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Physiological Relevance of Quantifying Segmental Contraction Synchrony

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Abstract

Background—Most current indices of synchrony quantify left ventricular (LV) contraction pattern in terms of a single, global (integrated) measure. We report the development and physiological relevance of a novel method to quantify LV segmental contraction synchrony.

Methods—LV pressure-volume and echocardiographic data were collected in seven anesthetized, opened-chest dogs under several pacing modes: right atrial (RA) (control), right ventricular (RV) (dyssynchrony), and additional LV pacing at either apex (CRTa) or free wall (CRTf). Cross-correlation-based integrated (CCSI_{int}) and segmental (CCSI_{seg}) measures of synchrony were calculated from speckle-tracking derived radial strain, along with a commonly used index (maximum time delay). LV contractility was quantified using either E_{es} (ESPVR slope) or ESPVR_{area} (defined in the manuscript).

Results—RV pacing decreased CCSI_{int} at LV base (0.95 ± 0.02 [RA] vs 0.64 ± 0.14 [RV]; $P < 0.05$) and only CRTa improved it (0.93 ± 0.03 ; $P < 0.05$ vs RV). The CCSI_{seg} analysis identified anteroapical and septal segments as being responsible for the low CCSI_{int} during RV pacing and inferior segment for poor resynchronization with CRTf. Changes in ESPVR_{area}, and not in E_{es}, indicated depressed LV contractility with RV pacing, an observation consistent with significantly decreased global LV performance (stroke work [SW]: 252 ± 23 [RA] vs 151 ± 24 [RV] mJ; $P < 0.05$). Only CRTa improved SW and contractility (SW: 240 ± 19 mJ; ESPVR_{area}: 545 ± 175 mmHg•mL; both $P < 0.01$ vs RV). Only changes in CCSI_{seg} and global LV contractility were strongly correlated ($R^2 = 0.698$, $P = 0.005$).

Conclusion—CCSI_{seg} provided insights into the changes in LV integrated contraction pattern and a better link to global LV contractility changes.

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Keywords

canine dyssynchrony model; cardiac resynchronization; echocardiography; segmental contraction; global contractility

Introduction

The COMPANION and CARE-HF trials established the therapeutic benefit of cardiac resynchronization therapy (CRT) in patients with refractory heart failure^{1,2}; however, about 30% of patients still do not respond.^{3,4} These disappointing results have prompted investigators to develop better criteria that identify CRT responders before pacemaker implantation. Despite its use as an indicator for CRT,⁵ QRS duration poorly predicts response to CRT.^{6,7} With this knowledge, emphasis has shifted toward refining dyssynchrony criteria for CRT by using mechanical indices of dyssynchrony.

Several small single-center studies have shown that echocardiography-derived mechanical markers of dyssynchrony, such as standard deviation of time to peak regional strain assessed among myocardial segments in the longitudinal or mid-axis cross-sectional view, predict both short-⁶ and long-term^{4,8–10} response to CRT. However, despite these promising results, when 12 different echocardiographic parameters were used to quantify ventricular dyssynchrony in a prospective, multicenter, nonrandomized clinical trial (PROSPECT), none of these measures were able to significantly distinguish CRT responders from nonresponders.¹¹ The discrepancy between the PROSPECT trial and other small, single-center studies may be a result of several factors: (1) technological issues surrounding tissue Doppler imaging (TDI) methods leading to significant interobserver variability, (2) high variability with measures derived from longitudinal imaging,¹² and/or (3) variable definitions for study end points that identified responders (e.g., clinical status parameter or an echocardiographic variable, such as a reduction in end-systolic volume [ESV], which was presumed to reflect reverse remodeling). It is also possible that indices of contraction dyssynchrony used in these studies may not have been adequate, thus contributing to the observed discrepancy. For example, most current mechanical indices use an integrated measure to quantify dyssynchrony, but information may be lost in using these “global” approaches, masking the mechanisms underlying changes in contraction patterns with CRT. The present study was focused on addressing the potential limitation of the global approach by developing a novel method to quantify segmental dyssynchrony and identifying the physiological relevance of segmental quantification.

In a previous study, we proposed a cross-correlation-based analysis to quantify integrated synchrony utilizing the entire systolic period of left ventricular (LV) myocardial time-strain curves, as opposed to focusing on a single point during the cardiac cycle.¹³ These time-strain data were collected using short-axis, echocardiographic tissue Doppler images obtained at the mid-LV level. A disconnect was observed between the changes in integrated dyssynchrony index and global LV contractile behavior during RV pacing-induced dyssynchrony and subsequent CRT using simultaneous pacing at two LV sites.¹³ We had speculated that the potential reasons underlying this disconnect were (1) inadequate characterization of LV contraction afforded by tissue Doppler-derived strain at the mid-LV axis,¹³ (2) inadequate characterization of synchrony based on the integrated measure and data obtained in a single cross-sectional plane, and (3) incorrect assumptions about how to assess global LV contractility in the setting of dyssynchronous contraction. Accordingly, in the present study, LV contraction pattern was measured using speckle tracking, instead of TDI, and data were acquired at two cross-sectional planes. We extend our previously validated cross-correlation-based analysis to quantify segmental contraction synchrony

within each cross-sectional plane. We tested the hypothesis that the analysis of segmental synchrony at multiple cross-sectional planes will provide (1) insights into the changes in the integrated measure of synchrony and (2) a better link to the changes in global LV contractile performance under a variety of experimental conditions (i.e., induction of dyssynchrony and subsequent CRT).

Materials and Methods

Surgical 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. Seven mongrel dogs, weighing 20.6 ± 1.5 kg, were studied after an overnight fast. All dogs were anesthetized with sodium pentobarbital (30 mg/kg induction; 1.0 mg/kg/h with intermittent boluses, as needed), their tracheas intubated (8-Fr Portex endotracheal tube) and mechanically ventilated (Harvard dual-phase animal ventilator) with a 10-mL/kg tidal volume. Frequency was adjusted to maintain an arterial $p\text{CO}_2$ between 35 and 40 mmHg. A 6-Fr 11-pole multielectrode conductance catheter (Webster Laboratories, Irvine, CA, USA) and an LV micromanometer catheter (MPC-500, Millar, Houston, TX, USA) were placed for LV pressure-volume analysis via the right internal carotid artery and the left common carotid artery, respectively, as previously described.¹⁴ After a median sternotomy, a snare occluder was placed around the inferior vena cava (IVC) to transiently alter preload. The pericardium was opened and epicardial pacemaker leads were placed on the right atrium, right ventricular (RV) free wall near the anterior infundibulum, LV mid-free wall near the mid-posterior-lateral wall, and LV apex. The placement of ventricular pacing leads is shown in the schematic in Figures 1A and B (star symbols). The pericardium was reopposed with multiple interrupted sutures and positive end-expiratory pressure (PEEP) applied to reexpand the lungs. Thereafter, 5-cm H_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 values similar to where they were prior to sternotomy.

Experimental Protocol

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, right atrial (RA) pacing was performed at frequencies 5–10 beats/min above the intrinsic rhythm. RA pacing is defined as normal ventricular contraction for subsequent comparisons. All succeeding ventricular pacing studies were done with sequential pacing at an atrioventricular (AV) delay of 20 ms. This pacing delay prevented ventricular fusion beats from contaminating the effects of ventricular pacing. Contraction dyssynchrony was created by simultaneous RA and high RV free wall (i.e., RV outflow tract) pacing, which induced a left bundle branch block-like contraction pattern. We then compared the impact of counter pacing at two different LV sites on the RV pacing-induced dyssynchronous contraction pattern. CRT was attempted by adding simultaneous pacing to the RV pacing mode at either the LV apex (CRTa) or posterior-lateral LV free wall at the mid-ventricular level below the left circumflex artery (CRTf). The order of CRTa and CRTf pacing was alternated in consecutive experiments to eliminate any sequencing effects.

Echocardiographic Imaging and Speckle-Tracking Algorithm

An echocardiographic system (Aplio 80, Toshiba Medical Systems Corp., Tokyo, Japan) was used to obtain images with a 3.0-MHz transducer directly applied to the heart. Digital routine gray-scale two-dimensional images from three consecutive beats were obtained at end-expiratory apnea from the LV basal and mid-LV short-axis views at depths of 8 cm

using a fixed transducer position. The two short-axis views were identified using the following anatomical landmarks: mitral valve plane for LV base and top of the papillary muscle for mid-LV. Great care was taken to orient the images to the most circular geometry possible. Gray-scale images were collected at frame rates of 49 Hz and gain settings were adjusted to optimize endocardial definition. Importantly, images were collected without LV conductance or pressure catheters to eliminate the shadowing effects associated with these instruments.

Speckle-tracking analysis¹⁵ was used to generate regional LV strain-time waveforms¹⁶ from routine B-mode gray-scale echocardiographic images at each of the two LV short-axis levels. Strain-time waveforms were generated using novel software (Toshiba Medical Systems Corp.) for frame-by-frame movement of stable patterns of natural acoustic markers present in ultrasound tissue images over the cardiac cycle as previously described.¹⁶ Briefly, a circular region of interest was traced on the endocardial and epicardial border of each LV short-axis image, using a point-and-click approach. The software automatically divided the region of interest into six equal radial segments: inferior (I), posterior (P), lateral (L), anterior (A), antero-septal (AS), and septal (S) (Fig. 1C). The segments automatically created by the software were adjusted as needed, and speckles within each segment were tracked in subsequent frames by the imaging software. The location shift of these speckles from frame to frame represented tissue movement and provided the spatial and temporal data. Radial strain was calculated as change in length/initial length between speckles as L/L_0 . Myocardial thickening was represented as positive strain and thinning as negative strain. Radial strain values from multiple circumferential points within each segment were calculated and averaged into segmental strain-time curves, as previously validated in humans.¹⁶ Quantification of radial synchrony was then performed offline.

Integrated Measure of Synchrony

Radial synchrony was quantified by analyzing the speckle-derived strain waveforms with our proprietary algorithm “Cross-Correlation Analysis: A Novel Bedside Tool to Quantify LV Contraction Dyssynchrony” (©2008 University of Pittsburgh). This algorithm has been described in detail elsewhere.¹³ Briefly, pairwise cross-correlation analysis of regional strain waveforms was used to develop an integrated cross-correlation synchrony index (CCSI_{int}) for each of the two cross-sectional levels (i.e., LV base and mid-LV). Given that strain data were acquired for six segments at the LV base and mid-LV, there are 15 segment pairs for each of those levels. Within each level, cross-correlation coefficients were obtained for each of the 15 pairwise correlations, summed, and normalized to the number of correlations (i.e., 15 for the base and mid-LV). A value of 1.0 for CCSI_{int} would imply perfect synchrony and lower values would correspond to progressively greater dyssynchrony. We also calculated a commonly used index of contraction dyssynchrony—maximum time delay. Specifically, the time delay between QRS and time of maximal strain (shortening) for each of the six segments was measured. Maximum time delay was the difference between the largest (latest contracting segment) and smallest (earliest contracting segment) time delay—a higher value of maximum time delay would imply greater dyssynchrony.

Segmental Measure of Synchrony

For the segmental analysis, a CCSI was calculated for each segment (CCSI_{seg}) from pairwise correlations of that segment with all other segments within the same cross-sectional level. For example, CCSI_{seg} for segment I at the mid-LV level contained the following pairwise correlations: (1) I versus P, (2) I versus L, (3) I versus A, (4) I versus AS, and (5) I versus S. Cross-correlation coefficients derived for each of these pairs were then summed and normalized by the total number of correlations (i.e., five). A value of 1.0 for CCSI_{seg} would imply perfect synchrony for a given segment with respect to all other segments within

the same cross-sectional level, and lower values would correspond to progressively greater segmental dyssynchrony. This was repeated for the other five segments within its respective level to obtain six $CCSI_{seg}$ values for each of the two cross-sectional levels. Given that $CCSI_{int}$ and $CCSI_{seg}$ are based on the same pairwise cross-correlation analyses, these indices are related. It can be shown mathematically that $CCSI_{int}$ is equal to the average of the six $CCSI_{seg}$ values.

Global LV Performance

LV pressure-volume data were collected at 250 Hz and stored for off-line analysis. 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.¹⁴

Global LV Contractility

Transient pressure-volume data obtained during IVC occlusion were used to quantify LV intrinsic mechanical properties. Specifically, LV contractility was quantified in terms of end-systolic pressure (ESP)-end-systolic volume (ESV) relationship, ESPVR ($ESP = E_{es}[ESV - V_d]$, where E_{es} and V_d are parameters). The slope of ESPVR, or end-systolic elastance (E_{es}), is commonly used as an index of contractility.¹⁷

Several investigators have documented that ESPVR is shifted to the right and may have an increased E_{es} with dyssynchronous contractions. Such dilation connotes failure whereas increased E_{es} connotes improved contractility. Therefore, we propose a new index that simultaneously considers both slope (E_{es}) and intercept (V_d) values for proper evaluation of contractile state. LV contractility was quantified by the area enclosed by ESPVR and the pressure axis (Y-axis) over the ESP range of 60–120 mmHg ($ESPVR_{area}$). This range was chosen based upon the working ESP range identified throughout the entire study. A larger $ESPVR_{area}$ (e.g., rightward shift of ESPVR) would correspond to lower contractility and vice versa (Fig. 2, shaded areas).

Statistical Analysis

Data are expressed as mean $\pm$ standard error of mean (SEM). One-way analysis of variance (ANOVA) with repeated measures was used to evaluate the effects of different pacing modalities on regional LV synchrony and indices of global LV performance. Tukey-Kramer test was employed for *post hoc* pairwise comparisons following each ANOVA. Significance was determined as $P < 0.05$. Linear regression analysis was used to examine the relationship between changes in synchrony indices (integrated or segmental) and global LV contractility.

Results

Integrated Synchrony

Using the integrated approach, a synchronous contraction pattern was observed with RA pacing as indicated by a $CCSI_{int}$ near 1.0 at the LV base (Fig. 3A). Synchrony was adversely affected with RV pacing reflected by a significant decrease in basal $CCSI_{int}$ compared to RA pacing (0.95 ± 0.02 to 0.64 ± 0.14 ; $P < 0.05$ RA to RV pacing). Interestingly, counter pacing to cause resynchronization was only successful with CRTa as shown by an increase in $CCSI_{int}$ at the LV base (0.93 ± 0.03 ; $P < 0.05$ vs RV pacing). Although CRTf tended to improve synchrony compared to RV pacing, the increase in basal $CCSI_{int}$ did not reach statistical significance. Similar changes in $CCSI_{int}$ were observed at the mid-LV level (Fig. 3B); however, the magnitudes of these changes tended to be less pronounced as compared to those at the LV base (Figs. 3A vs B).

Similar observations were made on the basis of maximum time delay as the measure of contraction synchrony (Figs. 3C and D), with one exception: improvement in contraction synchrony with CRTf with respect to RV pacing did reach statistical significance.

Segmental Synchrony

The synchronous contraction pattern observed with RA pacing can be better appreciated from the data presented in Figure 4A (left panel), where all $CCSI_{seg}$ values are similar and close to 1.0. To better illustrate this pattern, mean $CCSI_{seg}$ values were color-coded and displayed in a Bull's Eye representation shown in Figure 4A (right panel), with basal and mid-LV segments circling the outer ring and inner rings, respectively. A relatively homogeneous yellow Bull's Eye plot was observed for RA pacing, indicating almost complete synchrony across all segments at each of the two cross-sectional levels (Figure 4A, right panel).

$CCSI_{seg}$ values were significantly less with RV pacing, with a greater variation among various segments (Fig. 4B). The anteroseptal (AS) and septal (S) segments at the LV base appeared to be more dyssynchronous; however, this difference did not reach statistical significance.

CRTa improved $CCSI_{seg}$ for all segments at both the basal and mid-LV short-axis levels (Fig. 4C). In contrast, a heterogeneous pattern was observed with CRTf, such that $CCSI_{seg}$ for the inferior (I) segment was significantly less than that for all other segments (Fig. 4D).

Global LV Performance

Because we used a short AV delay in our AV paced beats (RV, CRTa, and CRTf), these conditions had reduced diastolic filling compared to the RA-paced baseline. Therefore, pairwise statistical comparisons for performance indices did not include intrinsic RA pacing. We compared RA and RV pacing only to document pacing-induced dysfunction, with awareness that some systolic depression may be due to short AV delay-induced lower end-diastolic volumes. RV pacing significantly impaired global LV performance as indicated by marked decreases in cardiac output (CO: 2.9 ± 0.3 to 2.3 ± 0.2 L/min; $P < 0.05$) and stroke work (SW: 252 ± 23 to 151 ± 24 mJ; $P < 0.05$) as well as other global LV performance indices (Table I).

Similar to the patterns observed with changes in synchrony indices, global LV performance was improved with CRTa but not CRTf (Table I). Compared to RV pacing, ESV was significantly improved with CRTa that led to a marked increase in CO (3.2 ± 0.2 L/min; $P < 0.05$ vs RV pacing) and SW (240 ± 19 ; $P < 0.05$ vs RV pacing). However, following CRTf, the only global LV performance index that showed improvement compared to RV pacing was dP/dt_{min} (Table I).

Global LV Contractility

Compared to RA pacing, E_{es} increased with RV pacing (2.7 ± 0.5 to 5.1 ± 0.7 mmHg/mL; $P < 0.05$; Fig. 5A), a pattern inconsistent with our expectation and changes in global LV performance. In contrast, the volume-axis intercept of ESPVR, V_d , was significantly shifted to the right with RV pacing (-26 ± 5 to -2 ± 5 mL, RA to RV pacing; $P < 0.05$; Fig. 5B), thus making it difficult to quantify global LV contractility using E_{es} alone. In association with the rightward shift of V_d , the $ESPVR_{area}$ increased with RV pacing (697 ± 153 to $1,019 \pm 202$ mmHg•mL, RA to RV pacing; $P < 0.05$; Fig. 5C), consistent with depressed global LV contractility.

The effect of resynchronization on global LV mechanics was also not clear when comparing either E_{es} or V_d alone (Figs. 5A and B). Compared to RV pacing, CRTa decreased both E_{es} and V_d , once again indicating opposite effects on global LV contractility. In contrast, $ESPVR_{area}$ was significantly less with CRTa than that with RV pacing (Fig. 5C), indicating improved LV contractility with CRTa. Finally, CRTf was not associated with improved contractility relative to RV pacing, in that neither E_{es} and V_d , nor the $ESPVR_{area}$, were different (Figs. 5A–C).

It is well known that dP/dt_{max} is a strong function of LV end-diastolic volume.¹⁸ However, LV end-diastolic volume was not different among RV pacing, CRTa, and CRTf groups (Table I) and therefore, one can use dP/dt_{max} as an alternative index with which to assess LV contractility changes among these three groups. The conclusion based on dP/dt_{max} data (Table I) is the same as that based on the $ESPVR_{area}$ data: CRTa, but not CRTf, increased LV contractility with respect to RV pacing.

Correlation of Synchrony Indices and Global LV Function

The segmental cross-correlation analysis ($CCSI_{seg}$) identified specific segments that were responsible for the failure of CRTf to resynchronize LV ejection. We first investigated whether this analysis provided a link between changes in global LV function (i.e., SW) and segmental contraction synchrony. Specifically, the change in $CCSI_{seg}$ during CRT relative to RV pacing was calculated for the most dyssynchronous segment, and this was compared to the change in SW. Univariate linear regression analysis revealed that neither LV base nor mid-LV $CCSI_{seg}$ changes significantly correlated with changes in SW (LV base: $R^2 = 0.029$, $P = 0.594$; mid-LV: $R^2 = 0.001$, $P = 0.908$) and multiple linear regression analysis using LV base and mid-LV as independent variables did not make any difference ($R^2 = 0.111$, $P = 0.588$; Fig. 6A). Similar observations were made when maximum time delay was used as the measure of contraction synchrony (Fig. 6C).

Correlation of Synchrony Indices and Global LV Contractility

Univariate linear regression analysis revealed that although both LV base and mid-LV $CCSI_{seg}$ changes correlated with changes in $ESPVR_{area}$, the degree of correlation with LV base $CCSI_{seg}$ changes was greater (LV base: $R^2 = 0.683$, $P = 0.001$; mid-LV: $R^2 = 0.339$, $P = 0.047$). Multiple linear regression analysis using LV base and mid-LV $CCSI_{seg}$ as independent variables did not significantly improve the univariate correlation (R^2 increased from 0.683 to 0.698; Fig. 6B). When maximum time delay was used as the index of contraction synchrony, we observed no significant correlations between changes in maximum time delay and $ESPVR_{area}$, both by univariate (LV base: $R^2 = 0.150$, $P = 0.213$; mid-LV: $R^2 = 0.142$, $P = 0.227$) and multiple ($R^2 = 0.207$, $P = 0.352$; Fig. 6D) regression analyses.

Discussion

There are two primary findings of the current study: (1) the segmental synchrony analysis ($CCSI_{seg}$) provides insights into the changes in integrated LV contraction pattern and a link to the changes in global LV contractility. (2) $ESPVR_{area}$ is a better index of global LV contractility than E_{es} in the setting of pacing-induced contraction dyssynchrony. Secondarily, we found that combining data from LV base and mid-LV cross-sectional levels does not provide any additional information. We will first compare the current observations with those from our previous study with the same experimental design, followed by a discussion of the primary findings.

TDI versus Speckle Tracking: Comparison with Previous Study

In our previous study,¹³ CRTf improved mid-LV $CCSI_{int}$ without improving SW, which is not consistent with the present observations. We hypothesized that this inconsistency was due to the technical limitation of TDI in the previous study relative to speckle tracking used in the present study. TDI-derived strain analysis cannot be performed for segmental movement obtuse to the echo beam; thus, no contraction information can be obtained from anterior and inferior segments. This limitation does not exist for the speckle-tracking-based strain data.¹⁹ To further investigate this hypothesis, we derived $CCSI_{seg}$ for TDI-derived strain waveforms from the previous study. Due to the above-mentioned technical limitation of TDI, the segment definitions were slightly different in the previous study (see Fig. 1 in Ref. 13). Consistent with the current study, TDI-based $CCSI_{seg}$ data revealed that RA pacing was associated with synchronous contraction across all segments and RV pacing induced significant dyssynchrony at the mid-septal (MS) and anteroseptal (AS) segments (Figs. 7A and B). However, resynchronization appeared to be successful with both CRTa and CRTf as indicated by the near normalization and homogeneous distribution of $CCSI_{seg}$ values (Figs. 7C and D). Therefore, unlike the current study, dyssynchronous contractions at inferior and anterior regions with CRTf could not be identified on the basis of TDI-derived strain. We conclude that speckle-tracking derived strain more comprehensively quantifies contraction patterns than TDI-derived strain.

Quantification of Synchrony: Integrated versus Segmental Approach

Most echocardiography-based measures use an integrated approach to quantify dyssynchrony. For example, dyssynchrony metrics have been derived from time to peak systolic velocity using TDI from apical or short-axis views and expressed principally as either the standard deviation of times to peak velocity of all myocardial segments in the acquired image or the time difference between times to peak velocity of earliest and latest contracting segments.^{20–23} Our $CCSI_{int}$ also falls in the category of integrated synchrony measures. It is not possible to determine the roles of individual segments in the overall contraction based on these integrated measures of synchrony. To address this issue, we developed a cross-correlation based index to quantify segmental contributions to the integrated measure of contraction synchrony, $CCSI_{seg}$. Importantly, $CCSI_{seg}$ characterizes the synchrony of a particular segment with respect to all other segments within the same cross-sectional level, providing insight into the mechanism behind overall contraction patterns. For example, we determined that the basal anteroseptal and septal segments were primarily responsible for the overall decrease in synchrony with RV pacing. Furthermore, resynchronization failure with CRTf was due to contraction disparities at the basal and mid-LV inferior segments. The color-coded, Bull's Eye plot of $CCSI_{seg}$ (Fig. 4) enables one to readily identify segments responsible for overall dyssynchrony and this presentation may have potential clinical applications because of the ease of interpretation. In the future, this method may be utilized to guide placement of LV leads in the setting of CRT device implantation. For example, if it is known that a particular region of the LV is more dyssynchronous than the others, placement of the LV lead near that particular site may yield an optimal response to CRT. Although future studies will need to address this hypothesis, segmental synchrony analysis has been shown to be a useful tool in identifying the most dyssynchronous segments in the current study. We acknowledge that some of the previous studies have used dyssynchrony measures that can be classified as segmental indices (e.g., time delay of maximal contraction (tissue velocity or strain) with respect to the peak of electrocardiogram QRS for each segment or time delays computed using contraction data of opposing wall segments).^{24,25} However, unlike $CCSI_{seg}$, which utilizes data from the entire systolic period, these indices focus on a single time point during systole (e.g., time for maximum tissue velocity or maximum strain). As discussed below (see section “Does the

cross-correlation-based synchrony index provide advantage over the conventional indices?”), this focus on a single time point may be problematic.

Although many studies have focused on developing echocardiography-derived measures to quantify dyssynchrony and identify patients for CRT,^{4,10,16,20,26} due to conflicting results, a standard approach to quantifying dyssynchrony has yet to be established. It is therefore not surprising that utilization of an echocardiography-derived dyssynchrony parameter is presently not recommended to identify patients for CRT.²⁷ Given the sole focus on integrated synchrony metrics in these studies, it is likely that segmental disparities were diluted when all pieces were incorporated into a single index, resulting in the lack of correlation between changes in integrated dyssynchrony measures and response to CRT. Our data support this conjecture. Changes in the most dyssynchronous segment as determined by $CCSI_{seg}$ predicted changes in global LV contractility.

Although the patterns of changes in $CCSI_{int}$ and $CCSI_{seg}$ were similar between the two cross-sectional levels (LV base and mid-LV), the magnitudes of changes at LV base tended to be greater (Figs. 3 and 4). In addition, changes in $CCSI_{seg}$, and not $CCSI_{int}$, correlated with changes in global LV contractility. Surprisingly, combining information from the two cross-sectional planes did not improve the link between changes in synchrony (integrated and/or segmental) and global LV contractility. Perhaps our focus on radial contraction synchrony is the reason for this negative outcome; it may be necessary to include measures of longitudinal synchrony.

Quantification of Global LV Contractility: E_{es} versus $ESPVR_{area}$

E_{es} , the ESPVR slope, is commonly used as an index of global LV contractility. However, this may only be accurate if all regions of the myocardium are contracting synchronously. In the current study, E_{es} -based inferences regarding LV contractility were problematic. There were several instances where both E_{es} and V_d increased (Fig. 2, dashed ESPVR). Based on E_{es} alone, this would imply increased contractility. But the rightward shift of ESPVR (i.e., increased V_d) indicates depressed contractility requiring a greater volume to produce the same pressure. Recently, Burkhoff et al.²⁸ have discussed the problems associated with using E_{es} alone as the index of LV contractility, particularly for *in vivo* data obtained over a limited range of loading conditions. Although they recommended the use of analysis of covariance for simultaneous assessment of changes in E_{es} and/or V_d , this analysis does not rank order the contractile states of the various conditions being analyzed. The $ESPVR_{area}$ metric yielded a physiologically consistent pattern of changes in LV contractility under various pacing modes in our study, including a clear and consistent depression of LV contractility (i.e., larger $ESPVR_{area}$) with RV pacing. Others have also reported a decrement in LV contractility following RV pacing in canines.^{29,30} However, one study observed a decrease in E_{es} with little change in V_d ²⁹ and the other study noted a rightward shift of ESPVR (i.e., increased V_d) without a change in E_{es} .³⁰ Thus, using $ESPVR_{area}$ might reduce these inconsistencies in assessing changes in global contractile function.

Does the Cross-Correlation-Based Synchrony Index Provide Advantage over the Conventional Indices?

In terms of quantifying the overall (integrated) contraction synchrony under various pacing modalities, both the cross-correlation-based index ($CCSI_{int}$) and the conventional index (maximum time delay) yielded essentially the same observations (Fig. 3). In addition, both approaches indicated that there was low correlation between the changes in LV function (i.e., SW) and the changes in contraction synchrony (i.e., changes in $CCSI_{seg}$ or in maximum time delay; Figs. 6A and C). However, the changes in $CCSI_{seg}$ seem to be predictive of the changes in LV contractility (Fig. 6B), while similar link was not seen with

the changes in maximum time delay (Fig. 6D). Both approaches represent an attempt to quantify the relative temporal patterns of two or more waveforms. The cross-correlation approach uses the entire systolic strain waveform to calculate $CCSI_{int}$ and $CCSI_{seg}$. In contrast, the maximum time delay index (or any other current index that uses time delay in its calculation) utilizes information from a single time point during systole (i.e., the time of maximum strain or shortening), making it more susceptible to noise in the strain waveform. This noise susceptibility may have contributed to some of the variability in the maximum time delay data, although this issue warrants further investigation. Lamia et al.³¹ found that the changes in area under the average strain curve explained most of the RV pacing-induced loss of global LV function, which supports the notion that utilizing contraction (strain) data from the entire systolic period may be better than focusing on a single time point during systole.

CRTa versus CRTf

Our data showing superiority of LV apical pacing (CRTa) to LV free wall pacing (CRTf) are in agreement with some studies¹² and at odds with others²² with respect to the optimal pacing site to achieve maximal LV contraction improvement. However, we believe this finding is probably due more to our model of pacing-induced dyssynchrony than to defining a universal optimal pacing site. We support the view of Bleeker et al.³² that the optimal site for resynchronization will be primarily defined by the ability of the resynchronization therapy to achieve resynchronization and this optimal site can vary significantly among patients, depending on a number of factors, such as the nature of the baseline dyssynchrony (regional differences in contraction), intrinsic heart failure, or fibrosis. Thus, it is better to interpret our data as demonstrating that the cross-correlation-based analysis allows for the accurate assessment of resynchronization such that global LV function is better when the cross-correlation-based index is increased.

Methodological Limitations

We used a short AV delay during all ventricular pacing modes, which restricts diastolic LV filling. Therefore, a direct functional comparison of intrinsic activation (i.e., RA pacing) and ventricular pacing (i.e., RV, CRTa, and CRTf) could not be performed. However, LV EDV was not different among the three ventricular pacing groups (Table I) and therefore, comparisons of LV functional indices of CRTa and CRTf groups with the RV group are valid. Second, the study consisted of healthy hearts with normal ejection fractions and an RV pacing-induced dyssynchrony model. These results contribute knowledge in the context of patients with normal ventricular function who receive ventricular pacing. The relevance of this study, particularly the differential effects of CRTa and CRTf, to heart failure patients or those with intrinsic infra-AV nodal His-Purkinje system defects may be questioned. However, we recently reported that the robustness of $CCSI_{int}$ in a chronic pacing-induced heart failure model.³³ Specifically, we demonstrated that RV pacing-induced dyssynchrony, as quantified by $CCSI_{int}$, increased over time with the development of heart failure. As the LV recovered following the cessation of tachypacing, the RV pacing-induced dyssynchrony decreased. Although the cause of dyssynchrony (intrinsic vs pacing-induced), the prevailing LV contractile state, or specific pacing mode used for resynchronization may yield different contraction patterns (magnitude and/or phase), we believe that $CCSI_{seg}$ will be equally efficacious in quantifying segmental synchrony in all cases, identifying segments responsible for overall (integrated) dyssynchrony and predicting changes in global LV contractility. Future experimental studies should focus on examining the potential confounding effects of baseline heart failure. Third, several indices can be derived from comparing two waveforms using the cross-correlation method. For each segmental pair, cross-correlation coefficients can be derived for a number of time delays. Specifically, a cross-correlation spectrum can be obtained by time shifting one segment with respect to the

other. For the current study, we used the coefficient at zero time shift, which represented the raw data (i.e., unshifted data). Other studies have used the time shift that yields maximum correlation coefficient as an index of synchrony.³⁴ A disadvantage of this method is that the maximum correlation coefficient of extremely different waveforms (e.g., a scarred segment compared to a healthy segment) will be low. In this case, the waveforms will never optimally “match” and the maximum correlation, which will be far from 1.0, may occur at a minimal time delay. As a result, the delay associated with the maximum correlation coefficient lacks information about the true temporal concordance of two waveforms. In the current study, the coefficient at zero time shift yielded the most useful information regarding regional analysis. Lastly, the pairwise cross-correlation analysis used here and by others³⁴ strictly focuses on the relative temporal patterns of two signals (i.e., phase information only); there is no contribution of the amplitudes of these two signals. In other words, the cross-correlation coefficient will be unchanged if only the amplitudes of segmental contractions were changed (up or down), without any changes in the relative temporal patterns of contraction. Thus, there can be dissociation between changes in cross-correlation-based indices and changes in global function when only contraction amplitudes are altered—for example, reductions in segmental strain amplitudes only (associated with global depression in contractility) will cause a reduction in global LV function without any changes in $CCSI_{int}$ or $CCSI_{seg}$ values. Future efforts will focus on combining the phase- and amplitude-related information for a more comprehensive characterization of segmental contractions.

Overall Summary and Conclusions

The present study introduced a cross-correlation-based measure of segmental contraction synchrony ($CCSI_{seg}$) and demonstrated its physiological relevance in the context of a canine model of pacing-induced dyssynchrony and subsequent resynchronization therapies. Segmental-based analysis provided insights into the changes in integrated LV contraction pattern, both during induction of dyssynchrony and resynchronization. In addition, the change in $CCSI_{seg}$ was predictive of the change in global LV contractility.

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Figure 1.

Schematic of pacing sites and short-axis echocardiographic imaging levels. Ventricular pacing leads were placed at the RV outflow tract, LV free wall, and LV apex (stars), shown for LV (A) short-axis and (B) long-axis views. (C) Echocardiographic short-axis images at the LV base and mid-LV showing radial segmentation. LV = left ventricular; RV = right ventricular; LVa = LV apex; LVf = LV free wall; I = inferior; P = posterior; L = lateral; A = anterior; AS = antero-septal; S = septal.

Figure 2.

Example of calculation of $ESPVR_{area}$. Compared to RA pacing (solid line), $ESPVR$ for RV pacing (dashed line) has a greater slope. However, $ESPVR$ for RV pacing is shifted to the right and pressure-volume loops are smaller, signifying a more depressed ventricle. To quantify the contractility by taking both $ESPVR$ slope and intercept into account, $ESPVR_{area}$ calculated from the RV pacing $ESPVR$ to Y-axis (gray) is larger than that for RA pacing (gray hatched). The greater $ESPVR_{area}$ indicates depressed contractility. RA = right atrial; RV = right ventricular; LV = left ventricular; $ESPVR$ = end-systolic pressure-volume relationship.

Figure 3.

Integrated measures of contraction synchrony under various pacing modes and for two short-axis views. Data for two indices are shown: CCSI_{int} (A and B) and maximum time delay (C and D). Data: mean $\pm$ SEM, n = 7, *P < 0.05 versus RA pacing, †P < 0.05 versus RV pacing. CCSI_{int} = cross-correlation-based integrated contraction synchrony index; RA = right atrial; RV = right ventricular; CRTa = resynchronization at the LV apex; CRTf = resynchronization at the LV free wall.

Figure 4.

Segmental synchrony indices ($CCSI_{seg}$) and corresponding Bull's Eye plots. $CCSI_{seg}$ at the LV base (filled circles) and mid-LV (open circles) under (A) RA pacing, (B) RV pacing, (C) CRTa, and (D) CRTf. Color-coded representations of $CCSI_{seg}$ are to the right of each plot with black corresponding to values ≤ 0.5 and yellow representing 1.0. Data: mean $\pm$ SEM, $n = 7$, * $P < 0.05$ (vs all other segments). $CCSI_{seg}$ = segmental cross-correlation synchrony index; other abbreviations same as in Figures 1 and 3.

Figure 5.

Indices of global LV contractile properties. Compared to RV pacing, E_{es} was lower with CRTa (A), indicating depressed LV contractility; however, the volume-axis intercept was lower with CRTa (B), suggesting improved contractile behavior. As a combined index of E_{es} and V_d , $ESPVR_{area}$ was significantly less with CRTa than that with RV pacing (C), indicating improved contractility, a pattern consistent with changes in regional synchrony and global LV performance. Data: mean $\pm$ SEM, $n = 6$; * $P < 0.05$ versus RA pacing, † $P < 0.05$ versus RV pacing. E_{es} = slope of the end-systolic pressure-volume relationship, ESPVR; V_d = volume intercept of the ESPVR; $ESPVR_{area}$ = area enclosed by the ESPVR and pressure axis between the end-systolic pressure values of 60 and 120 mmHg; other abbreviations same as in Figure 3.

Figure 6.

LV stroke work and global contractility versus contraction synchrony indices. (Panels A and C) Relationships between changes in LV stroke work (% Δ Stroke Work) and changes in CCSI_{seg} (% Δ CCSI_{seg}, panel A) or in the maximum time delay (% Δ Maximum Time Delay, panel C). (Panels B and D) Relationships between changes in LV global contractility (% Δ ESPVR_{area}) and % Δ CCSI_{seg} (panel B) or % Δ Maximum Time Delay (panel D). Filled and open circles represent LV base and mid-LV data, respectively. All percentage changes were calculated with respect to RV pacing. Regression statistics are shown for the multivariate analysis (i.e., using LV base and mid-LV data as two independent variables). CCSI_{seg} = cross-correlation-based segmental contraction synchrony index; ESPVR = end-systolic pressure-volume area.

Figure 7.

CCSI_{seg} for tissue Doppler imaging (TDI) derived strain. CCSI_{seg} at the mid-LV for TDI-derived strain waveforms under (A) RA pacing, (B) RV pacing, (C) CRTa, and (D) CRTf. Data: mean $\pm$ SEM, n = 7, *P < 0.05. I = inferior; P = posterior; PL = posterolateral; AL = anterolateral; MS = mid-septum; AS = antero-septal; other abbreviations same as in Figure 4.

Table I

Global LV Performance Values for Various Pacing Modes

	Dyssynchrony		Resynchronization	
	RA Pacing	RV Pacing	CRTa	CRTf
HR (beats/min)	139 ± 3	139 ± 3	139 ± 3	139 ± 3
LV ESP (mmHg)	109 ± 3	92 ± 5 *	94 ± 2	95 ± 3
LV EDP (mmHg)	12 ± 2	11 ± 2 *	9 ± 2 †	10 ± 2
MAP (mmHg)	96 ± 4	78 ± 5 *	83 ± 4	83 ± 4
EDV (mL)	40 ± 1	34 ± 2 *	34 ± 2	34 ± 2
ESV (mL)	19 ± 2	18 ± 2	11 ± 2 †	16 ± 2
SV (mL)	21 ± 2	17 ± 2 *	23 ± 1 †	18 ± 2
CO (L/min)	2.9 ± 0.3	2.3 ± 0.2 *	3.2 ± 0.2 †	2.5 ± 0.2
dP/dt _{max} (mmHg/s)	2,063 ± 172	1,603 ± 160 *	1,946 ± 244 †	1,699 ± 163
dP/dt _{min} (mmHg/s)	-2,325 ± 175	-1,684 ± 182 *	-2,061 ± 166 †	-1,973 ± 178 †
SW (mJ)	252 ± 23	151 ± 24 *	240 ± 19 †	175 ± 18

Data: mean ± SEM, n = 7;

* P < 0.05 RV versus RA pacing,

† P < 0.05 CRTa or CRTf versus RV pacing.

RA = right atrial; RV = right ventricular; CRTa = resynchronization therapy with LV apical pacing; CRTf = resynchronization therapy with LV free wall pacing; HR = heart rate; LV = left ventricular; ESP = end-systolic pressure; EDP = end-diastolic pressure; MAP = mean arterial pressure; EDV = end-diastolic volume; ESV = end-systolic volume; SV = stroke volume; CO = cardiac output; dP/dt_{max} = maximum rate of pressure rise; dP/dt_{min} = minimum rate of pressure rise; SW = stroke work.