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Establishing the optimal dose of nitric oxide in acute vasoreactivity testing in patients with pulmonary hypertension with use of the Bronchial Control Treatment System (RCD code: II)

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Abstract

The key point in the diagnostic algorithm for pulmonary hypertension plays pulmonary reactivity testing. The agent most frequently used in the test is inhaled nitric oxide (iNO). Various dosages of iNO have been used in acute vasoreactivity testing so far. Our aim was to determine the most effective dose of iNO for this procedure. Ten consecutive patients were enrolled in the open label study. To assess the most effective dose of iNO increasing concentrations of iNO: 10 ppm, 20 parts per million (ppm) and 30 ppm were administered. The study showed significant reduction in mean pulmonary artery pressure after each dose of iNO as compared to baseline was found. There were no significant differences in mean pulmonary artery pressure between subsequent iNO doses (10 ppm vs. 20 ppm, 20 ppm vs. 30 ppm). Additionally, significant reduction of systolic pulmonary artery pressure after iNO at the dose of 20 ppm as compared to a dose of 10 ppm was also observed. No significant side effects during iNO administration were observed. We concluded that the dose of inhaled nitric oxide used for acute vasoreactivity testing should not exceed 20 ppmas it proved to be both safe and effective. JRCD 2015; 2 (4): 109–114

Key words: PAH, reactive pulmonary hypertension, iNO, right heart catheterization

Introduction

Pulmonary hypertension (PH) is a progressive disease with heterogeneous etiology and poor prognosis, characterized by progressive increase in pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR), leading to right heart failure and death. According to current guidelines, the key point in the diagnostic algorithm for PH is the acute pulmonary vasoreactivity testing (APVRT). Its result determines prognosis and treatment of PH [1]. Patients with idiopathic pulmonary arterial hypertension (PAH) and positive result of APVRT should be treated with calcium channel antagonists; patients with PH caused by left heart failure may be subjected to cardiac transplantation because of low risk of right heart failure in donor heart. Also patients with PH due to congenital heart defects with systemic-to-pulmonary shunts may be subjected to corrective surgery [2,3]. According to data from the International Society of Heart and Lung Transplantation about 20% of early deaths after heart transplantation develop due to the right heart failure in transplanted heart [4].

APVRT in patients with PH in the course of left heart failure is recommended when systolic PAP is equal to or greater than 50 mm Hg, transpulmonary gradient equal to or greater than 15 mm Hg and PVR exceeds 3 Wood units. No reduction of PVR below 2.5 Wood units and systolic pressure in the aorta exceeding 85 mm Hg indicate high risk of right ventricular failure in donor heart [5]. In patients with PAH positive result of APVRT is defined as reduction in mean PAP below 40 mm Hg and more than 10 mm Hg from baseline without any reduction in cardiac output [1].

The most frequently used agent in acute pulmonary vasoreactivity testing is inhaled nitric oxide (iNO) because of its short half-life,

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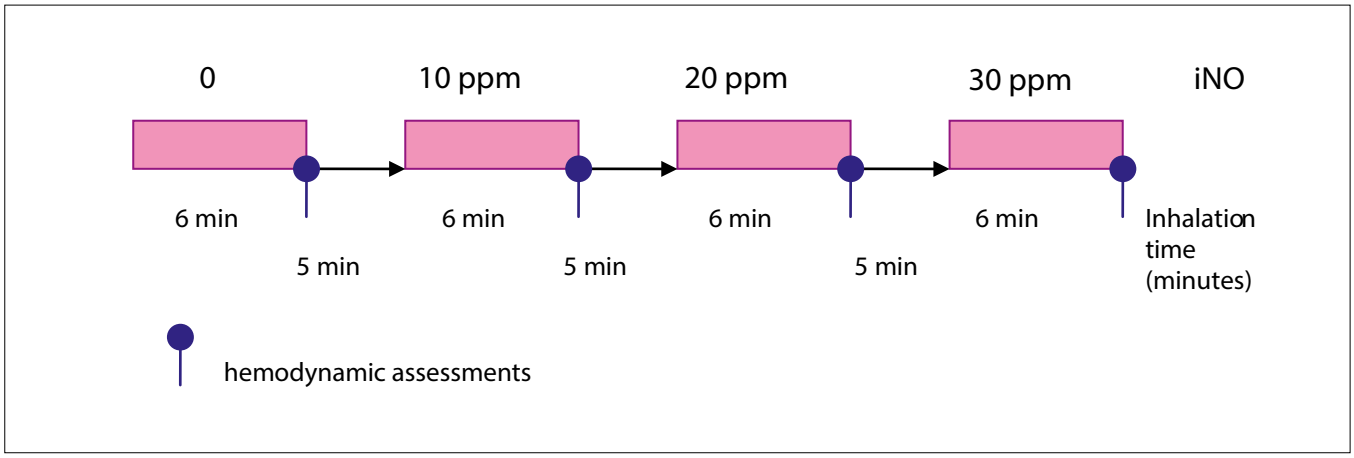

Figure 1. Evaluation of the most effective dose of inhaled nitric oxide. iNO: inhaled nitric oxide, ppm: parts per million

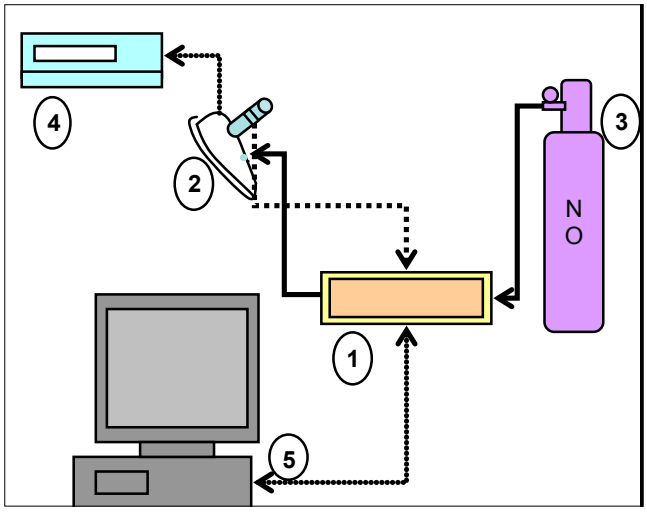

Figure 2. A suite for administration of inhaled nitric oxide in Bronchial Control Treatment System method. 1. pneumodozimeter (NOx PNEUMONEB® abcMED; 2. BCTS head – a mask with a pneumotachograph; 3. cylinder with nitroc oxide (NO) reducer; 4. NO and NO2 analyzer; 5. Computer with software for iNO administration by BCTS method

Table 1. The study group characteristics

characteristics	mean/number	range/percent (%)
Age (years)	45.49	27 – 70
Etiology		
PAH	6	60%
IPAH	4	40%
CHD	2	20%
LHD-PH	4	40%
WHO		
I	1	10%
II	4	40%
III	4	40%
IV	1	10%
6MWD (m)	335	150 – 550

PAH – pulmonary arterial hypertension, IPAH – idiopathic pulmonary arterial hypertension, CHD – congenital heart defect, LHD-PH – pulmonary hypertension due to left heart disease, 6MWD – six minute walking distance, m – meters

convenient method of administration and selective, restricted to the pulmonary circulation effect. In previously published studies different concentrations of inhaled nitric oxide (between 10 to 80 parts per million [ppm]) were used, so it is necessary to optimize the dose of iNO for this procedure [6,7,8]. Therefore the objective of the study is to determine the most effective dose of iNO for APVRT.

Materials and methods

Study group

The open label study enrolled 10 consecutive patients diagnosed for suspected PH. The inclusion criteria were: diagnosis of PAH or PH due to left heart disease. Exclusion criteria were: systolic blood pressure below 85 mm Hg and exacerbation of heart failure. To assess the clinical category of PH all patients underwent clinical examination, laboratory tests, ECG, echocardiography and lung perfusion scan or computed tomography of the chest.

The study protocol was approved by the institutional ethics committee.

Right heart catheterization

All patients underwent routine right heart catheterization (RHC) in supine position with access *via* the right femoral vein using a Swan-Ganz catheter. The following parameters were measured: systolic PAP (sPAP), diastolic PAP (dPAP), pulmonary capillary wedge pressure (PWP) and cardiac index (CI), cardiac output (CO), mean PAP (mPAP), PVR and systemic vascular resistance (SVR) were calculated. Pressures in the pulmonary arteries

Table 2. Mean values of hemodynamic parameters at baseline and after administration of increasing doses of iNO: 10 ppm, 20 ppm, 30 ppm

iNO dose	Parameter	Mean Value	Standard deviation	Minimum value	Maximum value
0	sPAP	88,5	31,81	61	167
	dPAP	36,7	11,71	23	57
	mPAP	56,0	16,36	41	95
	PVR	1243,9	1028,1	238,0	3947,1
	CI	1,5	0,745	0,9	2,7
10 ppm	sPAP	82,4	31,37	52	151
	dPAP	35,9	9,19	25	54
	mPAP	52,9	15,08	36	85
	PVR	1165,7	816,1	491,3	3175,7
	CI	1,3	0,6	1,1	2,7
20 ppm	sPAP	77,3	34,78	33	153
	dPAP	32,8	13,34	8	57
	mPAP	49,2	19,31	18	89
	PVR	1060,2	1018,1	289,8	3336,2
	CI	1,4	0,7	1,1	2,4
30 ppm	sPAP	82,0	35,14	48	153
	dPAP	34,8	9,83	23	57
	mPAP	52,2	17,1	36	88
	PVR	1246,3	1191,0	326,9	4068,6
	CI	1,4	0,6	1,1	2,3

sPAP – systolic pulmonary artery pressure, dPAP – diastolic pulmonary artery pressure, mPAP – mean pulmonary artery pressure, PVR – pulmonary vascular resistance, CI – cardiac index, ppm – parts per million

were acquired at the end of expiration. Heart rate was based of ECG recordings. PVR was calculated according to the formula: mPAP-PWP/CO. All calculation of hemodynamic parameters and average pressures were performed using Siemens software on a Cathcor 4.2B workstation. Pulmonary blood flow was calculated by Fick oxygen consumption method.

Pulmonary vasoreactivity testing

All patients underwent APVRT with iNO. To assess the most effective dose of iNO increasing concentrations of iNO: 10 ppm, 20 ppm and 30 ppm were administered. Inhalation time of each dose was 6 minutes and the intervals between inhalations lasted five minutes (Figure 1). After administration of each dose of iNO standard hemodynamic parameters were assessed; any change in the mPAP and sPAP after administration of increasing doses of iNO was subjected to further detailed analysis.

During inhalation each patient was observed for potential side effects such as hypotension, dyspnoea, drop in arterial oxygenation or pulmonary oedema.

NO was administered by using BCTS method (Bronchial Control Treatment System) NOx PNEUMONEB® abcMED. This method allows for continuous measurement of respiratory cycle, registration of the beginning of inspiration and delivers the proper dosage of iNO exactly in the early stage of inspiration. This method guarantees the highest deposition of the gas in the peripheral part of the respiratory system. Diagram of the device for controlled administration of iNO is shown on Figure 2.

Statistics

Continuous variables were reported as mean values and standard deviation. Categorical variables were described as counts and percentages. Continuous variables describing hemodynamic parameters at baseline and after 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 version 7.1.

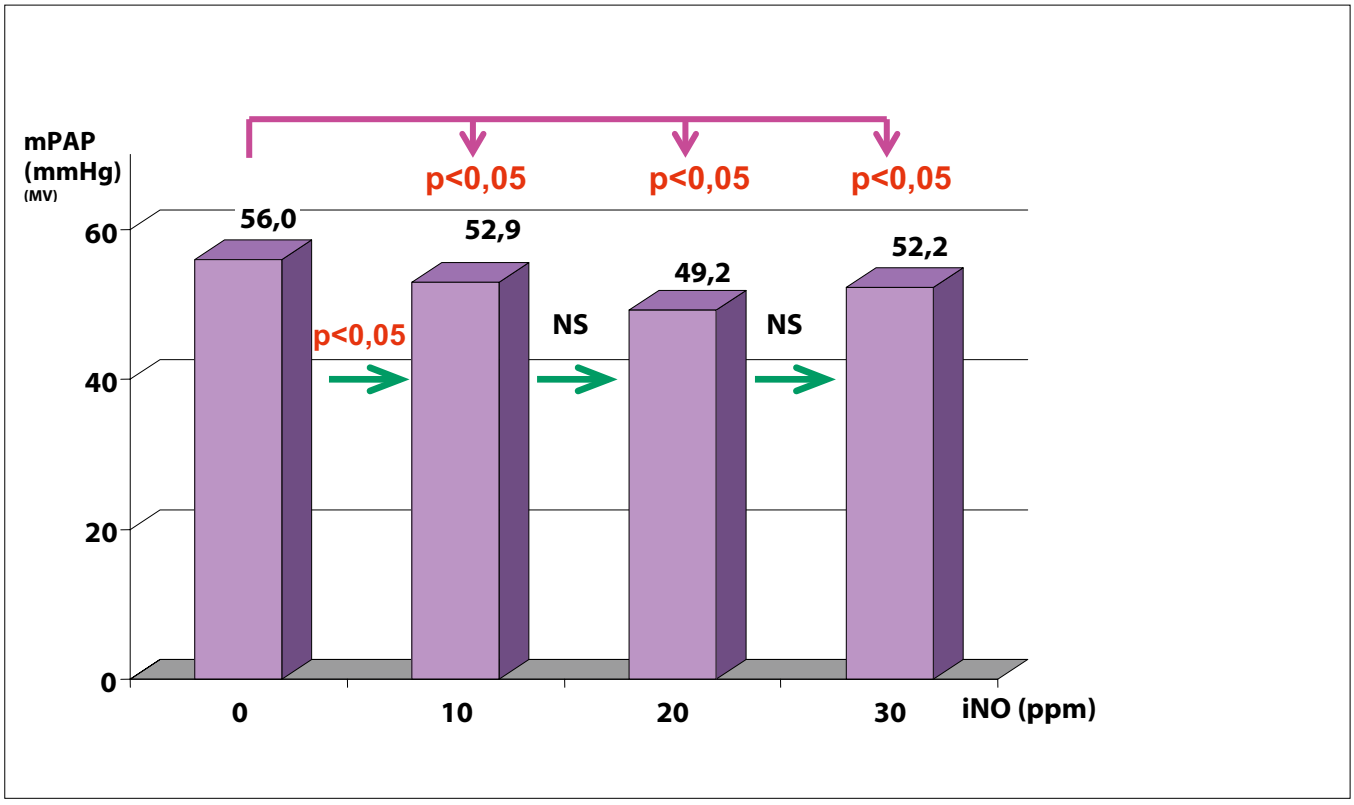

Figure 3. Mean pulmonary artery pressure after the administration of increasing doses of inhaled nitric oxide: 10 ppm, 20 ppm, 30 ppm. mPAP – mean pulmonary arterial pressure, iNO – inhaled nitric oxide, MV – mean value

Results

Ten patients with diagnosed PH, aged 27–70, average 45.9 years were enrolled in the study. PAH was diagnosed in 6 (60%) patients, PH due to left heart disease was recognized in 4 (40%) patients. The characteristics of the study group is shown in Table 1.

On the basis of performed measurements statistically significant reduction in mPAP after each dose of iNO as compared to baseline was found (Figure 3). There were no significant differences between the change of mPAP obtained by using subsequent iNO doses (10 ppm vs. 20 ppm, 20 ppm vs. 30 ppm). However, there was a statistically significant reduction of sPAP after iNO at the dose of 20 ppm as compared to 10 ppm (Figure 4). The results of hemodynamic measurements are shown in table 2. No significant side effects during iNO administration were observed. No true responders were found in the study group.

Discussion

According to the guidelines of European Society of Cardiology [1] and recommendations of the International Society for Heart and Lung Transplantation [5] the key point in diagnostic and therapeutic algorithm for PH is pulmonary APVRT. The agents most frequently used are sodium nitroprusside, oxygen, epoprostenol, adenosine, inhaled NO and iloprost. Due to selective effect on pulmonary vascular bed, no side effects during administration, short half-life and low cost, inhaled nitric oxide (iNO) remains the most widely used agent. Commonly perceived as a teratogenic and toxic substance, iNO is one of the most important factors involved in blood vessels relaxation, activation of platelets and leukocytes. iNO is also a mediator in inflammation and immune processes and a neurotransmitter in the central and peripheral nervous system [9,10,11].

In previously published studies various dosages of iNO were used (10–80 ppm). According to some researchers each of the iNO doses caused reduction in PAP and PVR, with higher doses being more potent. In the study published by Budts et al. iNO at the dose of 40 ppm caused decrease in PVR of 18% and 80 ppm up to 29% compared to baseline value [7]. Krasusky et al. found, that in patients with primary PH escalation of iNO dose results in slight decrease of PAP and PVR while in patients with secondary PH consecutive administration of 10 vs 20 vs 40 ppm caused stronger effect [8]. It was also shown that high iNO doses, ie. 80 ppm, caused stronger hemodynamic effects while inducing significantly more complications such as pulmonary edema.

In the current study there was no statistically significant change in the mPAP after administration 10 ppm vs. 20 ppm and 20 vs. 30 ppm of iNO. In contrast, sPAP after dosage of 20 ppm versus 10 ppm was significantly lower. No significant changes in pressures and PVR after administration of iNO in dose of 30 ppm were observed. Based on the obtained results, we think that the dose of iNO used in APVRT should not be greater then 20 ppm.

Similar results were shown by Sitbon et al., they proved that reversibility of PH is not iNO dose-dependent [12]. During escalation of iNO doses from 10 ppm to 20 ppm and 40 ppm the criteria of reversibility were met already after the first iNO dosage of 10 ppm

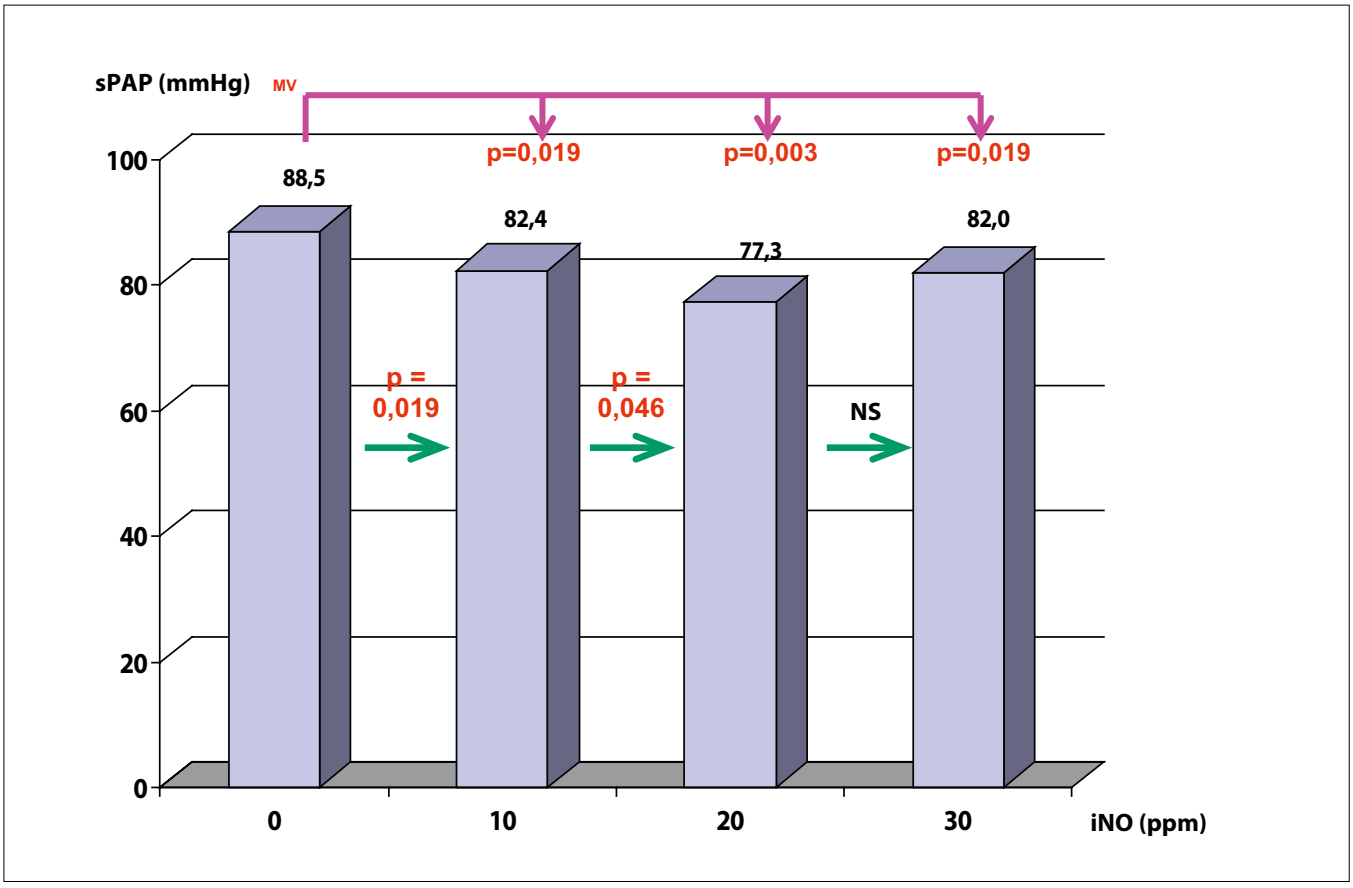

Figure 4. Systolic pulmonary artery pressure after administration increasing doses of inhaled nitric oxide: 10 ppm, 20 ppm, 30 ppm. mPAP – mean pulmonary arterial pressure, iNO – inhaled nitric oxide, MV – mean value

and the degree of pressure reduction was higher, but not significantly, after dosage of 20 ppm. In patients with positive APVRT PAP reduction was recorded in the first seconds of inhalation. The pressures returned to baseline values within 2 minutes after iNO was discontinued. In some patients with negative result of APVRT after administration of higer iNO doses an increase in pressures and vascular resistance was observed.

In the current study, during the iNO administration neither reduction in systemic pressures nor significant cardiac arrhythmias were observed. The administration of iNO using BCTS method is safe in patients with PH regardless of the dose.

Limitations of the study

The main limitation of the study is a relatively low number of study subjects, however the response was very similar in all patients, therefore we think, that increasing the number of patients would not have significantly changed the study results. Also using Fick method with approximation of O2 consumption can be a limitation of the study in patients with high cardiac output states, or lung injury.

Conclusions

The study showed that the dose of iNO used in APVRT should not exceed 20 ppm. This is the most effective and safe dose, which cause no side effects.

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