Published in final edited form as:

Ann Biomed Eng. 2016 August ; 44(8): 2364–2376. doi:10.1007/s10439-015-1534-x.

Identification of Dominant Excitation Patterns and Sources of Atrial Fibrillation by Causality Analysis

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Abstract

Burden of atrial fibrillation (AF) can be reduced by ablation of sources of electrical impulses driving AF but driver identification is still challenging. This study presents a new methodology based on causality analysis that allows identifying the hierarchically dominant areas driving AF.

Identification of dominant propagation patterns was achieved by computing causal relations between intracardiac multi-electrode catheter recordings of 4 paroxysmal AF patients during sinus rhythm, pacing and AF. In addition, realistic mathematical models of the atria during AF were used to validate the methodology both in the presence and absence of dominant frequency (DF) gradients.

During electrical pacing, sources of propagation patterns detected by causality analysis were consistent with the location of the stimulating catheter. During AF, propagation patterns presented temporal variability, but a dominant direction accounted for significantly more propagations than other directions ($49 \pm 15\%$ vs. $14 \pm 13\%$ or less, $p < 0.01$). Both in patients with a DF gradient and in mathematical models, causal maps allowed the identification of sites responsible for maintenance of AF.

Causal maps allowed the identification of atrial dominant sites. In particular, causality analysis resulted in stable dominant cause-effect propagation directions during AF and could serve as a guide for performing ablation procedures in AF patients.

Key terms

hierarchical pattern; Granger causality; atrial fibrillation; dominant pattern; ablation

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INTRODUCTION

Ablation strategies for atrial fibrillation (AF) are based on the isolation of areas presumably responsible for the initiation or maintenance of the fibrillatory process [1–3]. Widely used clinical practice to terminate AF prefers the ablative isolation of the pulmonary veins (PVs) based on empirical evidence for triggered activity in that region [3], but has a limited success rate that ranges from 28% in persistent AF patients up to 85% in paroxysmal patients [4].

The failure to terminate AF by PV isolation in some AF patients can be attributed to the presence of AF drivers outside the PV area [5–6] or lack of specific drivers all together. Recent AF panoramic mapping studies providing multiple signals obtained simultaneously across the atria support the former; either multipolar catheter baskets [2] or noninvasive recordings [7] have been identifying AF sources to guide ablation procedures. However, these panoramic mapping approaches totally rely on wave-by-wave analysis over wide areas and are still controversial [8–10]. The more commonly used cardiac mapping techniques are sequential and thus cannot use the wave-by-wave analysis to identify precisely the mechanisms of AF initiation and maintenance. The main problem is that the propagation of the electrical activity from possible sources to the rest of the atrial tissue during AF is irregular with beat-to-beat variation in propagation patterns. Moreover, even if specific atrial sources exist, they may be in the form of dynamic ectopic or reentrant activity that localizes to unspecified atrial regions and thus mapping that is not fully panoramic, detailed and account for the complex dynamicity of AF waves does not guarantee their identification. In this context of the complex electrical activation during AF, the use of sequential mapping devices comprising a small number of electrodes (<20) spanning only a couple of cm wide is not allowing accurate characterization of the underlying propagation pattern. This limitation has led to the development of different strategies for identification of AF sources. One such approach proposed the localization of regions with fractionated electrograms [11], assuming that fractionation occurs at arrhythmogenic areas, however its application has not been shown to be more effective than PV isolation alone [12]. Another approach is based on the localization of atrial sites with highest activation rates, presumably harboring AF drivers, and has been shown to be effective only in some, but not all, AF patients [6, 13–15].

Thus, the aim of this work is to study the feasibility of a novel tool for better localization of the electrical sources driving AF based on the search for the strongest causality relations between multiple electrograms [16]. The analysis of the cause-effect relationship between different electrical signals, obtained by either simultaneous or sequential mapping of the atria, is demonstrated here to enable estimation of the dominant propagation patterns of organized or fibrillatory activity and can potentially locate the region that is the dominant source of electrical activations during AF.

MATERIALS AND METHODS

Human atrial electrograms

Intracardiac electrograms (EGMs) were obtained during atrial electroanatomic reconstruction prior to the ablation procedure in 4 patients with paroxysmal AF. All patients

gave informed consent and the protocol was approved by the Institutional Ethics Committee. Antiarrhythmic agents were withheld >5 half-lives before the electrophysiological study. Two catheters were positioned at the high right atrium and distal coronary sinus and an ablation catheter was located at the pulmonary veins (PV). The 3-dimensional geometry of the left atrium (LA) was reconstructed with an electroanatomic navigation system (NavX, St. Jude Medical, Minneapolis, Minnesota). The posterior left atrial wall (PLAW) and the PVs were mapped with a 20 pole-spiral catheter covering an area of $2\text{--}5\text{ cm}^2$ (AFocus, St. Jude Medical Minneapolis, Minnesota) and 10 bipolar electrograms were recorded for off-line analysis (see Figure 1A). Segments without contact with the atrial wall ($>1\text{ cm}$ between atrial wall and electrodes) or without spatial information were excluded.

Mathematical models of the atrial electrical activity

An ensemble of 32 different mathematical models was simulated (see Supplemental Material for detailed methods), composed of 14 AF patterns driven by a single rotor at varying locations of the LA (PVs, PLAW and LA appendage), 17 AF patterns driven by a single rotor at varying locations of the RA (free RA wall and RA appendage) and 1 AF pattern driven by multiple drivers.

Definition of Causality Maps

We base our source detection strategy on cause-effect relationships between atrial electrograms obtained simultaneously with multipolar catheter roving in sequential regions across the atria. These cause-effect relationships are used to obtain local information of both the underlying propagation pattern and the source likelihood at each recorded site. Local and regional measurements are then integrated to generate global propagation patterns and source likelihood map across the entire sequentially mapped atria. Overall causal analysis maps consist of generating the causality propagation direction (CPD) map, a discrete vector map indicating the dominant cause-to-effect propagation direction for each EGM location; and the causality recurrence index (CRI) map, which is the interpolated scalar map showing the local level of dominance of the dominant propagation direction. The source(s) location is selected at the sites with highest CRI and the origin of the cause-to-effect flow along the dominant propagation trajectory. Additionally, the temporal consistency of the detected patterns is measured with the propagation organization index (POI).

Calculation of Local Causal Relationships

We adopted Granger's definition of causality [17] that assumes that causal relationships can be estimated from an autoregressive model. Accordingly, causal relations were searched between N simultaneous neighbouring signals, which were divided into K_n overlapping time segments of length equal to the inverse of the local dominant frequency. In the mathematical models data, neighbouring signals were from sites 2 cm or less apart, whereas in patient data neighbouring signals were all those simultaneously recorded by the spiral catheter.

Under the assumption that a given EGM signal can be estimated from signals in neighbouring locations at previous instants, their relationship can be represented by a univariate autoregressive model (ARM) following Granger's definition of causality [17] as:

$$x_i(t) = \sum_{\tau=t_{min}}^{t_{max}} a_{\tau} \cdot x_j(t-\tau) + \varepsilon_{ij}(t) \quad (1)$$

where $x_i(t)$, is the local EGM signal at location i at time instant t and $x_j(t-\tau)$ is the neighbour EGM signal at location j at τ previous time instant, a_{τ} 's are the ARM coefficients and $\varepsilon_{ij}(t)$ is the error in the prediction of the EGM at location i based on the EGM at location j . In short, previous time instants of the j^{th} EGM are used to estimate the current value of the i^{th} EGM. The variance $\sigma_{\varepsilon_{ij}}^2$ in predicting local EGM from a neighbour EGM is used as a measure of causality [17] since there is an inverse relation between the prediction error from the ARM model and their causal dependency. Importantly, the causality relationships between locations i and j are not necessarily symmetric (that is, in general $\varepsilon_{ij} \neq \varepsilon_{ji}$) which constitutes a unique direction of cause and effect between neighbouring locations.

The order of the ARM model is given by $t_{max}-t_{min}$, where $t_{min} = d/v_{max}$, $t_{max} = d/v_{min}$, d is the distance between electrodes, and v_{max} and v_{min} are the maximum and minimum conduction velocities respectively. This definition of v_{max} and v_{min} prevent from searching for causal relationships beyond physiologically possible solutions (e.g., finding strong causal relations between two distant nodes that are simultaneously activated by an equidistant source). The values of v_{max} and v_{min} were 120 and 20 cm/s respectively [18] and ARM coefficients were estimated by using the least-squares method [16].

Local causality measurements

Since variances in the prediction error $\sigma_{\varepsilon_{ij}}^2$ can be inversely attributed to a dependency between source and destiny signals, $\sigma_{\varepsilon_{ij}}^2$ is used to assess the degree of causality between two signals (i.e., large variance is associated with a weak dependency). However, in order to compare on equal terms the degree of causality between signals with inherent differences in their variance, we use a statistical approach based on influence measure [19]. This measure compares the variance measured by applying the ARM model with source and destiny signals $\sigma_{\varepsilon_{ij}}^2$ with the variance value $\sigma_{\varepsilon_{ii}}^2$ obtained by applying the model on the signal itself. We defined the Influence Ratio matrix (IR), computed for a given pair of signals (i,j) as the ratio between variances of the error of ARM models for the source signal ($\sigma_{\varepsilon_{ij}}^2$) and for itself ($\sigma_{\varepsilon_{ii}}^2$) (see Figure 1C):

$$IR_{ij} = \frac{\sigma_{\varepsilon_{ii}}^2}{\sigma_{\varepsilon_{ij}}^2}. \quad (2)$$

In order to evaluate causal relationships on an entire recording, the IR is measured for all K_n overlapping intervals ($IR_{j,k}$). The influence of a signal x_j in a signal x_i is then summarized by normalizing the IR matrix (IRN) so that $\sum_{i=1}^N IRN_{ij} = 1$:

$$IRN_{ij} = \frac{\frac{1}{K_n} \sum_{k=1}^{K_n} IR_{ij,k}}{\frac{1}{K_n} \sum_{k=1}^{K_n} \sum_{i=1}^N IR_{ij,k}} \quad (3)$$

Propagation Organization Index

The temporal stability of the propagation pattern in each electrode is estimated by measuring a local propagation organization index (*POI*):

$$POI_i = \left| \frac{\frac{1}{K_n} \sum_{k=1}^{K_n} \sum_{j=1}^{J_n} IR_{ij,k} \cdot \hat{u}_{ij}}{\sum_{j=1}^{J_n} IR_{ij,k} \cdot \hat{u}_{ij}} \right| \quad (4)$$

where $\hat{u}_{ij}$ is the unit spatial vector connecting nodes i and j and J_n is the number of neighbours of node i . The propagation organization index (POI), which reflects the temporal stability of the whole atria, is defined as the average of local POI_i values:

$$POI = \frac{1}{N} \sum_{i=1}^N POI_i. \quad (5)$$

POI values range from 0 (random propagation) to 1 (stable propagation) and can be interpreted as the time reproducibility of the global estimated pattern.

Construction of Causality Maps

The causality propagation direction (CPD) is a vector at each recording site which indicates the dominant propagation direction of cause-effect flow in that site over the period of time analyzed. The $\vec{v}_i$ vectors that compose the CPD vector map are the sum of IR indices projected on the direction of the unitary vector that connects each pair of recording electrodes ($\hat{u}_{ij}$), as depicted in Figure 1D, according to the following expression:

$$\vec{v}_i = \frac{1}{K_n} \sum_{k=1}^{K_n} \sum_{j=1}^{J_n} IR_{ij,k} \cdot \hat{u}_{ij}. \quad (6)$$

The source strength, quantified by the causality recurrence index (CRI), represents the permanent regime of a Markov process in which each location (or recording site) would represent a Markov state and the transition between the independent states is given by the causality measurements. The CRI quantifies the probability of a given location of acting as a source (CRI=1 represents a consistent electrical source and CRI=0 an electrical sink). The CRI is computed as follows for simultaneous (local) recordings:

$$CRI = M^\infty \times P_0; \quad (7)$$

where M^∞ is the permanent regime value of transition state matrix M and P_0 is the initial probability distribution where $P_{0i} = 1/N$. M^∞ is computed as follows:

$$M^\beta = M^{\beta-1} \times M^{\beta-1} \quad (8)$$

$$\xi = \text{var}(P^\beta - P^{\beta-1}). \quad (9)$$

M^∞ is obtained when the value of ξ reaches an upper threshold (10^{-10}). Initial values of the transition matrix for each pair of sites –or states– ($M_{i,j}^0$) is set to the corresponding IRN value for constructing local recurrence maps at which all EGMs are recorded simultaneously. For non-simultaneous recordings, the value of the transition matrix ($M_{i,j}^0$) is constructed by using the local values of the CPD and POI:

$$M_{i,j}^0 = \frac{\vec{v}_i \cdot \hat{u}_{ij} \cdot POI_i}{\sum_{i=1}^{N^r} \vec{v}_i \cdot \hat{u}_{ij} \cdot POI_i} \quad (10)$$

where $N^r = N^p \cdot N^s$, N^p is the amount of poles in the multipolar catheter and N^r is the amount of sequential recordings obtained. An example of a causality map is given in Figure 1F.

Dominant regions of sources were defined as those areas with CRI values above 40% of the maximum CRI value based on noise analysis in simulations.

Statistical analysis

Continuous variables are reported as mean $\pm$ SD. The t-Student test was used for assessing the statistical significance of continuous data and a value of $p < 0.01$ was considered statistically significant.

RESULTS

Propagation Patterns and Direction of Causality

Figure 1 illustrates the methodology of the causality analysis in a sample region during AF in a patient. The 10 simultaneously recorded bipolar signals in Panel A are shown to describe a beat-by-beat variation in propagation patterns in Panel B, originating generally in the right side of the map. Calculation of IR indices between sample EGMs is displayed in Figure 1C. As can be observed, EGM #10, with consistent earliest activations in the catheter, present the strongest IR values over neighbouring EGMs (red), whereas lack of consistent earliest activation in EGMs #5 and #3 results in lower IR (blue). Figure 1D further illustrates the combination of the IR between EGM #10 and all the other EGMs into a single dominant direction of cause-effect vector (CPD). The time course of the dominant direction for each EGM, as shown in Figure 1D, was then quantified with a propagation organization index (POI) and causality recurrence index (CRI) in Figure 1E to indicate the cumulative spread of

directions and the level of dominance of the dominant flow direction, respectively. Accordingly, EGM #10 with POI=0.87 and CRI=0.67 has a flow direction that is more consistent along a dominant direction in comparison to EGM #5 with POI=0.37 and CRI=0.56. To summarize the causality flow analysis, the CPD vectors at each EGM location are superimposed on the CRI map as shown in Figure 1F. Figure 1F shows the CRI to be highest (red, EGM #6) on the right side of the map of the same region and the CPD arrows to point from the cause (right) to the effect, on the left side of the map consistent with the general visual notion by Figure 1B.

During organized atrial rhythms, causality maps (CRI and CPD) were always consistent with the underlying propagation pattern of activation. During sinus rhythm causality maps in the PLAW exhibited a uniform propagation from the roof of the LA, as can be seen in Figure 2A. During pacing, causality analysis results in a uniform propagation pattern originating at the pacing site (Figure 2B) whereas during induced AF in the same patient, the detected causality pattern differed from those during sinus rhythm and stimulation (Figure 2C) and was suggestive of an activation originating at the center of PLAW.

Identification of Pacing Sites in AF Patients

The accuracy of the presented method was evaluated during pacing in AF patients (Figure 3), where the regional incoming direction of the waves is known. During pacing which induced AF, however, the expected direction of the incoming AF waves cannot be presumed to be the induced pacing site. In order to quantify the similarity of the detected directions during AF with the pacing site inducing AF, we divided the recorded signals into three different segments: (I) Pacing not inducing AF, defined as the last 5-seconds of electrical pacing that did not induce AF (n=17); (II) Pacing inducing AF, defined as the last 5-seconds of electrical pacing that triggered AF, including several seconds of arrhythmia (n=17); and (III) AF, defined as the first 5-seconds of induced AF, after cessation of pacing (n=17, see Figure 3A). For each individual segment, the location of highest CRI value was estimated and compared with the location of the pacing catheter (Figure 3B) that was active during the studied segment (in groups I and II) or immediately before the analyzed segment (group III). As expected, in all segments during pacing with no fibrillatory activity (group I) the propagation had an ipsilateral propagation (defined as a direction with an angular deviation with the stimulation catheter below 90° [20], see Figure 3C) and the direction of the incoming wavefronts showed a divergence of $24.1 \pm 28.9^\circ$ with the actual location of the catheter, which is below the average interelectrode angular distance. Interestingly, in the segments including pacing with simultaneous AF (group II), most segments (82%) presented an ipsilateral propagation, indicating that most atrial waves originated at the pacing site, with a divergence between the detected wavefronts and the stimulating electrode of $33.9 \pm 47.6^\circ$, again below the interelectrode angular difference. A few seconds after cessation of pacing (group III), an ipsilateral propagation direction with the previously active pacing site was still predominant (65%) but contralateral directions were frequently observed, which could either reflect drifting of the driving site after a few activations or wavefront fragmentation that results in varying activation patterns at the recording catheter.

The regularity of the detected patterns was dependent on the organization degree in the atria and was estimated by comparing the detected direction of wavefronts over time. The propagation organization index (POI) was computed for each analyzed segment. As shown in Figure 3D, during sinus rhythm the POI was significantly higher (0.86 ± 0.14) than during either AF (0.42 ± 0.12 , $p < 0.01$) or pacing during AF (0.48 ± 0.17 , $p < 0.01$). POI during pacing without AF showed similar values than those during sinus rhythm (0.82 ± 0.13), and was higher than both pacing during AF ($p < 0.01$) and AF ($p < 0.01$).

Stability of Causality Measurements in Human AF

The temporal stability of the detected patterns was evaluated on episodes of sustained AF (>30 s) in order to establish the reproducibility of the detected patterns over time. Eighteen AF episodes with durations between 35 and 100 seconds (87.5 ± 22.3 s) were divided into 5-seconds sections (17.5 ± 4.5 segments per AF episode). The incoming wave directions were divided into 60° angle sections (Figure 4A), where #1 was the dominant incoming direction and areas #6 and #2 its neighboring areas. Results of this directionality analysis are summarized in Figure 4B. It is noticeable that although the mean organization propagation index was relatively low (0.43 ± 0.12 , Figure 3D), the main propagation direction was maintained in $49.12 \pm 15.71\%$ of the analyzed segments, whereas activations from each of the non-dominant directions accounted for less than 15% of the analyzed segments ($p < 0.01$, Figure 4B). These results suggest that, although the organization during AF is significantly lower than during sinus rhythm, the activation pattern presents some degree of temporal stability and activations are not completely random.

Electroanatomical Identification of Dominant Sources in Human AF

With the purpose of locating the atrial areas acting as dominant sources, the LA was mapped by sequentially re-positioning the spiral catheter across the atrium. Since the causality method allows the identification of the most recurrent propagation pattern at each location, maps obtained using causality analysis may serve as a guide for AF sources exploration, by indicating the direction of incoming waves. Figure 5 shows a sample case of the causality analysis performed while the catheter was roving inside different pulmonary veins. Analysis at the RIPV (Figure 5A) suggests that recorded wavefronts do not originate at the mapped vein. When the catheter was placed inside the LSPV (Figure 5B), the detected propagation pattern suggested that most wavefronts came from the LIPV. Finally, when the spiral catheter was located inside the LIPV (Figure 5C), CPD showed a centrifugal pattern away from the LIPV which suggested that electrical waves had their origin at this PV. Consistent with the causality analysis, dominant frequency (DF) maps obtained at the LIPV demonstrated that the highest activation rate was also found at the LIPV (11 Hz).

Results from the causality analysis performed at several locations across the atria during AF can be summarized into a single map (Figure 6A) that allows identifying the global propagation pattern and the main source driving the AF. The CPD showed a propagation pattern originating at a small region in the left PVs (4.5 cm^2) with the highest CRI values consistent with the outcome of ablation at the LIPV, which resulted in termination of the arrhythmia. Furthermore, it can be observed that the estimated CPD vectors are consistent with the recorded EGMs shown in Figure 6B: EGM from site #1 demonstrate a fast and

regular activation at the left PVs while the activations at #2 and #3 are regular but a slower rate, consistent with a centrifugal activation emanating from #1. EGM at #4, however, shows fractionation, which is consistent with a collision of waves from #1 and #3.

Causality Analysis for the Identification of Rotors Driving AF

To illustrate that our causality analysis method allows locating rotors driving AF we used 3 electrical signal patterns from the anatomically realistic mathematical models of the 2 atria: a functional rotor at the LA roof with (Figure 7A–C) and without (Figure 7D–F) a LA-to-RA DF gradient, and a complex activation pattern without a single driving rotor (two functional reentries at the left atrial roof, two functional reentries at right atrium and an anatomical reentry around the RIPV, Figure 7G–I). Driving rotors appear in our CPD maps as small areas (8 cm^2) with increased CRI values regardless of the presence or absence of a DF gradient (see Figure 7C and Figure 7F). A more complex activation pattern with multiple, non-driving reentries is reflected as a more widespread region (48 cm^2) of high CRI values (Figure 7I). These results suggest that causality analysis may be independent of the activation rate of the atrial sources and may assist in identification of AF sources in cases of uniform activation rates across the atria and also in multiple sources scenarios.

The ability of our causal method to locate atrial drivers was evaluated in an ensemble of 31 mathematical atrial models driven by a single driver at varying locations. AF signals from 227 non-simultaneous sites covering both atria were evaluated. At each site, signals from 7 nodes were used for extracting causal relations. In these models, extension of the hierarchically dominant regions was found to be $17.1 \pm 6.6 \text{ cm}^2$ and in 100% cases encompassed the pre-assigned known source site. Distance from the highest CRI site and the actual source was $1.63 \pm 1.63 \text{ cm}$.

For comparison with other methods used for locating atrial drivers in clinical practice, we compared our source detection with a detection based on the highest DF region identification. Figure 8 summarizes the measurements obtained with each of the two methods. We first confirmed that noise of up to 20% of the EGMs amplitudes doesn't alter the $\text{CRI} > 0.4 * \text{CRI}_{\text{max}}$ spatial distribution (Panels A and B). Using this threshold for highest CRI and 0.5 Hz threshold for highest DF regions [21] we found the highest DF areas and highest CRI areas to overlap with 82% of the highest CRI areas encompassed inside highest DF areas. Overall the high CRI regions spread over smaller areas than highest DF areas (Panel C, 17.1 ± 6.6 vs. $115.1 \pm 82.7 \text{ cm}^2$, respectively, $p < 0.001$). Importantly, the distances to actual drivers locations (distance of highest CRI site vs. average of each point of the highest DF area) were also significantly smaller for the causality-based identification than for the DF method (Panel D, 1.6 ± 1.6 vs. $4.0 \pm 1.4 \text{ cm}$, $p < 0.001$).

DISCUSSION

A novel method to locate AF drivers based on causality analysis has been presented. This method follows the Granger approach [17] and allows identification of the atrial sites responsible for the perpetuation of AF by locating atrial electrical sources causing activity elsewhere. Hierarchical recurrence maps highlight those driving regions across the entire atria by calculating the most probable cause-effect direction in consecutive activations

recorded simultaneously by a multi-electrodes catheter and then integrating the analysis of sequential recordings obtained at different regions in the atria into a single map.

AF Mechanisms and Causality Analysis

Several clinical studies have provided evidence for the existence of discrete sources responsible for the maintenance of AF that can be located either at the pulmonary veins [3] or elsewhere in the atria [5, 6]. These atrial sources have been postulated to consist of either ectopic activity [3], reentries or rotors [1] and can be considered as the origin of a hierarchical process in the fibrillatory activity across the atria [22]. Our proposed methodology is designed to localize such origins of activation patterns, regardless whether the underlying mechanism is focal or reentrant.

Methods for AF ablation guidance

Identification of drivers remains a challenging task due to the irregular electrical activity during AF. However, in spite of the irregular nature of the electrical activation some degree of spatiotemporal consistency in AF activations [23] can be used as guidance for source identification. For example, driver detection is proposed based on the fact that EGMs near atrial sources present generally a faster and more regular morphology than EGMs elsewhere [14, 24]. Driver identification can also rely on waves directionality based on isochronal maps [25]. Recently, Narayan et al. showed that isochronal maps computed from intracardiac recordings allow localizing reentrant drivers whose ablation interrupts the arrhythmia [2]. However, the construction of isochronal maps requires the detection of activation times, which is somewhat subjective during fibrillation, and is limited to a single activation wave. As an alternative, computation of phase maps [26] does not require the detection of activation times, but is still limited to a simultaneous mapping approach with significant difficulties in low signal to noise ratio [8–9].

As opposed to morphology-based strategies of isochronal or phase analysis, our causality method does not require neither activation time detection nor a simultaneous mapping and thus it promises objective robustness against noise or complex EGM morphologies, as has been described in Figure 1. In our causal method, first principles of Granger true causality are applied on regional time series to obtain a global causal map that combines a vector field of cause-effect flow and a recurrence index. These parameters in turn, account for the dominant propagation directions and their likelihoods, respectively, and summarize the causal relations between regions even when recorded sequentially. Thus, roving the regional mapping catheters, in which a good electrodes contact is more attainable than in full panoramic mapping, to the origin of the causality directions may be an efficient guidance for localization of the source of a complex AF. We have shown here that the detected dominant direction is reproducible during a period of few minutes in our paroxysmal AF patients. The applicability of our approach to all patients with AF remains to be studied.

The stationarity of our recurrence maps over a period of various minutes is consistent with the presence of a predominant activation direction and a non-random AF nature. It is also consistent with sources identified by dominant frequency (DF) analysis [13]. Atienza et al. [1, 6] demonstrated that AF sources often present the highest DFs and ablation abolishing

DF gradients has a favorable long-term outcome [15]. Naturally, in AF without a DF gradient this approach is null [6]. Here we demonstrate in computer simulations that in the presence of a DF gradient, both DF and causality analyses offer similar results; the causality analysis points retrogradely to the AF origin source site which coincides with the highest DF site. Nevertheless, the causality analysis method presents an advantage over the DF analysis alone as it allows detecting the origin of AF activations even in the absence of DF gradients, or with increased specificity than the DF approach (Figures 7 and 8).

Methodological Considerations

Identification of causal relationships during irregular activations would benefit from a multipole catheter with as many recording electrodes as possible. However, the existing panoramic mapping balloon or basket multi-electrodes catheters are expensive, difficult to use and not readily available. In the present study we demonstrate feasibility of using our causal method using a 20 pole-spiral catheter which allows recording of a sufficient number of simultaneous signals for regional causal directionality analysis.

Study limitations

First, our analysis excludes evaluating the causality relations between EGMs recorded at two sites that would imply the electrical impulse to travel at non-physiological speeds, but thresholds may need adjustments based on further studies. Second, EGMs may have been contaminated by far-field artifacts, which is a common limitation in all electrical recordings during AF. Nevertheless, our causality approach is inherently overcoming this limitation as it is considering several sequential activations in which the distal contributions are likely to be un-synchronized with the local activity. Finally, our clinical results have been presented on a limited number of patients and encompassing the left atrium only. Validation in a larger number of patients, possibly with more complex AF and mapping both atria is the required next step.

Clinical perspective

A novel methodology based on the causality theory for the identification of the atrial sites which are responsible of AF maintenance has been presented. This method allows summarizing simultaneous and sequential electrical recordings in the atria during AF into a single map where dominant atrial regions and the dominant propagation patterns are shown. The methodology could be useful for better guiding ablation procedures in AF patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported in part by: Universitat Politècnica de València through its research initiative program; Generalitat Valenciana Grants (ACIF/2013/021); the Instituto de Salud Carlos III (Ministry of Economy and Competitiveness, Spain: PI13-01882, PI13-00903 and PI14/00857); Spanish Society of Cardiology (Grant for Clinical Research in Cardiology 2015); Spanish Ministry of Science and Innovation (Red RIC, PLE2009-0152) and the Centro Nacional de Investigaciones Cardiovasculares (CNIC-13).

FA served on the advisory board of Medtronic and has received research funding from St. Jude Medical Spain. OB received research support from Medtronic and St. Jude Medical. He is a Scientific Officer of Rhythm Solutions, Inc. and a consultant to Acutus Medical, inc. The other authors have no conflict of interest. None of the companies disclosed financed the research described in this manuscript.

Acronyms

AF	Atrial Fibrillation
ARM	Auto-Regressive Model
CPD	Causality Propagation Direction
CRI	Causality Recurrence Index
DF	Dominant Frequency
EGM	Electrogram
IR	Influence Ratio
LA	Left Atria
LIPV	Left Inferior Pulmonary Vein
LSPV	Left Superior Pulmonary Vein
POI	Propagation Organization Index
PLAW	Posterior Left Atrial Wall
PV	Pulmonary Vein
RA	Right Atria
RIPV	Right Inferior Pulmonary Vein
RSPV	Right Superior Pulmonary Vein

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Figure 1.

Illustration of the causal analysis method. **(A)** Atrial bipolar electrograms recorded with the spiral catheter during AF. Five successive activations segments are highlighted. **(B)** Isochronal map for each of the five time segments in **A** show variability in the general direction of propagation (arrows). Circled numbers indicate locations of electrodes recording the electrograms in **A**. **(C)** Time course of Influence Ratio (IR) between signals in sample electrodes 5–10 and 10–3 (Red traces: $IR_{10,5}$ and $IR_{10,3}$. Blue traces: $IR_{5,10}$ and $IR_{3,10}$; see Equation 2). Sample overlapping time segments used for the analysis are marked with two black arrows at the top. **(D)** Construction of the Causal Propagation Direction (CPD, pink arrow) for electrode #10 based on vector summation of the IR values with the simultaneously recorded EGMs at neighboring locations (black arrows) during a single time segment (see Equation 6). **(E)** Calculation of the Propagation Organization Index (POI, Equation 4) for sample electrodes 5 and 10 based on the time-course variation in CPD. **(F)** Complete causal map obtained with the signals in **A**. Causality Recurrence index (CRI; Equation 7) is color-coded red (high) to blue (low) with superimposed causal propagation direction (CPD; Equation 6) for each electrode represented by pink arrows pointing from cause (tail) to effect (head). Arrows lengths in different panels are not in same scale.

Figure 2. Causality Recurrence Index (CRI) maps with superimposed Causality Propagation Directions (CPD) during different rhythms projected on the posterior view of the left atrial shell. **(A)** Sinus rhythm; **(B)** Pacing (square pulse); **(C)** Spontaneous atrial tachycardia. The Causal Propagation Direction (CPD) is represented by black arrows. The location of the spiral and pacing catheters are depicted.

Figure 4. Temporal stability of incoming propagation directions during sustained AF. **(A)** Illustration of the angular sectors defined. **(B)** Temporal distribution of the incoming propagation directions for each angular sector.

Figure 5. Causality and DF maps obtained for three different pulmonary vein junctions mapping. (A) Right Inferior Pulmonary Vein (RIPV). (B) Left Superior Pulmonary Vein (LSPV); (C) Left Inferior Pulmonary Vein (LIPV). Left, color-coded Causality Recurrence Index (CRI) with superimposed causal propagation direction (CPD) represented by black arrows. Right, corresponding color-coded DF maps.

Figure 6.

Causal map of the entire left atrium obtained by summarizing sequential regional mapping of the entire chamber by a roving multi-electrode catheter. **(A)** Color-coded CRI with superimposed CPD arrows. **(B)** EGMs recorded sequentially at locations 1–4 in **A**.

Figure 7.

Anterior and posterior views of 3 simulations with different propagation patterns of activity in a realistic mathematical model of the atria. **(A–C)** Fibrillatory pattern sustained by a stable rotor at the roof of the left atrium (LA) with a left to right DF gradient. **(D–F)** Fibrillatory pattern sustained by a stable rotor at the roof of the left atrium (LA) with no DF gradient. **(G–I)** Complex fibrillatory pattern with multiple functional and anatomical reentries. **(A, D, G)** DF maps. **(B, E, H)** Snap shots of transmembrane potentials. **(C, F, I)** Causality Recurrence Index (CRI).

Figure 8.

Comparison between DF and causal measurements for driver localization in 32 different realistic mathematical models of the atria. **(A and B)** Causality Recurrence Index (CRI) maps of the simulation presented in Figure 7G-I **(A)** and the same simulation with additional 20% noise in the EGMs **(B)**. The regions with highest CRI values seem to be conserved at values $>0.4 \cdot \text{CRI}_{\text{max}}$. **(C)** Extension (in cm²) of the driver region detected by Dominant Frequency method (DF, $|\text{DF} - \text{DF}_{\text{driver}}| < 0.5 \text{ Hz}$) and with the high CRI ($\text{CRI} > 0.4 \cdot \text{CRI}_{\text{max}}$) region. **(D)** Distance to the rotor core (in cm) from source location estimated by the CRI and DF maps.