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Variability in Tissue Doppler Echocardiographic Measures of Dyssynchrony is Reduced with Use of a Larger Region of Interest

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Abstract

Background—Doppler tissue imaging (DTI) based dyssynchrony parameters failed to predict response to cardiac resynchronization therapy (CRT) in the multicenter Predictors of Response to CRT (PROSPECT) trial. Large variability during interpretation of DTI data was one of several factors thought to contribute to this failure.

Hypothesis—We *hypothesized* that using larger regions of interest (ROIs) to generate velocity curves from Doppler tissue images would significantly reduce the variability of DTI dyssynchrony parameters.

Methods—The variability of three ROI sizes (6×6, 18×6, 30×6mm) was compared in 30 patients undergoing CRT. Variability due to manual ROI placement was determined for each ROI size by placing 3 ROIs in each myocardial segment, 6mm apart from each other. Thus, 3 velocity curves were generated for each segment and each ROI size. Four published dyssynchrony parameters were calculated from all permutations of the 3 ROI positions per segment. A mean modified coefficient of variation was calculated for each parameter and ROI size.

Results—The 6×6mm ROI had a mean coefficient of variation of 27%. The 18×6 and 30×6mm ROIs had significantly lower coefficients of variation (17% and 14%, respectively) than the 6×6mm ROI (both $p < 0.01$). The 30×6mm ROI also reduced the diagnostic inconsistency of dyssynchrony parameters by 44% ($p = 0.024$) versus the 6×6mm ROI.

Conclusion—Using a 30×6mm region of interest instead of a 6×6mm region of interest to quantify tissue Doppler dyssynchrony reduces variability by 47% and diagnostic inconsistency by 44%. We recommend using a 30×6mm region of interest in future trials to minimize variability.

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Disclosures Brandon Fornwalt, Derek Fyfe, and John Oshinski have applied for a patent on using cross-correlation methodology to quantify dyssynchrony. This is one of the 4 techniques used to quantify dyssynchrony in the manuscript.

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INTRODUCTION

Tissue Doppler echocardiographic dyssynchrony parameters failed to predict response to cardiac resynchronization therapy (CRT) in the international, multicenter Predictors of Response to CRT (PROSPECT) trial¹. The PROSPECT investigators concluded that “efforts aimed at reducing variability arising from technical and interpretative factors may improve the predictive power of these echocardiographic parameters in a broad clinical setting.” For most echocardiographic dyssynchrony parameters, velocity curves from Doppler tissue images (DTI) of two or more left ventricular (LV) myocardial regions are compared. The velocity curves are generated by manually placing regions of interest (ROIs) within the myocardium. Manually adjusting the ROI slightly within the myocardium can substantially alter the shape of the velocity curve generated from that ROI. These changes in the velocity curves can lead to large variability when calculating dyssynchrony parameters.

The ROI represents the area over which the DTI data is averaged in order to generate the velocity curve that is then used to quantify dyssynchrony. The size and shape of this ROI can be adjusted in most commercially available DTI post-processing packages. Recent guidelines released by the American Society of Echocardiography and Heart Rhythm Society suggest using a ROI size of 10×5mm to 15×7mm². However, no scientific justification is given for this range. A review of the 10 most commonly cited tissue Doppler dyssynchrony studies revealed that 8 out of the 10 studies failed to mention the size of the ROI used³⁻¹⁰, while one study documented using a 6×6mm ROI¹¹ and another used a 2×2mm ROI¹².

We *hypothesized* that using larger ROIs would significantly reduce the variability associated with operator placement of the ROIs. We tested this hypothesis by quantifying the variability due to manual placement of 3 different ROI sizes in 30 patients undergoing CRT.

METHODS

Patient population

Thirty patients were randomly selected from a database of patients who have received CRT at Emory University Crawford Long Hospital. Inclusion criteria were: 1) left ventricular ejection fraction < 35%, 2) QRS duration > 120ms, 3) New York Heart Association (NYHA) class III or IV heart failure and 4) tissue Doppler echocardiogram at baseline prior to CRT implantation. Characteristics of the 30 patients are shown in Table 1. This study was approved by the Institutional Review Board of Emory University.

Tissue Doppler data acquisition

Apical 2-, 3- and 4-chamber Doppler tissue images of the myocardium were acquired with the patient in the lateral decubitus position (Vivid 7, GE Vingmed, Horten, Norway). The myocardial walls were aligned parallel to the Doppler beam to minimize the angle of insonation, and frame rate was optimized from 100 to 140 Hertz. Pulsed Doppler images of the aortic outflow tract were acquired for definition of systole.

Tissue Doppler dyssynchrony parameters

No segments were excluded from analysis. Post-processing software (EchoPAC PC, Version 6.0.0, GE Vingmed) was used to export velocity curves from the DTI data which were used to calculate 4 published dyssynchrony parameters:

1. basal septal-to-lateral delay in time-to-peak systolic velocity (SLD)⁸
2. maximum difference in times-to-peak systolic velocity between any 2 of the basal septal, lateral, anterior and inferior LV segments (MaxDiff)¹³

3. the standard deviation of times-to-peak systolic velocity in the 12 basal and mid-wall segments of the LV (Ts-SD)¹⁴
4. cross-correlation delay (XCD)¹⁵

To quantify XCD, a normalized cross-correlation function was used to calculate the time delay between velocity curves from opposing ventricular segments. One velocity curve was shifted relative to the other curve, and the normalized cross-correlation was computed for each time shift. The median time shift of the positive correlation between the two curves was defined as the cross-correlation delay between them. XCD was defined as the maximum of the three cross-correlation temporal delays between myocardial velocity curves from opposing basal sections in apical 2-, 3- and 4-chamber views.

Effect of ROI size on the variability of dyssynchrony parameters

Variability of each dyssynchrony parameter was determined for three ROI sizes (6×6, 18×6 and 30×6mm). The 6×6mm ROI was chosen because it is the default size in the EchoPAC software. The 30×6mm ROI was chosen because it is approximately large enough to cover one myocardial segment in a typical adult heart (i.e. the 30×6mm ROI covers one-third of the length of a typical ventricle that is 90mm long). The 18×6mm ROI size was chosen because its area is halfway between that of the 6×6 and 30×6mm ROIs.

Variability for each ROI size was determined in each patient by having a single observer place 3 ROIs of the same size in each myocardial segment (Figure 1). One ROI was placed at the center of the segment, another was placed 6 mm upward along the myocardial wall from the center, and a third ROI was shifted 6mm downward. Thus, each ROI size was used to generate 3 velocity curves for each of the 12 myocardial segments.

The four dyssynchrony parameters were calculated multiple times for each patient and ROI size using all permutations of the 3 ROI positions. For example, the SLD parameter utilizes only 2 myocardial segments to quantify dyssynchrony and was therefore calculated $3^2 = 9$ different ways for each patient and ROI size (Figure 2). The Ts-SD parameter utilizes 12 myocardial segments and was therefore calculated $3^{12} = 531,441$ different ways for each patient and ROI size. The MaxDiff parameter utilizes 4 segments and was calculated $3^4 = 81$ different ways while the XCD parameter utilizes 6 segments and was calculated $3^6 = 729$ different ways for each patient and ROI size.

An average velocity curve was generated from three cardiac cycles of velocity data prior to measuring dyssynchrony parameters. This averaging was done with the cine-compound function in the EchoPAC software to improve the signal-to-noise ratio of the extracted velocity curves¹⁶. All velocity data was exported using stationary ROIs. Pulsed Doppler of the aortic outflow tract was used to define systole for identification of the peak systolic velocity.

Effect of ROI size on the diagnosis of dyssynchrony

Threshold values to diagnose dyssynchrony have been published for all of the dyssynchrony parameters quantified in this study: SLD = 60ms⁸, MaxDiff = 65ms⁶, Ts-SD = 34.4ms¹¹ and XCD = 31ms¹⁵. Manual adjustments in the ROI location can cause the measured level of dyssynchrony to cross these thresholds, which leads to inconsistency in the diagnosis of dyssynchrony over a small region in the myocardium (Figure 3). The effect of ROI size on the *diagnostic inconsistency* according to each parameter was investigated.

Statistics

A mean modified coefficient of variation (CoV) was calculated to determine variability for each ROI size and dyssynchrony parameter using the following equations:

$$SD_{\text{parameter},ROI,\text{patient}} = \sqrt{\frac{1}{N_{\text{parameter}}} \sum_{\text{permutation}=1}^{N_{\text{parameter}}} \left(x_{\text{permutation},\text{parameter},ROI,\text{patient}} - \bar{x}_{\text{parameter},ROI,\text{patient}} \right)^2} \quad (1)$$

where $N_{\text{parameter}} = 3^2, 3^4, 3^{12}$ and 3^6 for SLD, MaxDiff, Ts-SD and XCD, respectively, and $x_{\text{permutation},\text{parameter},ROI,\text{patient}}$ represents the value of a dyssynchrony parameter for a given ROI size, patient and permutation of ROI locations.

$$\bar{x}_{\text{parameter},ROI,\text{patient}} = \sqrt{\frac{1}{N_{\text{parameter}}} \sum_{\text{permutation}=1}^{N_{\text{parameter}}} x_{\text{permutation},\text{parameter},ROI,\text{patient}}} \quad (2)$$

$$CoV_{\text{parameter},ROI} = \frac{\frac{1}{30} \sum_{\text{patient}=1}^{30} SD_{\text{parameter},ROI,\text{patient}}}{\frac{1}{30} \sum_{\text{patient}=1}^{30} \bar{x}_{\text{parameter},ROI,\text{patient}}} \quad (3)$$

Coefficients of variation and diagnostic inconsistency values for each ROI size were compared using a repeated measures ANOVA with a Huynh-Feldt correction followed by a Bonferroni multiple comparison post-hoc test. A value of $p < 0.05$ was defined as statistically significant.

RESULTS

Effect of ROI size on the variability of dyssynchrony parameters

The 30×6mm region of interest had the lowest CoV for 3 of the 4 dyssynchrony parameters (Table 2). The 18×6mm ROI reduced the mean CoV by 38% compared to the 6×6mm ROI (Bonferroni corrected $p < 0.01$, Figure 4). The 30×6mm ROI reduced the mean CoV by 47% relative to the 6×6mm ROI (Bonferroni corrected $p < 0.01$, Figure 4). However, there was no significant difference in CoV between the 18×6mm and 30×6mm ROI sizes ($p = 1.00$). Ts-SD had significantly lower variability compared to SLD and MaxDiff for the 6×6mm ROI (Table 2). There was no significant difference in variability between the parameters for the 30×6mm ROI (Table 2). Figure 3 shows Doppler velocity curves from a patient where a large change in the SLD parameter occurred due to a small shift in the 6×6mm ROI.

Effect of ROI size on the diagnosis of dyssynchrony

The 30×6mm region of interest had the lowest diagnostic inconsistency for 3 of the 4 dyssynchrony parameters (Table 3). The 30×6mm ROI reduced the mean diagnostic inconsistency by 44% relative to the 6×6mm ROI ($p = 0.024$, Figure 5). There was no significant difference in the diagnostic inconsistency between the 6×6mm ROI and the 18×6mm ROI ($p = 0.054$). In addition, there was no significant difference in the diagnostic inconsistency between any of the four parameters (Table 3). Figure 3 shows an example of a small shift in the 6×6mm ROI causing a change in the diagnosis of dyssynchrony according to the SLD parameter.

DISCUSSION

Echocardiographic assessment of left ventricular dyssynchrony using Doppler tissue imaging (DTI) has shown promise in predicting response to cardiac resynchronization therapy (CRT) in multiple single-center studies¹⁷. However, the predictors of response to CRT (PROSPECT) trial showed that only one out of seven DTI-based methods demonstrated “modest, statistically significant value” in predicting clinical response to CRT¹. This failure was thought to be due *in part* to the large variability in the analysis of the dyssynchrony parameters, and it was concluded that methods aimed at reducing this variability may improve the predictive power of echocardiographic dyssynchrony parameters in a broad clinical setting.

We have shown that using a 30×6mm region of interest (ROI) instead of a 6×6mm ROI to quantify dyssynchrony from DTI reduces the variability in the magnitude of dyssynchrony by 47%. In addition, we showed that the 30×6mm ROI reduced the diagnostic inconsistency by 44% compared to the 6×6mm ROI. Utilizing a 30×6mm ROI instead of a 6×6mm ROI can be done easily with current, commercially available DTI post-processing packages.

Explanation for using larger ROIs

Regions of interest (ROIs) are placed on Doppler tissue images (DTI) to generate velocity curves that can be analyzed to quantify dyssynchrony. These ROIs represent the area over which the DTI data is averaged to generate a velocity curve from the raw data, i.e. every pixel that falls inside of this ROI is averaged to produce a single velocity value at each time point. Our results suggest that an ROI size of 30×6mm minimizes the variability in the measured level of dyssynchrony and also reduces the diagnostic inconsistency. This is not surprising as the 30×6mm ROI averages 5 times more data than the 6×6mm ROI. Thus, moving the 30×6mm ROI a small amount will not change the shape of the velocity curve as significantly as moving a 6×6mm ROI the same distance. This is apparent in the significant overlap of the larger ROIs that can be seen in Figure 1.

Comparison to existing studies

To our knowledge, only one study has investigated the effect of small movements in the region of interest on quantification of tissue Doppler dyssynchrony parameters. De Boeck et al¹⁸ reported Bland-Altman limits of agreement of 129ms for quantifying SLD from 6×6mm ROIs at two different locations within 1.5 – 2cm of each other. We found similar results with a high coefficient of variation for SLD when measured 9 different ways for each patient using the 6×6mm ROI. To improve upon this, we showed that using a 30×6mm ROI reduces variability for SLD by 59%.

While some of the first DTI dyssynchrony studies reported low inter and intra-observer variabilities^{14, 19}, many studies did not perform any formal reproducibility analysis^{5, 6, 8, 9, 20}. Several recent studies have shown high variability in DTI dyssynchrony parameters leading to poor reproducibility^{1, 18, 21}. This high variability is in agreement with the high variability we documented with the use of 6×6mm ROIs (two of these studies documented using 6×6mm ROIs^{18, 21} while the third utilized a 10×10mm ROI¹).

Standardization of ROI size in future dyssynchrony studies

It is difficult to determine which ROI size is most commonly used as 8 of the 10 most cited DTI dyssynchrony studies failed to mention the size of the ROI used³⁻¹⁰. One study documented using a 6×6mm ROI¹¹ while another used a 2×2mm ROI¹². The PROSPECT study utilized a 10×10mm ROI (personal communication with Emory University core lab). Only one study has documented using a 30×6mm ROI to quantify dyssynchrony²². Clearly,

there is a wide range of ROIs that are utilized, and this technical step in DTI analysis could benefit from standardization.

Guidelines released by the American Society of Echocardiography and endorsed by the Heart Rhythm Society suggest using an ROI size from 10×5mm to 15×7mm². These guidelines also mention that manual adjustment of the ROIs can lead to different peak locations and substantially alter the velocity curves. As a solution, the guidelines recommend that users “manually adjust the regions of interest within the segment both longitudinally and side-to-side within the LV wall to identify the site where the peak velocity during ejection is most reproducible.” This type of manual adjustment is further described as “manual spatial averaging” in another review article²³. Using a 30×6mm ROI *automatically* performs spatial averaging while minimizing human error and should become the standard for quantifying dyssynchrony with DTI.

Diagnostic inconsistency

We showed that using a 30×6mm ROI instead of a 6×6mm ROI reduces variability in the measured level of dyssynchrony by 44%. However, dyssynchrony parameters are typically used to categorize, or “diagnose” a patient with dyssynchrony based on whether or not the patient has a level of dyssynchrony above or below a pre-defined threshold. Therefore, it was important to investigate: 1) how often the variability in dyssynchrony parameters leads to a different diagnosis and 2) if this diagnostic inconsistency was also reduced by using the larger ROIs. We showed that a 6mm shift of a 6×6mm ROI can change the diagnosis of dyssynchrony an average of $14 \pm 20\%$ of the time. Using the larger 30×6mm ROI reduced this inconsistency to $8 \pm 15\%$, resulting in a 44% reduction in the diagnostic inconsistency. Using an 18×6mm ROI did not significantly reduce the diagnostic inconsistency ($p = 0.054$).

Observer variability

Our study design is actually more powerful than an inter- or intra-observer study since we numerically simulated numerous observations for each patient and dyssynchrony parameter by using all possible permutations of ROI locations within each myocardial segment (Figure 2). Inter or intra-observer studies typically estimate variability with a simple difference between 2 measurements. Our study utilized a standard deviation across numerous measurements (9 measurements for SLD, 81 for MaxDiff, 729 for XCD, and 3¹² measurements for Ts-SD) to obtain a more precise estimate of variability.

Study limitations

We only examined the variability of 3 ROI sizes: 6×6mm, 18×6mm and 30×6mm. A wide range of ROI sizes has been used in the literature and we could not test every size. However, we selected the 6×6mm ROI because it is the default size in the EchoPAC software. We chose the 30×6mm ROI size because it is approximately large enough to cover one myocardial segment in a typical adult heart. We chose the 18×6mm ROI size because it was midway between the 6×6 and 30×6mm ROIs.

We used a 6mm shift of the ROIs to simulate the variability in manual operator placement of ROIs. The actual difference in ROI locations between multiple observers may be larger than 6mm. However, larger shifts should lead to increased variability in all 3 ROI sizes, and we would expect to document the same general trend that larger ROIs reduce the variability in DTI dyssynchrony parameters.

This study was a retrospective, single center study with a relatively small number of patients (30). In addition, we utilized a single ultrasound platform, which may significantly reduce the variability of measurements. However, the study was adequately powered to detect the

difference in variability between the 6×6 and 30×6mm ROIs. Future, prospective, multi-center studies should be performed to further validate our results.

Since SLD is calculated using 2 regions of interest, we utilized 9 permutations of the ROI locations to estimate its CoV in each patient. However, Ts-SD uses 12 regions of interest and we therefore utilized 3¹² permutations to estimate its CoV in each patient. Therefore, we are less confident in our estimate of the variance of the SLD parameter than the Ts-SD parameter.

Increasing the size of the ROI increases the spatial averaging of the tissue Doppler data, which may decrease the sensitivity to detect regional heterogeneity of timing. Future trials will be needed to confirm the ability of the 30×6mm ROI to predict response to CRT. For a more detailed discussion of this issue, please see the supplemental materials.

The PROSPECT study was unsuccessful for a multitude of reasons including 1) high levels of observer variability, 2) suboptimal image quality precluding accurate DTI measurements, 3) training standards, 4) use of multiple ultrasound platforms, and 5) inclusion of many subjects who did not satisfy enrolment criteria (20.2% had an ejection fraction > 35% when measured by the core labs)¹. Our study only focused on one of these limitations, namely, reducing observer variability. Future studies will need to address the additional limitations of the PROSPECT trial.

Conclusions

Using a 30×6mm region of interest instead of a 6×6mm region of interest to quantify tissue Doppler dyssynchrony reduces variability by 47%. In addition, a 30×6mm region of interest reduces the diagnostic inconsistency by 44% while an 18×6mm region of interest does not. We therefore recommend using a 30×6mm region of interest in future trials to minimize variability in a broad clinical setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

An exploded view of the basal septal wall shows placement of the 6×6mm regions of interest (ROIs). Three ROIs were placed in each myocardial segment: one at the center (yellow), one shifted 6mm up (blue), and one shifted 6mm down (red). This procedure was also performed for the 18×6 and 30×6mm ROIs (Figs C and D). Note that ROIs were also placed in the mid-wall segments (not shown).

Figure 2.

An image of the basal 4-chamber ROIs shows the 9 permutations used to quantify the septal-lateral delay dyssynchrony parameter.

Figure 3. Shifting a 6×6mm ROI slightly within the basal septum causes a change in the septal-lateral delay (SLD) parameter which results in a different diagnosis of dyssynchrony. Note that the threshold for diagnosing dyssynchrony is 60ms for SLD.

Figure 4.

Larger regions of interest (ROIs) reduce the variability in measuring tissue Doppler dyssynchrony parameters.

Figure 5.
Larger regions of interest (ROIs) reduce the diagnostic inconsistency of tissue Doppler dyssynchrony parameters.

Table 1

Characteristics of the patient population.

Variable (units)	Value*
Age (years)	61 ± 15
Male gender (%)	60%
Ischemic etiology (%)	48%
LV end systolic volume (ml)	126 ± 30
LV end diastolic volume (ml)	177 ± 65
LV ejection fraction (%)	29 ± 9
QRS duration (ms)	172 ± 32

* Values are means ± SD, $n = 30$.

Table 2

Comparison of coefficients of variation for each dyssynchrony parameter and ROI size.

	6×6mm ROI	18×6mm ROI	30×6mm ROI
SLD	43 ± 42%	25 ± 41%	18 ± 27%
MaxDiff	25 ± 22% *	19 ± 24%	15 ± 19%
Ts-SD	11 ± 10% *, [†]	6 ± 5% [‡]	8 ± 12%
XCD	28 ± 26%	17 ± 10%	16 ± 10%

Values are means ± SD, $n = 30$. *MaxDiff*, maximum difference in times-to-peak systolic velocity between any 2 of the basal septal, lateral, anterior and inferior left ventricular segments; *SLD*, septal-to-lateral delay in peak systolic velocity; *Ts-SD*, standard deviation of times-to-peak systolic velocity in the 12 basal and mid-wall segments of the left ventricle; *XCD*, cross-correlation delay.

* $p < 0.05$ vs SLD.

[†] $p < 0.05$ vs MaxDiff.

[‡] $p < 0.05$ vs XCD.

Table 3

Comparison of diagnostic inconsistency for each parameter and ROI size.

	6×6mm ROI	18×6mm ROI	30×6mm ROI
SLD	21 ± 25%	10 ± 17%	5 ± 11%
MaxDiff	12 ± 17%	12 ± 20%	9 ± 16%
Ts-SD	8 ± 15%	7 ± 14%	9 ± 17%
XCD	16 ± 21%	10 ± 15%	10 ± 14%

Values are means ± SD, $n = 30$. There were no statistically significant differences between the parameters after Bonferroni correction. *MaxDiff*, maximum difference in times-to-peak systolic velocity between any 2 of the basal septal, lateral, anterior and inferior left ventricular segments; *SLD*, septal-to-lateral delay in peak systolic velocity; *Ts-SD*, standard deviation of times-to-peak systolic velocity in the 12 basal and mid-wall segments of the left ventricle; *XCD*, cross-correlation delay.