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LifeShirt® Acquisition System to Monitor ECG from Ambulatory Swine and the Implementation of an Arrhythmia Detection Algorithm

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Abstract—**A wearable cardiopulmonary monitoring system, a LifeShirt®, was used to acquire continuous electrocardiograms (ECGs) from ambulatory swine. The animals received intracoronary injections of autologous mesenchymal stem cells, and the LifeShirt® was used for long-duration ECG monitoring in pre-defined periods post cell infusion. The system used here was developed for measurements from non-human primates and canines; however, we demonstrated that it could be used to non-invasively measure ECGs from swine without creating undue stress or restricting movement. A MATLAB-based analysis algorithm was developed to automatically detect premature ventricular contractions (PVCs) that arose 8-10 hours after cell delivery with spontaneous resolution 2-3 days post-infusion. Template based cross-correlation was used to detect the PVCs and identify regions of consecutive ventricular rhythm. The final algorithm was highly specific and sensitive when tested on records from the MIT-BIH arrhythmia database. The algorithm was subsequently used to automatically identify and quantify PVCs from over 200 hours of ECG data obtained from nine ambulatory swine.**

I. Introduction

Non-invasive, ambulatory electrocardiogram (ECG) monitoring of large animals requires a robust acquisition system that will detect a subject's ECG without inducing stress or distress. In this study, a LifeShirt® Pre-Clinical system, a wearable cardiopulmonary monitoring device, was used to continuously measure the ECGs from unanesthetized swine. This study represents a novel use of the LifeShirt®: The system was developed for monitoring physiological signals from canines and non-human primates [1]-[3]. The work described herein presents the first known use of this monitoring system in ambulatory swine, which are routinely used as test animals for pre-clinical evaluation of cell treatments targeted for human trials.

The animals received intracoronary infusions of autologous mesenchymal stem cells derived from adipose tissue. It was found that the cell injections triggered premature ventricular contractions (PVCs) in the previously healthy myocardium. The PVCs did not acutely occur with the cell delivery; the onset of the arrhythmias typically occurred 8-10 hours post-cell infusion. The LifeShirt® was used to non-invasively monitor the pro-arrhythmic effects of the cell treatment in pre-defined periods post-injection (details in Ref [4]). The ECGs were continuously measured during periods longer than three days post cell delivery. Thus, it was untenable to manually analyze these records. To quantify the arrhythmic events, we developed an algorithm to automatically detect PVCs and to identify regions of consecutive ventricular rhythm. The PVC detection algorithm employed a template-based cross-correlation technique similar to those described in Refs. [5]-[7]. The methodology, testing, and efficacy of the PVC detection algorithm for long duration ECGs are also described in this report.

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II. Materials and Methods

A. ECG Measurements Using LifeShirt®

The LifeShirt® (VivoMetrics Inc., Ventura, CA) is comprised of a wearable jacket that contains electrodes and transducers for measurement of the ECG, respiratory activity, heart rate and various other physiological signals. Given the extended duration ECGs, it was necessary to obtain measurements from unrestricted animal subjects. Additionally, there was concern that implanted electrodes for continuous monitoring would cause undesirable animal distress, possibly compromising the data. Finally, MR images were obtained post cell infusion from several of the experimental subjects, precluding the use of standard implantable systems for continuous monitoring. Accordingly, the LifeShirt® was selected as a preferable non-invasive monitoring method. For this study, a modified limb Lead I ECG configuration worked well in the ambulatory swine.

Nine specific pathogen-free (Michigan State University) Yorkshire cross domestic swine (28 – 38 kg) of mixed gender were used in the study. The LifeShirt® was applied to each animal during anesthesia and initial measurements were performed to verify that the device accurately measured the ECG. ECGs were acquired at 200 Hz and digital data were stored on a flash memory card that contained at least 26 hours of memory. Measurements were performed for 3-10 days. The flash cards were replaced and data was uploaded toa PC at semi-regular intervals. After uploading, the digital data was decrypted and displayed using VivoMetrics' VivoLogic software. For subsequent analysis, the data was converted to MATLAB-compatible data files.

B. QRS Detection and PVC Identification

The digital ECG data are analyzed post-acquisition in two phases: preliminary QRS identification and template-based cross-correlation for PVC detection. The QRS complexes have larger up- and down-strokes than the other ECG waves, i.e., the QRSs have greater slew rates than the P- or T-waves. Therefore, in order to identify QRS complexes, the digital ECG voltage data (V) is differentiated with respect to time, $\delta V/\delta t$:

$$\frac{\delta V}{\delta t} = \frac{V(k) - V(k-1)}{t(k) - t(k-1)}, k = 2, .3, .., end(V) \quad (1)$$

Where k represents a discrete data point of the ECG or time series (t). Differentiation effectively high-pass filters the ECG; retaining the high frequency QRS complexes and attenuating the P- and T-waves and low frequency noise. The differentiated ECG record is subsequently squared in order to rectify and nonlinearly augment the peaks in the signal [7]. The differentiated QRS peak values are typically 2-3 orders of magnitude greater than the other waves, making QRS peaks clearly discernible from the other ECG waves. A user-defined threshold is set at a value that is expected to be exclusively exceeded by differentiated ECG voltage values corresponding to QRS complexes. A sliding window is used to identify the maximum value in each ECG cycle that exceeds the prescribed threshold. The time points corresponding to each QRS peak are stored for subsequent analysis and the QRS waves are marked in the raw ECG record.

Time domain cross-correlation is performed to morphologically compare each beat to a normal beat template. In the initial step, the user defines a QRS template from a sinus-originated beat, which is stored for subsequent analysis (*temp*). The template is not compared to the entire ECG record; instead, it is compared to each QRS by cross correlating each cycle with respect to the fiducial points identified by the differentiation step [8]. Comparison was performed using a normalized covariance function in order to remove any DC components or baseline drift from the correlation calculation:

$$r_{QRS-temp} = \max\left\{ \frac{\sum_{i=1}^{M}\left(QRS_i - \overline{QRS}\right)\left(temp_i - \overline{temp}\right)}{\sqrt{\sum_{i=1}^{M}\left(QRS_i - \overline{QRS}\right)^2}\sqrt{\sum_{i=1}^{M}\left(temp_i - \overline{temp}\right)^2}} \right\} \quad (2)$$

Where $r_{QRS-temp}$ is the maximum cross-correlation coefficient value, M is the length of QRS template, $\overline{QRS}$ and $\overline{temp}$ are the arithmetic means of the QRS under examination and QRS template, respectively. PVCs typically have larger amplitudes and longer durations than the normal beats; therefore, the morphological similarity between the template and each beat are quantified by the $r_{QRS-temp}$. As the level of agreement between the QRS and the QRS template increases, the $r_{QRS-temp}$ value approaches 1, indicating that the QRS is a sinus-originated beat. Conversely, the cross-correlation coefficient approaches 0 at QRS complexes that are dissimilar, i.e., PVC beats. The maximum values of the cross-correlation coefficients for each QRS are plotted as a function of time and threshold levels for normal and PVC beats are defined. QRS complexes whose $r_{QRS-temp}$ values are greater than the high PVC threshold limit are classified as normal beats, and those that are within the PVCs threshold bands are classified as PVC beats (see Fig. 1). The frequency and time stamps of each beat type are stored for subsequent analysis for consecutive ventricular rhythm (cVR).

The algorithm was initially tested on ECG records from the MIT-BIH arrhythmia database [9]. The database contains 48-30 minute excerpts of two channel ECG recordings obtained from ambulatory human subjects. The recordings were independently analyzed by two cardiologists and arrhythmias are annotated and time stamped. We selected nine records where PVCs were evident and compared the algorithm performance with the cardiologist annotations (Record ID# 103, 106, 116, 119, 200, 208, 215, 223, and 233.) The following parameters were used for comparing the algorithm PVC detection with annotations in the recordings:

1. Percent difference between the total number of normal QRSs and PVCs,
2. Sensitivity and specificity of the detection algorithm
3. Average magnitude of the time discrepancy between the algorithm and MIT-BIH annotated PVC time stamps.

The algorithm was employed using MATLAB 7.0.1.

C. Statistics

Discrepancies between the MIT-BIH annotations and algorithm detections are presented as percent difference (%). The overall trends are presented as mean ± standard error of the mean (SEM).

III. Results and Discussion

A. Algorithm Compared with MIT-BIH Database

The average error between the algorithm and database annotated beats, including normal beats and PVCs, was 0.832% ± 0.141%. The accuracy of the method was attributable to the two-phase approach to QRS detection. The differentiation provided an estimate of the QRS occurrences while the final QRS identification was performed using cross-correlation. The QRS complexes identified by the algorithm were time stamped, and the markings were used to calculate ECG parameters including R-R intervals and beat-to-beat heart rate.

Normal QRS beats typically exhibited high (> 0.9) cross-correlation coefficient values, while the PVC beats had noticeably reduced coefficient values. Thresholds were set to classify beats as normal or PVCs (see Fig. 1). The algorithm accurately detected the quantity and temporal location of PVCs in the MIT-BIH records. The average error between the PVC occurrences detected by the algorithm compared to the annotations was 3.07% ± 1.14%

(see TABLE I). The algorithm-detected PVCs were typically within 20 ms of the MIT-BIH PVC annotations (19.3 ms ± 6.64 ms).

False positive and false negative PVC detections were quantified by comparing the time stamps of the algorithm-detected PVCs with MIT-BIH annotations. Both the average sensitivity and specificity of the algorithm exceeded 95%, indicating that the algorithm could accurately detect PVCs and discern the PVCs from normal beats (see TABLE II).

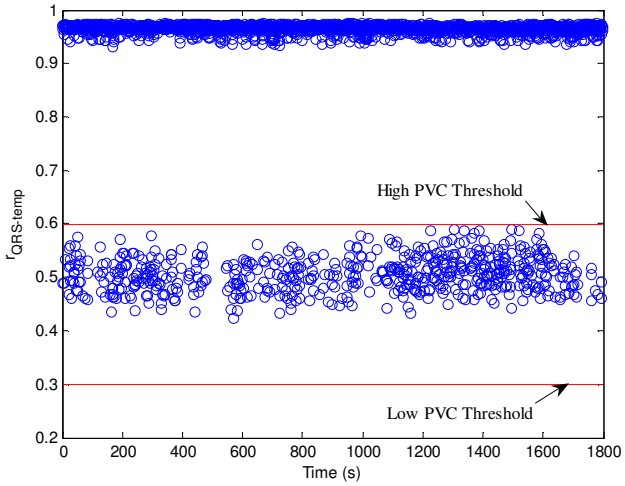

Fig. 1 Maximum cross-correlation coefficient values vs. time for each cardiac cycle. Upper and lower threshold limits for PVCs are marked in the plot (MIT-BIH Record #119).

TABLE I
ALGORITHM PVCS COMPARED WITH THE MIT-BIH ANNOTATED PVCS

Database Record #	*MIT PVC (True +)*	*Algorithm PVC*	*% Diff*
103	0	0	0%
106	520	506	2.69%
116	109	110	0.917%
119	444	444	0%
200	826	761	7.87%
208	992	925	6.75%
215	165	168	1.82%
223	473	506	6.98%
233	831	826	0.602%
Average			3.07%
SEM			1.07%

TABLE II
FALSE POSITIVES, FALSE NEGATIVES, SENSITIVITY, AND SPECIFICITY OF PVC ALGORITHM COMPARED WITH MIT-BIH ANNOTATED PVCS

Database Record #	*MIT PVC (True +)*	*False +*	*False -*	*Sensitivity*	*Specificity*
103	0	0	0	N/A	N/A
106	520	34	46	91.9%	97.7%
116	109	2	1	99.1%	99.9%
119	444	0	0	100%	100%
200	826	20	85	90.7%	98.9%
208	992	19	83	92.3%	99.0%
215	165	6	2	98.8%	99.8%
223	473	63	40	92.2%	97.1%
233	831	13	16	98.1%	99.4%
Average				95.4%	99.0%
SEM				1.31%	0.356%

B. Algorithm Applied to LifeShirt® ECG Data

After preliminary testing, the algorithm was applied to records obtained from nine animals that received cell infusions. Digital ECG data recorded from the LifeShirt® acquisition system on ambulatory swine were de-crypted and converted into MATLAB compatible data files. The data sets were segmented into 60 minute epochs and analyzed using the PVC detection algorithm.

The LifeShirt® data were subject to greater levels of noise than the MIT-BIH records. This was attributable to motion artifacts or electrodes becoming dislodged or damaged during the recording periods. Interference from noise was manifested by false positive or negative QRS detections during the differentiation phase, decreased cross-correlation-coefficient values for normal QRS complexes, and/or decreased cross-correlation coefficient values not commensurate to PVC occurrences (see Fig. 2). These noisy periods affected the algorithm accuracy, but the effects of the noise were mitigated by qualitatively examining the recordings before applying the algorithm. Excessively noisy regions, i.e., regions where neither normal nor arrhythmic QRSs were evident, were excluded from the algorithm analysis.

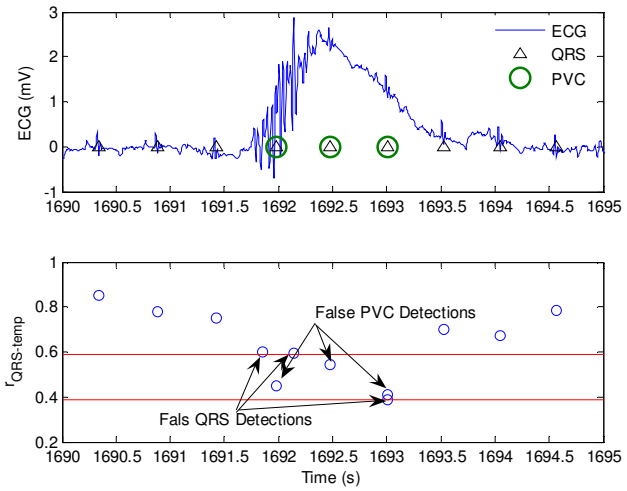

Fig. 2 False QRS and PVC detections due to noise and motion artifacts inducing decrease in cross-correlation coefficients in ECG measured from an ambulatory swine.

The algorithm was used to examine over 200 hours of swine ECG data. The techniques were found to significantly reduce analysis time compared to manual examination of the recordings. Additionally, a second MATLAB subroutine was developed and was used to identify regions of cVR. cVR was identified by areas of three or more consecutive PVCs, and the second subroutine was utilized the time stamps of the PVCs to detect: the on- and offset of cVR regions; duration and number of beats in the cVR regions; and beat-to-beat cycle lengths and heart rates of the cVR regions. The cVR data were used to identify regions of accelerated idioventricular rhythm (AIVR, cVR with heart rate < 100 bpm) and ventricular tachycardia (VT, cVR with heart rate > 100 bpm). These data, along with the frequency

of PVCs, were used to quantify the arrhythmias that occurred due to the myocardial cell therapy. From these analyses, we demonstrated that the infusion of cells into healthy porcine myocardium triggered self-limiting arrhythmias that typically occurred within 6.4 ± 1.4 hours to 28.9 ± 5.6 hours post cell delivery (see Fig. 3 and Ref [4] for detailed results).

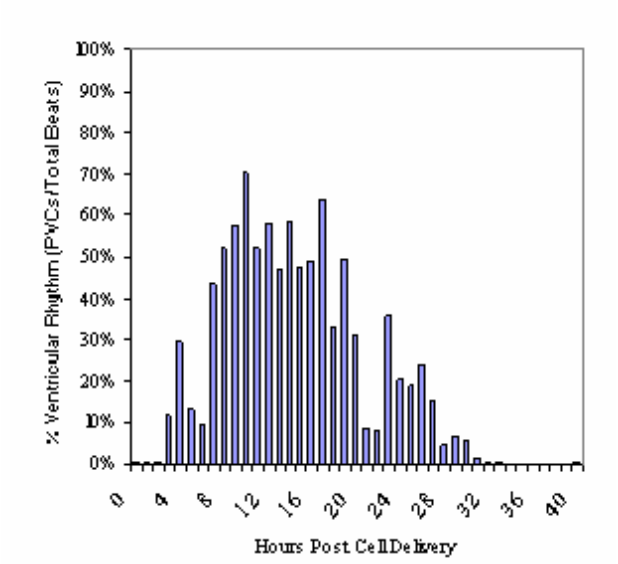

Fig. 3 % Ventricular rhythm vs. time post cell delivery for swine with ECG monitored using LifeShirt®.

IV. Conclusions and Future Work

In this study, ECGs were continuously monitored from ambulatory swine using a LifeShirt® acquisition system. We have demonstrated here for the first time that the system can be used to accurately measure ECG in a porcine animal model. We utilized this device because it facilitated continuous monitoring of the ECGs from the swine; providing ECG data for significant time periods without restricting animal motion or creating additional distress. There were some inherent difficulties in using this method. Portions of the ECGs were lost or compromised due to motion artifacts or dislodged leads. To combat these issues, we examined the integrity of the recorded data at semi-regular intervals (< 12 hours) and omitted noisy portions from subsequent analysis. We were able to demonstrate that the LifeShirt® can be successfully used to continuously measure porcine ECG in an ambulatory setting.

To quantify the frequency and onset of arrhythmias that arose in the days following cell infusion, an offline PVC detection algorithm was developed. Template-based cross-correlation techniques have been previously used to detect arrhythmic events in shorter duration, noise-free records. We chose to utilize this method here because of its ease of implementation; the results were easily interpreted compared to more complex ECG analysis techniques, e.g., wavelet analysis or time-frequency domain techniques; and this method does not require signal averaging or high resolution ECG data. The method was tested against cardiologist-annotated records from the MIT-BIH arrhythmia database and demonstrated to be highly sensitive and specific. We were able to use the algorithm for robust identification and quantification of PVCs.

In future iterations of the algorithm, the template-based cross-correlation technique can be further employed to detect other inter-wave components, i.e., the P- and T-waves. T-wave marking is of particular interest because it can be used to quantify the QT interval, an important diagnostic parameter for studies of pharmacological agents. Additionally, the R-wave peak and the T-wave can be used to quantify ST segment elevation or depression, which is indicative of myocardial ischemia. This could be used to determine if there is some correlation between the ST segment level and the onset of cVR, implying that ectopic beats are attributable to ischemia. The development of practical ambulatory electrocardiographic monitoring and analysis for swine provides a new aspect for future pre-clinical cell and drug evaluation.

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