Dynamics of T-peak-to-T-end Morphology Changes in an Open-chest Porcine Model, and its Relation to Arrhythmic Events

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Abstract

In this work, we use a time-warping-based morphology variation index, $d^{\text{PCA}}_{w,\text{T}_{pe}}$, computed between the peak and the end of the T-wave, and assess its association with the occurrence of ventricular fibrillation (VF) episodes (VF group) in ECG recordings from 20 pigs undergoing a 40-minute coronary occlusion. The $d^{\text{PCA}}_{w,\text{T}_{pe}}$ series was obtained by quantifying the morphological differences between the final part of the T wave at different stages of the occlusion and that of a reference T wave from a control recording. During occlusion, the absolute value of $d^{\text{PCA}}_{w,\text{T}_{pe}}$ followed a gradual increasing trend as ischemia progressed. At 0-5, 5-10, 10-15 and 15-20 minutes after the occlusion onset, $d^{\text{PCA}}_{w,\text{T}_{pe}}$ median values were significantly higher in the VF group than in the non-VF group (10.2, 11.7, 18.2 and 19.0 vs 1.8, 2.4, 3.2 and 2.4 ms), with p-values from the Kruskal-Wallis test of 0.017, 0.041, 0.045 and 0.013, respectively. In contrast, the $\text{T}^{\text{PCA}}_{pe}$ index did not present significant differences in any of the intervals between VF and non-VF groups. In conclusion, dynamic increases of the $d^{\text{PCA}}_{w,\text{T}_{pe}}$ index during ischaemia progression in pigs are associated with VF occurrence.

1. Introduction

Ventricular repolarization abnormalities have been linked to the formation of an arrhythmogenic substrate [1], prompting the investigation of several ECG-based indices to measure the increase in ventricular repolarization dispersion and predict ventricular arrhythmias. In particular, time-warping-based morphological ECG indices have been proposed and tested to overcome the restrictions of time-interval-based indices relying solely on temporal measurement differences. T-wave morphology restitution (TMR) [2] and T-wave morphology variations with respect to a normal reference (TMV) [3] are examples of such indices.

Under ischemia and myocardium infarction settings, the delineation of the T wave is particularly susceptible to annotation errors due to ST elevation, especially impacting the identification of the T wave onset. The T_{pe} interval has been widely recognized as a predictive marker of arrhythmic risk both in experimental models [4] and in clinical studies [5], and does not require determining the onset of T waves. More recently, the ability of the time-warping-based d_w index proposed by Ramírez et al. [6], adapted exclusively to the T_{pe} interval, $d^{\text{PCA}}_{w,\text{T}_{pe}}$, was evaluated during short-time induced ischemia in humans [7]. The $d^{\text{PCA}}_{w,\text{T}_{pe}}$ index showed significant effectiveness in quantifying ischemia-induced VRD changes in a 5-minute human ischemia model. Moreover, in order to overcome the restrictions of insufficient ischemia duration to evaluate the potential of $d^{\text{PCA}}_{w,\text{T}_{pe}}$ for arrhythmia risk prediction we demostrated in [8] that the evolution of the index predicts impending VF in a porcine myocardial infarction model. However, the exact mechanisms underlying the increased risk of arrhythmias could not be elucidated from the study based on the closed chest myocardial infarction model. The present study aims to evaluate if the T_{pe} interval warping-based $d^{\text{PCA}}_{w,\text{T}_{pe}}$ index is associated with ventricular fibrillation (VF) in a long-time open-chest porcine infarction model.

2. Materials and Methods

The study population included 20 domestic pigs (35.4 $\pm$ 7.5 kg body weight) undergoing an open-chest myocardial infarction model, see details in [9]. The procedures adhered to the guidelines for the Care and Use of Laboratory Animals, National Academies Press (US) 2011, and received approval from the ethical committee of the

Institute of Physiology at the Komi Science Centre, Ural Branch of the Russian Academy of Sciences. In order to induce left anterior descending (LAD) coronary occlusion, pigs were anesthetized, followed by intubation and mechanical ventilation, and a midsternal incision was made to access and cut the pericardium. A polycaproamide ligature (No 3-0) was placed (not tied first) in each pig and 12-lead body surface ECG recordings were recorded before ligation (Control stage) and throughout the 40-minute occlusion period (Occlusion stage). ECG recordings were digitized at a sampling rate of 250 Hz, an amplitude resolution of 1.18 μV per bit and dynamic range ±310 mV. Of the total study population, 12 pigs did not suffer from VF (Non-VF group) and 8 pigs suffered a VF episode that started later than 7 min after ligation (VF group).

2.1. Quantification of T-peak to T-end wave morphology changes

The ECG pre-processing involved several key steps. First, linear filtering was applied using a low-pass filter with a 40 Hz cut-off frequency to remove electrical and muscle noise, followed by a high-pass filter with a 0.5 Hz cut-off frequency to reduce baseline wander. Both filters were sixth-order Butterworth. The delineation of the ECG signals was achieved through a wavelet-transform-based method [10], focusing on a single lead to identify QRS fiducial points. A multi-lead selection strategy [11] was then used to refine these marks across all eight leads, resulting in a multilead QRS delineation. Next, spatial Principal Component Analysis (PCA) was applied to the eight standard leads, particularly emphasizing the T-wave by learning from it. The first principal component lead was subsequently delineated, and each segmented T-wave underwent additional low-pass filtering at 20 Hz with a sixth-order Butterworth filter for further analysis.

Changes in the T-peak to T-end wave morphology over time were measured using the d_w index, originally proposed by Ramírez in [6] and later adapted in [7] for restrictive analysis of the T_{pe} interval, $d^{\text{PCA}}_{w,\mathrm{T}_{pe}}$. For each s-th 15-second moving signal window along the recording (with 10-s overlap between windows), T waves were extracted and a mean warped T-peak to T-end wave (MWTPE) was computed. Initially, all T waves within a given window were transformed to positive polarity waves. The dominant class between biphasic or monophasic T waves was defined for each window as the class having the highest number of occurrences. Only those T waves belonging to the dominant class one were considered to compute the MWTPE. The reference MWTPE was computed from the first 60 seconds at the beginning of the control stage so that $d^{\text{PCA}}_{w,\mathrm{T}_{pe}}$ represents the T_{pe} interval morphological changes relative to the initial state. For each window, the index $d^{\text{PCA}}_{w,\mathrm{T}_{pe}}(s)$ is estimated as the temporal reparametrization between two T_{pe} intervals, a MWTPE, $\boldsymbol{f^s}(\boldsymbol{t^s}) = [f^s(t^s(1)), ..., f^s(t^s(N_s))]^T$, where $\boldsymbol{t^s} = [t^s(1), ..., t^s(N_s)]^T$, together with a selected reference MWTPE, $\boldsymbol{f^r}(\boldsymbol{t^r})$. $d^{\text{PCA}}_{w,\mathrm{T}_{pe}}$ index is the level of warping representing the amount of time stretching (or widening) needed to minimise the time domain differences among these different MWTPE, the one under study $\boldsymbol{f}^s(\boldsymbol{t}^s)$, and the reference $\boldsymbol{f}^r(\boldsymbol{t}^r)$.

Estimation of the $d^{\text{PCA}}_{w,\mathrm{T}_{pe}}$ series through warping functions: Let $\gamma(\boldsymbol{t}^r)$ be the warping function that relates $\boldsymbol{t}^r$ and $\boldsymbol{t}^s$ such that the composition $[\boldsymbol{f}^s \circ \gamma](\boldsymbol{t}^r) = \boldsymbol{f}^s(\gamma(\boldsymbol{t}^r))$ denotes the re-parameterization, or time-warping, of the $\boldsymbol{f}^s(\boldsymbol{t}^s)$ using $\gamma(\boldsymbol{t}^r)$. Following the approach in [6], the square-root slope function (SRSF) was utilized in place of the original signals to determine the optimal warping function, thereby preventing the "pinching effect". The optimal warping function, $\gamma^*(\boldsymbol{t}^r)$, is the one that minimizes the amplitude difference between the SRSF of $\boldsymbol{f}^r(\boldsymbol{t}^r)$ and $\boldsymbol{f}^s(\gamma(\boldsymbol{t}^r))$.

The $d^{\text{PCA}}_{w,\mathrm{T}_{pe}}$ index measures the amount of warping needed by calculating the average of the absolute differences between $\gamma(\boldsymbol{t}^r)$ and $\boldsymbol{t}^r$:

$$d^{\text{PCA}}_{w,\mathrm{T}_{pe}} = \left(\frac{S_d}{|S_d|}\right) \frac{1}{N_r} \sum_{n=1}^{N_r} |\gamma^*(\boldsymbol{t}^r(n)) - \boldsymbol{t}^r(n)|. \quad (1)$$

$$S_d = \sum_{n=1}^{N_r} \boldsymbol{t}^r(n) - \gamma^*(\boldsymbol{t}^r(n)) \quad (2)$$

A positive (negative) sign means that $\boldsymbol{f}^s(\boldsymbol{t}^s)$ must be widen (narrowed) to match the reference wave $\boldsymbol{f}^r(\boldsymbol{t}^r)$.

The time-course changes induced by ischemia, as captured by $d^{\text{PCA}}_{w,\mathrm{T}_{pe}}$, were computed for each $\boldsymbol{f}^s(\boldsymbol{t}^s)$ MWTPE estimated within each s-th 15-second window at the PCA lead. This produced a series $d^{\text{PCA}}_{w,\mathrm{T}_{pe}}(s)$ ($s \in \{1, \ldots, S\}$), sampled every 5 seconds relative to the initial reference, during both the control and occlusion stages. The T_{pe} interval was additionally estimated to provide a reference for comparing the added value of the $d^{\text{PCA}}_{w,\mathrm{T}_{pe}}$. It was determined for each i-th beat and a median filter was subsequently applied to the T_{pe} series, using a 15-second sliding window with a 10-second overlap, to match the resolution of the $d^{\text{PCA}}_{w,\mathrm{T}_{pe}}$ index, resulting in a $\mathrm{T}^{\text{PCA}}_{pe}(s)$ ($s \in \{1, \ldots, S\}$ series. Results were compared between the VF group and the non-VF group using the Kruskal-Wallis test. Statistical significance was assumed when p-value ≤ 0.05.

3. Results and discussion

No strong changes were observed by visual inspection in the interval T_{pe} waveform (quantified by $d^{\text{PCA}}_{w,\mathrm{T}_{pe}}$) over time in the control stage for the entire study population,

with a intra-recording median value ranging from -10.8 to 1.87 ms [median: 0, IQR:1.87]. The fact that $d^{\text{PCA}}_{w,\text{T}_{pe}}$ remains almost stationary during baseline suggests that the small $d^{\text{PCA}}_{w,\text{T}_{pe}}$ values just reflect natural ECG variability. In contrast, strong ischemia-induced alterations, indicated by changes in the T_{pe} shape and a higher $d^{\text{PCA}}_{w,\text{T}_{pe}}$ magnitude were observed during the occlusion stage in the majority of the pigs. These changes included variations both in width and amplitude. The intra-recording median $d^{\text{PCA}}_{w,\text{T}_{pe}}$ values ranged from -32.71 to 3.33 ms [median: -5.92, IQR: 12.21].

Figure 1 illustrates the $d^{\text{PCA}}_{w,\text{T}_{pe}}$ time course during control and occlusion stages for two specific pigs, one belonging to the VF group and the other to the non-VF group. The dynamic alterations in T_{pe} waveform morphology as ischemia advanced were effectively captured by the evolution of the $d^{\text{PCA}}_{w,\text{T}_{pe}}(s)$ index, which exhibited a downward trend triggered by artery occlusion, starting immediately after the initial minutes of occlusion. This increasing trend was more pronounced in the VF pig compared to the Non-VF pig, with values ranging from 0 to -33.33 ms and from 0 to -11.71 ms, respectively.

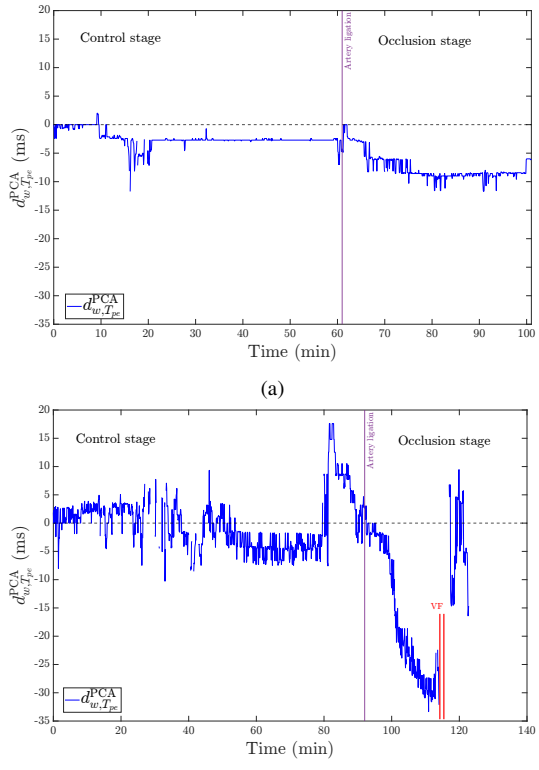

Figure 1: Time course of $d^{\text{PCA}}_{w,\text{T}_{pe}}(s)$ along time during occlusion stage for two particular pigs: from non-VF group (panel (a)) and from VF group (panel (b)). The purple dotted line indicates the onset of the artery ligation and the red dotted line the occurrence of the VF episode.

During the occlusion stage, $d^{\text{PCA}}_{w,\text{T}_{pe}}(s)$ index exhibited similar temporal patterns across the pigs, showing an initial decrease at the onset of ischemia in the majority of pigs, with the most significant changes occurring within the first 5 minutes, followed by a period of relative stability thereafter. The average time course (blue line) and standard deviation (red line) of the $d^{\text{PCA}}_{w,\text{T}_{pe}}(s)$ index for both the non-VF and VF groups, aligned to the start of the artery ligation onset, are shown in Fig 2. Note how the variations in the T_{pe} interval waveform caused by ischemia are specifically able to be captured by the average time-course of $d^{\text{PCA}}_{w,\text{T}_{pe}}(s)$. Note also the negative values of $d^{\text{PCA}}_{w,\text{T}_{pe}}(s)$ over ischemia time indicating that the T_{pe} intervals become larger relative to the reference interval as time progresses and thus a narrowing is necessary to optimally fit the reference interval, represented with a negative sign.

The median $d^{\text{PCA}}_{w,\text{T}_{pe}}$ and $\text{T}^{\text{PCA}}_{pe}$ values measured in different 5 minutes intervals (at 0-5, 5-10, 10-15, 15-20, 20-25, 25-30 minute intervals after occlusion onset and during 5 minutes prior to a VF episode), clustered for non-VF and VF groups are presented in Fig 3 At 0-5, 5-10, 10-15 and 15-20 minutes after the occlusion onset, $d^{\text{PCA}}_{w,\text{T}_{pe}}$ absolute median values were significantly higher in the VF group than in the non-VF group (Kruskal-Wallis test), with values of 10.2, 11.7, 18.2 and 19.0 vs 1.8, 2.4, 3.2 and 2.4 ms, and p-values of 0.017, 0.041, 0.045 and 0.013, respectively. In contrast, the $\text{T}^{\text{PCA}}_{pe}$ index did not present significant differences in any of the intervals between VF and non-VF groups. $d^{\text{PCA}}_{w,\text{T}_{pe}}$ index showed changes statistically significant for VF group already from the first 5 minutes after artery ligation onset, while $\text{T}^{\text{PCA}}_{pe}$ index did not, denoting superiority of $d^{\text{PCA}}_{w,\text{T}_{pe}}$ for early risk warning. The significant increase in $d^{\text{PCA}}_{w,\text{T}_{pe}}$ for the VF group relative to the non-VF group as ischemia progress indicates that increments in $d^{\text{PCA}}_{w,\text{T}_{pe}}$ magnitude beyond some threshold are associated with the occurrence of VF episodes.

4. Conclusions

The time-warping-based morphology index from the T-peak-to-end, $d^{\text{PCA}}_{w,\text{T}_{pe}}$, can track ischemia-induced changes. Larger dynamic changes of the $d^{\text{PCA}}_{w,\text{T}_{pe}}$ index during ischemia progression are associated with VF episodes suggesting the need for more clinical studies in humans to evaluate its power as a trigger for VF risk alarm.

Acknowledgments

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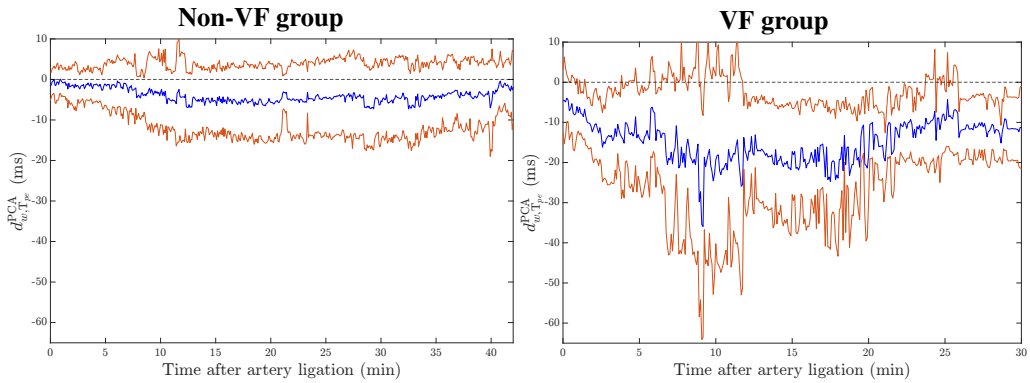

Figure 2: Average of $d^{\text{PCA}}_{w,\text{T}_{pe}}$ time course (blue line) $\pm$ standard deviation (red line) for the Non-VF group in the left panel and for the VF group (Right panel).

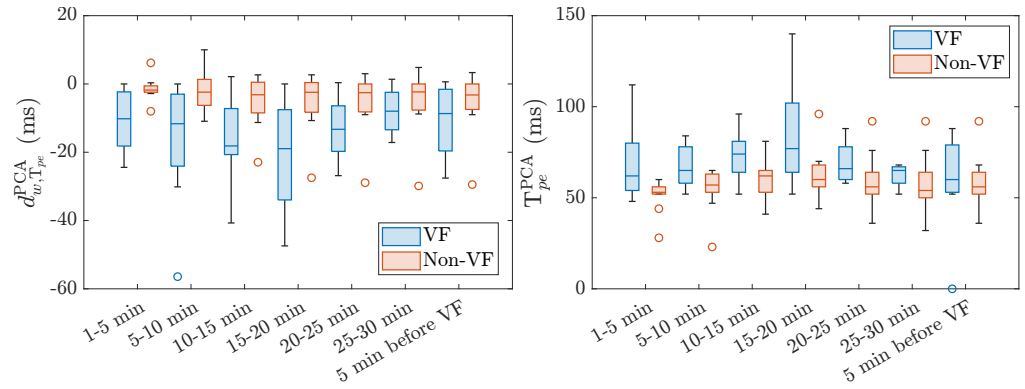

Figure 3: Box plots distributions of $d^{\text{PCA}}_{w,\text{T}_{pe}}$ (Left panel) and $\text{T}^{\text{PCA}}_{pe}$ (Right panel) indices for the Non-VF group (red) and VF group (blue) measured in different 5 minutes segments.

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