

## Response: can a simulation study of T-wave alternans (TWA) resolve whether TWA is T-wave amplitude dependent?

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Dear Editor,

We appreciate the interest in our article by Prof. Dr. Madias. The purpose of our paper was to present a methodological contribution, namely, an improved algorithm for analysis of T-wave alternans (TWA). Specifically, we described a method to improve the accuracy of Modified Moving Average (MMA) TWA analysis based on continuous dynamic time warping (CDTW) curve alignment. Unfortunately, there is no gold standard public TWA database annotated by experts. Consequently, we had to conduct our assessment study using synthetic ECG registers with known parameters. In order to achieve a high degree realism, we used the synthetic ECG generator that enabled us to specify parameters of the ECG signal such as the mean and standard deviation of the heart rate, morphology of the PQRST cycle, amplitude, sampling frequency, and the power spectrum of the RR tachogram.

While the primary objective of our paper was to provide a purely technical/methodological contribution exclusively focused on advancing the performance of the methods available for TWA analysis, and not to answer any fundamental clinical question, our contributions including (1) an improved algorithm for quantitative TWA analysis, (2) synthetic generation of TWA signals, and (3) a simulation study involving TWA are necessary methodological

advancements required in order to tackle the important clinical questions. For instance, in order to answer the question of “whether TWA is T-wave amplitude dependent?”, it is first necessary to have signal analysis methods capable of automatic TWA analysis and quantification of features such as TWA amplitude. Additionally, TWA models and synthetic generators can also serve as useful tools to generate hypothesis, assess new methods of analysis, and make possible insightful simulation studies.

Whether a simulation study can be used to resolve if TWA is T-wave amplitude dependent remains to be studied. In real cases, at the moment there is only a speculation about such dependence [1], and therefore, a simulation based on a speculation would also be speculative in nature.

However, with a proper experimental setup, a simulation study could contribute to shed light on this problem. For example, it could be used to model real signals [2] that exhibit TWA and generate additional synthetic signals that facilitate the application of extensive tests if real signals are lacking, noisy, or too heterogeneous. Additionally, a simulation study could be designed to generate different sets of signals that show the hypothesized features and help researchers gain insight into the feasibility of each hypothesis.

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