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ORIGINAL PAPERS, CLINICAL CARDIOLOGY

Lung Function, Cardiopulmonary Exercise Capacity and Lung Perfusion in Patients with Corrected Tetralogy of Fallot

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Study objectives: Patients after total repair of tetralogy of Fallot (TOF) often have residual abnormalities of lung perfusion. It was suggested that interventions such as stenting of the stenotic vessels would improve exercise capacity. The purpose of the study was to compare lung function and cardiopulmonary functional capacity in patients with and without lung perfusion disturbances.

Patients: Fifty patients (33 men, 17 women) of age 29 ± 11 years who were operated 8–10 years prior to the study. They were divided into two groups: 32 patients with normal lung perfusion and 18 patients with abnormal lung perfusion.

Methods: Patients performed full lung function testing, progressive cardiopulmonary exercise, echo-Doppler assessments of pulmonary pressure, and quantitative perfusion ventilation.

Results: Lung function: Patients post TOF show mild restriction (FVC = 80 %) with normal oxygen saturation (97 %) and six minute walking distance (600 m). Total lung capacity was slightly higher in the normal perfusion group 95 ± 15 % vs. 85 ± 12 % however; no statistical difference was seen between both groups. Echocardiography showed normal pulmonary pressure and normal LVEF (62 %). Cardiopulmonary exercise showed mild limitation of exercise capacity with VO_2 of 75–78 % predicted in both groups.

Conclusions: Patients post correction of TOF have mild restriction in their lung function, moderate limitation in their exercise capacity and normal pulmonary arterial pressure. As patients with abnormal lung perfusion scan have good exercise capacity, invasive intervention with angioplasty and/or stent insertion may not be justified. ***J Clin Basic Cardiol 2004; 7: 11–4.***

Key words: *tetralogy of Fallot, lung perfusion, cardiopulmonary exercise test, pulmonary artery pressure*

Patients with surgically corrected tetralogy of Fallot (TOF) are characterized by a decrease in pulmonary function [1, 2] and a diminished cardiopulmonary exercise capacity compared with healthy controls [3, 4]. One of the main reasons for the depressed cardiac and pulmonary function at rest and during exercise is a disturbance in pulmonary perfusion [5, 6]. The reason for the perfusion disturbances is narrowed or hypoplastic pulmonary arteries [7, 8].

To prevent the decrease in cardiopulmonary function in postoperative patients with TOF, researchers developed new angioplasty techniques with or without the insertion of stents to the narrowed or hypoplastic pulmonary arteries. However, it remains unclear whether the outcome of these invasive procedures, namely widening of the blood vessels and thereby increased perfusion to the hypoperfused lung, indeed leads to improved cardiopulmonary exercise capacity [9–12].

The aim of the present study was to determine lung function and exercise capacity of patients post TOF, and to find whether there is a relationship between lung perfusion and cardiopulmonary exercise capacity.

Methods

Patients

Fifty patients with documented TOF participated in the study. The study sample was composed of 33 men and 17 women aged 17 to 55 years (mean ± SD; 28.9 ± 11.22 years). Additional ten patients were excluded from the study protocol for the following reasons: constrictive pericarditis, refusal to undergo lung perfusion scan, development of atrial flutter following cardiopulmonary exercise testing, presence of Down syndrome (1 patient each), and refusal to sign the informed consent form (6 patients). All patients had undergone intracardiac repair of TOF without additional invasive procedures, such as stenting or percutaneous transluminal angioplasty. The surgical correction was performed between the ages of 1 and 43 years (mean ± SD; 10 ± 11): nine patients had a pulmonary systemic shunt (Blalock-Taussig in 8; Waterston-shunt in 1). Ten patients required repeated (re-do) surgery for full TOF correction at age 4.5 to 46 years (23 ± 16). Of the 50 patients, 10 were found to have a small residual shunt between the ventricles (VSD) on echocardiography, and four had right bundle branch block.

Patients were divided into two groups by the presence of normal and abnormal lung perfusion. Abnormal perfusion was defined as perfusion of < 45 % or > 58 % in the right lung and < 42 % or > 55 % in the left lung [5, 13].

Procedure

All patients underwent a comprehensive medical history and a complete physical examination including electrocardiogram and chest x-ray, echo-Doppler assessment, pulmonary perfusion test, pulmonary function test and cardiopulmonary exercise test. The protocol was approved by the institutional ethics committee and review board. Written informed consent was obtained from all patients.

Echo-Doppler

Echo-Doppler assessment was performed with a Hewlett-Packard system (Sonos 5500, USA) equipped with 2.5 MHz transducer with a use of a protocol previously reported [14]. Results were recorded on a super-VHS videocassette and analyzed independently by two experienced cardiologists (RH, LB). Pulsed wave Doppler ultrasound was used to detect valvular stenosis and valvular regurgitation. Right ventricular outflow velocity was recorded with a 3 MHz nonimaging continuous wave transducer. The maximal instanta-

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neous and mean systolic right ventricular outflow pressure gradients were calculated by the modified Bernoulli equation.

Lung Perfusion
Scintigraphy was performed after the intravenous administration of 111 MBq (3 mCi) of Tc-99m macroaggregated albumin (Pulmolite, Dupont, Billerica, MA, USA). A single-head gamma-camera (SPX-4, Elscint Ltd., Haifa, Israel) fitted with an all purpose parallel hole collimator was used. Anterior, posterior, left and right posterior oblique views were obtained, collecting 400,000 counts per view. The posterior view was used for the calculation of the relative perfusion. Right and left lung counts were separately obtained from rectangular region of interests. The ratios between the transplanted lung counts and the total lungs counts were called relative perfusion (RP).

Pulmonary function
The complete pulmonary function test (PFT) included spirometry, lung volumes, maximal voluntary ventilation (MVV) and diffusion capacity by single breath technique (DLco). For calibration, a 3-L syringe was used at the beginning of each session on each day. PFT measurements were corrected for body temperature and pressure saturated (BTPS). Testing was performed with the Medical Graphics Pulmonary Function System (1070-series 2, St. Paul, MN, USA). Lung volumes were obtained by body plethysmography (model 1085, Medical Graphics, St. Paul, MN, USA). MVV was assessed by asking the patient to breathe as fast and deeply as possible for 12 seconds. DLco was performed with a gas mixture that contained air, 10 % helium, and 0.3 % carbon monoxide. Each DLco measurement was adjusted to standard temperature and pressure and corrected for breath-holding time and effective alveolar volume as determined by inspired vital capacity. DLco values were not corrected for hemoglobin or smoking history. The predicted values of the parameters were obtained from the regression equations of the European Union [15].

6-Minute Walking Test
Following the PFT assessment, each patient underwent a 6-minute walking test to measure 6-minute walking distance (6MWD), as previously described [16]. A 50-meter corridor in the chest clinic area was used for testing and the maximum distance that could be walked was measured. The test was repeated twice, and the longer distance walked was used in the analysis.

Exercise Protocol
The exercise protocol was conducted between 08:30 am and 12:00 noon in the exercise physiology laboratory. Patients were encouraged to take their regular medications. Each participant underwent an incremental exercise test according to the protocol of Wasserman et al [17] on an electrically braked cycle ergometer (Ergoline 800). After a 3-minute rest period, unloaded paddling was performed at a rate of 60 rpm for 2 minutes. The effort was then progressively increased by 10–20 W/min. until the patient could no longer maintain a cycling frequency of at least 40 rpm. Cardiopulmonary parameters as heart rate (HR), minute ventilation (VE), oxygen uptake (VO_2), carbon dioxide production (VCO_2), and oxygen pulse (O_2P) were recorded, analyzed and stored by an exercise metabolic unit (CPX, Medical Graphics). Multiple-lead electrocardiogram (ECG) system (Cardiofax, Nihon Kohden, Tokyo, Japan) and a single lead V_5 ECG monitor (VC–22, Nihon Kohden, Tokyo, Japan) were used for continuous ECG monitoring. Oxygen saturation (SaO_2) was monitored separately with a pulse oximeter (Nellcor, NPB–190, CA, USA). Blood pressure was measured manually with a sphygmomanometer (Tycoss, USA) at rest, every 2 minutes, and at peak exercise.

Statistics
Results are expressed as mean ± standard deviation. Statistical analysis was done with statistical analysis software (SAS) [18] and consisted with Student's unpaired t-test to determine significant differences between the groups in demographic (age, age of repair, height, weight) and physiological parameters measured at rest (pulmonary function testing, 6MWD) and at peak exercise (HR, VO_2, VE, O_2P, etc.). A p-value of less than 0.05 was considered significant.

Results

Lung perfusion scan was normal in 32 patients (21 men, 11 women; group 1), and abnormal in 18 patients (12 men, 6 women; group 2). Comparison of their physical characteristics yielded no significant differences between the groups in present age, height, weight or male/female ratio (Table 1). Age at time of surgical correction of the TOF was significantly higher in group 1 (12.3 ± 12.9 years) than in group 2 (6.3 ± 5.1 years).

Estimated pulmonary pressure were 22 ± 19 and 20 ± 13 mmHg in both groups and LVEF was 63 ± 6 % and 62 ± 6 % in both groups respectively. There were also no significant differences in cardiothoracic ratio, conduction disturbances, pulmonary gradient, degree of tricuspid regurgitation or left ventricular ejection fraction (LVEF) between groups (Table 1).
Pulmonary function testing: (Table 2). Both groups showed mild restriction with FEV1 of 83 % and 82 % predicted in both groups with forced vital capacity of 80 %. Total lung capacity was slightly higher in the normal perfusion group (95 % vs. 85 %), however this has not reached statistical significance. Diffusion capacity was similar in both groups 86 % vs. 85 %. Oxygen saturation was normal in all patients (97 %). Six minutes walking distance was excellent both in the normal and abnormal lung perfusion and was around 600 m.

Exercise capacity: Patients have shown mild limitation in their exercise capacity with 75 % maximal oxygen consump-

Table 1. Physical and echo-Doppler characteristics of the two groups of subjects

Variable	Lung perfusion: Normal (n = 32)	Abnormal (n = 18)
Age (yr)	29.3 ± 11.8	28.2 ± 10.4
Age at repair (yr)	12.3 ± 12.9	6.3 ± 5.1*
Male/female	21/11	12/6
Height (cm)	173 ± 12	175 ± 14
Weight (kg)	67 ± 18	65 ± 19
Cardiothoracic ratio (%)	51.6 ± 6.1	53.47 ± 4.4
Conduction disturbances (%)†	75 ± 44	94 ± 24
Pulmonary gradient (mmHg)	22.14 ± 19.1	20.29 ± 13.4
Pulmonary tricuspid regurgitation (mmHg)	28.67 ± 11.95	31.76 ± 8.82
LVEF (%)	62.8 ± 5.9	62.4 ± 6.4

* Significantly different from normal lung perfusion group ($p < 0.05$)
† Conduction disorders: including right bundle branch block and left anterior hemiblock; LVEF = left ventricular ejection fraction

Table 2. Pulmonary function test results in the two groups of subjects

Variable	Lung perfusion: Normal (n = 32)	Lung perfusion: Abnormal (n = 18)
FEV_1 (% of pred.)	83.38 ± 16.35	81.93 ± 16.67
FVC (% of pred.)	80.64 ± 15.93	79.64 ± 16.70
FEV_1/FVC (%)	88.41 ± 10.72	87.37 ± 8.70
DLco (% of pred.)	86.23 ± 15.85	85.41 ± 14.80
TLC (% of pred.)	95.13 ± 15.07	84.7 ± 11.79
SaO_2 (%)	96.90 ± 2.56	96.74 ± 2.62
6MWD (m)	603 ± 101	597 ± 76

FEV_1 = forced expiratory volume in the first second; FVC = forced vital capacity; Dlco = single breath diffusion lung capacity; TLC = total lung capacity; SaO_2 = oxygen saturation of arterial blood; 6MWD = six minute walking distance

Table 3. Cardiopulmonary exercise test results in the two groups of subjects

Variable	Lung perfusion: Normal (n = 32)	Lung perfusion: Abnormal (n = 18)
Work (% of pred.)	58.62 ± 19.65	61.71 ± 21.05
VO_2 (% of pred.)	75.73 ± 23.43	78.82 ± 17.95
VO_2@AT (% of pred.)	51.1 ± 12.3	49.7 ± 11.5
HR (% of pred.)	78.44 ± 11.75	77.67 ± 12.47
VE (l)	47.65 ± 17.98	44.95 ± 10.61
O_2P (% of pred.)	96.23 ± 19.13	97.65 ± 19.19
VE/VCO_2 (l/l)	61.95 ± 13.19	60.54 ± 9.5

% of pred = percent of predicted; VO_2 = oxygen uptake; AT = anaerobic threshold; HR = heart rate; VE = minute ventilation; O_2P = oxygen pulse; VE/VCO_2 = ventilatory equivalent for carbon dioxide

tion without evidence for ventilatory or cardiac limitation. This suggests mostly poor effort or low exercise training. Nevertheless there was no difference between the groups with normal or abnormal perfusion (Table 3).

Discussion

Patients after correction of TOF show mild restrictive lung function mechanics and mildly reduced exercise capacity. No hypoxemia nor significant pulmonary hypertension was noted in any patients. This was true for both groups those with normal or abnormal lung perfusion scan. The age at repair was significantly different. A younger age at surgery could indicate greater severity of the pulmonic stenosis and more disturbed cardiopulmonary function; on the other hand, surgery done earlier in life, patients could have a greater impact on functional capacity than surgery done later; Joransen et al [19] noted better cardiac function when the repair was done before age of 2 years. In the present study, the group with abnormal lung perfusion demonstrated more frequent conduction disturbances such as bundle brunch block or left anterior hemiblock than the group with normal perfusion. Nevertheless, there is no evidence of more frequent arrhythmias or worse prognosis in association with such complications [20], but only of complete A-V block [21], which did not appear in our patients.

Our findings showed no significant differences in cardiopulmonary functional parameters between the groups. By contrast, Rhodes et al [12] reported a good correlation between lung perfusion abnormalities and exercise-increased minute ventilation, as well as low peak VO_2 in patients with narrowed pulmonary arteries. Wessel et al [9] have found poor exercise capacity in patients with reduced lung perfusion compared with patients with normal perfusion. Other studies have reported that abnormal pulmonary artery flow, enlargement of the heart, and elevated right ventricular pressure are the best predictors of post-repair outcome and exercise capacity [7, 9]. An elevated heart/lung ratio (> 60 %) was described by Kusuhara et al [22] in 42 patients with abnormal exercise capacity with a high frequency in the symptomatic patients. However, our study did not confirm these observations. Furthermore, Chaturverdi [6] and Singh [23] argued that abnormal function due to pulmonary insufficiency can appear only after very long-term follow-up (30–40 years), whereas our patients were tested on average only 20 years after surgery. Hosking et al [24] reported only a 35 % success rate in angioplasty or stenting of narrowed arteries in patients undergoing repair for TOF.

In the present study, there was no evidence that better lung perfusion in patients after repair of TOF improves cardiopulmonary function. Therefore, in patients with narrowed peripheral pulmonary arteries but without elevated pulmonary artery pressure, an invasive procedure such as percutaneous transluminal angioplasty with or without stents may be unnecessary.

We conclude that there is no relationship between lung perfusion capacity and cardiopulmonary exercise indices in patients after TOF repair. These findings suggest that the therapeutic procedure should not be dictated merely by the anatomical abnormality disturbance in lung perfusion but rather by the functional (i.e. cardiopulmonary indices and function) status.

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