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Physiologic determinants of exercise capacity in patients with different types of right-sided regurgitant lesions: Ebstein's malformation with tricuspid regurgitation and repaired tetralogy of Fallot with pulmonary regurgitation

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ABSTRACT

Background: Exercise capacity relates to right ventricular (RV) volume overload in congenital heart disease and may improve after surgery. We herewith investigate the relation between exercise capacity, cardiac index, and RV volume overload due to tricuspid regurgitation (TR) in Ebstein's malformation and pulmonary regurgitation (PR) after repair of tetralogy of Fallot (rToF).

Methods: We measured cardiac index and tricuspid/pulmonary regurgitant fraction by cardiovascular magnetic resonance in patients with Ebstein's malformation (n = 40) or rTOF (n = 53) with at least moderate TR/PR and 24 healthy controls. Exercise tolerance was determined by peak oxygen consumption (peak VO_2) during cardiopulmonary exercise testing.

Results: TR and PR fraction were similar in Ebstein and rTOF patients (43 ± 17% versus 39 ± 12%, respectively). Cardiac index was reduced in Ebstein (2.7 ± 0.6 L/min/m^2 compared to controls 3.5 ± 0.9 L/min/m^2, $p < 0.001$) but not in rToF patients (3.2 ± 0.5 L/min/m^2). Multiple regression analysis revealed a significant correlation between peak VO_2 and cardiac index in Ebstein. Furthermore, peak VO_2 correlated with peak heart rate in both groups but not with regurgitation fraction.

Conclusions: Despite comparable amounts of regurgitation from a right sided heart valve in patients with Ebstein and rToF, reduction of cardiac index was observed only in the former group. Greater physiologic complexity and adverse ventricular interaction with chronotropic incompetence in Ebstein's malformation may account for this.

1. Introduction

Exercise intolerance is common in adults with congenital heart disease and predicts hospitalisation and free survival [1]. Exercise tolerance is influenced both by cardiac anatomy and pathophysiology [2]. In Ebstein's malformation, apical displacement of the tricuspid valve and ensuing tricuspid regurgitation lead to changes in atrial and ventricular size and function. A recent study showed improved exercise capacity after tricuspid valve replacement in Ebstein's malformation which may have been related to the observed increase in cardiac output after surgery [3]. In contrast, exercise capacity failed to improve in a recent study from our group [4] following successful pulmonary valve replacement in repaired tetralogy of Fallot (rToF).

We examined herewith these two models of significant right heart valve regurgitation and volume overload, namely Ebstein's malformation with tricuspid regurgitation (TR) and rToF with pulmonary regurgitation (PR) and the relationship between regurgitant fraction, cardiac output and exercise capacity.

2. Methods

2.1. Study population

The clinical data of one hundred and five patients who had undergone clinical CMR and cardiopulmonary exercise testing within 6 months of each other at the Royal Brompton Hospital with either a diagnosis of native non-operated Ebstein with TR (n = 52) or rToF with PR (n = 53) were reviewed. Twenty-four healthy control subjects (age 34 ± 13 years, 12 males and 12 females) underwent CMR assessment

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for comparison with the patient population. The healthy volunteers gave informed consent. As the study involved retrospective review of medical records, individual patient consent was not required and this was approved by the Ethics Committee.

2.2. CMR protocol

CMR was performed on a 1.5T scanner (Siemens Sonata or Siemens Avanto, Siemens Medical Solutions, Erlangen, Germany) using an 8-element phased-array receiver coil. Subjects were positioned resting supine in the magnet and scout images obtained. Cardiac long-axis cine imaging using steady-state free precession imaging (True FISP, TR 40.2, TE 1.13, matrix 1.7 × 1.7 mm, slice thickness 7 mm) was performed in the four-chamber orientation. A routine set of LV and RV short-axis cine images, 7 mm slice thickness, were acquired at 10 mm intervals from base to apex using a breath-hold retrospective ECG-gated balanced steady state free precession (SSFP) gradient echo sequence, and volumetric analysis was performed using CMRtools (Cardiovascular Imaging Solutions, UK) [5,6]. The cardiac output at rest was measured using aortic flow analysis from through-plane phase contrast velocity mapping (TR 60, TE 2.32, matrix 1.3 × 2.5 mm, slice thickness 10 mm) in a plane transecting the aorta at the sino-tubular junction. The cardiac index at rest (CI) was obtained by indexing the cardiac output to body surface area. Pulmonary artery (PA) flow analysis from through-plane phase contrast velocity mapping in a plane transecting the pulmonary trunk was used to obtain the pulmonary regurgitant fraction [7], and the pulmonary artery effective stroke volume, which is the total pulmonary artery stroke volume less the pulmonary regurgitation volume at rest. The PA effective stroke volume was also indexed to body surface area to obtain the PA effective stroke volume index, or the PA cardiac index. The tricuspid regurgitant fraction was measured as the difference between RV stroke volume and systolic forward flow in the pulmonary artery.

2.3. Tricuspid valve displacement

Mitral and tricuspid valve offsetting was measured in the four-chamber image as the distance between the LV attachment of the anterior mitral valve leaflet and the septal attachment of the septal leaflet of the tricuspid valve, and indexed to the body surface area. Normal offsetting was defined as <8 mm/m^2 [8].

2.4. Cardiopulmonary exercise testing

All patients underwent symptom limited cardiopulmonary exercise testing using a treadmill step protocol. The ramp was elevated every 3 minutes by increments initially of 5% for the first 6 minutes, and then by 2% thereafter. Medgraphics VO_{2000} was used to assess gas and flow volume. Intermittent non-invasive blood pressure monitoring and continuous pulse oximetry were performed during exercise.

Peak oxygen consumption (peak VO_2) was used as the measure of exercise tolerance [1,9]. Predicted values for peak VO_2 according to sex, weight, height and age were calculated using the Wasserman protocol. Interpretation of peak VO_2 data was done by comparing patient MVO_2 to predicted values. Exercise performance was deemed to be adequate for analysis when the respiratory exchange ratio (the ratio of carbon dioxide to oxygen uptake) under steady state conditions was >1.0. A measure of ventilatory efficiency, the VE/VCO_2 ratio was also calculated. A value of <34 was taken as normal [10].

Respiratory function was assessed by spirometry prior to exercise. The FEV1, FVC and FEV1/FVC ratio were measured. The FEV1 and FVC are presented as percentages of predicted for age and height. A FEV1/FVC ratio of >0.7 of predicted was taken as normal.

2.5. Statistical analysis

Normality of data distributions in the patient and control groups was tested using the Kolmogorov–Smirnov method. Data was expressed as mean ± SD and as frequencies for categorical data. Stepwise multiple regression analysis was performed to assess for independent predictors of peak VO_2. In all cases, a two-tailed value of $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS (V.19.1, SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1. Study population

A total of 93 patients (47% male, and mean age 32 ± 13 years) were suitable for analysis and constituted the study population, after exclusion of 12 of 52 Ebstein patients as they also had a patent foramen ovale or an atrial septal defect, which may confound the results of exercise testing. There were 40 patients with Ebstein's malformation (43% male and mean age 35, range 16–55 years) and 53 patients with rToF (51% male and mean age 28, range 15–53 years). There were no significant differences between the groups with respect to sex and body surface area. The rTOF group tended to be younger relative to Ebstein ($p = 0.012$) but were not significantly different to the control group (Table 1).

In Ebstein patients, the septal leaflet was significantly displaced towards the apex, 55 ± 11 mm/m^2 versus 6 ± 1 mm/m^2 in normal controls, $p < 0.001$ (Fig. 1). Various degrees of RV atrialization were encountered.

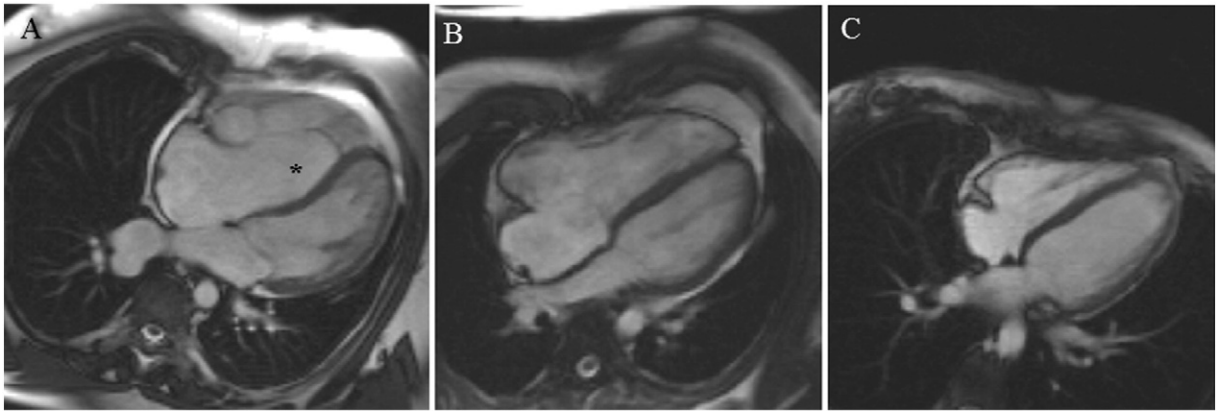

Fig. 1. Four-chamber image of Ebstein's (A), rToF (B) and control (C) hearts. The septal leaflet of the tricuspid valve in Ebstein's is severely displaced towards the apex. There is significant atrialisation of the right ventricle (*) with leftward interventricular septal shift. Normal septal leaflet attachment to the interventricular septum in rToF and control.

Table 1
Patient characteristics, data expressed as means ± std.

Overall patient population	
Male, n (%) and age, years (±SD)	44/93 (47), 32 ± 13
Ebstein's Anomaly with tricuspid regurgitation	
Male, n (%) and age, years (±SD)	17 (43), 35 ± 13
Tricuspid regurgitation fraction, % (±SD)	43 ± 17
Other cardiac defects or co-morbidities:	
Bicuspid aortic valve (no stenosis or regurgitation), n	3
Coarctation of the aorta (repaired, no residual stenosis), n	3
Haemoglobin (g/dL)	14 ± 2
Repaired ToF with pulmonary regurgitation	
Male, n (%) and age, years (±SD)	27 (51), 28 ± 11
Pulmonary regurgitation fraction, % (±SD)	39 ± 12
Other cardiac defects or co-morbidities:	
RV-PA conduit stenosis, n	1 mild, 3 moderate
RPA stenosis, n	3 mild, 1 moderate
LPA stenosis, n	2 mild, 4 moderate
Small residual VSD (QP:QS = 1.1:1), n	2
Haemoglobin (g/dL)	14 ± 3

There was significant right heart valve regurgitation in both groups, and the mean regurgitant fraction of TR and PR was similar, 43 ± 17% versus 39 ± 12% respectively (p = NS). Otherwise, none of the patients had additional significant structural heart disease nor other medical conditions including respiratory disease or previous pulmonary embolism. None of the patients had arrhythmia during CMR study or exercise testing.

3.2. Aortic and PA cardiac indices

The aortic cardiac index in Ebstein patients was significantly lower than in the control and rToF groups (2.7 ± 0.6 L/min/m^2 versus 3.5 ± 0.9 L/min/m^2 and 3.2 ± 0.5 L/min/m^2 respectively, p < 0.001 for both, Table 2), whereas no difference was found between rToF and controls.

The cardiac indices measured from the aortic and PA flow rates were equal to one another in all three groups and the PA cardiac index (or PA 'effective' stroke volume which is the forward flow in the PA minus the regurgitant volume) differences between the groups followed the same pattern.

3.3. Right and left ventricular volumetric analysis

Indexed right ventricular volumes were significantly larger and RV ejection fraction decreased in both patient groups compared to controls, p < 0.001 (Table 2), and did not differ between Ebstein and rToF. In contrast to the right ventricle, the indexed left ventricular end-diastolic volume in Ebstein was much reduced compared to control and to rToF. Despite a smaller indexed end-diastolic volume, the left ventricular ejection fraction in Ebstein was preserved. Indexed left ventricular stroke volume was therefore low when compared to control and rToF, p < 0.001.

In rToF however, indexed left ventricular end-diastolic volume did not differ significantly to control, whereas ejection fraction was reduced (61 ± 8% versus 67 ± 5%, p = 0.001). The resting heart rate was significantly higher in rToF compared to both controls (84 ± 12 beats/minute versus 73 ± 7 beats/minute, p = 0.001) and Ebstein (77 ± 14 bpm, p = 0.036). There was no significant difference in heart rate between the control and Ebstein groups.

3.4. Cardiopulmonary exercise testing

Adequate exercise was achieved in all patients. Mean peakVO_2 was lower than predicted for gender, age and body surface area in both patient groups (65 ± 18% in Ebstein and 71 ± 15% in rToF, Table 3). Although the peakVO_2 as a percentage predicted against a nomogram was similar for Ebstein and rToF, the actual peakVO_2 was lower in Ebstein compared to rToF patients (22 ± 7 ml/kg·min and 27 ± 8 ml/kg·min respectively, p = 0.003), suggesting that decreased exercise tolerance may also be affected by the relative older age of Ebstein rather than to cardiac physiology alone. Ventilatory efficiency or the VE/VCO_2, was higher in Ebstein than in rToF patients (p < 0.001, Table 3).

Resting heart rate were both lower in Ebstein compared to rToF (p = 0.036). Although the peak heart rate expressed as percentage predicted for age (Astrand Formula [11]) was above 90% in 20 (50%) Ebstein and 26 (49%) rToF patients, chronotropic response was less in Ebstein than rToF with absolute peak heart rate lower in Ebstein compared to rToF (158 ± 25 bpm versus 171 ± 20 bpm, p = 0.009).

Resting oxygen saturations did not differ between the groups. Neither group desaturated at peak exercise. Similar respiratory function values were obtained in Ebstein and rToF patients (Table 3).

3.5. Relation between peak VO_2 and cardiac parameters

Stepwise multiple regression analysis was performed to assess the relationship between peak VO_2 and cardiac parameters. The variables tested were the TR or PR regurgitant fraction, left ventricular ejection fraction, cardiac index, and peak heart rate. Initial analysis for Ebstein showed a R^2 of 0.54, and p < 0.001. Only cardiac index and peak heart rate showed significance, p < 0.05. Forward stepwise analysis using only these parameters confirmed R^2 of 0.50, p < 0.001. Cardiac index and peak heart rate showed positive correlation, p = 0.006 and <0.001 respectively.

Initial multiple regression analysis for rToF showed R^2 of 0.40, and p < 0.001. Only peak heart rate showed significance, and confirmed in stepwise analysis, R^2 = 0.40, p < 0.001.

Table 2
CMR findings in the 3 groups. Data expressed as mean ± std.

Characteristic	Ebstein (n = 52)	rToF (n = 53)	Control (n = 24)	p, Ebstein vs control	p, rToF vs control	p, Ebstein vs rToF
Male, n (%)	17 (43)	27 (51)	12 (50)	0.918	0.889	0.898
Age, years ± SD	35 ± 13	28 ± 11	34 ± 13	0.633	0.061	**0.012**
BSA (kg/m^2)	1.8 ± 0.3	1.8 ± 0.2	1.7 ± 0.2	0.192	0.352	0.829
LV-EDVi	64 ± 14	80 ± 14	78 ± 11	<**0.001**	0.883	<**0.001**
LV-ESVi	23 ± 8	31 ± 10	26 ± 7	0.251	**0.036**	<**0.001**
LV-SVi	41 ± 10	48 ± 9	52 ± 7	<**0.001**	0.170	<**0.001**
LV-EF	64 ± 9	61 ± 8	67 ± 5	0.136	**0.001**	0.443
LV-Mass Index	60 ± 17	63 ± 4	54 ± 8	0.207	**0.004**	0.482
RV-EDVi	132 ± 49	149 ± 40	77 ± 13	<**0.001**	<**0.001**	0.139
RV-ESVi	68 ± 35	77 ± 36	31 ± 10	<**0.001**	<**0.001**	0.461
RV-SVi	65 ± 23	72 ± 14	46 ± 7	<**0.001**	<**0.001**	0.136
RV-EF	49 ± 11	49 ± 9	61 ± 9	<**0.001**	<**0.001**	1.000
Cardiac Index, L/min/m^2	2.7 ± 0.6	3.2 ± 0.5	3.5 ± 0.9	**0.001**	0.217	**0.001**
PA effective stroke volume index, L/min/m^2	2.8 ± 0.7	3.2 ± 0.7	3.5 ± 0.8	**0.004**	0.170	**0.010**
Resting heart rate, beats/minute	77 ± 14	84 ± 12	73 ± 7	0.232	**0.001**	**0.036**

Table 3
CPET findings in Ebstein's and rToF groups. Data expressed as mean ± std.

Characteristic	Ebstein's (n = 52)	rToF (n = 53)	P value
Peak VO_2, % of predicted	65 ± 18	71 ± 15	ns
Peak VO_2, ml/kg·min	22 ± 7	27 ± 8	**0.003**
Respiratory exchange ratio	1.1 ± 0.1	1.2 ± 0.1	ns
VE/VCO_2	36 ± 11	29 ± 6	<**0.001**
Resting heart rate (beats/minute)	77 ± 14	84 ± 12	**0.036**
Peak heart rate (beats/minute)	158 ± 25	171 ± 20	**0.009**
Peak heart rate (% of predicted for age, normal >90%)	86 ± 10	90 ± 8	ns
Oxygen saturation at rest, %	98 ± 1	98 ± 1	ns
Oxygen desaturation >5%: n (%) and desaturation, %	0	0	ns
Rest SBP (mm Hg)	118 ± 14	113 ± 16	ns
FEV1, L/s	3.1 ± 0.9	2.9 ± 0.8	ns
FVC, L/s	3.6 ± 1.1	3.3 ± 1.0	ns
FEV1, % of predicted	76 ± 16	70 ± 16	ns
FVC, % of predicted	76 ± 18	69 ± 15	ns
FEV1/FVC	0.8 ± 0.1	0.9 ± 0.1	ns

4. Discussion

This study demonstrates significant differences in the pathophysiology of different types of right-sided regurgitant valve lesions. Despite comparable severity of right heart valve regurgitation in the Ebstein and rToF patient groups, cardiac index was significantly reduced only in the Ebstein group. It is clear that valve regurgitation and the subsequent RV volume overload are not the only mechanisms influencing exercise capacity. A complex interplay of ventricular overload, interventricular interaction, and other mechanisms are likely to impact on exercise capacity and should be kept in mind when deciding on the indications and timing of intervention.

Regurgitation of an atrioventricular valve is likely to have a different impact on the preload and afterload of a ventricle compared to a regurgitant outflow valve. Moreover, in Ebstein's malformation there are further anatomical and physiological features that may affect ventricular function and cardiac index. The atrialized portion of the RV typically results in part of the basal septum, which has been shown to be relatively devoid of myocardial tissue, bulging to the left both in systole and diastole [12,13]. This can significantly affect LV size and filling, and thus, reduce cardiac index [14]. The relatively low LVEDV in the our Ebstein group is in keeping with this hypothesis and, although adverse ventriculo-ventricular interaction is also likely present in rToF with significant PR [7], the pronounced changes in septal structure and movement in Ebstein anomaly (paradoxical motion of the interventricular septum) may explain the greater impact on cardiac index and as a result, of exercise capacity.

Another factor that may limit cardiac output and exercise capacity in Ebstein's malformation is chronotropic incompetence. In fact, despite a reduction in LV stroke volume in this group, no compensatory increase in either resting or peak exercise heart rate was seen when compared to the rToF, in whom LV stroke volume was normal. Chronotropic incompetence has been described in many congenital cohorts, is multifactorial and is closely related to a lower peak VO_2.

Ebstein patients had, on average, a significantly raised VE/VCO_2 slope, which was higher than that of ToF patients. A raised VE/VCO_2 slope reflects a high physiological dead space, which, in the absence of right-to-left shunting, provides evidence of impaired pulmonary perfusion, presumably secondary to the impairment of cardiac output. The VE/VCO_2 slope is an important exercise parameter and is closely related to outcome in non-cyanotic ACHD patients, independent of peak VO_2 [15]. A higher VE/VCO_2 slope in Ebstein compared to rTOF patients is further evidence of the physiological disparity between these two right-sided regurgitant lesions.

Overall, our findings appear to be consistent with the study by Kuhn et al. [3], who found that Ebstein's patients who have had tricuspid valve replacement for severe regurgitation had improved exercise tolerance compared to their pre-operative exercise tolerance. The improvement was attributed to increased cardiac output from competent valve action after surgery.

4.1. Limitations

This study was performed retrospectively, by the inclusion of patients who had been referred for clinical study according to the criteria described in the methods section. Although we selected patients with comparable tricuspid versus pulmonary regurgitant fractions, a number of factors, including age, previous surgery involving pericardotomy in the rToF group, and arguably more extensive intracardiac malformation in the Ebstein's group, could contribute to differences between the groups and potentially confound interpretation. Exercise testing, with associated measurements of heart rate, was not undertaken in the control group, in whom the Wasserman scale was used as a basis for the prediction of normal values.

5. Conclusion

Regurgitant lesions of comparable severity in Ebstein and rToF groups appear to affect the cardiac index differently, with a significant reduction in resting cardiac index only seen in Ebstein patients. Possible reasons for this include a greater physiologic complexity in Ebstein malformation, resulting in marked ventricular interaction, and the apparently compromised ability to compensate by elevating the heart rate. Deep understanding of the anatomic and pathophysiologic features of these two conditions is paramount for effective management.

Conflict of interest statement

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

Financial disclosure summary

Dr. Sheehan is a founder and Chief Scientist of VentriPoint, Inc. and holds equity in the company.

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