Experimental Measures of Ventricular Activation and Synchrony

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Background: *A widened QRS complex as a primary indication for cardiac resynchronization therapy (CRT) for heart failure patients has been reported to be an inconsistent indicator for dyssynchronous ventricular activation. The purpose of this study was to conduct a detailed experimental investigation of total ventricular activation time (TVAT), determine how to measure it accurately, and compare it to the commonly used measure of QRS width. In addition, we investigated a measure of electrical synchrony and determined its relationship to the duration of ventricular activation.*

Methods: *Unipolar electrograms (EGs) were recorded from the myocardial volume using plunge needle electrodes, from the epicardial surface using "sock" electrode arrays, and from the surface of an electrolytic torso-shaped tank. EGs were analyzed to determine a root mean square (RMS)-based measure of ventricular activation and electrical ventricular synchrony.*

Results: *The RMS-based technique provided an accurate means of measuring TVAT from unipolar EGs recorded from the heart, the entire tank surface, or the precordial leads. In normal canine hearts, a quantification of ventricular electrical synchrony (VES) for normal ventricular activation showed that the ventricles activate, on average, within 3 ms of each other with the left typically activating first.*

Conclusion: *Conclusions from this study are: (1) ventricular activation was reflected accurately by the RMS width obtained from direct cardiac measurements and from precordial leads on the tank surface and (2) VES was not strongly correlated with TVAT. (PACE 2008; 31:1560–1570)*

mapping, electrophysiology—basic, CRT, pacing, animal studies

Introduction

Over the past decade, cardiac resynchronization therapy (CRT), a ventricular pacing treatment aimed at restoring synchronous contraction of the ventricles, has been shown to improve outcomes for heart failure patients.[1–3] CRT utilizes ventricular stimulation, an electrical therapy, in response to mechanical insufficiency. A primary indication for CRT is a widened QRS complex, taken as a measure of increased duration of the electrical activation of the ventricles.[4,5] In the past, one of the indications of successful CRT was shortening of the QRS complex, inferring more synchronous activation and contraction.[6] However, some research indicates that there is a much more complex relationship between conduction delays and mechanical dyssynchrony in diseased hearts.[3]

The important clinical success from electrical therapeutic approaches has created a need for a basic understanding and detailed quantification of electrical activation of the ventricles, as well as a need to develop a measure of electrical synchrony to enhance our knowledge of the relationship between electrical and mechanical synchrony. While the working definition of electrical synchrony is the simultaneous activation of the left and right ventricles, this assumption of the natural sequence of activation has not been verified with experimental measurements. Despite a widely accepted relationship between QRS width and ventricular synchrony, there are few data on how well the QRS width relates to total ventricular activation time (TVAT) and the implications toward electrical synchrony. In addition, there is no validated measure of synchrony that can be related to TVAT. Therefore, the purpose of this study was to conduct a detailed experimental investigation of TVAT, determine how to measure it accurately, and compare it to QRS width as measured from the electrocardiogram (ECG). In addition, we investigated a recently published measure of electrical synchrony applied to patients undergoing CRT that examines differences in the mean activation

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times between the left and right ventricles[7] and determined its relationship with the ventricular activation time.

Experimental data were obtained from high-resolution electrical imaging, achieved by recording unipolar electrograms (EGs) from throughout the myocardial volume using plunge needle electrodes, from the epicardial surface using "sock" electrode arrays, and from the surface of an electrolytic torso-shaped tank. A maximum curvature algorithm was applied to a computed root mean square (RMS) signal from multiple, simultaneously collected EGs from the heart or torso surface to investigate accurate determination of ventricular activation. These results were compared with measures of TVAT obtained from high-resolution electrical recordings directly from the myocardial volume and with QRS width measured from the ECG. Also using EGs measured directly from the myocardial volume, we carefully computed the average activation times of each ventricle and investigated how the difference was related to TVAT.

By establishing accurate measures of ventricular activation time and ventricular electrical synchrony (VES), this study endeavored to use experimental measurements to give a more definitive understanding of the effectiveness and accuracy of the measure of QRS width as a surrogate for TVAT and a quantitative definition to electrical synchrony.

Methods

Experimental Preparation

All 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. A total of 24 mongrel dogs (13 males, 11 females, 25.4 ± 5.1 kg) were anesthetized with 30 mg/kg pentobarbital I.V. with additional amounts administered as needed and included in one of three separate experimental protocols.

The first experimental protocol consisted of nine studies in which each heart was rapidly excised and perfused using a modified Langendorff procedure.[8] Ninety-six (n = 6), 147 (n = 2), or 152 (n = 1) transmural plunge needle electrodes with 10 electrodes along each shank were then placed throughout the entire ventricular myocardial volume (Fig. 1A).[9] The needles were carefully inserted into the ventricles to avoid major vessels and the electrode locations were digitized using a Microscribe 3D digitizer (Immersion, San Jose, CA, USA). Endocardial data sets were obtained by selecting EGs recorded from electrodes 1 and 2 from each needle. Similarly, epicardial data sets were defined as electrodes 9 and 10 from each needle. Unipolar EGs were referenced to a remote electrode placed at the aortic root. Recordings were made during different activation sequences: atrial drive, and anterior left and right ventricular endocardial and epicardial pacing under normal conditions. The average distance between electrodes in these experiments was 4.5 ± 3.1 mm, with the largest measured distance between electrodes on the epicardial surface of 41.6 mm. In six of the experiments, after conducting the pacing protocol, both ventricular cavities were flushed with Lugol solution for 3–5 minutes to inactivate the specialized Purkinje conduction system and the pacing protocol was repeated.[10] Four additional isolated Langendorff-perfused experiments were conducted to study left ventricular (LV) activation and the timing of the activation of the septal wall. In this preparation, previously described,[11] the right ventricular (RV) wall was removed to expose the septum. Intramural needles were inserted in the LV free wall as well as the exposed septal wall.

The second set of six experiments used isolated hearts perfused with oxygenated blood

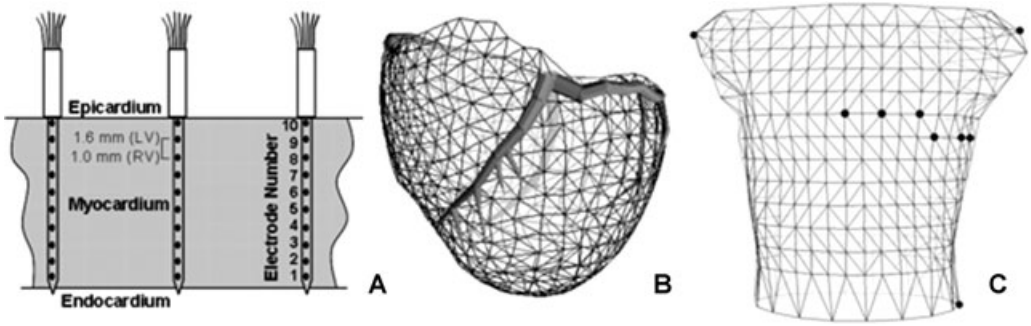

Figure 1. *Graphical representations of the various experimental protocols employed. (A) Schematic of plunge needle electrodes oriented in the myocardium. (B) Geometric mesh of a 490-electrode epicardial array electrode covering both ventricles. (C) Torso tank geometric mesh with the pseudo-12-lead ECG electrodes marked.*

provided by a support dog. The hearts were placed in the appropriate anatomical position in a small human torso-shaped electrolytic tank described previously in detail.[12,13] Unipolar EGs were recorded from a 490-electrode sock array placed over the ventricular surface and from the entire surface of the torso tank (384 electrodes) (Figs. 1B and C) with respect to Wilson's Central Terminal. The Lead II, three bipolar limb leads, precordial leads, and the 12-lead ECGs were derived from selected electrodes sites located on the torso tank surface (Fig. 1C). Activation sequences included right atrial pacing as well as anterior left and right ventricular epicardial pacing under normal conditions.

In a third set of five experiments, the hearts were exposed via a medial thoracotomy and suspended in a pericardial cradle.[14] A 247-electrode sock array was placed over the heart covering the surface of both ventricles. Unipolar EGs were recorded from the heart with respect to a remote lead placed on the left leg. A three-lead (three bipolar limb leads) or a single Lead II ECG was simultaneously recorded during various activation sequences, including atrial drive, left and right ventricular pacing and biventricular pacing.

Data Collection and Analysis

Signals, amplified and bandpass filtered from 0.03 to 500 Hz, were either simultaneously recorded (n = 20)[15] or recorded in consecutive banks of 192 (n = 4)[16] at a 1-kHz sampling rate with 12-bit resolution and stored on a Macintosh computer. Potential values were gain-adjusted and linear base lines were established between consecutive T-P intervals. Signals with an activation downstroke characterized by a substantially smaller modulus of the derivative than the other signals from the same needle, suggesting they were located outside the myocardium, or with poor signal quality were removed from the data set.

Local excitation time was estimated as the time of the minimum derivative of the unipolar EG.[14,17,18] All excitation times were referenced to the time of the pacing artifact or the onset of ventricular electrical activity for nonventricularly paced beats. Activation time (AT) was defined as the difference between the earliest and latest measured excitation times from any set of EGs. Maps were analyzed to ensure high electrode density in the early and late regions of activation to minimize errors in the estimation of TVAT. As shown in the examples in Figures 2A and B, with the earliest excitation time of 13.1 ms on the anterior epicardium and latest excitation time of 86.8 ms on the posterobasal epicardium, the AT was 73.7 ms as measured on the epicardial surface. Ideally defined as the duration from the time of the first depolarizing (activating) ventricular cell to that of the last depolarizing ventricular cell, TVAT provides a quantitative representation of the timing of the spread of activation throughout the ventricles.[17] We estimated TVAT as the latest minus the earliest excitation time as measured from 92 to 150 plunge needle electrodes distributed throughout the ventricular free walls. Excitation time irregularities were identified and eliminated from the data set using the arrival of the depolarization wave front seen in the time series of isopotential maps[14] visualized using Map3D software (http://www.sci.utah.edu/ncrr/software/map3d.html).[19]

To calculate the RMS of potentials (V_{RMS}) from the heart or body surface, an analysis tool

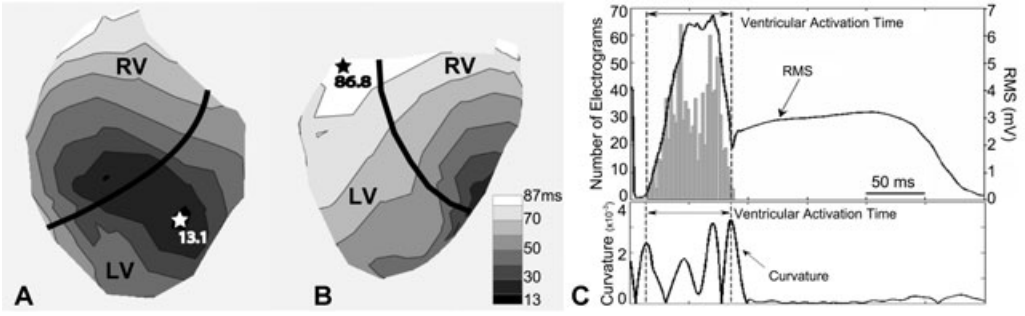

Figure 2. *Isochronal maps of (A) anterior and (B) posterior aspects of the epicardial surface with the onset and termination of activation marked by a white and black star, respectively. (C) The resultant RMS signal generated from 960 EGs with ventricular activation time marked, overlaid on a histogram of activation time from each EG in the ventricular myocardial volume. Below the RMS signal is the computed curvature showing the marking of the earliest and latest peaks. Data shown in all panels are from the same anterior left ventricular epicardially paced beat.*

was developed utilizing MATLAB® (MathWorks, Inc., Natick, MA, USA) using Equation (1):

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

where n is the number of EGs sampled and $v_i(t)$ is the potential of EG i at time t.[20]

Curvature of the RMS waveform was calculated by Equation (2):

$$\text{Curvature}(t) = \left|\frac{d^2V_{RMS}}{dt^2}\right| \Bigg/ \left[1 + \left(\frac{dV_{RMS}}{dt}\right)^2\right]^{3/2} \quad (2)$$

where V_{RMS} is the RMS potential and t is time.[14,21] Peaks in the curvature waveform represented significant deviations from baseline in the RMS signal allowing regions of the RMS waveform to be selectively marked. The onset and end of ventricular activation was marked using the first and last peaks associated with ventricular electrical activation exceeding a threshold of three standard deviations above the noise level in the RMS-based curvature signal as shown in Figure 2C.[21]

VES was measured as the mean right ventricular activation time (RVAT) minus the mean left ventricular activation time (LVAT).[7] Each ventricular mean AT was calculated as the average ATs from all EGs recorded within the respective ventricular free walls.

Statistical Analysis

Statistical calculations were made using Instat® (GraphPad Software, La Jolla, CA, USA) to compute both the repeated measures analysis of variance (ANOVA) with Tukey–Kramer multiple comparisons, and the nonparametric Spearman's correlation coefficient, R, via simple linear regression. For each test, P-values less than 0.05 were considered significant. All values are expressed as mean ± standard deviation.

Results

Quantifying TVAT from the Heart

Figure 2 shows an anterior view (panel A) and posterior view (panel B) of an epicardial excitation time map computed from EGs recorded from electrode 10 (outermost) of 96 plunge needles for a beat paced from the anterior LV epicardium. For this example, both the earliest (indicated by a white star) and the latest (indicated by a black star) excitation times measured from all 960 electrodes occur on the epicardial surface, resulting in the same value of 73.7 ms for epicardial AT and TVAT. Panel C shows the RMS curve for the same beat computed from the 960 EGs recorded from the myocardial volume. Under the RMS curve are histograms of the associated excitation times from the entire ventricular volume. Panel C demonstrates that excitation times begin and end with the onset and end of the portion of the RMS signal relating to ventricular electrical activity as marked with vertical bars in the figure using the maximum curvature technique. Throughout this paper, this marked region is referred to as the RMS width for brevity.

We first assessed the accuracy of ATs estimated from EGs recorded from the left and right ventricular free walls with only a few EGs from the septal wall (those which were accessible from the epicardium at the interventricular groove) as a measure of TVAT. For this measurement we used four isolated hearts with the RV free wall removed and placed needles in both the LV free wall and the exposed septal wall. Results showed that total septal activation fell entirely within the AT of the LV free wall following atrial stimulation (see, for example, Fig. 3A). On average, the LV free wall activated 2.1 ± 4.0 ms before the septal wall and continued 3.5 ± 4.0 ms beyond the last septal excitation time. For epicardial and endocardial LV pacing, the septal wall began activation 30.6 ± 9.8 ms after the LV free wall. The latest septal excitation time as measured from the needles was very close to that of the latest excitation for the LV free wall for both LV epicardial and endocardial pacing sequences (average difference, 0.4 ± 0.8 ms) in three of four hearts. For the remaining heart, septal activation finished 14 ms and 12 ms later than the LV for epicardial and endocardial pacing, respectively. In this heart, the pacing site was directly opposite the septal wall on the left lateral free wall, ensuring that the septum was the last area to be reached by the excitation wave front. Figure 3B contains an example of the timing of the septum and LV free wall activation for LV epicardial pacing.

LV free wall and septal excitation times obtained from the exposed septum model were then compared with those from intact isolated hearts under both LV and atrial stimulation in six separate experiments. Beats were matched for pacing site and activation onset and offset for comparability with the exposed septum model experiments. Figures 3C and D show an example of RV excitation times that were later than LV excitation times for both atrial stimulation and LV epicardial pacing in intact isolated hearts. On average, the latest RV excitation times following LV pacing of the epicardium and the endocardium were 32.6 ± 9.6 and 23.7 ± 8.7 ms longer, respectively, than the latest of the LV excitation times. From these six hearts, results always showed RV free wall ATs followed the LV free wall activation by even longer than

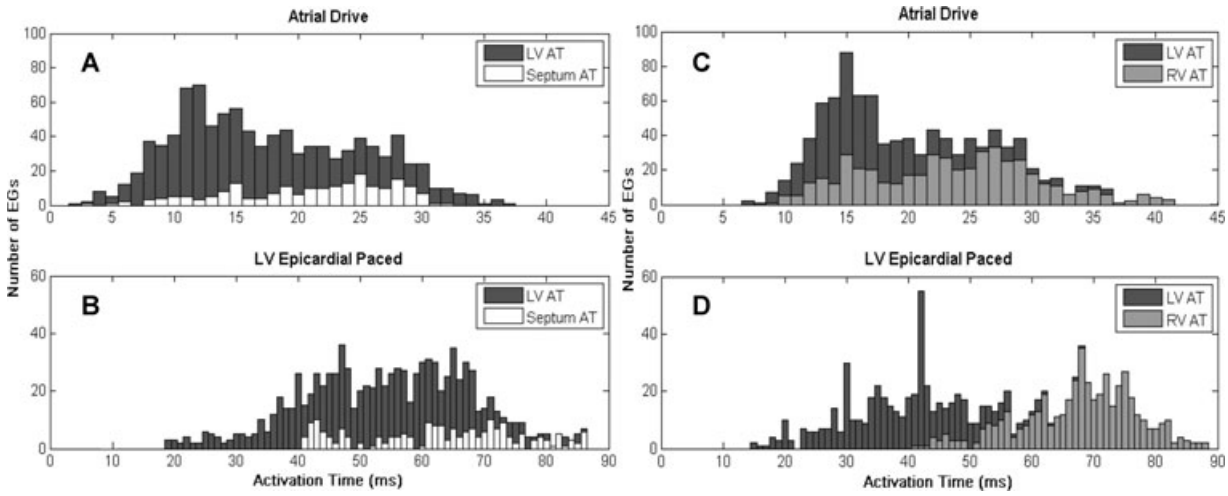

Figure 3. *Summed excitation time histograms from left ventricular free wall (black) and septal wall (white) during (A) atrial drive and (B) LV pacing. Similar histograms for the left ventricular (black) and right ventricular (gray) free walls during (C) atrial drive and (D) LV pacing.*

that seen in the exposed septal studies. Therefore, we concluded that the inclusion of only a few EGs from the septal wall would not significantly affect the measured value of TVAT in these studies.

In the first set of experiments with transmural needle recordings from the total ventricular volume, EGs were recorded when pacing from the right atrium, LV, or RV. RMS widths were computed from EGs measured from only the epicardial or endocardial surfaces as well as from the entire ventricular volume. TVAT was computed from the latest minus the earliest excitation times measured from the entire myocardial volume. The mean RMS widths and TVATs for various activation sequences are provided in Table I. Calculating the RMS width from EGs recorded from the entire myocardial volume, only epicardial, or only endocardial surfaces all accurately reflected TVAT. A multivariate repeated measures ANVOA yielded no significant differences between measured TVAT and RMS widths from the epicardium, endocardium, and myocardial volume ($P = 0.4562$, NS). Figure 4 shows an example in which histograms of the excitation times from all ventricular needle electrodes are plotted under the RMS curves generated from the ventricular volume (panel A), epicardial surface (panel B),

Table I.

Average RMS Widths in ms Obtained from the Myocardial Volume, and Epicardial and Endocardial Surfaces with the Total Ventricular Activation Time (TVAT) in ms for Various Activation Sequences Plus or Minus Standard Deviation

Pacing Location (Number of Runs)	TVAT	Volume RMS Width	Epicardial RMS Width	Endocardial RMS Width
Right atrium (6)	37.7 ± 4.1	37.5 ± 3.1	36.7 ± 2.1	38.2 ± 3.3
LV Epi (6)	84.7 ± 8.9	84.8 ± 8.9	83.5 ± 9.1	83.5 ± 10.6
LV Endo (7)	81.6 ± 9.5	81.6 ± 8.0	83.1 ± 8.1	83.6 ± 8.6
LV Epi PPI (6)	96.8 ± 13.3	93.8 ± 12.8	95.5 ± 13.0	93.5 ± 15.6
LV Endo PPI (6)	101.0 ± 10.9	100.5 ± 11.5	100.0 ± 11.1	100.3 ± 15.5
RV Epi (6)	93.9 ± 14.3	88.8 ± 15.3	93.3 ± 20.0	86.8 ± 12.8
RV Endo (4)	84.5 ± 14.1	86.3 ± 12.6	86.3 ± 11.6	85.0 ± 11.4
RV Epi PPI (4)	108.8 ± 15.1	104.5 ± 21.8	103.5 ± 23.1	101.8 ± 23.3
RV Endo PPI (4)	99.4 ± 23.4	105.3 ± 24.5	103.5 ± 23.1	101.0 ± 23.2
Mean difference from TVAT	–	2.3 ± 2.3, NS	2.0 ± 1.6, NS	2.6 ± 2.6, NS

Ventricular pacing sites were located on the anterior aspect of the heart (n = 47).
Abbreviations: PPI = Post-Purkinje inactivation; NS = not significantly different ($P > 0.05$).

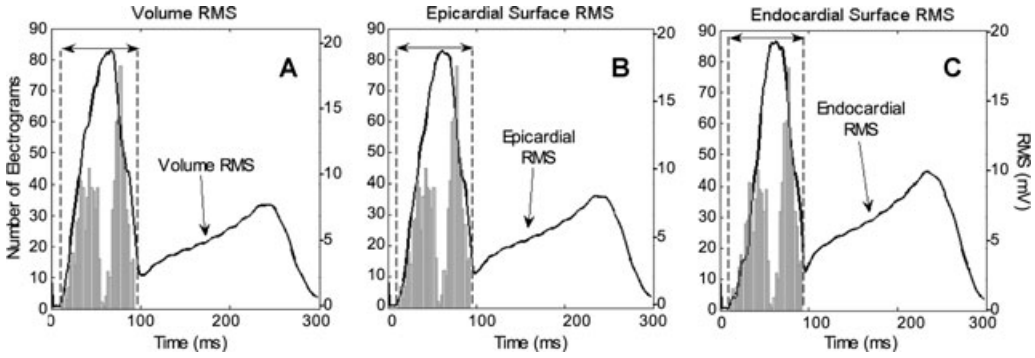

Figure 4. *Excitation time histograms from the myocardial volume overlaid on RMS curves with marked widths. Histograms remain constant for all three panels while the calculated RMS signals are derived from the (A) myocardial volume, (B) epicardial surface, and (C) endocardial surface. All three panels are from the same anterior left ventricular endocardially paced beat.*

and endocardial surface (panel C). For the three panels in Figure 4, the histograms remained the same while the subset of EGs used for RMS calculation varied. The marked duration of ventricular electrical activity from the RMS waveforms is equal to the span of the excitation times in all three cases.

Table II shows that, for various activation sequences, in contrast to RMS curves, ATs obtained from either the endocardial or the epicardial surfaces differed significantly from TVAT. However, AT calculated from combining EGs from both the epicardial and endocardial surfaces provided a statistically accurate estimate of TVAT. When AT of either the epicardial or endocardial surfaces was compared to TVAT, the greatest mean difference was 21.5 ms (see Table II, LV epicardial pacing) compared to a maximum difference of only 7.1 ms when the RMS widths were used (see Table I, RV epicardial pacing). Results from a multivariate repeated measures ANOVA with posttests showed endocardial and epicardial ATs to be significantly different from TVAT ($P < 0.0001$).

To illustrate the inability of epicardial or endocardial ATs alone to reflect TVAT adequately, Figure 5 depicts ATs measured from a beat paced from the endocarium on the anterior LV. Figure 5A shows an excitation time histogram from all myocardial volume EGs overlaid with an RMS signal computed from the same EGs depicting the alignment of earliest and latest excitation with the width of the RMS signal. Figures 5B and C,

Table II.

Average Activation Times (AT) in ms Obtained from the Epicardial and Endocardial Surfaces with the Total Ventricular Activation Time (TVAT) for Various Activation Sequences Plus or Minus Standard Deviation

Pacing Location (Number of Runs)	TVAT	Epicardial AT (ms)	Endocardial AT (ms)	Endo + Epi AT (ms)
Right atrium (6)	37.7 ± 4.1	30.8 ± 3.8	28.4 ± 3.8	36.4 ± 2.9
LV Epi (6)	84.7 ± 8.9	84.4 ± 9.3	63.2 ± 5.4	84.4 ± 9.3
LV Endo (7)	81.6 ± 9.5	69.7 ± 7.6	73.1 ± 5.6	80.9 ± 9.7
LV Epi PPI (6)	96.8 ± 13.3	95.1 ± 13.9	83.0 ± 13.0	95.1 ± 13.9
LV Endo PPI (6)	101.0 ± 10.9	89.5 ± 15.1	96.2 ± 12.8	100.1 ± 10.4
RV Epi (6)	93.9 ± 14.3	93.9 ± 14.3	75.7 ± 9.6	93.9 ± 14.3
RV Endo (4)	84.5 ± 14.1	76.3 ± 13.7	75.3 ± 10.2	84.5 ± 14.1
RV Epi PPI (4)	108.8 ± 15.1	108.2 ± 15.0	96.0 ± 10.3	108.8 ± 15.1
RV Endo PPI (4)	99.4 ± 23.4	91.2 ± 22.3	97.7 ± 25.1	98.8 ± 24.1
Mean Difference from TVAT	–	5.8 ± 4.9**	11.3 ± 6.2**	0.8 ± 0.6, NS

Ventricular pacing sites were located on the anterior aspect of the heart (n = 47).
**$P < 0.001$.
Abbreviation: PPI = Post-Purkinje inactivation; NS = not significantly different ($P > 0.05$).

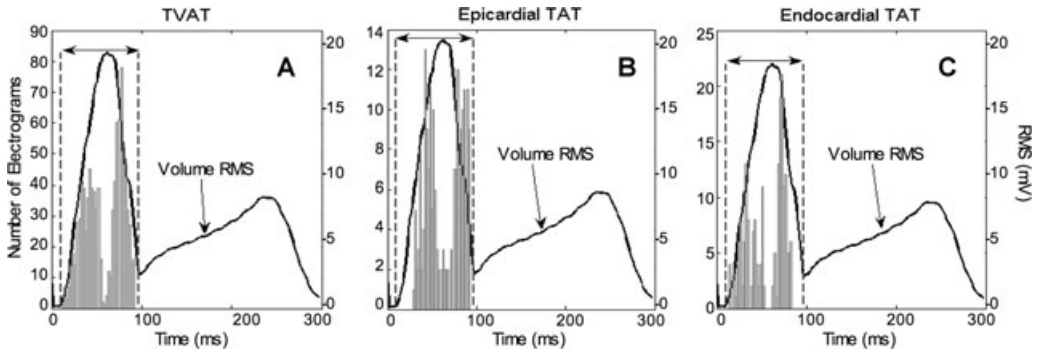

Figure 5. *Myocardial volume RMS signal overlaid on excitation time histograms. The RMS signal remains the same in each panel while the histograms are determined from the (A) myocardial volume, (B) epicardial surface, and (C) endocardial surface. All three panels are from the same anterior left ventricular endocardially paced beat.*

in contrast, show the same volume RMS signal overlaid on the histograms of excitation times obtained only from the epicardial or endocardial surfaces, respectively. For the three panels in this figure, the RMS signal was held constant while the data set used to calculate the excitation time histograms varied. Epicardial (panel B) and endocardial (panel C) excitation time histograms are subsets of the entire myocardial volume histograms (panel A). The epicardial surface excitation time histogram (panel B) reveals a 19-ms delay between the peak curvature marker in the RMS signal and the earliest measured excitation on the epicardium (start of the histograms). This gap results from the time required for transmural propagation of this endocardially paced beat to reach the epicardial surface. Similarly, Figure 5C shows the latest endocardial excitation (last histograms) to occur 13 ms prior to the second peak curvature marker in the RMS signal, again due to timing of transmural conduction. The gaps revealed in these figures indicate the inability of the ATs from either surface alone to accurately reflect TVAT.

Quantifying TVAT from the Body Surface

Having established that the width of the RMS signal from cardiac EGs is an accurate measure of TVAT, we next evaluated the ability of RMS signals generated from recordings from the body surface to represent TVAT by comparing RMS widths computed from epicardial and tank surface EGs. Results of repeated measure ANOVA followed by multiple comparisons showed significant differences in measures of the RMS widths for the 12-lead, three-lead, and lead II ECGs (Table III) when compared to the measures of RMS widths from epicardial EGs. In contrast, measures from the full set of tank surface leads or all precordial leads showed no significant differences. Table III also summarizes the results of linear regression comparisons between RMS widths computed from epicardial surface EGs and various sets of tank surface EGs. As the number of body surface EGs included in the RMS decreased, the accuracy of body-surface estimates of TVAT decreased, with the exception of the precordial leads which

Table III.

Linear Regressions and ANOVA Comparisons Results of RMS Widths Obtained from the Epicardial Surface Tested Against Those from the Tank Surface, 12-Lead ECG, Precordial Leads, 3-Lead ECG, and Lead II ECG

RMS Comparison	Mean Difference (±Standard Deviation)	P-Value	Correlation (R)	Slope	Intercept
Epicardial surface vs tank surface	7.15 ± 9.90	NS	0.9046	0.9364	11.804
Epicardial surface vs 12-lead ECG	8.70 ± 10.68	<0.05	0.8944	0.8760	17.578
Epicardial surface vs precordial ECG	5.50 ± 9.90	NS	0.9094	0.8894	13.770
Epicardial surface vs three-lead ECG	11.40 ± 17.98	<0.01	0.7485	0.6430	36.001
Epicardial surface vs lead II ECG	11.25 ± 16.63	<0.01	0.7805	0.6813	33.257

Mean difference defined as epicardial surface minus the body surface measurement (n = 20).

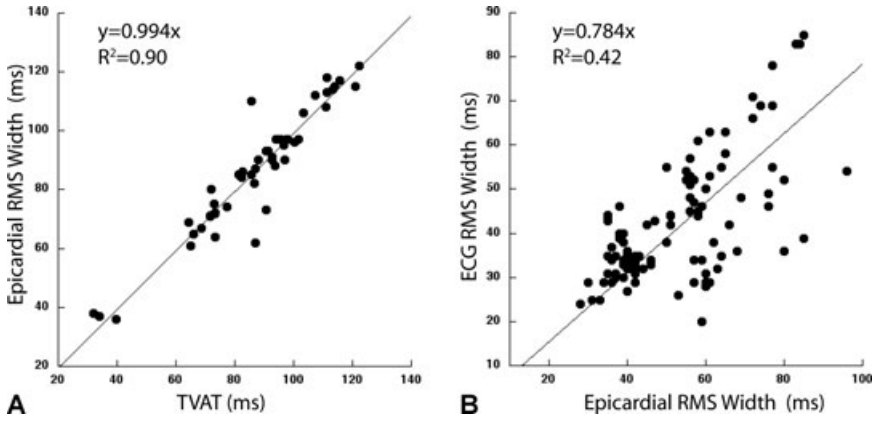

Figure 6. *(A) RMS width calculated from epicardial electrograms (EGs) plotted against TVAT obtained from plunge needle EGs (n = 50). (B) RMS widths from the body surface three-lead and lead II ECGs versus RMS widths determined from epicardial EGs (n = 101).*

exhibited the lowest mean difference (highest accuracy) when compared to the RMS widths computed from the epicardial surface EGs.

To further test the relationship between the QRS width and TVAT, three-lead ECGs were recorded from *in situ* canine experiments and compared with the RMS width measured from simultaneously recorded epicardial EGs during varied pacing regimens. The basis for this comparison is shown in Figure 6A, which displays the RMS widths obtained from the epicardial surface EGs versus the TVAT calculated from transmural needle EGs from the myocardial volume. Building on this relationship, using data from separate studies in which EGs were not recorded from transmural needle electrodes but from epicardial "sock" electrodes, RMS widths computed from epicardial EGs were compared with RMS determined from QRS widths calculated from the three-lead ECG (Fig. 6B). The resulting correlation (R = 0.42) is weaker (panel B) than that seen between TVAT and epicardial surface RMS width (R = 0.90, panel A). Using a linear fit forcing the intercept to be zero, the resulting slope for panel B has a much smaller value (0.784 vs 0.994) compared to panel A, indicating that the three-lead ECG tends to underestimate TVAT. On average, errors in the estimates of TVAT based on the three-lead ECG were 10.06 ± 12.26 ms, ranging from a maximal overestimation of up to 9 ms to a maximal underestimation of 47 ms (n = 101 sequences).

Measuring VES

Measurements of VES were obtained from the EGs recorded from plunge needles distributed throughout the ventricular volume. For electrical sequences initiated via atrial stimulation (n = 6), VES ranged from −2.48 ms to 8.74 ms (mean 2.68 ± 4.31 ms). Mean VES values were 36.0 ± 8.7 ms and −39.2 ± 9.8 ms for left ventricular (n = 25) and right ventricular (n = 16) pacing sites, respectively. Figure 7 shows the VES values from epicardial and endocardial surfaces versus those from the myocardial volume for several types of activation sequences (n = 47). The results from atrially paced beats were grouped near the origin reflecting small values of VES and ventricular synchrony. The left ventricular paced beats were grouped in the upper right quadrant reflecting LV followed by RV activation. Likewise, the right ventricular paced beats were in the lower left quadrant (negative values), indicating RV activation prior to LV activation.

Although values for VES obtained from the endocardial surface were statistically different

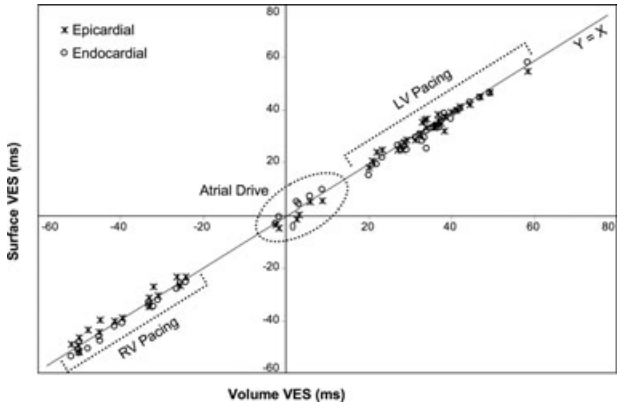

Figure 7. *VES calculated from the myocardial volume plotted versus the VES from the epicardial and endocardial surfaces with pacing types delineated into three groups: right ventricular pacing, atrial drive, and left ventricular pacing.*

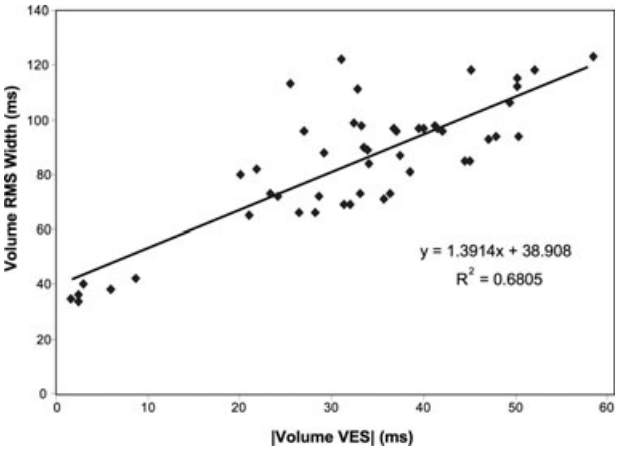

Figure 8. *RMS width measured from the myocardial volume plotted versus the absolute value of VES from the myocardial volume.*

($P < 0.001$) from the values derived from the myocardial volume, they exhibited a small mean difference (1.739 ms) and high correlation ($R = 0.9987$). VES values from the epicardial surface were statistically similar to the myocardial volume ($P = NS$) and produced a smaller mean difference (0.4235 ms) and similarly high correlation ($R = 0.9980$).

Relationship of VES to TVAT

Comparisons of volume RMS-based widths and VES values (Fig. 8) showed a correlated trend with some outliers ($R = 0.825$, $P < 0.0001$). Besides having different ventricular ATs, beats with small values of VES typically produced narrow, monophasic RMS waveforms while dyssynchronous beats showed wider RMS signals that were often multiphasic in shape.

Discussion

The study addressed the assumption that QRS width is an accurate measure of ventricular AT. The technique of measuring the duration of ventricular activation in an RMS signal from unipolar EGs recorded from the heart or the body surface was found to be an extremely accurate means of determining TVAT. By applying the RMS technique to body surface measurements, we have used an objective, reproducible, and accurate method for determining QRS width from the ECG.[20,21] This technique, as introduced by Fuller et al. as a means to measure repolarization dispersion from the cardiac and body surfaces,[20,21] provides a powerful means to sum all of the information recorded from multiple unipolar EGs in a way that makes detection of slight deviations from baseline accurate. The strength of this technique as applied to unipolar EGs allows the exploitation of far-field information present in each signal to indicate excitation and current flow at other, even distant locations in the heart. The results of this study suggest that cardiac mapping techniques, which measure electrical signals directly from the heart, may provide an accurate measure of TVAT if the RMS technique is applied. In measuring QRS width using the RMS technique from body surface measurements studied here, it appears that the use of a single-lead ECG may provide the least accurate measure of TVAT. Results showed large differences between measured TVAT and the QRS width measured from a single-lead ECG or the three bipolar limb leads. However, QRS widths from the precordial leads and entire tank surface did provide a reasonably accurate measure of TVAT.

We also investigated a metric of the difference between the mean ATs of both ventricles as introduced by Jia et al.[7] as a measure of synchrony. In normal canine hearts, a quantification of VES for normal ventricular activation determined that the LV and RV activate, on average, within 3 ms of each other with the LV typically activating slightly before the RV, although they are nearly simultaneous. Published CRT studies have suggested optimal LV pacing sites range from the lateral to the posteriolateral aspect of the LV for improving synchrony.[1,2] Pacing from the anterior endocardial LV, far from these suggested locations, in a heart following Purkinje inactivation, exhibited a VES value of 59 ms (rightmost data point in Fig. 6) and an RMS width of 122 ms, indicating an electrically dyssynchronous beat. This specific case exemplifies the more general result that VES values were consistent with anticipated degrees of asynchrony based on the applied pacing sequence. Jia et al.[7] used only epicardial excitation times to compute VES; our results suggest that this is sufficient to accurately estimate the volume VES.

These results may provide some practical insight as to why QRS width has not always been a strong predictor for synchrony and enables some reflection on how one might better use clinical measures in the future to provide more accurate measures of ventricular AT and synchrony. While the ECG is the most widely used clinical electrical signal from the body, the results from this study show that QRS widths measured from the single- or three-lead ECG provide an inaccurate indication of TVAT, yielding QRS widths that were considerably shorter than those obtained from epicardial signals. Results showed that a full body surface map or even just the precordial leads may provide a better measure of TVAT. The precordial leads showed the smallest mean difference when compared to the epicardial source signals, reflecting

longer measured QRS widths than those in the distant limb leads. The close proximity of the precordial leads to the source signals provides higher amplitude and signal-to-noise ratio for more accurate measurement of the QRS width. The fact that the precordial leads are a component of the 12-lead ECG would explain why the correlation with TVAT was higher for the 12-lead than the three- or single-lead measurements; however, averaging with the distant limb leads decreased the signal-to-noise ratio and slightly reduced the overall accuracy of the 12-lead ECG for predicting TVAT. These findings may raise the question as to whether the precordial leads might be investigated for a more consistently accurate measure of ventricular activation.

In this experimental study, TVAT was not strongly correlated with our measure of synchrony, VES. The data show that the duration of activation is not directly related to the synchronous activation of both ventricles. This finding advocates consideration of new methods to determine synchrony using clinical methods which differentiate the ATs of the individual ventricles rather than implying the more general measure of total activation time from both ventricles combined.

High-resolution electrical measurements are requisite to define and understand electrical activation and synchrony but only have value if one can estimate these quantities from clinically available measurements. There are other methods for obtaining electrical data from patients that, although less common than the ECG, are still feasible. These include endocardial potential mapping using catheter-based techniques,[4,22–26] epicardial potential mapping,[7,13,27–29] and endocardial and epicardial activation mapping via inverse solutions from body surface potential measurements.[22,30,31]

Based on the results of this study, endocardial potential mapping may potentially provide an accurate measure of TVAT using the RMS technique from the potentials. However, traditional AT measurement of the endocardial surface provides a poor surrogate measure for TVAT. Also, accurate measure of VES may be obtained from the endocardial excitation times if both ventricles are mapped; however, this is not usual practice in a clinical setting.

Indirectly determining the epicardial potentials from inverse calculations based on body surface potential measurements is still experimental, but has achieved some success in the clinic and has been applied to CRT patients.[7] The work presented here suggests that this technique may provide feasible and appropriate ways to measure TVAT and VES. TVAT could be computed from the RMS width of the epicardial potentials and VES could be determined from excitation times on the epicardial surface, provided the data from the left and right ventricles can be properly distinguished. A different approach to solving the inverse solution estimates excitation times on the endocardial and epicardial surfaces from body surface potentials.[31] While this technique does not compute potential values, but rather, only ATs, our results suggest that TVAT could be determined from the combined ATs from both the epicardial and endocardial surfaces. In addition, VES may also be determined from these two surfaces with accuracy, again, provided the geometry can accurately distinguish the LV from the RV.

Limitations of Study

The use of plunge needle electrodes introduces another consideration involving the injury sustained by the heart due to needle insertion. However, in addition to our own validation studies, other investigations have shown that the insertion of these needles has no significant effect on myocardial function, structure, or activation sequence.[32,33] Recording of the ECG following a medial thoracotomy, as reported here, may have an affect on the morphology of the ECG; however, this possibility was evaluated in this study. Finally, an important limitation of this study is that the electrical synchrony measurements presented were not compared with measures of mechanical synchrony or hemodynamics. This study has established accurate means of determining the relevant electrical parameters and future research will be necessary to establish relationships with mechanical synchrony. It is worth noting, however, that results from recently published randomized clinical trials have demonstrated heterogeneity of mechanical synchrony[34] and challenges associated with a lack of measurement standards for mechanical synchrony and dyssynchrony.[35]

Conclusion

Through the findings of this study, some electrical measures central to our understanding of CRT and other pacing strategies have been defined and characterized in an experimental model. As QRS width is often assumed to represent ventricular activation timing[3] and synchrony, it was necessary to assess these assumptions experimentally. There are two conclusions from this study; the first is that ventricular activation was reflected most accurately by the RMS width obtained from direct cardiac measurements, precordial signals, or from the tank surface, but less accurately from a single- or three-lead ECG. The second is that our measure of synchrony was not strongly correlated

with TVAT. These experimental findings serve to provide an improved understanding of the electrical foundation for cardiac activation, which may ultimately help improve the ability to properly apply and evaluate pacing therapies.

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