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Cardiac Action Potential Wavefront Tracking Using Optical Mapping

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***Abstract*—A wealth of knowledge is available about the effect of diabetes on the heart but very little has been done to quantify the conduction velocity of the diabetic heart. This study intends to develop a technique for tracking the cardiac wavefront across the heart in order to achieve the total activation time as well as the conduction velocity of the heart at any point during its activation, to compare the newly determined activation times with previously determined activation times, and to also compute the average conduction velocity of the heart from diabetic and control rats. The technique developed for tracking the action potential wavefront across the heart extracts the wavefront and provides the activation time as well as the conduction velocity – both instantaneous and average – successfully. The method reproduces previously measured activation times well, with a correlation of $R^2 = 0.875$, which suggests that this technique is reliable and that its determination of conduction velocity will allow for the examination of healthy and diseased hearts using a new criterion. In addition, the method for determining the conduction velocity of the heart allows direct comparison of the baseline conduction velocity in control and diabetic hearts. The results of this comparison indicated that conduction velocity in the diabetic hearts is slower (0.47 ± 0.02 m/s) than in control hearts (0.55 ± 0.02 m/s) (p = 0.001).**

I. Introduction

DIABETES is an increasing problem throughout the world with far reaching medical repercussions in every organ of the body [1]. An estimated 3.5% of the average worldwide population is affected by this chronic and incurable disease. A great deal is known about the implications of diabetes on the mechanics [2] and the electrical function [3] of the heart, but very little is known and very few studies have been conducted to understand the effect of diabetes on the propagation of electrical activation through the heart.

In current practice [4], the heart is imaged with a high-speed video camera as the electrical signal, a series of action potentials (APs), propagates through it. The heart is stained with a voltage-sensitive dye which emits a fluorescent, wavelength-specific light, the intensity of which is proportional to membrane voltage. The propagation of the wavefront of the electrical signal through the heart is imaged using this technique and as the AP at each cell activates, a change in the intensity of the emitted light is observed. The activation time can be determined by measuring the time it takes for a complete activation of the heart to occur, where the electrical signal propagates from the top of the heart to the bottom, and is normalized to a baseline measurement for analysis.

The impetus for this research is to first, determine a new method for tracking the propagation of the wavefront to give an instantaneous description of the velocity and to secondly, determine the fitness of the current method being used in comparison with the new technique. The driving force behind this research is to allow for the analysis of the effects of diabetes on the heart using the average wavefront velocity and the time to activation of the heart as standard measurements of analysis.

A. Current State of the Field & Literature Review

Optical imaging of the heart using voltage-sensitive dyes has made it possible to record cardiac APs with high spatial and temporal resolution but the susceptibility of optical imaging to motion artifacts is ever present [4][6][7]. Conversely, at an individual cell level, the cardiac AP can be measured by a micro-electrode where the occurrence of motion artifacts is limited, but the spatial resolution suffers greatly due to its utilization. Optically recorded signals have individual properties that differ quite uniquely from individual cell measurements recorded with extracellular electrodes or APs recorded with microelectrode techniques [5]. Given the benefit of high spatial resolution, optical imaging is an excellent choice for the recorded observation of APs across the heart. Previous research completed by Nygren et al. [4] has used this technique of imaging to record the propagation of the electrical wavefront across the surface of the heart to observe its behavior in various situations. Data from this previous study [4] is used in this study to develop a method for wavefront tracking. Currently, the techniques used to analyze cardiac imaged data range from determining the overall activation time for the heart to calculating the localized velocity vectors for each step of a propagating wavefront from initial upstroke to rest [4][7].

The electrical behaviour, specifically the AP wavefront behaviour, of the heart is well documented and has been proven to be very reproducible. The tracking of such has not had the same depth of research and of the methods researched; the most congruent methods make use of localized velocity calculations such as the previously discussed methods [7]. The amount of data associated with

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the determination of localized velocity is daunting and is also an unnecessary amount for the analysis used in the determination of the effects of diabetes on the electrical behaviour of the heart.

B. Aim of Research

This study tests the hypothesis that a new method based on wavefront tracking will outperform the existing technique because it will be less susceptible to motion artifacts when the heart is imaged as it expands and contracts during a heartbeat. Further, it is hypothesized that the new method for wavefront detection proposed here will give a more accurate description of the behaviour of the wavefront and will also offer a spatially averaged sequence of images to mitigate the effects of motion artifacts at various points on the heart.

We aim to reproduce the same results as those that have been published [4] using the current method of determining the activation time of the heart, as well as to prove the new technique to be a better indicator of the effect of diabetes on the electrical behaviour of the heart when compared to the current technique.

II. Materials and Methods

A. Source of data and previous experiments

The source of the data used for the development of the wavefront detection algorithm in this study comes from previous research completed by Nygren et al. [4]. The research makes use of healthy and diabetic rats in comparisons for determining the effect of a number of factors on the conduction velocity of the heart. Measurements of total ventricular activation time in the presence of heptanol (gap junction uncoupler) or elevated extracellular K^+ concentration (reduced excitability) are normalized to control (baseline) measurements for both healthy and diabetic rat hearts. The rationale for this experimental paradigm is described in detail in a previous publication [4]. The data used for the development of the algorithm and the determination of the wavefront velocity is averaged over the length of the entire movie to suppress noise inherent in the recording method.

B. Automated wavefront tracking algorithm

Using the signal averaged movies from the available data set, a method was developed for tracking the cardiac action potential wavefront and calculating its velocity on a frame-by-frame basis. Initially, the whole movie is temporally filtered using a 10^{th} order low pass digital Butterworth filter at a cutoff frequency determined by discriminating the power spectral density of the entire movie above 0 dB/Hz.

Next, a spatial filtering of the movie is done using a 2D median filter by which the data in the 2D matrix A – each frame of the movie in this case – is averaged on an individual pixel basis where the reference data for the individual pixel is the 3x3 neighborhood surrounding it. This method was chosen because the noise appearing in the movies is better suppressed than with a Gaussian distributed de-noising function. It is a non-linear operation and it is a very robust method of de-noising images with "salt and pepper" noise which is the case with these movies.

After this processing of the movie is completed, the position of the cardiac wavefront is determined by performing a first order differentiation of the data to be able to clearly differentiate the propagation of the wavefront from the resting level of the heart. Due to the discrete nature of the data, it is easily achieved by performing a subtraction of the present frame by the previous frame in the movie. As a result of the frame subtraction, the movies again becomes noisy and by performing another low pass filtering on the resulting data – this time at a cut off frequency of 50 Hz – the propagating wavefront is clearly distinguished from its surroundings and the automated detection is performed with greater ease and less ambiguity.

To best segment the frame subtracted data (Fig. 1A) from the remaining noise and artifacts, an algorithm named Block-matching and 3D filtering [9], BM3D, is used. BM3D is an algorithm for attenuation of additive white Gaussian noise from both grayscale and RGB images. In this case, the BM3D algorithm is configured to segment the wavefront from the rest of the signal in each frame (Fig. 1C). The median filtering method (Fig. 1B) is not adequate in determining the bounds of the wavefront due to its one-dimensional filtering method. The reason for choosing the BM3D method is that it intelligently determines the nearest neighbors which are most likely to be a part of the wavefront by both looking at the surroundings of each block of pixels – 8x8 blocks in this case – and also sliding along the direction of least difference in order to intelligently predict where the bounds of the wavefront is.

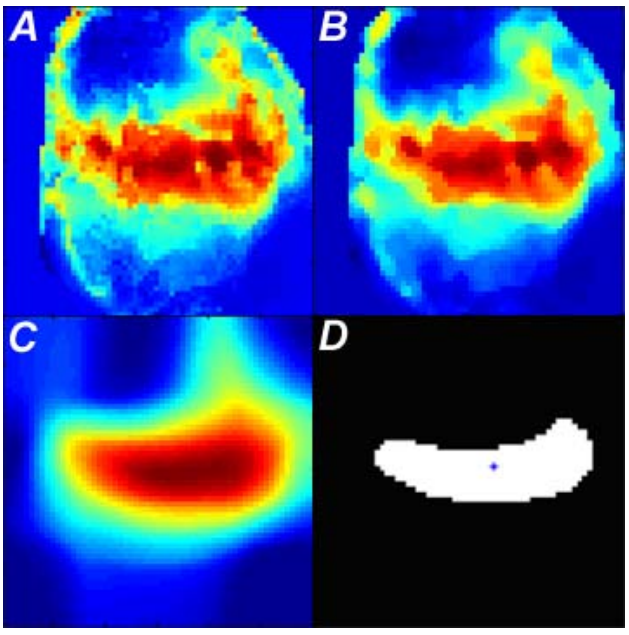

Fig. 1. Filtering and segmentation methods. *A*) Frame subtracted and low-pass filtered (no spatial filtering), *B)* Median filtered, *C)* BM3D filtered, and *D)* Binary segmentation of wavefront and corresponding centroid. The advantage of using the BM3D filter over median filtering is clearly seen in the comparison of *B* and *C*.

Binary thresholding (Fig. 1D) of the frame enables us to segment the wavefront from its surroundings and allow for the determination of the wavefront centroid. Initially, our intention was to track the wavefront using a straight line on the leading edge of the wavefront. However, this was found to not accurately describe the direction and orientation of the wavefront. This is why the recording of the position and behaviour of the wavefront has been chosen to be done by determining its centroid.

Given the camera frame rate of 950 Hz [8], the pixel geometry as 250 µm x 250 µm, and also knowing the position of each centroid, we can determine both the instantaneous velocity and the average velocity of the propagating wavefront.

III. Results

A. Activation time measurements

As discussed in the aims of the research, other than the creation of a method for tracking a wavefront propagating through the heart, an equally important goal of this research (for the purpose of validation of the method) was to reproduce the results obtained by the method previously used [4]. The existing technique has been used to measure the time it takes for a wavefront to propagate across the heart. In this previous study, a normalized measure was computed for each heart by comparing recordings in which conduction was perturbed using either elevated extracellular K^+ or heptanol to measurements under control conditions. From the published data [4], there are 33 activation time records available. Of these 33 records, we failed to reliably detect the wavefront in seven movies, thereby leading us to perform our analysis on the remaining 26 records. There are five main subsets of data on which the existing and new methods are used for the determination of the activation time and the comparison of the percent change from their respective baseline values:

1. Six control rats at 9 mM K^+ concentration.
2. Three control rats at 11 mM K^+ concentration.
3. Three diabetic rats at 9 mM K^+ concentration.
4. Six control rats at 0.5 mM heptanol concentration.
5. Eight diabetic rats at 0.5 mM heptanol concentration.

The comparison of the mean slowing of activation times, and associated standard errors, from the five subsets between the two methods are as follows:

1. 24.52 ± 5.06 % (original) vs. 19.89 ± 5.30 % (new).
2. 42.91 ± 14.64 % (original) vs. 37.88 ± 16.74 % (new).
3. 52.60 ± 11.85 % (original) vs. 40.56 ± 8.99 % (new).
4. 10.91 ± 3.86 % (original) vs. 13.90 ± 4.22 % (new).
5. 28.63 ± 5.40 % (original) vs. 26.01 ± 4.16 % (new).

Fig. 2 shows graphically the correlation between the 26 pairs, from all five subsets, of normalized activation times corresponding to the quantities achieved from the existing and new methods, respectively. This comparison shows that the correlation is high ($R^2 = 0.8748$) and that on average, the activation time measurements resulting from the new technique are determined to be about 15-20% longer than the activation time measurements determined from the original method (see Discussion).

B. Conduction velocity measurements

The technique described in section II. *B*. allows for the calculation of many different parameters and as already discussed, the activation time is determined by segmenting the wavefront from the rest of the heart and tracking it through its passage across the heart. The fact that the centroid of the wavefront is tracked from one frame to the next is a feature of the new method which allows for the calculation of the conduction velocity at any point during the activation of the heart. Fig. 3 shows the time varying velocity plotted against the position in the movie file of a wavefront propagating across the heart. Since the velocity is known throughout the conduction of the wavefront, the average velocity is easily computed. Although this was not part of the initial aims and hypotheses, the fact that another comparative measure is available for analysis allows for data sets to be analyzed and compared independently on the basis of a standard average velocity calculation. The limitation of using the activation time is such that any time measurement must be normalized with a baseline measurement and then compared to a normalized quantity which is not the case with the average velocity calculation; which can be used independently without normalization.

C. Statistical analysis of conduction velocity dataset

The ability to independently compute the average conduction velocity allows for the side-by-side comparison of the average conduction velocity of 16 control and 15 diabetic rat hearts. The mean of each set of average velocities is calculated as well as the p-value from a standard two-tailed t-test. This analysis shows that the mean of the average velocities of control and diabetic rat hearts are 0.55 ± 0.02 m/s and 0.47 ± 0.02 m/s, respectively. This result was found to be highly statistically significant ($p = 0.001$). Thus, the potential for the use of average velocity under control conditions as a criterion of analysis is very high.

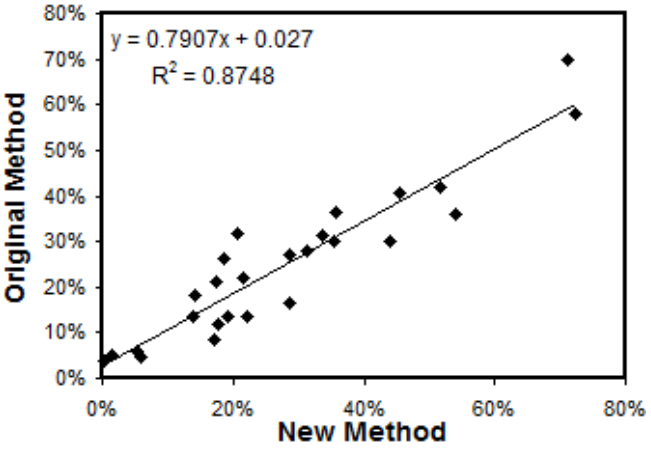

Fig. 2. Normalized average difference comparison for 26 separate activation time pairs.

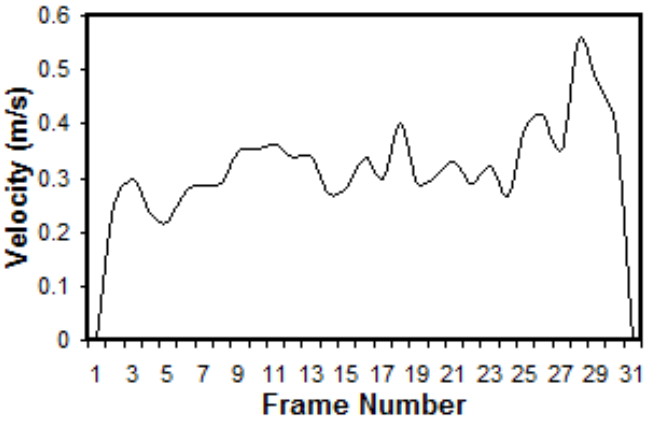

Fig. 3. Graph of instantaneous conduction velocity

IV. Discussion of Results

A. Discussion of results

When the processed data is compared to the existing data it indicates the strength of the method developed for the segmentation and tracking of cardiac wavefronts. On average, the normalized activation times are roughly 15-20% longer than the times from the original method. This fact can be clearly seen by examining the slope of the line fitted to the data in Fig. 2, where the slope is expected to be 1 starting from the origin in a perfectly reproduced scenario. However, the scatter plot in Fig. 2 is indicative of highly correlated data pairs. It shows the comparison of every data pair and the resulting correlation coefficient of 0.8748 and a linear regression fit line with a slope of 0.79 which almost passes through the origin (y = 0.027). It can thus be concluded that this method produces data which is closely correlated with data from the existing analysis method, albeit affected by a "scale factor" of 0.79. This quantitative difference between the two measures can be easily explained, considering that the previous activation time-based method purposely excludes part of the field of view as a way of improving robustness [4]. Thus, the goal of reproducing existing observations using the newly developed analysis method has been met.

The use of average velocity measurements for the analysis of cardiac wavefront propagation shows that diabetic hearts, on average, exhibit a 15% slowing in baseline conduction velocity compared to the average conduction velocity of control hearts. This result is highly statistically significant (p = 0.001). The ability of the new method to compare conduction velocities directly is a significant improvement over our previous methods in that it allows comparisons to be made without the need for an experimental "perturbation" of conduction velocity. The observation that baseline conduction velocity is significantly slowed in the diabetic rat heart is a new observation (based on our existing data) and has the potential to simplify future experiments aiming to quantify differences in conduction velocity due to reduced intercellular coupling.

B. Conclusion

The initial aim of this research was to prove the new technique to be a better indicator of the effect of diabetes on the electrical behaviour of the heart when compared to the current technique. The resulting data and subsequent statistical analysis shows the level of accuracy and ability of the new wavefront tracking technique to reproduce data when compared to the existing method. The results produced with the new method, which mirror the published data [4], combined with the capability to express the conduction of the heart in terms of an average and/or time-varying velocity measurement, not only succeed in outperforming the existing technique but also allow for an added number of usable parameters to describe the cardiac function of healthy, diseased, and drug treated hearts.

In meeting our aims, the research in this paper is a compromise between the rigorous determination of velocity vector fields and the basic measure of activation time. It offers the field another method of quantifying the behaviour of the cardiac conduction velocity in optical mapping recordings.

References

[1] A. D. Mooradian, "Cardiovascular disease in type 2 diabetes mellitus," *Archives of Internal Medicine*, vol. 163, pp. 33-40, Jan. 2003.

[2] D. L. Severson, E. Aasum, D. D. Belke, T. S. Larsen, L. M. Semeniuk, and Y. Shimoni, "Diabetes and cardiac dysfunction," in *Atherosclerosis, Hypertension and Diabetes*, illustrated ed., G.N. Pierce, M. Nagano, P. Zahradka and N.S. Dhalla, Ed. Boston: Kluwer Academic Publishers, 2003, pp. 373-385.

[3] K. Abo, Y. Ishida, R. Yoshida, T. Hozumi, H. Ueno, H. Shiotani, K. Matsunaga, and T. Kazumi, "Torsade de pointes in NIDDM with long QT intervals," *Diabetes Care*, vol. 19, pp. 1010, Sept. 1996.

[4] A. Nygren, M. L. Olson, K. Y. Chen, T. Emmett, G. Kargacin, and Y. Shimoni, "Propagation of the cardiac impulse in the diabetic rat heart: reduced conduction reserve," *The Journal of Physiology*, vol. 580, pp. 543-560, Dec. 2006.

[5] S. D. Girouard, K. R. Laurita, and D. S. Rosenbaum, "Unique Properties of Cardiac Action Potentials Recorded with Voltage-Sensitive Dyes," *Journal of Cardiovascular Electrophysiology*, vol. 7, pp. 1024-1038, April 2007.

[6] I. R. Efimov, V. P. Nikolski, and G. Salama, "Optical Imaging of the Heart," *Circulation Research*, vol. 95, pp. 21-33, April 2004.

[7] G. E. Morley and D. Vaidya, "Understanding conduction of electrical impulses in the mouse heart using high-resolution video imaging technology," *Microscopy Research and Technique*, vol. 52, pp. 241-250, Jan. 2001.

[8] A. Nygren, R. Kondo, B. Clark, and W. R. Giles, "Voltage-sensitive dye mapping in Langendorff-perfused rat hearts," *American Journal of Physiology – Heart and Circulatory Physiology*, vol. 284, pp. 892-902, March 2003.

[9] K. Dabov, A. Foi, V. Karkovnik, and K. Egiazarian, "Image denoising with block-matching and 3D filtering," in *Proceedings of SPIE*, 2006, pp. 354-365.