ARTICLE

Longitudinal Evaluation of Right Ventricle Function after Right Ventricle-Pulmonary Artery Shunt *vs.* Blalock-Taussig Shunt

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ABSTRACT

Background: Still little is known about the impact on right ventricle function of the 2 main approaches to Norwood palliation in Hypoplastic left heart syndrome, the right ventricle-pulmonary artery shunt (RVPAS) and the modified Blalock-Taussig shunt (mBTS). **Methods:** The cohort included 27 patients with Hypoplastic left heart syndrome (10 in the mBTS group, 17 in the RVPAS group). Longitudinal strain, tricuspid annulus peak systolic excursion and fractional area change were evaluated before Norwood and in four different breakpoints in the steady-state after Norwood procedure (30-days, 90-days, 140-days and 200-days after Norwood). **Results:** No significant differences were found in all standard echocardiographic functional parameters between the two groups at any times. However, when we compared right ventricle function before and after Norwood procedure, longitudinal strain significantly improved in mBTS group compared to pre-surgical assessment (after 90-days: mBTS +27,35% ± 43,47 *vs.* RVPAS −8,20% ± 25,25, *p* = 0,03; after 200-days: mBTS +10.19% ± 36.58 *vs.* RVPAS −21.64% ± 30.43, *p* = 0.04). **Conclusion:** The mBTS group, which did not receive any ventriculotomy, showed a significant increase in right ventricle longitudinal strain during convalescence. These data support the use of longitudinal strain in Hypoplastic left heart syndrome evaluation and may suggest potential value in terms of cardiac mechanics in using mBTS, preserving the right ventricle integrity.

KEYWORDS

Hypoplastic left heart syndrome; speckle tracking echocardiography; congenital heart disease

1 Introduction

Almost four decades after its description [1], the Norwood procedure still represents the cornerstone of Hypoplastic left heart syndrome (HLHS) staged palliation. Very early in life, neonates with HLHS receive reconstruction of neo-aorta and connection of systemic and pulmonary circulations (Norwood stage I). After pulmonary vasculature maturation, the systemic venous return is redirected toward pulmonary arteries through two surgical stages performed at 4 to 6 months of age and 18 to 48 months of age [2].

Essentially, two are the techniques allowing the connection of systemic and pulmonary circulations in the first stage:

- *The Modified Blalock–Taussig Shunt (mBTS)*, where a tube is placed from the innominate or subclavian artery to the pulmonary arteries to supply pulmonary blood flow. This tube provides a continuous systo-diastolic flow towards pulmonary circulation with a possible result in "coronary steal" during diastole.
- *The Right Ventricle-to-Pulmonary Artery Conduit (RVPAS)*, where a valveless conduit is placed from the right ventricle (RV) to the pulmonary arteries to supply pulmonary blood flow. Possible complications are related to the right ventriculotomy and scar creation [3].

As a consequence of "coronary steal" elimination, it is thought RVPAS conducts to a very stable early post-operative course [4]. On the other side, RVPAS presupposes an antero-basal right ventriculotomy with the creation of ventricular scar and alteration in local contractility [5] and, even though RVPAS has demonstrated to be a better choice for the early post-operative transplantation-free survival, this approach lost its superiority on the long run [6]. Indeed, RVPAS seems to be associated with a lower ventricular function when compared to mBTS in some studies on longer follow-up after second surgical stage [7,8], but a direct correlation with RVPAS placement at the time of Norwood procedure is not demonstrated yet [8–10].

Evaluation of RV function is challenging due to no exact geometric model existing for volume measurements, with 2D and Doppler echocardiographic measurements modestly correlating with magnetic resonance estimates of ejection fraction [11,12]. Furthermore, classical functional echocardiographic parameters have failed to demonstrate RV function differences in early and mid-term follow up of patients who underwent RVPAS or mBTS [13].

Speckle-tracking echocardiography derived longitudinal strain (LS) has been demonstrated to be a reliable technique, allowing the assessment of RV deformation without geometric assumption and the influence of acute preload and afterload changes [14,15], with good correlation with cardiac magnetic resonance imaging-derived RV ejection fraction in patients with HLHS [9,16].

Different studies have focused on speckle tracking-analysis to study ventricular function in patients with HLHS [16–20], but just a few tried to demonstrate postoperative ventricular deformation differences in the two types of shunt [9].

In our study, we used speckle-tracking echocardiography over standard echocardiographic parameters to evaluate changes in RV function in HLHS patients after RVPAS and mBTS.

2 Methods

This is a retrospective observational case-series on 27 consecutive paediatric patients. We conducted a re-analysis of a retrospective study on patients who underwent Norwood palliation between June 2015 and April 2019 at Royal Brompton Hospital of London, United Kingdom.

We collected patients' data between July 2018 and July 2019. Only patients with a diagnosis of "pure HLHS" were considered eligible for the study. Exclusion criteria were "HLHS variants" (e.g., critical aortic stenosis, double-outlet RV with mitral atresia, unbalanced atrioventricular septal defect, and heterotaxic syndrome; n = 6), and initial procedures different from Norwood operation. Patients were divided in two groups on the basis of Norwood surgical technique received: RVPAS group and mBTS group (Suppl. Fig. 1).

Demographic, clinical management, and outcome data were obtained from patients' medical recordings.

Informed consent was obtained from patients' parents before the enrolment when data were collected retrospectively. The study protocol conformed the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the local research committee.

Five different follow-up time points were chosen for the study purpose: (1) A pre-Norwood assessment "baseline"; (2) A 30-days post-Norwood assessment; (3) A 90-days post-Norwood assessment; (4) A 140-days post-Norwood assessment; (5) A 200-days post-Norwood assessment.

The 90-days and 140-days post Norwood evaluations were done after the first but before the second surgical step (Glenn procedure); the 200-days post-Norwood assessment was done after the second surgical step.

Echocardiographic recordings were obtained using a GE E95 ultrasound machine (GE Healthcare, Wauwatosa, WI) and Philips EpiQ 7 ultrasound machine (Koninklijke Philips N.V., Amsterdam, The Netherlands) and, then, kept digitally for offline analyses. Uncompressed data were stored on an Xcelera platform (Koninklijke Philips N.V., Amsterdam, The Netherlands) and then analysed offline with TomTec system (TomTec Imaging System GMBH, Unterschleissheim, Germany) by one blinded physician.

From the apical window, we measured: tricuspid annulus peak systolic excursion (TAPSE), fractional area change (FAC), and peak LS.

TAPSE was measured as the difference between end-diastolic and end-systolic tricuspid annulus displacement. FAC was measured as the difference between end-diastolic and end-systolic RV area tracing manually the endocardial boundary in a focused apical four-chamber view; values were expressed in percentage.

The RV LS analysis was obtained from grayscale optimized images while in apical 4-chamber view. To be included in the analysis, the image quality had to have a frame rate >50 frames per second with a good definition of the RV wall. The region of interest was selected using three point-click method, with three points manually placed on each side of tricuspid anulus and at apex. The endocardium contour was semi-automatically traced, manually adjusted as needed, and then the LS was automatically evaluated by the software algorithm. A 6-segment model was used for the study purpose. Peak strain was defined as the highest strain value within the cardiac cycle [16,21].

Moreover, we evaluated variations in LS, FAC, and TAPSE between echocardiograms at 30-days, 90-days, 140-days, and 200-days post-Norwood and baseline, as follow:

$$\Delta LS = [\text{30-days (or 90-days or 140-days or 200-days) post Norwood LS} - \text{baseline LS}]$$
$$/\text{baseline LS} \times 100$$

The same method was used for ΔFAC and ΔTAPSE.

Tricuspid regurgitation was classified from 0 to 3 as follow: 0 = none/trivial (single narrow jet), 1 = mild (multiple narrow jets), 2 = moderate (wide jet reaching the midportion of the right atrium), and 3 = severe (wide jet reaching the back wall of the right atrium). This method has been used in previous studies on HLHS patients by our group [20] and other authors [16,22].

Clinical and echocardiographic data were indicated as median and interquartile ranges or mean and standard deviation as appropriate. Normality was tested using the Shapiro-Wilk method. Comparisons were made with the Mann-Whitney U test or unpaired T-test, on MedCalc, version 18.11 (MedCalc Software, Mariakerke, Belgium). A p-value < 0.05 was considered statistically significant.

We measured TAPSE, FAC, and LS intra- and inter- observer variability in 10 randomly selected exams by using Bland-Altman scatterplot analysis. To evaluate intra-observer variability, the same observer who performs all the echocardiographic measurements reassessed the same parameters at least 4 weeks later to avoid recall bias. To evaluate inter-observer variability, another observer, independent and blinded to the original measurements, evaluated also the RV parameters. We calculated the relative mean absolute

difference between intra- and inter- observer measurements and then performed regression testing for proportional bias. Finally, we calculated intraclass correlation coefficients.

3 Results

In the time-study period, 27 patients (17/27 male patients, 63%) with HLHS fulfilled the enrolment criteria and were included in the study. Ten patients (37%) received mBTS, while 17 patients (63%) received RVPAS.

All patients (100%) early survived the Norwood stage 1 operation (RVPAS and mBTS). Three patients died before the second surgical stage: Two of them (2/17 patients, 12%) belonged RVPAS group, one of them (1/10 patients, 10%) belonged mBTS group. At the time of the second surgical stage, 21/24 patients were treated with a straightforward Glenn operation, while in one case Glenn operation was associated with tricuspid valve repair. The patient who received tricuspid valve repair belonged RVPAS group. Since this repair could influence longitudinal RV performance, we excluded the patient from the analysis at the fifth evaluation, after Glenn operation. There were no differences in terms of weight or age at the time of Norwood operation between the two groups. Patients' demographic and clinical characteristics are summarized in Tab. 1.

Echocardiographic images' frame rate was 65 ± 15 frames per second. Thirty-two echocardiograms (13/27 patients, 48%) showed a moderate or severe tricuspid regurgitation, but no significant difference was found between mBTS and RVPAS group. Tab. 2 and Fig. 1 present the population's echocardiographic data.

Table 1: Patient's demographic and clinical characteristics

Characteristics	RVPAS	mBTS	p
No. of infants	17	10	
Age–days			
Pre-Norwood	1.00 (0–3.00)	1.00 (0.25–2.50)	0.98
30-days post Norwood	55.50 (40.25–67.25)	45.00 (37.00–58.00)	0.29
90-days post Norwood	99.00 (97.00–115.00)	109.50 (97.00–123.75)	0.49
140-days post Norwood	148.00 (136.50–183.00)	143.00 (123.25–162.50)	0.40
200-days post Norwood	204.00 (180.50–256.50)	184.50 (171.50–236.75)	0.49
Male sex - %	59	70	0.56
Race or ethnic group—%			
White	29	70	0.04
Black	23	10	0.38
Hispanic	6	0	0.03
Asian	6	0	0.03
Other	35	20	0.40
Birth weight–kg	3.04 ± 0.39	3.13 ± 0.36	0.55
Size of ascending aorta–cm	0.30 (0.20–0.43)	0.52 (0.51–0.60)	0.07

There were no differences in TAPSE, FAC, and LS between the RVPAS group and the mBTS group in all the echocardiographic time points (Fig. 2). At 90-days and 200-days post-Norwood assessment, the mBTS group showed a significant improvement in LS compared to pre-Norwood assessment (ΔLS). This

finding, albeit present, was no statistically significant at 30-days and 140-days post-Norwood assessment. At 200-days post Norwood evaluation mBTS group showed a significantly smaller RV compared to RVPAS group.

Table 2: Patient's echocardiographic data

Variables	Pre-Norwood "baseline"			30-days post-Norwood			90-days post-Norwood			140-days post-Norwood			200-days post-Norwood		
	RVPAS	mBTS	p	RVPAS	mBTS	p	RVPAS	mBTS	p	RVPAS	mBTS	p	RVPAS	mBTS	p
Weight—kg	3.04 ± 0.39	3.13 ± 0.36	0.55	3.51 ± 0.45	3.60 ± 0.74	0.73	4.69 ± 0.75	5.41 ± 0.58	**0.03**	6.02 ± 0.98	6.48 ± 0.64	0.28	6.74 ± 1.11	7.16 ± 0.56	0.36
TR—grade 0-3	0 (0–1)	0.5 (0–1)	0.47	1 (0.75–1.25)	1 (1–1)	0.54	1 (1–2)	1 (1–2)	1.00	2 (1–2)	1 (0.75–1.25)	0.23	1 (0–2)	1 (0.75–2)	0.94
TAPSE—cm	0.8 (0.7–0.8)	0.8 (0.62–0.9)	0.38	0.55 (0.47–0.6)	0.55 (0.5–0.6)	0.74	0.7 (0.5–0.8)	0.7 (0.6–0.8)	0.50	0.7 (0.6–0.8)	0.7 (0.65–0.92)	0.51	0.7 (0.5–0.77)	0.7 (0.57–0.82)	0.55
FAC—%	35.14 ± 7.77	33.10 ± 6.89	0.50	34.62 ± 8.81	36.27 ± 6.76	0.62	34.81 ± 9.25	38.49 ± 6.51	0.32	30.30 ± 8.40	38.12 ± 6.96	0.28	28.27 ± 10.47	36.62 ± 6.80	0.06
LS—%	−16.82 ± 3.53	−14.62 ± 4.36	0.16	−15.19 ± 5.13	−14.80 ± 3.36	0.83	−16.01 ± 4.03	−16.69 ± 2.00	0.67	−15.72 ± 3.53	−16.09 ± 2.75	0.80	−12.96 ± 5.60	−15.04 ± 2.33	0.33
ΔLS—%	–	–	n/a	−10.32 ± 28.73	+6.48 ± 25.10	0.14	−8.20 ± 25.25	+27.35 ± 43.47	**0.03**	−4.90 ± 27.97	+13.81 ± 21.99	0.12	−23.14 ± 30.99	+10.19 ± 36.58	**0.03**
ΔTAPSE—%	–	–	n/a	−23.70 ± 21.20	−20.76 ± 29.08	0.77	−14.24 ± 24.90	+0.68 ± 44.68	0.33	−5.73 ± 24.51	+11.43 ± 68.62	0.39	−8.86 ± 29.03	+2.33 ± 63.33	0.57
ΔFAC—%	–	–	n/a	+4.56 ± 36.73	+13.57 ± 29.30	0.52	+0.74 ± 31.82	+19.95 ± 41.32	0.23	+2.05 ± 29.42	+20.25 ± 40.27	0.23	−16.72 ± 35.27	+16.91 ± 48.39	0.07
RV ED area	5.30 ± 1.24	4.67 ± 0.91	0.17	7.15 ± 1.80	6.10 ± 2.00	0.18	7.97 ± 2.62	8.81 ± 2.78	0.48	12.16 ± 3.24	8.19 ± 2.99	0.11	10.81 ± 3.58	7.75 ± 1.68	**0.03**
RV ES area	3.48 ± 1.06	3.09 ± 0.54	0.30	4.71 ± 1.49	3.85 ± 1.28	0.15	5.34 ± 2.19	5.52 ± 2.04	0.85	10.48 ± 19.98	5.00 ± 1.68	0.33	7.81 ± 2.90	4.90 ± 1.26	**0.01**

RVPAS, right ventricle-pulmonary artery shunt; mBTS, modified Blalock-Taussig shunt; TR, tricuspid regurgitation; TAPSE, tricuspid annulus peak systolic excursion, FAC, fractional area change; LS, longitudinal strain, LSR, longitudinal strain rate; LV, left ventricle; RV, right ventricle; RV ED, right ventricle end-diastolic; RV ES, right ventricle end-systolic.

Inter-observer agreement of our data was very good for TAPSE and LS with an ICC of 0.84 and 0.85 respectively. Intra-observer reproducibility was also very good for TAPSE and LS with an ICC 0.95 and 0.91, respectively. FAC showed poor inter- and intra-observer reproducibility with an ICC of 0.55 and 0.52, respectively (Fig. 3).

4 Discussion

With this study, we want to describe the effect on cardiac mechanics of the two main initial approaches to HLHS palliation, the RVPAS and the mBTS [23]. Identifying patients with single ventricle initial dysfunction is crucial because RV damage correlates with intermediate and overall poor outcomes [24]. RV function, currently, remains best assessed by conductance catheterization [25], however, in patients with HLHS, studies with magnetic resonance imaging and conductance catheter have shown RV speckle tracking indices are relatively preload independent and correlates well with end-systolic elastance and ventricular contractility [16,26].

In our knowledge, our study is the first using LS over classical echocardiographic parameters to recognize variations over time in RV function early after the 2 main Norwood shunts. Very few studies used speckle tracking in this clinical setting [16–20] and even less compared ventricular function after the

two types of Norwood shunt [9]. Indeed, Hill et al. [9] analysed speckle tracking differences at one specific time point, when the shunt was already taken down, at 14 months of age.
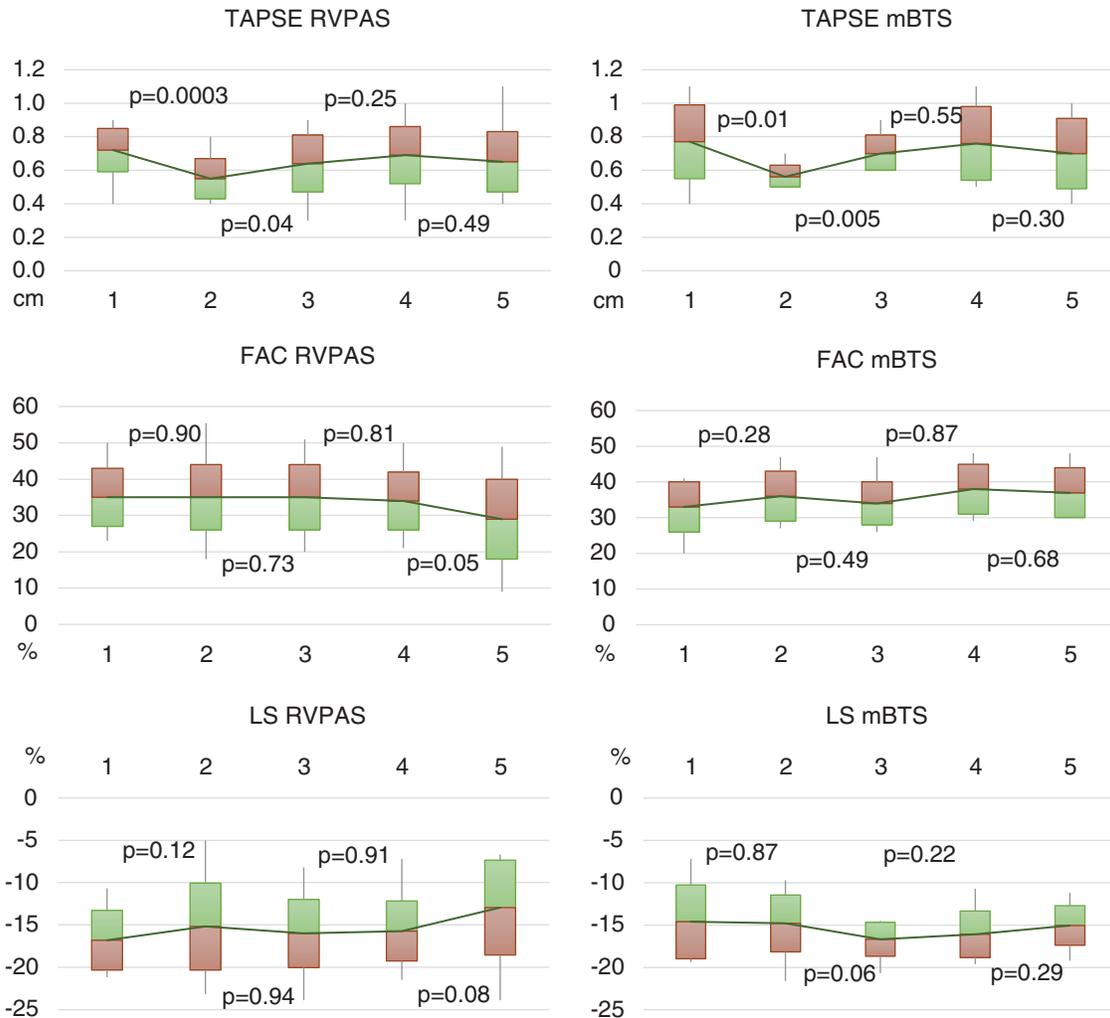

Figure 1: Box-and-whisker plots for comparison between RVPAS and mBTS groups of TAPSE (cm), FAC (%) and LS (%). RVPAS, right ventricle-pulmonary artery shunt; mBTS, modified Blalock-Taussig shunt; TAPSE, tricuspid annulus peak systolic excursion, FAC, fractional area change; LS, longitudinal strain. 1, pre-Norwood assessment; 2, 30-days post Norwood assessment; 3, 90-days post Norwood assessment; 4, 140-days post Norwood assessment; 5, 200-days post Norwood assessment

In line with the observations of Frommelt et al. [13], we did not find differences in standard functional echocardiographic parameters at any time in the early post-operative course. A straight evaluation of LS differences between the two groups revealed no statistically significant differences at any time points analysed. However, when we compared right ventricle myocardial deformation parameters before and after RVPAS/mBTS, we found an improvement of LS in the mBTS group. This amelioration was already present 30-days after mBTS but became statistically significant only 90-day after mBTS.

At 140-days post mBTS operation, this gain in LS was still present, but it lost its statistical significance. However, 200-days post mBTS, after all patients received Glenn operation (II stage), it was confirmed ΔLS

statistical difference between the two groups. We speculated that the loss of statistical significance at 140-days post mBTS might be related to the small volume sample, but, also, to RV outset of dysfunction and be a red-flag for early second intervention.
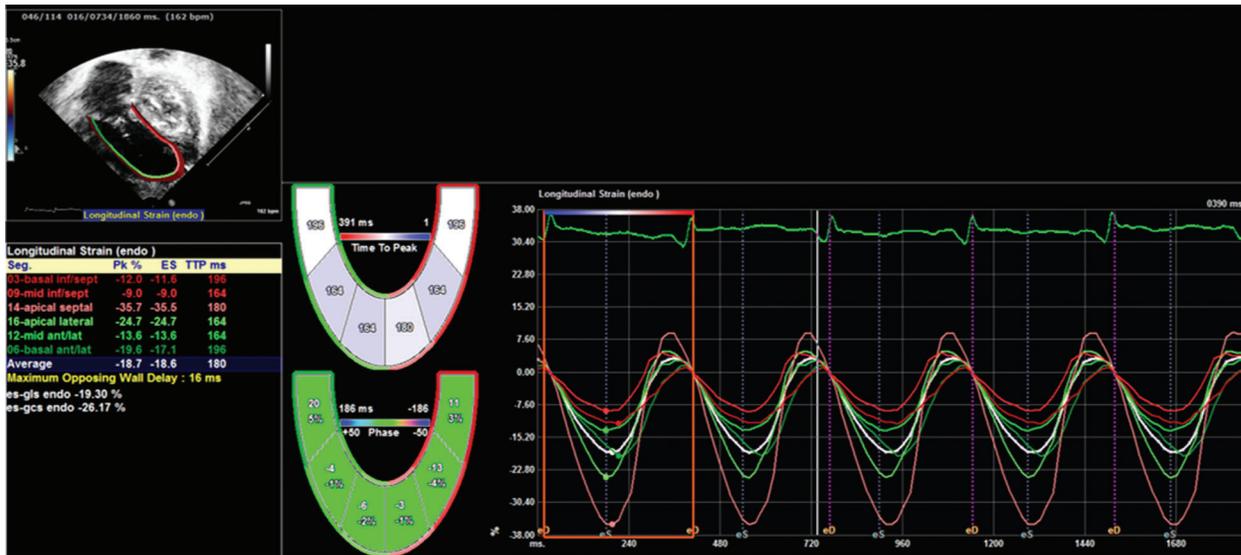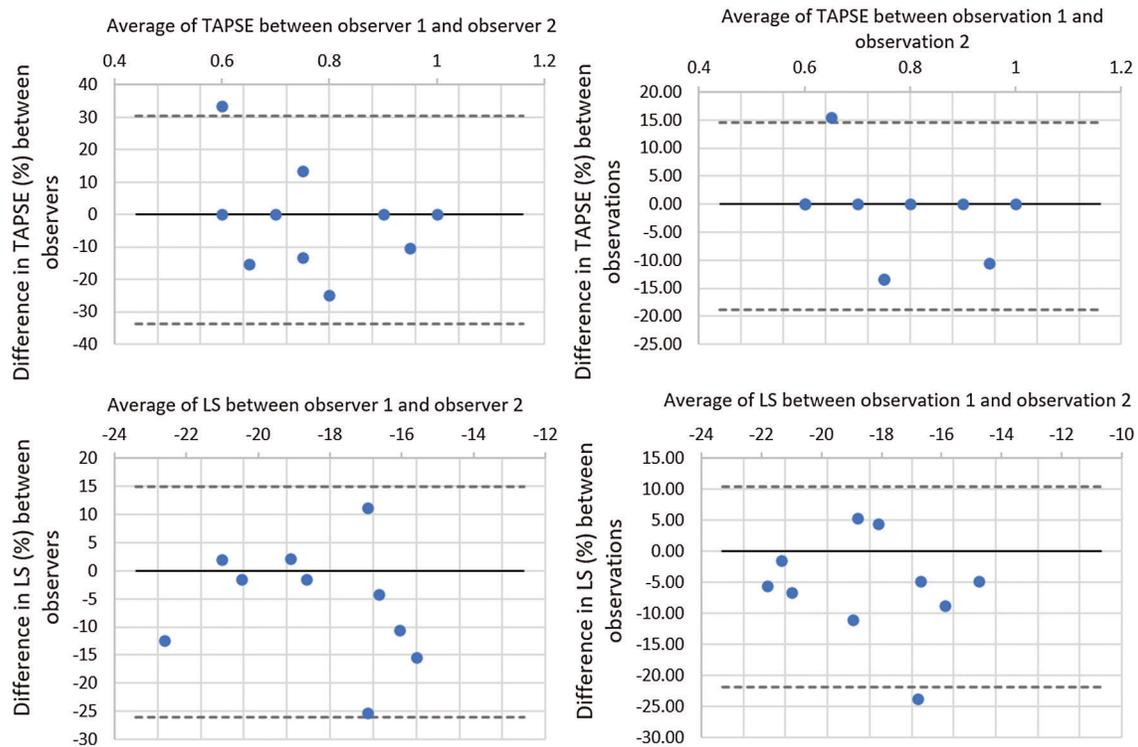

(a)
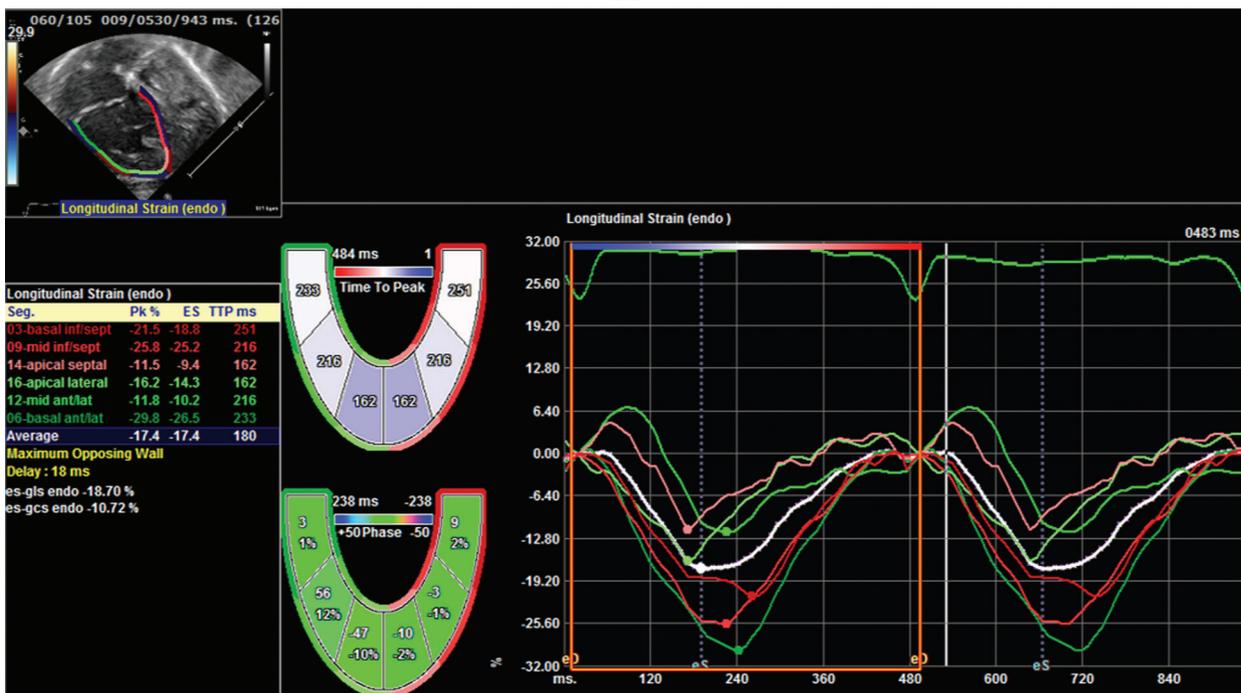
(b)

Figure 2: LS measurement at 90-days post Norwood evaluation. Image a shows LS in a patient treated with BTS. Image b shows LS in a patient treated with RVPAS

Figure 3: Bland-Altman scatterplots showing intra- and interobserver agreement for TAPSE and longitudinal strain (LS). TAPSE, tricuspid annulus peak systolic excursion, LS, longitudinal strain

On the other hand, RVPAS showed a constant, but not significant, reduction in LS in all post-Norwood assessments compared to pre-Norwood assessment.

No statistical differences were found between post-Norwood FAC and TAPSE and the baseline evaluation (ΔFAC and ΔTAPSE) in the two groups. This finding is probably related to a greater sensibility [27,28] and reproducibility of LS compared to the other functional parameters (greater intra- and inter-observer reproducibility compared to FAC and greater interobserver reproducibility compared to TAPSE).

Notably, 200-days post Norwood, RV dimensions were significantly smaller in mBTS group compared to RVPAS group. This finding was related to the well-known RV volume overload due to the regurgitation from the valveless RVPAS [6].

Other authors previously reported that RVPAS ventriculotomy may be responsible of RV damage and this may cause the loss of survival benefits over mBTS with time [9]. Similarly, we hypothesize that RV intactness in the mBTS group may favour a precocious LS improvement and may be beneficial for cardiac mechanics over RVPAS.

Moreover, since we found this result only analysing echocardiographic differences between pre- and post-surgical times, our study suggests the noteworthy value of serial LS measurements in the assessment of patients with HLHS.

There were some limitations in this study. The main one was represented by the small population size. However, given the rarity of the condition, the monocentric character of the study, and the strict inclusion criteria, the volume sample was fairly substantial. The quality of images in some cases was not enough to allow speckle tracking analysis, as a result, some echocardiographic data were cut off from the study.

However, considering the retrospective nature of the study and the complex cardiac anatomy of HLHS, these losses were random and very few with no prejudice on the analysis.

Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

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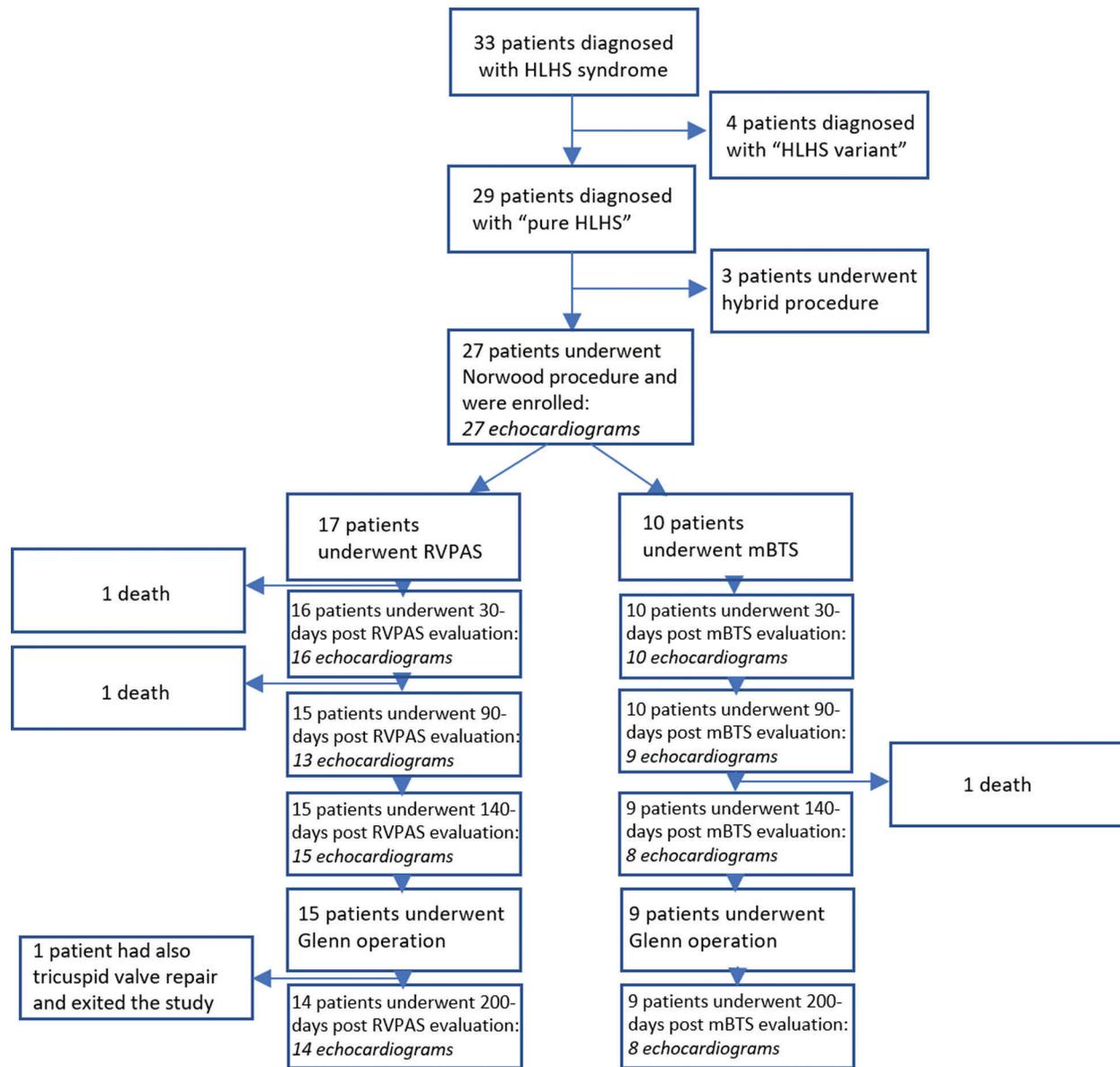
Supplement Figure 1: Flow diagram of patients' selection and outcome. The number of echocardiographic available loop was included for each follow-up