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Effect of calcium channel blockers evaluated by cardiopulmonary exercise testing in idiopathic pulmonary arterial hypertension responding to acute pulmonary vasoreactivity testing

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ABSTRACT

Background: The baseline exercise capacity evaluated by cardiopulmonary exercise testing (CPET) and the change after administration of calcium channel blockers (CCB) therapy in patients with vasodilator-responsive idiopathic pulmonary arterial hypertension (VR-IPAH)are unknown.
Methods: 25 patients with newly diagnosed VR-IPAH from 1 January 2012 to 16 November 2015 were prospectively enrolled, and 28 age, sex and pulmonary vascular resistance matched newly diagnosed patients with vasodilator-nonresponsive idiopathic pulmonary arterial hypertension (VNR-IPAH) were enrolled. CPET was performed before and after 3.5 ± 0.8 months of CCB or sildenafil therapy.
Results: Ventilatory efficiency at rest, anaerobic threshold (AT), and peak were significantly higher (lower in $\dot{V}E/\dot{V}CO_2$@AT and higher in $PETCO_2$@AT) in VR-IPAH group than that in VNR-IPAH group. Peak $\dot{V}O_2$ (13.9 ± 2.9 mL $kg^{-1}\cdot min^{-1}$ vs 16.4 ± 4.1 mL $kg^{-1}\cdot min^{-1}$, p = 0.001), peak O_2 pulse (5.5 ± 0.8 mL $min^{-1}\cdot beat^{-1}$ vs 6.9 ± 1.3 mL $min^{-1}\cdot beat^{-1}$, p = 0.001), $\dot{V}E/\dot{V}CO_2$@AT (34.2 ± 5.0 vs 31.6 ± 3.1, p = 0.02) and $PETCO_2$@AT (33.1 ± 4.0 mmHg vs 35.3 ± 3.2 mmHg, p = 0.02) were significantly improved after high dose of CCB therapy, along with improvement of WHO functional class, 6-min walking distance, NT-proBNP and tricuspid regurgitation pressure gradient.
Conclusions: Ventilatory efficiency in patients with VR-IPAH is better than that in patients with VNR-IPAH. CCB can improve aerobic capacity and ventilatory efficiency during exercise in patients with VR-IPAH.
Clinical trial registration number: ClinicalTrials.gov:NCT02061787.

1. Introduction

Pulmonary arterial hypertension (PAH) is a devastating disease characterized by increased pulmonary vascular resistance that leads to right heart failure and death. The REVEAL registry of pulmonary arterial hypertension study showed that the 5-year survival rate for newly diagnosed group 1 PAH was 61.2% [1]. However, a subset of idiopathic pulmonary arterial hypertension (IPAH)

Abbreviations: AT, anaerobic threshold; CCB, calcium channel blockers; CI, Cardiac index; CPET, cardiopulmonary exercise testing; DBP, diastolic blood pressure; HR, heart rate; LVED, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide; PCWP, pulmonary capillary wedge pressure; $PETCO_2$@AT, endtidal partial pressure of carbon dioxide at anaerobic threshold; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RER, respiratory exchange ratio; RHC, right heart catheterization; RVED, right ventricular end-diastolic diameter; RVEDP, right ventricular end-diastolic pressure; SBP, systolic blood pressure; S_PO_2, arterial oxygen saturation; SvO_2, mixed venous oxygen saturation; TRPG, ricuspid regurgitation pressure gradient; $\dot{V}E$, ventilation; $\dot{V}E/\dot{V}CO_2$@AT, ratio of ventilation to carbon dioxide output at anaerobic threshold; $\dot{V}O_2$, oxygen consumption; VR-IPAH, vasodilator-responsive idiopathic pulmonary arterial hypertension; VNR-IPAH, vasodilator-nonresponsive idiopathic pulmonary arterial hypertension; WHO-FC, World Health Organization Functional Class; 6WMD, 6 min walk distance; 6MWT, 6 min walk test.

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characterized by acute vasodilator responsiveness for vasodilator agents (VR-IPAH), who has excellent survival time under the treatment of calcium channel blockers (CCB), has a 5-year survival rate of 98% [2]. The effects of CCB in patients with VR-IPAH is mainly evaluated by right heart catheterization (RHC), 6 min walking distance (6WMD),NT-proBNP, electrocardiogram and WHO function class [2,3].

Recently, cardiopulmonary exercise testing (CPET) has been widely used in patients with PAH, as it can accurately quantify cardiorespiratory fitness and formulate function-based prognostic stratification [4]. Study also showed that peak $\dot{V}O_2$ rather than resting hemodynamic parameters obtained from RHC is an independent and strong predictor of survival in patients with IPAH [5].The effects of sildenafil on exercise capacity in patients with PAH have already been evaluated by CPET [6].However, the characteristics of CPET in patients with VR-IPAH and the change after CCB therapy have not been previously studied. The main aim of our study was to investigate the characteristics of CPET before and after the treatment of high doses of CCB in patients with VR-IPAH.

2. Material and methods

2.1. Study sample

Patients aged over 18 years old with newly diagnosed IPAH who demonstrated a significant acute response to aerosolised iloprost at Fuwai Hospital from 1 January 2012 to 16 November 2015 were prospectively enrolled, meanwhile, patients aged over 18 years old with newly diagnosed IPAH who did not demonstrate a significant acute response to aerosolised iloprost (VNR-IPAH) and treated with sildenafil from 1 January 2012 to 1 January 2014 were also prospectively enrolled. IPAH was defined according to 2009ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension [7]. Patients with the following conditions were excluded: (1) other types of pulmonary hypertension; (2) hemodynamic instability; (3) NYHA class IV; (4) restrictive or obstructive pulmonary disease. The study complies with the Declaration of Helsinki and was approved by the Ethics Committee of Fuwai Hospital (No. 2011−331). All written informed consents were obtained from participants.

2.2. Cardiopulmonary exercise testing

Symptom-limited CPET was performed on all recruited patients with VR-IPAH and patients with VNR-IPAH at baseline. Gas exchange measurements (Cosmed, Italy) were performed continuously during the 3 min of resting time, 3 min of unloaded pedaling at 60 rpm followed by a progressively increasing work rate exercise of 5−20 W/min to maximum tolerance, and then 5 min of recovery. Oxygen consumption ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$) and minute ventilation ($\dot{V}E$) were computer-calculated breath by breath and averaged over 10s intervals. AT (anaerobic threshold) was detected by a combination of the V-slope method and ventilatory equivalents for oxygen.O_2 pulse was calculated by dividing the $\dot{V}O_2$ by heart rate (HR). Pulmonary gas exchange was assessed by measuring the ratio of ventilation to carbon dioxide output ($\dot{V}E/\dot{V}CO_2$) and end tidal partial pressure of carbon dioxide ($PETCO_2$). Pulse oximetry (SpO_2), HR, 12-lead ECG and blood pressure were monitored and recorded. The equipment was calibrated in a standard procedure using reference gases prior to each test.

2.3. Right heart catheterization

Diagnostic RHC with standard hemodynamic measurements was performed at baseline within 5 days of each patient's CPET study. Aerosolised iloprost was used when subjects underwent acute pulmonary vasodilator testing according to the methods reported previously [8]. After baseline hemodynamic parameters and blood gases have been obtained, 20 μg iloprost (Bayer-Schering Pharma) was delivered by a PARI LC STAR nebulizer (PARI GmbH) driven by a PARI TurboBOY-N compressor (PARI GmbH) for 10−15min. Following that, another set of hemodynamic measurements and blood gases was obtained. Blood gas analysis was performed using a blood gas analyzer (Nova Biomedical). A positive acute response was defined as a decrease of mean pulmonary arterial pressure (mPAP) by more than 10 mmHg to below 40 mmHg with an increased or preserved cardiac output (CO). CO was calculated by Fick's method and cardiac index (CI) was calculated by dividing cardiac output by body surface area. Pulmonary vascular resistance (PVR) was calculated as dividing (mPAP−PCWP) by pulmonary blood flow.

Spirometry and body plethysmography were performed with the use of a constant volume body plethysmograph (Cosmed, Italy) to exclude underlying restrictive or obstructive pulmonary disease. Anthropometry data, blood pressure, 6 min walk test (6MWT), electrocardiograms, echocardiograms, routine blood examinations, N-terminal pro-brain natriuretic peptide (NT-proBNP) were also evaluated at baseline.

2.4. Calcium channel blockers or sildenafil therapy and follow -up

Oral CCB therapy was initiated in patients with newly diagnosed VR-IPAH. Diltiazem or amlodipine was used, which depended on the patient's heart rate at rest (diltiazem for heart rate $\geq$100 bpm, amlodipine for heart rate <100 bpm) [3]. Patients were recommended to add 1.25 mg or 2.5 mg of amlodipine (once a day), 7.5 mg or15 mg of diltiazem (three times a day) every three or five days on the basis of previous drug doses until they exhibited side effects such as hypotension or bradycardia after they were discharged. Patients with newly diagnosed VNR-IPAH received sildenafil, which was given at a dose of 20 mg three times a day. For both groups, warfarin was prescribed to patients if they did not have any contradiction or adverse effects. Diuretics and digoxin were prescribed to patients based on physician's judgement of patient's condition.

Patients were followed up 3−6 months after treatment with CCB or sildenafil. CPET, 6MWT, WHO function class, NT-proBNP, echocardiography were performed again except RHC. In addition, cardiovascular events, the dose of the CCB, the side effects, blood pressure, heart rate, routine blood examinations, chest X-ray electrocardiograms were also performed.

2.5. Statistical analysis

Continuous variables with normal distribution were expressed as mean ± SD and as median and interquartile range with non-normal distribution, while categorical variables were presented as percentages or absolute numbers. Comparisons between VR-IPAH group and control group were made using chi-square tests for categorical variables, independent-samples Student's t tests for normally distributed continuous variables, and Mann−Whitney U tests for non-normally continuous distributed variables. A paired Student's t tests was used to compare variables between baseline and follow-up. All testing was 2 tailed at a significance level of 0.05. All statistical analyses were performed using SPSS version 19.0(SPSS, Inc., Chicago, IL, USA).

3. Results

Twenty-five patients met the criteria of IPAH who also