

Peri-operative changes in diastolic function and outcomes in congenital aortic valve surgery

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Abstract

Background: The ratio of early diastolic mitral inflow velocity (E) to early diastolic mitral annular tissue velocity (e'), or E/e', is an echocardiographic measure of left ventricular filling pressure. Peri-operative changes in E/e' and association with outcomes have been demonstrated in adults undergoing surgery for aortic stenosis (AS). We sought to explore changes in E/e' and other diastolic indices in the setting of congenital AS surgery and to assess for association with post-operative outcomes among children and young adults.

Methods: A retrospective, single-center study was performed among patients 6 months to 30 years of age who underwent congenital AS surgery from 2006 to 2018. Tissue Doppler indices were collected from pre- and post-operative echocardiograms. Post-operative outcomes were reviewed.

Results: Sixty-six subjects with subvalvar (45%), valvar (47%), and supra-valvar (8%) AS underwent surgery at a median age of 9.5 years (IQR: 4.0–14.8). Pre-operatively, the lateral E/e' ratio was 8.6 (6.7–11.0); 33% had E/e' ≥ 10. Post-operatively, the lateral e' decreased to 9.9 cm/s (8.0–11.4), the E/e' ratio increased to 10.4 (8.3–13.1); and 53% had E/e' ≥ 10 (*p*-values < 0.0001, 0.0072, and < 0.001, respectively). Pre-operative lateral e' correlated modestly with duration of intubation ($\rho = -0.24$, *p*-value 0.048) and post-operative lateral e' correlated modestly with duration of intubation and length of hospital stay ($\rho = -0.28$ and -0.26 , *p*-values = 0.02 and 0.04, respectively).

Conclusions: Children and young adults who underwent congenital AS surgery had echocardiographic evidence of diastolic dysfunction pre-operatively that worsened post-operatively. Lateral e' may be a sensitive indicator of impaired ventricular relaxation in these patients and may impact duration of intubation and hospital stay.

KEYWORDS

aortic valve, aortic valve, congenital heart disease, congenital heart surgery, echocardiography, left, repair, replacement, ventricle

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1 | INTRODUCTION

Patients with aortic stenosis (AS) are exposed to chronic pressure overload that may result in left ventricular (LV) remodeling, diastolic dysfunction, and elevated LV filling pressure. Echocardiographic indices of diastolic function have proven to have prognostic value in many disease states, including AS.¹⁻³ One specific tissue Doppler index, the ratio of early diastolic mitral inflow velocity (E) to early diastolic mitral annular tissue velocity (e'), or E/e' , serves as a validated non-invasive index of LV filling pressure⁴ and, importantly, is less impacted by variable loading conditions, including the presence of aortic valve disease.⁵ Adult studies have described the changes in pre- and post-operative E/e' and shown associations between pre- and post-operative E/e' and post-operative clinical outcomes, including mortality, in those undergoing aortic valve replacement.^{6,7}

Children and young adults undergoing congenital aortic valve surgery have a range of post-operative clinical outcomes.^{8,9} While E/e' and other tissue Doppler indices have been shown to correlate with LV filling pressures in pediatric patients,¹⁰ the peri-operative changes in these measures have not been well-described. Moreover, the utility of these measures in assessing operative risk and post-operative outcomes in the setting of congenital aortic valve surgery has not been evaluated. Therefore, we sought (1) to describe the changes in E/e' and other diastolic indices by echocardiography among children and young adults undergoing congenital aortic valve surgery; and (2) to assess whether pre- or post-operative E/e' may serve as a non-invasive marker for early post-operative outcomes, including duration of intubation and hospital stay.

2 | PATIENTS AND METHODS

We performed a retrospective study of children and young adults between the ages of 6 months and 30 years who underwent surgery for congenital AS at Morgan Stanley Children's Hospital and Milstein Hospital of Columbia University Irving Medical Center from 2006 to 2018. Patients with primary diagnoses of subvalvar, valvar, and/or supra-valvar AS were abstracted from our congenital cardiac surgical database. Since it is not uncommon for congenital patients with obstructive aortic lesions to have mixed disease, those with a secondary diagnosis of aortic insufficiency (AI) at the time of surgical intervention were included. Similarly, given that a substantial number of patients with congenital valvar AS undergo balloon aortic valvuloplasty as an initial intervention, these patients were also included if the primary indication for surgical re-intervention was AS. Patients were excluded if they had (1) concomitant complex congenital heart disease (including hemodynamically significant ventricular septal defect and more than mild mitral stenosis or regurgitation), (2) prior surgical aortic valve intervention, or (3) insufficient tissue Doppler imaging available. This study was approved by the Institutional Review Board with a waiver of informed consent.

Demographic, clinical, and echocardiographic data were collected for each patient. Demographic and clinical variables included age,

gender, presence of a genetic syndrome, prior aortic valve interventions, primary surgery type, and cardiopulmonary bypass time. Complete pre-operative echocardiograms within 3 months prior to the operation and post-operative echocardiograms within 14 days after the operation and prior to discharge were reviewed. The severity of AS, presence of AI, and aortic valve morphology were noted. LV size, hypertrophy, and function were assessed both qualitatively and quantitatively, measured by M-mode and shortening fraction (SF). Early (E) and late (A) mitral inflow velocities were measured from the standard apical four-chamber view. Tissue Doppler imaging was reviewed, and the following measurements were also performed from the standard apical four-chamber view: septal e' , lateral e' , isovolumic relaxation time (IVRT), mitral valve inflow time (MVIT), and deceleration time. The septal and lateral E/e' ratios were determined, and a lateral E/e' ratio ≥ 10 was characterized as abnormal. Age-based E, E/A, septal and lateral e' and E/e' z-scores were derived using the Boston Z-score calculator.^{11,12}

The primary post-operative outcome measures were duration of intubation and length of hospital stay. Given the known low operative mortality in children and young adults undergoing congenital aortic valve surgery, mortality was noted but not included as an outcome measure.

Data are presented as median (inter-quartile range) or frequency (%) where appropriate. Non-parametric analyses were employed. To assess the changes in pre- to post-operative E, E/A, septal and lateral e' and E/e' , IVRT, MVIT, and deceleration time, the Wilcoxon signed-rank test was used. Comparisons between these indices and post-operative outcomes (duration of intubation and length of hospital stay) were performed using Spearman's rho and Wilcoxon rank-sum. A p -value < 0.05 was considered statistically significant. Analyses were performed with Stata (College Station, TX, USA).

3 | RESULTS

Sixty-six patients met inclusion criteria at a median age of 9.5 years (4.0–14.8). As demonstrated in Table 1, most were male ($n = 47$ or 71%). Patients underwent surgery for subvalvar ($n = 30$, 45%), valvar ($n = 31$, 47%), or supra-valvar ($n = 5$, 8%) AS; six patients had relief of multi-level AS. The most common primary surgeries performed included subaortic membrane resection ($n = 30$, 45%), Ross with or without Konno procedure ($n = 20$, 31%), supra-valvar AS repair ($n = 8$, 12%), and aortic valve replacement ($n = 4$, 6%). A small group of patients required secondary interventions including VSD closure ($n = 2$, 3%), mitral valve intervention ($n = 2$, 3%), and coarctation repair ($n = 1$, 2%). Median cardiopulmonary bypass time was 96.0 minutes (51.8–139.0).

The pre-operative echocardiograms were performed at a median of 7 days (4.4–15.9) prior to surgery. As demonstrated in Table 2, most patients had moderate ($n = 31$, 47%), moderate to severe ($n = 8$, 12%), or severe ($n = 18$, 27%) AS, with median peak and mean gradients of 65.0 mm Hg (50.0–78.4) and 34.5 mm Hg (25.5–44.0), respectively. Most patients had LV hypertrophy ($n = 46$, 70%) and no or mild LV dilation ($n = 49$, 74%), consistent with a primary diagnosis of AS. Most

TABLE 1 Patient characteristics (n = 66)

	Median or n	IQR or % ^a
Age (years)	9.5	4.0–14.8
Weight (kg)	31.9	17.0–59.9
Height (cm)	133	100.3–160.4
Gender		
Male	47	71.2
Female	19	28.8
Presence of genetic syndrome	7	10.6
Primary type of aortic stenosis		
Subvalvar	30	45.5
Valvar	31	46.9
Supravalvar	5	7.6
Prior intervention	27	40.9
Balloon aortic valvuloplasty	21	31.8
Coarctation repair or stent	8	13.6
Primary surgery		
Subaortic membrane resection	30	45.5
Aortic valve repair	1	1.5
Aortic valve replacement	4	6.1
Ross +/- Konno	20	30.3
Ozaki	2	3.0
Bentall	1	1.5
Supravalvar repair	8	12.1

^aAll percentages represent the proportion of the entire study population.

had qualitatively normal to hyperdynamic LV systolic function (n = 63, 95%); the median SF was 43.2% (38.4–46.6).

The pre- and post-operative diastolic findings are displayed in Table 3. Pre-operatively, subjects demonstrated mild diastolic dysfunction. The median medial e' and lateral e' z-scores of –1.5 and –1.8, respectively, were relatively low, and the median medial and lateral E/e' z-scores were slightly higher than age-based norms with z-scores of +2.3 and +2.0, respectively. One-third of patients (n = 22) had lateral E/e' ≥10.

The post-operative echocardiograms were performed at a median of 3 days (2.6–4.0) after surgery. The medial and lateral e' and e' z-scores decreased significantly, and the lateral E/e' increased from a median of 8.6 pre-operatively to 10.4 post-operatively (p = 0.007); see Table 3 and Figure 1. Similarly, the proportion of patients with lateral E/e' ≥10 rose from 33% to 53% (p < 0.001). MVIT shortened from a median of 332.8 msec pre-operatively to 223.5 msec post-operatively (p-value < 0.0001). There was no significant pre- to post-operative change in median E, E/A, IVRT, or deceleration time.

Most (n = 41, 62%) were extubated on post-operative day 0 (0.0–1.0) and only one-third required inotropic support for a median duration of 0 days (0.0–1.0). The median length of hospital stay was 4.0 days (3.0–5.8). There was no early mortality. A lower pre-operative lateral e' (ρ = –.24, p-value 0.048), shorter pre-operative MVIT (ρ = –.27, p-value 0.03), and shorter deceleration time (ρ = –0.25, p-value 0.047)

TABLE 2 Pre-operative echocardiographic findings (n = 66)

	Median or n	IQR or %
Time to echocardiogram (days)	7.0	4.4–15.9
Aortic stenosis		
None	0	0
Mild	7	10.6
Mild-moderate	2	3.0
Moderate	31	47.0
Moderate-severe	8	12.1
Severe	18	27.3
Peak gradient (mm Hg)	65.0	50.0–78.4
Mean gradient (mm Hg)	34.5	25.5–44.0
Aortic insufficiency		
None	20	30.3
Mild	22	33.3
Mild-moderate	3	4.5
Moderate	5	7.6
Moderate-severe	9	13.6
Severe	7	10.6
LV systolic function		
Normal	55	83.3
Hyperdynamic	8	12.1
Mildly decreased	1	1.5
Moderately decreased	1	1.5
Severely decreased	1	1.5
Shortening fraction (%)	43.2	38.4–46.6
LV hypertrophy		
None	20	30.3
Mild	24	36.4
Mild-moderate	10	15.2
Moderate	9	13.6
Moderate-severe	1	1.5
Severe	2	3.0
LV dilation		
None	41	62.1
Mild	8	12.1
Mild-Moderate	2	3.0
Moderate	6	9.1
Moderate-Severe	2	3.0
Severe	7	10.6
Aortic valve morphology		
Tricuspid	42	63.6
Bicuspid	23	34.8
Unicuspid	1	1.5

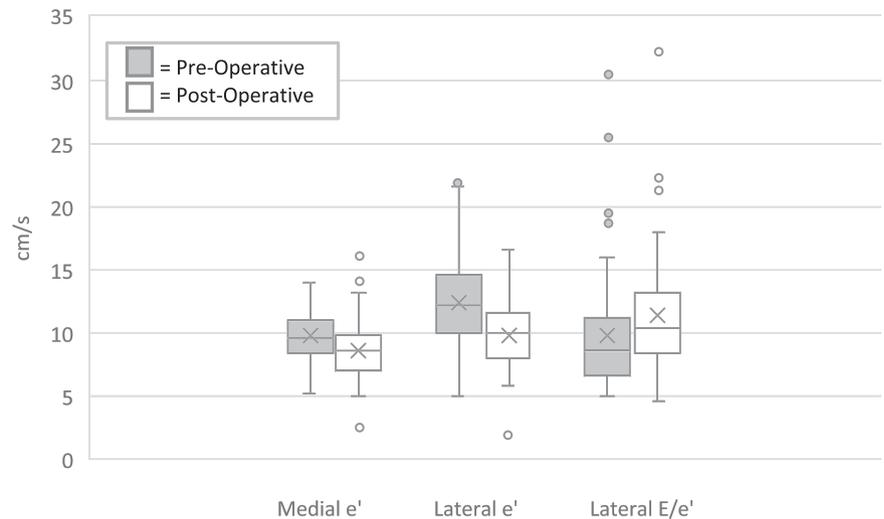
Abbreviations: LV, left ventricle; LVOT, left ventricular outflow tract.

TABLE 3 Pre- and post-operative tissue doppler indices (n = 66)

	Pre-operative		Post-operative		p-value
	Median or n	IQR or %	Median or n	IQR or %	
E (cm/s)	108.0	92.9 - 121.8	99.1	85.8 - 118.5	0.073
E z-score	+0.9	0.0 - +1.7	+0.4	-0.2 - +1.5	0.11
E/A	1.7	1.4 - 2.0	1.6	1.1 - 2.1	0.36
E/A z-score	-0.7	-0.1 - -1.1	-0.9	-0.2 - -1.4	0.35
Medial e' (cm/s)	9.6	8.4 - 11.0	8.6	7.0 - 9.7	0.0003
Medial e' z-score	-1.5	-0.7 - -2.4	-2.2	-1.3 - -3.0	0.0002
Medial E/e'	11.3	8.9 - 12.9	11.8	9.2 - 14.8	0.12
Medial E/e' z-score	2.3	+1.0 - +3.4	2.6	+1.0 - +4.7	0.11
Lateral e' (cm/s)	12.1	10.0 - 14.4	9.9	8.0 - 11.4	<0.0001
Lateral e' z-score	-1.8	-0.9 - -2.8	-2.5	-1.8 - -3.4	<0.0001
Lateral E/e'	8.6	6.7 - 11.0	10.4	8.3 - 13.1	0.0072
Lateral E/e' z-score	+2.0	+0.8 - +3.6	+3.0	+1.8 - +4.9	0.0074
Lateral E/e' ≥ 10	22	33	35	53%	<0.001
IVRT (msec)	70.4	63.4 - 88.0	71.3	56.3 - 84.5	0.63
MVIT (msec)	332.8	241.0 - 421.6	223.5	179.6 - 288.5	<0.0001
Deceleration time (msec)	137.3	119.0 - 181.6	140.4	115.1 - 167.2	0.10

Abbreviations: A, Late diastolic (atrial) mitral inflow velocity; E, early diastolic mitral inflow velocity; e', early diastolic mitral annular tissue velocity; IVRT, isovolumic relaxation time; MVIT, mitral valve inflow time.

FIGURE 1 Peri-operative change in tissue Doppler indices. The box-whisker plot demonstrates worsening of the medial and lateral e' velocities (centimeters/sec) and the lateral E/e' ratio following congenital aortic valve surgery. E = early diastolic mitral inflow velocity, e' = early diastolic mitral annular tissue velocity



correlated modestly with longer duration of intubation. A lower post-operative lateral e' correlated modestly with both longer duration of intubation ($\rho = -0.28$, p -value 0.02) and length of hospital stay ($\rho = -0.26$, p -value 0.04). A shorter post-operative deceleration time also correlated modestly with longer duration of intubation ($\rho = -0.31$, p -value 0.01) and length of hospital stay ($\rho = -0.26$, p -value 0.03).

4 | DISCUSSION

In this series of children and young adults undergoing congenital aortic valve surgery, the majority had at least mild left ventricular hypertro-

phy pre-operatively and one-third had evidence of diastolic dysfunction by the lateral E/e' ratio. Peri-operatively, various indices of diastolic dysfunction worsened, including the absolute and age-normalized medial and lateral e' measurements, and over half developed abnormal E/e' ratios. There were modest but significant correlations of worse pre- and post-operative indices of diastolic function with longer duration of intubation and length of hospital stay, including the lateral e' measurement, MVIT, and deceleration time.

Patients with congenital AS are at risk of developing diastolic dysfunction secondary to chronic pressure overload on the LV and compensatory development of LV remodeling. LV diastolic dysfunction is routinely assessed by echocardiogram with tissue Doppler

imaging,¹³ which measures low-velocity, high-amplitude velocities of the myocardium. These are typically performed at the medial (septal) and lateral aspects of the mitral valve. The ratio of early diastolic mitral inflow velocity (E) to early diastolic mitral annular tissue velocity (e'), or E/e' , has emerged as a surrogate measure of LV filling pressure. Many studies have correlated E/e' with invasive measurement of LV filling pressure, including a 2017 European multi-center study that demonstrated E/e' , among other echo indices, to be independently associated with invasive LV end-diastolic pressure (LVEDP).^{14–18} Ommen *et al.* demonstrated that in adult patients, E/e' values < 8 and > 15 accurately predicted normal and elevated mean LV diastolic pressure, respectively, with wide variability in those with E/e' between 8 and 15.⁴ However, Friedman *et al.* went on to show that in children and young adults with AS, lateral $E/e' > 9.5$ accurately predicted an LVEDP ≥ 15 mm Hg.¹⁹

As a reliable surrogate of LV filling pressure, E/e' has been studied as a clinical and operative prognosticator. In the adult literature, E/e' has been shown to be predictive of survival and reduced exercise capacity after acute myocardial infarction, decreased ventricular function and mortality after off-pump coronary artery surgery, morbidity and mortality in patients with congestive heart failure, primary cardiac events in hypertensive patients, and mortality in end-stage renal disease.^{20–27} Specific to AS, E/e' has been used to assess risk in unrepaired adult patients, including the development of symptoms and event-free survival.^{28–30} In those undergoing aortic valve replacement, both pre- and post-operative E/e' have been shown to be associated with post-operative morbidity, including heart failure and acute kidney injury (AKI), and mortality.^{1,6,7}

This study is the first, to our knowledge, in the pediatric literature to describe the changes in tissue Doppler measurements in the setting of congenital aortic valve surgery and to assess the association with early post-operative outcomes. Eidem *et al.* previously showed that children with unrepaired AS have significantly increased medial and lateral E/e' ratios when compared to healthy controls.³¹ Our results support this finding, demonstrating baseline elevations in both the absolute pre-operative lateral E/e' and the age-normalized z-scores. Both the medial and lateral e' and e' z-scores decreased significantly in the peri-operative period, resulting in a further increase in lateral E/e' and the associated z-scores. Interestingly, the E and E/A did not change significantly, suggesting that tissue Doppler imaging may have a greater sensitivity to detect changes in diastolic dysfunction peri-operatively.

In our series, a lower pre-operative e' , shorter pre-operative MVIT, and shorter pre-operative deceleration time correlated modestly with longer duration of intubation, while a lower post-operative e' and shorter post-operative deceleration time correlated modestly with both longer duration of intubation and length of hospital stay. Although deceleration time was associated with pre- and post-operative outcomes, it did not significantly change peri-operatively. E/e' was not associated with short-term post-operative outcomes, presumably because E did not change significantly as previously mentioned. This suggests that the absolute e' value, in particular, may be a more sensitive and clinically relevant indicator of impaired relaxation and recov-

ery following congenital aortic valve surgery in children and young adults.

Evidence of diastolic dysfunction on echocardiogram may be partly attributable to the surgery itself, as several studies have shown associations between cardiopulmonary bypass and aortic cross-clamp times with reductions in tissue Doppler velocities.^{32–34} Cardiopulmonary bypass and cross-clamping are known to induce myocardial injury. In addition to direct injury, there is a well-described systemic inflammatory response associated with exposure to exogenous materials, which exacerbates endothelial dysfunction. Cellular ischemia also occurs, which results in the depletion of high-energy phosphates, increases of intra-cellular calcium stores, and build-up of toxic metabolites.^{35,36} Reperfusion injury adds to this insult. Patients with pre-operative diastolic dysfunction may be both more susceptible to this injury and/or slower to recover.

Vassalos *et al.* demonstrated recovery of pre-operative LV peak systolic velocities by tissue Doppler by 15 hours after cardiac surgery in most children, suggesting that abnormal measurements beyond this time more likely represent true abnormalities. In this same study, reduced pre- and post-operative LV systolic velocities were associated with longer duration of intubation.³ Similarly, Nam *et al.* showed that among adults undergoing cardiac surgery, post-operative lateral $E/e' > 15$ was independently associated with post-operative AKI and mortality at 1 and 5 years. The authors proposed that, in addition to underlying diastolic dysfunction, elevated peri- and post-operative LV filling pressure may be indicative of more significant hemodynamic instability, resulting in an increased risk of post-operative complications. They went on to show that 92.4% of patients with elevated E/e' measured within 10 post-operative days continued to have abnormal values at 1 year, suggesting prolonged disturbances in diastolic dysfunction.⁷ Together, these studies and ours suggest that LV tissue Doppler indices may have prognostic value in determining both short-term and long-term post-operative outcomes.

There were several limitations to our study. Although we included patients with a primary diagnosis of AS, there was heterogeneity in the level of AS and the degree of AI. The LV, however, is likely exposed to similar conditions regardless of the type of outflow obstruction. Moreover, the appearance of the LV pre-operatively in our cohort—predominantly hypertrophied and not significantly dilated—supports our inclusion of patients with primary AS. Given the retrospective nature of the study, a minority of subjects could not be included due to lack of tissue Doppler acquisition. We chose to focus on indices of diastolic function measured by tissue Doppler and, therefore, did not examine other parameters, such as left atrial volume. Most importantly, our single-center study was performed at a large academic medical center in which our subjects had very favorable post-operative outcomes. Because of the short duration of intubation and length of hospital stay, there was limited ability to detect marked associations between diastolic indices and outcomes. That being said, there were significant peri-operative changes and associations noted that suggest that tissue Doppler indices may be useful prognosticators in children, as they are in adults. Long-term follow-up to assess for serial changes in diastolic indices and their relationship to symptoms and outcomes

in a multi-center cohort of children and young adults may prove to be quite informative.

Ultimately, the goal of aortic valve surgery is to prevent irreversible LV changes and long-term diastolic dysfunction.³⁷ The early presence of diastolic dysfunction in children and young adults may impact the decision regarding timing of intervention or impact risk-stratification with regard to post-operative care. In our study, we found that the lateral e' measurement may be the most sensitive indicator of not only peri-operative changes in diastolic function but also impaired relaxation and recovery following congenital aortic valve surgery. Moving forward, a multi-center, collaborative approach would be worthwhile to elucidate the utility of this measurement and its relationship to both short- and long-term outcomes.

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