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Methods for Accurate Measures of Total Ventricular Activation Time

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***Abstract*—The purpose of this study was to determine improved measures of total ventricular activation time for the diagnosis and treatment of patients undergoing cardiac resynchronization therapy (CRT). This work investigates the accuracy of a root mean square (RMS) based QRS width computed from unipolar electrograms (EGs) measured in heart for representing true total ventricular activation time (TVAT). The study also investigated the use subsets of EGs obtained from the endocardial and epicardial surfaces as indicators of TVAT. Transmural needle electrodes (96) were used to obtain 960 EGs from six normal isolated canine hearts. RMS-based QRS-widths from the endocardial and epicardial surfaces and volume were compared to the TVAT measured from all 960 EGs. No statistically significant differences were found in RMS-based QRS-widths obtained from all three sets of electrograms when compared with true TVAT. Activation times obtained from endocardial and epicardial surfaces were found to be poor indicators of true TVAT. The results support the use of RMS techniques for providing more accurate measures of TVAT.**

I. Introduction

CARDIAC resynchronization therapy (CRT) is becoming a widely used clinical therapy for patients presenting with heart failure and QRS durations of greater than 120 ms and a left bundle branch block morphology. The clinical benefits from pacing therapies have preceded experimental optimization and a thorough understanding of the component mechanisms. Recent reports suggest, some 40% of heart failure patients treated with CRT do not show benefits [1]. Even patients that do not show benefits in cardiac output as assessed by echocardiography still show reductions in QRS width as measured in the body surface ECG[2]. There is a strong need to develop better methods of assessing the electrical activity of the heart to provide better insight into the mechanisms of CRT therapy benefits.

Currently, only the standard electrocardiogram (ECG) is *widely* used to provide insight into the heart's electrical activity. More recently, results of inverse calculations have provided epicardial activation maps from body surface EGs [3-5] from patients. Techniques introduced by Fuller *et al*. make use of the root mean square (RMS) of EGs to derive more accurate information about the activation and recovery sequences of the heart [6, 7]. Utilizing the RMS of any set of electrograms, the effective strength of the signals can be analyzed. Specific intervals of the RMS signals can be selected consistently based upon points of local maxima of the curvature function [6]. By this process an objective, and perhaps more accurate, measure of true ventricular activation time can be obtained.

The QRS-width is assumed to be physiologically similar to TVAT as it represents the depolarization of the ventricles. Thus the purpose of this study was to investigate the use of RMS-based techniques to 1) determine if QRS-width is an accurate measure of true TVAT and 2) assess if TVAT can be accurately determined from various subsets of ventricular EGs. It was hypothesized that true TVAT can be accurately obtained the RMS-based QRS-width from the myocardial volume or endocardial and epicardial surfaces EGs. This study attempts to answer these questions from data obtained from normal canine hearts.

II. Methods

A. Software Development

An analysis tool was developed utilizing MATLAB® version 7.0.4 (The MathWorks, Inc., Natick, Massachusetts) to interactively analyze EG data. This tool determines interval widths based on the maximum curvature of the electrograms. The program first calculates the RMS of the using equation (1),

$$\mathrm{RMS}(t) = \sqrt{\frac{\sum_{i=1}^{n} v_i^2(t)}{n}} \quad , \tag{1}$$

where n is the number of leads sampled and $v_i(t)$ is the potential from EG *i* at time t [7]. The curvature of the RMS waveform was then calculated based on a method for approximating derivatives utilizing a least-squares fit of a quadratic function [13] with the equation:

$$\mathrm{Curvature} = \left|\frac{\mathrm{d}^2 v}{\mathrm{d}t^2}\right| \Bigg/ \left[1 + \left(\frac{\mathrm{d}v}{\mathrm{d}t}\right)^2\right]^{3/2} \quad , \tag{2}$$

where v is the RMS voltage and t is time[6, 8].

B. Experimental Preparation

Six experiments were conducted in accordance with the University of Utah Institutional Animal Care and Use Committee and conformed to the Guide for the Care and Use of Laboratory Animals (NIH 1985). Mongrel dogs, weighing 23.0 ± 3.85 kg (mean ± standard deviation, 4 males, 2 females), were anesthetized with 30 mg/kg pentobarbital I.V. with additional amounts added as necessary. The heart was then rapidly excised and perfused in a modified Langendorff procedure. Ninety-six transmural needle electrodes, each with

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10 electrodes along the shank, were placed throughout the left and right ventricles spanning the free wall from endocardium to epicardium. The interelectrode spacing along the needle shank was 1.6 mm for the left ventricle and 1.0 mm for the right ventricle [9]. The recorded unipolar EGs were referenced to a remote electrode placed at the aortic root. Although injury current can be seen in the electrograms in the form ST-segment elevation, insertion of needle electrodes has been shown to have undetectable effects on myocardial activation, function, and structure [10, 11].

B. Data Collection and Analysis

Recordings were made during activation sequences: atrial pacing and anterior ventricular pacing from the endocardial and epicardial surfaces of the right and left ventricles under normal conditions and after simulation of total heart block. Flushing both ventricular cavities with Lugol solution for three minutes to inactivate the specialized Purkinje conduction system simulated total heart block. Signals, amplified and bandpass filtered from 0.03 to 500 Hz, were digitized at a 1 kHz sampling rate with 12-bit resolution and stored on a Macintosh computer [12]. Potential values were gain-adjusted using calibration signals and linear base lines were established between consecutive T-P intervals.

Activation time was determined as the time of the minimum of the time derivative in the QRS complex [13]. Total ventricular activation time (TVAT) was defined as the difference between the earliest and latest measured activation time from all 960 EGs recorded from the entire volume. For the endocardial and epicardial surfaces, total activation time (TAT) was calculated similarly by using the earliest and latest activation times from only the 192 subendocardial EGs or 192 subepicardial EGs, respectively.

C. Statistical Analysis

Values of total activation time were compared via simple linear regression and repeated measures analysis of variance (ANOVA) with $p < 0.05$ indicating significant differences. All values are expressed as the mean ± the standard deviation.

III. Results

Fig. 1 shows typical output from the developed software for RMS-based QRS-width determination using the maximum curvature. The top panel shows all 960 EGs plotted as a function of time. The middle panel shows the RMS computed from the 960 EGs and the bottom panel shows the computed curvature of the RMS signal with the dashed lines indicating the QRS width. All values of QRS width reported in this paper were determined by the maximum curvature of the RMS signal.

A. QRS-Width and TVAT Relationships

Values of QRS widths measured from the volume EGs, epicardial EGs and endocardial EGs were compared with the TVAT via linear regression. These results are presented in terms of the correlation coefficient, R, in Table 1 along with *p*-values. The results indicated very strong correlation in all cases. Moreover, the results of a repeated measures ANOVA test of the mean differences of the three measures of QRS width and TVAT provide a *p*-value of 0.92.

B. Volume TVAT and Surface TAT

Table 2 presents the values of QRS width and TAT determined from the endocardial EGs, epicardial EGs and the volume. Repeated measures ANOVA test of the mean differences of the ventricular volume, endocardial surface and epicardial surface TATs resulted in a *p*-value less than 0.001. Post hoc comparisons indicated that the TAT measured from the endocardial or epicardial surfaces are poor indicators of the activation time for the entire ventricular volume.

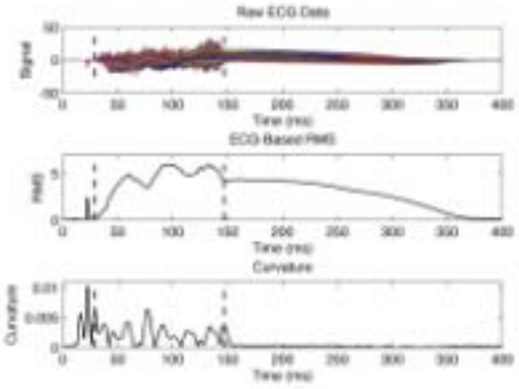

Fig. 1. Top panel - 960 EGs recorded from the ventricular volume during right ventricular endocardial pacing after simulation of total heart block. Middle panel – Computed RMS signal. Bottom panel – Curvature computed from the RMS signal. Dashed lines indicate QRS width.

IV. Conclusion

The purpose of this study was to investigate the use of RMS-based QRS-widths as accurate indicators of total ventricular activation time. It was hypothesized that a RMS-based QRS-width obtained from any subset of EGs would accurately represent TVAT. The results show through quantitative statistical analyses that true TVAT is strongly and accurately represented by endocardial, epicardial or

Comparison	Correlation (*R*)	*p* - Value
Volume and Endocardial QRS Widths	0.9798	p < 0.0001
Volume and Epicardial QRS Widths	0.9869	p < 0.0001
Volume QRS Width and TVAT	0.9685	p < 0.0001
Endocardial QRS Width and TVAT	0.9491	p < 0.0001
Epicardial QRS Width and TVAT	0.9681	p < 0.0001

TABLE 1. Linear regression comparisons of ventricular volume or epicardial and endocardial surface QRS widths with each other and with total ventricular activation time (TVAT).

Activation Sequence	Volume QRS Width	Endocardial QRS Width	Epicardial QRS Width	Volume TVAT	Endocardial TAT	Epicardial TAT
Atrial Pacing	52.3 ± 15.8	53.8 ± 17.0	50.2 ± 15.7	50.9 ± 17.3	41.0 ± 14.9	44.7 ± 16.9
Endocardial Pacing	85.4 ± 10.8	83.7 ± 10.8	84.5 ± 10.9	82.2 ± 10.8	71.1 ± 9.2	74.7 ± 11.4
Epicardial Pacing	86.4 ± 10.9	85.2 ± 9.0	87.8 ± 13.2	88.9 ± 11.3	71.2 ± 8.5	85.3 ± 13.9
Endocardial Pacing Post Total Heart Block	103.1 ± 17.0	101.5 ± 17.2	100.5 ± 15.5	103.8 ± 11.7	97.2 ± 15.2	97.5 ± 13.0
Epicardial Pacing Post Total Heart Block	97.8 ± 15.4	96.6 ± 17.4	97.1 ± 15.0	100.8 ± 13.5	89.9 ± 12.3	95.6 ± 16.6

TABLE 2 - Average QRS widths and total ventricular activation times (TVAT) or total activation times (TAT) from the ventricular volume, endocardial surface and epicardial surface in ms for five types of activation sequences.

myocardial volume RMS-based QRS-widths.

Additionally, statistical analysis has shown that TAT obtained on the epicardial or endocardial surfaces may be a significantly inaccurate representation of actual TVAT. When the means of the various TATs, TVATs, and RMS-based QRS-widths are compared by pacing type (Table 2), it can be noted that endocardial or epicardial TAT can underestimate true TVAT by about 20 ms depending on pacing and activation sequence. It can also be seen from Table 2 that the means of the RMS-based QRS-widths from the various surfaces are consistently representative of true TVAT. Results presented by Punske *et al*. state endocardial TAT may not be representative of TVAT and that the accuracy of epicardial TAT is highly dependant upon the location of the pacing site [14]. The results presented here extend these findings to note that TAT from both surfaces are poor indicators of TVAT. The RMS-based QRS-width, however, is a reliable indicator of TVAT from both surfaces. The results by Fuller *et al*. suggested that the QRS width of the RMS may be a good indication of TVAT [6], but lacked the measurements from the volume to show this to be true.

Clinically, the QRS-width is commonly used to approximate the duration of ventricular activation. However, the QRS-width has not been proven to be an accurate indicator of true TVAT, which is the focus of our current work. However, these results indicate that very accurate measures of TVAT can be obtained clinically through the use of a RMS based measures obtained from EGs recorded from balloon catheters in the endocardium [15] to measure endocardial TAT or from epicardial potentials computed via inverse calculations from the body surface ECG [3-5] to measure the epicardial surface TAT. For clinical cases, such at assessment of patients receiving CRT, where accurate measures of electrical activity are warranted, these techniques can provide this important information with demonstrated accuracy.

V. References

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