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Original article

Effects of long-term iloprost treatment on right ventricular function in patients with Eisenmenger syndrome

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ABSTRACT

Background: Right ventricular (RV) function is an important prognostic factor of pulmonary arterial hypertension (PAH), but there is insufficient data regarding RV function after long-term inhaled iloprost treatment. We evaluated the effect of long-term iloprost treatment on RV function in patients with Eisenmenger syndrome (ES).

Methods: Eleven consecutive patients with ES associated with congenital heart disease underwent echocardiographic measurements at baseline and 48 weeks after iloprost therapy. In addition, we recorded World Health Organization (WHO) functional class, 6-minute walk distance (6MWD), systemic arterial oxygen saturation (SaO₂), and laboratory values such as hemoglobin, serum creatinine, and N-terminal pro-B natriuretic peptide.

Results: After 48 weeks of iloprost therapy, mean pulmonary arterial pressure (mPAP), pulmonary arterial systolic pressure (PASP), and pulmonary vascular resistance (PVR) were significantly decreased [mPAP, 42.5 (38.5–61.0) to 36.5 (29.1–40.0) mmHg; PASP, 92.6 ± 19.9 to 74.5 ± 23.8 mmHg; PVR, 23.4 (19.8–26.0) to 23.4 (19.8–26.0) Wood unit respectively, all $p < 0.05$]. There was also significant improvement in RV myocardial performance index [0.68 (0.61–0.80) to 0.52 (0.51–0.62), $p = 0.003$] and RV longitudinal strain ($-15.7 ± 1.6$ to $-18.1 ± 1.5%$, $p < 0.001$). In clinical assessment, WHO functional class ($p = 0.006$), 6MWD ($310.6 ± 44.7$ to $399.7 ± 80.8$ m, $p < 0.001$), and SaO₂ ($90.9 ± 6.0%$ to $92.5 ± 6.0%$, $p = 0.022$) were significantly improved.

Conclusion: The improvement in echocardiographic parameters of the RV function after 48 weeks of iloprost therapy may provide insight on the efficacy of long-term iloprost treatment for RV functional improvement, which is a prognostic factor in patients with ES.

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Introduction

Eisenmenger syndrome (ES) represents a congenital heart disease with left-to-right shunting that induces severe pulmonary arterial hypertension (PAH) and finally results in right-to-left shunt with hypoxemia [1,2]. Although patients with ES usually have better clinical outcomes than patients with idiopathic PAH, their life expectancy is significantly reduced [3,4]. ES patients have

increased pulmonary vascular resistance (PVR), leading to chronic pressure overload of the right ventricle (RV) with subsequent dilatation and failure. RV function has been identified as one of the main prognostic factors in patients with PAH [5,6]. Previously, treatment for ES was mainly supportive care or heart-lung transplantation [7,8], and there have been recent developments in the management of PAH with the introduction of new groups of drugs: phosphodiesterase inhibitors, prostacycline analogs, endothelin-receptor antagonists, and nitric oxide [9,10]. However, there is lack of evidence of the benefit of PAH-specific drugs on the RV function except endothelin-receptor antagonist, bosentan [9]. Previously, we showed that 24 weeks of inhaled iloprost therapy improved exercise capacity and quality of life outcomes, but there was no significant change in RV function with the

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exception of RV myocardial performance index (MPI) [11]. Here, in the present study, we evaluated RV functional change after 48 weeks of iloprost inhalation in patients with PAH related to congenital heart disease (CHD) comorbid with Eisenmenger physiology.

Methods

Study design

This study is a prospective, multicenter, single-arm trial. Inclusion and exclusion criteria, inhalation protocol, and medication method were as follows. Patients with exertional dyspnea World Health Organization (WHO) functional Class III–IV and Eisenmenger physiology (non-restrictive intra-cardiac or extra-cardiac communication with a right-to-left shunt at rest) were recruited between December 2010 and November 2012. Patients greater than 20 years of age with congenital heart defects such as univentricular heart, patent ductus arteriosus, ventricular septal defect, atrial septal defect, atrioventricular septal defect, or patients with persistent PAH after previous closure of a CHD defect were included for further study. Exclusion criteria included severe left ventricular (LV) dysfunction [ejection fraction (EF) $\leq 40\%$]; pulmonary venous congestion as measured invasively or by echocardiography; obstruction of the RV outflow tract, pulmonary valve, or pulmonary arteries; glibenclamide or cyclosporine treatment; known coronary artery disease; planned surgical procedure during the study period; systolic blood pressure ≤ 85 mmHg; inability to perform a 6-minute walk distance (6MWD) test and/or comply with the study protocol; serum creatinine ≥ 1.5 mg/dL; patients who had started or discontinued treatment for PAH within 1 month of screening; and anticoagulant use.

Patients inhaled iloprost via the prodose adaptive airway device. The acceptable target dose of iloprost is 2.5–5 μg administered divided by 6–9 times per day. In this study, patients inhaled 2.5 μg of iloprost twice a day in the first 4 weeks because of the safety and tolerability. After 4 weeks, dosage was increased to the target level if they could tolerate the medication, and the therapeutic dose was titrated according to patient compliance. Baseline medications including renin–angiotensin system inhibitors, calcium channel blocker, digoxin, diuretics, and antithrombotic agents were allowed to continue during study period. Use of phosphodiesterase inhibitors, prostanoids, and investigational endothelin-receptor antagonists was not allowed during the study. Women were advised to use reliable contraceptive methods (barrier-type devices, intrauterine devices, or oral contraceptives in combination with barrier methods).

Clinical information was collected at baseline and after 48 weeks of iloprost treatment and included blood pressure, heart rate, 6MWD, WHO functional class, systemic oxygen saturation (SaO_2), and echocardiography. Laboratory tests such as hemoglobin, uric acid, creatinine, and N-terminal pro-B natriuretic peptide (NT-proBNP) were followed to monitor clinical status and treatment side effects. Local ethics review committees approved the study protocol, and written informed consent was obtained from all patients.

Echocardiographic measurements

Echocardiography was performed at baseline and at 48 weeks after iloprost treatment. Two-dimensional and Doppler analysis was conducted according to the recommendations of the American Society of Echocardiography (ASE). Average values were taken for analysis. LVEF was estimated using modified Simpson's methods. Transmitral peak early (E) and atrial (A) diastolic velocities were

measured with pulsed wave Doppler in the apical 4-chamber view positioning the sampling volume at the tips of the mitral valve. Early diastolic mitral annular velocities (E') were obtained from the tissue Doppler apical 4-chamber view with the sampling volume placed at the medial (septal) corners of the mitral annulus. The maximal tricuspid regurgitation velocity (TR Vmax; in m/s) was obtained from continuous wave Doppler of the TR signal. The RV outflow tract (RVOT) time-velocity integral (TVI_{RVOT} ; in cm) was obtained by positioning the sample volume of the pulsed wave Doppler at the RVOT. PVR was calculated by a simple ratio such as the $\text{TR Vmax}/\text{TVI}_{\text{RVOT}} \times 10 + 0.16$. The Doppler-derived pulmonary artery systolic pressure (PASP; in mmHg) was then calculated from the maximal TR Vmax using the simplified Bernoulli formula as follows: $\text{PASP} = 4 \times (\text{TR Vmax})^2 + \text{right atrial (RA) pressure}$. RA pressure was estimated by measuring the diameter and the inspiratory collapse of the inferior vena cava (IVC). RA pressure was estimated as 5 mmHg if the IVC diameter was ≤ 2.1 cm and did collapse $>50\%$ with a sniff, 15 mmHg if the IVC diameter was >2.1 cm and collapsed $<50\%$ with a sniff, and 10 mmHg if the IVC diameter and collapse did not fit this paradigm. Mean pulmonary arterial pressure (mPAP) was calculated by tracing the TR time-velocity integral plus RA pressure. PAH was defined as the mPAP of at least 25 mmHg.

RV function was measured using tricuspid annular peak systolic velocity (S'), RV MPI, RV fractional area change, and RV strain. Tricuspid annular peak systolic velocity was measured by placing the pulsed Doppler sample volume in the tricuspid annulus of the free RV wall. To calculate RV MPI, isovolumic contraction time (ICT), isovolumic relaxation time (IRT), and ejection time derived from pulsed wave Doppler imaging data were obtained at the tricuspid inflow and RV outflow, and the RV MPI was defined as the sum of ICT and IRT divided by ejection time. RV fractional area change was measured by tracing the RV endocardium in both systole and diastole. Strain is defined as the percentage change in myocardial deformation. Two-dimensional RV strain (speckle-tracking analysis) was studied at the apical 4-chamber view to measure regional (basal, mid-ventricular, and apical segments of the RV free wall) and global contractility. All echocardiographic examinations were performed by an experienced operator and analyzed off-line with an EchoPAC Dimension system (General Electric, Horten, Norway) at a central laboratory by an operator blinded to the clinical status of the study subjects.

Statistical analysis

Statistical analysis was performed with SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Comparisons of variables between baseline and after iloprost therapy were performed using the Wilcoxon signed-rank sum test and paired t-test according to the normality of parameters. Results are presented as the mean \pm standard deviation in parametric analysis and the median (interquartile range) in non-parametric analysis. Categorical variables are presented as number and percentage and are compared by Pearson's chi-square analysis. Correlations between variables were tested using Spearman's rank correlation tests. Statistical significance was set as a p-value less than 0.05.

Results

Baseline characteristics

All of the eleven patients with ES completed 48 weeks of iloprost treatment according to the study protocol. There were no major adverse effects or significant declines in arterial oxygen saturation for the duration of the study period. Table 1 shows baseline demographics of enrolled patients. The mean age was

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