Effects of single- and biventricular pacing on temporal and spatial dynamics of ventricular contraction

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In the normal heart, the Purkinje system rapidly conducts the action potential to all parts of the heart, which results in a rapid and uniform contraction of the left ventricle. Conduction disturbances and ventricular pacing, however, cause ventricular activation to progress more slowly because impulses bypass the Purkinje system and travel predominantly through the slower-conducting myocardium (21). A slower electrical activation, which is indicated by a longer QRS duration, leads to a slower rate of rise of left ventricular (LV) pressure (dP/dt max) (2, 16). However, temporal measures alone may be inadequate in characterizing pump function, because recent experimental studies have shown a poor correlation between QRS duration and contractility when different pacing sites were compared (20). Recently, pacing therapy has been used in an attempt to resynchronize cardiac contraction in patients with heart failure and abnormal activation due to left bundle branch block (1, 3, 6, 7, 14). In these studies, the ventricles were paced at the LV base only or at the right ventricular apex (RVA) and the LV base to increase the temporal synchrony of contraction. These clinical studies also showed that the hemodynamic improvements from pacing were poorly correlated with QRS duration (14).

The poor correlation between QRS duration and pump function may exist because QRS measures electrical and not mechanical activation, and because QRS duration measures only the temporal synchrony and not the spatiotemporal synchrony of activation. With a single ectopic ventricular pacing site, contraction starts at the pacing site and then progresses slowly around the heart to the opposite wall (24). This wavefront of contraction leads to a temporally and spatially asynchronous contraction characterized by the early-activated regions stretching the passive myocardium of the late-activated regions, which causes work to be done on the heart walls instead of the blood (18, 19). This study focuses on the potential role of the intraventricular spatial coordination of contraction as a factor for efficient pumping.

It would appear that proper application of pacing therapy would require detailed knowledge of the temporal and spatial characteristics of LV contraction on a patient-by-patient basis. For example, it is not known to what extent biventricular (BiV) pacing normalizes the activation compared with RVA pacing with respect to both the temporal synchrony and spatial distribution of activation. The degree of normalization of activation is likely to be dependent on the degree of coupling of the ectopically generated impulses to the Purkinje system (13). Until now, the spatial character-
istics of electrical or mechanical activation during BiV pacing were not known. However, the technique of magnetic resonance imaging (MRI) tagging allows for noninvasive quantification of LV contraction under normal and paced conditions (4, 11, 12, 19, 24), which makes measurements of the spatial and temporal distributions of mechanical activation feasible.

The present work expands on the use of mechanical activation mapping (24), which maps the regional onset of contraction in the left ventricle to compare BiV pacing with single-ventricular-site pacing and atrial pacing. Also, a new measure of heart function, the activation delay vector (ADV), which characterizes the spatiotemporal pattern of contraction, is derived from the mechanical activation maps.

**METHODS**

The canine heart was paced from each of the following locations: the right atrium, the apex of the right ventricle, and simultaneously from the LV base (LVb) and RVa sites (BiV). Tagged MRIs were acquired during each of the pacing protocols and then processed to determine 1) the temporal evolution of myocardial strain during systole, 2) the mechanical activation times, and 3) the spatiotemporal pattern of contraction.

**Animal Preparation**

Eight mongrel dogs (body wt 20–25 kg) were initially anesthetized with Pentothal Sodium (20 mg/kg) and then ventilated with O₂ supplemented with air and isoflurane (0.8–1.25%) to maintain anesthesia. A magnetic resonance-compatible Millar catheter-tip micromanometer (model SPC-350MR; Millar Instruments, Houston, TX) was inserted into the left ventricle via the carotid artery to monitor chamber pressure. The chest was opened and nonferromagnetic biopolar pacing leads were sewn on the heart at the right atrial (RA) free wall, the LVb free wall, and through the RV wall on the endocardial RVa. For the last five pacing experiments, a pacing catheter (Bard custom magnetic resonance-compatible catheter) was inserted into the femoral vein or jugular vein and guided by fluoroscopy to the RVa. The catheter permitted endocardial pacing of the RVa site, which resulted in a pacing protocol that better resembled the methods used clinically. After the experiment, the animal was killed with an overdose of pentobarbital sodium. The experiments were performed with approval of the Johns Hopkins Animal Care and Use Committee.

**Pacing Protocol**

Details of the pacing protocol have been previously described (24). The stimulus levels at each pacing site were individually adjusted to ensure consistent capture as verified by electrocardiogram (ECG) and LV pressure. The normal electrical activation of the heart was suppressed by using AV-synchronous pacing at a rate above the spontaneous rate, and the same pacing rate was used for all three pacing protocols within each experiment. For the eight studies, the pacing rate ranged from 91 to 137 beats/min with an average pacing rate of 111 beats/min. For RVa and BiV pacing, the AV delay was 0 ms.

**MRI Protocol**

As previously described (10, 24), tagged cine MRIs were acquired on a GE SIGNA 1.5 T scanner during breath-hold periods. During each breath-hold, the respirator was stopped at an identical point in the cycle; this minimized any image misregistration resulting from respiratory motion. The scanner was synchronized with the pacing such that tagging took place 5 ms after the pacing signal in the ventricular paced experiments. This timing permitted a couple of images to be taken in late diastole before the pacing signal initiated the onset of contraction. For the atrial paced experiments, the tagging occurred at late diastole as determined from the cine sequence of MRIs. In each case, the first image occurred 6 ms after tagging. A total of 14–20 images were taken from late diastole through systole at 16–23 ms intervals. The scanning parameters used were field of view, 28–32 cm; repetition time, 4.3–6.5 ms; echo time, 1.4–2.1 ms; acquisition matrix, $256 \times 96–110$; bandwidth, ±32 kHz; readouts per movie frame, 3–5; in-plane spatial resolution, $1.25 \times 3$ mm; and slice thickness, 7 mm.

For each of the three pacing protocols, seven to nine tagged short-axis slices were acquired using a parallel-line tagging pattern with the tags perpendicular to the frequency encoding direction; the same set of short-axis slices were then acquired with both the tags and the readout gradient rotated 90° (8, 10, 15). Nine long-axis slices oriented radially from the center of the LV cavity and spaced 20° apart were imaged with the tags parallel to the short-axis imaging planes. The acquisition took ~40–50 min for the complete three-dimensional series for one pacing protocol. Examples of short-axis slices during the various pacing protocols are shown in Fig. 1.

**Data Processing**

**Calculation of mechanical activation times.** From the tagged MRIs, displacements and strains were calculated and used to determine the mechanical activation times or onset of contraction (24). The circumferential strain ($E_{cc}$) at the midwall was calculated at each imaging time (every 16–23 ms at 14–20 time points) on a mesh of between 7 and 9 longitudinal ($l$) and 24 circumferential ($c$) points using the method of O’Dell (15). B splines (17) were then used to interpolate the Ecc data over time. From the fitted Ecc data, the mechanical activation time ($t_{act}(c,l)$) was determined as the onset of shortening, which generally was the peak of the maximum prestretch. The mechanical activation time was calculated at each mesh point defined by $c$ and $l$.

**Mechanical activation width.** To quantify the temporal asynchrony of the mechanical activation, the duration of the LV activation was estimated with a parameter called the mechanical activation width (MA width). This is analogous to estimating electrical asynchrony using the QRS width. The MA width was computed from the maps of $t_{act}(c,l)$ for the midwall myocardium and corresponds to the time required to mechanically activate 70% of the myocardial mass. From the mechanical activation data, it was observed that the time to activate the initial 20% and the final 10% of the myocardial mass was somewhat variable; hence these portions of the mechanical activation were not used to calculate the MA width. Figure 2 shows this calculation for the three different pacing protocols in one heart.

**Activation delay vector.** Although MA width reflects the overall asynchrony, it does not express the spatial progression of the wavefront of mechanical activation over the left ventricle. To characterize both the spatial and temporal aspects of activation, the ADV was created. The ADV measures the spatial imbalance indicative of mechanical activation between opposite sides of the LV wall.

The ADV was generated by summing a vectorized representation of the $t_{act}(c,l)$ values at each mesh point; the mag-
nitudes were equal to $t_{\text{act}}(c,l)$, whereas the phases were determined from the spatial locations of the mesh points. Larger ADV values indicate a greater imbalance in contraction from one side of the left ventricle to the other, and smaller ADV values indicate a spatially and temporally balanced contraction. The ADV was calculated by

$$\text{ADV} = \frac{4}{CL} \sum_{c=1}^{C} \sum_{l=1}^{L} t_{\text{act}}(c,l) \cdot \frac{r_c}{r_{c,l}}$$

where the summations are across all circumferential ($C = 24$) and longitudinal ($L = 7–9$) or base to apex mesh indices. The last term is a unit vector in the direction of the spatial location of $t_{\text{act}}(c,l)$. Although the ADV could have been calculated as a vector in three-dimensional space, it was reduced to the circumferential plane by using $r_c$ instead of $r_{c,l}$ in the last term of Eq. 1. This was done because the spatiotemporal asynchrony observed in the mechanical activation in the longitudinal direction was much smaller than in the circumferential direction. The last term of Eq. 1 was determined by

$$\frac{r_c}{r_{c,l}} = [\cos(\phi_c), \sin(\phi_c)] = \left[\cos\left(\frac{2\pi c}{C}\right), \sin\left(\frac{2\pi c}{C}\right)\right]$$

where $\phi_c$ is the circumferential angle of the mesh point with the circumferential index $c$. Equation 2 indicates the phase or direction of the imbalance indicated by the ADV. Phase angles were measured from the reference vector between the septum and the LV free wall with vectors pointing toward the anterior wall considered positive and vectors pointing toward the posterior wall considered negative.

The data are expressed as means ± SD. Comparisons between pacing protocols were made using one-way ANOVA and Fisher's least-squared-difference test. Differences were considered statistically significant for $P < 0.05$.

RESULTS

Magnetic Resonance Images

Figure 1 shows the tagged MRIs of the same short-axis slice for each of the pacing protocols at regularly spaced intervals from late diastole to end systole. The synchronous contraction of the RA paced heart is demonstrated by a decreased intertag spacing and the motion of the tags bowing toward the LV cavity. In RVa pacing during early systole, a rapid contraction occurred near the pacing sites while on the opposite side of the left ventricle the wall bulged outward. This outward bulge can be seen in the RVa paced heart (see Fig. 1, middle column; 134 ms) as an outward bending of the tags on the wall opposite from the pacing site. These late-activated regions contracted later in systole, restretching the myocardium near the pacing site and creating a second, smaller, bulging of the heart. For the BiV-paced heart, rapid contraction occurred near the two pacing sites, and there was a less-pronounced bulging between the two pacing electrodes. In BiV pacing, there was no second bulging at the pacing site as seen in the single-site ventricular-pacing exper-
iments. The far-right column demonstrates a greater contraction at end systole from the RA and BiV pacing protocols.

**Strain Maps**

Examples of the LV strain maps generated for each pacing protocol are shown in Fig. 3. The strain map for RA pacing (Fig. 3A) has two main distinguishing features. First, the start of contraction occurred fairly synchronously for different regions. Second, the extent of shortening during systole was consistent throughout the left ventricle.

The RVa pacing strain maps (Fig. 3B) had a characteristic rapid but small contraction near the pacing site and a subsequent rebound stretch before it contracted once again in late systole. The late-activated regions of the left ventricle on the wall opposite from the pacing sites, however, demonstrated a significant prestretch before a large systolic contraction. BiV pacing (Fig. 3C) reduced the magnitude of the prestretch and the size of the region with prestretch compared with RVa pacing.

Another way of visualizing the spatiotemporal evolution of the strain was to map the strain onto a volume reconstruction of the left ventricle for each time point in systole (9). Figure 4 shows the strain rendering of the LV midwall for each of the pacing protocols at different points in the imaging cycle. The strain rendering of the RA paced heart demonstrates the uniform contraction by the spatially homogeneous color throughout systole. The RVa paced hearts, on the other hand, show a wave of contraction moving around the heart. The region of prestretch emerged on the opposite side of the heart from the pacing site as shown by the yellow color. In the strain rendering for the BiV paced hearts, two waves of contraction were seen moving from each of the pacing sites.

**Mechanical Activation Maps**

An example of the mechanical activation maps for one experiment are shown in Fig. 5. The activation maps vividly demonstrate the uniformity of contraction during RA pacing. For RVa pacing, the initiation of contraction was seen at the pacing site and the wave of propagation moved around the left ventricle to the opposite wall. In the BiV paced hearts, early activation occurred at the two pacing sites and the waves of activation merged approximately halfway between the two pacing sites. The total delay for activation in the BiV paced hearts was shorter than what was found in the RVa paced hearts but was still greater than for RA pacing. The MA widths for all experiments \(n = 8\) are shown in Fig. 6A. During RA pacing, the MA width was significantly lower \(43.6 \pm 17.1\) ms than during RVa pacing \(77.6 \pm 16.4\) ms and BiV pacing \(67.4 \pm 15.2\) ms.

**Activation Delay Vectors**

The arrows on the activation maps of Fig. 5 are proportional to the magnitude of the ADV as calculated by Eq. 1. The direction of the ADV vector was determined from the phase of the ADV and illustrates the main direction of progression of mechanical activation. During RA pacing, the magnitude of the ADV was relatively small, which indicates only a small net im-
balance in the timing of contraction from one side of the heart to the opposite side. Also during RA pacing, the ADV generally pointed away from the septum or toward the posterior wall, which indicates that the net propagation of the contraction moved from the septum to the posterior wall. The angle of the ADV for RA pacing was $43 \pm 55^\circ$.

The ADV magnitude during BiV pacing was relatively small, which shows that there was little imbalance of contraction between a given side and the opposite side. In BiV pacing, the ADV generally pointed between the electrodes toward the latest activated region with an angle of $15 \pm 84^\circ$. For RVa pacing, the ADV was very large and pointed away from the pacing site toward the LV free wall.

Figure 6B shows the ADV values for all experiments ($n = 8$). The average ADV magnitudes ($n = 8$) were $18.9 \pm 8.1$ and $34.2 \pm 18.3$ ms for RA and BiV pacing, respectively, which were both significantly lower than the ADV for RVa pacing, $73.8 \pm 16.3$ ms. It should be noted that the two high outliers for the BiV paced experiments were from studies where the RVa and LVb electrodes were placed $\sim 90^\circ$ apart instead of the optimal $180^\circ$. The preferential direction of the ADV for RVa pacing is pointing away from the pacing site with an angle of $-2 \pm 39^\circ$.

**Hemodynamics**

Data of the maximum time derivative of LV pressure ($LV \frac{dP}{dt_{max}}$) for all experiments are shown in Fig. 6C. During RA pacing ($n = 6$), $LV \frac{dP}{dt_{max}}$ was $1,560 \pm 300$ mmHg/s and was significantly higher than during RVa pacing ($1,070 \pm 370$ mmHg/s) but not BiV pacing ($1,310 \pm 220$ mmHg/s).

**DISCUSSION**

The present study shows further evidence that the site or sites of pacing strongly influences the sequence of contraction within the LV wall. This was especially clear from the ADV data. In a previous study, it was shown that during ventricular pacing, mechanical activation gradually progressed through the myocardium (24). The “conduction velocity” of the mechanical acti-
vation matched the electrical conduction velocity of normal myocardium, which indicates limited involvement by the Purkinje system during ventricular pacing. The present study confirms the slow conduction during pacing and extends it to BiV pacing, where the mechanical activation originates from the two pacing sites and the waves of contraction merge in between the two electrodes.

The gradual progression of mechanical activation justifies the use of a vector approach for quantification of the spatiotemporal asynchrony of contraction; the size of the vector indicates the degree of spatiotemporal asynchrony and the direction of the vector indicates the main direction of conduction. For the single-ven-

![Fig. 5](image-url)  
Fig. 5. A representative set of mechanical activation maps for each protocol in one heart is shown: RA (A), BiV (B), and RVa (C) pacing. Center of each plot is the apex, and the outer ring is the base. Pacing sites for the ventricular paced experiments are marked with a white X. Arrows are proportional to the magnitude of the activation delay vector (ADV); phase of the ADV is indicated by arrow direction.

![Fig. 6](image-url)  
Fig. 6. Parameter data for all experiments for each pacing protocol: MA width (A), ADV magnitude (B), and maximum rise in pressure, $dP/dt_{max}$ (C). (Data were not collected for the RA pacing sites in one experiment and were not available for all sites in another experiment.) Symbols in each plot correspond to the same experiment.
tricular-site pacing protocol, the ADV pointed away from the pacing site, whereas during BiV pacing, the direction depended on the relative placement of the two electrodes. Thus the process of mechanical activation can be summarized using two variables. Because of the correlation between electrical and mechanical activation, this technique could be used to summarize electrical epicardial or endocardial mapping techniques (5, 22).

Compared with RVA pacing, BiV pacing reduced the temporal asynchrony and the spatiotemporal asynchrony of the LV midwall contraction. The temporal asynchrony as measured by the MA width was reduced by only 13%, which is a reduction similar to the reduction of QRS duration by BiV pacing in normal dogs (20). However, the spatiotemporal asynchrony as measured by the ADV magnitude was reduced by 51% during BiV pacing compared with RVA pacing. LV dP/dt_max was 37% higher during BiV pacing than RVA pacing. The reduction in the ADV magnitude that is seen in BiV pacing compared with RVA pacing paralleled the improvement in LV dP/dt_max better than the reduction in MA width. However, the variance in the dP/dt_max measurements was high, and this is potentially due to several factors. First, because AV synchronous pacing was used for the ventricular pacing experiments, the normal atrial contribution to filling was suppressed. As a result, the filling and hence the preload were most likely reduced for the ventricular pacing experiments compared with RA pacing, which potentially reduced dP/dt_max. Second, although attempts were made to maintain a consistent blood volume throughout the experiment, variations were unavoidable. In experiments with shorter pacing protocols and more consistent loading conditions, dP/dt_max was significantly greater for BiV pacing compared with RVA pacing (20).

The effects of LV wall prestretch were important because a large amount of prestretch decreases the efficiency of contraction (19). During RVA pacing, the amount of prestretch seen in each region was proportional to the activation time of that region. BiV pacing significantly reduced this prestretch and also reduced the rebound contraction seen in the strain maps (see Fig. 3) for RVA pacing, which resulted in a contraction pattern that more closely resembled RA pacing. The ADV indicated that BiV pacing approached the spatiotemporal pattern of contraction seen in RA pacing, whereas the temporal-only measure, MA width, indicated a less-pronounced improvement. Thus the spatial information provided by ADV improved the characterization of the heart function over temporal-only measures such as MA width.

It should be noted that Eq. 1 is equal to twice the amplitude of the first harmonic of the Fourier expansion of t_check(c) and hence is equal to the time delay between the late-activated region (peak) and the early-activated region (trough). In BiV pacing, this peak-to-trough time difference was greatly reduced by the placement of the two electrodes on opposite sides of the left ventricle. Higher-order Fourier harmonics could be calculated to differentiate BiV pacing from RA pacing (23).

Pacing the diseased heart is complicated by the competing intrinsic heart rhythm and by a partially functioning Purkinje system. However, the methods of mechanical activation mapping from magnetic resonance-tagged images presented in this study could be helpful in designing effective pacing strategies in the diseased heart. Improving cardiac output requires not only increasing the rate of contraction but also reducing the spatial imbalance of contraction, both of which are noninvasively mapped by this technique. Either single-site pacing in conjunction with the intrinsic contraction or BiV pacing could be used to accomplish this goal.

When using AV synchronous pacing in the healthy dog heart, BiV pacing improved the temporal synchrony of contraction (as measured by the MA width) with an even greater improvement in the spatiotemporal synchrony of contraction (as measured by the ADV) over RVA pacing alone. BiV pacing reduced the spatiotemporal asynchrony by eliminating the prestretch in the late-activated region opposite the pacing site.

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