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ORIGINAL RESEARCH

Functional Echocardiographic and Serum Biomarker Changes Following Surgical and Percutaneous Atrial Septal Defect Closure in Children

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BACKGROUND: Ventricular performance is temporarily reduced following surgical atrial septal defect closure. Cardiopulmonary bypass and changes in loading conditions are considered important factors, but this phenomenon is incompletely understood. We aim to characterize biventricular performance following surgical and percutaneous atrial septal defect closure and to relate biomarkers to ventricular performance following intervention.

METHODS AND RESULTS: In this multicenter prospective study, children scheduled for surgical or percutaneous atrial septal defect closure were included. Subjects were assessed preoperatively, in the second week postintervention (at 2-weeks follow-up), and 1-year postintervention (1-year follow-up). At each time point, an echocardiographic study and a panel of biomarkers were obtained. Sixty-three patients (median age, 4.1 [interquartile range, 3.1–6.1] years) were included. Forty-three patients underwent surgery. At 2-weeks follow-up, right ventricular global longitudinal strain was decreased for the surgical, but not the percutaneous, group (–17.6±4.1 versus –27.1±3.4; P<0.001). A smaller decrease was noted for left ventricular global longitudinal strain at 2-weeks follow-up for the surgical group (surgical versus percutaneous, –18.6±3.2 versus –20.2±2.4; P=0.040). At 1-year follow-up, left ventricular performance returned to baseline, whereas right ventricular performance improved, but did not reach preintervention levels. Eight biomarkers relating to cardiovascular and immunological processes differed across study time points. Of these biomarkers, only NT-proBNP (N-terminal pro-B-type natriuretic peptide) correlated with less favorable left ventricular global longitudinal strain at 2-weeks follow-up.

CONCLUSIONS: Right, and to a lesser degree left, ventricular performance was reduced early after surgical atrial septal defect closure. Right ventricular performance at 1-year follow-up remained below baseline levels. Several biomarkers showed a pattern over time similar to ventricular performance. These biomarkers may provide insight into the processes that affect ventricular function.

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Key Words: atrial septal defects ■ biomarkers ■ cardiopulmonary bypass ■ congenital heart disease ■ speckle tracking echocardiography

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CLINICAL PERSPECTIVE

What Is New?

- Biventricular function is temporarily decreased following surgical, but not percutaneous, atrial septal defect closure; and several serum biomarkers developed in a similar pattern to cardiac function.

What Are the Clinical Implications?

- Serum biomarkers may provide insight into the recovery from periprocedural injury, which includes trauma related to septal defect closure and injury related to perioperative conditioning, including cardiopulmonary bypass.

Nonstandard Abbreviations and Acronyms

COBRA^3	Congenital Heart Defects: Bridging the Gap Between Growth, Maturation, Regeneration, Adaptation, Late Attrition and Ageing
CPB	cardiopulmonary bypass
FABP4	fatty acid binding protein 4
GLS	global longitudinal strain
ITGB2	integrin β-2
RVEDD	right ventricular end-diastolic diameter
T1	preoperatively
T2	2-weeks follow-up
T3	1-year follow-up
uPA	urokinase-type plasminogen activator

Approximately 9.0 per 1000 live-born children experience congenital heart disease (CHD).[1] Interventions at a young age are commonly required to correct the abnormal loading conditions and shunting caused by CHD. Depending on the specific congenital defect, this may require one or several interventions. Perioperative conditioning, including cardiopulmonary bypass (CPB), is required to perform intracardiac surgery.[2] This inevitably leads to ischemic and reperfusion damage to cardiac tissue, which may result in myocardial stunning or even cardiomyocyte death.[2] Reduced ventricular performance is observed shortly following surgery for CHD, followed by a recovery over months.[3–5] Although ventricular function generally recovers in the early stages after interventions in the heart, concerns about the long-term consequences of perioperative injury have been raised and mechanisms of tissue damage and repair have been incompletely studied in congenital heart disease.

CPB use and CPB duration have been recognized as factors associated with long-term prognosis in more complex CHD, suggesting that recovery after surgical trauma and CPB may be incomplete.[6] It is well known that CPB is followed by an immune response characterized by activation of the humoral and cellular immune system, the coagulation system, and fibrinolytic system.[7] Wound healing following surgical trauma similarly requires an immune response contributing to removal of debris and preparation for wound healing.[8–10] The immune response following CPB may relate to temporarily impaired ventricular function and recovery from perioperative injury.

Novel cardiovascular and immunological biomarkers might provide more insight in the biological processes involved in postoperative reduced ventricular performance and subsequent recovery and might help identify targets for improved myocardial protection and/or markers to identify patients with CHD with poor prognosis.

Patients with atrial septal defects (ASDs) can be treated percutaneously by transcatheter devices, or surgically by direct ASD closure. Surgical ASD closure is performed with cardiopulmonary bypass, percutaneous closure without, allowing the study of the differences in functional and biochemical response between these approaches.

We performed an exploratory prospective observational study comparing echocardiographic markers and a panel of multiple cardiovascular serum biomarkers in patients undergoing surgical and percutaneous closure for a type II ASD.

We aimed to answer the following questions:

- How does biventricular function develop over 1-year follow-up following percutaneous and surgical ASD closure?
- What serum biomarkers are associated with the adaptation of cardiac function following up to 1 year after intervention?

METHODS

Study Design and Subjects

We performed a multicenter prospective observational exploratory study (COBRA^3: Congenital Heart Defects: Bridging the Gap Between Growth, Maturation, Regeneration, Adaptation, Late Attrition and Ageing; Netherlands trial register NL5129). From December 2015 to September 2019, we included subjects scheduled to undergo interventional or surgical closure of a secundum ASD from 4 tertiary centers in the Netherlands: Erasmus MC Sophia Children's Hospital, Rotterdam; Willem Alexander Children's Hospital,

Leiden; Wilhelmina Children's Hospital, Utrecht; and Beatrix Children's Hospital, Groningen. Indication for ASD closure was based on interdisciplinary team discussions of the participating centers. In general, closure of an ASD was indicated if there was evidence of right ventricular (RV) volume overload (eg, increased size, paradoxical motion or abnormal position of interventricular septum, or pulmonary to systemic flow ratio (Qp/Qs) >1.5). Indications for surgical closure over percutaneous closure were, among others, multiple defects, defects too large for occlusion devices, or proximity of the ASD to the aortic rim. Severe intellectual disability and comorbid congenital heart defects were exclusion criteria. Subjects were assessed at 3 time points: preoperatively (T1); at first outpatient follow-up following ASD closure, or at 1 to 2 weeks postintervention in case of prolonged hospital stay (at 2-weeks follow-up [T2]); and at outpatient follow-up 1 year after ASD closure (at 1-year follow-up [T3]). At each time point, subjects underwent standard clinical examination, echocardiography, and blood sampling. The study protocol was approved by the institutional medical ethical review board of the participating centers (MEC-2014-326). All subjects and/or their legal guardians gave written informed consent, according to Dutch legislation. The data that support the findings of this study are available from the corresponding author on reasonable request.

Echocardiography

All subjects underwent transthoracic echocardiographic studies by an experienced cardiac sonographer. All studies were performed according to the study protocol, which included 2-dimensional grayscale, color Doppler, M-mode, and pulsed wave tissue Doppler imaging.[11] All studies were performed on a Vivid7 or Vivid E9 cardiac ultrasound system (General Electric Vingmed Ultrasound, Horten, Norway). No sedation was used during echocardiography studies. Studies were analyzed offline using commercially available software (EchoPac; General Electric Vingmed, Horten, Norway) by 1 of 4 trained observers from 2 core laboratories (Erasmus MC–Sophia Children's Hospital and Willem Alexander Children's Hospital–Leiden University Medical Center). All M-mode and pulsed wave tissue Doppler parameters were averaged over 3 consecutive heart beats. The presence of tricuspid regurgitation was assessed using color Doppler imaging and graded subjectively. Speckle tracking analysis was used to determine myocardial strain using vendor-specific software (Echopac version 11.2; General Electric Vingmed Ultrasound), as previously described by our group.[12] Timing of end systole was defined by the software. Global longitudinal peak systolic strain of the left ventricle was averaged from available segments from the apical 2-, 3-, and 4-chamber views. RV longitudinal peak systolic strain was assessed from the RV free wall on the apical 4-chamber view.

Strain is considered a more sensitive marker for systolic failure, compared with conventional echocardiographic parameters.[13] Furthermore, in contrast to conventional echocardiographic parameters, strain measurements rely on few geometric assumptions, which may be uncertain in CHD. As such, left ventricular (LV) and RV longitudinal peak systolic strain (global longitudinal strain [GLS]) were considered the primary outcome for systolic function. Lateral atrioventricular valve tissue Doppler S' and tricuspid annular plane systolic excursion were considered secondary outcomes. RV end-diastolic diameter (RVEDD) was assessed from the 2-dimensional parasternal long-axis view. RVEDD *Z*-scores were computed from published age-related reference values.[14]

Serum Biomarkers

At the specified study time points, venous or capillary blood samples were collected. Samples were collected in EDTA containers, centrifuged, and stored at −80 °C. Samples were analyzed with a protein biomarker panel with 92 biomarkers (OLINK Cardiovascular panel III; Olink Bioscience, Uppsala, Sweden).[15] The biomarkers included in the panel are related to cardiovascular or immunological function and have shown potential as cardiovascular biomarkers.[15] The biomarker panel uses a proximity extension assay, which is highly specific and sensitive.[16] A detailed description of the technique has previously been published.[16] In short, a biomarker-specific antibody is labeled with a specific oligonucleotide. The oligonucleotides of binded antibodies are amplified by polymerase chain reaction. The result of this process is a normalized protein expression, rather than exact quantification. Normalized protein expression is a logarithmic scale, where a 1-unit increase relates to a doubling in concentration. Normalized protein expression can be used to compare expression levels across samples within a study. For analyses with levels below the limit of detection, reported levels were used for analysis (in consultation with OLINK), as the limit of detection is a conservative estimate. If the limit of detection was not reached in >50% of subjects for a specific biomarker, that biomarker was excluded from analysis. NT-proBNP (N-terminal pro-B-type natriuretic peptide) was also assessed at the clinical laboratories of the participating centers to compare to panel biomarker analysis.

Statistical Analysis

Continuous data are presented as "mean±SD" for normal distributions or "median (interquartile range)" for nonnormal distribution. Nominal data are presented

as "count (percentage)." Differences between groups are assessed by a Student *t* test or Wilcoxon test (for nonparametric distributions). Differences between time points are assessed by paired tests and repeated-measures ANOVA. Corrections for confounders were performed by multivariable linear regression. To decrease the false detection rate, only biomarkers that differed between time points assessed by ANOVA are considered in the primary analyses. In a secondary analysis, all remaining biomarkers are considered. *P* values in the primary and secondary analysis are adjusted separately with the Benjamini-Hochberg procedure.[17] Corrections for multiple testing were stratified per statistical test and table (ie, all ANOVA tests and paired *t*-tests were adjusted separately for each table). Reproducibility is assessed by Bland-Altman analysis and intraclass correlation coefficient in a subset of 15 randomly selected echocardiography studies. All data analysis is performed in R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Subjects

Sixty-four children were included from December 2015 to September 2019. For one subject, no intervention was scheduled during the study time span because of parental concerns unrelated to the study. This subject was excluded from all analyses. Sixty-three patients (median age, 4.1 years; range, 0.4–18.2 years) were included for data analysis. Patient characteristics are shown in Table 1. Forty-three patients (68%) underwent surgical and 20 patients (32%) underwent percutaneous ASD closure. Nine surgical patients were previously listed for percutaneous closure, but were deemed unsuitable candidates periprocedurally. ASD closure was successful in all patients, with no relevant residual transatrial shunts. All patients were asymptomatic (New York Heart Association class I) following procedures. Patients who underwent surgical ASD closure, compared with percutaneous ASD closure, were generally younger and had larger ASD sizes. Five patients (8%) had extracardiac defects. For surgically treated patients, this included a congenital hearing disorder (n=1), rheumatic disease (n=1), and anterior cutaneous nerve entrapment syndrome (n=1). For percutaneously treated patients, this included Coffin-Siris syndrome (n=1) and Rieger syndrome (n=1). Assessment at T1 was performed at 1 (1–11) days before intervention. For T2, this was 6 (3–13) days after intervention, and 397 (314–455) days for T3.

Echocardiography

An echocardiogram was obtained for 56 subjects at T1, 56 subjects at T2, and 55 subjects at T3. In addition, strain measurements could not be attained for an additional 1 subject at T1, 2 subjects at T2, and 1 subject at T3. Six patients had missing echocardiographic data at 2 time points. Subjective contractility was good for each patient at each time point. Parameters of cardiac function and serum biomarkers at the specified

Table 1. Patient Characteristics Before Intervention

Characteristic	Study population (N=63)	Surgical ASD closure (N=43)	Percutaneous ASD closure (N=20)	*P* value
Age, y	4.1 (3.1–6.1)	3.6 (1.8–5.2)	4.8 (4.0–8.3)	0.005*
Male sex	22 (35)	14 (33)	8 (40)	0.333
Height, cm	103 (92–120)	99.0 (85.0–115.5)	112.8 (101.0–133.2)	0.007*
Weight, kg	15.4 (11.8–22.3)	14.0 (10.3–20.6)	18.9 (14.5–30.2)	0.006*
BMI, kg/m^2	15.3 (14.0–16.4)	14.8 (13.9–15.9)	15.6 (15.2–17.0)	0.061
BSA, m^2	0.67 (0.55–0.86)	0.63 (0.5–0.82)	0.76 (0.66–1.1)	0.006*
ASD size diameter, mm	15.0 (12.0–25.0)	21.0 (14.0–25.0)	11.0 (9.0–12.0)	<0.001*
Tricuspid insufficiency				0.660
None	20 (32)	15 (35)	5 (25)	
Mild	32 (51)	21 (49)	11 (55)	
Moderate	2 (3)	1 (2)	1 (5)	
Severe	0 (0)	0 (0)	0 (0)	
Age at diagnosis, y	1.5 (0.6–4.2)	1.6 (0.74–4.1)	1.1 (0.6–4.3)	0.765
Intervention duration, min	172 (130–211)	205 (170–222)	109 (90–124)	<0.001*
Perfusion time, min	…	38 (33–45)	…	
Aortic cross-clamp time, min	…	18 (14–23)	…	

Data are given as median (interquartile range) or number (percentage). ASD indicates atrial septal defect; BMI, body mass index; and BSA, body surface area.
*Indicates a statistically significant difference ($P < 0.05$).

time points are shown in Table 2. At baseline, surgically treated patients had higher indexed RVEDD compared with percutaneously treated ones (Z, 1.6±1.0 versus 0.7±1.1; P=0.044). For surgically treated patients, RVEDD decreased at T2 (to Z 0.5±0.8; adjusted P<0.001). For percutaneously treated patients, RVEDD did not differ across study time points (repeated measurements ANOVA; adjusted P=0.865).

Biventricular GLS at the study time points is shown in the Figure. At 2 weeks postintervention, RV GLS was decreased for the surgery group compared with baseline, but not for the percutaneous intervention group (T2 RV GLS, –17.6±4.1 versus –27.1±3.4; P<0.001). These differences remained statistically significant after correcting for age and ASD size (P<0.001 for surgery versus percutaneous intervention). Tricuspid valve tissue Doppler imaging S' and tricuspid annular plane systolic excursion, secondary parameters of RV systolic function, were also depressed at T2 for surgically treated patients, but not for percutaneously treated patients.

A similar, but less extensive, difference between surgical and percutaneous patients was seen for LV GLS at T2. After correcting for age and ASD size, this difference was not statistically significant (P=0.638 for percutaneous versus surgical repair). At T3, LV GLS had returned to baseline (Figure). RV GLS was decreased at T3 compared with T1 for surgically and percutaneously treated patients.

T3 LV GLS related to total intervention time for surgically treated patients (r=0.42; P=0.021). For percutaneously treated patients, total intervention time related to LV GLS at T2 (r=0.66; P=0.002) and T3 (r=0.55; P=0.022). Perfusion time and aortic cross-clamp time did not relate to biventricular GLS (for surgically treated patients).

Serum Biomarkers

During the preparation of biomarker panels, a protocol breach was noted for 2 samples. These samples were excluded from analysis. One biomarker (spondin-1) was below the limit of detection in 95% of samples and excluded from analysis. Serum biomarkers were obtained for 34 subjects at T1, 17 subjects at T2, and 36 subjects at T3.

NT-proBNP (measured as routine marker in the participating hospital's clinical laboratories) was considered above normal limits (defined as 15 pmol/L) for 47% of subjects at T1, and for 20% of subjects at T3. NT-proBNP was increased at T2 compared with T1 and T3 for both groups, although the increase was more pronounced in the surgical group. (Log-transformed) NT-proBNP measured by clinical laboratories and panel biomarker analysis correlated well (r=0.75; P<0.001).

Of 91 biomarkers, 8 differed across time points (shown in Table 3). Expression levels of integrin β-2

Table 2. Echocardiography Parameters at Study Time Points

	Surgical ASD closure						Percutaneous ASD closure					
Parameter	T1	T2	T3	P value ANOVA	P value (T1 vs T2)	P value (T2 vs T3)	P value (T1 vs T3)	T1	T2	T3	P value ANOVA	P value (T1 vs T2)	P value (T2 vs T3)	P value (T1 vs T3)
LV GLS	–20.2±2.9	–18.6±3.2*	–19.8±2.5	0.004†	0.003†	0.056	0.425	–19.9±2.2	–20.2±2.4*	–19.6±2.1	0.396	0.908	0.500	0.138
LV TDI MV S', cm/s^{-1}	10.0±2.9	7.4±2.5	7.6±1.4	<0.001†	<0.001†	0.856	<0.001†	9.0±2.5	8.6±2.8	8.4±2.5	0.625	0.500	0.359	0.542
RV GLS	–30.4±5.3	–17.6±4.1***	–24.0±5.7	<0.001†	<0.001†	<0.001†	0.001†	–29.2±4.4	–27.1±3.4***	–25.8±3.4	0.075	0.645	0.608	0.056
TDI TV S', cm/s^{-1}	13.3±3.4	6.8±1.7***	8.8±2.0***	<0.001†	<0.001†	<0.001†	<0.001†	13.3±2.8	11.8±1.4***	12.2±2.2***	0.205	0.224	0.908	0.258
TAPSE, mm	22.2±4.4	10.5±3.4***	13.7±3.5***	<0.001†	<0.001†	<0.001†	<0.001†	21.4±4.6	20.1±3.8***	19.5±2.7***	0.587	0.610	0.500	0.610
RVEDD, mm	24.4±6.1	18.0±4.3	22.4±4.5	<0.001†	<0.001†	<0.001†	0.359	22.7±6.2	22.1±6.0	22.7±6.2	0.823	0.956	0.610	0.908
RVEDD Z	1.6±1.0*	0.5±0.8	1.0±0.7	<0.001†	<0.001†	0.003†	0.138	0.7±1.1*	0.6±0.9	0.8±0.6	0.865	0.976	0.908	0.908

Reported ANOVA and paired t test P values are corrected for multiple testing. ASD indicates atrial septal defect; GLS, global longitudinal strain; LV, left ventricular; MV, mitral valve; RV, right ventricular; RVEDD, RV end-diastolic dimension; T1, preoperatively; T2, 2-weeks follow-up; T3, 1-year follow-up; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler imaging; and TV, tricuspid valve.

*P<0.05, **P<0.01, and ***P<0.001 for difference between surgical and percutaneous patients.

†Indicates a statistically significant difference (P < 0.05).

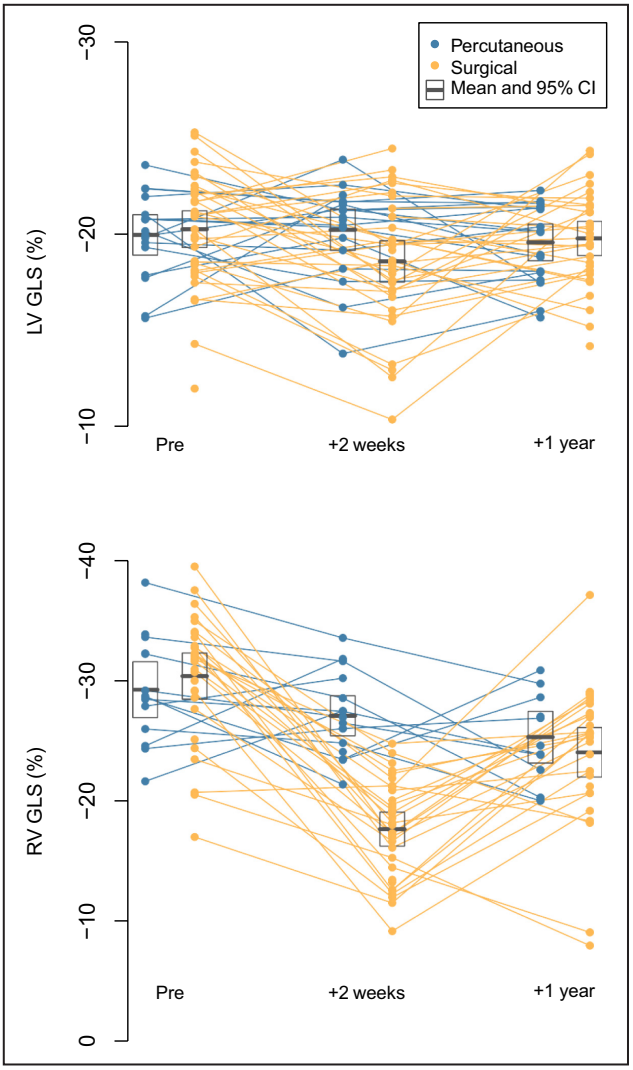

Figure. Biventricular global longitudinal strain (GLS) at the study time points.
Top: Left ventricular (LV) GLS. Bottom: Right ventricular (RV) GLS. Means and 95% CIs of means are provided. *P* values are provided in Table 2. Please note that axes scales differ between plots.

(ITGB2) and cadherin-5 were increased at T3, compared with T1 and T2. NT-proBNP was decreased at T3 compared with T1 and T2. FABP4 (fatty acid binding protein 4) and myoglobin were increased at T3 compared with T2. Chitotriosidase-1 and paraoxonase-3 were increased at T3 compared with T1. Urokinase-type plasminogen activator (uPA) was decreased at T2.

Increased NT-proBNP expression correlated with less favorable LV GLS at T2 (r=0.81; adjusted P=0.014). This correlation remained statistically significant after correcting for age, ASD size, and intervention type (P=0.041). No other biomarkers correlated with LV or RV GLS at any time point (see Tables S1 through S3 for correlation tests). In the secondary analysis, none of the other panel biomarkers differed in expression between surgical and percutaneously treated patients, and none correlated with RV or LV GLS after correcting for multiple statistical testing.

Reproducibility

Reproducibility has been assessed in a random sample of echocardiography studies (53% surgical patients; 47% percutaneous patients). Intraobserver and interobserver variabilities of speckle tracking echocardiography parameters are shown in Table 4. Intraclass correlation coefficient exceeded 0.91 for all parameters. The 95% limits of agreement of interobserver variability for RV GLS ranged from –3.4 to 4.1.

DISCUSSION

In this prospective observational study, we found reduced ventricular performance shortly after surgical, but not percutaneous, ASD closure. The right ventricle was more affected than the left ventricle at early follow-up. LV function returned to baseline at 1-year follow-up, whereas RV function remains slightly reduced compared with baseline. Several biomarkers were expressed in a similarly fluctuating pattern across study time points. Of all assessed biomarkers, only NT-proBNP related to LV function at T2. No correlations between biomarkers and biventricular function were present before intervention or at 1-year follow-up. Details about these biomarkers and their possible role in recovery following cardiac intervention are discussed below.

We found RV GLS was decreased at T3 compared with T1 for both surgically and percutaneously treated patients. Some studies found that RV systolic function remains reduced beyond the early postoperative period following surgical closure, but not following percutaneous closure.[18–21] Others found no differences in systolic function.[22,23] This may relate to the vulnerability of the right ventricle to the adverse effects of cardiopulmonary bypass.[5,24] In our present study, RV GLS at T3 appears well within normal range compared with published age-related reference values, whereas RV GLS at T1 seems increased.[25] RV GLS strain may be increased at T1 because of RV volume overload.[26] Surprisingly, RV size did not differ across study time points for percutaneously treated patients. This may relate to the limited RV dilation of percutaneously treated patients (preintervention RVEDD Z, 0.7±1.1) in our cohort, which consists of patients who are younger than most published cohorts.[27–29] Most studies in literature find RV volumes decrease following surgical and percutaneous ASD closure and continue to decrease in the first year following intervention.[27–29] In current practice, the preferred method to close ASDs is percutaneously, if the patient is a suitable candidate. Our

Table 3. Biomarkers at Study Time Points

Biomarker	Surgical ASD closure				Percutaneous ASD closure			
	T1	T2	T3	*P* value ANOVA	T1	T2	T3	*P* value ANOVA
Cadherin-5	3.3±0.6	2.9±0.9	3.5±0.4	0.156	3.3±0.4	3.3±0.5	3.6±0.5	0.304
Chitotriosidase-1	2.0±1.6*	1.7±1.9	2.4±1.3	0.156	3.0±0.7*	3.0±0.7	3.1±0.7	0.711
FABP4	2.8±0.9	2.4±1.6	3.0±0.7	0.250	3.0±0.4	2.5±0.6	3.2±0.4	0.091
ITGB2	5.3±1.0	4.5±1.8	5.7±0.4	0.156	5.5±0.4	5.2±0.5	5.6±0.5	0.156
Myoglobin	4.7±1.0	4.0±1.5	4.9±0.5	0.197	4.8±0.9	4.1±0.6	5.1±0.6	0.091
NT-proBNP	3.2±1.0	4.2±2.3	2.8±0.6**	0.322	2.7±0.5	3.5±0.9	2.3±0.3**	0.080
Paraoxonase-3	5.0±1.0	4.3±1.7	5.5±0.5	0.197	5.3±0.8	5.1±0.8	5.4±0.8	0.156
uPA	5.3±0.9	4.6±1.6	5.5±0.4	0.202	5.3±0.3	5.0±0.5	5.4±0.4	0.250

Reported ANOVA *P* values are corrected for multiple testing. ASD indicates atrial septal defect; FABP4, fatty acid binding protein 4; ITGB2, integrin β-2; NT-proBNP, N-terminal pro-B-type natriuretic peptide; T1, preoperatively; T2, 2-weeks follow-up; T3, 1-year follow-up; and uPA, urokinase-type plasminogen activator.

*$P<0.05$, **$P<0.01$, and ***$P<0.001$ for difference between surgical and percutaneous patients.

findings support this practice. Surgical and percutaneous closures of ASDs are both routinely performed with similar, excellent outcomes.[21,26] No differences in survival, risk of stroke or arrhythmia, and ventricular volumes between percutaneous and surgical ASD closure have been found after long-term follow-up.[30]

Biomarkers reported in this study may be expressed (1) in the heart, in response to altered loading conditions or perioperative injury; (2) in response to metabolic stress; and (3) as part of the general immune response following perioperative injury.

Several biomarkers may be predominantly expressed by the heart: NT-proBNP is expressed nearly exclusively in the myocardium. NT-proBNP is a well-established biomarker in congenital heart disease, reflecting increased myocardial stretch.[31] The biological half-life of NT-proBNP, ≈120 minutes, is too short for the increase in NT-proBNP to be considered related to the short-term effects of the intervention.[32] After ASD closure, LV filling is relatively increased and myocardial performance may be temporarily decreased, both of which may lead to increased NT-proBNP levels.[29,31,32]

FABP4 is generally considered to be expressed in adipocytes and macrophages, but may be expressed within the pericardial cavity in significant amounts for patients with cardiovascular disease.[33,34] Whether FABP4 is produced by cardiomyocytes, adipocytes in the pericardial fat, or cardiac resident macrophages in these cases is uncertain. It is a prognostic biomarker in adult acquired cardiovascular disease,[35] possibly related to (incipient) metabolic syndrome, and higher FABP4 levels relate to poorer exercise capacity in adolescents with tetralogy of Fallot[36] and Fontan circulations.[37] As such, it has been suggested to have a potential role as biomarker in these patients, which the current results might seem to confirm. However, the biological functions of FABP4 within the heart, and for patients with CHD, need further clarification.

Myoglobin is highly expressed in both cardiac and skeletal muscle, and is considered a marker of muscle injury.[38] Myoglobin may be released from the myocardium because of manipulation, such as during surgery and device placement.[39] In our present study, myoglobin concentrations were temporarily decreased, rather than increased, at T2. The cause of this temporarily decreased myoglobin is currently unclear, but may relate to exhaustion following periprocedural losses or hospitalization-related muscle wasting.

Last, uPA is expressed in the myocardium following cardiac injury and plays a role in wound healing and favorable remodeling.[40] The decreased uPA at T2 in our present study may relate to fibrinolysis, recruitment of

Table 4. Reproducibility of Speckle Tracking Echocardiography (N=15 Randomly Selected Echocardiography Studies)

Variable	Bias	Limits of agreement	Mean of measurements	COV, %	ICC	95% CI
Intraobserver variability						
LV GLS	−0.3	−3.4 to 2.8	−18.6	8.4	0.93	0.83–0.98
RV GLS	0	−5.0 to 5.0	−28.1	9.4	0.96	0.89–0.99
Interobserver variability						
LV GLS	0.2	−3.3 to 3.7	−17.66	1.2	0.91	0.74–0.97
RV GLS	0.3	−3.4 to 4.1	−27.9	6.9	0.97	0.93–0.99

COV indicates coefficient of variation; GLS, global longitudinal strain; ICC, intraclass correlation coefficient; LV, left ventricular; and RV, right ventricular.

circulating uPA to the injury zone, or depletion following increased use.[41]

Some of the biomarkers we noted are related to energy metabolism. During metabolic stress, the heart may preferentially use carbohydrates as fuel, rather than fatty acids.[42] This metabolic shift is required for favorable recovery from cardiac injury.[43] Expression of the following biomarkers may relate to such a metabolic shift. FABP4 is expressed in adipocytes and macrophages and functions at the intersection of metabolism and inflammation.[33] As a lipid-binding protein, it is considered to play a role in intracellular pathways involving adiposity-related disease processes.[35] Paraoxonase-3, an enzyme found in the high-density lipoprotein cholesterol complex, is involved in the lipid metabolism and has antioxidative properties, although its other biological properties have scarcely been studied.[44,45] The increased levels of paraoxonase-3 and FABP4 at T3 in our present study may relate to increased fatty acid metabolism (ie, less metabolic stress) at this time point. Chitotriosidase-1, a human chitinase that is generally understood as part of the innate immune system, has a carbohydrate binding domain and may play a role in carbohydrate metabolism.[46,47] As previously discussed, FABP4 is a prognostic biomarker in acquired and congenital heart disease.[35–37] Chitotriosidase-1 and paraoxonase-3 are less studied in cardiovascular disease. One study found chitotriosidase-1 was not associated with 3-month outcome following acute coronary syndromes.[48] More research is needed to ascertain the function of these biomarkers in a cardiovascular and perioperative setting.

Other biomarkers noted in our protein panel approach are not primarily expressed by the heart, but most likely relate to the systemic inflammatory response observed following CPB.[7] This response is characterized by, among others, immune cell activation and increased vascular permeability.[7] Chitotriosidase-1 is produced directly by macrophages and is considered a marker of macrophage activation.[49] Chitotriosidase-1 may itself have immunological regulatory functions, but these are currently poorly understood.[50] uPA and ITGB2 regulate neutrophil activity and may relate to neutrophil activation following CPB.[51–53] Cadherin-5 and ITGB2, both cell-cell adhesion proteins, are important regulators of vascular permeability.[7] Increased vascular permeability, as seen following CPB, affects end-organ function.[7] This may include the heart and relate to temporarily impaired ventricular function. In our present study, levels of cadherin-5, chitotriosidase-1, ITGB2, and uPA were surprisingly decreased at T2, compared with T1 and T3. This may relate to depletion following increased use or recruitment at injury sites, leading to lower circulating levels. Whether expression of these factors relates to (un)favorable recovery is largely unclear: uPA and ITGB2 have previously been demonstrated to increase the extent of ischemia and reperfusion injury, by either increased neutrophil extravasation or inflammation-mediating properties.[53,54] Increased neutrophil activity and transvessel migration may facilitate wound repair, but may induce an extended inflammatory response associated with unfavorable outcomes.[53–55] In our present study, none of these biomarkers related to ventricular function at any time point.

Reduced ventricular performance shortly following surgery for CHD, as demonstrated in the current study by the strain measurements, has previously been described, but the mechanisms behind these observations are incompletely understood.[5] Surgical ASD closure is a relatively minor procedure compared with more extensive surgeries for CHD, with limited CPB duration. Despite this, we found importantly lower ventricular strain following surgical ASD closure but not following catheter-based interventions. For comparison, the decrease in RV GLS following surgical ASD closure, ≈13 strain points, is similar to the mean difference between healthy subjects and patients with heart failure with reduced ejection fraction.[56] The temporarily impaired ventricular performance was well tolerated, as all patients were asymptomatic following procedures. Although selection bias plays a role (more volume overload in surgically treated patients), the temporarily impaired ventricular performance may also be explained by the effects of perioperative conditioning, including CPB. The response to CPB may lead to damage in multiple organ systems, including the kidney, liver, and brain. Many of the cytokines involved in the response to CPB have short biological half-lives.[57–59] However, reduced ventricular performance may persist over weeks to months following CHD surgery.[5] We found several biomarkers were disparate at T2 (1 to 2 weeks after the intervention), compared with T1 and T3. The biological functions associated with these biomarkers might play a role in the development of temporarily reduced ventricular function, its subsequent recovery, and myocardial repair. Improving our understanding of perioperative cardiac damage, temporarily reduced ventricular function, and subsequent recovery might identify new targets for treatment, such as improved myocardial protection strategies or immunomodulation for beneficial recovery following surgery. This might be especially relevant in complex congenital heart disease, for which patients may require multiple and extensive surgeries during childhood.

Limitations

In this prospective exploratory study, we systematically assessed percutaneously and surgically treated patients with ASD using novel echocardiographic and

serum biomarkers and with a relatively long follow-up. Despite this study's strengths, some limitations of this research should be considered. Our study was subject to selection bias as children (deemed) unsuitable for percutaneous closure were selected for surgical closure. Surgical patients were younger, had larger ASDs, and had more dilated RVs, which may confound our results. Correcting for these confounders did not affect our findings with regard to RV function. The reduction in function of the left ventricle was less extensive, and did not remain statistically significant after correcting for confounders. We only considered 3 time points for the evaluation of ventricular function, as previous research found a minor difference between ventricular function at 1 day after surgery, compared with 2 weeks after surgery.[4] Our study population was relatively healthy and homogeneous. Differences across subjects are relatively small, which may limit our ability to assess more subtle differences and associations.

For biomarker analysis, we used a commercially available proximity extension assay. This results in a normalized expression rather than absolute concentrations. The reported expression cannot be directly compared across different study populations or with healthy reference levels. Biomarker expression may vary with age. Olin et al found the expression of all reported markers in our current study, with the exception of NT-proBNP, was increased at the age of 6 months, compared with birth.[60] We found serum levels of several biomarkers differed across study time points. This may relate to reduced expression, but may also relate to increased use or recruitment at injury sites (reducing circulating biomarkers). Furthermore, serum levels do not directly reflect biological activity. Despite these limitations, the biomarker analysis provided in our present study may provide insight into their behavior in the perioperative setting and, in light of the aforementioned limitations, should be considered exploratory. Further experimental studies are needed to elucidate the associated biological functions hypothesized in our present study.

CONCLUSIONS

In our observational study, ventricular function was reduced at short-term (1 to 2 weeks) after ASD closure for surgically, but not for percutaneously, treated patients. The right ventricle was more affected than the left ventricle. At 1-year follow-up, LV performance had returned to baseline, whereas RV performance remained slightly reduced compared with baseline, probably relating to different loading conditions. Several biomarkers of cardiac function, energy metabolism, and systemic inflammatory response to perioperative injury were abnormal at 1 to 2 weeks postintervention. These findings might provide insight into the processes that influence reduced ventricular performance and recovery in the weeks following cardiac surgery with CPB.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S3

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SUPPLEMENTAL MATERIAL

Correlations between biomarkers and biventricular GLS at study time points

Table S1

	LV GLS p			*RV GLS*		
				r	*p*	*Adjusted p*
Biomarker	*r*		*Adjusted p*			
CDH5		.356				
CHIT1	-0.18	.076	.743	-0.26	.260	.676
FABP4	-0.34	.214	.340	-0.07	.765	.918
ITGB2	-0.24	.814	.676	-0.28	.227	.676
MB	-0.05	.074	.930	-0.15	.509	.872
NT-	-0.34	.560	.340	-0.03	.912	.956
proBNP	-0.12	.952	.872	-0.41	.063	.340
PON3	0.01	.610	.956	-0.12	.617	.872
uPA	-0.10		.872	-0.28	.227	.676

Table S2

	LV GLS p			*RV GLS*		
				r	*p*	*Adjusted p*
Biomarker	*r*		*Adjusted p*			
CDH5		.409				
CHIT1	0.23	.304	.818	-0.59	**.043**	.340
FABP4	0.28	.237	.694	-0.59	**.041**	.340
ITGB2	0.33	.591	.676	-0.72	**.008**	.102
MB	0.15	.475	.872	-0.72	**.008**	.102
NT-	0.20	**<.001**	.872	-0.53	.078	.340
proBNP	0.81	.270	**.014**	-0.34	.282	.676
PON3	0.30	.338	.676	-0.54	.071	.340
uPA	0.27		.738	-0.72	**.008**	.102

Table S3

	LV GLS p			*RV GLS*		
				r	*p*	*Adjusted p*
Biomarker	*r*		*Adjusted p*			
CDH5		.521				
CHIT1	-0.12	.675	.872	-0.02	.915	.956
FABP4	0.08	.932	.908	0.07	.738	.908
ITGB2	0.02	.244	.956	-0.08	.701	.908
MB	-0.22	.600	.676	-0.14	.487	.872
NT-	0.10	.693	.872	0.24	.223	.676
proBNP	0.07	.956	.908	0.01	.944	.956
PON3	0.01	.552	.956	-0.05	.790	.924
uPA	-0.11		.872	-0.07	.720	.908

GLS: global longitudinal strain; CDH: cadherin-5; CHIT1: chitotriosidase-1; FABP4: fatty acid binding protein 4; ITGB2: integrin beta 2; MB: myoglobin; NT-proBNP: N-terminal pro brain natriuretic peptide; PON3: paraoxonase-3; uPA: urokinase type plasminogen activator.