

Left Ventricular Dysfunction is Associated with Intraventricular Dyssynchrony by 3-Dimensional Echocardiography in Children

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Introduction. We used 3-dimensional (3D) echocardiography to identify and quantify left ventricular (LV) dyssynchrony in children with LV dysfunction compared with control subjects.

Methods. The 3D echocardiography LV full volumes were acquired in 18 children, 9 with LV dysfunction and 9 control subjects. The LV was subdivided into 16 segments (apex excluded). Time from end diastole to the minimal systolic volume for each segment was expressed as a percent of the R-R interval. The SD of these times provided a 16-segment dyssynchrony index (16-SDI). The second index (12-SDI) was similarly calculated using 6 basal and 6 mid segments. The third index consisted of 6 basal segments (6-SDI).

Results. The dysfunction group exhibited significantly increased 16-SDI ($P = .008$) and 12-SDI ($P = .01$). The 16-SDI was negatively correlated with 3D ejection fraction and 2-dimensional fractional shortening.

Conclusions. Children with LV dysfunction demonstrate increased intraventricular LV dyssynchrony by 3D echocardiography, in a pattern that is negatively correlated with LV systolic function.

The relationship between left ventricular (LV) dyssynchrony (DSY) and heart failure has been well demonstrated in adult patients.¹ Both interventricular and intraventricular DSY contribute to heart failure by decreasing ventricular efficiency and performance. Intraventricular DSY causes blood to undulate between early and late contracting regions of the LV rather than being ejected. Cardiac resynchronization therapy (CRT) targets ventricular DSY and has been shown to improve symptoms and quality of life, while reducing complications and risk of death.² However, despite the application of conventional selection criteria, such as prolonged QRS duration, a significant proportion of patients do not experience clinical benefit.³ In a recent study, adult patients with heart failure and normal QRS duration demonstrated significant ventricular DSY and benefited from CRT.⁴ These findings indicate the need for improved measures of DSY and a deeper understanding of the relationship between ventricular DSY and dysfunction.

A recent multicenter study found that pediatric patients and those with congenital heart disease undergoing CRT exhibited a significant increase in mean ejection fraction (EF); however, long-term results regarding percentage of responders and degree of benefit are not yet available.⁵ Although CRT is increasingly used in this population, there is currently few published data that evaluate

DSY in healthy children, or in children with ventricular dysfunction.

Echocardiography has emerged as the modality of choice for assessment of DSY. Many echocardiographic methods have been used to evaluate patients for DSY, however, there is still no clear gold standard. Recently, 3-dimensional (3D) echocardiography (3DE) has undergone significant technologic advancements. DSY can now be assessed at the bedside by using sophisticated 3D volumetric software, which allows for temporal analysis of dispersion in segmental ventricular volumes during the cardiac cycle. In addition, 3DE does not require correct acquisition axis or time-consuming analyses.

This prospective study examines the feasibility of using 3DE to identify and quantify DSY in children with LV dysfunction as compared with body surface area-matched control subjects. It also examines the relationship between ventricular DSY and dysfunction in this population.

METHODS

Study Population

From May 2005 to May 2006, we performed 3DE and 2-dimensional (2D) echocardiography on 9 children with LV dysfunction with a median age of 14.1 years (range 4.9-18.6 years) and 9 body surface area-matched ($\pm 10\%$) healthy control subjects with a median age of 12.5 years (range 4.5-16.2 years). This study was an ancillary study of the Pediatric Heart Network Ventricular Variability Study. As part of the protocol of this study, LV dysfunction was defined as a fractional shortening of less than or equal to 28%. Patients with structural congenital heart disease were excluded. The diagnoses in the LV dysfunction group were as follows: dilated cardiomyopathy ($n = 7$), supraventricular tachycardia-induced cardiomyopathy ($n = 1$), and transplant rejection ($n = 1$). Control

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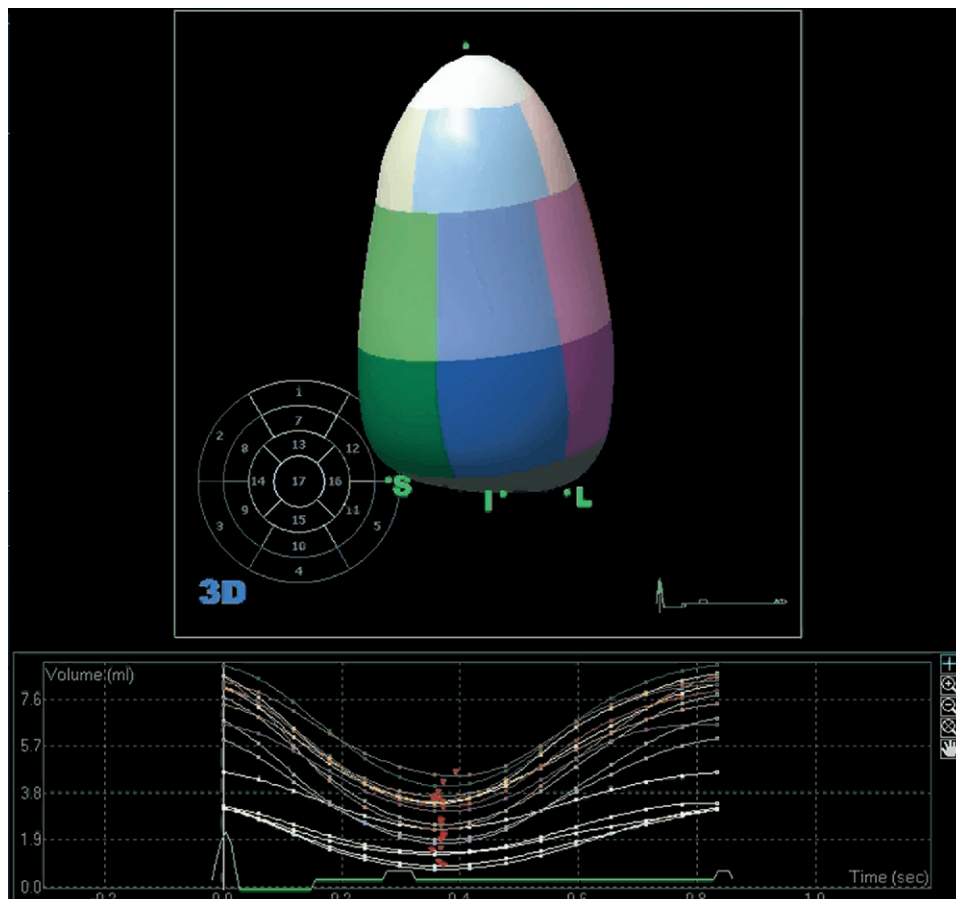


Figure 1 Three-dimensional echocardiographic left ventricular segmental analysis software illustrating 16-segment model and graphic display of each segment's volume throughout cardiac cycle.

subjects were selected from patients referred to a university-based pediatric cardiology clinic, and were found to have a normal echocardiogram with no history of cardiovascular or systemic disease. There were 4 male and 5 female patients in each group. The median body surface area for patients and control subjects was 1.5 m² and 1.4 m², respectively. The study was approved by the institutional review board.

3DE Imaging and Analysis

In all patients, 3D full-volume data sets were acquired from the apical window using either an iE33 or Sonos 7500 imaging system and X3-1 or X4-2 full matrix-array transducer, respectively (Philips Medical Systems, Bothell, WA). The full-volume data sets consisted of 4 real-time subvolumes acquired during 4 cardiac cycles merged together to create a larger 3D pyramidal data set. The data sets were briefly examined immediately after acquisition for inclusion of the entire LV endocardium and clear endocardial borders. At least two data sets were acquired in each patient and the highest quality data set was selected for analysis.

The 3D data sets were analyzed using volumetric quantification software (QLAB, Version 4.2, 3DQ Advanced, Philips Medical Systems). All analyses were performed in triplicate and results averaged. The volumetric analysis proceeded as follows: (1) three 2D orthogonal planes (apical 4-chamber, apical 2-chamber, and ventricular short-axis) were oriented to bisect the LV and incorporate the true ventricular apex; and (2) 5 anatomic landmarks were set (the hinges

of the mitral valve in the two orthogonal apical views, and the apical endocardium) in both end diastole and end systole.

Once these steps were completed, the automated border detection algorithm created a 3D model of the endocardial border at end diastole and end systole. The accuracy of the endocardial border detection was examined and manually edited if necessary. The software was then initiated to perform the volumetric analysis, providing a cast of the LV cavity throughout the cardiac cycle.

For segmental volume analysis, the LV was divided into 16 segments (American Society of Echocardiography recommended model).⁶ The volume of each segment was graphed as a function of time throughout the cardiac cycle (Figure 1). The time from end diastole to the minimal systolic volume was measured for each segment. To control for heart rate, these times were then expressed as a percent of the R-R interval. Three separate indices of DSY were calculated using the standard deviation (SD) of these times: for 16 LV segments (apex excluded) (16-SD%), for 12 LV segments (6 basal and 6 mid segments) (12-SD%), and for 6 basal segments (6-SD%). This method has been previously used for LV segmental volume analysis in adults.^{7,8}

Statistics

Given that the data were not normally distributed, nonparametric statistical methods were used in the analysis. Continuous variables were described using median and range. Differences in variables between groups were analyzed using Wilcoxon rank sum tests. Correlation between variables was assessed using Spearman correla-

tion coefficients. A *P* value of less than .05 was considered statistically significant. Descriptive statistics and analyses were performed using software (SAS 9.1, SAS Institute Inc, Cary, NC).

RESULTS

Acquisition of 3DE full-volume data sets was feasible in all patients with LV dysfunction. In two potential matched control subjects, the data sets acquired were not of adequate quality for volume analysis. Therefore, these were discarded and two additional control subjects were selected. Time required for acquisition of data sets was estimated at 2 to 3 min/echocardiogram. Time required for analysis was approximately 3 to 4 min/data set, similar to previously published data on time-resource use for this modality.⁹

As described in Table 1, the median end-diastolic volume in the dysfunction group was 139.9 mL (range 63.5-230.8 mL), compared with control subjects, 88.3 mL (range 35.4-155.2 mL). The median end-systolic volume in the dysfunction group was 96.9 mL (range 20.4-195.2 mL), as compared with control subjects, 29.3 mL (range 12.1-57.6 mL). The median 3D EF in the dysfunction group was 36.3% (range 12.8%-58.8%), compared with control subjects, 60.8% (range 44.3%-72.1%). The median QRS duration in the dysfunction group was 92 milliseconds (range 80-128 milliseconds), compared with control subjects, 80 milliseconds (range 72-102 milliseconds) and was not significantly different between groups (Table 2). QRS duration did not correlate with 16-SD% ($r = -0.003$).

Compared with control subjects, the dysfunction group exhibited significantly increased 16-SD% and 12-SD% (Table 2). The median 16-SD% was 4.37% (2.29%-14.77%) in the dysfunction group and 2.1% (0.71%-2.78%) in control subjects ($P = .008$). The median 12-SD% was 2.82% (0.99%-12.26%) in the dysfunction group and 1.15% (0.77%-2.23%) in control subjects ($P = .01$). The median 6-SD% was 1.97% (0.97%-12.52%) in the dysfunction group and 1.28% (0.53%-2.33%) in control subjects ($P = .08$).

To examine the relationship of 16-SD% to measures of ventricular function we combined the dysfunction and control groups. In the combined population, 16-SD% was negatively correlated with 3D LV EF ($r = -0.81$, $P < .001$) (Figure 2) and 2D fractional shortening ($r = -0.61$, $P = .01$).

DISCUSSION

In our study group, we found that 3DE effectively identified and quantified DSY in pediatric patients. Patients with LV dysfunction demonstrated significantly higher intraventricular DSY compared with healthy control subjects as measured by the 12- and 16-segment 3DE indices. However, the difference between the two groups in the 6 segment index did not reach statistical significance. This suggests that global segmental analysis may allow for a more sensitive and robust evaluation of DSY.

The QRS duration was not significantly different between the groups and there was no correlation between 16-SD% and QRS duration. Larger studies are needed to better elucidate the relationship between QRS duration and DSY in children; however, our findings suggest that QRS duration may be an insensitive measure of intraventricular DSY. This is in agreement with the findings of a recent study, which found that adult patients with heart failure and normal QRS duration can exhibit significant ventricular DSY.⁴

Table 1 Comparison of 3-dimensional volume indices between patients with left ventricular dysfunction and control subjects

	LVD	Control
3D-EDV	139.9 mL (63.5-230.8 mL)	88.3 mL (35.4-155.2 mL)
3D-ESV	96.9 mL (20.4-195.2 mL)	29.3 mL (12.1-57.6 mL)
3DEF	36.3% (12.8%-58.8%)	60.8% (44.3%-72.1%)

LVD, Left ventricular dysfunction; 3D-EDV, 3-dimensional end-diastolic volume; 3DEF, 3-dimensional ejection fraction; 3D-ESV, 3-dimensional end-systolic volume.

Table 2 Comparison of dyssynchrony indices between the patients with left ventricular dysfunction and control subjects

	LVD	Control	<i>P</i> value
QRS duration	92 ms (80-128 ms)	80 ms (72-102 ms)	.16
16-SD%	4.37% (2.29%-14.77%)	2.1% (0.71%-2.78%)	.008
12-SD%	2.82% (0.99%-12.26%)	1.15% (0.77%-2.23%)	.01
6-SD%	1.97% (0.97%-12.52%)	1.28% (0.53%-2.33%)	.08

LVD, Left ventricular dysfunction; 16-SD%, 16-segment dyssynchrony index; 12-SD%, 12-segment dyssynchrony index; 6-SD%, 6-segment dyssynchrony index.

The 16-SD% showed a strong negative correlation with both 2D fractional shortening and 3D EF. This is consistent with the findings of a recent study by Zeng et al,⁸ in which multiple indices of DSY in adult patients with dilated cardiomyopathy were compared with healthy control subjects. They found 16-SD% to have the strongest negative correlation with 3D EF. This suggests a reproducible, inverse relationship between this global index of intraventricular DSY and EF.

Interestingly, all 4 patients in the dysfunction group with a 3D EF less than 35% had a 16-SD% greater than 7.3%. These findings are in agreement of those with Kapetanakis et al,⁷ who found that adult patients with moderately and severely depressed LV EF had a mean 16-SD% of 10% and 15.4%, respectively. As intraventricular DSY increases and the volume of intraventricular blood displacement increases, the ventricle may reach a threshold of DSY at which adequate ventricular systolic function is difficult to maintain. The relationship between DSY and dysfunction is clearly complex and further study is needed in both the adult and pediatric population.

An important component of successful CRT is optimal ventricular lead placement. The unique ability of 3DE to simultaneously demonstrate location and timing of segmental contraction delay throughout the entire LV could prove useful in guiding lead placement. Moreover, with the availability of live transesophageal 3DE and on-scanner analysis software, lead guidance could be performed during lead implantation providing real-time feedback to the surgeon or electrophysiologist.

Limitations

The reviewer was not blinded to the diagnoses while performing the ventricular volumetric analysis. The study population was small as a result of the relative infrequency of LV dysfunction in anatomically normal hearts in children. Because of the small sample size, only 4 patients had DSY by 3DE. Although the results were statistically significant, a larger sample size is needed to confirm these findings.

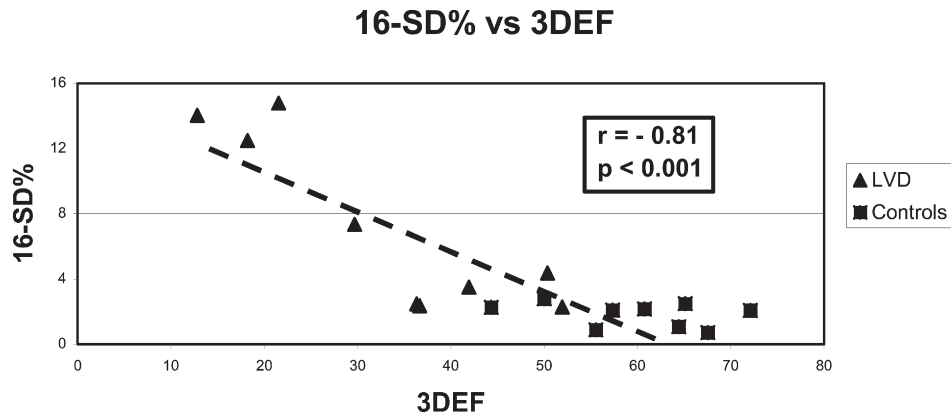


Figure 2 Correlation between 16-segment dyssynchrony index (16-SD%) and 3-dimensional ejection fraction (3DEF) demonstrating increasing 16-SD% with decreasing 3DEF. LVD, Left ventricular dysfunction.

Results regarding the interobserver and intraobserver variability for the segmental volumetric analysis are not presented, but are part of an ongoing study. An extensive review of the interobserver/intraobserver variability for nonsegmental ventricular volume analysis is available in a recent publication by the authors.⁹ The 3DE indices of DSY were not compared with other methods of DSY analysis, such as Doppler tissue imaging. This observational study did not examine the effects of CRT.

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