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ORIGINAL ARTICLE
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Nitric oxide vs Sildenafil for pulmonary artery reactivity testing in heart transplantation candidates

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Abstract

In idiopathic pulmonary arterial hypertension (IPAH) nitric oxide (NO) is an agent of choice for pulmonary artery (PA) reactivity testing. Contrary, currently there is no standardized protocol for PA reactivity testing in patients with pulmonary hypertension (PH) associated with left heart disease and several vasodilator agents are suggested for this procedure. We aimed to assess whether standard protocol of PA reactivity testing used in IPAH is useful in patients with severe PH due to severe systolic dysfunction of a left ventricle. During right heart catheterization we assessed hemodynamic parameters in 14 patients at baseline, during NO inhalation and 30 minutes after oral administration of sildenafil. We observed a significant decrease in PA pressure and resistance, and increase in cardiac index after sildenafil but not after NO administration. We conclude that standard protocol for PA reactivity in IPAH is not useful in patients with PH due to severe left ventricular systolic dysfunction. JRCD 2012; 1: 7–9

Key words: Pulmonary hypertension due to left heart disease; Qualification for heart transplant

Background

Pulmonary hypertension due to left heart disease (LHD-PH) is the most common type of pulmonary hypertension (PH) [1]. LHD-PH is a consequence of various pathologies such as systolic left ventricular (LV) dysfunction, diastolic LV dysfunction and mitral or aortic valve disease.

Heart transplantation (HTx) is usually considered in patients with severe LV systolic dysfunction and peak oxygen consumption (peak VO2) of ≤12 ml/kg/min, as measured in cardio-pulmonary exercise test (CPET). However, a vast number of patients is disqualified from the HTx due to severe PH. This is mainly associated with high risk of right heart failure after HTx and thus, high mortality.

Contemporary registry data from the International Society of Heart and Lung Transplantation (ISHLT) indicate, that approximately 20% of early deaths after HTx in patients with PH associated with LV systolic dysfunction are attributable to right ventricle (RV) failure [2]. Therefore, right heart catheterization (RHC) accompanied by pulmonary artery (PA) reactivity testing is indicated in every patient with LHD-PH who is considered for HTx to assess the risk of RV failure after transplantation.

According to the ISHLT guidelines [3], all HTx candidates with PA systolic pressure of ≥50 mm Hg and, either with transpulmonary gradient (TPG) of ≥15 or with pulmonary vascular resistance (PVR) of >3 Wood units if the systolic arterial blood pressure >85 mm Hg, should undergo PA reactivity testing on the RHC procedure.

In idiopathic pulmonary arterial hypertension (IPAH) nitric oxide (NO) is mostly used for PA reactivity testing. In contrast, there is no standardized protocol for PA reactivity testing in patients with LHD-PH and several vasodilator agents are suggested for this procedure.

The aim of this study was to assess, whether standard protocol of PA reactivity testing used in IPAH is useful in patients with severe PH due to severe systolic dysfunction of the LV.

Material and methods

In this open label study consecutive patients with PH associated with LV systolic dysfunction, who were previously disqualified from the HTx due to severe PH (pulmonary artery systolic pressure

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of ≥50 mm Hg and, either TPG of ≥15 or PVR of >3 Wood units) were enrolled. Other inclusion criteria were: chronic heart failure (New York Heart Association – NYHA class III-IV), peak VO2 of <12 ml/kg/min, left ventricle ejection fraction (LVEF) <25% as measured in cardiac echo study. The exlusion criteria were: known allergy to the study drug, systolic blood pressure <85 mm Hg and acute exacerbation of the heart failure.

Patients were classified as having LV dysfunction due to coronary artery diseases (CAD), when at least one atherosclerotic plaque narrowing the lumen diameter of at least one coronary artery of ≥50% was noted in coronary angiography or a history of acute myocardial infarction, coronary angioplasty or coronary arteries by-pass grafting was positive. Otherwise the patients were assigned to the group of dilated cardiomyopathy (DCM). DCM was diagnosed according to the guidelines of the European Society of Cardiology Working Group on myocardial and pericardial diseases [4]. The protocol was approved by the Ethics Committee of the Jagiellonian University in Krakow, Poland and written informed consent was obtained from all patients.

Transthoracic echocardiography, coronary angiography and right heart catheterization was performed in all patients.

Vivid 7 ultrasound machine, equipped with 2.5–5.0 MHz probe was used for the echocardiographic evaluation. Standard M-mode, 2D, and Doppler blood flow measurements were assesed according to the guidelines of the European Association of Echocardiography. LVEF was calculated with the biplane method of discs (modified Simpson's rule) [5].

Coronary angiography was executed in all patients with the application of standard techniques.

RHC was performed in a supine position from the right femoral vein access using a Swan-Ganz catheter. Pressures were acquired at end expiration. Heart rate (HR) was captured from the ECG recording. Cardiac output (CO) was specified using Fick oxygen consumption method. PVR was calculated as the difference between mean pulmonary artery pressure (mPAP) and pulmonary capillary wedge pressure (PCWP) divided by the CO. Haemodynamic measurements were gained at baseline, and 5 minutes after the start of inhaled nitric oxide (NO) administration (at dose of 20 ppm). Following that, 50 mg of sildenafil was given to the patient orally and the haemodynamic analysis was repeated after 30 minutes. We recorded the following parameters: right atrium pressure (RAP), systolic pulmonary artery pressure (sPAP), diastolic pulmonary artery pressure (dPAP), mPAP, PCWP, mean systemic pressure (mSP), pulmonary artery blood oxygen saturation (PA-SpO_2), and calculated: cardiac index (CI), CO, PVR, systemic vascular resistance (SVR) and TPG.

Statistics

Continuous variables were reported using median and interquartile range (IQR). Categorical variables were described as counts and percentages. Continuous variables describing haemodynamic parameters at baseline and after PA reactivity testing were compared using Wilcoxon test for paired samples. The significance level was set at $p < 0.05$. Statistical analysis was performed with *Statistica PL* software [StatSoft, Inc. (2010). STATISTICA (data analysis software system), version 9.1. Tulsa, USA www.statsoft.com].

Table 1. Baseline characteristics (n = 14)

parameter	median (IQR) (n [%])
Age (years)	53.5 (50.0–57.0)
Male	13 (92.8)
Etiology	
CAD	10 (71.4)
DCM	4 (28.6)
NYHA class III	9 (64.3)
NYHA class IV	5 (35.7)
LVEF (%)	18.0 (14.0–21.0)
peak VO_2 (ml/kg/min)	10.1 (9.0–11.6)
Risk factors	
Hypertension	1 (7)
Hyperlipidemia	7 (50)
Diabetes	5 (36)
Smoking	9 (64)
Drugs	
ACEI	10 (71)
ARB	2 (14)
Beta-blocker	14 (100)
Statins	10 (71)
ASA	10 (71)
Loop diuretics	13 (93)
Spironolactone	7 (50)
Eplerenon	5 (36)
Digoxin	8 (57)
ICD	13 (93)

CAD – coronary artery disease, DCM – dilated cardiomyopathy, NYHA – New York Heart Association, LVEF – left ventricle ejection fraction, peak VO_2 – peak oxygen consuption in cardio-pulmonary exercise test, ACEI – angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker, ASA – acetylsalicylic acid, ICD – implantable cardioverter-defibrillator

Results

We enrolled 14 patients (13 men), aged 52.8 ±5.4 years. All patients had been symptomatic despite the optimal medical treatment which was stable for at least three months before inclusion to the study. Clinical characteristics of the study group are summarized in Table 1.

Administration of sildenafil was associated with a significant reduction of the sPAP, mPAP and PVR without decrease of mSP. Vasodilatory effect of sildenafil was accompanied by the increase of CO, CI and PA-SpO_2. Sildenafil administration resulted in TPG decrease without PCWP elevation. In contrast, we did not observe any significant change in hemodynamic parameters after NO inhalation.

Hemodynamic results are summarized in Table 2.

Discussion

This study compares acute hemodynamic effects of NO and sildenafil in HTx candidates with severe PH due to LV systolic dysfunction. We have shown that a standard protocol for PA reactivity with NO inhalation which is recommended for IPAH patients is not useful to detect PA reactivity in this group of patients since

its application does not change PVR or PA pressure. Both parameters on the contrary, are significantly lowered by sildenafil.

Increased afterload of RV and the high end-diastolic LV pressure are the principal findings in patients with PH due to LV systolic dysfunction. In our study sildenafil decreased both RV and LV afterload which was expressed by lowering of PVR and SVR. It further resulted in a rise of CI without systolic blood pressure fall. Despite lowering of SVR we did not observed any decrease in PCWP after sildenafil which we believe is a result of increased flow through pulmonary circulation into the noncompliant LV. Concomitant influence of sildenafil on systemic and pulmonary circulation makes this agent not only effective but also safe option for PA reactivity testing. Use of an agent specific for pulmonary vasculature would pose a significant risk for pulmonary oedema.

In the ISHLT guidelines different agents have been proposed for testing PA vasoreactivity such as nitroprusside, nitroglycerin, nesiritide, prostacyclin and NO without designation of a preferred one. In our study NO was not effective in decreasing PVR which was in contrast to some previous studies in patients with left ventricular systolic dysfunction [6,7]. In those studies however higher doses of NO e.g. 80 ppm over 10 min were used and the decrease in PVR was at cost of increased filling pressure of LV which may pose a risk of acute lung oedema.

Although sildenafil was shown to effectively reduce PVR in our study we do not have any data on how this response predicts the risk of RV failure after heart transplantation. Further head-to-head studies are needed to compare the effects of sildenafil and other vasoactive agents on PVR and the heart transplantation risk in patients with PH due to LV systolic dysfunction.

Conclusion

A standard protocol for PA reactivity with NO used in IPAH patients is not useful to detect PA reactivity in heart transplant candidates with severe PH due to LV systolic dysfunction. Sildenafil when compared to NO is superior for detecting PA reactivity, however, further head to head studies are needed to indicate the vasodilator of choice for PA reactivity testing in this group of patients.

Conflict of interest: non declared.

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Table 2. Hemodynamic parameters

parameter	baseline	NO	sildenafil	p*	p**
RAP [mm Hg]	11.3 (4–17)	10.5 (3–17)	12.2 (5–16)	0.73	0.69
sPAP [mm Hg]	63.0 (55.0–75.0)	65.5 (59.0–73.0)	57.7 (52.0–70.0)	0.54	<0.001
dPAP [mm Hg]	26.0 (21.0–30.0)	29.5 (26.0–34.0)	26.0 (20.0–29.0)	0.51	0.21
mPAP [mm Hg]	43.0 (40.0–48.0)	42.5 (35.0–48.0)	38.5 (31.0–43.0)	0.51	<0.001
PCWP [mm Hg]	23.0 (18.0–28.0)	21.5 (19.0–28.0)	22.5 (19.0–25.0)	0.73	0.96
mSP [mm Hg]	78.0 (73.0–87.0)	81.0 (74.0–86.0)	78.0 (73.0–88.0)	0.22	0.58
SaO_2 PA [%]	55.6 (50.1–63.4)	57.4 (49.0–60.2)	59.7 (53.0–66.6)	0.62	0.005
CO [l/min]	3.0 (2.7–3.3)	3.0 (2.9–3.1)	3.5 (3.3–3.6)	0.68	0.003
CI [l/min/m^2]	1.6 (1.4–1.7)	1.6 (1.4–1.8)	1.8 (1.7–1.9)	0.57	0.003
PVR [dyn*s*cm-5]	489.0 (343.0–578.0)	461.0 (367.0–553.0)	312.0 (230.0–352.0)	0.76	<0.001
SVR [dyn*s*cm-5]	1837.0 (1609.0–2266.0)	2229.0 (1836.0–2384.0)	1522.0 (1393.8–1605.5)	0.31	0.03
TPG [mm Hg]	19.0 (16.0–22.0)	17.5 (13.0–21.0)	13.0 (7.0–23.0)	0.85	0.002

p* for the difference between baseline hemodynamic data and after NO inhalation; p**for the difference between baseline hemodynamic data and after sildenafil
RAP – right atrium pressure, sPAP – systolic pulmonary artery pressure, dPAP – diastolic pulmonary pressure, mPAP – mean pulmonary pressure, PCWP – pulmonary capillary wedge pressure, mSP – mean systolic pressure, SaO_2 PA – pulmonary artery oxygen saturation, CO – cardiac output, CI – cardiac index, PVR – pulmonary vascular resistance, SVR – systemic vascular resistance, TPG – transpulmonary gradient