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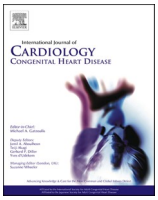

Left ventricle function after arterial switch procedure for D-transposition of the great arteries: Long term evaluation by speckle-tracking analysis

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ABSTRACT

Aim: The objective of this study was to assess left ventricle (LV) function in patients underwent arterial switch procedure (ASO) for transposition of great arteries (TGA) in long-term follow-up.
Methods: We studied 59 asymptomatic patients (43 male) who have undergone single-stage ASO for TGA, aged 13.9 ± 4.8 years, with a normal LV ejection fraction, compared to healthy peers. We evaluated LV volume, function and myocardial deformation in asymptomatic patients with normal ejection fraction by using speckle-tracking echocardiography (STE).
Results: Global longitudinal strain (GLS) was lower in patients compared to healthy peers throughout all age groups (5–9 years: −20.03 ± 0.65% vs 21.00 ± 1.30%, p = 0.083; 10–14 years: −19.43 ± 1.75% vs −21.80 ± 1.30%, p < 0.0001; 15–19 years: −19.05 ± 1.65% vs −22.50 ± 1.30%, p < 0.0001; 20–24 years: −17.90 ± 0.85% vs −20.90 ± 1.30%, p < 0.0001; >25 years: −18.60 ± 0.42% vs 20.60 ± 1.20%, p = 0.041). At the univariate analysis GLS resulted significantly related only to the presence of restrictive patent foramen ovale at birth (p = 0.0016). At the multivariate analysis GLS was significantly related to prenatal diagnosis, restrictive patent foramen ovale and by-pass time.
Conclusion: Children and young adults late after ASO demonstrate normal ejection fraction, but present sub-clinical signs of myocardial dysfunction, such as reduction of longitudinal strain. Our findings support the usefulness of STE to detect it precociously.

1. Introduction

Transposition of the great arteries (TGA) is a conotruncal abnormality in which the aorta arises from the right ventricle (RV) and the pulmonary artery arises from the left ventricle (LV) resulting in discordant ventriculoarterial connections. TGA occurs in approximately 31.5 in 100,000 live births and it is the 10th most common congenital heart defect and the second most common cyanotic lesion after tetralogy of Fallot [1]. Without surgical correction, preoperative mortality in the neonate is approximately 30% within the first week of life and up to 90% within the first year [2].

The arterial switch operation (ASO), first described by Adib Jatene in 1976, is currently the procedure of choice when the anatomical conditions and the timeline are appropriate; it is performed in the first month of life [3,4]. Current perioperative mortality is under 4% and long-term survival is around 97% at 25 years follow-up. However, long-term morbidity after ASO is substantial and between 25 and 30% of patients require re-interventions [5]. The most common late complications include coronary artery stenosis, right ventricular outflow tract obstruction, neoaortic dilation and neoaortic insufficiency. Aortic regurgitation and the development of gothic arch [6] cause altered loading conditions, that could affect LV function. Moreover recent studies have shown that coronary artery abnormalities [7], decreased coronary artery vasoreactivity [8], reduced coronary flow reserve, proximal intimal proliferation [9], and reversible myocardial perfusion defects are present in patients who have undergone ASO [10–12] and sub-optimal coronary perfusion could lead to chronic ischemia, inducing LV damage and remodeling. For all these reasons, as recommended by

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the American Society of Echocardiography (ASE) guidelines on Multimodality Imaging Guidelines of Patients with TGA, the assessment of ventricular function, including more quantitative techniques as speckle-tracking echocardiography (STE), is an important component of the clinical evaluation during follow-up [13,14].

LV systolic function in patients who have undergone ASO has largely been found to lie within the normal range when assessed by using standard echocardiographic indices (such as Shortening Fraction, Ejection Fraction) [15,16]. Deformation imaging is a more sensitive tool to detect early ventricular dysfunction and it has shown to accurately predict a decline in LV function in a variety of conditions, including heart failure in cardio-oncology [17]. Limited data are published on deformation imaging of the LV in patients after ASO for TGA. Impaired deformation expressed by Global Longitudinal Strain (GLS) and torsion of the LV, despite normal EF, has been reported in pediatric patients after ASO in studies by Pettersen et al. [18] and Di Salvo et al. [19] Only few data on deformation imaging in older patients after ASO have been reported [20]. Van Wijik et al. studied GLS both in children and in older patients but their patient population was heterogenic, including one- and two-stage arterial switch ASO patients and patients with EF reduction.

The aim of our study is to assess LV function in children and young adults after one-stage ASO for TGA during long-term follow-up. In particular, our purpose is to evaluate LV function and myocardial deformation in asymptomatic patients through STE compared with standard echocardiographic measures.

2. Methods

2.1. Study design and patients selection

A prospective cross-sectional cohort study was performed between May 2019 and August 2019. We studied patients who have undergone single-stage ASO for d-TGA, with or without ventricular septal defect (VSD) associated, regularly followed at Pediatric Cardiology and Adult Congenital Unit of University of Bologna, Italy.

Inclusion criteria were: age $\geq$5 years, no symptoms (New York Heart Association class I) and normal LV EF ($\geq$55%), measured by modified Simpson's method. Exclusion criteria were: presence of LV akynesia or hypokinesia and hypertension and/or metabolic disordes at the time of the study.

Informed consent was obtained from all patients and additional consent by parents if aged <18 years of age.

Patients underwent clinical examination, electrocardiography, standard Doppler echocardiography and STE study.

2.2. Echocardiography data

Transthoracic echocardiography was performed on a Philips EPIQ7 machine (Philips, Bothell, Washington, USA) with a 5 MHz transducer, using a standard protocol including 2D imaging, pulsed-wave Doppler velocities, and tissue Doppler imaging. QLAB software version 9.0 (Philips) was used for offline analysis of echocardiographic cine-loops stored. A certified medical analyst (A.B.) with echocardiographic experience performed the echocardiographic exams while offline analysis was performed by a single experienced examinator (G.B.).

LV and left atrial dimensions were taken from 2D tracings. LV mass indexed for body surface area (BSA) was calculated using the Devereux-modified American Society of Echocardiography formula [21]. LV ejection fraction was determined using modified Simpson's biplane method. Mitral inflow velocities (peak early diastolic velocity, peak late diastolic velocity, their ratio E/A, and early diastolic wave deceleration time) were obtained using pulsed-wave Doppler. Myocardial velocities were analyzed using Tissue Doppler imaging from the apical four-chamber view at the septal and lateral mitral annulus level. Peak velocities at the septal and lateral mitral annulus during early diastole were measured and the ratio of peak early transmitral velocity to early diastolic mitral annular velocity (E/e' average) was calculated. Peak early systolic velocities at the same levels were also measures.

For STE analyses, two-dimensional grayscale images of the left ventricle in the apical four-, two-, and three-chamber views were acquired. Aortic valve closure was visually determined by apical three-chamber view [18]. Four consecutive endexpiratory cardiac cycles using a frame rate higher than 50 Hz harmonic imaging in each echocardiographic view were acquired. Offline analysis was performed using 2D speckle tracking software (Automated Cardiac Motion Quantification, aCMQ, QLAB, Philips) [22]. The software automatically tracked the endocardial surface during the cardiac cycle. Manual adjustments of region of interest and automated trackings were performed when necessary. From the apical views longitudinal peak systolic strain was assessed through basal, mid, and apical wall segments. The mean global longitudinal strain (GLS) was obtained and reported as percentage (Fig. 1).

Reference values for healthy peers were obtained from the study of Marcus et al. [23], that reports age-dependent reference values using 2DSTE imaging in a large pediatric and young adult cohort.

2.3. End-points

Primary endpoints were the detection of subclinical LV dysfunction, expressed as a reduction of GLS compared to reference values, and its relation to surgical, clinical and echocardiographic variables in patients who underwent neonatal ASO.

2.4. Statistical analysis

Categorical variables are expressed as percentages, continuous variable are presented as mean $\pm$ standard deviation if normally distributed. For comparison of age groups, independent samples *t*-test or ANOVA was used for continuous variables as appropriate and chi-square test for was use for categorical variables. Univariate and multivariate analyses were performed to assess relationship between global longitudinal strain and demographic, anatomical and surgical factors, based on clinical relevance and potential impact on cardiac function. For all tests, a p value of <0.05 was accepted as statistically significant. All analyses were performed using STATA/IC version 15.

3. Results

A total of 59 consecutive patients participated in this study. Two patients were affected by TGA and coarctation of the aorta and they underwent a complete repair with ASO and coartectomy and end-to-end anastomosis. No residual systemic outflow obstruction was documented.

All 59 patients (43 male, 72%) were asymptomatic and none had undergone further surgery since the initial operation. The median age of participants was 13.9 $\pm$ 4.8 years. All were in sinus rhythm without electrocardiographic changes at rest suggesting myocardial scar or ischemia. 6 patients showed complete bundle branch block. 10 patients were treated with ACE inhibitors or sartans and/or betablockers for aortic dilatation.

At birth 22 (37%) patients had TGA with VSD, 54 (91%) had restrictive PFO (defining restrictive a PFO when maximal diameter is < 5mm) and 56 (94%) had PDA. 36 patients (62%) had usual coronary anatomy at diagnosis, 22 (37%) had unusual coronary anatomy at diagnosis according to the Yacoub classification (4 patients type B, 1 type C, 12 type D and 5 type E). One had no anamnestic details about the anatomy at birth, because underwent surgery in an another country.

The median age of intervention was 9.4 $\pm$ 6.1 days. 12 patients (20%) had a VSD closure with a patch, 5 (8%) by suture (5 patients had a spontaneous closure during the first week. The cardio-pulmonary bypass time and the aortic cross-clamp time were 149.88 $\pm$ 31.75 and 100.58 $\pm$ 16.92 min. Few post-procedure complications occurred. One patient

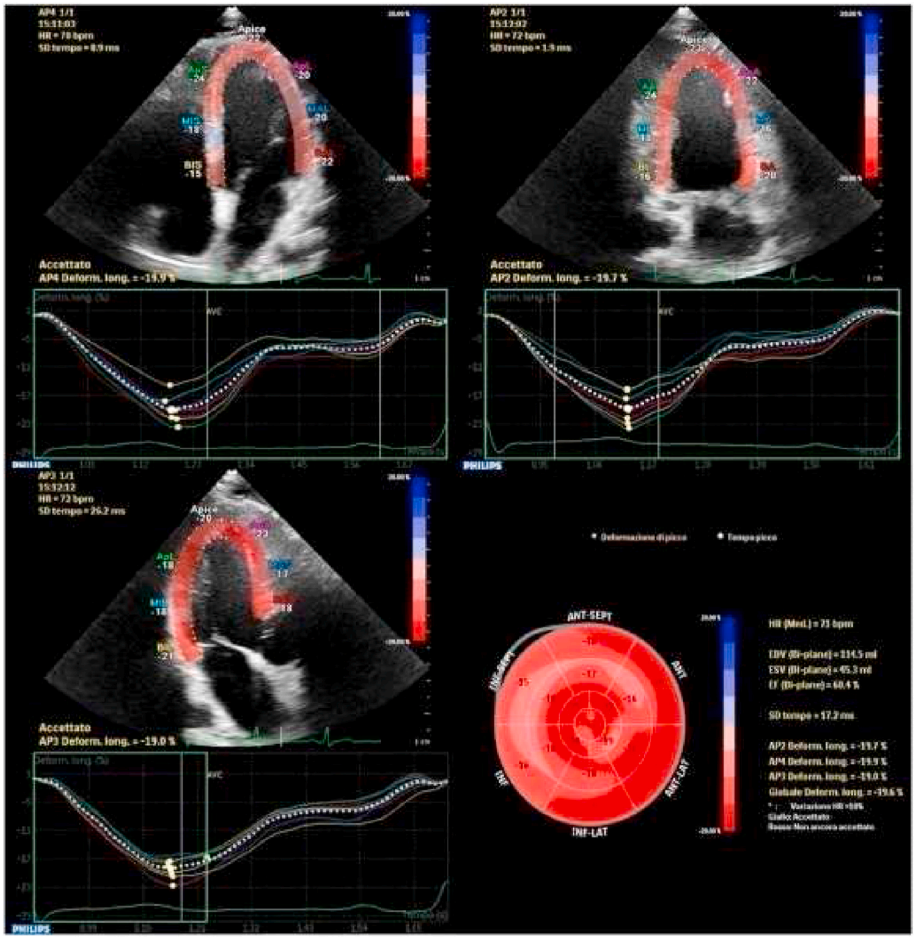

Fig. 1. Global Longitudinal Strain (GLS) was obtained from apical views.

underwent sternal closure in a second stage due to hemodynamic instability. 2 patients had hemi-diaphragmatic paralysis, 1 had sustained supraventricular arrhythmia and 1 developed pericardial effusion 3 months after the surgery.

A coronary angiography was performed in all patients between 12 and 24 months after the surgery. 6 (10%) patients showed coronary occlusion, 3 of these had adequate collateral circulation, one underwent left main and anterior descending artery angioplasty (5.7 years after the ASO) for the evidence of inducible ischemia and two underwent angioplasty with stenting, one on the anterior descending and right coronaries and one on the right coronary (14.9 and 11.9 years after ASO respectively) for angina and for evidence of septal hypokinesia, respectively. 10 patients (17%) developed pulmonary stenosis, of these 2 underwent angioplasty and one angioplasty with stenting (time from ASO 71.06 ± 69 months). Only one patient required a surgical plasty of left pulmonary branch 3 years after. Table 1 shows general and surgical data.

3.1. Standard echocardiographic evaluation

All patients had normal ejection fraction, measured by modified Simpson's method (mean 60.81 ± 3.44%) with LVEDD mean of 43.74 ± 5.27 mm and a LV mass index mean of 67.17 ± 17.91 g/m2. LVEDD z-score was within normal range, except for 2 patients, that showed mild LV dilatation (LVEDD z-score +2.57 and + 2.64). At the Doppler analysis no one had diastolic dysfunction (E/A mean 2.31 ± 0.78 with E/e' average mean 8.36 ± 2.19). At Pulsed-wave TDI peak early systolic velocities at the septal and lateral mitral annulus were at the lower normal limit (S′ mit 6.99 ± 0.99 and 8.46 ± 1.44 cm/s respectively). Normal left atrium dimension (Left atrial volume indexed, LAVI, 21.29 ± 6.29) and normal right ventricular longitudinal function (S′ tric 8.74 ± 1.45 cm/s) were documented in all patients.

At the Color-doppler analysis, of note, 40 patients had trace-to-mild aortic regurgitation, and 4 (6.8%) had moderate aortic regurgitation.

Comparison of main standard echocardiographic data across age groups was performed (Table 2). Of note, significant differences were documented in LV dimension parameters, but not in indexed values for BSA (LV mass index 66.76 ± 17.38 g/m2, p = 0.194; LVEDV biplane index 64.87 ± 10.94 ml/m2, p = 0.908). E/e' lat and E/e' average had significant difference across age group.

3.2. Speckle-tracking echocardiography study

In patients who have undergone ASO, GLS was significantly lower compared to reference data across age groups, except in the youngest group (Table 3 and Fig. 2). An ancillary analysis was made excluding patients with moderate aortic regurgitation (n = 4) and patients with history of coronary stenosis (n = 6). In this subpopulation GLS remained significantly lower when compared to reference values by age (Table 4). Comparison of GLS across age groups was performed (Table 5), showing a tendency to statistical significance (p = 0.0878), in particular we observed a reduction of GLS in older patients. Longitudinal deformation had lowest values in the anterior septal wall at the basal and mid levels (−15.85 ± 3.37 and −15.56 ± 3.34, respectively) and in the basal infero-lateral wall (−15.63 ± 3.98). Univariate analysis showed no statistical significant correlation between decreased GLS values and main clinical and anatomical characteristics at birth, surgical details and coronary complications. GLS resulted significantly related only to the

Table 1
General and surgical data.

Clinical Characteristics at birth	**N = 59**
Sex (male %)	43 (72.88)
Gestational age (weeks)	38.74 ± 1.51
Prenatal Diagnosis (%)	29 (50.88)
SpO2 at birth (%)	72.33 ± 12.20
Weight at birth (gr)	3263.36 ± 500.55
Age at surgery (days)	**9.41 ± 6.14**
Anatomical Characteristics at birth	
PDA (%)	56 (94.92)
Restrictive PFO (%)	**54 (91.53)**
VSD (%)	**22 (37.29)**
Usual coronary anatomy (%)	**36 (62.07)**
Urgent Rashkind (%)	42 (72.41)
Surgical details	
Bypass time, min	**149.88 ± 31.75**
Aortic clamp, min	100.58 ± 16.92
VSD closure by suture (%)	5 (8.62)
VSD closure by patch (%)	**12 (20.69)**
Post-procedural complications (%)	5 (8.62)
Pulmonary and coronary stenosis during follow-up	
Pulmonary stenosis (%)	10 (17.24)
Pulmonary angioplasty (%)	3 (5.17)
Time to angioplasty from ASO (months)	71.06 ± 69
Coronary stenosis (%)	**6 (10.16)**
Coronary angioplasty (%)	3 (5.17)
Time to angioplasty from ASO (years)	10.85 (4.76)
Clinical characteristics at the study	
Age (years)	**13.94 ± 4.88**
BSA	1.47 ± 0.34

PDA, patent ductus arteriosus; VSD, ventricular septal defect; ASO, arterial switch operation; BSA, body surface area; NYHA, New York Heart Classification; PFO, patent foramen ovale.

presence of restrictive patent foramen ovale at birth (p = 0.0016, R^2 0.1620).

At the multivariate analysis GLS was significantly related to prenatal diagnosis, restrictive patent foramen ovale and by-pass time (Table 6). Of note, by-pass time was not significantly related to coronary pattern (p = 0.8584).

4. Discussion

Although long-term outcomes after the ASO for TGA are excellent and the majority of pediatric survivors are asymptomatic and have normal EF, our study demonstrates that there are significant reduction of systolic longitudinal myocardial deformation when compared to healthy reference values.

4.1. Abnormal global longitudinal strain

Across age groups, longitudinal deformation was significantly reduced in patients who underwent ASO, when compared to normal values reported in previously published data [23]. Only the youngest group (5–9 years) showed no significant difference but only a trend (p = 0.083), probably due to small number of patients of the group.

Moreover, GLS remained significantly reduced in all age groups, except in the youngest (p = 0.0575), even when patients with confounding factors, such as moderate aortic regurgitation and/or coronary stenosis, were excluded.

This result is in line with previous studies [18–20]. Di Salvo et al. showed a significant reduction in longitudinal myocardial deformation in pediatric patients after ASO (average age 8.7 years) and Van Wijk et al. demonstrated GLS reduction in older patients (average age 20.6 years). These myocardial alterations could be explained by the presence of coronary artery abnormalities, previously reported in ASO patients, such as abnormal coronary arterial vasomotor response, reduced coronary flow reserve or cardiac autonomic neuropathy, that may result in myocardial ischemia [7,24,25]. Moreover, as demonstrated in other conditions, the longitudinally oriented endocardial fibers, responsible for the LV longitudinal deformation, are the most susceptible to hypoperfusion [26].

In our study, the decrease in GLS resulted significantly related to the presence of restrictive PFO at birth (p = 0.0016). Of interest, no relationship was found between GLS and presence of VSD, coronary anatomy and/or the development of coronary stenosis. No correlation was observed between GLS and surgical VSD closure, probably of the small number of patients. Moreover at the multivariate analysis GLS resulted related also to prenatal diagnosis and surgical by-pass time (p = 0.0030). It is known that the presence of restrictive PFO may compromise survival after birth. This restriction, reported in approximately 20% of fetuses with TGA, leads to progressive severe hypoxia and acidosis, as the ductus arteriosus closes after birth [27,28]. It is also demonstrated that inadequate mixing and chronic hypoxia predisposes to neurological

Table 3
Global longitudinal strain of age groups compared to reference values.

Age group	n	GLS, %	GLS reference, % (n)	p-value
5 - 9 y	6	−20.03 ± 0.65	−21.00 ± 1.30 (36)	0.083
10 - 14 y	31	−19.43 ± 1.75	−21.80 ± 1.30 (29)	**<0.0001**
15 - 19 y	12	−19.05 ± 1.65	−22.50 ± 1.30 (21)	**<0.0001**
20 - 24 y	8	−17.90 ± 0.85	−20.90 ± 1.30 (25)	**<0.0001**
>25 y	2	−18.60 ± 0.42	−20.60 ± 1.20 (13)	**0.041**

GLS, global longitudinal strain; Y, years.

Table 2
Comparison of standard echocardiographic data across age groups.

	5–9 y (n = 6)	10–14 y (n = 31)	15–19 y (n = 12)	20–24 y (n = 8)	>25 y (n = 2)	total	p-value
LVEDD (mm)	37.83 ± 1.47	42.93 ± 4.99	46.33 ± 3.84	46.12 ± 6.29	49.0 ± 1.41	43.75 ± 5.27	0.0028
ISV (mm)	6.33 ± 1.34	6.97 ± 1.08	7.33 ± 0.65	7.75 ± 1.03	9.5 ± 0.71	7.17 ± 1.15	0.003
LV mass index (g/m2)	70 ± 15.24	68.54 ± 15.86	56.75 ± 16.84	68.75 ± 23.47	81.5 ± 17.38	66.76 ± 17.38	**0.194**
LVEDV 4c (ml)	54.17 ± 12.53	86.68 ± 25.94	113.25 ± 19.37	115.25 ± 35.33	118 ± 11.31	93.71 ± 30.61	0.0000
LVESV 4c (ml)	18.67 ± 5.16	32.93 ± 10.86	46.33 ± 7.84	46.12 ± 13.12	47.5 ± 2.12	36.49 ± 13.13	0.0000
LVEDV 2c (ml)	57.5 ± 10.76	89.93 ± 28.69	116.83 ± 21.25	113.75 ± 36.56	122.5 ± 6.36	96.44 ± 31.84	0.0002
LVESV 2c (ml)	22.33 ± 4.88	34 ± 13.57	46.58 ± 12.29	47.25 ± 15.99	51.5 ± 0.71	37.76 ± 14.97	0.0006
LVEDV biplane (ml)	57.33 ± 11.00	89.52 ± 27.42	115.75 ± 19.69	115.62 ± 35.40	123.5 ± 9.19	96.27 ± 31.03	0.0000
LVEDV biplane index (ml/m2)	61.97 ± 11.06	64.93 ± 10.14	65.23 ± 10.29	67.27 ± 16.67	61.09 ± 2.84	64.87 ± 10.94	**0.908**
EF biplane (%)	62.33 ± 2.42	61.87 ± 3.09	58.92 ± 3.53	58.5 ± 1.93	58.5 ± 2.12	60.75 ± 3.29	0.0074
S′ mit lat (cm/s)	7.88 ± 1.22	8.50 ± 1.52	8.4 ± 1.35	8.79 ± 1.74	8.5 ± 0.56	8.46 ± 1.44	0.8774
S′ mit med (cm/s)	6.94 ± 1.16	7.09 ± 0.93	6.9 ± 1.20	6.85 ± 1.10	6.75 ± 0.64	6.99 ± 0.99	0.9561

LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; IVS, interventricular septum; LVEDV, left ventricular end-diastolic volume; LVESV, left vetricular end-systolic volume; EF, ejection fraction; E/A, transmitral early/late diastolic velocity ratio; E/e' avg, early transmitral/early diastolic mitral annular velocity ratio average; lat, lateral; med, medial; DT, deceleration time; LA, left atrium; LAVI, left atrial volume indexed for BSA; S′, peak early systolic velocity; mit, mitral; y, years.

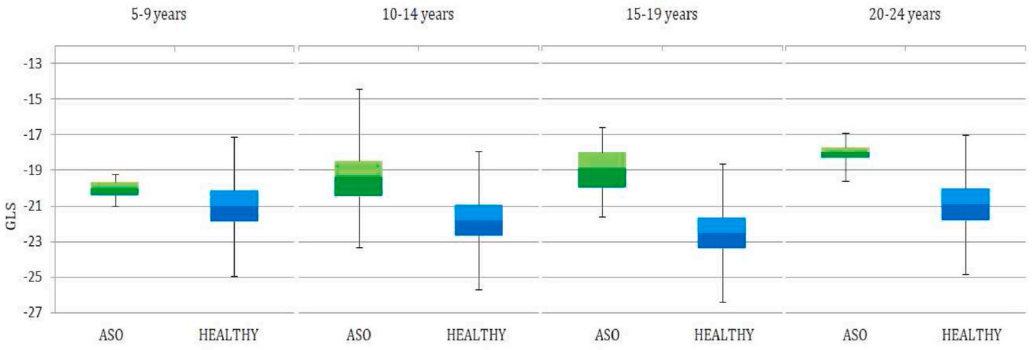

Fig. 2. Global longitudinal strain (GLS) of age groups in patients underwent Arterial Switch Procedure (ASO) and healthy references.

Table 4
Global longitudinal strain of age groups, without patients with moderate aortic regurgitation and/or history of coronary stenosis, compared to reference values.

Age group	n	GLS, %	GLS reference, % (n)	p-value
5–9 y	5	−19.84 ± 0.50	−21.0 ± 1.3 (36)	0.0575
10–14 y	31	−19.44 ± 1.75	−21.8 ± 1.3 (29)	**<0.0001**
15–19 y	8	−18.50 ± 1.59	−22.5 ± 1.3 (21)	**<0.0001**
20–24 y	4	−17.60 ± 0.48	−20.9 ± 1.3 (25)	**<0.0001**
>25 y	1	−18.30 ± 0	−20.6 ± 1.2 (13)	.

GLS, global longitudinal strain; Y, years.

injuries [29]. Porayette et al. [30] demonstrated reduced oxygen delivery to the coronary arteries and the brain in TGA fetuses, predisposing to fetal myocardial hypoxia. We hypothesized that patients with restrictive PFO, and so with severe hypoxia, may have myocardial injury.

In our population 91% patients had restrictive PFO, but only 72% had urgent (within 12 h) balloon atrial septostomy (Rashkind procedure). This could be explained due to scarce prenatal diagnosis in the past years (50% in our population), as suggested by our findings at the multivariate analysis. Indeed, prenatal diagnosis of TGA was shown to be efficient in reduction early mortality by decreasing the required time for Rashkind procedure [31]. Moreover, it is associated with decreased neonatal morbidity, including decreased use of mechanical ventilation, antibiotics, and emergent surgery [32].

In our study at the multivariate analysis by-pass time seems to be related to long-term GLS reduction. Surgical times are associated to fibrotic remodeling, as demonstrated in MRI studies on patients with repaired Tetralogy of Fallot [33].

In addiction our patients showed lowest values of longitudinal strain mainly in anteroseptal wall, in particular at the basal and mid levels, irrespectively of the presence of VSD. One explanation may be a hypoplastic left anterior descending coronary artery present in many of the TGA patients, as demonstrated in previous studies [7].

Finally comparison of GLS across age groups showed a tendency to reduction in older patients, according to studies on healthy subjects [34].

4.2. Clinical implications

Even though long-term clinical outcome is considered excellent in patients after ASO for TGA for the duration of follow-up now available, the decrease in GLS gives rise to concern for long-term preservation of LV function. This subclinical sign may help to select patients at higher risk to develop earlier ventricular dysfunction and to provide them stricter follow-up and/or second level examinations.

Moreover, reduced exercise capacity is relatively common in children and young adults who have undergone ASO and more data are needed to correlate GLS to functional capacity.

Based on these results strain analysis should be incorporated in routine evaluations. Long-term longitudinal follow-up studies are needed to confirm if these abnormalities predispose for clinically significant dysfunction and adverse clinical outcome.

Finally, our results confirm the advantage of prenatal diagnosis to detect factors, such as restrictive PFO, that may influence clinical outcome. Promoting prenatal diagnosis predispose adequate treatment and timing after birth.

4.3. Limitiations

The present study carries some limitations. First, this study includes patients with VSD at birth and patients with aortic regurgitation and/or coronary stenosis during the follow-up. Subgroup analysis showed no significant differences between these groups. We decided to include these patients to best represent the entire heterogenic population of patients after ASO. Second, we used a different speckle tracking software compared with one used for reference data.However, many studies showed good comparability in GLS between vendors [35].

Furthermore, given the cross-sectional nature of our cohort study,

Table 6
Multivariate analysis of clinical, anatomical characteristics at birth, surgical details and GLS (global longitudinal strain).

	p-value	R [2]
Prenatal diagnosis + restrictive PFO	**0.0008**	0.2322
Prenatal diagnosis + restrictive PFO + By-pass time	**0.0030**	0.2326

GLS, global longitudinal strain; PFO, patent foramen ovale.

Table 5
Comparison of global longitudinal strain and four-, two-, three-chambers longitudinal strain across age groups.

Age	5-9 y (n = 6)	10-14 y (n = 31)	15-19 y (n = 12)	20-24 y (n = 8)	>25 y (n = 2)	Total	p-value
4C LS (%)	−20.05 ± 1.52	−19.76 ± 2.02	−19.46 ± 1.75	−18.42 ± 1.46	−19.30 ± 0	−19.53 ± 1.84	0.4248
2C LS (%)	−20.08 ± 1.45	−20.05 ± 2.43	−19.52 ± 1.78	−18.86 ± 1.04	−17.55 ± 2.62	−19.70 ± 2.12	0.3475
3C LS (%)	−20.02 ± 0.49	−18.50 ± 2.60	−18.16 ± 2.19	−17.21 ± 1.43	−19.05 ± 1.34	−18.43 ± 2.28	0.2389
GLS (%)	−20.03 ± 0.65	−19.43 ± 1.75	−19.02 ± 1.65	−17.90 ± 0.85	−18.60 ± 0.42	−19.18 ± 1.60	**0.0878**

Y, years; GLS, global longitudinal strain; LS, longitudinal strain.

any progression of findings or prognostic value in terms of clinical outcome could therefore not be assessed.

Ultimately, as 2DE was assessed by single observer, interobserver variability could not be evaluated.

5. Conclusion

Even though children and young adults late after the ASO demonstrate normal ejection fraction, subclinical signs of myocardial dysfunction, such as reduction of global longitudinal strain, are present.

Our findings support the usefulness of longitudinal strain to detect LV dysfunction precociously. Long-term longitudinal follow-up studies are needed to confirm if these abnormalities predispose for clinically significant dysfunction and adverse outcome.

Lastly, restrictive PFO at birth, prenatal diagnosis and surgical times may influence long-term LV remodeling.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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