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Effects of inhaled salbutamol in primary pulmonary hypertension

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ABSTRACT: Although lung function is grossly normal in patients with primary pulmonary hypertension (PPH), mild-to-moderate peripheral airflow obstruction can be found in the majority of patients with this disease. Therefore, β_2-agonists may affect pulmonary function, blood gases and haemodynamics in patients with PPH.

Pulmonary function testing, blood gas measurements and right heart catheterisation was performed in 22 patients with PPH and the acute effects of inhaled salbutamol (0.2 mg) were measured.

Salbutamol caused an increase in the forced expiratory volume in one second (FEV_1) from 2446±704 to 2550±776 mL. The mean expiratory flow at 50% of the vital capacity (MEF_{50}) rose from 58±17 to 66±21% pred. The pulmonary artery pressures remained unchanged after inhalation of salbutamol, but the cardiac output increased significantly from 3.9±1.4 to 4.2±1.4 L·min^{-1} accompanied by significant increases in stroke volume and mixed venous oxygen saturation as well as a significant decrease in pulmonary vascular resistance. The arterial oxygen tension rose from 9±2.4 kPa (68±18 mmHg) at baseline to 9.7±2.8 kPa (73±21 mmHg) after inhalation of salbutamol, the alveolo-arterial oxygen gradient values improved from 6±2.5 kPa (45±19 mmHg) to 5.1±2.9 kPa (38±22 mmHg), respectively.

Inhaled salbutamol has beneficial acute effects on pulmonary function, blood gases and haemodynamics in patients with primary pulmonary hypertension.

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Primary pulmonary hypertension (PPH) is caused by progressive obliteration of the pulmonary vascular bed leading to increasing pulmonary vascular resistance and eventually right heart failure [1]. The cause of PPH is unknown even if recently discovered mutations in the bone morphogenetic receptor protein 2 (BMPR2) gene in patients with familial and sporadic disease may indicate a proliferative disorder of pulmonary vascular cells as a principal pathogenetic mechanism [2–4]. Clinically, the diagnosis of PPH is one of exclusion, since other diseases causing secondary forms of pulmonary hypertension have to be ruled out [5]. Therefore, one diagnostic criterion for the diagnosis of PPH is the exclusion of obstructive and restrictive pulmonary disease. Nevertheless, one common, but widely overlooked feature of PPH is mild-to-moderate peripheral airflow obstruction which can be detected in up to 80% of patients [6]. To the present authors' knowledge there is only one study so far which has described airway responsiveness to inhaled β_2-agonists in children with pulmonary hypertension [7]. It has not been previously investigated whether β_2-agonists may yield a clinical benefit for patients with PPH in terms of improved oxygenation and haemodynamics.

Therefore, the present authors initiated a pilot trial to test the acute effects of inhaled salbutamol, a selective β_2-agonist, on lung function, blood gases and haemodynamic variables in patients with PPH.

Methods and patients

Patients

A total of 22 patients with PPH were studied. The diagnosis was established in accordance with the criteria recently formulated by a World Health Organization-sponsored meeting of experts in the field of pulmonary hypertension [5]. The female:male ratio was 1:1 and the mean age was 45±21 yrs. Six out of the 22 patients were former smokers and none had a history of asthma.

The study protocol was approved by the institutional ethics committee and all patients gave informed consent.

Pulmonary function studies

Spirometric variables, lung volumes, flow/volume curves and single-breath diffusion capacity for carbon monoxide (corrected for haemoglobin levels) were obtained using a Ganshorn bodyplethysmograph (Ganshorn, Muennerstadt, Germany). All measurements were made in a seated position. After these measurements were completed, the patients received two puffs of 0.1 mg salbutamol (Sultanol®, GlaxoSmithKline GmbH & Co. KG, Munich, Germany) resulting in a total dose of 0.2 mg salbutamol.

Spirometry and flow/volume curves were recorded again 10 min later, according to the present authors' guidelines to test reversibility of bronchoconstriction. Normal values were obtained from published references [8–10]. The pulmonary function studies were performed 1–3 days before or after the haemodynamic assessments.

Haemodynamic assessment and blood gas measurements

All patients received a Swan-Ganz catheter and a femoral arterial line for diagnostic reasons unrelated to this study. During the investigation, the acute haemodynamic effects of aerosolised iloprost were usually assessed. Details of heart catheterisation and iloprost challenge have been described elsewhere [11–13]. After drug challenge with iloprost, haemodynamic stability was documented at least 1 h later for a minimum period of 15 min before salbutamol was applied. A set of haemodynamics was recorded and blood was obtained from the pulmonary artery and the arterial line and immediately sent for blood gas measurement (ABL 520; Radiometer, Copenhagen, Denmark). The values obtained at this time were used as baseline values for the purposes of this study. Haemodynamic assessment and blood gas analyses were repeated 10 min after inhalation of 0.2 mg salbutamol, performed in a 30 seated position. The alveolo-arterial oxygen gradient ($D_{A\text{-}a,O_2}$) was calculated according to standard formula assuming a respiratory ratio (R) of 0.8 [14].

Statistical analysis

The results are given as mean±SD. Changes in lung function, blood gases and haemodynamics after inhalation of salbutamol compared to baseline were compared using a paired t-test. All tests were two-sided. The significance level was set at $p<0.05$. The correlation between independent variables was expressed by the correlation coefficient r.

Results

Results of pulmonary function testing, blood gas analysis and heart catheterisation were available from all 22 patients. All studies were completed without complications and none of the patients experienced any side-effects from inhalation of salbutamol.

Pulmonary function testing

Lung volumes were normal in all patients. The total capacity was 93±13% pred. The corresponding results for vital capacity, functional residual capacity and residual volume were 90±12, 99±18 and 99±29%, respectively. The airway resistance was also normal in most patients (2.5±1.0 $cmH_2O{\cdot}L{\cdot}s^{-1}$; normal <3.5 $cmH_2O{\cdot}L{\cdot}s^{-1}$). The diffusion capacity for carbon monoxide was 65±17 % pred.

Although the forced expiratory volume in one second (FEV_1) was normal in all of the patients in this study (2,446±704 mL, 89±12% pred), the flow/volume curves indicated considerable peripheral airflow obstruction (fig. 1). The peak expiratory flow (PEF) was 91±18 % pred but the mean expiratory flow rates at 50% and at 25% of the vital capacity (MEF_{50} and MEF_{25}) were 58±17% pred and 45±14% pred, respectively. In eight patients, the MEF_{50} was <50% pred.

As shown in table 1, inhalation of salbutamol caused a mild but significant increase in FEV_1, MEF_{50} and MEF_{25}. There was no differences in the degree of peripheral airflow obstruction between former and never smokers.

Haemodynamics and blood gases

The results of haemodynamic assessment and blood gas measurements are shown in table 2. All patients suffered from severe pulmonary hypertension. After inhalation of salbutamol, the mean pulmonary artery pressure remained unchanged, but there was a significant increase in the cardiac output (fig. 2) accompanied by a significant increase in the stroke volume, and a slight rise in mixed venous saturation as well as a significant decrease in the pulmonary and systemic vascular resistance. The heart rate remained unchanged. In addition to the haemodynamic changes, inhalation of salbutamol caused a slight but statistically significant increase in the arterial oxygen tension.

The $D_{A\text{-}a,O_2}$ was 6.0±2.5 kPa (range 2.3–8.6 kPa) (45±19 mmHg (range 17–65 mmHg)) before and 5.1±2.9 kPa (range 0.9–8.3 kPa) (38±22 mmHg (range 7–63 mmHg)) after inhalation of salbutamol ($p=0.004$). Chronic hyperventilation was detected in all patients (carbon dioxide tension in arterial blood 4.0±0.4 kPa (30±3 mmHg)) but was not affected by salbutamol (table 2).

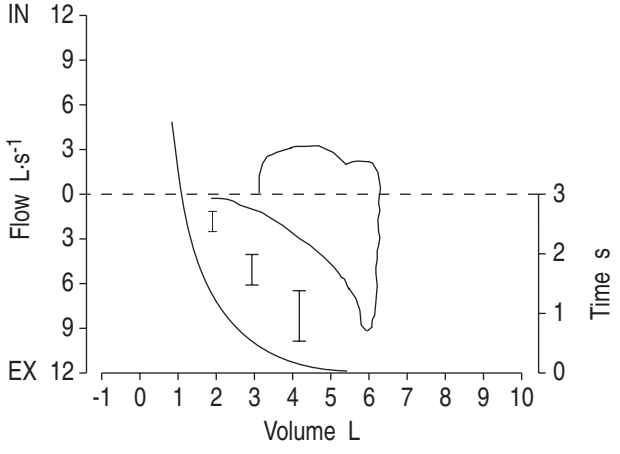

Fig. 1.–A representative picture of a flow/volume curve in a patient with primary pulmonary hypertension.

Table 1. – Results of pulmonary function testing in 22 patients with primary pulmonary hypertension before and after challenge with 0.2 mg salbutamol

	Baseline	After salbutamol	p-value
VC mL	3500±977	3504±1002	NS
VC % pred	90±12	91±13	NS
FEV_1 mL	2446±704	2550±776	p=0.0051
FEV_1 % pred	89±12	91±10	NS
FEV_1 % VC	73±10	74±8	NS
PEF $L \cdot s^{-1}$	6.9±2.1	6.9±2.3	NS
PEF % pred	91±18	92±22	NS
MEF_{50} $L \cdot s^{-1}$	2.6±0.9	2.9±1.1	p=0.0001
MEF_{50} % pred	58±17	66±21	p=0.0002
MEF_{25} $L \cdot s^{-1}$	0.8±0.4	1.0±0.4	p<0.0001
MEF_{25} % pred	45±14	52±17	p<0.0001
TLC mL	5188±1077	ND	
TLC % pred	93±13	ND	
FRC mL	2912±634	ND	
FRC % pred	99±18	ND	
RV mL	1775±362	ND	
RV % pred	99±29	ND	
R_{aw} $cmH_2O \cdot L \cdot s^{-1}$	2.5±1.0	ND	
$D_{L,CO}$ mL·min·$mmHg^{-1}$	18.4±7.4	ND	
$D_{L,CO}$ % pred	65±17	ND	

Data are presented as mean±SD. VC: vital capacity; FEV_1: forced expiratory volume in one second; PEF: peak expiratory flow; MEF_{50}: maximum flow at 50% of VC; MEF_{25}: maximum flow at 25% of VC; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; R_{aw}: airway resistance; $D_{L,CO}$: carbon monoxide diffusing capacity of the lung; NS: nonsignificant; ND: no data.

There was no correlation between the increase in cardiac output after salbutamol and the increase in cardiac output after acute challenge with iloprost (r=-0.04). In addition, there was no significant correlation between the haemodynamic response and the increase in expiratory flow rates or the arterial oxygen tension (data not shown).

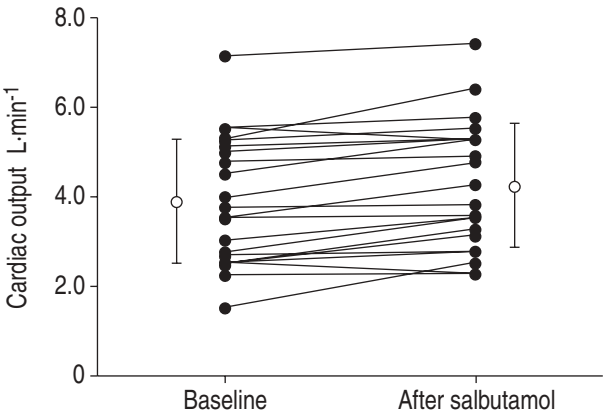

Fig. 2. – Cardiac output in 22 patients with primary pulmonary hypertension before and after the inhalation of 0.2 mg salbutamol. ●: individual variables; ○: mean±SD values.

Discussion

This study confirms previous observations that peripheral airflow obstruction is a common finding in patients with PPH [6, 7, 15]. Even if the FEV_1 and airway resistance were normal or only mildly abnormal in the patients in this study, peripheral airflow obstruction was indicated by reductions in the MEF_{50} and MEF_{25} to 58±17% and 45±14% pred, respectively.

MEF_{50} has been used by many authors as a sensitive variable of peripheral airflow limitation in chronic obstructive pulmonary disease, in post-transplant patients with bronchiolitis obliterans or in occupational lung disease [16–19].

A larger study on 171 patients with PPH corroborates the present data that peripheral airway obstruction is common in PPH [6]. As in the patients here, the airway resistance as a whole did not differ significantly from healthy controls. This is plausible since an increase in airway resistance is more sensitive to obstruction of the larger airways than to small airways disease. Data from asthmatics show that even major obstruction of the peripheral airways can occur

Table 2. – Results of right heart catheterisation and blood gas analysis in 22 patients with primary pulmonary hypertension before and after challenge with 0.2 mg salbutamol

	Baseline	After salbutamol	p-value
Heart rate beat·min^{-1}	83±12	84±12	NS
Mean pulmonary arterial pressure mmHg	6.8±1.5	6.8±1.5	NS
Mean systemic arterial pressure mmHg	12.1±1.5	12.2±1.7	NS
Cardiac output $L \cdot min^{-1}$	3.9±1.4	4.2±1.4	p=0.0003
Stroke volume mL	48±18	53±19	p=0.04
Pulmonary vascular resistance dynes×s×cm^{-3}	1011±495	910±411	p=0.015
Systemic vascular resistance dynes×s×cm^{-3}	1992±857	1817±697	p=0.005
Right arterial pressure mmHg	0.9±0.8	0.9±0.8	NS
Pulmonary capillary wedge pressure mmHg	0.9±0.4	1.1±0.4	0.01
Oxygen tension in arterial blood mmHg	9.0±2.4	9.7±1.6	0.03
Carbon dioxide tension in arterial blood mmHg	4.0±0.4	4.0±0.4	NS
pH	7.45±0.02	7.46±0.02	NS
Alveolo-arterial oxygen tension mmHg	6.0±2.5	5.1±2.9	p=0.004
Mixed venous oxygen saturation %	60±9	61±9	p=0.046

without recognisable increases of airway resistance [16].

It is possible that peripheral airflow limitation may contribute to exercise limitation and dyspnoea in patients with pulmonary hypertension. In a study on patients with congestive heart failure, KIDMAN *et al.* [20] showed a marked improvement of MEF_{25-75} in response to ipratropium bromide which resulted in a substantial increase in the maximum voluntary ventilation and a decrease in dyspnoea [20]. Peripheral airflow obstruction may therefore contribute to work of breathing and exertional dyspnoea.

The cause of airflow obstruction in patients with PPH is unknown. There is limited data on a histomorphological correlate. FERNANDES-BONETTI *et al.* [15] described pathological observations in necropsy and lung biopsy specimens of patients with PPH that showed signs of small airway disease. Other authors interpreted the findings of peripheral airflow obstruction as merely a result of the pathological changes present in the pulmonary vasculature [21].

Interestingly, the current study showed that peripheral obstruction in patients with PPH was partly, albeit incompletely reversible by applying β_2-agonists. This observation was first described in children with PPH by O'HAGAN *et al.* [7].

It is possible that small airways are affected as innocent bystanders in patients with PPH. It is well known that endothelial dysfunction is a major pathogenetic factor in PPH [22–25]. Several studies suggest that abnormalities in endothelial function, including impaired production of prostacyclin and nitric oxide and excessive synthesis of endothelin eventually lead to vasoconstriction and subsequent vascular growth and remodelling. Yet all these mediators also have well-known effects on the bronchial system. Endothelin-1 mimics several features of asthma, including bronchospasm, airway remodelling, inflammatory cell recruitment and activation, oedema, mucus secretion and airway dysfunction [26]. It possesses mitogenic effects on smooth muscle cells and fibroblasts and is a very potent bronchoconstrictor. Thus, the observed peripheral obstruction may be a result of some spill over of endothelin from the vasculature into the airway system. A recent study examining the effect of the endothelin receptor ET(A)/ET(B) antagonist bosentan on endothelin-induced bronchoconstriction showed that bosentan completely prevented the ET(B)-receptor agonist (IRL1620) induced bronchoconstriction [27].

In addition to the effects on airflow limitation, salbutamol had beneficial acute haemodynamic effects in the PPH patients in this study. The mean pulmonary artery pressure remained unchanged but the cardiac output rose significantly resulting in a decline in pulmonary vascular resistance. The increase in cardiac output was not caused by a chronotropic effect of salbutamol since the cardiac frequency remained unchanged. The stroke volume, in contrast, increased suggesting that salbutamol had a positive inotropic effect in the patients. Alternatively, inhalation of salbutamol may have caused some pulmonary vasodilation that was answered by a rise in the cardiac output. Pulmonary arterial smooth muscle cells carry β_2-receptors [28] so that some pulmonary vasodilatory effect of inhaled β-agonists may well be expected. Conversely, BRISTOW *et al.* [29] have shown that the right ventricle, in patients with pulmonary hypertension, shows an altered expression of cellular receptors when compared to normal subjects and patients with left heart failure. One of the characteristic features of the right ventricle in patients with PPH is an increase in the expression of myocardial β_2-receptors [30]. Therefore, it is quite possible that inhaled β_2-agonists may have a positive inotropic action in patients with PPH. There may be a dose-dependent dissociation of the inotropic and chronotropic actions of salbutamol. ZIMMER *et al.* [31] showed, in studies with rat hearts, that certain doses of salbutamol produced an inotropic effect without any chronotropic effect.

In the group of patients present here with PPH, inhaled salbutamol had a positive effect on mixed venous oxygen saturation and arterial oxygenation. The current authors speculate that improvement of arterial oxygenation was presumably due to some positive effects of inhaled salbutamol on ventilation-perfusion matching although this study was not designed to address this question.

The increase in mixed venous oxygen saturation was primarily a result of the increase in cardiac output. It is striking, however, that the rise in cardiac output observed by thermodilution was considerably greater than the rise in mixed venous oxygen saturation. The reason for this observation might be an increase in oxygen consumption due to β-adrenergic activation, as it has been shown in several studies [20, 32–34].

The present study has several potential limitations. There was no control group and no blinding, so that any bias can not be fully excluded. The study was not designed to address long-term effects of inhaled β_2-agonists in PPH. It is unclear whether the demonstrated acute effects have any substantial meaning for long-term treatment.

In conclusion, this pilot trial on the effects of inhaled salbutamol in patients with primary pulmonary hypertension showed beneficial acute effects on lung function, blood gases and haemodynamics. Although it is unlikely that inhaled β_2-agonists will significantly affect the course of primary pulmonary hypertension, they deserve further evaluation as adjunctive treatment in this disease. However, since β_2-agonists may cause systemic side-effects such as hypokalaemia, tachycardia and arrhythmia among others, its routine use in patients with primary pulmonary hypertension cannot be recommended at this time.

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