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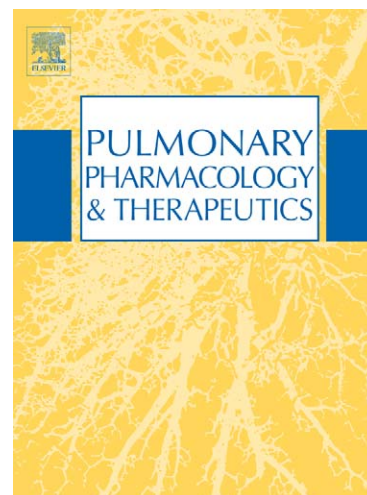
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DOPPLER ECHOCARDIOGRAPHIC ASSESSMENT OF THE EFFECTS OF INHALED LONG-ACTING β_2 -AGONISTS ON PULMONARY ARTERY PRESSURE IN COPD PATIENTS

Mario Cazzola¹, Antonio Mantero², Pierachille Santus³, Paolo Carlucci³, Michele Mondoni³, Laura Bosotti², Stefano Centanni³

¹Unit of Pneumology and Allergology, A. Cardarelli Hospital, Naples, Italy, ²Unit of Cardiology and ³Unit of Respiratory Medicine, San Paolo Hospital, University of Milan, Milan

Correspondence and requests for reprints should be addressed to: Mario Cazzola, Via del Parco Margherita 24, 80121 Napoli, Italy, Tel. +39 081 7473334, Fax +39 081 404188, Email mcazzola@qubisoft.it

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Running head: LABAs and pulmonary artery pressure in COPD

Abstract

Increase in pulmonary artery pressure (PAP), which is common in severe COPD, is a predictor of mortality independent of airflow limitation. β -agonists might slightly attenuate this increase because they exert a vasodilating effect on pulmonary circulation when systematically administered. We have investigated the acute effects of salmeterol and formoterol on echocardiographic systolic pulmonary artery pressure (sPAP) in 20 patients with COPD and a sPAP greater than 20 mmHg at rest. Acute haemodynamic responses to inhaled formoterol or salmeterol were assessed in all patients, in a randomized, double-blind double-dummy fashion. On two consecutive days, patients received, in a randomized order, formoterol 12 μ g via Turbuhaler plus placebo via Diskus or salmeterol 50 μ g via Diskus plus placebo via Turbuhaler. Transthoracic Doppler echocardiography measurements of sPAP were made before and 15, 30, 60 and 180 min after bronchodilator inhalation. Lung function, pulse oximetry and heart rate were also monitored at the same times. Mean sPAP significantly ($p < 0.05$) decreased in comparison with baseline at 15, 30, and 60 min post inhalation but returned towards control levels at 180 min after both salmeterol and formoterol. There was no correlation between the maximum increase in FEV₁ and maximum decrease in sPAP either after inhalation of salmeterol ($r_2 = 0.071$) or after that of formoterol ($r_2 = 0.0006$). The increases in FEV₁ in comparison with baseline were always significant ($p < 0.05$) from 15 to 180 min post inhalation after either salmeterol or formoterol. Neither pulse oximetry nor heart rate changed in a significant manner ($p > 0.05$). This study demonstrated that salmeterol and formoterol were equally beneficial for pulmonary haemodynamics in patients with COPD. A direct vasodilatation due to the activation of β -adrenoceptors that are present in pulmonary vessels is a more likely mechanism of their action in inducing the decrease in sPAP.

Key Words: Salmeterol; formoterol; COPD; transthoracic Doppler echocardiography; pulmonary artery pressure.

Accepted manuscript

Introduction

Elevated pulmonary artery pressure (PAP) is the main cardiovascular complication in severe chronic obstructive pulmonary disease (COPD). It is a predictor of mortality independent of airflow limitation [1], and the best independent predictor of hospitalization for acute exacerbation [2]. These findings suggest that patients with an abnormal pulmonary vascular bed might have fewer functional reserves to overcome the potential complications that occur during the evolution of the disease, hence needing hospital admissions more frequently [3].

Chronic hypoxic pulmonary vasoconstriction is generally assumed to be the cause of the increase in PAP in COPD [4, 5]. In patients with COPD, there is a negative correlation between PAP and oxygen saturation (SaO_2) [6]. Chronic hypoxia leads to muscularization of a subset of arterioles in the lung, the so-called precapillary "resistance vessels," which are particularly sensitive to the effects of hypoxia [7]. This structural alteration can explain why an increase in PAP following chronic hypoxia may occur even in the absence of vasoconstriction [7], although it progresses slowly, with an average annual raise of only 0.5 mmHg [4]. However, PAP can rise suddenly and markedly during episodes of acute respiratory failure [4]. This increase results mainly from vasoconstriction [7].

Many agents have been tried to reverse the elevated PAP, but consensus exists only on the use of oxygen therapy [3], although vasodilators may be useful in patients with acute exacerbation of COPD and cor pulmonale [3].

Although β -agonists generally produce trivial changes in PAP [3], some reports suggest that these agents decrease PAP when administered intravenously [8-10]. Unfortunately, these effects are frequently accompanied by worsening of arterial oxygenation, due to the inhibitory effect of β -agonists on hypoxic pulmonary vasoconstriction [11, 12]. Such

a detrimental effect of these agents on gas exchange is not seen when they are administered by inhalation [12].

To our best knowledge, there has been no clinical study to address the effects of long-acting β_2 -agonists formoterol and salmeterol on PAP in COPD patients. Therefore, we have conducted a pilot trial to test the acute effects of salmeterol and formoterol on lung function and echocardiographic systolic pulmonary artery pressure (sPAP) in this type of patients. Previous studies have, in fact, demonstrated that sPAP can be determined non-invasively by Doppler echocardiography [13-16], but apparently no study has investigated the effects of bronchodilators on this parameter using this technique.

Patients and Methods

Patients

This study was made up of 20 severe-to-very severe COPD patients with an echocardiographic sPAP > 20 mmHg at rest. The diagnosis of COPD was consistent with the diagnostic standards of American Thoracic Society/European Respiratory Society for the management of COPD [17]. All the patients were smokers or ex-smokers with a history of smoking equivalent to at least 20 pack-years. None of the patients had a history of atopy or a significant reversibility of airflow obstruction (FEV1 increasing by > 20% when compared to baseline value after inhalation of 200 Bg salbutamol via a metered-dose inhaler). Patients with severe obesity (BMI > 35 kg/m²), left heart disease, known obstructive sleep apnea syndrome, other chronic pulmonary disease, or any other severe disease were excluded. Demographics, smoking history, pulmonary function and basal PAP are presented in Table 1.

The institutional Ethics Committee approved the study protocol and all patients gave informed consent.

Study Protocol

Acute haemodynamic responses to inhaled formoterol or salmeterol were assessed in all patients, in a randomized, double-blind double-dummy fashion. On two consecutive days, at the same hour, 9 A.M., the patients received, in a randomized order, formoterol 12 µg via Turbuhaler plus placebo via Diskus or salmeterol 50 µg via Diskus plus placebo via Turbuhaler. The Ethics Committee did not give the authorization for a placebo arm.

Oral bronchodilators were not permitted during the study. Short acting inhaled β_2 -agonists were unrestricted soon after each test when required. All patients were under an inhaled steroid (budesonide 800 µg or fluticasone 500 µg twice daily). No patient received drugs susceptible of having vasodilator effects (calcium channel blockers, nitrates, angiotensin-converting enzyme inhibitors), theophylline or oxygen supplementation.

Transthoracic Doppler echocardiography measurements of sPAP were made before and 15, 30, 60 and 180 min after bronchodilator inhalation. Lung function, pulse oximetry (SpO₂) and heart rate (HR) were also monitored at the same times.

Echocardiographic studies were performed using an Acuson SEQUOIA C256 ultrasound machine and a 3V2c-MHz phased-array transducer. The same experienced cardiologist performed all echocardiographic investigations. Patients were imaged during quiet respiration in the left lateral decubitus position. Echocardiographic assessment was done by using all standard echocardiographic windows (parasternal long-axis view, parasternal short-axis view, apical four chamber view, subcostal view). Initially, tricuspid regurgitation jet was localized with colour flow Doppler and then interrogated with image

directed continuous-wave Doppler. A systematic search was performed to identify the best recording of the greatest maximal velocity. sPAP was measured from the continuous-wave Doppler signal of the tricuspid regurgitation gradient by the simplified Bernoulli equation ($Dp = 4v^2$, where Dp is the peak pressure difference between right ventricle and right atrium, and v is the peak flow velocity of the tricuspid regurgitant jet) [18] added to the right atrial pressure. This last was estimated by studying the degree of collapse of the proximal inferior vena cava by echocardiography during voluntary deep inspiration [19-21]. Only Doppler signals resulting in a clearly defined envelope of velocities were considered suitable for analysis. The recordings were stored on SVHS videotape for analysis by an investigator who was unaware of the treatment assignments. Measurements represent an average of 3 to 5 beats for patient.

Intra-observer measurements of variability for the sPAP, determined by one observer on two occasions, was assessed in 20 subjects, while inter-observer variability (another observer measured the same selected sPAP independently and blindly) was assessed in 8 randomly selected patients. Intra and inter-observer reproducibility of sPAP were analysed using the method of agreement as described by Bland and Altman [22].

Statistical analysis

Unless otherwise stated, all values are for mean and 95% confidence interval (CI). Statistical analysis of the data was performed with ANOVA to determine differences within groups and Student's t test to determine differences between groups. The significance level was set at $p < 0.05$. The correlation between independent variables was expressed by the correlation coefficient r .

Results

Intra-observer variability of sPAP derived from echocardiographic tricuspid regurgitation had good precision. The mean difference between the values obtained by the same reader during two different days was close to zero (Figure 1 A). Also inter-observer variability of sPAP was close to zero. In fact, the second observer measured similar peak tricuspid regurgitation velocities in comparison to the first observer (Figure 1B).

The inhalation of either salmeterol or formoterol led to a significant short-term decrease in sPAP (figures 2 and 3). Mean sPAP, was 38.4 mmHg (95% CI: 30.7 – 46.1) before salmeterol, and 36.0 mmHg (95% CI: 30.7 – 41.3) before formoterol. It significantly decreased in comparison with baseline values at 15 min (-3.6 mmHg, 95% CI: -1.5 – -5.8, $p = 0.002$, after salmeterol; -2.8 mmHg, 95% CI: -1.2 – -4.5, $p = 0.002$, after formoterol), 30 min (-3.9 mmHg, 95% CI: -2.4 – -5.5, $p < 0.001$, after salmeterol; -3.6 mmHg, 95% CI: -2.3 – -4.8, $p < 0.001$, after formoterol) and 60 min (-4.0 mmHg, 95% CI: -1.2 – -6.7, $p = 0.0067$, after salmeterol; -3.2 mmHg, 95% CI: -1.7 – -4.6, $p = 0.002$, after formoterol) post inhalation. It approximately returned to control levels 180 min after inhalation of each agent (mean sPAP: 36.1 mmHg; 95% CI: 29.8 – 42.5 after salmeterol; 34.3 mmHg; 95% CI: 29.7 – 38.9 after formoterol).

The increases in FEV₁ in comparison to baseline were always significant ($p < 0.05$) from 15 to 180 min post inhalation after both salmeterol and formoterol (figure 4). There was no correlation between the maximum increase in FEV₁ and maximum decrease in sPAP either after inhalation of salmeterol ($r_2 = 0.071$) (figure 5A) or that of formoterol ($r_2 = 0.0006$) (figure 5B).

Neither SpO₂ (figure 6A) nor HR (figure 6B) changed in a significant manner ($p > 0.05$) (figure 6B).

The differences in sPAP, FEV₁, SpO₂, and HR between salmeterol and formoterol were always not significant at each time point ($p > 0.05$).

Discussion

The present trial demonstrated that inhaled long-acting β_2 -agonists could have a significant short-term effect of sPAP in COPD patients. Salmeterol and formoterol were equally able in reducing sPAP in these patients. β_2 -Agonists have been suggested to induce a fall in pulmonary vascular resistance because of an increase in cardiac output [8, 23] and in right ventricular ejection [23, 24]. However, Eliassen et al. [10] documented that intravenous terbutaline did not modify mean PAP, at least during rest, although it resulted in an increase in left ventricular ejection fraction, augmented right ventricular ejection fraction and decreased right ventricular end-diastolic volume.

We are unable to confirm or reject these findings. A full assessment of pulmonary haemodynamics requires measurement of pressure and flow, which involves invasive cardiac catheterization. However, due to ethical reasons that did not allow us to perform right-heart catheterization for experimental aims on two consecutive days, we were only authorized to evaluate sPAP by Doppler echocardiography. Nevertheless, this non-invasive technique can be considered adequate for the aim of our study. In fact, although one rather old study [25] of 51 patients found a relatively poor correlation between right ventricular systolic pressure (RVSP) estimated from tricuspid jets (sPAP is considered equal to RVSP) and haemodynamic right-heart catheterization values, nine studies [26-34] reported statistically significant correlation. Moreover, we must highlight that in this study the intra- and inter-observer variabilities were close to zero.

A direct vasodilatation due to the activation of β -adrenoceptors that are present in pulmonary vessels [35] is a more likely mechanism of action of salmeterol and formoterol in inducing the decrease in sPAP. It is well known that increased β -adrenergic activity is associated with marked reductions in the pulmonary vasoconstrictor responses to hypoxia [36]. In fact, pulmonary arterial smooth muscle cells carry β_2 -adrenoceptors [37] that mediate vasodilating effects of endogenous catecholamines. These β -adrenoceptors cause vasodilatation by activating adenyl cyclase that is followed by an increase in the intracellular adenosine 3',5'-cyclic monophosphate (cAMP) content [38].

In this our trial, we have for the first time documented that inhaled long-acting β_2 -agonists can influence sPAP in patients with COPD. This finding apparently contrasts with some other few reports in literature. Recently, Sartori et al. [39] showed that prophylactic inhalation of salmeterol at very high dosage (125 μ g twice daily) reduced the risk of high altitude pulmonary edema, but this effect was not associated with an attenuation of altitude-induced increase in PAP. Also Spiekerkoetter et al. [40] were unable to show an effect of an inhaled β_2 -agonist in primary pulmonary hypertension, although this agent induced a significant decrease in pulmonary vascular resistance. We have no real explanation for this discrepancy, but it is like that the different pathologies might have influence the vascular response to these agents.

We must highlight that the sample size of our study was not calculated because this was a pilot investigation, but we have always reported the confidence intervals around the means that represent the plausible range in which the true treatment effect may lie [41]. We also must emphasize that the study was not designed to address long-term effects of inhaled long-acting β_2 -agonists on pulmonary haemodynamics in COPD. Therefore, it is unclear

whether the demonstrated acute effects have any substantial meaning for long term treatment.

In conclusion, this pilot trial on the acute effects of inhaled long-acting β_2 -agonists in patients with COPD has clearly shown that these agents are able to elicit beneficial acute effects on pulmonary haemodynamics. This finding confirms and enlarges our opinion that the use of these agents in this disease is important [42]. The study has also documented the possibility of using a non-invasive technique for exploring the impact of drugs on pulmonary vascular bed in COPD patients and this finding suggests the possibility of considering the evaluation of changes in sPAP as a further outcome in these patients.

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Figure 1 - Intra-observer (A) and inter-observer (B) variability of sPAP derived from echocardiographic tricuspid regurgitation.

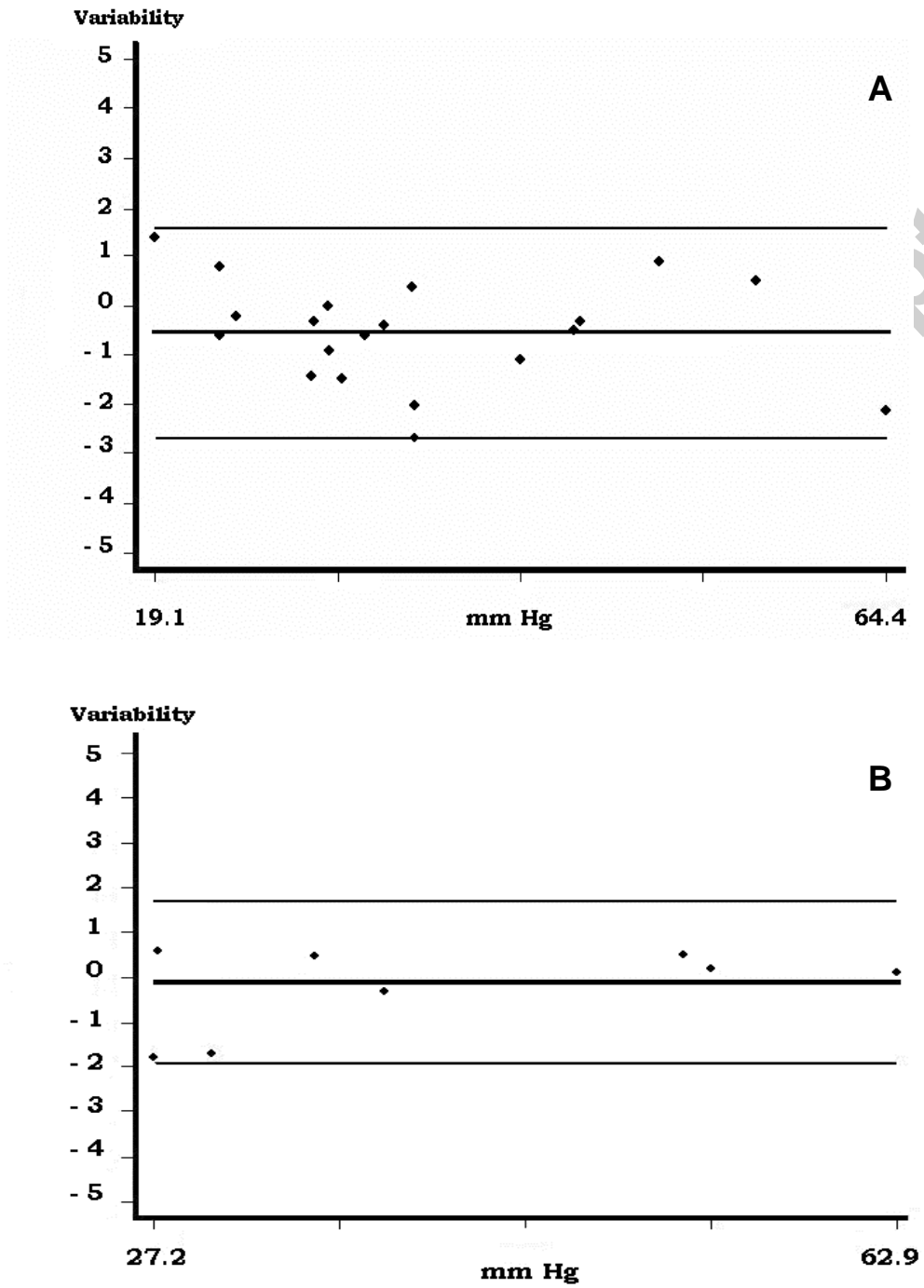


Figure 2 - Mean changes of sPAP from baseline after inhalation of salmeterol 50 µg Diskus or formoterol 12 µg Turbuhaler. Values are mean. ** p<0.01; *** p<0.001 vs baseline.

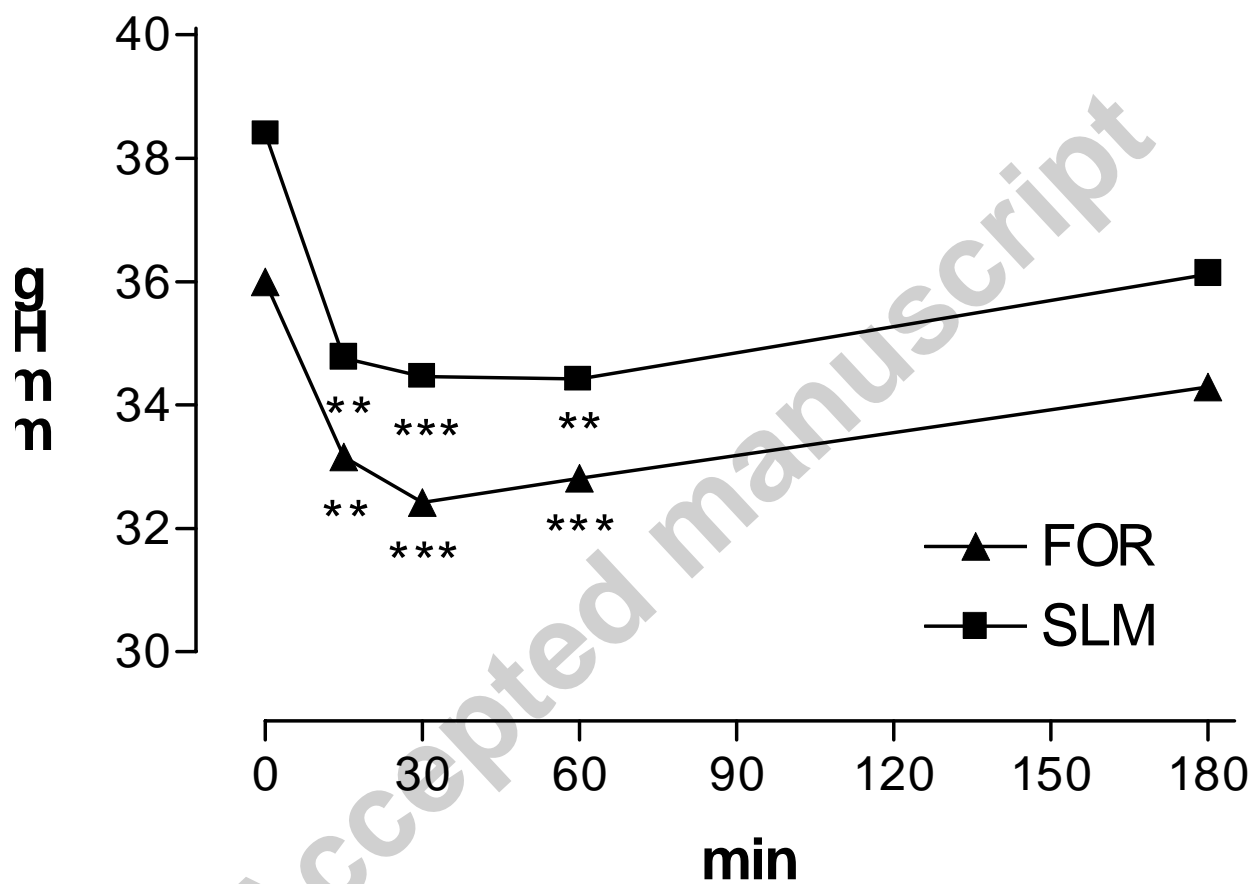
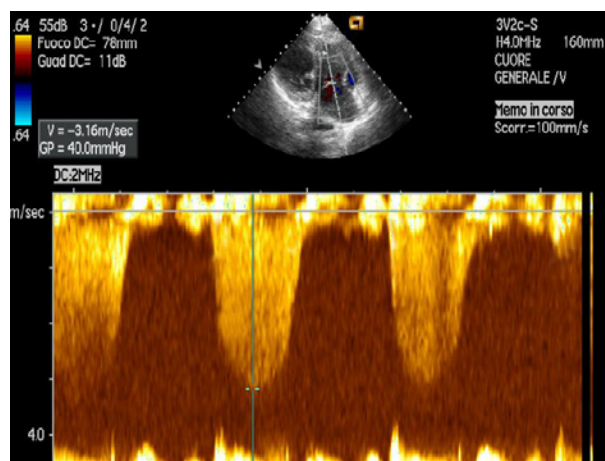
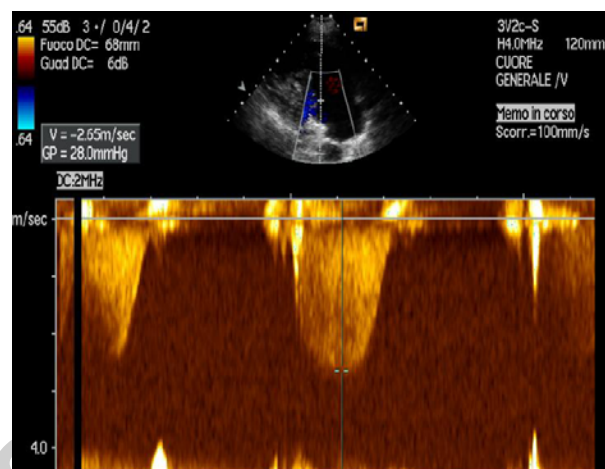


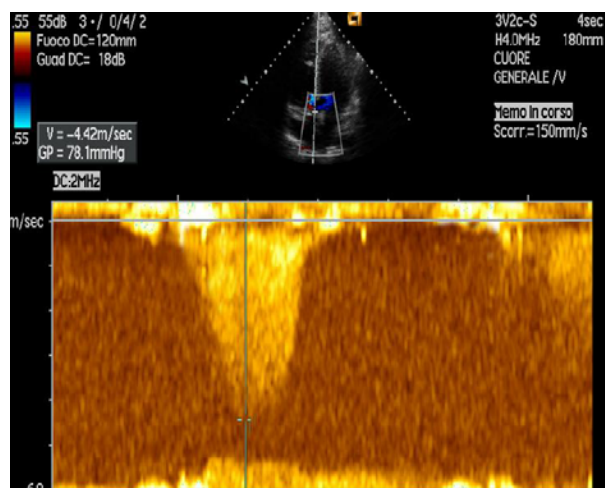
Figure 3 – Echocardiograms showing the effect of both salmeterol (A before, and B 30 min after inhalation) and formoterol (C before, and D 30 min after inhalation).



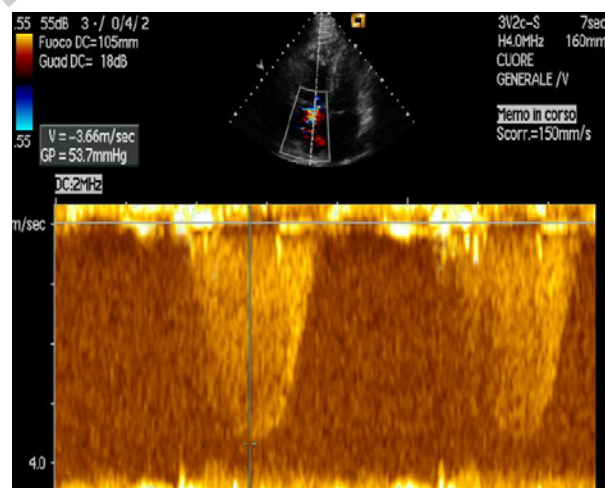
A



B



C



D

Figure 4 - Mean changes of FEV₁ from baseline after inhalation of salmeterol 50 µg Diskus or formoterol 12 µg Turbuhaler. Values are mean. *** p<0.001 vs baseline.

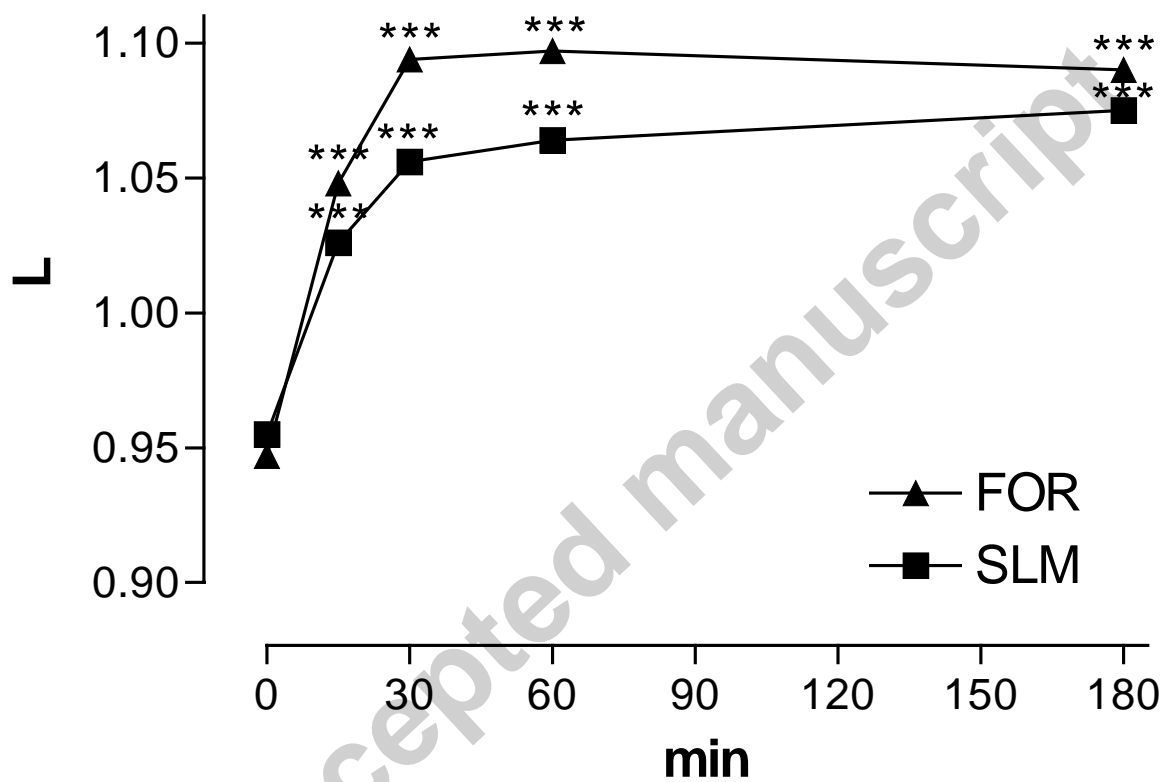


Figure 5 - Correlation between the maximum increase in FEV₁ and maximum decrease in sPAP after inhalation of salmeterol 50 µg Diskus (A) or formoterol 12 µg Turbuhaler (B).

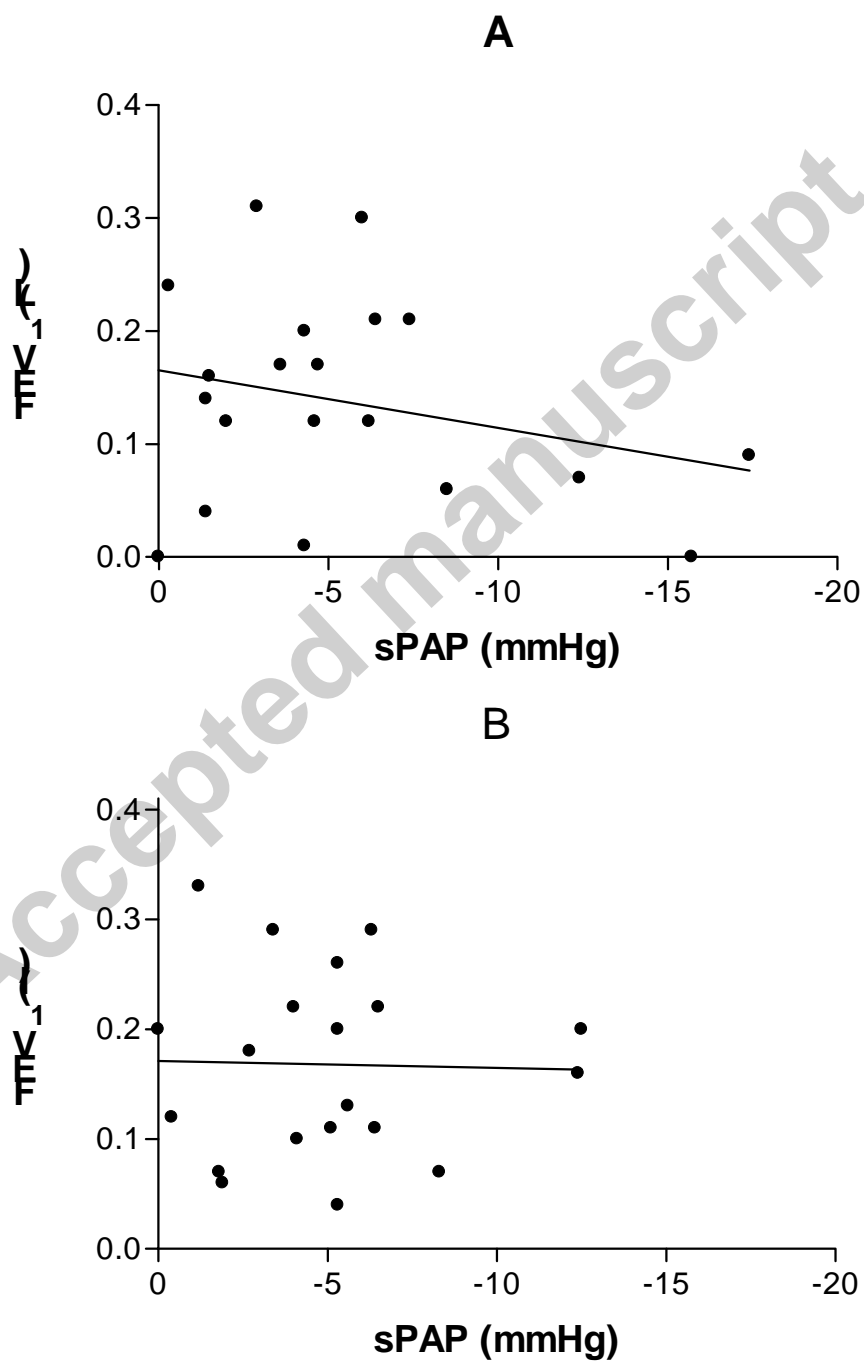


Figure 6 - Mean changes of pulse oximetry (SpO₂) and heart rate (HR) from baseline after inhalation of salmeterol 50 µg Diskus or formoterol 12 µg Turbuhaler.

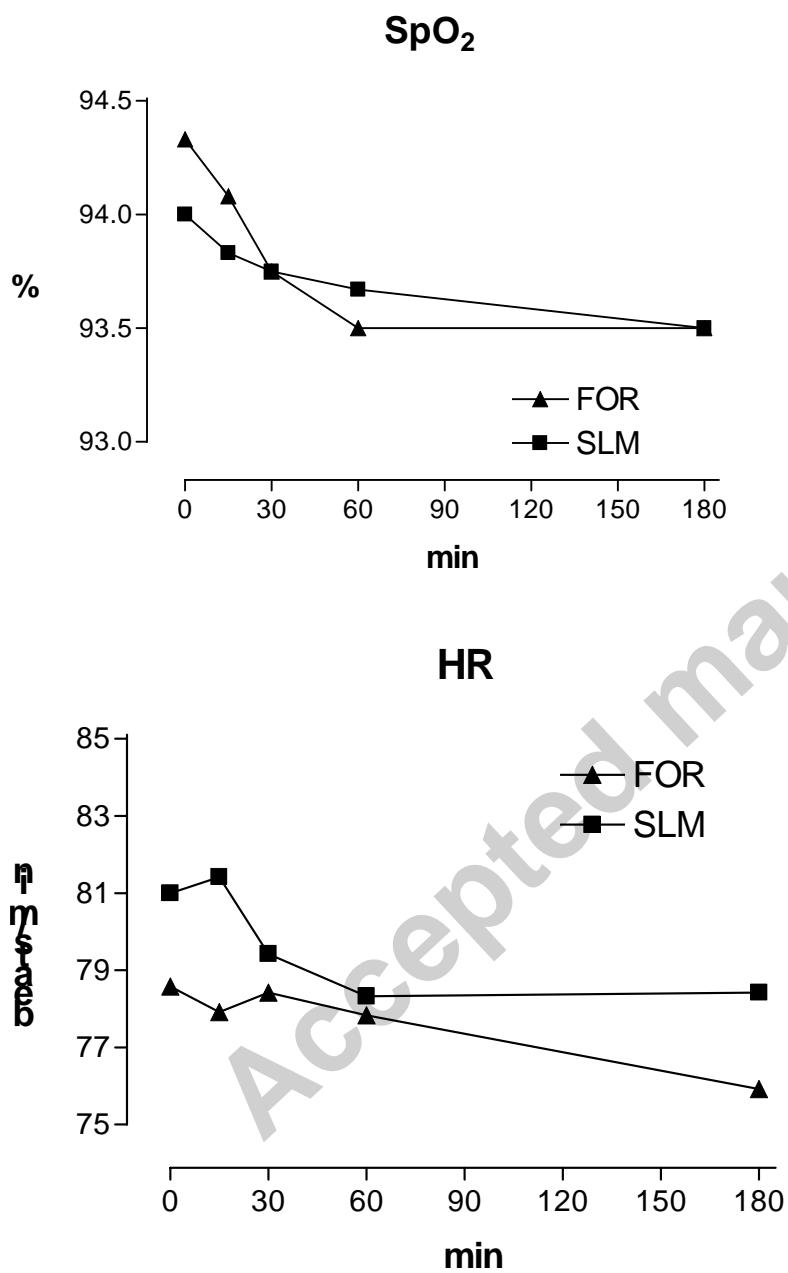


Table 1- Characteristics of enrolled patients

Patient n.	Sex	Age (years)	Smoking history (pack/year)	Basal FEV ₁	Basal sPAP (mmHg)
1	m	72	60	0,99	24,4
2	m	68	52	1,02	30,9
3	m	75	45	0,52	36,0
4	m	76	58	1,78	29,7
5	m	78	54	0,81	29,0
6	m	72	50	0,61	41,5
7	m	70	60	0,92	38,9
8	f	58	50	0,48	20,1
9	m	79	60	1,27	63,6
10	m	81	55	0,55	45,7
11	m	80	45	1,34	24,9
12	f	62	42	1,08	31,7
13	m	80	50	0,54	77,4
14	f	72	48	1,75	33,0
15	m	67	75	0,44	33,7
16	f	58	30	0,73	29,9
17	m	62	40	1,56	29,8
18	m	60	60	0,52	55,3
19	f	70	80	0,89	44,4
20	m	66	50	0,8	35,0