International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Left ventricular outflow tract obstruction and its impact on systolic ventricular function and exercise capacity in adults with a subaortic right ventricle☆

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ARTICLE INFO

Article history:
Received 28 February 2017
Received in revised form 9 May 2017
Accepted 12 June 2017
Available online xxxx

Keywords:
Transposition of great arteries
Ventricular outflow obstruction
Ventricular function
Exercise capacity

ABSTRACT

Background: In biventricular hearts the filling and contractility of one ventricle affects the performance of the other. In this study, we compared right ventricular systolic function and exercise capacity in patients with a subaortic right ventricle (RV) in relation to the presence of a left ventricular outflow tract obstruction (LVOTO).
Methods: Retrospective chart review of adults with congenitally corrected transposition of the great arteries (ccTGA) or with a previous atrial switch procedure for complete TGA (D-TGA). A LVOTO was defined by a peak instantaneous systolic gradient > 20 mm Hg. Right and left ventricular ejection fraction (EF) were measured by cardiac magnetic resonance imaging (CMR), and exercise capacity as the predicted peak oxygen consumption (peak VO_2) on a cycle ergometer.
Results: We identified 79 clinically stable adults (age 33 ± 10 years, 70% male). Nine patients (11%) had cc-TGA and 70 patients had (89%) D-TGA. Thirteen patients (16%) had a LVOTO with a mean peak instantaneous systolic gradient of 43 ± 22 mm Hg. Patients with a LVOTO had higher left (68 ± 7% vs. 60 ± 9%, $p = 0.01$) and right ventricular EF (52 ± 8 vs. 46 ± 9%, $p = 0.05$) by CMR compared to patients without LVOTO. In a multivariate regression analysis with left ventricular EF and LVOTO as predictors, only left ventricular EF was independently associated with right ventricular EF (correlation coefficient 0.41, $p < 0.01$). The presence of a LVOTO was not associated with improved exercise capacity.
Conclusions: In adults with a subaortic RV, a pressure loaded subpulmonary left ventricle has a beneficial effect on systemic right ventricular EF.

1. Introduction

In Europe and North America, there are an estimated 30–50 adults per 1 million inhabitants living with a subaortic right ventricle [1–3]. These are adults with complete transposition of the great arteries (D-TGA) repaired with an atrial switch operation, and adults with congenitally corrected transposition of the great arteries (ccTGA). Although midterm survival is favorable, late outcome is compromised by progressive impairment of subaortic right ventricular function, tricuspid regurgitation, decompensated heart failure, atrial and ventricular arrhythmias and premature death [3–6]. Our knowledge how to prevent or treat progressive subaortic right ventricular failure in transposition patients is scarce [7]. The only double-blind placebo-controlled randomized clinical trial performed so far with Valsartan as heart failure medication showed no effect of this drug on right ventricular ejection fraction in D-TGA patients [8].

Intrinsic left ventricular outflow tract obstruction (LVOTO) is common in adults with transposition of the great arteries, and increases subpulmonary left ventricular afterload [9,10]. In biventricular hearts, the filling and contractility of one ventricle affect the performance of the other by myocardial cross-talk due to shared myofibers [11]. Case reports in adults with ccTGA have suggested that pulmonary artery banding and its resulting increase in subpulmonary left ventricular pressure improves subaortic right ventricular function and reduces tricuspid regurgitation [12,13]. According to this concept, an intrinsic

☆ The authors did not receive any financial support for the study and declare that they have no conflict of interest.

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http://dx.doi.org/10.1016/j.ijcard.2017.06.050
0167-5273/

LVOTO may also exert a beneficial effect on subaortic right ventricular function in transposition patients.

In this study, we aimed to assess the impact of "naturally" occurring LVOTO on subpulmonary and subaortic ventricular function in adults with a subaortic right ventricle. The primary hypothesis of this study was that adults with transposition and an associated LVOTO have better left and right ventricular function on cardiac magnetic resonance imaging (CMR) than corresponding adults without LVOTO. Second, we hypothesized that this improve in ventricular function translates into a better exercise capacity in adults with LVOTO compared to adults without LVOTO.

2. Methods

In 2014, a nation-wide registry of adults with congenital heart disease was launched in Switzerland (Swiss Adult Congenital HEart disease Registry, SACHER, ClinicalTrials.gov Identifier NCT 02258724). All adults with congenital heart defects were eligible to participate. Patients were recruited from specialized adult congenital heart disease clinics. After informed consent was obtained, anonymized clinical data were entered in an online registry. The ethics review boards of all participating medical centers approved the registry and subsequent analysis of data. From May 2014 to December 2015, 2077 patients had been recruited, including 169 patients with a biventricular circulation and a subaortic right ventricle. Patients were divided into 2 groups: patients with a LVOTO and controls with no LVOTO. A LVOTO was defined by peak instantaneous systolic gradient of >20 mm Hg measured by transthoracic echocardiography (TTE). The cutoff of 20 mm Hg was chosen in analogy to a previous study [14].

As modality for cardiac imaging, cardiac magnetic resonance imaging (CMR) for assessment of biventricular function and TTE for assessment of LVOTO were required, unless a CMR was contraindicated. Exclusion criteria for this study were: 1) no cardiopulmonary exercise testing (CPET) data or no CMR imaging data in the absence of specific contraindications; 2) >18 months time interval between CPET and imaging studies; 3) history of previous tricuspid valve replacement, 3) pulmonary arterial hypertension, 4) no stable clinical course between the exercise and imaging tests. No stable clinical course was defined as a decrease in functional class, hospitalization for heart failure, or the occurrence of new arrhythmias requiring medical or electrophysiological therapies. Out of the 169 patients in the registry with a subaortic right ventricle, 90 patients were excluded from further analysis: n = 73 patients had either no CMR assessment of biventricular function despite no contraindications for a CMR or had no CPET data; n = 8 patients had a time interval of >18 months between the imaging and CPET studies; n = 4 patients had a replaced tricuspid valve; n = 2 patients suffered severe pulmonary hypertension; n = 3 patients did not have a stable clinical course between the imaging test and the CEPT study.

We analyzed differences in ventricular volumes and systolic function between adults with and without LVOTO by CMR, and differences in the degree of tricuspid regurgitation by TTE. In the absence of established criteria for the grading of regurgitation in a tricuspid valve of a subaortic right ventricle, we used similar grading criteria as for mitral regurgitation [15]. CMR was performed according to a standardized protocol, defined by cardiologists and radiologists performing routinely CMRs in congenital heart disease patients [16]. In pacemaker patients with contraindications for CMR but TTE data, only the impact of LVOTO on exercise capacity was studied.

Cardiopulmonary exercise testing (CPET) was used to analyze exercise capacity. We measured exercise capacity as the predicted maximum in Watt and predicted peak oxygen consumption (peak VO_2). All patients used a cycle ergometer to perform continuous measurements of minute ventilation, oxygen consumption, carbon dioxide production, heart rate, blood pressure and electrocardiography. Workload was increased by 5 to 15 W in a stepwise manner, depending on the individually predicted maximum exercise capacity, in such a way that the maximal possible effort was attaint in 10–15 min. Peak VO_2 was defined as the highest value of oxygen consumption during the last 30 s of peak exercise [17].

Data were analyzed using STATA 12 statistical software (Stata Corporation, College Station, TX, USA) and are expressed as mean and standard deviation for normally distributed variables and as median and interquartile range for non-normally distributed data. Between-group comparisons were performed using an unpaired Student's *t*-test. Multivariate linear regression analysis was used to identify independent predictors of right ventricular ejection fraction (EF) or exercise capacity. According to our study hypothesis and the study design, we pre-defined left ventricular EF, the presence of LVOTO and the transposition anatomy (D-TGA vs. ccTGA) as potential predictors of subaortic right ventricular EF. In order to assess the effect of LVOTO on predicted exercise capacity, we used the presence of a LVOTO, transposition anatomy and the presence of a pacemaker as predictors of peak VO_2. In all analyses, the null hypothesis was rejected for p-values < 0.05.

3. Results

Baseline characteristics of the 79 patients included in the analysis are reported in Table 1. Patients were followed in the specialized adult congenital heart disease clinics of the Universities of Basel (n = 11), Bern (n = 34) and Zurich (n = 34). The median time interval between CMR or transthoracic echocardiography and cardiopulmonary exercise testing was in both instances 0 months (interquartile range [IQR] - 6 to 6 months). Twenty-one patients (27%) had a pacemaker. The underlying anatomy of patients with pacemakers was D-TGA in 18 cases (18/70 or 26%) and ccTGA in 3 cases (3/9 or 33%; p = 0.69). A subpulmonary LVOTO was present in 13 patients (16% of all patients); 1 with ccTGA as underlying anatomy (11% of all ccTGA patients) and 12 patients (17% of all D-TGA patients) with an atrial switch procedure. The mean age of patients with LVOTO was 31 ± 11 years and did not significantly differ from the mean age of patients without LVOTO (33 ± 10 years; p = 0.48). The peak LVOTO gradient ranged from 20 to 80 mm Hg (mean 43 ± 22 mm Hg; median 30 mm Hg, IQR 23–54 mm Hg). There was no significant difference in patients with and without LVOTO in respect to gender, type of baffle repair, pacemaker, degree of tricuspid regurgitation, and their baseline medication. Betablockers were used in 32% of patients without LVOTO and in 22% of patients with LVOTO. For the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers, the corresponding proportions were 42% and 45%, respectively. The p-value for the chi-square tests of the different drugs between both groups was 0.41.

Table 1
Patient characteristics.

Gender, m/f	55/24 (70%/30%)
Age at last follow-up, years	33 ± 10
Anatomy	
ccTGA	9 (11%)
D-TGA, Mustard procedure	23(29%)
D-TGA, Senning procedure	47 (59%)
Age at atrial switch procedure, years	1.9 ± 0.8
LVOTO	13 (16%)
Pacemaker	21 (27%)
Tricuspid regurgitation on TTE	
None	14 (18%)
Mild	42 (53%)
Moderate	22 (28%)
Severe	1 (1%)
Cardiac medication at last follow-up	
No medication	35 (44%)
Beta-blockers	9 (11%)
ACE-inhibitor or ARB	19 (24%)
Beta-blocker and ACE-inhibitor/ARB	16 (20%)

Abbreviations: ACE-inhibitor – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; ccTGA – congenitally corrected transposition; D-TGA – complete transposition; LVOTO – left ventricular outflow tract obstruction with peak instantaneous systolic gradient > 20 mm Hg; TTE – transthoracic echocardiography.

3.1. Systolic ventricular function

The imaging results are presented in Table 2. Patients with a LVOTO had significantly higher left and right ventricular EF by CMR compared

Table 2
Imaging parameters.

Parameter	No LVOTO	LVOTO	p-Value
Magnetic resonance imaging			
No Pacemaker, data available (n, %)	46/66 (70%)	12/13 (92%)	0.09
LV EDV indexed to BSA (ml/m^2)	83 ± 34	82 ± 29	0.91
RV EDV indexed to BSA (ml/m^2)	116 ± 34	97 ± 28	0.08
LV EF (%)	60 ± 9	68 ± 7	0.01
RV EF (%)	46 ± 9	52 ± 8	0.05
Transthoracic echocardiography			
Data available (n, %)	66	13	
Tricuspid regurgitation			0.903
– None	12 (18%)	2 (15%)	
– Mild	34 (52%)	8 (62%)	
– Moderate	19 (29%)	3 (23%)	
– Severe	1 (2%)	0 (0%)	

Abbreviations: BSA – body surface area; EF – ejection fraction; EDV – end-diastolic volume; FAC – fractional area change; LV – left ventricular; LVOTO – left ventricular outflow tract obstruction; RV – right ventricular; TAPSE – tricuspid annular plane systolic excursion.

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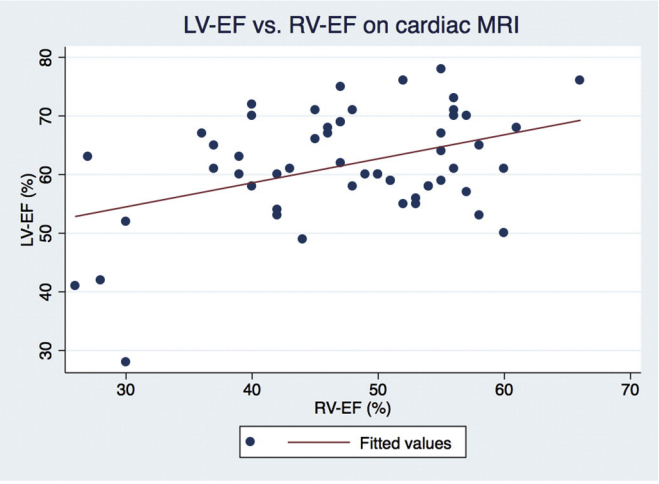

Fig. 1. Correlation of left and right ventricular ejection fraction. There was a weak but statistically significant correlation between right and left ventricular EF assessed by CMR ($y = 0.42 \times$ right ventricular EF + 42%, $p = 0.002$, $r = 0.4$).

to patients without LVOTO. In the pre-defined multivariate regression analysis with left ventricular EF, LVOTO, and transposition anatomy as predictors of right ventricular EF, only left ventricular EF was an independently associated with systemic ventricular function (adjusted correlation coefficient 0.41, $p = 0.007$). The positive association between left and right ventricular EF on CMR in a univariate regression analysis model is depicted in Fig. 1 ($r = 0.42$, $p = 0.01$). The exclusion of the $n = 9$ adults with ccTGA from the analysis did not affect the results of the impact on LVOTO on ventricular function (right ventricular EF of 47 ± 8% in D-TGA adults without LVOTO vs. 51 ± 7% in adults with LVOTO) but the corresponding p-value was not significant any more ($p = 0.12$) due to the lower number of analyzed patients.

3.2. Exercise capacity

The results of exercise testing are presented in Table 3. Mean exercise capacity was 152 ± 51 W and mean peak VO_2 was 25 ± 7 ml/min/kg, corresponding to a predicted exercise capacity in Watt of 81 ± 22% and predicted oxygen consumption of 69 ± 18%. There was no difference in any of the exercise parameters between patients with and without LVOTO, nor between patients with and without pacemakers. In the pre-defined multivariate regression analysis with LVOTO, transposition anatomy and the presence of a pacemaker as predictors of oxygen consumption, none of the variables showed a statistically significant association with the predicted peak VO_2.

Table 3
Exercise capacity.

Parameter	No LVOTO (n = 66)	LVOTO (n = 13)	p-Value
Age at CPET, years	34 ± 10	31 ± 11	0.43
Female sex	20 (30%)	2 (15%)	0.20
Watt	152 ± 57	151 ± 44	0.98
Predicted Watt (%)	83 ± 23	77 ± 20	0.45
PeakVO_2 (ml/min/kg)	24 ± 7	25 ± 4	0.66
Predicted peakVO_2 (%)	69 ± 19	68 ± 14	0.87
VE/VCO_2 slope	28 ± 7	30 ± 5	0.33
Peak RER	1.2 ± 0.1	1.1 ± 0.1	0.38
Oxygen saturation at rest (%)	97 ± 2	96 ± 3	0.36
Oxygen saturation at peak exercise (%)	96 ± 3	94 ± 7	0.25

Abbreviations: CPET – cardiopulmonary exercise study; LVOTO – left ventricular outflow tract obstruction; RER – respiratory exchange ratio; VE/VCO_2 slope – slope of ventilation vs. CO_2 production.

4. Discussion

This study demonstrated a positive association between left and right ventricular systolic function in patients with subaortic right ventricles. Adults with intrinsic obstruction to the subpulmonary outflow tract had better biventricular systolic function compared to those without, independent of the amount of tricuspid regurgitation. These findings support the study hypothesis of biventricular interdependence in transposition patients with a subaortic right ventricle.

Our findings complement recent studies in ccTGA patients, describing a positive impact of pulmonary (i.e. left ventricular) outflow tract obstruction on tricuspid regurgitation and clinical outcome [12,13,18]. Helsen et al. analyzed 62 patients with ccTGA and showed that the ones with a LVOTO had less tricuspid regurgitation and less subaortic right ventricular dysfunction than patients without LVOTO. Patients with LVOTO did not experience a clinical adverse during a mean follow-up of 10 years, compared to an adverse event rate of 40% in the remaining patients [18]. Similar benefits of LVOTO had also been reported in another clinical scenario with ccTGA: after relief of LVOTO, i.e. after replacement of an obstructed left ventricular to pulmonary artery conduit, worsening tricuspid regurgitation and a reduction in exercise capacity was observed [19]. In all of these studies, the beneficial effect of pulmonary banding or an intrinsic LVOTO on subaortic right ventricular function was to be secondary to ventricular interactions related to the positioning of the interventricular septum.

Compared to these previous studies, the present analysis has its focus on the concept of ventricular interdependence, i.e. that the function of one ventricle is influenced by the function of the second ventricle. Fogel et al. investigated the impact of left ventricular function on the subaortic right ventricle in 18 children and adolescents, of whom 11 had D-TGA and 7 had a single right ventricle with Fontan physiology [20]. Using CMR, the presence of a subpulmonary left ventricle was found to augment subaortic right ventricular function and improved ventricular strain in 7 of 8 studied regions of the right ventricle in D-TGA patients compared to single ventricle patients. In the present study with adults with biventricular physiology and a subaortic right ventricle, we found a similar ventricular interdependence: a LVOTO had a positive effect on subaortic right ventricular EF by improving left ventricular EF. Sustained changes in afterload are associated with a homeometric contractility adaptation, as described by Anrep's law of the heart [21,22]. This law describes a slow force response of the heart to increased afterload, independent of the rapid changes in myofilament calcium-sensitivity as response to increased preload (Frank-Starling mechanism). Our findings are in line with this hypothesis: left ventricular volumes in adults with LVOTO were similar to in adults without LVOTO (i.e. there was no potential role for the Frank-Starling mechanism), but left ventricular EF was nevertheless significantly higher in LVOTO patients compared to patients without LVOTO. In the multivariate analysis, the increase in left ventricular EF was the only independent predictor of an increased subaortic right ventricular EF. Neither the presence of a LVOTO nor the underlying transposition anatomy had by itself an effect on subaortic EF. A similar increase in subaortic EF in relation to the presence of a LVOTO was also seen in this subgroup of adults with D-TGA, i.e. after exclusion of ccTGA patients. Due to the smaller number of patients, this difference did not reach statistical significance.

5. Study limitations

In the present study, a LVOTO had no direct impact on exercise capacity, despite its beneficial effect on subaortic EF. We acknowledge that the sample size was small and exercise capacity depends on many factors. Therefore, we cannot draw firm conclusions regarding the effects of LVOTO on exercise capacity. Our population of adults with LVOTO was also too small to differentiate the effects of a moderate to severe versus severe LVOTO on biventricular function and exercise capacity. Due to the retrospective study design, we had to rely on

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reported ventricular volumes and ejection fraction. This decreases the diagnostic accuracy of the imaging studies compared with a prospective analysis of imaging studies by the same investigators, and by performing measurements twice and using mean results for study purposes.

6. Conclusion

In adult congenital heart disease patients with a subaortic right ventricle, there is ventricular interdependence. A pressure loaded subpulmonary left ventricle has a beneficial effect on subaortic right ventricular EF. Based on our findings, we recommend a conservative approach when discussing interventions to relief a LVOTO in a subpulmonary ventricle. In this situation, the positive effect of a subpulmonary obstruction on right ventricular EF should be kept in mind.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgements

We are very thankful to Karin Spring and André Frenk from the clinical trial unit of the Department of Cardiology, University Hospital Inselspital, for their help and support.

We also thank all SACHER investigators for supporting this registry. Participating centers are: Basel University Hospital – D. Tobler; Bern Inselspital – M. Schwerzmann, F. Schwitz, K. Wustmann; Geneva University Hospital – J. Bouchardy; Lausanne University Hospital – J. Bouchardy, T. Rutz; Lucerne Kantonsspital – C. Auf der Maur, H.P. Kuehn; St. Gallen Kantonsspital – R. Engel, D. Stammbach; Zurich Klinik im Park – C. Attenhofer Jost; Zurich University Hospital – F. Bonassin, G. de Pasquale, M. Greutmann, A. Oxenius, T. Seeliger.

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