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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.

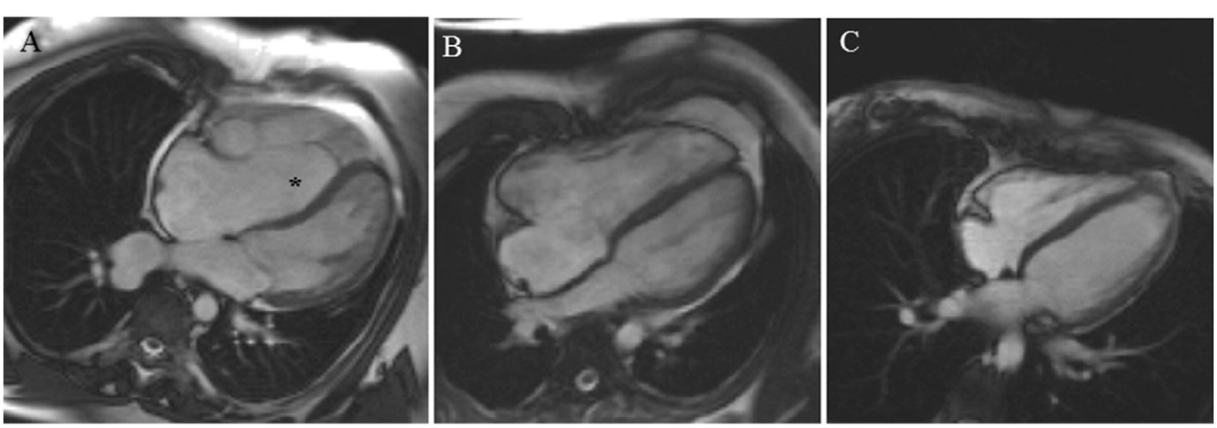

Fig. 1. Four-chamber image of Ebstein's (A), rToF (B) and control (C) hearts. The septal leaflet of the tricuspid valve in Ebstein's is severely displaced towards the apex. There is significant atrialisation of the right ventricle (*) with leftward interventricular septal shift. Normal septal leaflet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