Published in final edited form as:

J Cardiothorac Vasc Anesth. 2016 June ; 30(3): 709–715. doi:10.1053/j.jvca.2016.01.024.

Differential Effects of Left Ventricular Pacing Sites on Regional Contraction Patterns and Global Performance

Michael R. Pinsky¹, Hyung Kook Kim¹, Sven Zenker^{1,3}, Lauren Johnson², and Sanjeev Shroff²

¹Cardiopulmonary Research Laboratory, Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA

²Cardiovascular Systems Laboratory, Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA

Abstract

Objective—To define the differential effect of site-specific ventricular counter-pacing efficacy during cardiac resynchronization therapy (CRT) so as to identify the most informative views to quantify it. Cross sectional and long axis views are commonly used to assess left ventricular (LV) contractility.

Design—We assessed the effect of LV apical (LVa) and free wall (LVfw) pacing during cardiac resynchronization therapy (CRT) on long and short-axis contraction, cardiac output (CO) and stroke work (SW) in 10 open-chested acute canine model, hypothesizing that LVa and LVfw would induce earlier apical and free wall than basal or septal shortening, respectively. We also studied apical (CRTa) and free wall (CRTfw) using right ventricular (RV) pacing-induced dyssynchrony.

Setting—University large animal research laboratory

Participants—Acutely anesthetized and instrumented open-chested purpose-bred dogs

Interventions—Right ventricular (RV) pacing served as our model of cardiac dyssynchrony. Selective left ventricular (LV) free wall (LVfw) and apical (LVa) pacing alone or with RV (CRTfw and CRTa, respectively) we studied relative to right atrial pacing (RA) as control.

Measurements and Main Results—Two pairs of three ultrasonic crystals were placed along the LV longitudinal axis: apex, mid to base pairs along septal and free wall lines. Conductance catheter-defined longitudinal LV segmental volumes and pressure-volume data were collected. RV decreased CO and SW compared to RA (2.0 ± 0.3 vs. 1.4 ± 0.1 L•min⁻¹; 137 ± 22 vs. 60 ± 14 mJ; $P < 0.05$, respectively). LVfw but not LVa decreased SW [130 ± 35 mJ] while CRTa but not CRTfw, improved both (2.1 ± 0.2 L•min⁻¹; 113 ± 13 mJ; $P < 0.01$ vs. RV pacing). No difference in time to

Corresponding Author: Michael R. Pinsky, MD, 606 Scaife Hall, 3550 Terrace Street, Pittsburgh, PA 15261, Phone: (412)-647-3587, FAX: (412)-647-8060, pinskymr@upmc.edu.

³Dr. Zenker's current address is Department of Anesthesiology and Intensive Care Medicine, University of Bonn, 53105 Bonn Germany

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

minimal length free wall-to-septal crystal was seen with pacing. Both LVa and CRTa displayed increased apical to basilar shortening delay compared to RA, RV, LVfw (42 ± 47 , 9 ± 105 , and 1 ± 46 msec, respectively, $p < 0.05$). No matching regional LV volume changes were seen during LVa.

Conclusions—LV functional analysis from only a cross-sectional plane may be insufficient to characterize improved LV contraction synchrony during multisite CRT.

Keywords

cardiac resynchronization therapy; segmental shortening; canine model; LV performance; dyssynchrony

Introduction

Effective myocardial contraction requires both shortening of contractile myocardial elements and synchronization among these elements. Myocardial contraction dyssynchrony can occur from structural changes to the His-Purkinje system, such as left bundle-branch block (LBBB) or other intra-ventricular conduction defects, manifested as non-specific widening of the QRS (1, 2), as well as by functional changes in regional myocardial contractility, such as myocardial ischemia, stunning, hibernation, and infarction (3). Dyssynchronous myocardial contraction decreases left ventricular (LV) ejection efficiency by a variety of mechanisms, including having regional segments reach their maximal shortening at different times and dysfunction of the mitral valve apparatus leading to incompetence through dyssynchronous papillary muscle contraction. LV performance is often evaluated using 2D-echocardiographic techniques. Assessment of counter-pacing efficacy during cardiac resynchronization therapy (CRT) requires imaging contraction in the most informative views. Cross sectional and long axis views are commonly used to assess LV performance. Presently there is no established method of assessing regional dyssynchrony over multiple image planes.

CRT using selective ventricular multi-site pacing is used to minimize LV contractile dyssynchrony and improve LV mechanical function (4, 5, 6, 3, 2). CRT improves functional status and survival in heart failure patients with pre-existing dyssynchrony (1, 7, 8, 9, 11, 12, 13), but 20-30% of patients do not benefit from this therapy (1, 7, 8). We recently documented that both LV apical and LV free wall pacing improve global LV performance in a canine model of LBBB but that the improved performance was not completely explained by a detailed analysis of mid-myocardial radial strain analysis (14). In that study we used mid-myocardial cross-sectional 2D echocardiographic tissue Doppler imaging and strain analysis, as previously validated by our group (15, 16). That imaging plane excludes apical and basilar radial movement, which might behave differently between LV apical and free wall pacing sites. Potentially, contraction dyssynchrony along the long axis (apex to base) or along the short axis (free wall to septum) that are outside the mid-myocardial cross-sectional plane may be occurring during multisite CRT and not captured by this common imaging mode. Since minimizing LV contractile dyssynchrony is directly correlated with improved survival and increased reverse remodeling (9), defining the optimal effect of resynchronization lead placement is important. Thus, in this study we measured regional LV segmental short axis contraction from apex to base and regional LV longitudinal axis

contraction free wall to septum, respectively, during LV apical or free wall pacing alone or combined as CRT using highly accurate ultrasonic crystals to quantify regional length changes using a subgroup of the animals reported earlier (14). We hypothesized that LV apical or free wall pacing would result in earlier apical than basilar LV radial contraction and earlier free wall than septal contraction, respectively.

Materials and Methods

Preparation

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. Ten mongrel dogs (20.2 ± 1.2 kg body weights) were studied after an overnight fast. Anesthesia was induced with a bolus of 30 mg/kg sodium pentobarbital and maintained with a continuous infusion of 0.1 mg/kg/min sodium pentobarbital. A triple-lumen intravenous catheter was inserted into a femoral vein, and 20-gauge catheter inserted into a femoral artery for blood pressure monitoring and blood sampling. A balloon-tipped pulmonary artery catheter was inserted for monitoring of blood temperature and cardiac output by the continuous thermal technique. All medications were administered intravenously. The trachea was intubated and the lungs mechanically ventilated (Harvard dual-phase animal ventilator, Harvard Apparatus, Cambridge, MA) with a 10 ml/kg tidal volume. Frequency was adjusted to maintain an arterial PCO_2 between 35 and 45 mm Hg. Acid-base status was adjusted with intermittent bolus of sodium bicarbonate to maintain arterial blood pH between 7.35 and 7.45. Body temperature was maintained between 36°C and 38°C using a heat blanket.

A 6-Fr 11-pole multielectrode conductance catheter (Webster Laboratories, Irvine, CA) and a 5-Fr high-fidelity micromanometer catheter (MPC-500, Millar, Houston, TX) were placed for LV pressure-volume analysis via the right internal carotid artery and left common carotid artery, respectively. The conductance catheter method of Baan for measuring ventricular volume has been described and validated previously (17). Briefly, a 20-kHz, constant-amplitude current of 30 μA RMS is passed between the electrodes of the distal and proximal extremes of the multielectrode catheter in a dual-field format. The change in conductance sensed during ventricular contraction in any one of these discs is caused by a change in resistance in the cross-sectional area of the disc. A sternotomy was performed. The pericardium was opened and the heart was suspended in a pericardial cradle. Epicardial pacemaker leads were placed on the right atrium (RA), right ventricular (RV) outflow track below the pulmonary valve, LV free wall near the mid posterior-lateral wall, and LV apex for multi-site stimulation. To analyze circumferential and longitudinal movement, three sonomicrometric crystals (Sonomicrometry, Sonometrics Corp., London, Ontario, Canada) were inserted in the subepicardium along the interventricular septum and another matched set of three crystals were inserted in the subepicardium along the LV lateral wall. The angle between two crystal rows was maintained with 90 degrees (Figure 1). The pericardium was closed with multiple interrupted sutures. Afterward, 5 cmH_2O PEEP was applied to maintain end-expiratory lung volume for the remainder of the experiment. Fluid resuscitation was performed prior to starting the protocol to restore apneic LV end-diastolic volume to value similar to where they were prior to sternotomy.

Protocol

All measurements were made with respirations suspended at an end-expiration of 5 cm H₂O PEEP to control for the effects of cardiopulmonary interactions. The protocol consisted of pacing and then creating a stable apneic steady state for data acquisition. To avoid retrograde conduction for all pacing steps of the protocol, RA pacing was performed at frequencies 5-10 beats/min above the intrinsic rhythm. We compared the mechanical effects of RA to sinus rhythm (SR) to document that RA did not alter contraction synchrony. RA pacing is defined as normal ventricular contraction for subsequent comparisons. All succeeding ventricular pacing experiments were then done with sequential pacing at an atrioventricular (A-V) delay of 30 ms to prevent fusion beats. This resulted in a decreased LV end-diastolic volume during all ventricular paced beats because of the loss of the atrial contribution to LV filling. Contraction dyssynchrony was created by RA plus RV outflow tract pacing (RV pacing), which induced a LBBB-like contraction pattern. We then compared the impact of two different LV sites on simple RA pacing or RV pacing-induced dyssynchronous contraction pattern. We chose to pace at either the LV apex (LVa) or lateral LV free wall at the mid-ventricular level below the left circumflex artery (LVfw) during simultaneous RA pacing. We also performed LV apical and free wall pacing during RV-pacing induced dyssynchrony to mimic CRT to ascertain if the altered contraction pattern we expected to observe with isolated LV pacing would persist during similar LV pacing site CRT. These pacing states are referred to a CRTa and CRTfw, respectively. The sequence of apical or free wall pacing during both RA pacing and RV pacing was alternated among sequential animals to eliminate any sequential effects. Pacing was sustained for > 30 sec before measurements were made for each step so that a hemodynamic equilibrium could be established. In practice, hemodynamic stability usually took < 15 sec to occur. Between each ventricular pacing interval, the animals were returned to RA pacing, and all hemodynamic variables were stabilized to baseline levels before the next step in the protocol was initiated.

Data collection and analysis

LV pressure and volume, aortic pressure, pulmonary artery pressure, right atrial pressure, continuous cardiac output, and airway pressure data were digitized at 250 Hz and stored on disk for off-line analysis (Ponemah System, Gould, Cleveland, OH). The longitudinal and circumferential peak systolic stresses were obtained by calculation of the instantaneous distance between crystals normalized to the end-diastolic length and used to approximate strain. Sonomicrometric data were acquired simultaneously with LV pressure and volume data. The conductance catheter also reports segmental volume changes. We defined axial dyssynchrony as a significant time delay to minimal apical to basal segment length between septal and free wall crystals, and longitudinal dyssynchrony as a significant time delay to minimal septal to basal segment length between septal and free wall crystals.

Indices of global performance (e.g., LV stroke volume, LV stroke work, LV $dP/dt_{\max}$ and $dP/dt_{\min}$) were calculated from LV pressure-volume data obtained under steady-state apneic conditions for each pacing modality using standard formulae (18).

Statistical Analysis

Global LV performance values are expressed as mean $\pm$ SEM and Regional LV contraction data are expressed as mean $\pm$ SD. One-way analysis of variance (ANOVA) with repeated measures was used to evaluate the effects of different pacing modalities on regional LV segmental time to minimal distance or minimal synchrony and indices of global LV performance. Tukey-Kramer test was employed for *post hoc* pair-wise comparisons following each ANOVA. Significance was determined as $P < 0.05$. Linear regression analysis was used to compare the newly developed index of contraction synchrony with the existing dyssynchrony indices.

Results

Effect of Pacing of Performance

Global hemodynamic data for all pacing conditions are shown in Table 1. Heart rate was the same throughout RA, RV, LVa, LVfw, CRTa and CRTfw (133 ± 6 beats $\cdot$ min $^{-1}$). As expected, RV pacing induced decrements in global LV functional indices compared to RA [cardiac output (CO): 2.4 ± 0.7 to 1.7 ± 0.7 L $\cdot$ min $^{-1}$; stroke work (SW): 162 ± 58 to 80 ± 55 mJ; LV dP/dt $_{\max}$: 1346 ± 144 to 1087 ± 166 mm Hg $\cdot$ s $^{-1}$; LV dP/dt $_{\min}$: -1679 ± 221 to -1072 ± 165 ; all $P < 0.05$]. All pacing modalities decreased LV end-diastolic volume relative to RA. Although LVa was associated with similar CO and SW relative to RA, LVfw was associated with a reduced SW (109 ± 51 mJ, $P < 0.05$). CRTa were associated with improved CO and SW (all $P < 0.01$, CRTa vs. RV) whereas neither LV dP/dt $_{\max}$ nor LV dP/dt $_{\min}$ changed (LV dP/dt $_{\max}$: 1087 ± 166 to 1109 ± 116 mm Hg $\cdot$ s $^{-1}$; LV dP/dt $_{\min}$: -1072 ± 165 to -1218 ± 181 mm Hg $\cdot$ s $^{-1}$). CRTfw did not alter either CO or SW (1.9 ± 0.8 L $\cdot$ min $^{-1}$, 96 ± 42 mJ, respectively) and CO for both RV and CRTfw were less than CRTa ($P < 0.05$).

Effect of Pacing Site and CRT on Regional LV Contraction

Time to LV minimal volume was unaltered by pacing site (Table 2). Timing differences induced by pacing for axial dyssynchrony (free wall to septum) and longitudinal dyssynchrony (apex to base) are shown in Figures 2 and 3, respectively. SR and RA had similar levels of regional dyssynchrony. Despite inducing marked reductions in CO and SW, RV was not associated with a change in radial or longitudinal dyssynchrony. Similarly, neither LVfw nor CRTfw were associated with significant radial or longitudinal dyssynchrony. However, both LVa and CRTa displayed significantly longitudinal dyssynchrony as compared to both RV and CRTfw (148 ± 141 , 35 ± 138 , and 4 ± 117 msec, respectively, $p < 0.05$). Interestingly, the global LV pressure-volume relations for LVa as compared to CRTa and LVfw as compared to CRTfw displayed similar shapes (Figure 4) suggesting that the site of LV pacing in CRT alters both regional dyssynchrony and global LV performance.

Discussion

The principal findings of this study were that ventricular pacing profoundly alters not only global LV function but also only orthogonal contraction synchrony. RV-pacing induces a left bundle branch block-like contraction dyssynchrony (15) and the site of LV counter-pacing

CRT differentially alters global measures of LV performance and regional segmental dyssynchrony (5, 14, 18, 19). CRTa improves global LV performance but increases regional longitudinal contractile dyssynchrony whereas CRTfw improved LV performance less but was not associated with LV pacing-induced regional dyssynchrony. The novel findings of this study are that when regional dyssynchrony is assessed by longitudinal dyssynchrony (differences in time to minimal length in radial contracting ultrasonic crystal pairs apex to basal) longitudinal dyssynchrony occurs to a greater degree with LVa, as mirrored by CRTa, whereas neither RV, LVfw nor CRTfw displayed such phase differences in any orthogonal direction. Since most of the normal systolic LV wall movement occurs in a radial direction associated with torsion (5, 20), with minimal apical longitudinal shortening (21), our findings of selective longitudinal dyssynchrony with CRTa are relevant because this region normally moves the least and may explain the lack of tight concordance between mid-LV cross-sectional dyssynchrony measures and global LV performance during LV contraction dyssynchrony and CRT.

Presently, the impact of CRT in clinical trials on dyssynchrony is assessed by single plane echocardiographic 2D image processing (22). Although both longitudinal strain and radial cross-sectional mid-myocardial strain assess the impact of CRT on regional performance, both assume that this single plane view reflects global LV performance. We (6, 14, 23) and others (24) have used highly processed single plane echocardiographic analysis to quantify contraction effectiveness. In fact, most of the mechanical dysfunction seen with pacing-induced dyssynchrony and its improvement with CRT can be explained by the single regional segment with the greatest degree of dyssynchrony (5). Interestingly, when longitudinal dyssynchrony was assessed by regional long axis LV segmental volume measures, as we previously used in a contraction dyssynchrony model (18), these segmental crystal contraction differences are abolished. Presumably, regions of the LV not measured by the specific crystal placement summate to cause LV regional stroke volumes to remain unchanged. Since these apical to basal contraction dyssynchrony effects are not captured by radial mid-myocardial imaging, our findings of out of mid LV cross-sectional axis plane dyssynchrony may explain the often seen dissociation between quantitative measures of regional dyssynchrony and global LV performance during multi-site CRT (6, 18, 23). Clearly, the impact of CRT on LV performance is complex and not easily described by a single parameter or even multiple parameters if measured along a single plane. Our data reinforce this conclusion and suggests that multi-plane echocardiographic analysis is preferred to assess the impact of CRT on LV dyssynchrony. Or at a minimum, if changes in global LV performance do not match observed changes in dyssynchrony assessed by a single plane 2-D echocardiographic analysis, further analysis across other image planes must be made.

Methodological Considerations

Dyssynchrony Model—Our model is not one of structural contraction dyssynchrony or of heart failure, but rather pacing-induced contractile dyssynchrony caused by high outflow tract RV pacing. Right ventricular pacing is an established model that produces delayed LV contraction (25), LV contraction dyssynchrony, and decreased stroke volume, stroke work, and LV pressures (15, 25, 26). However, our regional segmental analysis remains valid as a

model of CRT and illustrates the need to assess multiple parameters of dyssynchrony when assessing the impact of CRT on regional LV performance.

Quantification of Dyssynchrony—There is no one standard method to quantify dyssynchrony. Quantification is a function of the method used. For example, we previously showed that regional dyssynchrony could be modeled as a cosine function of phase shifts amongst paired regions (18), regional strain assessed by tissue Doppler imaging could be analyzed by the regional differences in time to peak strain and in the cross correlation of all regional strain patterns in a mid-ventricular short axis view (14) and that maximal segmental dyssynchrony defined most of the mechanical inefficiency described by global LV contraction (5). In this study we add time difference to reach minimal length amongst different segments as a means to quantify dyssynchrony. One advantage of ultrasonic crystal data is that it makes no assumptions about strain or systole, only segmental length changes. Our data show that regional longitudinal dyssynchrony can be accurately assessed by differences in time to minimal distance between apical and basilar regions and that similar analyses using endomyocardial LV volumes with a conductance catheter are less sensitive. Potentially, regional intra-luminal LV volume changes during systole can be altered independent of an isolated segmental length change because other segments outside of those measured by the crystals may contract differently. The clinical utility of the assessment of regional LV volumes during CRT has not been defined.

LV Pacing Sites: Implications for CRT and Contraction Synchrony Analysis

—We previously reported using this model that global LV performance only improved during CRTa and not CRTfw (14). Thus, it appears that LV apical pacing is superior to LV free-wall pacing in CRT if no structural limitations to cardiac conduction co-exist. Those data agreed with those of Helm *et al.* (27) who also demonstrated better LV performance with LV apical pacing compared to more basal stimulation. Similarly, two other groups also reported beneficial effects on global LV performance following biventricular (RV apex + LV apex) pacing in healthy dogs (28, 29). Finally, Vanagt *et al.* (30) showed that the LV apex was the optimal pacing site in both canines and humans. Clinically, more basilar LV pacing sites are usually used because of convenience. Although this site selection bias is primarily due to site limitations created by retrograde coronary vein pacing probe placement, other factors may potentially make basilar pacing better in specific instances. For example, structural abnormalities following myocardial infarction or conduction defects may render LV free wall pacing more effective at creating optimal LV performance than LV apical pacing. Our study does not allow us to address these clinically relevant issues further.

Potentially, apical pacing may be more beneficial to global LV function in otherwise healthy hearts because it activates the Purkinje system at a point where further electrical conduction uses intrinsic pathways (31). Since impulses exit the Purkinje system in the lower third of the LV wall (25), apical stimulation should induce an activation pattern similar to intrinsic myocardial activation thus contributing to improved global LV performance. Interestingly, although global LV performance improved more with apical pacing, apical pacing was the only CRT pacing mode to induce independently regional dyssynchrony as quantified by ultrasonic crystal data. That only LV apical pacing and not LV free wall pacing causes

dyssynchronous contraction propagation, suggests that one needs to evaluate the three dimensional impact of pacing in all cases because its impact outside a 2-dimensional plane will not be otherwise appreciated. Thus, future studies of the impact of different pacing sites on global LV performance should also address dyssynchrony across more than a single plane. Otherwise relevant pacing-induced dyssynchrony may be missed.

Clinical significance—Echocardiographic analysis documenting improved LV contractile synchrony in response to CRT predicts long-term myocardial tissue reverse remodeling (32, 33) but only to the extent that global dyssynchrony is minimized (9). Thus, multi-view echocardiographic analysis may be needed to define optimal CRT lead placement since real-time documentation of resynchronization using intramyocardial markers is unrealistic.

Acknowledgement

The authors wish to thank Lisa Gordon and Don Severyn, MS for their expert technical assistance.

This study was supported in part by NIH awards HL04503, HL067181 and HL073198

References

1. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002; 346:1845–1853. [PubMed: 12063368]
2. Tavazzi L. Ventricular pacing: a promising new therapeutic strategy in heart failure. For whom? *Eur Heart J*. 2000; 21:1211–1214. [PubMed: 10924309]
3. Tang ASL, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL, for the Resynchronization-Defibrillation of Ambulatory Heart Failure Trial (RAFT) investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med*. 2010; 363:2385–2395. [PubMed: 21073365]
4. Gorcsan J 3rd, Kanzaki H, Bazaz R, Dohi K, Schwartzman D. Usefulness of echocardiographic tissue synchronization imaging to predict acute response to cardiac resynchronization therapy. *Am J Cardiol*. 2004; 93:1178–1181. [PubMed: 15110219]
5. Lamia B, Tanabe M, Tanaka H, Kim HK, Gorcsan J, Pinsky MR. Left ventricular systolic torsion correlates global cardiac performance during dyssynchrony and cardiac resynchronization therapy. *Am J Physiol (Heart Circ)*. 2011; 300:H853–H858.
6. Tanabe M, Lamia B, Suffoletto MS, Pinsky MR, Gorcsan J III. Validation of Novel Echocardiographic Speckle Tracking Radial Strain to Assess Ventricular Dyssynchrony: Comparison with Angle corrected Tissue Doppler Strain Imaging. *J Am Soc Echocardiol*. 2008; 21:1382–1388.
7. Auricchio A, Stellbrink C, Butter C, Sack S, Vogt J, Misier AR, Bocker D, Block M, Kirkels JH, Kramer A, Huvelle E. Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. *J Am Coll Cardiol*. 2003; 42:2109–2116. [PubMed: 14680736]
8. Auricchio A, Stellbrink C, Sack S, Block M, Vogt J, Bakker P, Huth C, Schondube F, Wolfhard U, Bocker D, Krahnefeld O, Kirkels H. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol*. 2002; 39:2026–2033. [PubMed: 12084604]
9. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. Cardiac-resynchronization therapy with or

- without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004; 350:2140–2150. [PubMed: 15152059]
10. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, Garrigue S, Kappenberger L, Haywood GA, Santini M, Bailleul C, Daubert JC. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med*. 2001; 344:873–880. [PubMed: 11259720]
 11. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005; 352:1539–1549. [PubMed: 15753115]
 12. Reuter S, Garrigue S, Barold SS, Jais P, Hocini M, Haissaguerre M, Clementy J. Comparison of characteristics in responders versus nonresponders with biventricular pacing for drug-resistant congestive heart failure. *Am J Cardiol*. 2002; 89:346–350. [PubMed: 11809441]
 13. Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, Canby RC, Schroeder JS, Liem LB, Hall S, Wheelan K. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *JAMA*. 2003; 289:2685–2694. [PubMed: 12771115]
 14. Johnson L, Kim HK, Tanabe M, Gorcsan J, Schwartzman D, Shroff S, Pinsky MR. Differential Effects of Left Ventricular Pacing Sites in an Acute Canine Model of Contraction Dyssynchrony. *Am J Physiol: Heart and Circ*. 2007; 293:H3046–H3055.
 15. Dohi K, Pinsky MR, Kanzaki H, Severyn D, Gorcsan J 3rd. 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]
 16. Dohi K, Suffoletto MS, Schwartzman D, Ganz L, Pinsky MR, Gorcsan J 3rd. Utility of echocardiographic radial strain imaging to quantify left ventricular dyssynchrony and predict acute response to cardiac resynchronization therapy. *Am J Cardiol*. 2005; 96:112–116. [PubMed: 15979447]
 17. Baan J, Van Der Velde ET, De Bruin H, Smeenk GJ, Koops J, van Dijk AD, Temmerman D, Senden J, Buis B. Continuous measurement of left ventricular volume in animals and man by conductance catheter. *Circulation*. 1984; 70:812–823. [PubMed: 6386218]
 18. Strum DP, Pinsky MR. Modeling ischemia-induced dyssynchronous myocardial contraction. *Anesth Analg*. 2006; 103:846–853. [PubMed: 17000791]
 19. Lamia B, Tanabe M, Kim HK, Gorcsan J III, Pinsky MR. Quantifying the role of regional dyssynchrony on global ventricular performance. *JACC Cardiovasc Imaging*. 2009; 2:1350–1356. [PubMed: 20083067]
 20. Zhou W, Benharash P, Chua JA, Nakahara S, Ho JK, Mahajan A. Acute effects of pacing at different ventricular sites on left ventricular rotational mechanics in a porcine model. *J Cardiothorac Vasc Anesth*. 29:1148–1154. [PubMed: 25824449]
 21. Grines CL, Bashore TM, Boudoulas H, Olson S, Shafer P, Wooley CF. Functional abnormalities in isolated left bundle branch block. The effect of interventricular asynchrony. *Circulation*. 1989; 79:845–853. [PubMed: 2924415]
 22. Bleeker GB, Mollema SA, Holman ER, Van De Veire N, Ypenburg C, Boersma E, van der Wall EE, Schalij M, Bax JJ. Left ventricular resynchronization is mandatory for response to cardiac resynchronization therapy: Analysis in patients with echocardiographic evidence of left ventricular dyssynchrony at baseline. *Circulation*. 2007; 116:1440–1448. [PubMed: 17785624]
 23. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J 3rd. 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]
 24. Toyoda T, Baba H, Akasaka T, Akiyama M, Neishi Y, Tomita J, Sukmawan R, Koyama Y, Watanabe N, Tamano S, Shinomura R, Komuro I, Yoshida K. Assessment of regional myocardial strain by a novel automated tracking system from digital image files. *J Am Soc Echocardiogr*. 2004; 17:1234–8. [PubMed: 15562260]

25. Little WC, Reeves RC, Arciniegas J, Katholi RE, Rogers EW. Mechanism of abnormal interventricular septal motion during delayed left ventricular activation. *Circulation*. 1982; 65:1486–1491. [PubMed: 7074805]
26. Kingma I, Tyberg JV, Smith ER. Effects of diastolic transseptal pressure gradient on ventricular septal position and motion. *Circulation*. 1983; 68:1304–1314. [PubMed: 6640880]
27. Helm RH, Byrne M, Helm PA, Daya SK, Osman NF, Tunin R, Halperin HR, Berger RD, Kass DA, Lardo AC. Three-dimensional mapping of optimal left ventricular pacing site for cardiac resynchronization. *Circulation*. 2007; 115:953–961. [PubMed: 17296857]
28. Peschar M, de Swart H, Michels KJ, Reneman RS, Prinzen FW. Left ventricular septal and apex pacing for optimal pump function in canine hearts. *J Am Coll Cardiol*. 2003; 41:1218–1226. [PubMed: 12679225]
29. Prinzen FW, Van Oosterhout MF, Vanagt WY, Storm C, Reneman RS. Optimization of ventricular function by improving the activation sequence during ventricular pacing. *Pacing Clin Electrophysiol*. 1998; 21:2256–2260. [PubMed: 9825329]
30. Vanagt WY, Verbeek XA, Delhaas T, Mertens L, Daenen WJ, Prinzen FW. The left ventricular apex is the optimal site for pediatric pacing: correlation with animal experience. *Pacing Clin Electrophysiol*. 2004; 27:837–843. [PubMed: 15189513]
31. Prinzen FW, Peschar M. Relation between the pacing induced sequence of activation and left ventricular pump function in animals. *Pacing Clin Electrophysiol*. 2002; 25:484–498. [PubMed: 11991375]
32. Chakir K, Daya SK, Tunin RS, Helm RH, Byrne MJ, Dimaano VL, Lardo AC, Abraham TP, Tomaselli GF, Kass DA. Reversal of global apoptosis and regional stress kinase activation by cardiac resynchronization. *Circulation*. 2008; 117:1369–77. [PubMed: 18316490]
33. Barth AS, Aiba T, Halperin V, DiSilvestre D, Chakir K, Colantuoni C, Tunin RS, Dimaano VL, Yu W, Abraham TP, Kass DA. Cardiac resynchronization therapy corrects dyssynchrony-induced regional gene expression changes on a genomic level. *Circulation: Cardiovascular Genetics*. 2009; 2:371–8. [PubMed: 20031609]

Figure 1.

Placement of sonomicrometer crystals along Interventricular Septal Groove (Septum) and Lateral Wall (Lateral) at a 90° arc of the left ventricular (LV) circumference and arrows showing vertical and horizontal contraction phase differences. Contraction phase differences between basal crystal pairs compared to apical crystal pairs were taken to reflect longitudinal axis contraction dyssynchrony. Whereas contraction phase differences between septal crystal pairs compared to lateral wall crystal pairs were taken to reflect horizontal (cross-sectional) contraction dyssynchrony.

Figure 2.

Contraction Time Delay between Base to Apex for Lateral-Septal Crystal Pairs reflecting longitudinal axis dyssynchrony. Positive time difference means apex reaches minimal length earlier than base. Individual subjects shown in different colors with mean $\pm$ SD shown for each step in grey. Abbreviations: sinus rhythm, SR; right atrial pacing control, RA; RA-right ventricular pacing, RV; RA-left ventricular apical pacing, LVa; RA-left ventricular free wall pacing, LVfw; cardiac resynchronization therapy combining RA, RV and LV apical or LV free wall pacing, CRTa and CRTfw, respectively.

Figure 3.

Contraction Time Delay between Septal to Lateral Wall Apical-Basal Crystal Pairs reflecting horizontal (cross sectional) axis dyssynchrony. Positive time difference means lateral wall reaches minimal distance before septum. Individual subjects shown in different colors with same color match per subject as in figure 2, with mean $\pm$ SD shown for each step in grey. Abbreviations: sinus rhythm, SR; right atrial pacing control, RA; RA-right ventricular pacing, RV; RA-left ventricular apical pacing, LVa; RA-left ventricular free wall pacing, LVfw; cardiac resynchronization therapy combining RA, RV and LV apical or LV free wall pacing, CRTa and CRTfw, respectively.

Figure 4.
Regional LV pressure-length relations during apnea for RA, RV, LVa, LVfw, CRTa and CRTfw for LV basal (A), mid (B) and apical (C) regions for one animal.

Table 1

Global LV performance values for different pacing modalities.

	RA Pacing	RV Pacing	LVa	LVfw	CRTa	CRTfw
HR (beats•min ⁻¹)	134±15	134±15	133±14	134±5	134±15	134±15
MAP (mm Hg)	92±18	73±19 [*]	77±14 [*]	75±17 [*]	75±19 [*]	75±19 [*]
LV EDP (mm Hg)	12 ± 7	12 ± 6	12 ± 6	11 ± 6	12 ± 6	11 ± 6 ^{‡#}
LV ESP (mm Hg)	98±20 [*]	81±22 [*]	66±37 [*]	74±32 [*]	82±22 [*]	73±36 [*]
LV EDV (mL)	52±22	42±22 [*]	47±20 [*]	42±15 [*]	44±20 [*]	40±18 [*]
LV ESV (mL)	33±16.6	29±18	27±15 [*]	26±13 [*]	25±17 [‡]	26±13 [§]
SV (mL)	18±6	13±5 [*]	20±10 [‡]	16±4	19±8 [‡]	14±6 [§]
CO (L•min ⁻¹)	2.4±0.7	1.7±0.7 [*]	2.6±1.1 [‡]	2.1±0.6	2.5±0.9 [‡]	1.9±0.8 [§]
dP/dt _{max} (mm Hg•s ⁻¹)	1389±373	1138±432 [*]	1274±342	1247±332	1174±338 [*]	1186±359 [*]
dP/dt _{min} (mm Hg•s ⁻¹)	—	—	—	—	—	—
	1712±549	1138±446 [*]	1365±449 [‡]	1275±554 [*]	1311±517 [‡]	1302±555 [*]
SW (mJ)	162±58	80±55 [*]	150±57 [‡]	109±51 [*]	141±59 [‡]	96±42 [§]

Data are means ± SD; n=8.

RA Pacing, right atrial pacing; RV Pacing, right atrial and right atrial-right ventricular pacing; LVa, right atrial-left ventricular apical pacing; LVfw, right atrial-left ventricular free wall pacing; CRTa, right atrial-right ventricular-left ventricular apical pacing; CRTfw, right atrial-right ventricular-left ventricular free-wall pacing; HR, heart rate; MAP, mean arterial pressure; LV EDP, LV ESP, left ventricular end-diastolic and end-systolic pressure, respectively; LV EDV, LV ESV, left ventricular end-diastolic and end-systolic volume, respectively; SV, stroke volume; CO, cardiac output; dP/dt_{max}, dP/dt_{min} maximum and minimum rate of change of LV pressure, respectively; SW, LV stroke work.

^{*} $P < 0.05$, vs. RA pacing

[‡] $P < 0.05$, vs. RV pacing

[§] $P < 0.05$, LVa vs. LVfw or CRTa vs. CRTfw

[#] $P < 0.05$, LVa vs. CRTa or LVfw vs. CRTfw

Table 2

Time to minimal regional volume or length difference between apex and base crystal pairs for RA, RV, LVa, LVfw, CRTa and CRTfw pacing modes in individual animals

DOG	Minimal volume time difference from conductance catheter (msec)						Minimal length difference from sonomicrometric crystals (msec)					
	RA	RV	LVa	LVfw	CRTa	CRTfw	RA	RV	LVa	LVfw	CRTa	CRTfw
1	-68	-60	-62	-40	-64	-52	42	-23	-	-95	-234	-55
2	-8	-84	-58	-52	-68	-40	151	60	-	28	-281	137
3							-12	-58	-10	24	-3	-35
4	-164	-112	-88	-26	-84	-76	-35	-191	-72	191	-210	254
5	116	-92	-47	-40	-60	-64	-30	-28	-	-27	-191	-25
6							-94	248	-67	0	-62	1
7	-20	28	-60	3	-68	12	-22	-61	-	182	-315	-159
8	-116	208	-42	-2	-68	8	13	15	-	77	-156	-59
9	-28	8	-12	-2	-20	12	-57	199	-	-21	153	-65
10	-40	36	-22	3	-20	0	-109	188	-	59	-185	42