rotor detections to the HDF area increased the rotor detection accuracy from 4.5±4.5 to 3.2±3.1cm ($p<0.05$) with 0 dB noise.

Conclusion: The combination of frequency and phase-derived measurements increases accuracy of non-invasive localization of atrial rotors driving AF in the presence of noise and uncertainties in atrial location or size.

Keywords: electrocardiographic imaging; inverse problem; dominant frequency; rotor; dominant region

INTRODUCTION

Personalized characterization of patterns of activation in atrial fibrillation (AF) patients with ~~the novel invasive [Narayan JACC 2013] or~~ the novel non-invasive electrocardiographic imaging (ECGI) method has reported successful ablation rates [1]. The method has been employed to ~~-~~identify the hierarchy of dominant AF regions by non-invasively measuring dominant frequencies (DF) [2] or rotors on the epicardial wall of the atria [1,3]. However, the propagation patterns that result from the inverse problem solution during AF appear to be simpler [1,3] than to those obtained with intra-cardiac contact electrodes and optical mapping experiments [4-5], with less and smoother simultaneous wavefronts. These discrepancies between contact and non-contact mapping techniques do raise some skepticism regarding the accuracy of the method in the characterization of the true propagation patterns and rotors during AF and for understanding of AF mechanisms ~~us,~~ despite the successful AF ablation guided by the inverse solution mapping [1], ~~the accuracy of the method in the characterization of the true propagation patterns during AF and for understanding of AF mechanisms in general is unclear.~~

In this work we use multiple computer simulations to quantify the accuracy of ECGI-based AF driver detection under uncertainties that are relevant to the clinical setting of its usage. Variations in the geometry of the computer model, including location, orientation and size of the atria, as well as varying electrical noise are introduced into the inverse problem solution of body surface potentials to assess the accuracy of the solutions relative to the atrial activity used to generate the surface potentials.

METHODS

Mathematical models

A realistic 3D model of the atrial anatomy was used to simulate the atrial electrical

activity ~~(see the Supplemental Material for further information)~~. Heterogeneity in electrophysiological properties of the atrial myocardium was introduced in form of changes in the ionic currents and in fibrosis distribution to generate AF maintained by rotors and fibrillatory activity exhibiting non-uniform propagation patterns and different shape and extension of the dominant region (see the Mathematical models section in Supplemental Material). An ensemble of 30 different AF episodes driven by a single rotor at varying locations was simulated (see Figures S1-S34~~2~~).

For each simulation, a uniform mesh of unipolar EGMs was calculated surrounding the epicardial surface. The ECG potentials on the torso model were calculated by solving the forward problem and then, the inverse-computed EGMs (icEGMs) were reconstructed on the atrial surface by solving the inverse problem by the zero-order Tikhonov's and L-curve methods (see Supplemental Material). Temporal series of EGMs and iCEGMs were compared in terms of correlation coefficients.

Addition of model and signal uncertainties for the inverse problem solution

To evaluate the robustness of the inverse solution approach against model uncertainties, we evaluated the accuracy of the solution under four uncertainty conditions: (i) noise, (ii) error in the atrial size, (iii) error in the location of the atria, and (iv) error in orientation of the atria inside the torso volume. Those uncertainties were generated by: (i) White Gaussian noise added to the surface ECG signals with a signal-to-noise ratio (SNR) between 60 dBs (low noise) and 0 dBs (high noise). (ii) Deviations in the atrial size from -20% to +20% (80% to 120% of its original dimension in each axis). (iii) Displacements in the atrial position from 0 cm to 5 cm in the lateral axis (X axis in Fig 1.A). And (iv) atrial rotations from 0º to 45º around the lateral axis.

Rotor and Dominant Frequency identification

Rotor localization was automated based on singularity points (SP) identification in the phase signal map obtained with the Hilbert Transform. Only long lasting SPs (>1 rotation) were considered as rotors and other SPs were discarded [6]. Histograms of atrial rotors presence were obtained by counting the number of rotors in each atrial model node, and the node with highest SP presence was considered as the rotor place.

For the dominant frequency (DF) analysis the power spectral density of all signals was computed using Welch periodogram to determine the local DFs [7]. Since a spatial correlation in our unstructured mesh does not accurately account for the discrete metric in the DF maps, we compared inverse-computed DF maps with the original DF maps in terms of the concordance of their Highest DF (HDF) regions, defined as the intersection between HDF regions (or regions within 0.5 Hz from the HDF) over the original HDF region. The distance between the barycenters of the original and the inverse-computed HDF regions was also calculated.

RESULTS

Illustrating sample cases

Epicardial maps based on inverse computed potentials always differed from those computed from the original EGMs. Figure 1.A illustrates a schematic view of the 3D torso model used for the inverse solution and the atrial surface at its reference position. The potential distributions for an AF episode driven by a stable rotor is depicted in Figure 1.B. Panel C shows the inverse-computed voltage map following the inverse solution under the best possible conditions, that is, with no added electrical noise to the ECGs and with the atria at their reference position. As shown, the inverse-computed voltage map is smoother than the original EGMs, due to the

inability of the inverse solution to reconstruct the wavefront irregularity produced by the fibrotic tissue [6]. However, the activating wavefront (transition from blue to red colors) around the rotor is at the same place.

Figure 1.D depicts the inverse-computed maps after inverse solution with noise added to the ECG (10dBs SNR). As expected, inverse-computed voltage map differed from the original map to a greater extent than those computed with no addition of uncertainties, but the potential map still retained some similarity with the original map. The inverse solution based on a mismatch in the atrial size used in the inverse solution (120%, Panel E), presented a potential distribution similar to the one obtained under the best conditions. Inverse-computed potential map with atrial displacement of 2 cm (Panel F) and rotation of 27º (Panel G) relative to the reference position and orientation also retained the main features of the original map, although some other incorrect wavefronts appeared on the inverse solution map.

EGM signals correlation

Figure 2.A shows the original (blue) and inverse-computed (red) EGM signals from a point near of the rotor core of the simulation in Figure 1 for two inverse solutions: with no noise (60dBs SNR) and under noisy conditions (0dBs SNR). Even for the best scenario (no noise), the inverse-computed signal notability differed from the original EGM signal, although it still retained the main activation sequence showing a correlation coefficient of 0.61. However, the addition of noise reduced the similarity between the original and inverse-computed signals, showing a correlation of 0.27. A summary of the measured correlation coefficients in the whole database is presented in Figure 2 showing that the correlation coefficient for EGM signals (0.45±0.12) was quite poor even in the absence of noise or model uncertainties. An addition of white noise to the surface ECGs before computing the inverse solution decreased this

correlation coefficient down to 0.18±0.1 for a 0dB SNR. Uncertainties in the atrial size moderately decreased the correlation coefficient down to 0.33±0.10 for 80%, as shown in Figure 2.C. Uncertainties in the location or orientation of the atria inside the torso volume, however, had a large impact on the correlation coefficients, as depicted in Figures 2.D-E. Correlation coefficients decreased from 0.41±0.13 for 0 cm down to 0.01±0.02 for a 3 cm displacement, and down to 0.03±0.05 for a 27º of rotation.

Notably, the correlation coefficient between icEGMs and original EGMs showed significantly higher values in the HDF regions than in the rest of the passively-activated atrial tissue (see Figure ~~S3~~S5). This trend was observed for all those scenarios in which the general correlation coefficient was significantly different from 0: for 60, 30, 20 and 10dB SNR in the ECG; for all the atrial sizes; for 1 cm, 2 cm and 3 cm of displacement and for rotations of 0º, 9º and 18º. These values could be explained by the more stable propagation patterns in the area of the rotor, where the propagation had clear wavefronts, relative to the peripheral passive tissue where there is fibrillatory conduction.

Highest Dominant Frequency Regions

Although the morphology of icEGMs and their original EGMs has been shown to be poorly related, they do allow for a robust estimation of the local activation rate (or DF) against signal or model uncertainties (see Figure 3). Inverse-computed DF map (Panel B) presented a high correlation with the original DF map (Panel A) in the absence of ECG noise, and the extent and position of the Highest DF (HDF) region was preserved following the inverse solution. In the presence of ECG noise (Panel C), identification of the HDF region was accomplished with a concordance above 75% for SNRs as low as 10 dB that decreased to 56.5±32.3% for 0 dB. Changes in

the atrial size did not result in noticeable changes in the HDF region concordance which remained stable around 85±10%. Notably, identification of the HDF region was very robust against uncertainties in the atrial location, with mean concordance values above 75.9±11.9% for uncertainty of 3 cm in location. Inverse-computed DF maps were more sensitive to angular deviations (but less sensitive than the EGMs), where the concordance of the HDF progressively decreased from 84.5±10.6% for 0º down to 56.2±23.0% for 45º.

The rationale behind the ability of the inverse solution to locate correctly HDF regions can be understood from data presented in Figure ~~S4~~ S6 showing that the HDF region is generally wider in the inverse-computed data as compared to the original HDF region. Indeed, the addition of noise increased the size of the HDF region by 26.8±32.2% for 60 dB and up to by 36.7±35.1% for 20 dB, and only followed by a decrease down to -4.8±53.0% for the largest level of noise at 0 dB SNR. Decreases in the atrial size also increased the HDF region (-10.4±83.6% for 80% size), whereas atrial enlargement did not significantly alter the HDF area size (15.2±27.3% for 120% size). In contrast, displacement in the atrial position resulted in a considerably higher increase in the HDF area, up to 202.1±169.9% for 5 cm whereas an angular deviation provoked a maximum increase of 59.0±78.6% for 45º.

Complementary to the data presented in Figure 3, the center of the original HDF maps and their inverse-computed counterparts were compared. Figure 4.A shows the original DF map with its barycenter (black cross), which suffered a displacement (black dot, Panel B) when compared with the barycenter of the HDF region of the inverse-computed DF map with a displacement of 2 cm in the atrial position. As can be observed in Figure 4.C, this deviation for the entire database presented values lower than 4 cm for every level of electrical noise added to the ECG, being the

average value 1.36±0.78cm for 0 dB SNR. Changes in the atrial size increased the error in the HDF region center location to 1.67±0.94cm for 80% and 0.81±0.56cm for 120%. When atrial displacements were present in the inverse calculation, the distance between HDF region centers increased gradually with the displacement, up to 3.12±1.11 cm for 5 cm (Panel 4E). Finally, the angular deviations also showed a constant increment in the error of HDF center region location, which reached 3.15±1.05 cm for 45º.

Incidence of SP detections

The low accuracy and tendency for simplification of propagation patterns by the inverse solution did not allow to fully estimate the complexity of the electrical patterns during our simulated AF. The original EGM maps presented more simultaneous non-driving, short-lasting, rotors (8.5±5.3) than their inverse-computed counterparts, even for high SNRs (i.e. 4.4±2.5 for 60 dB SNR), and this number further gradually decreased down to 1.4±0.3 for 0 dB SNR (see Figure ~~S5~~S7). Uncertainties in the atrial location or orientation, however, had the opposite effect in the detected number of non-driving rotors, with up to 5.6±2.6 for 1 cm or 14.6±1.1 for 5 cm displacements and 4.6±2.4 for 9º or 12.3±4.7 for 45º rotations.

However, despite the sensitivity of rotor detection to signal or model uncertainties, driving rotor identification, defined as the region with most frequently detected rotations, was quite robust. Figure 5 shows the phase map (top) and rotor location maps (bottom) for the original and the inverse-computed signals (Panels A and B respectively). Due to the smoothing effect of the inverse-solution, rotors tended to cluster in stable sites, and the rotor position (in red) was easily identified. In Figure 5.C-F, the accuracy of this estimation is presented for the entire database. Panel 5C shows this error both for the original phase maps (0.7±0.7 cm) and for the inverse-

computed maps under the effect of electrical noise. These average errors remained stable around 1 to 1.5 cm from 60 to 20 dBs. For higher noise level of 10 and 0 dB the average value of the error in rotor location increased to 2.4±3.6 cm and 4.5±4.5 cm respectively, but in both cases 50% of rotors were localized to <2 cm from their original location. Variations in atrial size (Figure 5.D) did not result in significant variations respect to the original location. Displacements in the atrial position provoked a similar error in the inverse-computed rotor position: from 0.9±1.3 cm for a displacement of 1 cm to 4.7±3.3 cm for a displacement of 5 cm (Figure 5.E). Rotations of the atria inside the thorax also resulted in incremental errors in the inverse-computed rotor position: from 1.2±1.3 cm for 9º to 4.9±2.6 cm for 45º (Figure 5.F).

Inverse identification of the driving atrium

Next, the overall ability of the inverse solution in identifying the dominant atrium responsible for AF maintenance was also evaluated both by SP and HDF analysis. The atrial surface was divided into 2 anatomical regions (LA and RA) and the match between the original and inverse-estimated dominant atrium was quantified. As shown in Figure 6.A, there was a good match in the SP detection and rotor site (>90%) for all SNRs except for the most noisy case where the matching ratio decreased to 73% for 0 dB. Atrial size again had little effect on rotor region identification. Rotor region identification was also accurate (>80%) for deviations lower than 4 cm or 36º.

Then the ability to identify the dominant atrium by measuring the extension of the HDF region was evaluated in Figure 7. Here it can be observed that there was a good match (>90%) for all SNRs except for the most noisy case where the match ratio decreased to 87% for 0 dB, results that outperform SP alone identification. The

analysis of the inverse-computed HDF region was able to properly identify the dominant atrium for more than 90% of cases when changes were present in the blood conductance (Online Supplement) or in the atrial location. However, changes in the atrial orientation decreased this match ratio down to 80% for angular deviations higher than 27º.

Combined SP and HDF approach for driver identification

Since driving rotors activate at the fastest rates in the atria and both DF and rotor measurements and localizations were robust against inverse problem uncertainties, these two parameters were combined in order to improve driver location. Figure 8 depicts the error in the atrial rotor location considering only those inverse-computed rotors present in the HDF region, compared with the error when all inverse-computed rotors were considered. As shown, the combination of information from both measurements can reduce the average error in the driver location. However, this reduction in the inverse-computed rotor location error is significant just for the extreme cases, as in the sample case shown in Figure 8.A-B.

DISCUSSION

Main findings

In this work we use mathematical models of the human torso and AF propagation to demonstrate that inverse-computed maps allow for an accurate identification of atrial drivers, even in the presence of noise or model uncertainties. Despite limited accuracy in the morphology of the inverse-computed epicardial potentials caused by noise and uncertainties in the heart position and orientation, atrial drivers can still be identified with significant accuracy because the predominant activation patterns and their frequencies are preserved. Overall, the identification of atrial drivers by

localization of SPs confined to highest DF regions outperforms drivers identification based on SP localization alone.

Accuracy of the inverse problem solution in AF

We have recently shown that icEGMs are poorly related to intracardiac contact electrograms (either measured experimentally or simulated), with large relative errors in the instantaneous phases [2]. In the present work we demonstrate that errors in reconstruction of the epicardial potentials can be mostly attributed to a loss of complexity in the surface potentials relative to the original epicardial potentials, quantified in terms of the number of simultaneous phase singularities. This loss of complexity is consistent with a mutual cancellation of extracellular potentials of propagating wavefronts with opposed directions [6] that is not be retrievable by solving the inverse problem.

Despite this loss of information at the body surface level, surface potentials have shown to keep some relevant attributes of AF drivers both in terms of their activation frequency [7] and rotor location [6]. However, other uncertainties may add computational errors to the inverse problem solution which may restrict the validity of such approach in the context of AF. These uncertainties include, among others, the presence of electrical noise of up to 32dB or the inaccuracies in the geometrical model used of up to 3 cm [8] due to either an inaccurate volume segmentation, the changes in chambers size due to treatment or the use of a static torso model that does not account for the dynamic position of the atria inside the thorax during heart contraction and respiration [9]. Although previous works [8-10] concluded that these uncertainties have a limited impact in inverse problem solutions in the context of non-fibrillating ventricular activity, they did not account for the more complex

scenario of AF, with multiple simultaneous activation wave-fronts and lower signal-to-noise ratios (which can reach 0 dB in a real clinical setting). Moreover, the impact of the anticipated atrial surface acquisition by image techniques could also have a significant impact on position of the atria inside the thorax [1].

We also found that the addition of electrical noise to the surface recordings results in an additional smoothening of the surface potentials, already smoothened by the inverse problem solution in the absence of noise, which results in a further decrease in the number of simultaneous phase singularities. However, despite the non-negligible effect of signal or noise inaccuracies on the reconstructed propagation patterns, we found that activation-based parameters, such as the activation frequency or rotor location, are robust against both signal and model uncertainties, with errors that allow identifying the AF driving atrium and mean errors in location of drivers below 2 cm for up to 20 dB of SNR or 2 cm displacement. This driver identification accuracy can also be expected for reduced and irregular geometries on the atrial shell or a reduced amount of sensing surface electrodes (see Figures ~~S6~~ S8 and ~~S7~~S9). The good performance of activation-based parameters suggests that the information underlying key features of propagation patterns reach the torso surface and can be inverse-reconstructed whereas the fibrillatory conduction that surrounds the main rotational activity cancels out, as we have previously described [6].

Targeting drifting rotors for ablation with some inaccuracy (comparable to rotor drift, 1.18 ± 0.55 cm in our population of models) may result in successful AF termination, since the rotational path can be interrupted by ablation (see supplementary Movie 1, with an error in rotor location of 1.7 cm). In contrast, ablation strategies based on larger identification errors may not result in AF termination (see supplementary

Movie 2, with an error in rotor location of 3.3 cm).

Combination of rotor and DF measurements, however, allows for an improved rotor identification in the most extreme cases of noise or displacement.

Inverse problem and AF mechanisms

There is still no agreement on which are the mechanisms responsible for AF maintenance [11-12]. A growing body of experimental and clinical evidence suggests that drivers in the form of rotors are responsible for AF maintenance [1,13-14]. The success of rotor-guided ablation strategies [1,13] has demonstrated the mechanistic role of rotors in AF maintenance. Nevertheless, other investigators disagree with rotors driving AF [5,12]. Indeed, even the clinical reports suggesting that rotors play a driving role in AF differ in their details. While Haissaguerre et al. [1] have reported on the identification of driving rotors by solving the inverse problem of electrocardiography, their activation maps were simpler and with fewer and less stable rotors as compared to intracardiac panoramic contact activation maps by Narayan [13]. Neither of these two systems has been independently validated for AF waves detection so we cannot know for sure which results are closer to the true, but those differences could be explained based on of the present study. According to our results, the reconstructed epicardial potentials using the inverse solution present a simplified version of the original epicardial potentials, however the presence of key patterns and rotors is preserved, albeit affected by secondary epicardial patterns as well [6].

Study Limitations

We used mathematical models in order to validate the noninvasive estimation of atrial drivers during AF because current technology does not allow validating such approach in a physiologically realistic scenario. An accurate validation would require

precise simultaneous measurements of the transmembrane voltage in the entire atrial tissue (i.e. as optical mapping recordings) with simultaneous torso potentials, which is unattainable.

The mathematical models used a simplistic representation of the torso and the atrial surface, with no intra-structural heterogeneities. Inclusion of uncertainties in the conductance of inner organs may add further errors in the estimation of AF driver locations (i.e., added errors of up to 1 cm for 100% error in lungs conductivity, see Figure ~~S8~~S10).

Finally, although our population of models may not represent the whole possible atrial substrates during AF, we employed a set of 30 different simulations to enhance the relevance of the study to the general AF population.

CONCLUSIONS

AF driver identification based on the inverse problem solution is possible despite the overall simplification of calculated epicardial potentials. The identification of drivers based on a combination of frequency and phase-derived measurements outperforms the identification of drivers based on rotor location only, especially under noise conditions.

ACKNOWLEDGEMENTS

This work was supported in part by Generalitat Valenciana Grants [ACIF/2013/021]; Instituto de Salud Carlos III, Ministerio de Ciencia e Innovación [PI13-01882, PI13-00903, PI14/00857and IJCI-2014- 22178]; Spanish Society of Cardiology [Clinical research Grants 2015]; Ministerio de Ciencia e Innovación [Red RIC RD12.0042.0001] and the National Heart, Lung, and Blood Institute [P01-HL039707, P01-HL087226 and R01-HL118304] and cofound by FEDER.

References

1. Haissaguerre M, Hocini M, Denis A, et al. Driver domains in persistent atrial fibrillation. Circulation 2014;130:530-8.
2. Cuculich PS, Wang Y, Lindsay BD, Faddis MN, Schuessler RB, Damiano RJ Jr, Li L, Rudy Y. Noninvasive characterization of epicardial activation in humans with diverse atrial fibrillation patterns. Circulation 2010;122:1364-72.
3. Berenfeld O, Mandapati R, Dixit S, Skanes AC, Chen J, Mansour M, Jalife J. Spatially distributed dominant excitation frequencies reveal hidden organization in atrial fibrillation in the Langendorff-perfused sheep heart. J Cardiovasc Electrophysiol 2000;11:869-879.
4. Allessie MA, de Groot NM, Houben RP, Schotten U, Boersma E, Smeets JL, Crijns HJ. Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: longitudinal dissociation. Circ Arrhythm Electrophysiol 2010;3:606-615
5. Pedrón-Torrecilla J, Rodrigo M, Climent AM, et al. Noninvasive estimation of epicardial dominant high-frequency regions during atrial fibrillation. J Cardiovasc Electrophysiol 2016;27:435-42
6. Rodrigo M, Guillem MS, Climent AM, Pedron-Torrecilla J, Liberos A, Millet J, Fernandez-Aviles F, Atienza F, Berenfeld O. Body surface localization of left and right atrial high-frequency rotors in atrial fibrillation patients: A clinical-computational study. Heart Rhythm 2014;11:1584-1591.
7. Guillem MS, Climent AM, Millet J, Arenal A, Fernández-Avilés F, Jalife J, Atienza F, Berenfeld O. Noninvasive localization of maximal frequency sites of atrial fibrillation by body surface potential mapping. Circ Arrhythm

Electrophysiol 2013;6:294-301.

8. Cheng LK, Bodley JM, Pullan AJ. Effects of experimental and modeling errors on electrocardiographic inverse formulations. IEEE Trans Biomed Eng 2003;50:23-32.
9. Jiang M, Xia L, Shou G, Wei Q, Liu F, Crozier S. Effect of cardiac motion on solution of the electrocardiography inverse problem. IEEE Trans Biomed Eng 2009;56:923-31.
10. Ramanathan C, Rudy Y. Electrocardiographic imaging: II. Effect of torso inhomogeneities on noninvasive reconstruction of epicardial potentials, electrograms, and isochrones. J Cardiovasc Electrophysiol 2001;12:241-252.
11. Narayan SM, Jalife J. CrossTalk proposal: rotors have been demonstrated to drive human atrial fibrillation. J Physiol 2014;592:3163-3166.
12. Allessie M, de Groot N. CrossTalk opposing view: rotors have not been demonstrated to be the drivers of atrial fibrillation. J Physiol 2014;592: 3167-3170.
13. Narayan SM, Krummen DE, Clopton P, Shivkumar K, Miller JM. Direct or coincidental elimination of stable rotors or focal sources may explain successful atrial fibrillation ablation. J Am Coll Cardiol 2013;62:138-147.
14. Hansen BJ, Zhao J, Csepe TA, et al. Atrial fibrillation driven by micro-anatomic intramural re-entry revealed by simultaneous sub-epicardial and sub-endocardial optical mapping in explanted human hearts. Eur Heart J 2015;36:2390-2401.
15. Li N, Csepe TA, Hansen BJ, Sul LV, Kalyanasundaram A, et al. Adenosine-induced atrial fibrillation: localized reentrant drivers in lateral right atria due to heterogeneous expression of adenosine A1 receptors and GIRK4 subunits in

the human heart. Circulation 2016;134(6):486-98.

Figure 1. Illustration of the numerical set-up and examples of uncertainties in inverse-computed maps. **(A)** Schematic view of the torso (green) and the reference atrial (red) surface at its original position. **(B)** Original potential map for an AF episode maintained by a rotor in the LA. **(C)** Inverse-computed potential map for the simulation in (B). Inverse-computed potential maps for the simulation in (A) solved: **(D)** with 10dB of signal-to-noise ratio; **(E)** with a 20% enlarged atria; **(F)** at displaced (2 cm) position; **(G)** at rotated (27º) position.

Figure 2. Correlation of inverse-computed EGMs with original EGMs. **(A)** Comparison between original (EGM) and inverse-computed signals (icEGM) from a point in the PLAW under two levels of ECG noise. Average correlation coefficients under variations in: **(B)** ECG noise; **(C)** Size; **(D)** Displacement; **(E)** Rotation.

Figure 3. Concordance of inverse-computed HDF region with original HDF region. **(A)** Original DF map. **(B)** Inverse-computed DF map solved with 60dB of Noise-to-Signal Ratio. Average concordance values under variations in: **(C)** ECG noise; **(D)** Size; **(E)** Displacement; **(F)** Rotation.

Figure 4. Error in non-invasive HDF center identification. **(A)** Original DF map with the barycenter of the HDF (black cross). **(B)** Inverse-computed DF map solved with 60dB of Noise-to-Signal Ratio with the barycenter of the HDF (black dot). Error average under variations in: **(C)** ECG noise; **(D)** Size; **(E)** Displacement; **(F)** Rotation.

Figure 5. Error in non-invasive rotor position identification. **(A)** Original EGM phase map for an AF episode maintained by a rotor in the LA (top) and the histogram quantifying the rotor presence (bottom). **(B)** ECGI phase map with 60dBs SNR for the simulation in (A) (top) and the histogram quantifying the rotor presence (bottom). Error average under variations in: **(C)** ECG noise; **(D)** Size; **(E)** Displacement; **(F)** Rotation.

Figure 6. Non-invasive identification of the dominant atrium by rotor histogram under variations in: **(A)** ECG noise; **(B)** Size; **(C)** Displacement; **(D)** Rotation.

Figure 7. Non-invasive identification of the dominant atrium by HDF region analysis under variations in: **(A)** ECG noise; **(B)** Size; **(C)** Displacement; **(D)** Rotation.

Figure 8. Rotor identification in the HDF region. **(A)** Non-invasive rotor histogram with 0dBs SNR and **(B)** with 0dBs SNR with only rotors inscribed inside the HDF region. Error in non-invasive rotor position identification by rotational activity (blue) and by rotational activity plus dominant frequency (red) under variations in: **(C)** ECG noise; **(D)** Size; **(E)** Displacement; **(F)** Rotation.