Causality in Atrial Fibrillation determined by transfer entropy

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Abstract

High level of complexity makes characterization of wave conduction during Atrial Fibrillation (AF) very difficult. Here we aim to use statistical approach characterizing AF as a system with determined information flow using a concept of transfer entropy.

Left and right atrial 60 s electrograms were recorded at high right atrium (HRA), coronary sinus (CS) and Left Atrial Appendage (LAA) in 42 patients undergoing catheter ablation of AF. Transfer entropy (TE) was used to asses causality calculating direction and extent of information flow between neighboring sites in the atria. TE was calculated between electrograms recorded along each catheter. Additionally, numerical analysis were performed on a set of unidirectionally coupled stochastic signals modeling electrical activity during AF. We found an asymmetry in information flow along the catheters. In HRA catheter, in general, information flows from proximal to distal portion of the catheter and in CS from the distal towards the proximal portion. The dominant flow of information from the base into the LAA was the most pronounced and in agreement with believed passive role of LAA in maintenance of AF.

Information flow in the atria during AF is asymmetric and it is possible to determine the direction of the flow using concept of entropy transfer.

1. Introduction

Atrial fibrillation (AF) is the most common and the most complex sustained arrhythmia [1]. The mechanisms of AF remain not fully understood and the treatment is suboptimal. Nowadays, one of the most frequently performed treatment procedures in patients with Atrial Fibrillation is catheter ablation [2], with the success rate up to 90% in paroxysmal AF and up to 64% in persistent AF (after multiple procedures) [3].

Catheter ablation evolves rapidly. One of the important challenges for this method of treatment is improving the identification of ablation targets [2] which is extremely difficult because of high level of complexity of wave conduction. Here, we aim to identify targets of ablation procedure using statistical approach, characterizing AF as a system with determined information flow using a concept of transfer entropy. This measure has been mostly used to determine the neurological connections in spiking models in biological networks [4]. Nowadays, the entropy transfer method is widely used in other fields [5], an example of which is the approach used in this study.

2. Methods

2.1. Study population

In the experimental part, left and right atrial electrograms at three different locations (high right atrium - HRA, coronary sinus - CS and in left atrial appendage – LAA) were recorded for 60 s in 42 patients undergoing catheter ablation of AF. The procedure ended in success (spontaneous termination of arrhythmia) in 21 patients and 21 underwent electrical cardioversion due to lack of response to ablation. For each patient in the CV group two ablation stages were identified: baseline (before the ablation) and POSTPVI (after isolation of the pulmonary veins), while the TERM group also included records of PRETERM stage (prior to termination of AF).

For each patient and each ablation stage 16 electrograms were available: 5 from catheter located in the coronary sinus, 2 from catheter placed high in the right atrium and 9 from LASSO catheter from left atrial appendage. For each catheter separable recordings for electrodes pairs of the catheter were available (for example for CS catheter CS 1-2, CS 3-4 etc.). The sampling frequency was 1 kHz.

All the data was collected in the University Hospital Eppendorf, Department of Electrophysiology, Hamburg, Germany.

To asses causality in the atria we used transfer entropy (TE).

2.2. Transfer entropy calculation

Transfer entropy was chosen as the method able to detect the **directed exchange** of information between two systems [6]. Since TE is defined on a binary data, we introduced three methods of signal transformation, one based on raw electrogram and two based on intervals between consecutive activations. Here, we present results only of a method replacing local activation with ones and the rest of the signal with zeroes (see Figure 1).

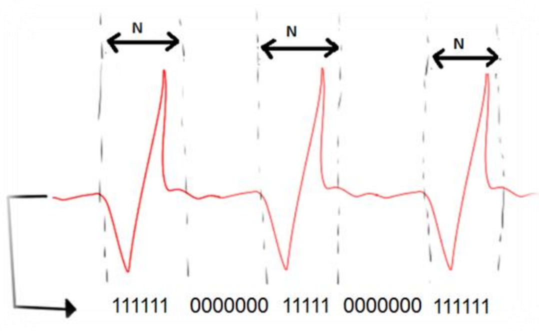


Figure 1. Illustration of chosen method of signal transformation. Each sample of the local activation (N-part) is converted to 1 and intervals between activations to 0.

For obtained binary strings, transfer entropy was calculated according to formula [6]:

$$TE_{J\to I} = \sum p(i_{n+1}, i_n^{(k)}, j_n^{(l)}) \log \frac{p(i_{n+1}|i_n^{(k)}, j_n^{(l)})}{p(i_{n+1}|i_n^{(k)})} \; ,$$

where:

$$i_n^{(k)} = i_n, i_{n-1}, \dots, i_{n-k+1} \; , \quad j_n^{(l)} = j_n, j_{n-1}, \dots, j_{n-l+1} \; ,$$

where k is the number of samples of receiving signal (j) and l of sending signal (i), based on which particular probabilities (p) are calculated.

Transfer entropy was calculated between pairs of electrograms recorded by each catheter.
Additionally, we used TE to quantify information flow in a chain of unidirectionally coupled oscillators with added noise, according to the formula:

$$\dots$$
$$CL_5(i+1)=CL_5(i)+\eta+k_{6\to 5} *(CL_6(i)-CL_6(i-1))$$
$$CL_6(i+1)=CL_6(i)+SD*\eta$$
$$CL_7(i+1)=CL_7(i)+\eta +k_{6\to 7} *(CL_6(i)-CL_6(i-1))$$
$$\dots ,$$

where i is the sample number, CL (cycle length) corresponds to time interval between consecutive activations, η is the Gaussian noise of standard deviation SD (set as SD=2) and k is the coupling parameter (set as k=0.5).

2.3. Transfer Entropy graphical presentation

Analysis of information flow was performed on a group of signals (recorded by individual catheter). For each pair of signals, value of TE was calculated. The results are presented using a square array denoted as Causality Diagram. An example is shown in Figure 2.

In order to make the interpretation of Causality Diagram easier, we introduced Causality Graph (Figure 3). Each node in the graph represents one signal and arrows between the nodes indicate the direction of information flow. In order to simplify the graph, only the most important directions of flow were presented.

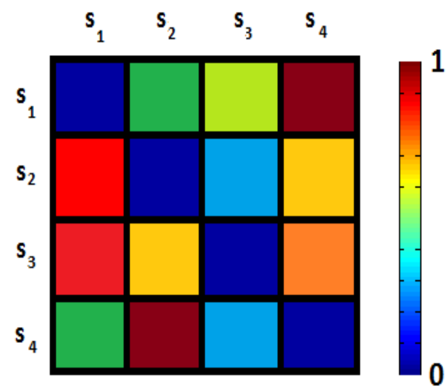


Figure 2. Example of Causality Diagram. It graphically presents values of transfer entropy in the group of signals. Colors correspond with the quantity of information that is transferred in each individual pair of signals (from the raw to the column signal).

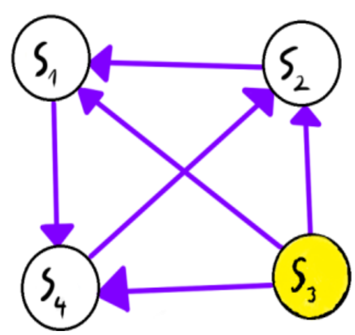


Figure 3. Example of Causality Graph. Each node corresponds to one signal. The arrows indicate the direction of the information flow.

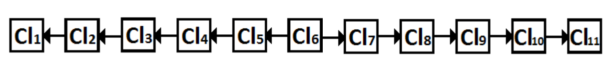


Figure 4. A schematic diagram presenting a set of unidirectionally coupled oscillators modeling intervals between consecutive activations at neighboring sites. Central element (CL6) is a "conductor" since as it is the only element influencing neighboring units without being influenced by any other element of the system

2.4. Artificial electrograms

To test whether TE method could be used in assessing causality in signals having properties of similar to electrograms recorded during Atrial Fibrillation, we generated the chain of synthetic signals. Signals were meant to model the cycle length variation in the electrograms recorded during Atrial Fibrillation.

AF is a very complex process, but with not fully understood dynamics. For this reason, the intervals between activations were modeled as a chain of unidirectionally coupled oscillators with added noise.

In Figure 4 a schema of coupling is presented. The middle signal (CL6) is a conductor and it controls other signals.

3. Results

3.1. TE calculated on artificial signals

Causality Diagram for chain of synthetic electrograms is presented in Figure 5. Causality can be noticed only between the neighbors, in a strictly defined direction, according to the structure of the model (unidirectional coupling; see Figure 4).

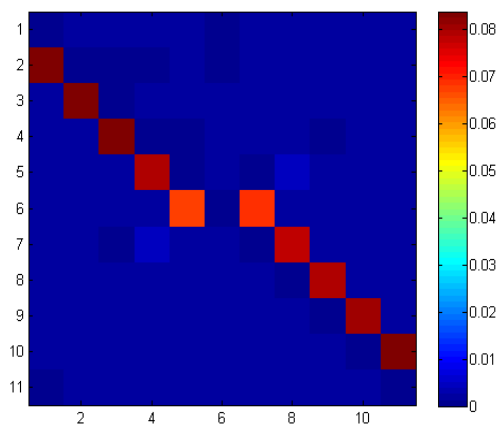


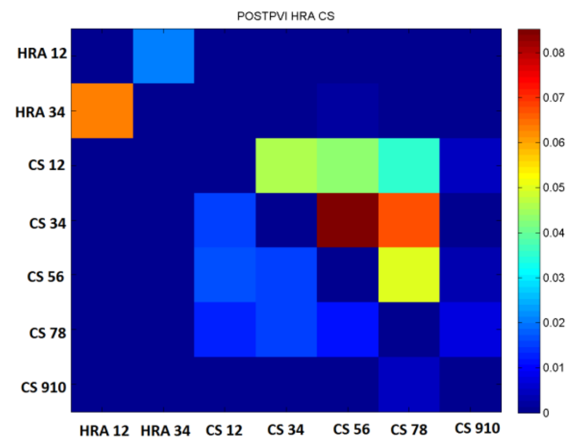
Figure 5. Causality Diagram for artificial signals corresponding with assumed coupling in the group of 11 signals presented in Figure 4.

3.2. TE calculated using patient data

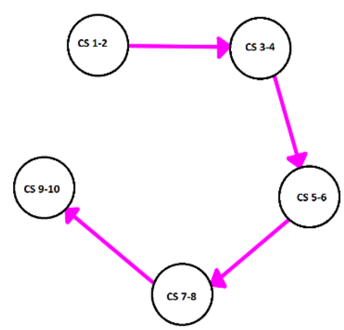
We found an asymmetry in information flow along the catheters. Averaged results for the group of patients show that in HRA catheter information flows from proximal to distal portion of the catheter (from bottom to top of the atria) and in CS from the distal towards the proximal portion (from left to right atria), see Figure 6.

Figure 7 presents an example of information flow across the atria in an individual patient, where conductor (the element from which majority of the information is flowing) cannot conductor was found and identified as electrogram CS9-10).

In Figure 9 an example of information flow in Left Atrial Appendage is presented. Signals were measured with LASSO catheter (which is curled into circular shape inside the appendage). Averaged results show that information propagates from the appendage entrance (corresponding to location of electrograms LAA 9-10 and LAA 1-2) to its distant part (where electrograms LAA 5-6, LAA 6-7 were recorded).

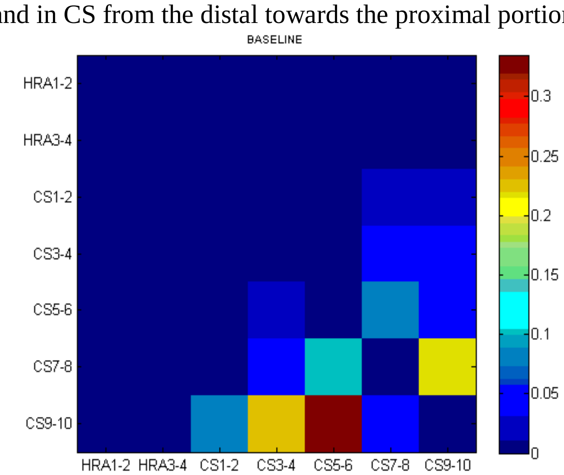


(6a)

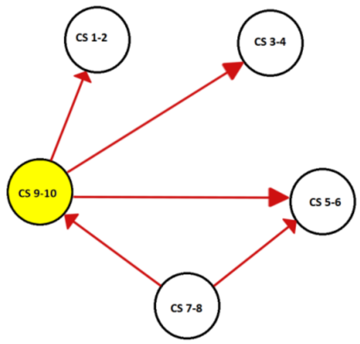


(6b)

Figure 6. Example of Causality Diagram (6a) and Causality Graph (6b) for averaged results of all patients from group TERM, POSTPVI stage. There is dominant information flow from proximal to distal portion of the catheter in HRA and in CS from the distal towards the proximal portion.

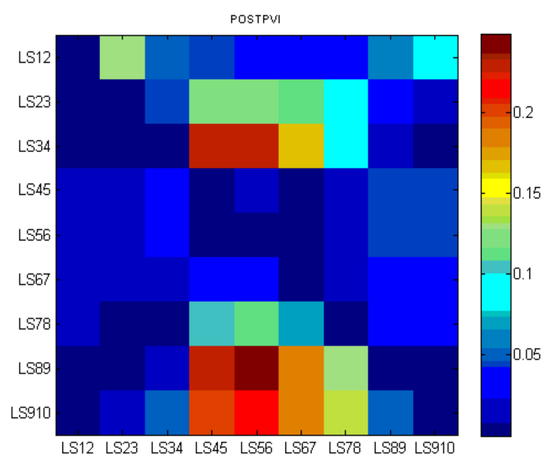


(7a)

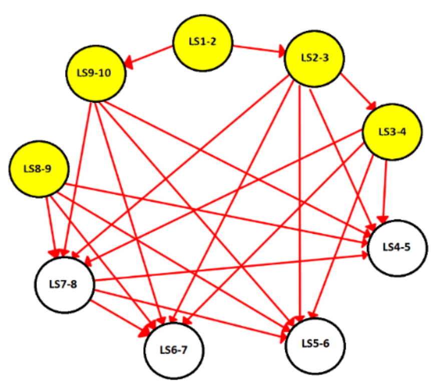


(7b)

Figure 7. Example of Causality Diagram (7a) and Causality Graph (7b) for a measurement in a patient, electrodes from HRA and CS. Information flows from the electrode CS 9-10 to electrodes CS 1-2, CS 3-4, CS-5-6. Based on the dominant direction of conduction flow, electrode CS9-10 was identified as a conductor.



(8a)



(8b)

Figure 8. Example of Causality Diagram 8(a) and Graph (8b) for a measurement in a patient using LASSO catheter in Left Atrial Appendage. In this case, a conductor is not a single electrode but a group of electrodes (LAA 8-9, LAA 9-10, LAA 1-2, LAA 2-3, LAA 3-4) from which there is an unidirectional information flow to remaining electrodes.

4. Discussion

TE diagrams calculated using artificial signals show clear direction of information flow from the center of the chain toward its ends.

We found a clear directionality of information flow in the atria during Atrial Fibrillation. In general, in HRA, information flows from the bottom to the top of the atria and in CS from the left to right atria. The dependencies found in Left Atrial Appendage are the most pronounced and they are in agreement with believed passive role of LAA in maintenance of AF. Note however, that for each patient the specific pattern of the flow of information varies. Exploration of the causes of this variability and relation with atrial structural pathology is an interesting direction of further research.

5. Conclusions

Information flow in the heart is asymmetric and it is possible to determine the direction of the flow using concept of transfer entropy. Analysis of the information flow may be an useful tool in identification of the atrial regions maintaining AF.

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