Changes in T-peak-to-T-end Morphology Measured by Time-Warping Are Associated with Ischemia-Induced Ventricular Fibrillation in a Porcine Model

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Abstract

In this work, we use a time-warping-based morphology variation index, d_w, computed between the peak and the end of the T-wave, and assess its association with the occurrence of ventricular fibrillation (VF) episodes in ischemic conditions. ECG recordings from 26 pigs undergoing a 40-minute coronary occlusion were analyzed. The d_w series was obtained by quantifying the morphological differences between the final part of the T wave at different stages of the occlusion and a reference T wave in the control recording. During control recordings, d_w remained stationary with a median value along each recording of 1.76 ms, IQR of 1.80, while during artery occlusion followed a well-marked gradual increasing trend as ischemia progressed, with median of 15.47 ms, IQR of 18.53. At the 20-to-25 min period from occlusion onset (and during 5 min prior to VF episode) d_w averages in the VF group was significantly higher than in the non-VF group with median values of 40.0 (and 34.4) vs 7.8 (and 7.7) ms, with p-values of 0.002 (and 0.001), respectively. In conclusion, dynamic increases of the d_w index during ischaemia progression in pigs are associated with VF occurrence.

1. Introduction

Ventricular repolarization alterations have been associated with the development of an arrhythmogenic substrate [1], leading to the study of several ECG-indices to quantify the increase in ventricular repolarization dispersion and predict ventricular arrhythmia. In particular, T-wave area dispersion [2], periodic repolarization dynamics (PRD) [3], the appearance of a J-wave pattern [4], QT interval variability [5], the distance from the peak to the end of the T-wave ($\mathrm{T_{pe}}$ interval) [6], T-wave morphology variations with respect to a normal reference (TMV) [7], and T wave morphology restitution (TMR) [8] are some examples of these indices.

Under ischemic conditions, T wave delineation is highly exposed to annotation errors as consequence of the ST elevation, particularly the T wave onset. The dispersion of ventricular repolarization reflected on the $\mathrm{T_{pe}}$ interval has shown potential in predicting arrhythmic risk [9], and does not require T wave onset determination. In addition, time intervals indices relying solely wave annotation measurements, do not capture all the possible morphological changes contained in the ECG morphology. To overcome these restrictions, the ability of the time-warping based index proposed by Ramírez *et al.* [10], adapted to restrict it application to the T-peak to T-end part of T wave, was evaluated during a human model of short time induced ischemia by percutaneous coronary intervention (PCI)[11]. In that study, the index capability in capturing ischemia induced T-peak to T-end waveform modification is reported. The present study aims to evaluate if this d_w index, restricted to T-peak to T-end is associated with ventricular fibrillation risk in a porcine model of prolonged ischemia.

2. Materials and Methods

The study population included 26 pigs undergoing a closed-chest myocardial infartion model by PCI intervention, see details in [12]. A balloon inflation in the left descending artery (LAD) to induce ischemia was performed in each pig. 12-lead ECG recordings, digitized at a sampling rate of 1024 Hz and an amplitude resolution of 1.18 μV per bit, were used to monitor the pigs before the balloon inflation (Control stage) and throughout the 40-minute occlusion period (Occlusion stage). From the total study population, 16 pigs did not suffer from VF (non-VT group) and 10 pigs suffered from VF (VT group), being afterwards defibrillated, after minute 15th from occlusion

onset. The occurrence time of VF events after occlusion onset ranged from 17:40 to 30:50 min with a mean of 21:20 min. The study conformed to the Guide for the Care and Use of Laboratory Animals by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996) and received approval from the local animal research ethics committee.

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

The ECG pre-processing included the following steps. Linear filtering, first with a low-pass 40-Hz cut-off frequency for electric and muscle noise removal, then with a high-pass 0.5-Hz cut-off frequency, for baseline wander attenuation, both Butterworth of sixth-order. The ECG delineation was performed using a wavelet-transform-based single-lead method [13] to obtain the QRS fiducial points. Subsequently, a multi-lead selection rule strategy [14] was applied over the 8 single-lead sets of marks to obtain the multilead delineated QRS marks. Then, spatial Principal Component Analysis (PCA) transformation was performed over the 8 standard leads, and learned over the T wave, in order to emphasize T-wave content. Finally, the first principal component lead was again delineated, and each segmented T-wave further low-pass filtered at 20 Hz cut-off frequency, with a sixth order Butterworth filter, for subsequent analysis.

The T-peak to T-end wave morphology changes along time were quantified by the d_w index proposed by Ramírez in [10], and adapted in [11] for the restricted second half of the T wave. 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 that were of the same class as the dominant 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_w represents the T-peak to T-end wave morphological changes relative to the initial state. For each window, the marker $d_w(s)$ is estimated as the temporal reparametrization between two waves, 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_w index is the mean amount of warping needed to minimise the time domain differences among these different MWTPE, the one under study $\boldsymbol{f}^s(\boldsymbol{t}^s)$, and the reference $\boldsymbol{f}^r(\boldsymbol{t}^r)$.

d_w series estimation 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 $\gamma(\boldsymbol{t}^r)$. As in [10], the square-root slope function (SRSF) was used instead of the original signals, to find the optimal warping function so avoiding the so called "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 level of warping represents the amount of time stretching needed to optimally fit the wave under study relative to the reference one. The d_w biomarker quantifies this level of warping required as the average of the absolute difference value between $\gamma(\boldsymbol{t}^r)$ and $\boldsymbol{t}^r$:

$$d_w = \frac{1}{N_r} \sum_{n=1}^{N_r} |\gamma^*(\boldsymbol{t}^r(n)) - \boldsymbol{t}^r(n)|. \quad (1)$$

The ischemia-induced time-course changes captured by $d_w(s)$ were calculated for each $\boldsymbol{f}^s(\boldsymbol{t}^s)$ MWTPE estimated for each s-th 15-second window at the PCA lead, resulting in a series $d_w^{\text{PCA}}(s)$ ($s \in \{1, \ldots, S\}$) sampled at each 5 seconds relative to the initial reference, both in the control and the occlusion stages. Results were compared between the VF group and the non-VF group and were compared using the Kruskal-Wallis test. Statistical significance was assumed when p-value ≤ 0.05.

3. Results and discussion

No significant T-peak to T-end waveform changes (as quantified by d_w) were found during the control recordings in the study population, with a intra-recording median value ranging from 0.11 to 4.98 ms [median: 1.76, IQR: 1.80]. This points to the fact that the small d_w values during baseline conditions just reflect natural ECG variability. On the contrary, strong ischemia-induced changes, reflected in T-peak to T-end shape changes (width and amplitude increases/decreases) and captured by an increased d_w magnitude were noted during the balloon inflation stage in most of the pigs with a intra-recording median value ranging from 1.58 to 47.80 ms [median: 15.47, IQR: 18.53].

Figure 1 shows an example of the $d_w^{\text{PCA}}(s)$ time course during control and occlusion stages for two particular pigs, one from the VF and other from the non-VF groups. Dynamic changes in the T-peak to T-end waveform morphology, induced by artery occlusion, were well reflected by the $d_w(s)$ index evolution, with an increasing trend as ischemia progressed starting immediately after the initial minutes of occlusion. The increasing trend is more emphasized for the VF pig than for the Non-VF pig, with values ranging from 4.92 to 44.51 and from 1.94 to 7.52 ms, respectively. In contrast, in both groups, $d_w^{\text{PCA}}(s)$ magnitude

remains almost stationary during the control stage, ranging from 0 to 8.67 and from 0 to 3.15 ms, respectively.

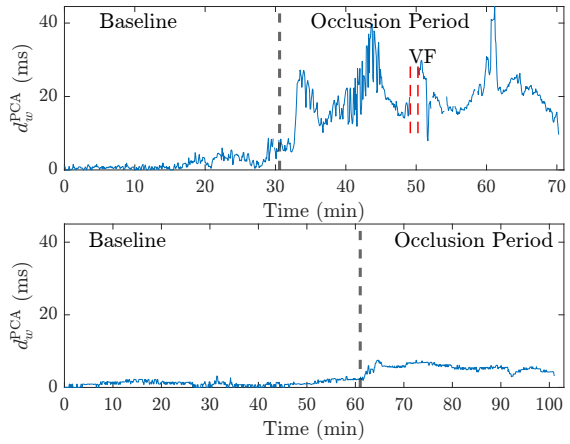

Figure 1: Time course of $d_w^{\mathrm{PCA}}(s)$ along time during control and occlusion stages from two particular pigs. The top panel shows the evolution for a VF group pig and bottom panel for a non-VF group pig. The black dotted line indicates the onset of the artery occlusion and the red dotted line the occurrence of the VF episode.

During occlusion stage, $d_w(s)$ index presented similar behavior across pigs when comparing temporal trends, characterized by an increase from the beginning of exposure to ischemia, with the greatest changes occurring in the first 5 minutes and remaining relatively stable thereafter. The average time course (blue line) and standard deviation (green line) of $d_w(s)$ index across pigs for the non-VF group and the VF group are displayed in Fig. 2, both during control and occlusion stages, aligned to the recording onset or to the balloon inflation onset, respectively. Note how the average time-course of the $d_w(s)$ is able to capture variations in the T-peak to T-end waveform, induced specifically by ischemia.

The average of $d_w(s)$ index measured in different 5 minutes intervals (last 5 minutes before the occlusion onset, at 1-5, 5-10, 10-15, 15-20, 20-25 minute intervals after occlusion onset and during 5 minutes prior to a VF episode), clustered for the two pig group are presented in Fig. 3. These $d_w^{\mathrm{PCA}}(s)$ averages was significantly higher for VF group than in the non-VF group with a median value of 0.82, 0.83, 6.25, 7.56, 8.02, 7.76, 7.81 and 7.65 vs 0.44, 2.35, 12.45, 18.78, 26.71, 23.96, 30.95 and 34.37, and p-value of 0.223, 0.011, 0.035, 0.001, 0.001, 0.007, 0.002 and 0.001, for each interval, respectively. d_w index showed changes statistically significant already from the 5 minutes prior to the occlusion onset, possible consequence of already modifications induced by catheter insertion. As occlusion time progresses, significant inter-individual differences were found in the magnitude of d_w changes for VF group from the first 5 minutes of balloon inflation, ranged from a negligible variation at the beginning of the occlusion to a pronounced magnitude as time elapses. The very significant increase in d_w for the VF group relative to the non-VF group as ischemia progress indicate that increases in d_w magnitude beyond some threshold are associated with the occurrence of VF episodes.

4. Conclusions

In a porcine myocardial infarction model, the time-warping-based shape marker, d_w, restricted to T-peak to T-end interval, allows to monitor ischemia-induced repolarization changes. Larger increase of d_w during ischaemia progression is associated with VF occurrence and suggest further evaluation in humans.

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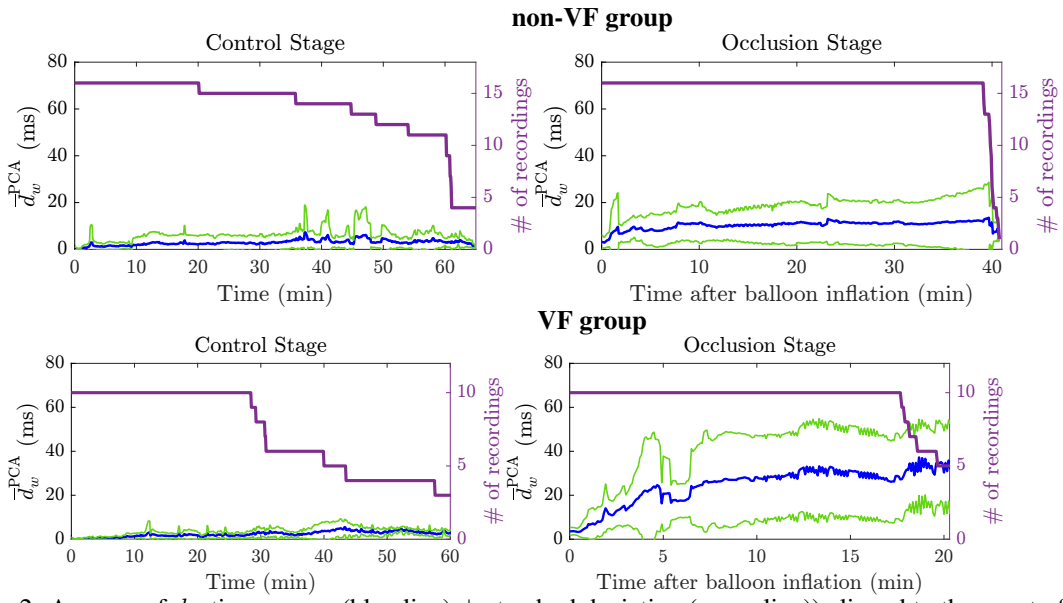

Figure 2: Average of d_w time course (blue line) $\pm$ standard deviation (green line)) aligned to the onset of the recording in control stage and to the occlusion onset during occlusion stage, for the non-VF group in panel (top) and for the VF group (botton). Purple line and the right y-axis represents the number of averaged recordings at each given time.

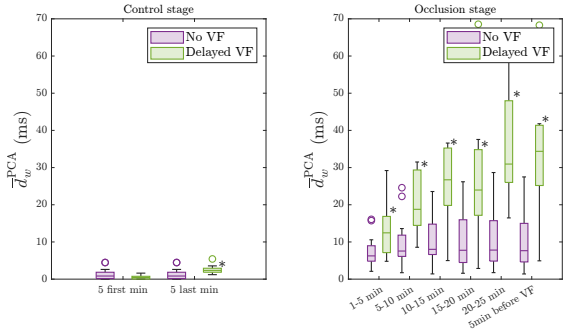

Figure 3: Comparison of d_w averages, for the VF subgroup (green color) and non-VF subgroup (purple color), measured in different 5 minutes segments. * indicates statistical significance for comparison between groups.

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