Transmural temporospatial left ventricular activation during pacing from different sites: potential implications for optimal pacing

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Aims Previous studies showed that right ventricular (RV) endocardial pacing can be deleterious even in individuals with initially normal left ventricular (LV) function. The mechanism(s) by which RV endocardial pacing may cause LV dysfunction is unknown. This study compares the temporospatial LV transmural activation profiles during sinus rhythm with normal His/Purkinje conduction vs. currently utilized and proposed cardiac pacing sites.

Methods and results Mongrel dogs were instrumented with transmural electrodes that tracked transmural activation sequences at five sites in the LV. Pacing/recording catheters were positioned in the RV apex and on the RV and LV sides of the ventricular septum. An epicardial pacing electrode was also sewn to the mid-lateral LV epicardium. Electrograms were recorded during sinus rhythm and pacing from the RV endocardium, LV septum, LV epicardium and during biventricular pacing. Compared to normal sinus/His/Purkinje rhythm (NSR), RV endocardial pacing significantly (P < 0.05) prolonged transmural activation (NSR endocardium 6.1 ± 1 ms vs. RV endocardium 23.0 ± 2.6 ms). The highly ordered temporospatial pattern of transmural activation during sinus rhythm was replaced with dispersion and intermingling of endo-, mid-, and epicardial activation. LV epicardial and biventricular pacing did not correct these abnormalities. Only LV septal pacing achieved the transmural and transseptal activation sequences similar to sinus rhythm.

Conclusion Clinically utilized pacing modalities, including biventricular pacing, cause abnormal transmural activation. LV septal pacing results in transmural activation patterns that closely resemble those seen in sinus rhythm.

KEYWORDS
Ventricular pacing; Transmural activation; Septal activation; Biventricular pacing

1. Introduction

More than 200 000 pacemakers are implanted annually in North America1 with the most frequent indication being sinus node dysfunction (58.8%).2 Dual-chamber pacing was developed to restore and maintain atrioventricular (AV) synchrony and is considered a ‘physiologic’ mode.3–6 However, trial results relative to heart failure have been inconsistent suggesting either modest or no benefit in limiting progression to heart failure.4–7 Analyses of randomized trials suggested that right ventricular (RV) pacing, with or without maintenance of AV synchrony, can lead to higher rates of new or progressive heart failure and increased mortality.6,8 This was recently verified in the MOST trial9–11 which was the largest (2010 patients) randomized trial to compare single-chamber vs. dual-chamber pacing (the RV was paced in both) in patients with sinus node dysfunction.4 Heart failure occurred least frequently in patients randomized to dual-chamber pacing but with a very low cumulative % of RV pacing.5 Despite maintaining AV synchrony, dual chamber pacing with >40% ventricular pacing was associated with a 2.6-fold increase in risk of hospitalization for heart failure.5,9,10 Similarly, during single-chamber RV pacing with a high cumulative per cent pacing, the probability of heart failure increased by nearly 40-fold.5 Thus, a new (untested) strategy has been recommended for physiologic ventricular pacing—if ventricular or AV conduction is abnormal, RV septal, left ventricular (LV) epicardial, or biventricular pacing should be considered instead of RV apical pacing.3

This canine study systematically compares LV temporospatial transmural activation profiles in normal sinus/His/Purkinje rhythm (NSR) with both clinically utilized and proposed pacing sites with a view to identifying the site(s)
which result in the most physiological transmyocardial activation.

2. Methods

2.1 Animal preparation

Five mongrel dogs weighing 20–25 kg were premedicated with 25 mg/kg sodium thiopental. Anaesthesia was maintained with intravenous fentanyl citrate (0.04 mg/mL; given to effect), followed by an infusion of ~4 mg/h which was adjusted as necessary to maintain a surgical plane of anaesthesia. The animals were intubated and ventilated with a constant volume ventilator (Harvard apparatus, Natick, MA, USA) with 50% O₂/50% N₂O. Through a median sternotomy, the pericardium was opened with a base-to-apex incision. The tip of a quadrapolar-pacing catheter was positioned in the RV apex via the right external jugular vein under fluoroscopic guidance. Medtronic 5076 52 cm active fixation leads (6 F) were inserted through the LV and RV free walls and screwed into the LV and RV sides of the septum, respectively, using fluoroscopic guidance. Five short bevelled 20 gauge needles, each containing 3 Ag/AgCl electrodes with a 4 mm inter-electrode distance (2 electrodes in the shaft and the third in the phenolic base) were inserted into the LV (Figure 1) [anterior base (AB), the posterior base (PB), the lateral free wall (LFW) halfway between apex and base, the mid-anterior free wall (AFW), and the LV apex]. An Ag/AgCl epicardial pacing electrode was sutured to the middle of the lateral LV free wall. The pericardium was then closed, and chest wall was opposed. A 6 F catheter was inserted into the femoral artery for continuous arterial pressure monitoring and to obtain samples for blood gas analysis. A three-lead electrocardiogram was recorded throughout procedure. All studies were approved by the institutional Animal Welfare Committee at the University of Calgary and carried out in accordance with the Canadian Council on animal care guidelines as well as the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

2.2 Experimental protocol

Electrograms were recorded during NSR, RV endocardial (septal and apical), LV epicardial, LV septal, and biventricular pacing (RV septal+LV epicardial pacing). Each site was paced at twice diastolic threshold for 2 min at a rate just above the sinus rate so that there was 1:1 capture. Pacing sequences were randomized to minimize the potential impact of time-dependent changes. There was a minimum interval of 5 min between pacing from each site. Electrograms recorded with the distal plunge electrodes were considered to be recorded from the endocardium. Electrograms recorded with the mid-plunge electrodes were considered to be recorded from the mid-myocardium and those recorded with the proximal or surface plunge electrode were categorized as epicardial in origin.

2.3 Data acquisition

Unipolar signals from each recording electrode were referenced to the chest wall using a 4 mm sintered disk electrode and DC coupled, amplified, filtered (0.2–5000 Hz), simultaneously sampled at 16 kHz, and analogue-to-digitally converted with 12 bits of resolution. The input impedance of the amplifiers was 10¹² Ω. Unipolar electrogram signals were stored together with ECG signals. Five-point, second-order data-fit was used to calculate all derivatives. Location of peak negative dV/dt (maximum change in voltage over time) for unipolar electrograms was automatically determined and was used to indicate time of activation. Myocardial regional activation time was defined as the mean of the electrogram activation times recorded by the plunge electrodes in the individual regions (e.g. mean of endocardial recordings, etc). The total duration of myocardial activation was defined as the length of time between the earliest and latest myocardial activation. The envelope of activation is defined as the mean of the electrogram activation times. Regional myocardial dispersion of activation was defined as the time difference between earliest and latest activation in each myocardial region; that is endo- is separately analysed from mid- and epi-data.

2.4 Statistical analysis

Data are expressed as mean ± SE unless otherwise indicated. Mean values were compared between NSR and the different pacing sites using ANOVA followed by the Dunnett correction factor. Differences with P < 0.05 were considered statistically significant.

Figure 1 Recording electrodes and anatomical locations. (A) Each plunge electrode consisted of three unipolar recording sites, 4 mm apart to record from endocardium, mid-myocardium, and epicardium. (B) Plunge electrodes were inserted basally in the anterior (AB) and posterior (PB) paraseptal regions, the LV apex, lateral free wall (LFW) midway between the base and apex and the anterior free wall (AFW). Recording electrodes were also positioned on the right ventricular septum and left ventricular septum.
3. Results
3.1 Envelope of activation

*Figure 2A–E* shows typical transmural electrograms recorded during NSR and during pacing at each site. Left column shows transmural electrograms referenced to the surface ECG. The middle and right columns show expanded views of the transmural electrograms during depolarization and repolarization, respectively. During NSR (*Figure 2A*, middle column), activation of endocardium (red) was rapid; activation of the mid-myocardium (blue) occurred soon after and was complete prior to epicardial activation (black).

LV septal pacing (*Figure 2B*, middle column) produced an envelope of activation that was very similar to that in NSR. In addition to similar endo-, mid-, epicardial, and total activation durations, the transmural spatial activation...
sequence was also similar. This was not true with biventricular (Figure 2C, middle column), LV epicardial (Figure 2D, middle column), and RV endocardial (Figure 2E, middle column) pacing where the total duration of activation and the activation duration of individual regions were prolonged compared with NSR and LV septal pacing. In addition, the organized sequence of activation observed during NSR (Figure 2B, middle column) was replaced by intermingling of endo-, mid-, and epicardial activation (Figures 2C–E, middle column). RV endocardial pacing (Figure 2E, middle column) caused the most prolonged regional activation durations as well as the most disorganized sequence of activation.

The right column in Figure 2 shows the envelopes of repolarization associated with the envelopes of activation in the middle column. The signal-to-noise ratio is much smaller for repolarization than depolarization. As expected, repolarization varies with the different pacing modes. Figure 3 shows representative samples of repolarization during NSR and the various pacing modes. The signal-to-noise ratio is very poor.

3.2 Transmural activation sequence

Transmural activation sequence is more formally presented as a radial plot for NSR and for each pacing site (Figure 4). Each arm of the plot represents an anatomical recording site. During NSR (Figure 4A), the LV septum (red symbol) was activated first followed rapidly by activation of the remaining LV endocardium (red symbols) and sequential activation of midmyocardium (blue symbols) and epicardium (black symbols). During NSR, the RV septum was activated later than all the LV endocardial sites. With LV septal pacing (Figure 4B), transmural activation was very similar to that during NSR. With biventricular pacing (Figure 4C), LV endocardial activation was markedly prolonged compared to that during NSR. There was intermingling of endo-, mid-, and epicardial activation with some epicardial areas predictably activating before some endocardial areas. LV endocardial activation was also prolonged during LV epicardial pacing (Figure 4D) compared to that during NSR. There was also intermingling of endo-, mid-, and epicardial activation. Pacing from RV endocardial sites caused prolonged and disordered (intermingling of endocardial, mid-myocardial, and epicardial activation) transmural LV activation. LV septal activation was markedly delayed compared to that in NSR.

3.3 Mean transmymocardial activation times

Figure 5 shows the mean transmural regional activation times (± SE) for NSR and for each pacing site. Endocardial activation during NSR was significantly more rapid (6.1 ± 1.0 ms) than during pacing at the other sites (RV endo, 23.0 ± 2.6 ms; LV epi, 15.3 ± 2.2; BIV, 14.5 ± 1.9 ms; P < 0.05) with the exception of LV septal pacing (11.7 ± 2.6 ms; NS compared to NSR). Importantly, the pattern of transmural activation during NSR and LV septal pacing was similar. The activation wave sequentially and progressively moved from endo- to mid- to epi- sites in NSR and during LV septal pacing. Mean endocardial activation times were 6.1 ± 1.0 ms, for NSR; and 11.7 ± 2.6 ms, for LV septal pacing. Mean mid-myocardial activation times were 10.7 ± 0.8 ms for NSR and 15.9 ± 2.8 ms for LV septal pacing (P < 0.05 compared to endocardium) while mean epicardial activation times were 21.6 ± 0.8 ms for NSR and 24.9 ± 3.1 ms for LV septal pacing (P < 0.05 compared to mid-myocardium). Because of intermingling of activation in the endo-, mid-, and epicardial regions, this sequential and progressive transmymocardial activation relationship did not exist with pacing at the other sites.

During NSR, no time-dependent changes were observed in QRS amplitude in Lead II (0.57 ± 0.20 mV at the start of the protocol vs. 0.46 ± 0.13 mV at the end, P=ns) or duration (49.8 ± 6.3 ms at the start vs. 49.1 ± 5.5 ms at the end, P=ns). There was no significant difference in arterial pressure during NSR and the different modes of pacing.

3.4 Dispersion of activation

Figure 6 shows the mean dispersion of activation (± SE) for endo-, mid-, and epicardial regions during NSR, LV septal,
biventricular, and RV endocardial pacing. The greatest dispersion of activation in all three myocardial regions (endo-, mid-, epi-) was observed during RV endocardial pacing. There was no significant difference in dispersion of activation between RV endocardial pacing and biventricular pacing. The least dispersion of activation occurred during NSR. Dispersion of activation in all three myocardial regions (endo-, mid- and epi-) was significantly greater during RV endocardial pacing (30.1 ± 5.4 ms for endo; 39.4 ± 3.9 ms for mid; and 45.5 ± 2.2 ms for epi) compared
to either NSR (5.9 ± 0.8 ms for endo; 6.6 ± 0.8 ms for mid; and 7.0 ± 0.4 ms for epi) or LV septal pacing (13.0 ± 5.3 ms for endo; 16.3 ± 5.4 ms for mid; and 17.7 ± 5.5 ms for epi).

3.5 Septal activation

Figure 7 shows RV and LV septal activation times during NSR and during pacing at the other sites. The LV and RV septal
activation relations and times were very similar during NSR and LV septal pacing. During RV endocardial and biventricular pacing, the septal activation sequence was reversed with the RV septum being activated initially and LV septal activation being significantly delayed compared to during NSR. In fact, during RV endocardial pacing, LV septal activation time was similar to that of the LV free wall endocardium (Figure 4E). The LV septum was the last endocardial site to be activated during biventricular pacing (Figure 4C).

4. Discussion

In the present study, we have shown that the timing, sequence, and duration of myocardial activation vary substantially with pacing sites. This work adds to that of Medina-Ravell et al.14 with respect to LV epicardial and biventricular pacing. During NSR, activation is rapid and uniform with the LV endocardium being activated first, followed by the mid-myocardium and then, the epicardium. However, activation duration and sequence are substantially altered during pacing at all other sites except the LV septum, which resulted in a transmural activation duration and sequence similar to those observed during NSR. RV endocardial pacing caused marked prolongation and a disordered sequence of endo-, mid-, and epicardial activation. Biventricular pacing did not correct these abnormalities. Additionally, septal activation was reversed during both RV endocardial and biventricular pacing compared to NSR.

4.1 Envelope of activation

The importance of the temporospatial activation pattern for optimal myocardial performance was recognized by Wiggers15 and has been referred to as the ‘idioventricular kick’.16 Assessment of LV activation should include total duration as well as duration of endocardial, mid-myocardial, and epicardial activation and the sequence of transmural activation. The most obvious difference between activation through the normal His-Purkinje system and RV endocardial pacing is the prolonged duration of activation. Ventricular activation via the Purkinje network normally occurs within approximately 40 ms, whereas with RV endocardial pacing, the altered activation sequence creates delays of up to 100 ms.17 During RV endocardial, LV epicardial, and biventricular pacing, the spatial activation is substantially different than during NSR. The progression of activation from endocardium to mid-myocardium to epicardium is replaced by an intermingling of activation in all three regions.

The consequences of long-term RV endocardial pacing are potentially harmful. Myocardium which is activated early can stretch not-yet-depolarized muscle, which in turn, when activated, can stretch repolarized earlier activated segments.16–18 The resulting contraction is thus mechanically and metabolically inefficient.19 Reduced myocardial blood flow and increased wall thickness have been demonstrated in early-activated regions.17,18 This can result in LV remodelling with asymmetric hypertrophy, mitral regurgitation, decreased ejection fraction, and increased left atrial size.1,16,17 These changes appear to be reflected in clinical outcomes—despite maintaining AV synchrony, patients with the greatest amount of pacing are hospitalized more often for heart failure than those who are paced less.5

Not surprisingly, during this acute study in animals with normal hearts, the brief periods of pacing did not produce any significant changes in aortic pressure despite the changes in the transmural envelope of activation. LV epicardial pacing showed intermingling of endo-, mid-, and epicardial activation rather than the normal activation sequence seen during NSR. Endocardial activation was also prolonged and there was marked epicardial dispersion of activation. Resynchronization therapy, which combines RV endocardial and LV epicardial pacing to optimize mechanical synchrony, is recommended in patients with moderate to severe LV dysfunction who require pacing or have poorly controlled heart failure.20,21 During biventricular pacing, there was also intermingling of endo-, mid-, and epicardial activation; endocardial activation was slower than during NSR, though faster than during RV endocardial pacing. Clinically, in patients with abnormal LV dysfunction, biventricular pacing is ineffective in ~30% of patients.22 It is possible that the sequence of transmymocardial activation plays a role in limiting the effectiveness of this therapy.

4.2 Septal activation

During normal conduction, the left mid-septal endocardium is activated first23,24 in keeping with our findings. Purkinje fibres do not penetrate the septum and conduction through the remainder of the septum is syncytial.24,25 Pacing from a point source results in the contralateral ventricle not being activated normally and the impulse may enter the contralateral ventricle through multiple pathways.25 During RV endocardial pacing, the septal activation sequence was reversed with left septal activation being markedly delayed compared to during NSR. The earliest LV activation commonly occurred close to the septum, either anterior or posterior, before activation of the mid-LV septum. LV epicardial activation resulted in delayed RV and LV septal activation. Biventricular pacing resulted in a septal activation pattern similar to RV endocardial pacing. Thus, these results suggest that optimal septal activation is not achieved with presently used or proposed clinical pacing sites.

4.3 Left ventricular septal pacing

LV septal pacing achieved a temporospatial activation envelope that closely resembled that during NSR, whereas pacing at all other study sites, including biventricular pacing, did not. No changes in aortic pressure were demonstrated during the short episodes of pacing in the various pacing
modes. Peschar et al., who also paced the LV septum in dogs demonstrated no deterioration in stroke work, end-systolic, and end-diastolic volumes compared with NSR but were unable to explain the favourable haemodynamics as the QRS duration was still prolonged compared with NSR. Effective LV septal pacing has been achieved experimentally, which suggests that such a strategy may be clinically feasible. Since pacing from the LV septal site produces an envelope of activation that most closely resembles normal sinus rhythm, further work to determine if LV septal pacing can prevent or minimize the impact of pacing on the development or progression of heart failure appears justified.

4.4 Limitations

Relatively few recording electrodes were used in this study; thus there may be earlier and later myocardial activation sites than those recorded. However, this study did include transmural and septal recordings during NSR and pacing from presently utilized and proposed sites. Our results during NSR were similar to those previously reported and demonstrated the disarray of temporospatial patterns of activation associated with pacing. It has previously been shown that even large numbers of plunge electrodes do not alter activation sequence.

This was an acute study and episodes of pacing in all modalities were brief, thus the potential long-term consequences of structural remodelling and its haemodynamic effectscould not be addressed by this study.

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