CORRESPONDENCE

Response to the article by Sungnoon *et al*. "Atrial electrophysiological property analysis by sample entropy and atrial fibrillatory rate with cardiac autonomic derangements in acute ischemic stroke with atrial fibrillation"

We have read with interest the article by Sungnoon *et al*.[1], who studied the effect of cardiac autonomic derangements on the atrial activity (AA) organization during atrial fibrillation (AF). More precisely, the authors assessed the correlation between two features widely used to characterize AA from the surface electrocardiogram (ECG), such as the dominant atrial frequency (DAF), or its inverse the atrial fibrillatory rate (AFR)[2], and sample entropy (SampEn)[3], and the heart rate variability in two different scenarios: i) AF patients with acute ischemic stroke and ii) AF patients recovering from ischemic stroke.

From a clinical point of view, it seems very reasonable to consider that cardiac autonomic dysfunction in AF patients with acute stroke could lead to more disorganized AA patterns compared to those recovered from stroke.[4] However, despite the fact that previous works have reported that AFR and SampEn are accurate estimators of AF organization from the surface ECG[2,3], the authors did not find significant differences between groups of patients. In our modest opinion, this poor outcome might derive from an inaccurate estimation of the AFR and SampEn. As a consequence, some important methodological issues would deserve further attention as will be detailed next.

It can be first remarked that although AFR and SampEn seem to be computed from the AA signal, the approach used for its extraction from the ECG is unclear. On the one hand, the authors mention that AA from TQ intervals was analyzed, thus avoiding the use of any QRST cancellation technique. But on the other hand, they indicate that a QRST complex cancellation technique was used. Additionally, the authors include a figure to illustrate a QRST cancellation method which really displays the approach to obtain the AA from TQ intervals. Both methods are different ways to obtain an AA signal from the surface ECG[5,6] and therefore, only one of them should be used.

Another fundamental aspect that merits more careful attention is how AFR and SampEn were computed. The authors mention the use of at least 1 minute-length ECG signals, but metrics were obtained from 10 second-length AA intervals. As a consequence, it is unclear how the final AFR and SampEn values were computed for each patient. Furthermore, no indication is given about how noisy or useless AA intervals were managed in the global computation. To this respect, it is worth noting that the application of an adequate preprocessing to the ECG recordings plays a key role to obtain accurate estimates of AFR and SampEn from the AA signal.[7,8]

Additionally, in contrast to a wide variety of previous works in which SampEn has proven to be a more accurate estimator of AF organization than the DAF[3], Sungnoon *et al*.[1] surprisingly found that AFR may be more sensitive than SampEn to get influenced by cardiac autonomic derangements. Although they argue that both metrics could estimate different sides of AF organization, we would like to draw attention to important aspects that affect SampEn estimation.

Firstly, this nonlinear index depends strongly on two parameters (the length of the sequences to be compared, m, and the patterns similarity tolerance, r), which have to be appropriately selected.[9] Although we can image that the authors used the most typical values of $m=2$ and $r=0.25$ times the standard deviation of the original data, the normalization of r is a question that requires special attention.[9,10] Indeed, very different SampEn values can be obtained by normalizing r with the standard deviation

of the whole AA signal vector under study or with the standard deviation from each analyzed 10 second-length interval.[10] Bearing this in mind, we sincerely believe that an inappropriate normalization of *r* might be the main reason to obtain significantly lower SampEn values (around 0.12) than those reported in previous works in which AA from TQ intervals was also analyzed (around 0.25-0.35).[5] Indeed, the SampEn values presented by Sungnoon *et al*.[1] suggest that they analyzed AF signals with approximately, a 3-fold increase in organization compared to previous works, which is very unlikely from a clinical point of view.[3,5,9]

As a conclusion, the authors can be congratulated on the novel idea of analyzing non-invasively how AA organization during AF is influenced by cardiac autonomic derangements. However, it has to be remarked that the use of signal processing tools, such as AFR and SampEn, to characterize properly the surface ECG and reveal useful clinical information requires a careful consideration of many methodological aspects.

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