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Dynamic and site-specific impact of ventricular pacing on left ventricular ejection fraction

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Abstract

BACKGROUND—Some studies suggest that right ventricular (RV) pacing has an adverse impact on left ventricular ejection fraction (LVEF), particularly in subjects with preexisting left ventricular (LV) dysfunction, and that direct LV pacing may be relatively protective. Interactions between pacing site and LVEF remain unclear.

OBJECTIVE—The purpose of this study was to examine the relative impact of RV and LV pacing on LVEF by serial study during a period in which LV dysfunction, induced by tachypacing, was introduced and then resolved.

METHODS—In each of five dogs, RV, LV, and simultaneous RV and LV (BiV) pacing modes were compared to native ventricular activation (1) prior to tachypacing (baseline), (2) weekly during a 5-week continuous tachypacing period, and (3) weekly during a 3-week post-tachypacing recovery period. At each evaluation, LVEF and LV contraction synchrony were assessed during each pacing mode.

RESULTS—The decrease in LVEF during the tachypacing period was more pronounced during RV pacing than during native activation or LV or BiV pacing. The magnitude of this effect correlated with a diminishment in LV contraction synchrony that was not observed during native activation or LV or BiV pacing. During the post-tachypacing period, gradual reversal of these changes toward baseline was observed.

CONCLUSION—Compared to native activation, RV pacing worsens LVEF in a manner proportional to the severity of preexisting LV dysfunction, attributable to reduced LV contraction synchrony. In comparison, both LV and BiV pacing preserve LVEF and contraction synchrony.

Keywords

Contraction; Ejection fraction; Pacing; Resynchronization; Ventricle

Introduction

Although right ventricular (RV) pacing reportedly has an adverse impact on left ventricular ejection fraction (LVEF), clinical experience is mixed. Some have suggested that RV pacing is more likely to be detrimental in the setting of preexisting left ventricular (LV) dysfunction. It has also been suggested that, with a goal of protecting LVEF, LV pacing is preferable to RV pacing, particularly in the setting of preexisting LV dysfunction.^{1–3} Although tenable, the data supporting these conclusions are incomplete, in part because most of the data derived from subjects studied at a single point in time. In the present investigation, we sought to better characterize the interaction between pacing site, LV function, and LVEF by performing a serial study during a period in which LV dysfunction, induced by tachypacing, was introduced and subsequently resolved. We hypothesized that there would be a disparity in LVEF between native activation and RV pacing, which would become magnified as dysfunction worsened and which would subsequently diminish as function improved. We also hypothesized that the disparity would be less apparent during direct LV pacing. Although our assumption was that the amelioration associated with LV pacing would be attributable to initial excitation of the LV, given the common clinical practice of tandem LV and RV (“biventricular” [BiV]) pacing, we decided to examine both LV-alone pacing and BiV pacing.

Methods

The protocol was approved by the Institutional Animal Care and Use Committee and conformed to the position of the American Physiological Society on research animal use. Five healthy mongrel dogs weighing 19.9 ± 0.6 kg were studied.

Animal management

After animals were fasted overnight, anesthesia was induced by mask isoflurane followed by endotracheal intubation and continuous isoflurane. Each animal underwent left lateral minithoracotomy, limited pericardiotomy, and application of permanent pacing leads (model 4968, Medtronic, Inc., Minneapolis, MN, USA) to the epicardial surfaces of the left atrium (LA; from a small lateral thoracotomy, this was more convenient than right atrium), RV free wall, and LV free wall. The pericardial and thoracic incisions were closed. The lead bodies were tunneled subcutaneously to the abdomen, where they were attached to a commercial pacing device (model 8042, Medtronic), which was placed in a subcutaneous pocket. This system was used for LA, RV, LV, and BiV pacing (described later). During the same procedure, a second commercial pacing device (model 900, Medtronic) was placed in a subcutaneous pocket in the ventral region of the right neck and attached to a single lead (model 4480, Guidant, Inc., St. Paul, MN, USA), which was placed endocardially in the RV via the right internal jugular vein. This system was used for tachypacing (described later). Animals were allowed to recover without pacing for 7 days, by which point each had returned to its preoperative physical and behavioral state; this point is referred to as “baseline.”

Baseline study

Conscious sedation was induced using mask isoflurane. Transthoracic echocardiography and 12-lead ECG were performed during each of four pacing modes: (1) LA pacing alone, during which ventricular electromechanical activation was native (LA); (2) sequential LA–RV pacing (RV); (3) sequential LA–LV pacing (LV); and (4) sequential LA–simultaneous BiV pacing (BiV). For each of the sequential pacing modes, an AV delay of 20 ms was chosen to ensure capture of the entire ventricular mass by the paced activation wavefront as

confirmed by ECG QRS morphology (data not shown). The paced rate for all modes (132 ± 4 bpm, range 130–140 bpm) was approximately 10 bpm faster than the sinus rate.

After echocardiography was completed, the model 8042 system was deactivated. The model 900 system was activated and programmed to a fixed, asynchronous tachypacing rate of 200 bpm.

Subsequent studies

At weeks 1, 2, 3, and 4 after baseline, the tachycardia pacing device was briefly deactivated, and the animal was placed under conscious sedation. The model 8042 system was activated and programmed as necessary to permit acquisition of echocardiographic and ECG data (below) during each of the four pacing modes, with pacing at the same rate as during the baseline study. After completion of data collection, the model 8042 system was again deactivated and the model 900 system reactivated. At week 5, the same procedure was followed, except that after completion of data collection, the model 900 system was not reactivated (no further tachypacing was performed). Data were collected in identical fashion at weeks 6, 7, and 8. Data from weeks 1–5 form the “tachypacing period,” and data from weeks 6–8 form the “post-tachypacing recovery period.” The animal was euthanized on week 8.

Echocardiography

A commercial system incorporating a 3.0-MHz transducer (Aplio, Toshiba Medical Systems, Tokyo, Japan) was used. Manual tracing of apical four-chamber and two-chamber views was used to derive end-diastolic volume (EDV), from which LVEF was calculated using the biplane Simpson rule.⁴ Mitral regurgitation area was calculated as the proportion of the planimetered LA area (four-chamber view) occupied by regurgitant color Doppler signal. Each value was derived as the average of three consecutive beats.

Radial LV strain was derived by speckle tracking analysis using commercial software (Toshiba), as previously described.^{5–8} In brief, B-mode, gray-scale, short-axis images were obtained at the mid-LV level, identified by apices of the papillary muscles (depth 8 cm, frame rate 49 Hz, with gain settings adjusted to optimize endocardial definition). Digitized images were analyzed for movement of stable patterns of natural acoustic markers (speckles) present in the ultrasound images. Endocardial and epicardial borders were traced, and the LV myocardium was divided into six segments, three of which composed the interventricular septal region (septal, anteroseptal, anterior), and three of which composed the free-wall region (inferior, posterior, lateral; Figure 1). Speckles within each segment were tracked, and their location shift from frame to frame, portraying myocardial motion, yielded the spatial and temporal (time–strain) data reported here. By analyzing the motion of speckles across myocardial thickness, radial strain was calculated as the change in thickness divided by the initial thickness. Myocardial thickening was represented as positive strain. Strain values from multiple regions within each segment were calculated and averaged into a single time–strain curve for each segment, as previously validated (Figure 2).^{5,9} The interval from QRS to peak strain was measured for each segment.

Analysis of synchrony

Contraction synchrony was analyzed by using systolic time–strain data from each of the six mid-LV segments. Onset of systole was defined by the moment of the QRS complex, which was assigned a time of 0. In order to encompass the contractile motion of all segments, the end of systole was defined by the moment of peak strain of the latest segment. Synchrony was assayed using a cross-correlation method, as previously described.^{10,11} This method examines the entirety of systole (Figure 2) and thus may be more robust than other reported

methods, which depend upon a single moment therein.^{12–14} Pairwise correlation analyses performed between all segment combinations resulted in 15 cross-correlation coefficients. These coefficients range in value from 0.00 (perfect asynchrony) to 1.00 (perfect synchrony). All coefficients were averaged to yield the global synchrony index (GSI). In addition, a segmental synchrony index (SSI) was generated for each segment individually by averaging only the coefficients from the five analyses involving that segment. For example, the inferior segment produced coefficients from each of the following analyses: (1) inferior versus posterior, (2) inferior versus lateral, (3) inferior versus anterior, (4) inferior versus anteroseptal, and (5) inferior versus septal.

Electrocardiography

Twelve-lead ECGs were digitally recorded using standard filtering methods with a commercial system (LabSystem, Bard). The ECG QRS duration (QRSd) data reported here represents the maximal value from among all leads, averaged over three consecutive beats.

Histology

After animal sacrifice (week 8), myocardial sections were obtained from the septal and free-wall regions of the mid-LV, fixed in formalin, embedded in paraffin, sectioned at 5- μ m thickness, and stained with Masson trichrome. Tissue sections were visualized using a microscope (TE2000-U, Nikon, Tokyo, Japan), and areas (excluding endocardial and perivascular regions) occupied by blue pixels were quantified using Metamorph image analysis software (Molecular Devices, Sunnyvale, CA, USA). Collagen volume fraction was determined as described previously.¹⁵ Data generated from two dogs with healthy hearts were used as normal values.

Analytical methods

In each study, the order of pacing modes (LA, RV, LV, BiV) was random. The echocardiographic data were acquired and analyzed by personnel blinded to pacing mode. Synchrony analyses were performed by different personnel, who also were blinded to pacing mode.

Data are given as mean $\pm$ SEM, unless otherwise stated. Comparisons were assessed using two-way repeated measures analysis of variance with a Fisher least significant difference *post hoc* test. Correlations were performed using the Pearson product moment correlation. For all tests, $P < .05$ was considered significant.

Results

Native activation (LA pacing mode)

At baseline, a normal LVEF was associated with short QRSd, low EDV, no mitral regurgitation, and high GSI and SSI values.

During the tachypacing period, progressive increases in EDV and mitral regurgitant area and a decrease in LVEF were seen (Figure 3). These changes were not accompanied by a significant prolongation in QRSd (Figure 3), decreases in GSI or SSI values (Figure 4), or prolongation in the duration of systole (Figure 5).

During the post-tachypacing recovery period, there was marked reversal of the changes incurred during the tachypacing period (Figure 3).

RV pacing mode

At baseline, QRSd was significantly longer than during LA mode, but no significant differences were noted between these modes in EDV, LVEF, mitral regurgitant area, GSI, SSI, or duration of systole (Figures 3–5).

During the tachypacing period, the decrease in LVEF was significantly more pronounced than during LA mode, resulting in a significant difference by week 3 that grew progressively larger at weeks 4 and 5 (Figure 3). Despite an unchanging QRSd, this difference was associated with a progressively decreasing GSI (Figure 4). The diminishment in GSI was associated with a small but significant prolongation in the duration of systole, measured by the time to peak strain of the latest activating segment (Figure 5). At the end of the tachypacing period, the magnitude of the difference in LVEF between LA and RV pacing modes was correlated with the magnitude of the difference in GSI between these modes ($R = .78$, $P < .05$). The SSI analyses revealed that although all segments contributed to the progressive diminishment in GSI during the tachypacing period, those composing the interventricular septal region did so disproportionately (Figure 4).

During the post-tachypacing recovery period, as for LA mode there was reversal of the changes incurred during the tachypacing period. As an absolute, the improvement in LVEF was more marked than during the LA mode because of its lower nadir at the end of the tachypacing period (Figure 3). This improvement was associated with a significant improvement in GSI (Figure 4) and a decrease in the duration of systole (Figure 5). However, by the end of the recovery period, these indices clearly had not returned to baseline.

LV and BiV pacing modes

Observations made during the LV and BiV pacing modes were similar and thus are presented together. At baseline, QRSd was significantly longer for each of these modes than during LA pacing mode and was significantly shorter during BiV than LV pacing mode. QRSd during LV pacing mode was not significantly different from that during RV pacing mode (Figure 3). No significant differences across LA, BiV, and LV pacing modes were seen for EDV, LVEF, mitral regurgitant area, GSI, SSI, or duration of systole (Figures 3–5).

During the tachypacing period, the decrease in LVEF was not significantly different from that during LA mode (Figure 3). Akin to LA mode, no significant changes in QRSd, GSI, SSI, or duration of systole were seen (Figures 3–5).

During the post-tachypacing recovery period, there was reversal of the changes incurred during the tachypacing period in a pattern akin to that during LA mode (Figures 3–5).

Histology

Myocardium from animals sacrificed on week 8 revealed no significant difference in collagen volume fraction between septal ($2\% \pm 2\%$, range 1%–6%) and free-wall ($4\% \pm 2\%$, range 1%–6%) sections. Combined, these myocardial data demonstrated no significant difference compared to myocardium obtained from control animals ($1\% \pm 1\%$, range 1%–2%, $P = .32$).

Discussion

In the setting of accruing LV dysfunction induced by tachypacing, RV pacing mode produced a greater decrease in LVEF than did native ventricular activation (LA pacing mode), with the magnitude of the difference proportional to the severity of dysfunction. This

observation confirms and extends those in prior reports, which have suggested that the detrimental effect of RV pacing on LVEF is “magnified” in the presence of preexisting LV dysfunction.³ These reports generally attributed the magnification phenomenon to prolonged electromechanical activation of diseased ventricular tissue but could not examine this issue fully because data were derived from subjects at a single point in time.^{3,16–18} By using a within-subject serial study format during a period in which LV dysfunction accrued, we observed that the magnitude of prolongation in the duration of systole was small relative to the magnitude of the disorder induced in the synchrony of contraction among its various segments, as quantified by GSI. The degree of diminishment in contraction synchrony was not homogenous across the ventricle; rather, it was more marked among segments composing the interventricular septum. This observation is consistent with previous reports demonstrating that RV pacing undermines interventricular septal motion in particular and supports the notion that efficient septal motion is a key to normal LV contraction.^{19–22}

In contrast, LV pacing modes (LV and BiV) were akin to native activation in that the magnification phenomenon was not observed as LV dysfunction accrued, an observation that was associated with like preservation of GSI. A general equivalence of LVEF during LV and BiV modes has been noted previously.^{23–28} Based on our findings, it is reasonable to hypothesize that LV pacing modes would be more protective of LVEF than RV pacing modes in the setting of an intercurrent cardiac insult. This concept might be supported by recent data demonstrating the potential benefit of “preemptive” LV pacing in patients with LV dysfunction and disordered native ventricular mechanical activation akin to RV pacing (left bundle branch block).²⁹

Study limitations

Our study have several limitations. First, the cohort is small; thus, the study may have missed other important differences between pacing modes that would have surfaced in a larger cohort. However, because each animal served as its own control, undergoing multiple studies as LV dysfunction accrued and then resolved, and because the findings were consistent across animals, we posit that the differences that we did detect are robust. Second, tachycardia-induced LV dysfunction is not a typical clinical substrate. Our primary goal was to better understand the potentially dynamic interaction between pacing site and LVEF. We believe that it was important to demonstrate that changes engendered by LV dysfunction would reverse once function began to improve. This would not have been feasible with a more typical substrate. Consistent with the nonfibrotic pathology observed in this study was the stability of QRSd throughout. The marked evolution in LVEF observed in the face of this is a reminder of the limited utility of QRSd for divining LV mechanical function.³⁰ Third, LVEF, a load-dependent index, is an inconsistent arbiter of intrinsic LV contractility. Given the immediate nature and random order of the comparisons between pacing modes, and given the fact that their mitral regurgitant magnitudes were not significantly different, it is likely that the differences in LVEF demonstrated here reasonably portrayed differences in intrinsic contractility. Fourth, AV asynchrony (AV delay 20 ms) induced during sequential pacing (RV, LV, and BiV modes) may have served to accentuate differences between these modes and native activation (LA pacing, in which AV synchrony was preserved). However, given that we did not observe significant differences between LA and LV or BiV modes, it seems less likely that this limitation would have altered our conclusions. Fifth, our motion analysis was limited to a single (radial) planar motion of a limited aspect of the LV myocardium and as such was highly simplistic. Finally, the RV pacing site used in this study (free wall) was at a distance from the interventricular septum. This site is different than the clinically standard site for permanent pacing (RV apex), which is adjacent to the interventricular septum. As opposed to the early septal electromechanical activation characteristic of RV apical pacing, it is possible that during BiV (RV free-wall) pacing,

septal activation was dominated by the wavefront proceeding from the LV lead. This may have contributed to the observed equivalence between LV and BiV modes.

Conclusion

The adverse impact of RV pacing on LVEF increases progressively in the setting of accruing LV dysfunction induced by tachypacing due to a decrease in LV contraction synchrony that is proportional to the degree of dysfunction. This process has a disproportionate effect on the interventricular septal region. The absence of an adverse impact during LV or BiV pacing was due to the ability of these modes to preserve synchrony. Thus, LV or BiV pacing may be preferable to RV pacing for maintaining LVEF against intercurrent disease that would threaten LV function.

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ABBREVIATIONS

BiV	biventricular (simultaneous RV and LV)
EDV	end-diastolic volume
GSI	global synchrony index
LA	left atrium
LV	left ventricle
LVEF	left ventricular ejection fraction
QRSd	electrocardiographic QRS duration
RV	right ventricle
SSI	segmental synchrony index

References

1. Tops L, Schalij M, Bax J. The effects of right ventricular apical pacing on ventricular function and dyssynchrony. *J Am Coll Cardiol*. 2009; 54:764–776. [PubMed: 19695453]
2. Chen L, Hodge D, Jahangir A, et al. Preserved left ventricular ejection fraction following atrioventricular junction ablation and pacing for atrial fibrillation. *J Cardiovasc Electrophysiol*. 2008; 19:19–27. [PubMed: 17971146]
3. Sweeney M, Prinzen F. Ventricular pump function and pacing: physiological and clinical integration. *Circ Arrhythmia Electrophysiol*. 2008; 1:127–139.
4. Lang R, Bierig M, Devereux R, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005; 18:1440–1463. [PubMed: 16376782]
5. Suffoletto M, Dohi K, Cannesson M, Saba S, Gorcsan J. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. *Circulation*. 2006; 113:960–968. [PubMed: 16476850]

6. Tanabe M, Lamia B, Tanaka H, Schwartzman D, Pinsky M, Gorcsan J. Echo-cardiographic speckle tracking radial strain imaging to assess ventricular dys-synchrony in a pacing model of resynchronization therapy. *J Am Soc Echocardiogr.* 2008; 21:1382–1388. [PubMed: 19041581]
7. Gorcsan J III, Tanabe M, Bleeker G, et al. Combined longitudinal and radial dyssynchrony predicts ventricular response after resynchronization therapy. *J Am Coll Cardiol.* 2007; 50:1476–1483. [PubMed: 17919568]
8. Tanaka H, Hara H, Saba S, Gorcsan J III. Prediction of response to cardiac resynchronization therapy by speckle tracking echocardiography using different software approaches. *J Am Soc Echocardiogr.* 2009; 22:677–684. [PubMed: 19501326]
9. Atria T, Sorescu G, Schuler B, et al. Speckle-tracking strain echocardiography for detecting cardiac dyssynchrony in a canine model of dyssynchrony and heart failure. *Am J Physiol (Heart Circ Physiol).* 2007; 293:H735–H742. [PubMed: 17449554]
10. Johnson L, Kim H, Tanabe M, et al. Differential effects of left ventricular pacing sites in an acute canine model of conduction dyssynchrony. *Am J Physiol (Heart Circ Physiol).* 2007; 293:3046–3055.
11. Silva E, Mont L, Delgado V, et al. Quantification of left ventricular asynchrony throughout the whole cardiac cycle with a computed algorithm: application for optimizing resynchronization therapy. *J Cardiovasc Electrophysiol.* 2009; 20:1130–1136. [PubMed: 19549037]
12. Dohi K, Pinsky M, Kanzaki H, Severyn D, Gorcsan J III. Effects of radial left ventricular dyssynchrony on cardiac performance using quantitative tissue Doppler radial strain imaging. *J Am Soc Echocardiogr.* 2006; 19:475–482. [PubMed: 16644429]
13. Yu C-M, Zhang Q, Fung J, et al. A novel tool to assess systolic asynchrony and identify responders of cardiac resynchronization therapy by tissue synchronization imaging. *J Am Coll Cardiol.* 2005; 45:677–684. [PubMed: 15734610]
14. Aurichio A, Prinzen F. Update on the pathophysiological basis of cardiac resynchronization therapy. *Europace.* 2008; 10:797–800. [PubMed: 18482999]
15. Pickering J, Boughner D. Fibrosis in the transplanted heart and its relation to donor ischemic time. Assessment with polarized light microscopy and digital image analysis. *Circulation.* 1990; 81:949–958. [PubMed: 2306841]
16. Vassalo J, Cassidy D, Miller J, Buxton A, Marchlinski F, Josephson M. Left ventricular endocardial activation during right ventricular pacing: effect of underlying heart disease. *J Am Coll Cardiol.* 1986; 7:1228–1233. [PubMed: 3711479]
17. Varma N. Left ventricular conduction delays induced by right ventricular apical pacing: effect of left ventricular dysfunction and bundle branch block. *J Cardiovasc Electrophysiol.* 2008; 19:114–122. [PubMed: 17971145]
18. Sweeney M, Hellkamp A, Ellenbogen K, Lamas G. Reduced ejection fraction, sudden cardiac death, and heart failure death in the Mode Selection Trial: implications for device selection in elderly patients with sinus node disease. *J Cardiovasc Electrophysiol.* 2008; 19:1160–1166. [PubMed: 18554201]
19. Curtius J, Nowitzki G, Kohler E, Kuhn H, Loogen F. Left bundle branch block: inferences from ventricular septal motion in the echocardiogram concerning left ventricular function. *Z Kardiol.* 1983; 72:635–641. [PubMed: 6659640]
20. Grines C, Boshore T, Boudoulas H, Olson S, Shafer P, Wolley C. Functional abnormalities in isolated left bundle branch block: the effect of interventricular asynchrony. *Circulation.* 1989; 79:845–853. [PubMed: 2924415]
21. Verbeek X, Vernooy K, Peschar M, Cornelussen R, Prinzen F. Intra-ventricular resynchronization for optimal left ventricular function during pacing in experimental left bundle branch block. *J Am Coll Cardiol.* 2003; 42:558–567. [PubMed: 12906989]
22. Saleh S, Liakopoulos O, Buckberg G. The septal motor of biventricular function. *Eur J Cardiothorac Surg.* 2006; 29:S126–S138. [PubMed: 16564701]
23. Blanc J, Etienne Y, Gilard M, et al. Evaluation of different ventricular pacing sites in patients with severe heart failure. *Circulation.* 1997; 96:3272–3277.

24. Kass D, Chen C, Curry C, et al. Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. *Circulation*. 1999; 99:1567–1573. [PubMed: 10096932]
25. Auricchio A, Stellbrink C, Block M, et al. The effect of pacing chamber and atrio-ventricular delay on acute systolic function of paced patients with congestive heart failure. *Circulation*. 1999; 99:2993–3001. [PubMed: 10368116]
26. Touiza A, Etienne Y, Gilard M, Fatemi M, Mansourati J, Blanc J. Long-term left ventricular pacing: assessment and comparison with biventricular pacing in patients with congestive heart failure. *J Am Coll Cardiol*. 2001; 38:1966–1970. [PubMed: 11738301]
27. Nelson G, Berger R, Fetters B, Talbot M, Hare J, Spinelli J. Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. *Circulation*. 2000; 102:3053–3059. [PubMed: 11120694]
28. Hay I, Melenovsky V, Fetters B, et al. Short-term effects of right-left heart sequential cardiac resynchronization in patients with heart failure, chronic atrial fibrillation, and atrioventricular nodal block. *Circulation*. 2004; 110:3404–3410. [PubMed: 15557370]
29. Moss A, Hall W, Cannom D, et al. Cardiac-resynchronization therapy for the prevention of heart failure events. *N Engl J Med*. 2009; 14:317–318.
30. Leclercq C, Faris O, Tunin R, et al. Systolic improvement and mechanical resynchronization does not require electrical synchrony in the dilated failing heart with left bundle-branch block. *Circulation*. 2002; 106:1760–1763. [PubMed: 12356626]

Figure 1.

Short-axis, mid-left ventricular, end-systolic echocardiographic images from a single animal demonstrating left ventricular segments and morphologic changes observed during the course of the study. *Dotted line* in the baseline image indicates the right ventricular aspect of the interventricular septum. Scale line = 1 cm. A = anterior segment; AS = anteroseptal segment; I = inferior segment; L = lateral segment; LV = left ventricular cavity; P = posterior segment; pm = papillary muscle; RV = right ventricular cavity; S = septal segment.

Figure 2.

Examples of strain data derived from one animal during RV mode at baseline (**top**) and at the end of the 5-week tachypacing period (**bottom**). **Left:** Families of time-strain curves derived at each study interval. Each family is composed of six curves, each derived from a single left ventricular segment. **Right:** Cross-correlation analysis between inferior and antero-septal segments, which used the entirety of the time-strain curves generated during systole (shown). Each analysis produced a segmental synchrony index (SSI) value ranging from 0.00 (perfect asynchrony) to 1.00 (perfect synchrony). A = anterior segment; AS = antero-septal segment; ES = end-systole, defined by the moment of peak strain of the latest contracting myocardial segment; I = inferior segment; L = lateral segment; P = posterior segment; QRS = moment of ECG QRS complex, defined as time 0; S = septal segment.

Figure 3. Morphology and function data for each pacing mode (all animals combined). * $P < .05$. B = baseline; EDV = left ventricular end-diastolic volume; EF = left ventricular ejection fraction; QRSd = ECG QRS duration; MRA = proportional mitral regurgitant area. Pacing modes as defined in text.

Figure 4.

Cross-correlation data for each pacing mode (all animals combined). Data are presented for each segment separately. GSI = global synchrony index; SSI = segmental synchrony index. Pacing modes as defined in text.

Figure 5.

Duration of systole, defined as the interval beginning with the moment of the QRS complex and ending with the moment of peak strain of the latest contracting myocardial segment, for each pacing mode (all animals combined). Pacing modes as defined in text.