Impact of right ventricular geometry and left ventricular hypertrophy on right ventricular mechanics and clinical outcomes in hypoplastic left heart syndrome

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Abstract

Background: Right ventricular (RV) function is a major determinant of survival in hypoplastic left heart syndrome (HLHS). However, the relation of RV geometry to myocardial mechanics, and their relation to transplant-free survival are incompletely characterized.

Methods: We retrospectively studied 48 HLHS patients from the Hospital for Sick Children, Toronto, aged 2.2 IQR 3.62 years at different surgical stages. Patients were grouped by the presence (n=23) or absence (n=25) of RV "apical bulging" defined as a sigmoid shaped septum with the RV leftward apical segment contiguous with the LV lateral wall. Regional and global RV strain were measured using speckle-tracking echocardiography and regional strains analyzed for patterns and peak values. These were compared between HLHS anatomical sub-types and between patients with versus without apical bulging. We further investigated the association between RV geometry and dysfunction with the outcomes of heart-failure, death or transplant.

Results: RV global (-7.3±2.8 vs. -11.2±4.4%; *p*=0.001), basal septal (-3.8± 3.2 vs. -11.4 ± 5.8 %; *p=0.0001*) and apical-lateral (-5.1± 3.5 vs. -8.0 ± 5.8 %, *p=0.001*) longitudinal strain were lower in patients with versus without apical bulging, respectively. Apical bulging was equally prevalent in all HLHS anatomical variants. Twenty of 22 (91%) patients with apical

bulging displayed hypertrophy of the LV apical and lateral segments. Death or transplantation were approximately equal in both groups but related to reduced RV global strain in patients with (7/7), and not in those without apical bulging (2/8) (p= 0.022).

Conclusion: These results suggest that the finding of apical bulging is related to the presence of a hypertrophied hypoplastic LV, with a negative impact on regional and global RV function. Therefore, analysis of RV and LV geometry and mechanics may aid in assessment and prognostication of this high-risk population.

Key words: congenital heart disease; hypoplastic left heart syndrome; ventricular function; outcome

Bullet-points:

1. "apical bulging" describes a specific phenotype in HLHS patients
2. Apical bulging is consistent with lateral hypertrophy of the residual left ventricle.
3. Regional dysfunction is pronounced compared to the non-bulging phenotype.
4. Low transplant-free survival in reduced RV function in presence of apical bulging.

Abbreviations:

CPD: classic pattern dyssynchrony

FAC: fractional area change

HLHS: hypoplastic left heart syndrome

LV: left ventricle

RV: right ventricle

TR: tricuspid regurgitation

Introduction

Despite improvements in clinical care, morbidity and mortality remain high in children with hypoplastic left heart syndrome (HLHS) [1-4]. Surgical palliation typically occurs over the early years of childhood in 3 stages: Stage 1 (Norwood operation) consisting of aortic reconstruction, resection of the interatrial septum and placement of a systemic-pulmonary or right-ventricle (RV)- pulmonary shunt; Stage 2 surgery consisting of a bidirectional superior vena cava-pulmonary artery connection and Stage 3 consisting of the Fontan operation (inferior vena cava to pulmonary connection. RV dysfunction, tricuspid regurgitation (TR) and the size and hypertrophy of the hypoplastic left ventricle (LV) have been identified as important risk-factors for adverse outcomes in HLHS [2, 5-7]. Moreover, it has been proposed that certain anatomic variants, especially mitral stenosis with aortic atresia, or the presence of septal hypertrophy have worse outcomes [8, 9]. Thus, RV and LV factors, both of which affect RV geometry, may impact outcomes. In the normal heart, the RV has a complex shape [10], and interacts in an intimate fashion with the LV. In patients with HLHS, this interaction is affected by the absence of a normal LV, which influences RV geometry and mechanics and impacts normal ventricular interdependence [11].

Several studies have utilized strain imaging for assessment of regional and global function in HLHS [12-16] and to define adverse mechanics which may affect RV function. These studies have consistently shown reduced regional basal septal strain and strain rates across the surgical stages of single-ventricle palliation [13, 17-20]; while other studies have suggested that RV function is affected by LV size and hypertrophy [7, 19]. However, the impact of abnormal LV and RV geometry, and their impact on RV efficiency and function remain incompletely understood.

Accordingly, we sought to determine patterns of regional RV strain in patients with HLHS, and to investigate their association with RV geometry, anatomical HLHS variants and the clinical outcomes of heart failure, heart transplantation or death.

Methods

The institutional research ethics board approved this study with waiver of informed consent. We retrospectively identified children from the Hospital for Sick Children in Toronto with HLHS from our institutional database between 2008 and 2010 [12]. For this study, 'classic' HLHS was defined as usual atrial arrangement, atrioventricular and ventricular-arterial concordance and a LV deemed too small to support the systemic circulation leading to single-ventricle palliation [21]. Patients at all stages of surgical palliation were included if clinically stable at echocardiography. The clinical outcomes of need for heart failure medications, transplantation or death were recorded from the medical records.

Two-Dimensional Echocardiography

We retrospectively analyzed the last available complete echocardiogram in order to include a maximal number of patients with restituted volume-load. Anatomic subtype was recorded as mitral stenosis with aortic atresia, mitral stenosis with aortic stenosis, or mitral atresia with aortic atresia. TR severity was determined by the vena contracta width (summation of jets if more than one) and classified as none or trivial, mild or moderate to severe. Based on the Pediatric Heart Network Single Ventricle Reconstruction trial, a vena contracta width of ≤ 2.5 mm indicated mild TR and a vena contract width > 2.5 mm indicated moderate or severe TR [22]. RV function was assessed in an apical 4-chamber equivalent view by the RV fractional area change (FAC; [end-diastolic area-end-systolic area]/end-diastolic area) [23].

Assessment of segmental and global endocardial longitudinal strain

Longitudinal strain was analyzed using Digital Imaging and Communications in Medicine (DICOM)–format grayscale images by vector velocity imaging (TomTec Imaging Systems GmBH, Unterschleissheim, Germany) (**Figure 1**). The endocardium was manually traced in an apical four-chamber equivalent view, and adequate tracking was ensured throughout the cardiac cycle. Strain curves of 6 segments were displayed including the basal, medial and apical walls of the rightward lateral RV wall and the apical, medial and basal segments of the leftward lateral wall. When a LV was present, the

endocardial line followed the RV side of the septum. Segments were defined by equal lengths along the endocardial line from base to apex as automatically defined by the software. Peak systolic strain values were expressed as the highest peak during systole as either a peak positive or peak negative strain-value. "Global strain" was defined as the average of peak-systolic strain-values of the six segments. Due to the lack of normal-values for HLHS patients, we defined hypokinesia according to previous strain-measurements in patients with Fontan-surgery, as peak longitudinal strain values > (weaker than) -8% as hypokinetic [24]**.** Based on previous studies on patients with transmural myocardial scar tissue values > (weaker than) -4% were defined as akinetic [25]. Positive strain was defined when the absolute systolic value of a positive excursion of the strain curve was higher than the absolute value of a negative excursion.

Figure 1 displays different strain-patterns corresponding to dyssynchrony and different degrees of reduced contractility represented by reduced systolic myocardial shortening. Strain curves were assessed to be normal (Panel A) when peak strain and activation was simultaneous with peak-strain values <-8%, indicating normokinesia. According to previously established inter-segmental patterns [15], we evaluated for characteristic mechanical signs of early regional activation leading to "classic pattern dyssynchrony" (CPD) (Panel C) as manifested by an early systolic "flash" followed by a systolic rebound stretch of that segment at the time-point of late systolic shortening of the opposing wall [15, 26, 27]. Not classified as CPD was "delayed mechanical activation", defined as systolic stretch in one segment compared to early contraction of the opposing segments but without rebound stretch of the early activated segments (Panel D). "Mechanical dispersion" was assessed visually by non-simultaneous time to peak strain between several segments (Figure 1, panel B and C).

<u>RV and LV geometry</u>

All geometrical measurements were derived from the end-diastolic and end-systolic apical four-chamber view equivalent images. To quantify RV and LV geometry, the septal length and RV length were measured. RV length was measured from the center of the tricuspid annular plane to the RV apex, and the ratio of septal/RV length calculated. LV area was

measured at end-diastole including the myocardium of the septum and lateral wall. RV/LV area ratio was derived from the endocardial contour of the RV and LV cavities. LV myocardial area was used as a measure for myocardial mass of the residual LV and calculated from the difference of the (total) LV area minus the LV cavity area. Additionally, LV septal or apico-lateral hypertrophy was defined by visual assessment when the walls exceeded 1.5 times the maximal RV wall thickness. As shown in **Figure 2**, apical bulging was defined as a sigmoid shaped septum with the left lateral RV apical segment contiguous with the LV lateral wall and not with the septum. In these hearts, from the coronal/ apical 4-chamber view the septum is in a more horizontal position and the RV appears kidney like shaped. Hearts without apical bulging displayed either a flat septum when the septal length was >25% of the RV length with more ellipsoid-shape or a spherically shaped RV with a diminutive LV when the septal length measured <25% of the RV length.

Statistical Analysis

Data are displayed as mean ± SD for normally distributed variables or as medians with interquartile ranges. Fisher`s exact test was used for nominal dichotomous variables and the Chi Square test for frequencies of non-dichotomous nominal variables. Differences between continuous measures between groups or between anatomical variants were analyzed with Analysis of Variance (ANOVA). Post-hoc analysis testing the mean of one group against the mean of all other groups, was calculated for groups with at least 9 patients. *p*- values < 0.05 were considered statistically significant. For interobserver variability, using the same cardiac cycle, two independent observers drew new regions of interest.

Reproducibility

For the assessment of intra- and inter-observer variability, regions of interest were redrawn using the same DICOM loop. Intra-observer reliability was analyzed at least 1 month after the original measurements, blinded to previous results. For inter-observer reliability, observers were blinded to the other observer's analysis. Reproducibility of strain measurements was assessed using intraclass correlation coefficients of variation on data from 10 randomly selected patients.

Results

Forty-eight infants and children with HLHS (median age 0.75 years, range 0 - 14 years; interquartile range (IQR) 3.62 years; mean 2.2 years) were retrospectively analyzed. **Table 1** shows their clinical characteristics, prevalence and severity of TR and different anatomical variants of HLHS separately for apical bulging vs. non-apical bulging. There was no significant difference in clinical parameters between these groups. All patients underwent a BT shunt or hybrid procedure and no patients underwent a RV-PA conduit at stage 1. Apical bulging seems not to be associated with a certain type of anatomical variant. In addition to the last echocardiography included into the study, two to three repeated echocardiograms over 1-3 years were available in 12 children at different surgical states. Five out of 12 children displayed apical bulging and 7 did not. During this time the presence or absence of apical bulging did not change for any of the patients.

RV and LV geometry

Of 48 patients, 23 patients displayed apical bulging (**Figure 2,** Panel B), while 25 patients displayed no RV apical bulging with either a small residual or virtually absent LV (**Figure 2,** Panel A) or a flat septum (**Figure 2,** Panel C). **Table 2** describes the differences in RV and LV geometry and function. RVs without apical bulging displayed smaller septal/RV length, shorter septal length, smaller LV total area (cavity + myocardium) and a smaller LV/RV area ratio. **Table 2** also demonstrates that LV lateral-apical hypertrophy was associated with the presence of RV apical bulging, while septal hypertrophy was only seen in half of this group. All patients with apical bulging had either LV lateral-apical or septal hypertrophy. Apico-lateral hypertrophy was present in only three patients without apical bulging, all with a relatively sizeable LV and flat septum. One of these patients had a diminutive LV cavity with a flat basal septum and mild sigmoid curvature towards the apex. The LV myocardial area in patients with apical bulging was significantly larger compared to patients without apical bulging. Apical bulging with LV lateral-apical hypertrophy were evenly distributed across all anatomical variants. Septal hypertrophy was only seen in patients with mitral stenosis and in one out of four patients with aortic atresia.

Segmental function

Table 2 and Figure 3 illustrate differences in global and regional segmental function between patients with the presence versus absence of apical bulging. Patients with apical bulging showed highest strain in the "bulging" RV left apical segment and RV basal lateral wall, significantly reduced strain of the basal septum and RV apical right lateral wall and overall significantly reduced RV global strain. Patients without apical bulging showed more homogenous strain values, fewer abnormal strain patterns and less variation in strain patterns among segments. Patients with apical bulging had a higher proportion of akinetic and hypokinetic segments. Hypokinesia was present in the majority of hearts with apical bulging and a high percentage of these hearts displayed segments with positive strain (systolic stretch), reflecting inefficient myocardial contraction. In contrast, patients without apical bulging showed a more homogeneous contraction pattern, less hypokinetic segments, less stretched segments and overall better RV global strain.

Strain-patterns and signs of dyssynchrony

Next, we assessed all regional strain curves for inefficient contraction patterns including classic pattern dyssynchrony and/ or delayed onset of shortening. Delayed onset of shortening with normal peak segmental strain, as displayed in **Figure 1** panel D, was observed in 4/48 (8%) hearts. Classic pattern dyssynchrony (**Figure 1,** panel C) was not observed in any of the patients. Time-to peak strain within the 6 segmental strain-curves was visually assessed to display mechanical dispersion **(Figure 1*)** in 43/48 hearts (90%).

Regional RV mechanics and outcomes

Figure 4 compares the presence of transplant or death in patients with and without apical bulging in relation to the global RV strain-value. As opposed to patients without apical bulging, patients with apical bulging displayed lower strain when heart-failure medication was applied and RV strain decreased further in patients who experienced transplant or death.

Here, RV dysfunction with global strain > (weaker than) -8% was present in all 7 patients in the apical bulging group, significantly higher (p= 0.022) compared to 2/8 patients without apical bulging.

Table 3 illustrates the distribution of patients with reduced RV strain and TR in relation to heart-failure, and the outcome of transplantation or death; comparing patients with versus without apical bulging. In the apical bulging vs. non-bulging groups 5/7 vs 5/8 patients experienced death or transplant before completion of Stage 2 operation, respectively. Of the three transplanted patients with apical bulging, two had TR and reduced RV function and one had reduced RV function. One of the two transplanted patients without apical bulging had moderate to severe TR and none showed reduced RV function. In all patients, death or transplant was experienced in patients with apical bulging and severely reduced RV function, while death or transplant in the group without apical bulging was associated with different reasons including 2/8 patients with reduced RV function, 4/8 patients with TR and good RV function and 2/8 patients without TR and good RV function who died out of hospital from unascertained causes. The time-interval between death or transplant and the study-echocardiogram was recorded in 9 of 15 patients. Among the patients who died, the interval was 0; 0; and 17 months vs. 0; 3 and 4 months in the non-bulging vs. apical bulging group, respectively. The interval in the transplanted patients was 24 months in the non-bulging group vs. 0 and 2 months in the apical bulging group. After stage 1 operation, 6-18 months after the previous examination, patients with apical bulging showed a tendency to worsening global longitudinal strain with a reduction by +1.6 ±3.4%; vs. -3.5 ±7.5% (N.S.) increase in strain in the non-apical bulging group. Among patients experiencing death or transplant, 3 of those with repeat studies showed further reduced strains by +3.6 ±2.7%, while patients without apical bulging tended to have improved (more negative) strain by -6.9 ± 8.8% (N.S.).

Reproducibility: Intra-observer and inter-observer agreement for segmental strain were good, with intra-class correlation coefficients of 0.85 and 0.82, respectively

Discussion

The major findings of the study are: definition of an “apical bulging” HLHS phenotype which is related to apico-lateral hypertrophy of the hypoplastic left ventricle. 2. The association of this phenotype with more pronounced regional dysfunction and lower global RV strain compared with the non-apical bulging phenotype. 3. Transplant or death were related to reduced RV function in the apical bulging group.

Interpretation of the findings

The visual assessment of strain-curves showed predominantly non-simultaneous time-to peak values [12, 13, 17-20]. However, this “mechanical dispersion” was not related to CPD (**Figure 1,** panel C) as typical mechanical manifestation of electro-mechanical dyssynchrony [15, 26, 27]. As CPD or other types of delayed electrical activation with non-simultaneous peak-strains were not identified in any patient in this cohort, the observed regional functional inhomogeneity more likely reflects differences in contractile function or differences in regional wall stress perhaps due to the differing geometry. Our results are consistent with other HLHS studies which described reduced strain in the basal septum [13, 17-20]. Petko et al. suggested that this phenomenon may be associated with hypertrophy of the hypoplastic LV [19]. The current study shows that “apical bulging” was associated with reduced basal septal function. The current study shows that “apical bulging” was associated with reduced basal septal function. In these patients, septal mechanics seemed to be related to apical and lateral hypertrophy of the hypoplastic left ventricle, while septal hypertrophy was only seen in 50% of patients. Systolic stretching and absence of septal hypertrophy in the otherwise hypertrophied LV may occur due to isovolumetric contraction with pressure-generation and shortening of the (hypertrophied) lateral wall. Ventricles without apical bulging, and a flat septum, had neither septal nor apico-lateral hypertrophy of the hypoplastic LV, consistent with unrestrictive systolic volume shift (i.e. by mitral regurgitation or VSD), and LV deformation contributing to RV function. Overall, our results suggest that a hypertrophied, isovolumetrically contracting hypoplastic LV may negatively impact mechanical RV function.

Interestingly, in the RV, not only the basal septum, which in part reflects the function of the residual hypoplastic LV, but also the apical rightward (i.e. "free wall") segment shows similarly reduced deformation. Reduced contractile properties or increased afterload of this segment with flattened curvature might be possible explanations [28]. The more horizontal orientation of this segment in ventricles with an apical bulge may also lead to a reduction in longitudinal strain. Abnormal coronary anatomy, and specifically coronary-LV cavity sinusoids may potentially affect ventricular function and have been associated with an anatomical sub-type of mitral stenosis and aortic atresia. In our study there were insufficient cases to assess the relation to apical bulging, but as apical bulging was not related to anatomical sub-type we doubt that this was a significant factor in this cohort. Increased QRS duration and electromechanical dyssynchrony with non-simultaneous peak strains did not play a role in this patient population where QRS length was reported to be in the range between 58 and 122 ms **(Table 1)** and no patient had classic pattern dyssynchrony strain patterns.

HLHS anatomical variants

Our results suggest that hypertrophy of the hypoplastic LV is closely connected with apical bulging and associated with reduced global and segmental function. Although LV hypertrophy is often seen in the setting of mitral stenosis with aortic atresia, apical bulging was present in all anatomical sub-types. Our results are somewhat different from some previous studies that found tighter relations between functional parameters and HLHS anatomical variants [19]. However, these did not emphasize the configuration of apical bulging.

The presence of apical bulging did not correspond with anatomical sub-type. This may partly stem from limitations in the anatomical sub-type classification. For example, patients with MS/AA typically have a muscle-bound LV. However, there are patients with severe aortic stenosis and minimal prograde flow who are classified as MS/AS, but likely have a MS/AA anatomical subtype. These patients also differ from many MS/AS patients without an extremely hypertensive LV. There may be other patients with MS/AA during fetal life in whom the mitral valve ultimately closes. These patients are classified

as MA/AA, but may be different from patients with no identifiable LV. The developmental time point of valvular atresia and the degree of valvular stenosis during fetal life is important for the final configuration of the residual LV and might explain the varying degree of LV hypertrophy within the same anatomical variants. Description of apical bulging may circumvent some of these limitations.

Ventricular function, TR and outcomes in patients with and without apical bulging

Although global longitudinal and segmental strains are commonly reduced in HLHS [16, 29, 30], EF or FAC might not be affected if circumferential shortening compensates [31]. EF and FAC express the sum of strains in all directions, thus these measures for ventricular function cannot be interchangeably replaced. Additionally, radial and circumferential strain might not be as sensitive to early loss of myocardial function as longitudinal strain [14, 32]. In the current study, FAC was not different between those with versus without apical bulging; or between the different anatomical sub-types. However, all patients with significantly reduced FAC also displayed reduced RV global strain.

The number of patients with death or transplant outcome was similar in the groups with versus without apical bulging. However, while preliminary, our results might suggest that patients with the lowest RV strain might be at risk for death or transplant. As previously described, the presence of moderate to severe TR was associated with transplant or death, regardless of apical bulging [12]. The 3 patients with apical bulging and repeated echocardiography showed a tendency towards further reduced strains, while the 4 patients without apical bulging had a tendency towards improved strain-values after stage 1 surgery, perhaps indicating that impaired myocardial function after stage 1 palliation might manifest in the presence of apical bulging, but less so in its absence. Interestingly, the presence of TR with normal ventricular strain-values was not observed in patients with apical bulging. In this patient group, all 3 patients with TR had reduced RV function leading to transplant or death which raises the hypothesis that these ventricles may not be able to compensate for the additional volume-loading imposed by TR.

The presence of either reduced RV strain (predominantly in the apical bulging group) or moderate to severe TR was associated with 13/15 (86%) outcomes of death or transplant. Thus, reduced RV strain in patients with apical bulging and moderate to severe TR might constitute risk factors for adverse outcomes.

Limitations

This was a retrospective, cross sectional, descriptive study with inherent limitations. Serial study would have been stronger, but RV configuration in terms of presence or absence of apical bulging does not change or develop over time. Cardiac functional parameters were not analyzed for the influence of changing hemodynamics at differing surgical stages or the different surgical techniques or time-duration between the surgical palliative stages. Images were not specifically optimized for strain-analysis and analyzed at relatively low frame rates. Short-axis images for circumferential strain-measurements were not available, and LV strain-was not assessed. The number of patients overall was moderate and small in some sub-groups with a wide age range and echocardiography was performed at different surgical states. Therefore, conclusions need to be made cautiously. The availability of 3D or MRI derived RV EF would have strengthened the study but was unavailable. Although others have reported on circumferential RV strain in HLHS, we have not found this measurement consistently feasible or reproducible. The study predominantly investigated the association of myocardial function and geometry. Due to the small sub-group sample size, the ability to correlate functional and geometry results with death or transplant is limited and our findings are descriptive.

Conclusions

Apical bulging of the RV in HLHS is present in association with LV lateral wall and apical hypertrophy. Apical bulging is associated with reduced basal septal, and RV global longitudinal strain, possibly due to the impact of abnormal inter-ventricular interaction with a hypertrophied residual LV. The combination of apical bulging with low RV strain appears to be associated with transplant or death. Indeed, transplant or death occurred in most cases in patients with reduced RV-

strain associated with apical bulging or with moderate to severe TR. These results suggest that assessment of RV and LV geometry and mechanics may aid in prognostication of this high-risk population. This needs further investigation in longitudinal studies.

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Figure legends:

Figure 1

Cartoons depicting representative segmental strain-patterns encountered in the patient population

Panel A: Normal contractile myocardium in all segments with simultaneous peak and equal systolic peak strain-values.

Panel B: Strain curves with either differing contractile force or differing regional wall stress. The dark blue and yellow curve represent hypokinetic segments, the light blue and purple curve reflect akinesia, while the purple curve reflects no systolic stretch of non-elastic myocardium, scar tissue or prosthetic material, the light blue curve reflects systolic stretch of non-contractile myocardium with preserved tissue elasticity.

Panel C: Classic pattern dyssynchrony (CPD) with early systolic contraction and later systolic rebound stretch of the earliest activated segments, while late electrically activated segments stretch early during systole and still shorten after aortic valve closure (AVC)

Panel D: Dyssynchronous activation: Early segmental activation and stretching of other segments can be seen with simultaneous peak strains at the time-point of AVC.

*: Presence of mechanical dispersion (peak strain-values are not simultaneous) occurring either due to different contractile properties of the segments (Panel B) or CPD (Panel C).

Figure 2

Typical patient-examples: Types of right ventricular geometry in relation to the configuration of the hypoplastic left ventricle and longitudinal segmental strain~~-curves~~.

Panel A: “no apical bulging” with small left ventricle; Panel B: “apical bulging” with a hypertrophic hypoplastic left ventricle; Panel C: “no apical bulging” with ‘Larger’ LV with a flat septum

Figure 3

Segmental function in the 6 segments of an “apical 4 chamber view”. * $p<0.05$ between one segments and all other segments; † $p<0.05$ between the same segments of different groups

Figure 4

Relation of outcomes and global strain in patients with and without apical bulging

Table 1

Table 1: Patient characteristics

	All patients n = 48	**Apical Bulging n = 23**	**No Apical Bulging n = 25**	**P (Fisher`s exact test)**
	***n* (%)** or mean ± SD	***n* (%)** or mean ± SD	***n* (%)** or mean ± SD	
Male (*n*)	30	15	15	0.130
Age (y)	0.75 IQR 3.6	0.5 IQR 3.0	1.2 IQR 2.6	0.186
Weight (kg)	7.9±9.4	6.9±8.7	8.3±10.5	0.172
Echocardiography at Surgical stage (*n*)				0.586
At birth	1	0	1	
Before Stage 2	14	8	6	
Transplant	2	1	1	
Death	8	4	4	
After Stage 2 before Fontan completion	20	10	10	
Transplant	3	2	1	
Death	2	1	1	
After Fontan completion	13	5	8	
TV valve regurgitation (*n*)				0.566
no	9	4	5	
mild	30	16	14	
Moderate-severe	9	3	6	
QRS width (ms) Range (ms)	85 ± 18	82 ± 19 58-124	86 ± 17 58-122	0.394
Aanatomical variants				
Mitral Stenosis +Aortic Stenosis	16 (33%)	8 (50%)	8 (50%)	0.43
Mitral Stenosis +Aortic Atresia	16 (33%)	10 (63%)	6 (38%)	
Mital Atresia+Aortic Atresia	13 (27%)	5 (38%)	8 (62%)	

TV: tricuspid valve; Stage 1 surgery: Aortic reconstruction, resection of the interatrial septum and placement of a systemic-pulmonary shunt; Stage 2 surgery: Bidirectional cavo-pulmonary artery connection"

Table 2

Table 2: Right and Left Ventricular Geometry, segmental function and clinical outcome in both groups

	n	All	*n*	Apical Bulging	*n*	No Apical Bulging	*P*-value ANOVA or Fischer`s exact test
		***n* (%)** or mean ± SD		***n* (%)** or mean ± SD		***n* (%)** or mean ± SD	
Septal length (cm)	47	2.1 ± 1.0	22	2.4 ± 0.8	25	1.7 ± 1.0	0.021
RV Length (cm)	47	3.7 ± 1.0	22	3.9 ± 0.9	25	3.6 ± 1.0	0.232
Septal/RV length ratio	47	0.56 ± 0.22	22	0.62 ± 0.14	25	0.49 ± 0.26	0.029
RV end-diastolic area (cm^2)	47	9.8 ± 4.7	22	9.6 ± 4.5	25	10.0 ± 5.0	0.799
RV end-systolic area (cm^2)	47	6.0 ± 1.1	22	5.9 ± 3.0	25	6.1 ± 2.9	0.847
RV FAC (%)	47	36.0 ± 13.5	22	37.3 ± 13.2	25	34.8 ± 14.0	0.267
LV cavity area(cm^2)	45	1.0 0.9	22	1.1 ± 0.7	23	0.9 ± 1.0	0.698
LV cavity + myocardial area (cm^2)	45	2.7 ± 1.7	22	3.3 ± 1.5	23	2.1 ± 1.9	0.018
LV myocardial area (cm^2)	45	1.3 ± 1.9	22	2.2 ± 1.3	23	1.2 ± 1.2	0.008
LV/RV area ratio	45	0.32 ± 0.23	22	0.40 ± 0.20	23	0.24 ± 0.23	0.016
Septal hypertrophy, v.a. (*n*/%)	46	10 (22)	22	10 (45)	24	0 (0)	<0.0001
LV lateral-apical hypertrophy, v.a. (*n*/%))	46	23 (50)	22	20 (91)	24	3 (13)	<0.0001
Septal or lateral hypertrophy (*n*/%)	46	25 (54)	22	22 (100)	24	3 (13)	<0.0001
RV global longitudinal strain (%)	48	-9.5 ± 4.2	23	-7.3 ± 2.8	25	-11.3 ± 5.8	0.001
Basal Septum: Segmental strain (%)	48	-7.9 ± 6.0	23	-4.1 ± 3.4	25	-11.4 ± 5.8	0.0001
Percentage of segments with positive strain/heart (%)	48	14 ± 18	23	22 ± 22	25	7.3 ± 11	0.001
Percentage of segments with hypokinesia/heart (%)	48	41 ± 28	23	55 ± 22	25	30 ± 28	0.001
Number of hearts with at least 1 segment with positive strain	48	21 (44)	23	13 (59)	25	8 (32)	0.082
Number of hearts with at least 2 segments with positive strain	48	12 (25)	23	9 (41)	25	3 (12)	0.042
Number of hearts with at least 3 segments with hypokinesia	48	21 (44)	23	16 (73)	25	5 (20)	0.001

Number of hearts with at least 2 segments with hypokinesia	48	26 (54)	23	20 (91)	25	6 (24)	<0.0001
No Heart-failure medication	48	19 (40)	23	11 (48)	25	8 (32)	0.365
Heart-failure medication	48	14 (29)	23	5 (22)	25	9 (36)	

RV: Right Ventricular; LV: Left Ventricular; FAC: Fractional Area Change; v.a.= visually assessed: Hypertrophy was present, when the walls exceeded 1.5 times the maximal RV wall thickness.

Table 3: Clinical outcome and functional parameters

Clinical outcome	**RV global strain**	**TR**	**All Patients**	**Alive**	**Death or Transplant**	**Fisher`s exact test *p*-value**
No Apical Bulging	high <-8%	No TR	15	13	2	0.025
	high <-8%	TR	6	2	4	
	low > -8%	No TR	3	1	2	
	low > -8%	TR	1	1	0	
Apical Bulging	high <-8%	No TR	10	10	0	0.003
	high <-8%	TR	0	0	0	
	low > -8%	No TR	10	6	4	
	low > -8%	TR	0	0	3	

Outcome data were derived from the time-period of clinical follow-up until the last surgical stage. Heart failure was defined by prescription of heart-failure medication. TR: moderate to severe tricuspid regurgitation; global right ventricular (RV) strain was derived from strain of one long-axis view

Click here to access/download;Figure;Figure 1 patterns CMYG.ti

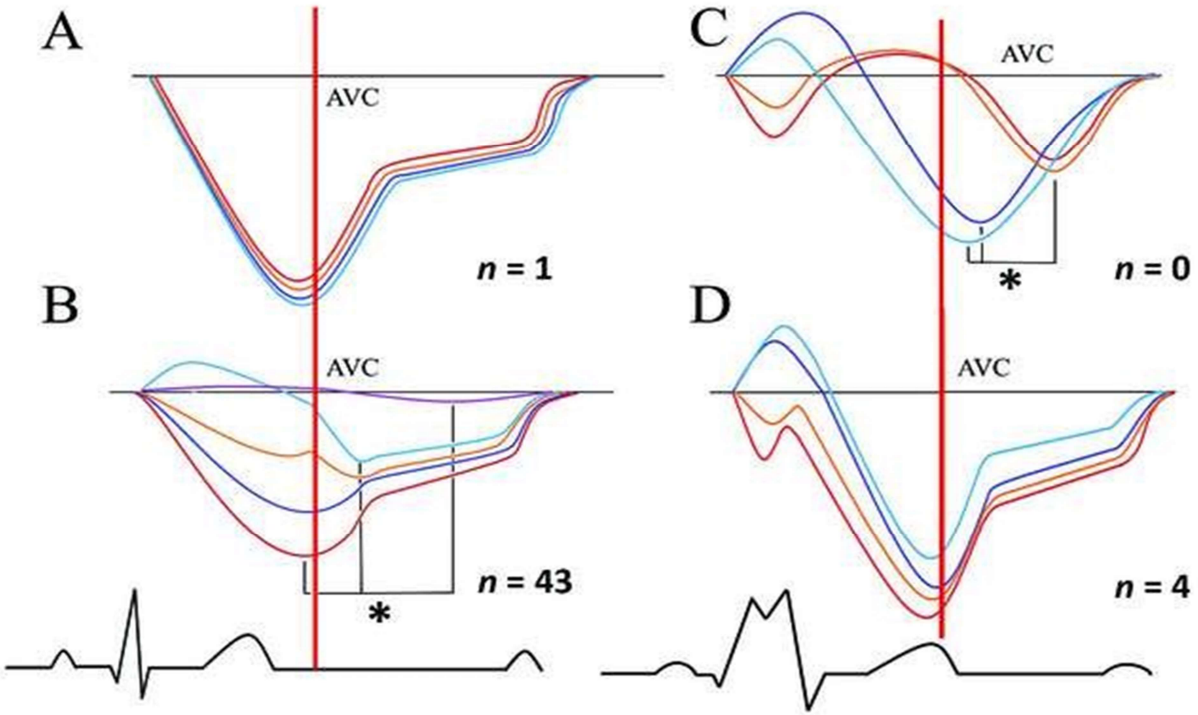


Figure 2

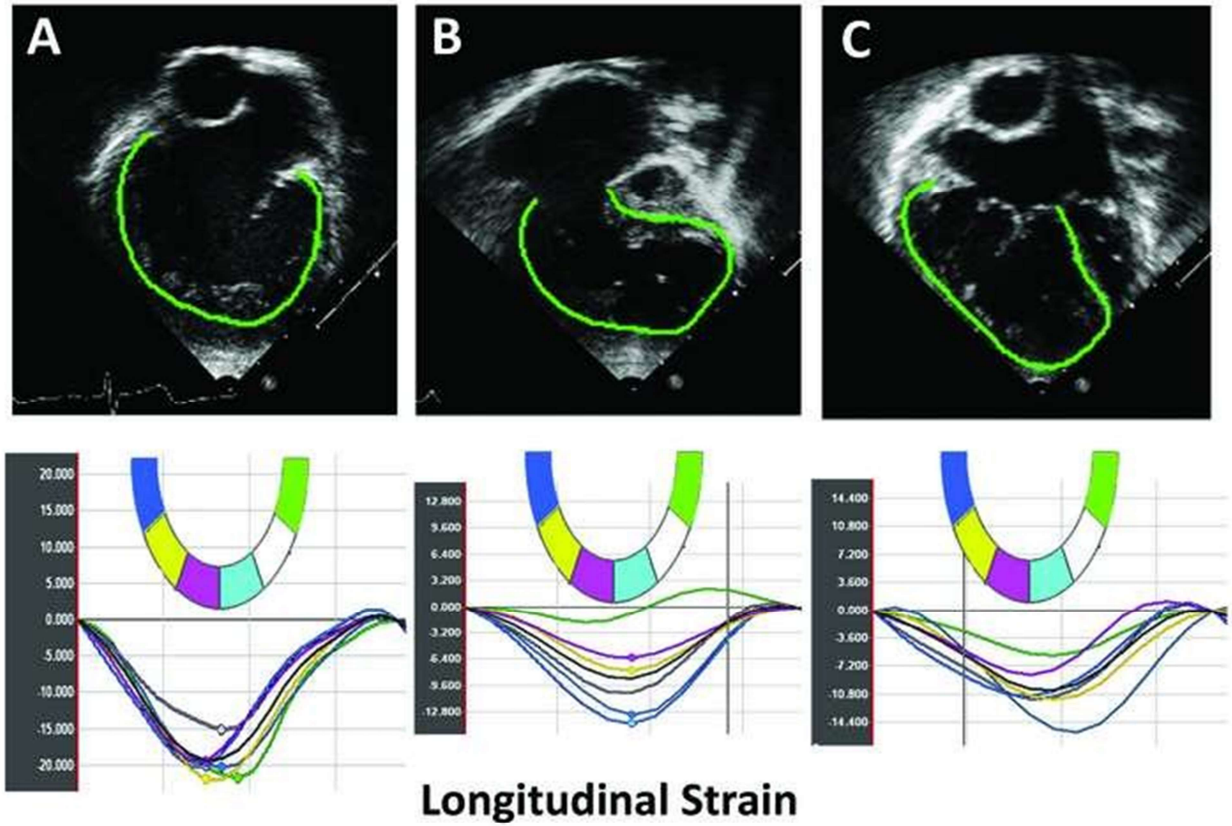
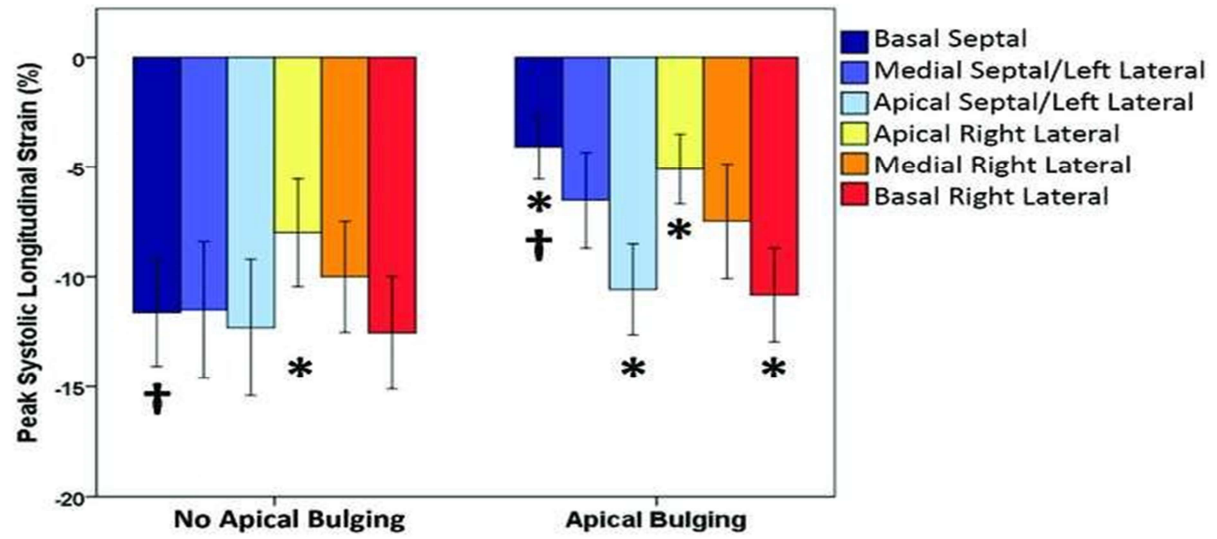
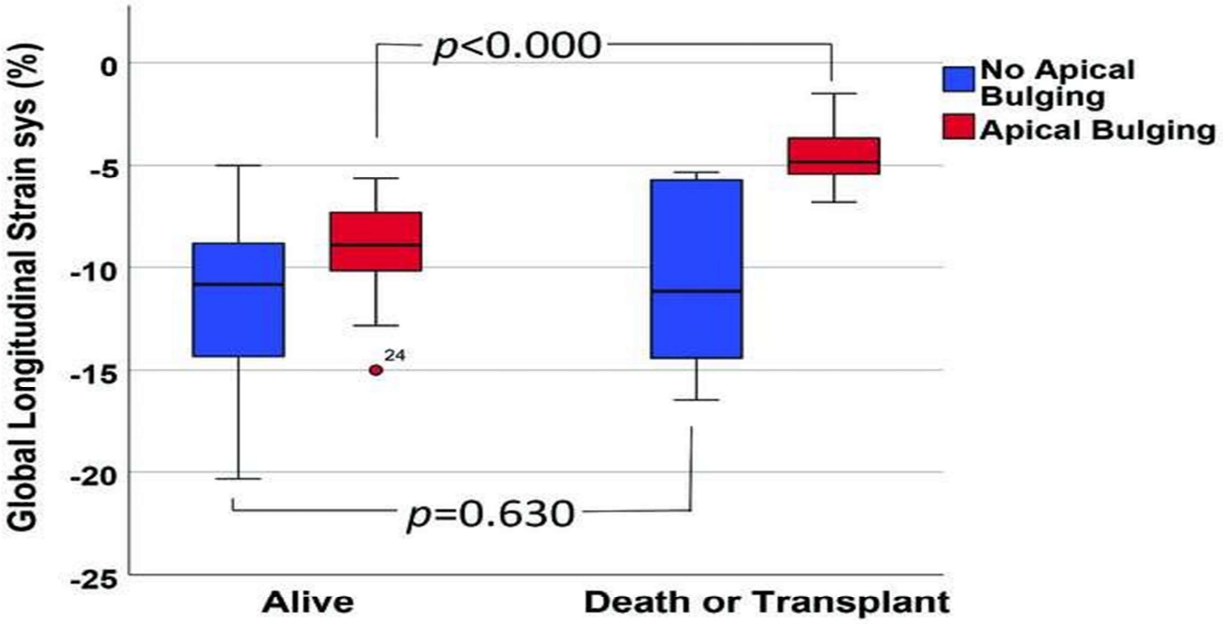

A
B
C
20.000
15.000
10.000
5.000
0.000
-5.000
-10.000
-15.000
-20.000
12.800
9.600
6.400
3.200
0.000
-3.200
-6.400
-9.600
-12.800
14.400
10.800
7.200
3.600
0.000
-3.600
-7.200
-10.800
-14.400
Longitudinal Strain

Figure 3


Peak Systolic Longitudinal Strain (%)
0
-5
-10
-15
-20
No Apical Bulging
Apical Bulging
Basal Septal
Medial Septal/Left Lateral
Apical Septal/Left Lateral
Apical Right Lateral
Medial Right Lateral
Basal Right Lateral


Global Longitudinal Strain sys (%)
0
-5
-10
-15
-20
-25
p<0.000
p=0.630
24
Alive
Death or Transplant
No Apical Bulging
Apical Bulging