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Tricuspid Annular Plane Systolic Excursion Correlates with Exercise Capacity in a Cohort of Patients with Hypoplastic Left Heart Syndrome After Fontan Operation

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Abstract

Objective—Tricuspid annular plane systolic excursion (TAPSE) is a reproducible measure of right ventricular systolic function. We sought to determine the reliability of TAPSE measurements, to evaluate TAPSE in patients with hypoplastic left heart syndrome (HLHS) relative to normal values, and to correlate values of TAPSE with measures of exercise performance.

Design—TAPSE measurements were performed offline in the cohort of patients with single right ventricle anatomy who had been enrolled in the Sildenafil After Fontan Operation clinical trial. These values were converted to z-scores using age-specific means and standard deviations according to published reference values. Reproducibility of measurements was assessed using the coefficient of variation between two readers. Comparisons between echo measurements and exercise outcomes were assessed using Pearson correlation coefficients.

Results—Forty-four echocardiograms from 11 subjects were included in this analysis. The median age of included subjects was 13 years (range 12–17). The coefficient of variation for TAPSE measurements was 5.0%. TAPSE was significantly diminished relative to reference values, with a median z-score of -7.6 . TAPSE values correlated with both maximal oxygen consumption ($R=0.64$; $p=0.033$) and oxygen consumption at the anaerobic threshold ($R=0.73$, $p=0.017$).

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Conclusions—In this small sample of children with HLHS, TAPSE was reproducible, substantially lower than reference values, and correlated well with measures of exercise performance. Further studies are needed to evaluate these findings in a larger cohort and in a longitudinal manner.

Keywords

Fontan; echocardiography; congenital heart disease

Introduction

For patients with hypoplastic left heart syndrome (HLHS), the right ventricle occupies an unnatural position as the sole driver of cardiac output for both the systemic and pulmonary circulations. The performance of the single right ventricle is therefore a crucial determinant of long-term outcome. While there have been numerous attempts to establish an echocardiographic imaging tool that would allow for simple and consistent assessment of right ventricular performance, none have gained general acceptance (1–5). Despite advances in technology, clinical evaluation of the right ventricle is often limited to the subjective assessment of an experienced echocardiographer. Given the importance of ventricular performance to the overall outcome for patients with HLHS, a measure of ventricular performance that is reliable, reproducible, and correlates with functional outcome would be of substantial value.

Tricuspid annular plane systolic excursion (TAPSE) is a simple, reproducible and validated measurement of the distance travelled by the tricuspid annulus in systole (6–9). This technique has been used to assess ventricular performance in a variety of disease states affecting the right ventricle, including heart failure and pulmonary arterial hypertension in adults, and in a variety of forms of congenital heart disease (10–13). While there are well-established normal values for TAPSE in patients with a two-ventricle circulation, there is less information on TAPSE in patients with single right ventricles and scarce data correlating TAPSE with functional outcomes in patients with HLHS (14, 15).

In this study we evaluated data from children and young adults with HLHS after Fontan operation that were previously enrolled in a randomized trial in which protocol-based echocardiograms were performed (16, 17). The objectives of the current study were to determine the reliability of TAPSE measurements, to evaluate TAPSE in patients with HLHS relative to normal values, and to correlate values of TAPSE with serum brain-type natriuretic peptide (BNP) levels and measures of exercise performance.

Methods

This analysis utilized data from a subset of children and young adults with single right ventricular morphology after Fontan operation who were enrolled in a randomized, double blind, placebo-controlled, crossover trial of oral sildenafil versus placebo ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00507819) identifier: NCT00507819). Only those subjects with HLHS who had echocardiographic images deemed suitable were analyzed for this study. This study was approved by the Institutional Review Board for the Protection of Human Subjects at The Children's Hospital

of Philadelphia and complies the Declaration of Helsinki. Informed consent was obtained from all subjects or their guardians, as appropriate.

TAPSE measurement was performed offline using 2-dimensional apical views with Syngo Dynamics software version 9.5 (Siemens, Ann Arbor, MI). We identified the lateral annulus of the tricuspid valve and measured the distance to the apex of the screen sector at end-diastole and end-systole. TAPSE was calculated as the difference in distance from end-diastole to end-systole. The electrocardiogram was used to determine accurately the phase of the cardiac cycle. This technique was shown to be similar to the distance measured by M-mode, which was not available in this study (8). The lateral tricuspid annular peak systolic velocity (S' velocity), an additional measure of right ventricular systolic performance, was also measured offline using previously acquired tissue Doppler imaging. TAPSE and S' values were quantified independently by two readers blinded to treatment assignment and study phase. Both readers obtained three measurements of TAPSE and S' velocity for each subject at each study phase. TAPSE values were standardized by the age-specific mean and standard deviation from a healthy population, obtained from published reference values (18).

The results of exercise tests, baseline serum BNP levels, and echocardiograms from the original trial were also used for this analysis. Exercise testing was performed according to a ramp exercise protocol as previously described (16). Exercise measurements were converted to percent-predicted values based on age and sex (19). Echocardiograms were performed by one of two echocardiographic sonographers with specific training for the study protocol. A Phillips IE33 (Phillips, Andover, MA) machine was used for image acquisition. Appropriate transducers were selected based on subject body habitus.

Participant characteristics at baseline were summarized using standard descriptive statistics. Qualitative assessment of ventricular function and atrioventricular valve regurgitation was abstracted from the original trial. Reproducibility of echocardiographic measurements made in this study were evaluated using the coefficient of variation (CV) between the two readers; the average of each reader's three measurements was used in the analysis. All pre-phase and post-phase values were used to calculate the CV. TAPSE and S' velocity were compared to baseline serum BNP level and to additional echocardiographic measures of ventricular function: the product of velocity time integral and heart rate ($VTI \times HR$), a surrogate of cardiac output, the myocardial performance index (MPI), a systolic and diastolic measure of right ventricular function, and right ventricular fractional area change. Comparisons to the following exercise variables were performed: oxygen consumption at peak exercise and oxygen consumption at the anaerobic threshold (VO_2 AT). Comparisons were made using Pearson correlation coefficients. Due to the repeated measures design (two pre-phase values for each of the two readers), the mean of the pre-phase values for each participant was used for correlation analysis (20). All analyses were conducted using R 3.0.2 (R Development Core Team, Vienna, Austria).

Results

Of the 28 participants initially recruited for the SAFO study, 11 had a diagnosis of HLHS and echocardiographic images from which TAPSE could be measured. The demographic

and baseline characteristics for the 11 participants included in the analysis are listed in Table 1. Of those included, 82% were male and 91% were white. The median age of included participants was 13 years, while the median age at the time of the Fontan operation was 1.7 years. The median baseline body mass index was in the normal range, and the mean serum BNP was 85 pg/ml. Ventricular function was characterized as normal or mildly diminished in all participants and no participants had more than mild AV valve regurgitation. The median percent-predicted VO₂ max was 76%, while the median VO₂ AT was 21 ml/kg/min. TAPSE was significantly diminished overall, with a median z-score of -7.6. All participants had a z-score for TAPSE that was more than two standard deviations below the normal population.

Association between TAPSE, S' velocity, serum BNP level, and markers of ventricular and exercise performance

TAPSE and S' velocity were both reproducible; the coefficient of variation for TAPSE and S' velocity measurements were 5.0% and 4.5%, respectively. The correlations between TAPSE and other measures of ventricular and exercise performance are listed in Table 2. There was modest correlation between the raw TAPSE value and the S' velocity ($R = 0.63$, $p=0.039$, Figure 1), but not between TAPSE and VTI $\times$ HR or MPI. Neither TAPSE nor S' velocity correlated with baseline serum BNP level. While the absolute TAPSE value did not correlate with measures of exercise performance, TAPSE z-scores were correlated with both VO₂ max ($R=0.64$; $p=0.033$) and VO₂ AT ($R=0.73$; $p=0.017$, Figure 2).

Discussion

In this study of a small sample of patients with HLHS, we demonstrate that TAPSE is a reproducible measure of right ventricular systolic function. All measured values for TAPSE were below the population mean derived from a healthy cohort, with the vast majority more than two standard deviations below the mean. As expected, TAPSE was strongly correlated with S' velocity, although it did not correlate with other metrics of ventricular function, including MPI, VTI $\times$ HR, and right ventricular fractional area change. Importantly, we also demonstrated a modest correlation between TAPSE and both VO₂ max and VO₂ AT, key measures of functional outcome.

Systolic function in the single right ventricle is complex and dependent on a combination of myocardial shortening and twisting produced by longitudinal, radial, and circumferential muscle fibers. However, although TAPSE is just one component of right ventricular function, previous studies in patients with HLHS that have used TAPSE as a tool to quantify function have also demonstrated diminished values relative to published z-scores (13–15). In part, the abnormalities in TAPSE z-score are expected given the increased importance of radial and circumferential function in the face of systemic afterload (21). Abnormalities in TAPSE z-score have also been demonstrated in other forms of congenital heart disease including tetralogy of Fallot and transposition of the great arteries (8, 12, 22, 23). Studies in adult populations with pulmonary arterial hypertension and systolic heart failure have shown that TAPSE values decrease as the disease state worsens (10, 11). Our study confirms that TAPSE is significantly abnormal in the cohort of patients with HLHS after Fontan operation.

The correlation between TAPSE and S' velocity demonstrated in this cohort was expected. TAPSE and S' velocity are measures of right ventricular function obtained by measuring either the distance of annular descent (TAPSE) or the peak velocity of the lateral tricuspid annulus (S' velocity). Indeed, the product of the time averaged mean velocity of the lateral tricuspid annulus and the ejection time should be quite similar to the measured TAPSE. In this study, the correlation serves as an internal control regarding measurements of these parameters. Not surprisingly, TAPSE did not correlate with MPI, $VTI \times HR$, right ventricular fractional area change, or subjective measures of ventricular function. TAPSE is strictly a measure of longitudinal systolic function while MPI is a measure of global ventricular performance, with both systolic and diastolic components. $VTI \times HR$ is a rough measure of cardiac output that may not correlate with TAPSE when the right ventricle is the systemic ventricle. A similar negative finding was previously demonstrated in a study that attempted to correlate TAPSE with cardiac output as measured by cardiac magnetic resonance imaging (13).

The relationship between TAPSE and exercise capacity may be important. Exercise performance for children with Fontan physiology is abnormally low throughout childhood and becomes progressively diminished as children pass through adolescence and into adulthood (24, 25). Diminished exercise performance is correlated with the onset of symptoms associated with heart failure in many forms of congenital heart disease, including in those with Fontan physiology (26). While TAPSE measures a specific component of overall right ventricular systolic function, it may be that a “healthier” right ventricle is able to maintain a more normal longitudinal shortening in the face of increased afterload. This, in turn, may relate to improved exercise capacity. A more detailed exploration of this relationship would be useful as a non-invasive measure that tracks with exercise performance would be of value as a tool to follow patients longitudinally and to monitor the impact of potential therapeutic interventions over time.

As with many forms of congenital heart disease, ventricular performance is a significant contributor to the long-term outcome of children and adolescents with single ventricle physiology who have undergone Fontan palliation. Echocardiographic assessment of the right ventricle is challenging related to the geometric configuration of the right ventricle and the conformational changes in right ventricular mechanics following single ventricle palliation. The ability to evaluate ventricular function by a simple measurement has potential value for clinicians who are faced with the task of following children from Fontan surgery into adulthood and need a qualitative tool for the serial assessment of the right ventricle. Many previous studies in patients with HLHS have evaluated techniques for estimating right ventricular performance beyond the subjective measurements obtained through standard qualitative echocardiography, but few have been adopted as part of routine clinical care (1–3, 27). While these echocardiographic descriptions of ventricular performance are helpful, a measure that is simple to obtain, has good reproducibility, and correlates with functional outcomes has substantial additional value.

Limitations

This study was performed retrospectively using a pre-determined patient population from a randomized trial. As such, our power to detect correlations was limited by the small number of included participants and we were limited to off-line measurements in previously obtained images. Further investigation is needed to determine whether the correlations that we identified are present across the larger HLHS population. Additional studies are likewise needed to determine the natural history of TAPSE over longitudinal follow-up, and whether this measure correlates with exercise performance over time.

Conclusion

Our study demonstrates the potential utility of TAPSE as a descriptor of ventricular performance in the population of children and adolescents with HLHS after Fontan operation. In our cohort, measurements of TAPSE were reproducible and were internally consistent with S' velocity, another measure of ventricular performance. As expected, TAPSE z-scores were substantially lower than those for healthy age-matched children and correlated well with exercise capacity, an important marker of function outcome. Additional studies are needed to evaluate our findings in a larger cohort and in a longitudinal manner. Nevertheless, this study supports the notion that TAPSE might be useful in routine measurement of ventricular performance in the cohort of children and young adults with HLHS after Fontan palliation.

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Figure 1. TAPSE versus S' velocity (correlation, 0.63; $p=0.039$). Gray circles indicate individual values. Black $\times$ s denote pre-phase mean values. Black lines indicate scatterplot smoother with 2 degrees of freedom.

Figure 2. TAPSE z-score versus oxygen consumption at anaerobic threshold (correlation, 0.73; $p=0.017$). Gray circles indicate individual values. Black 'x's denote pre-phase mean values. Black lines indicate scatterplot smoother with 2 degrees of freedom.

Table 1

Characteristics of study participants at baseline (n=11).

<i>Demographic and clinical characteristics</i>	
Age, years, median (IQR)	13 (12, 17)
Age at Fontan, years, median (IQR)	1.7 (1.6, 2.2)
Male, n (%)	9 (82)
Caucasian, n (%)	10 (91)
Body mass index, kg/m ² , median (IQR)	20.0 (17.7, 21.8)
Serum brain-type natriuretic peptide, pg/ml, median (IQR)	85 (54, 115)
<i>Echocardiographic measurements</i>	
TAPSE, cm, median (IQR)	1.00 (0.83, 1.06)
TAPSE z-score, median (IQR)	-7.6 (-8.8, -6.6)
S' velocity, cm/sec, median (IQR)	6.7 (6.3, 7.1)
Right ventricular FAC, %, median (IQR)	50 (45, 53)
Velocity time integral × heart rate, cm × beats/min, median (IQR)	1390 (1200, 1470)
Myocardial performance index, median (IQR)	0.46 (0.35, 0.53)
Ventricular dysfunction, n (%)	
Normal	8 (73)
Trivial or mild	3 (27)
Moderate or severe	0 (0)
Atrioventricular valve regurgitation, n (%)	
None	1 (9)
Trivial or mild	10 (91)
Moderate or severe	0 (0)
<i>Exercise measurements</i>	
Oxygen consumption at peak exercise, ml/kg/min, median (IQR)	36 (32, 38)
Oxygen consumption at anaerobic threshold, ml/kg/min, median (IQR)	21 (17, 24)

IQR, interquartile range; TAPSE, tricuspid annular plane systolic excursion; S' velocity, lateral tricuspid annular peak systolic velocity; FAC, fractional area change

Table 2

Correlation of TAPSE and S' velocity with markers of ventricular and exercise performance.*

	TAPSE Correlation (P value)	TAPSE z-score** Correlation (P value)	S' velocity Correlation (P value)
S' velocity	0.63 (0.039)	0.57 (0.069)	—
RV FAC	0.08 (0.83)	0.04 (0.91)	0.08 (0.82)
VTI × HR	0.19 (0.58)	0.15 (0.65)	0.08 (0.82)
MPI	−0.41 (0.21)	−0.17 (0.61)	−0.58 (0.063)
VO2 max	0.39 (0.23)	0.64 (0.033)	0.15 (0.65)
VO2 AT	0.57 (0.087)	0.73 (0.017)	0.41 (0.24)
BNP	−0.18 (0.60)	−0.32 (0.34)	−0.04 (0.90)

TAPSE, tricuspid annular plane systolic excursion; S' velocity, lateral tricuspid annular peak systolic velocity; RV FAC, right ventricular fractional area change; VTI × HR, the product of velocity time integral and heart rate; MPI, myocardial performance index; VO2 max, oxygen consumption at peak exercise; VO2 AT, oxygen consumption at the anaerobic threshold; BNP, serum brain-type natriuretic peptide level.

* Repeated measurements for each subject were summarized using the mean of the pre-phase values.

** TAPSE values standardized by the age-specific mean and standard deviation from a healthy population(18).