Published in final edited form as:

Pediatr Cardiol. 2019 February ; 40(2): 366–373. doi:10.1007/s00246-018-2018-1.

The Relationship Between Pre-operative Left Ventricular Longitudinal Strain and Post-operative Length of Stay in Patients Undergoing Arterial Switch Operation Is Age Dependent

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Abstract

Introduction—Post-operative length of stay (LOS) after the arterial switch operation (ASO) is variable. The association between pre-operative non-invasive measures of ventricular function and post-operative course has not been well established. The aims of this study were to (1) evaluate the relationship between pre-operative non-invasive measures of ventricular function and post-operative LOS and (2) evaluate the change in ventricular function after ASO.

Methods—Data were reviewed in consecutive ASO patients between 2010 and 2016. The primary outcome was post-operative LOS. Echocardiograms obtained during the pre-operative period and at the time of discharge were retrospectively analyzed using speckle-tracking echocardiography. Pearson's correlation between patient-specific, pre-operative, and echocardiographic data versus post-operative LOS was assessed.

Results—Fifty-two patients were included in analyses, 39 neonates and 13 infants. Left ventricular (LV) longitudinal strain correlated with post-operative LOS for infants age > 28 days ($r = 0.62$, $p = 0.03$), but not for neonates ($r = 0.14$, $p = 0.40$). Operative age ($r = -0.42$, $p = 0.003$), weight at surgery ($r = -0.48$, $p = 0.001$), and cardiopulmonary bypass time ($r = 0.30$, $p = 0.045$) also correlated with post-operative LOS. Standard 2D measures of ventricular function did not correlate with post-operative LOS. LV ejection fraction and longitudinal strain worsened post-operatively.

Conclusion—Higher pre-operative LV longitudinal strain (representing worse LV function) is associated with increased post-operative LOS after ASO in infants > 28 days, but not in neonates. LV ejection fraction and longitudinal strain worsened after ASO. Future studies should assess the utility of performing STE in risk stratifying patients prior to ASO.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Keywords

Speckle-tracking echocardiography; Transposition of the great arteries; Congenital heart disease; Neonatal surgery

Introduction

The arterial switch operation (ASO) is the preferred surgical repair for neonates and infants with dextro-position of the great arteries (d-TGA) and double outlet right ventricle (DORV) with malposed great arteries [1]. Overall, long-term outcomes are improving [2]. However, there remains significant post-operative morbidity and mortality; most recent data report a perioperative mortality rate of 2.2–5.1% [3]. Patient factors have been identified that are associated with increased morbidity and mortality [4–9]. For patients undergoing late ASO, there are conflicting reports as to the utility of echocardiographic data to predict post-operative outcomes [10–13]. Anecdotal evidence suggests that patients with pre-operative ventricular dysfunction experience increased morbidity including prolonged length of stay (LOS) after ASO. However, the relationship between pre-operative ventricular function and post-operative morbidity has not been well established.

Speckle-tracking echocardiography (STE) is a non-invasive modality for the assessment of myocardial deformation. Reference ranges have been published for the pediatric population [14, 15], and STE has increasingly been applied in patients with congenital heart disease [16–18]. STE has several characteristics that make it appealing for evaluation of ventricular function in this patient population. Measures derived from STE have geometry independence, good reproducibility, and have been shown to be more sensitive to changes in systolic function than standard measures such as ejection fraction [19–22]. The purposes of this study are to (1) evaluate the relationship between pre-operative and post-operative non-invasive measures of ventricular function and post-operative LOS and (2) evaluate the change in ventricular function after ASO.

Methods

A retrospective cohort study was performed identifying all patients who underwent ASO at the Medical University of South Carolina between January 1, 2010 and December 31, 2016. Patients were excluded if they underwent ASO at > 90 days of life or if their echocardiogram images were not sufficient to permit STE analysis. The primary outcome was post-operative LOS. This study protocol was approved by the Medical University of South Carolina's Institutional Review Board.

Echocardiographic Analysis

Clinical echocardiograms previously stored in Digital Imaging and Communications in Medicine format at 30 frames per second were analyzed on Xcelera (Philips, Andover, MA). The pre-operative echocardiogram was defined as the most recent echocardiogram prior to the surgical date. The post-operative echocardiogram was defined as the echocardiogram obtained prior to hospital discharge. A single blinded reviewer retrospectively analyzed all

echocardiograms. Standard 2D measurements were performed in accordance with the recommendations from the American Society of Echocardiography [23]. Left ventricular (LV) ejection fraction was calculated using the $(5/6 \times \text{area} \times \text{length})$ method. Right ventricular (RV) fractional area change was calculated as $[(\text{RV area diastole} - \text{RV area systole})/\text{RV area diastole}]$.

Speckle-tracking echocardiography was performed using vendor independent software, Cardiac Performance Analysis v3.0 (Tomtec Imaging Systems, Munich, Germany) on all echocardiograms. Longitudinal strain was obtained from an apical four chamber view. Circumferential strain was obtained from a parasternal short-axis view at the level of the papillary muscles or sub-valvular apparatus. In the absence of acceptable parasternal acoustic windows, circumferential strain was obtained from a subcostal short-axis view. The endocardial border was identified manually and automatically traced by the software throughout the cardiac cycle (Fig. 1). The ventricular myocardium was divided into six discrete segments. Segments that did not track the endocardium accurately were excluded. STE data were included if four out of six segments tracked appropriately. Longitudinal and circumferential strain represented an average of the included wall segments [22]. A more negative value for strain indicates better ventricular function.

Statistical Analysis

Shapiro–Wilk test was utilized to analyze the distribution of data. Independent *t*-tests, Chi-square tests, and Mann–Whitney *U* tests were used to identify differences between neonates (age < 28 days) and infants (age ≥ 28 days). Paired *t*-tests or Wilcoxon signed rank tests were used to evaluate for changes in measures of ventricular function before and after ASO. We used Pearson's correlation to assess relationship between LOS and echocardiographic measures of ventricular function. Log transformations were used to account for non-parametric distribution of data. Statistical significance was defined as *p*-value < 0.05. IBM SPSS Statistics software v 24 was used for statistical analysis.

Results

Sixty-nine patients underwent ASO at the Medical University of South Carolina between January 1, 2010 and December 31, 2016. Two were excluded based on age > 90 days at time of surgery. Fifteen were excluded based on inadequate echocardiogram images. Fifty-two patients were included in analysis and patient characteristics are represented in Table 1. No patients died prior to hospital discharge. The underlying lesion varied. Thirty-two (62%) of patients had d-TGA with intact ventricular septum (IVS), 13 (25%) had d-TGA with ventricular septal defect (VSD), and 7 (13%) had DORV with malposed great arteries and d-TGA physiology.

Neonates Versus Infants

Of the 52 patients included in the study, 39 (75%) were neonates and 13 (25%) were infants. Neonates had a longer median hospital LOS at 23 days (IQR 19, 27) compared to infants who had a median hospital LOS at 10 days (IQR 6, 49). However, the difference in post-operative LOS was not statistically significant. Neonates had a higher birth weight (3.4 ± 0.5

kg) than infants (2.7 ± 0.8 kg), but infants had a higher operative weight (5.3 ± 2.1 kg) than neonates (3.4 ± 0.4 kg) at the time of surgery. Neonates had more days intubated (5 [IQR 3, 8]) than infants (2 [IQR 1, 11]) although this did not reach statistical significance. There was no difference in standard measures of ventricular function between neonates and infants. Neonates had worse LV longitudinal strain [-14.5% (IQR -16.6% , -12.2%) vs. -17.6% (IQR -20.7% , -15.3%)] and LV circumferential strain [-15.8% (IQR -18.0% , -14.6%) vs -19.9% (IQR -21.4% , -16.3%)] than infants.

Predictors of Post-operative LOS

Among the full cohort, there was a weak correlation ($r = 0.30$, $p = 0.04$) between pre-operative LV longitudinal strain and post-operative LOS. We then evaluated this correlation for neonates and infants separately. For neonates, there was no correlation between pre-operative LV longitudinal strain and post-operative LOS ($r = 0.14$, $p = 0.40$) (Fig. 2). However there was a moderate correlation between pre-operative LV longitudinal strain and post-operative LOS in infants ($r = 0.62$, $p = 0.03$) (Fig. 3). Operative age ($r = -0.42$, $p = 0.003$), weight at surgery ($r = -0.48$, $p = 0.001$), and cardiopulmonary bypass (CPB) time ($r = 0.30$, $p = 0.045$) also correlated with post-operative LOS in the full cohort.

Change in Ventricular Function after ASO

Table 2 demonstrates changes in ventricular function after ASO. LV ejection fraction decreased from pre-operative echo to post-operative echo ($62 \pm 8\%$ to $58 \pm 7\%$), $p = 0.001$. LV longitudinal strain likewise worsened from -15.3% (IQR -18.3% , -13.1%) to -13.9% (IQR -16.1% , -12.6%), $p = 0.007$. End diastolic volume did not change. RV fractional area change increased from 0.28 ± 0.06 to 0.36 ± 0.09 , $p = 0.001$. There was no statistically significant change in RV longitudinal strain.

Discussion

There are few studies evaluating STE in patients who underwent ASO. Some of these studies focused on mid to long-term analysis of ventricular function [24, 25]. Others have evaluated the changes in pre-operative versus post-operative function [26]. To our knowledge, no studies have used clinical outcomes as a primary endpoint. This study shows that pre-operative LV function as measured by longitudinal strain correlates with post-operative LOS in infants > 28 days undergoing ASO, but not in neonates.

Neonates versus Infants

We divided patients into two groups, neonates and infants. There were statistically significant differences between these groups in characteristics that have been shown in other studies to be predictive of either post-operative morbidity or LOS.

Unsurprisingly neonates were smaller than infants, although none weighed less than 2.5 kg, a cut off which has been shown to be a risk factor for morbidity in previous studies [8]. Infants had a lower birth weight, but a higher operative weight. Infants also had longer aortic cross clamp (and trended toward longer CPB times). Of the patients undergoing ASO as infants, a VSD was present 92% (12 out of 13). Overall these data are consistent with our

institutions preference to perform ASO within the first week of life for standard risk patients. Patients with low birth weight and complicated intracardiac anatomy had delayed repair after a period of interval growth if they had a mechanism to keep the LV trained (such as an unrestrictive VSD).

It is unclear why neonates in the current study had abnormal pre-operative ventricular function as measured by STE. Pre-operative d-TGA patients in a previous study had normal pre-operative LV longitudinal strain [26]. It is possible that our echocardiograms were obtained in the setting of perinatal hypoxia and acidosis from a neonate during stabilization, and that repeat echocardiography obtained immediately pre-operatively would have shown improved ventricular function. LV “de-training” would be unlikely over this time period, as 97% (38/39) had the presence of either a VSD or a patent ductus arteriosus, which would expose the LV to systemic vascular resistance. Alternatively, STE was performed using different software packages and at different frame rates, which may account for the differences between studies. However, it is important to note that both studies showed worsened longitudinal strain after ASO.

Predictors of Post-operative LOS

Overall, pre-operative LV longitudinal strain correlated with post-operative LOS; however standard 2D measures of ventricular function did not. This correlation became stronger when we evaluated the infant separately from neonates. This suggests that infants who were identified as having normal function by standard 2D measures may indeed have had subclinical ventricular dysfunction that influenced the post-operative course. We suspect that subclinical ventricular function pre-operatively corresponds with worse cardiac output in the immediate post-operative period, requiring increased inotropic support, prolonging time to extubation, and delaying time until re-initiation of feeds, all of which prolong the post-operative LOS. This hypothesis should be investigated in future larger studies.

We did not find a correlation between pre-operative LV longitudinal strain and post-operative LOS in neonates undergoing ASO. This is not altogether surprising. There are multiple patient characteristics and perioperative factors that have been associated with the clinical course of patients undergoing ASO [4–9]. These factors appear to be stronger predictors of post-operative LOS compared to pre-operative myocardial deformation. Neonates also face unique post-operative considerations compared to infants including the development of feeding skills and family training that may play a significant role in post-operative LOS.

We have also shown that CPB time correlated with post-operative LOS, while operative age and weight inversely correlated with post-operative LOS. Unfortunately, the small sample size precluded multiple variable regressions, and therefore, identifying independent predictors of LOS was not feasible in this study.

Change in Ventricular Function After ASO

Overall LV function worsened after ASO when measured by LV ejection fraction and LV longitudinal strain. LV circumferential strain was unchanged. RV fractional area change improved while RV longitudinal strain worsened. This is consistent with previous studies

that have shown worsening biventricular function after undergoing CPB [26, 27]. Potential etiologies include CPB, changes in loading conditions, and myocardial ischemia–reperfusion. The RV seems particularly sensitive to CPB [21].

Implementation and Future Directions

STE is becoming more prevalent in the field of pediatric cardiology and congenital heart disease. It can easily be performed on standard echocardiographic views recommended as part of a complete pre-operative transthoracic echocardiogram [28]. If included in the pre-operative evaluation, it may help to risk stratify infants based on expected post-operative course and more accurately counsel families. As the correlation was strongest for infants, STE may have a role in the assessment of patients with delayed presentation for surgery. For example, in patients who undergoing a palliative surgery prior to the ASO, STE may be used to assess readiness or predict outcome after ASO. It is also worth noting that late ASO for TGA with IVS is not uncommon in countries with developing health systems; ASO may be useful to determine the degree of LV “training” prior to ASO in this setting. Further studies should evaluate the ability of STE to predict outcomes in patients undergoing ASO prospectively in a larger cohort.

Limitations

This was a retrospective study and by its nature could not establish causality. Our analysis required high quality echocardiographic images and complete studies. There was no defined echocardiogram protocol for pre-operative studies, and a thorough post-operative or “discharge” study only became standard later during our study period [29]. Anecdotally, many of the patients excluded from the study due to inadequate windows were from early during the study period, which may have affected results. Our definition of pre-operative and post-operative echocardiogram meant that there was some variability in the proximity of the echocardiogram to the operative date. This study type is susceptible to unmeasured confounders. The small sample size lacked the power to perform multiple variable regression analyses. The STE analysis was performed on DICOM images at 30 frames per second; potentially leading to underestimated strain values, though some studies purport the adequacy of these images in evaluating strain [22].

Conclusions

Pre-operative LV longitudinal strain correlates moderately with post-operative LOS in infants > 28 days undergoing ASO. LV longitudinal strain worsens after ASO. STE should be considered for inclusion in the standard pre-operative evaluation to help risk stratify patients prior to ASO, especially in patients undergoing late repair.

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Fig. 1.

Representation of STE with corresponding deformation curves: **a** analysis of LV longitudinal strain from apical four chamber view; **b** analysis of RV longitudinal strain from apical four chamber view; **c** analysis of LV circumferential strain from parasternal short-axis view

Fig. 2.

Neonates Pre-operative LV longitudinal strain on *x*-axis (more negative indicates better ventricular function), post-operative LOS on *y*-axis

Fig. 3.

Infants Pre-operative LV longitudinal strain on *x*-axis (more negative indicates better ventricular function), post-operative LOS on *y*-axis

Table 1

Patient characteristics

	Neonates (< 28 days) <i>n</i> = 39	Infants (> 28 days) <i>n</i> = 13	<i>p</i> Value
Male sex	22 (56%)	6 (46%)	
Operative weight (kg)	3.4 ± 0.4	5.3 ± 2.1	0.009
Height (cm)	50.2 ± 2.4	60.0 ± 9.1	0.003
Gestational age (weeks)	39 (38, 39)	39 (36, 39)	0.243
Birth weight (kg)	3.4 ± 0.5	2.7 ± 0.8	0.020
XCL time (min)	110 (94, 150)	156 (118, 175)	0.016
CPB time (min)	225 (197, 271)	261 (221, 288)	0.136
Days intubated	5 (3, 8)	2 (1, 11)	0.149
Post-op LOS (days)	15 (11, 21)	10 (6, 23)	0.133
Hospital LOS (days)	23 (19, 27)	10 (6, 49)	0.038
SBP (mmHg)	72 ± 10	88 ± 13	0.001
DBP (mmHg)	41 ± 9	53 ± 11	0.001
RV fractional area change	0.28 ± 0.06	0.30 ± 0.09	0.322
LV ejection fraction (%)	62 ± 8	63 ± 8	0.591
LV longitudinal strain	-14.5 (-16.6, -12.2)	-17.6 (-20.7, -15.3)	0.011
RV longitudinal strain	-14.5 ± 4.6	-14.9 ± 1.6	0.630
LV circumferential strain	-15.8 (-18.0, -14.6)	-19.8 (-21.4, -16.3)	0.024

Each value is expressed as mean ± SD or median (interquartile range)

XCL aortic cross clamp, CPB cardiopulmonary bypass, SBP systolic blood pressure, DBP diastolic blood pressure, RV right ventricle, LV left ventricle

Table 2

Change in non-invasive measures of function after ASO

	Pre-operative	Post-operative	<i>p</i> Value
SBP (mmHg)	76 ± 13	88 ± 15	0.001
DBP (mmHg)	42 (37, 50)	49 (42, 56)	0.059
EDV (mL)	10.0 (7.3, 12.7)	10.2 (7.8, 11.8)	0.703
RV fractional area change	0.28 ± 0.06	0.36 ± 0.09	0.001
LV ejection fraction (as %)	62 ± 8	58 ± 7	0.001
LV longitudinal strain	− 15.3 (− 18.3, − 13.1)	− 13.9 (− 16.1, − 12.6)	0.007
RV longitudinal strain	− 14.7 ± 4.2	− 12.4 ± 2.9	0.067
LV circumferential strain	− 17.1 (− 20.0, − 14.8)	− 16.8 (− 18.7, − 15.2)	0.648

Each value is expressed as mean ± SD or median (interquartile range)

EDV end diastolic volume, *RV* right ventricle, *LV* left ventricle