Cardiopulmonary interactions of salbutamol and hypoxaemia in healthy young volunteers

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- 1 Nebulised salbutamol is frequently used in the treatment of asthma and chronic obstructive pulmonary disease. Its effects on the cardiovascular system have been extensively investigated although as yet little is known concerning its effects on the pulmonary circulation, particularly during hypoxaemia. We have therefore examined the effects of nebulised salbutamol on pulmonary haemodynamics to see if it modifies hypoxic pulmonary vasoconstriction.
- 2 Eight healthy normal volunteers were studied on two separate occasions. After resting to achieve baseline haemodynamics patients were randomised to receive 5 mg salbutamol or placebo via a nebuliser. They were restudied after 30 min and then rendered hypoxaemic by breathing an N₂/O₂ mixture to achieve an SaO₂ of 75–80%. Doppler echocardiography was used to measure mean pulmonary artery pressure (MPAP), cardiac output (CO) and hence pulmonary vascular resistance (PVR).
- 3 Treatment with salbutamol significantly increased MPAP during normoxaemia and hypoxaemia compared with placebo at 12.0 ± 1.2 vs 8.0 ± 0.7 mm Hg and 28.6 ± 0.9 vs 25.2 ± 1.0 mm Hg, respectively ($P < 0.05$). Salbutamol caused a significant increase in heart rate compared with placebo and effects were additive to those of hypoxia at 74 ± 2 vs 67 ± 3 beats min⁻¹ during normoxaemia and 84 ± 3 vs 77 ± 4 beats min⁻¹ during hypoxaemia, respectively ($P < 0.05$). Whilst systemic vascular resistance fell in response to salbutamol, PVR was unchanged by salbutamol during either normoxaemia or hypoxaemia. Cardiac output was increased by salbutamol and by hypoxia.
- 4 Since PVR was not altered by salbutamol, this suggests that changes in CO rather than true pulmonary vasoconstriction were responsible for the observed increase in MPAP with salbutamol during normoxaemia and hypoxaemia. Thus, there appears to be no significant interaction between salbutamol and hypoxia in the human pulmonary vasculature, although combined chronotropic effects may be important.

Keywords hypoxaemia β -adrenoceptor agonists pulmonary circulation nebuliser

Introduction

Inhaled β -adrenoceptor agonists are known to have systemic effects [1, 2] as well as functioning as bronchodilators. The epidemiological finding that fenoterol was associated with an increased risk of sudden death in patients with severe asthma [3, 4] and the association of an increased risk of cardiac arrhythmias in patients with COPD receiving high dose nebulised bronchodilators [5] has aroused much

interest in the cardiovascular effects of β -adrenoceptor agonists. Indeed they are known to have inotropic, chronotropic and electrophysiological effects [6, 7]. Studies have also shown that hypoxaemia causes a dose dependent increase in cardiac output [8] as well as affecting myocardial repolarisation [6]. Although the interaction between hypoxia and the pulmonary circulation has been extensively investigated little is

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known of the interaction between β -adrenoceptor agonists and the pulmonary circulation.

Nebulised salbutamol is used in the treatment of both chronic hypoxic lung disease and asthma, conditions where hypoxia and high concentrations of β -adrenoceptor agonists frequently co-exist. Although hypoxic pulmonary vasoconstriction has adaptive effects in terms of ventilation-perfusion matching, the stimulus of chronic hypoxia results in an increase in pulmonary artery pressure with the development of cor pulmonale, and a poor prognosis [9]. If β -adrenoceptor agonists were to modify the hypoxic pulmonary vasoconstrictor response then the use of these drugs in obstructive airways disease could conceivably have deleterious consequences.

We have therefore studied for the first time the effect of salbutamol on the pulmonary circulation in the presence of both normoxaemia and hypoxaemia in normal subjects.

Methods

Subjects

Eight healthy male volunteers (six smokers, two non-smokers), age (mean $\pm$ s.d.) 26 ± 5 years were studied on two separate occasions. There was no abnormality present on clinical history, examination, 12 lead ECG, echocardiography, spirometry ($FEV_1 > 90\%$ predicted), biochemical or haematological screening. No subjects were taking any medications during the study period. Informed written consent to the study protocol, previously approved by the Tayside Committee for Medical Research Ethics, was obtained.

Study protocol

Subjects attended the laboratory at the same time of the day on two separate occasions, at least 1 week apart. They were asked to refrain from alcohol, caffeine and cigarettes for 12 h prior to each visit. An intravenous cannula was inserted into the left forearm for blood sampling. Subjects then rested supine for at least 30 min to obtain stable resting haemodynamics (t_0) and were randomised to receive either 5 mg of salbutamol or placebo (5 ml normal saline) via a face mask and a sidestream nebuliser (Medicard, Pagham, UK) driven by compressed air (CR 60 High flow Compressor) and were restudied 30 min post-dose (t_1). They were then rendered hypoxaemic by breathing a variable mixture of oxygen and nitrogen which rendered their arterial oxygen saturation between 75–80% (t_2) for 30 min. The hypoxic gas mixture was produced from separate cylinders of nitrogen and oxygen fitted with variable flow valves. Gases were mixed in a 25 l Douglas bag, from which the subjects breathed through a mouth-piece connected by a series of one-way valves, while wearing an occlusive nose clip. Measurements of pulmonary and systemic haemodynamic variables, and venous blood samples

for plasma renin activity (PRA), angiotensin II (ANG II) and electrolyte assays were taken at t_0 , t_1 and t_2 .

Measurements

Oxygenation Arterial blood oxygen saturation was continuously monitored by transcutaneous oximetry (CSI 503, Criticare Systems Inc, Waukesha, WI, USA).

Haemodynamics Heart rate (HR) was recorded on an electrocardiograph trace and an average rate over 1 min was obtained. Mean arterial blood pressure (MAP) was measured by semi-automatic sphygmomanometer (Vital Signs Monitor, Critikon, Tampa, FL, USA). Pulmonary acceleration time (PAT) in milliseconds was measured as previously described [10], from pulmonary arterial flow by pulsed-wave Doppler echocardiography (Vingmed SD50, Vingmed Sound, Horten, Norway) from the left 3rd/4th intercostal space. The mean of three consistent waveforms at each time point was used for the purpose of analysis. Mean pulmonary artery pressure (MPAP) in mm Hg was calculated as $MPAP = 73 - (0.42 \times PAT)$ [11]. Aortic cross-sectional area (CSA) was measured by M-mode echocardiography (Vingmed SD50). The aortic systolic velocity integral (SVI) was measured by on-line computer assisted determination using pulsed-wave Doppler echocardiography of ascending aortic blood flow from the suprasternal notch. On-line calculations of stroke volume ($SV = SVI \times CSA$) and cardiac output (CO) as the product of SV and HR were also made. Total pulmonary vascular resistance (PVR) was calculated as: $PVR = MPAP/CO \times 80 \text{ dyn s cm}^{-5}$. We have previously shown the short term coefficients of variability for measurement of PAT and SVI in our hands to be 1.7% and 1.2% respectively [10].

Electrolytes Samples for serum electrolytes were collected in chilled lithium-heparin tubes and were centrifuged at 4° C immediately and separated plasma was stored at –20° C until measured in one batch at the end of the study using an internal caesium standard flame photometer (Instrumentation Laboratory, Milan, Italy).

RAS activity Samples for measurement of PRA were collected into chilled EDTA tubes. They were centrifuged at 4° C immediately and separated plasma was stored at –20° C until assayed in one batch at the end of the study. PRA was assayed using commercially available r.i.a. kits (Sorin Biomedica, Saluggia, Italy) which assayed PRA by measurement of amount of angiotensin I generated per hour. Samples for ANG II assay were collected into chilled glass tubes containing 0.5 ml of a cocktail comprising 0.05 mmol l⁻¹ o-phenanthroline, 0.2 g neomycin, 0.125 mmol l⁻¹ EDTA and 2% (v/v) ethanol before centrifugation and separated plasma was stored at –70° C. ANG II assay was performed following separation from plasma proteins by ethanol extraction using a specific commercially available r.i.a. kit (Nichols

Institute Diagnostics, San Juan Capistrano, CA, USA). The lower limit for ANG II detection was 1.3 pmol l⁻¹. The intra-assay coefficient of variation for analysis of PRA was 7.6% and of ANG II was 11.2%.

Data analysis

Comparison of values between study days were made by multifactorial analysis of variance (MANOVA) [12]. Duncan's multiple range test was used to compare serial time points on the same study day. A probability value of $P < 0.05$ (two-tailed) was considered to be statistically significant. Data are presented in the text and figures as means and s.e. mean and where a difference between means is stated, the 95% confidence interval for this difference is given.

Results

Pulmonary haemodynamics

Treatment with salbutamol resulted in a significant ($P < 0.05$) increase in MPAP compared with placebo during both normoxaemia (t_1): mean difference 4.0 mm Hg (95% CI 0.7–7.1) and hypoxaemia (t_2): 3.4 mm Hg (95% CI 0.4–6.4) (Figure 1a). In contrast salbutamol compared with placebo had no significant effect on PVR during normoxaemia (t_1): 140 ± 20 vs 116 ± 16 dyn s cm⁻⁵ or hypoxaemia (t_2): 295 ± 17 vs 294 ± 22 dyn s cm⁻⁵ respectively. There was a significant ($P < 0.001$) increase in both MPAP and PVR in response to hypoxaemia on both study days.

Systemic haemodynamics

There was no significant difference in baseline (t_0) haemodynamic parameters between the two study days. Treatment with salbutamol resulted in a significant ($P < 0.05$) increase in heart rate compared with placebo during both normoxaemia (t_1): mean difference 8 beats min⁻¹ (95% CI 3–12) and hypoxaemia (t_2): mean difference 7 beats min⁻¹ (95% CI 1–12) (Figure 2a). There was also a significant ($P < 0.05$) increase in CO: mean difference 1.50 l min⁻¹ (95% CI 0.4–2.6) during normoxaemia (t_1) after salbutamol compared with placebo, although there was no significant difference between study days during hypoxaemia (t_2) (Figure 2b). Treatment with salbutamol resulted in a significant ($P < 0.05$), decrease in SVR compared with placebo during normoxaemia (t_1): 956 ± 65 vs 1203 dyn s cm⁻⁵ [mean difference 247 dyn s cm⁻⁵ (95% CI 25–470)] and a trend towards a decrease ($P = 0.06$) during hypoxaemia (t_2): 851 ± 51 vs 1029 ± 79 dyn s cm⁻⁵, respectively. There was a significant ($P < 0.01$) increase in CO and a significant ($P < 0.05$) decrease in SVR with hypoxaemia on both study days. There was no significant difference in MAP between study days at any time point or in MAP in response to hypoxaemia on both study days (Figure 1b).

Figure 1 a) absolute mean pulmonary artery pressure (MPAP) measured at baseline (t_0) and after treatment with placebo (clear bars) or salbutamol (hatched bars) during normoxaemia (t_1), or hypoxaemia (t_2). * $P < 0.05$ for difference between treatment with placebo and salbutamol. b) absolute mean arterial pressure (MAP) measured at baseline (t_0) and after treatment with placebo (clear bars) or salbutamol (hatched bars) during normoxaemia (t_1), or hypoxaemia (t_2). There was no significant difference between treatment with placebo and salbutamol at any of the time points.

Serum electrolytes

There was no significant difference in serum sodium between study days at baseline (t_0): placebo 139.0 ± 0.4 mmol l⁻¹ vs salbutamol 138.7 ± 0.4 mmol l⁻¹, at t_1 : placebo 138.9 ± 0.6 mmol l⁻¹ vs salbutamol 139.3 ± 0.5 mmol l⁻¹, or at t_2 : placebo 139.2 ± 0.4 mmol l⁻¹ vs salbutamol 139.5 ± 0.4 mmol l⁻¹. Compared with baseline (4.19 ± 0.11 mmol l⁻¹) nebulised salbutamol resulted in a significant decrease in serum potassium during normoxaemia (t_1): 3.89 ± 0.10 mmol l⁻¹ ($P < 0.05$), and hypoxaemia (t_2): 3.74 ± 0.07 mmol l⁻¹ ($P < 0.01$).

RAS activity

There was no significant difference in PRA between study days at baseline (t_0): placebo 1.01 ± 0.16 pmol l⁻¹ h⁻¹ vs salbutamol 0.85 ± 0.17 pmol l⁻¹ h⁻¹, at t_1 : placebo 1.16 ± 0.20 pmol l⁻¹ h⁻¹ vs salbutamol

Figure 2 a) absolute heart rate (HR) measured at baseline (t_0) and after treatment with placebo (clear bars) or salbutamol (hatched bars) during normoxaemia (t_1), or hypoxaemia (t_2). * $P < 0.05$ difference between treatment with placebo and salbutamol. b) absolute cardiac output (CO) measured at baseline (t_0) and after treatment with placebo (clear bars) or salbutamol (hatched bars) during normoxaemia (t_1), or hypoxaemia (t_2). * $P < 0.05$ difference between treatment with placebo and salbutamol.

0.96 ± 0.29 pmol l⁻¹ h⁻¹, or at t_2 : placebo 0.89 ± 0.15 pmol l⁻¹ h⁻¹ vs salbutamol 0.72 ± 0.16 pmol l⁻¹ h⁻¹. Similarly there was no significant difference in ANG II between study days at baseline (t_0): placebo 6.51 ± 1.67 pg ml⁻¹ vs salbutamol 7.34 ± 1.02 pg ml⁻¹, at t_1 : placebo 6.21 ± 1.38 pg ml⁻¹ vs salbutamol 6.69 ± 1.50 pg ml⁻¹, or at t_2 : placebo 5.05 ± 1.02 pg ml⁻¹ vs salbutamol 5.61 ± 0.59 pg ml⁻¹.

Discussion

Our results suggest that salbutamol has no effect on true pulmonary vasoconstriction since PVR was unchanged during treatment with salbutamol compared with placebo both in the presence of normoxaemia and hypoxaemia. Although there was an increase in MPAP, the unaltered PVR suggests that these pressure effects reflect an increase in cardiac output and hence pulmonary flow concomitant upon

treatment with salbutamol. There appears, therefore to be no significant interaction between salbutamol and hypoxaemia in health in the human pulmonary vasculature.

In terms of the systemic circulation we have demonstrated a significant chronotropic effect of salbutamol additive to that of hypoxaemia. Although this effect has been documented in those treated with i.v. salbutamol [13] it is perhaps not surprising that a single standard nebulised dose should have such a demonstrable effect. Salbutamol also increased CO and reduced SVR although in contrast to the chronotropic effects these effects were not additive to those of hypoxaemia. Previous studies on systemic haemodynamics with high dose inhaled salbutamol have shown that whilst the pulse pressure widens, the net effect is of unchanged mean arterial pressure [14]. In contrast to an increase in MPAP, salbutamol had no effect on MAP. This is likely to reflect the differences between the low pressure pulmonary circulation and the relatively high pressure systemic circulation where increases in flow will have proportionately less effect. In this respect the increase in CO observed with salbutamol will have a significantly larger effect on the pulmonary circulation. Likewise the decrease in SVR but not PVR might also be explained by vascular geometry, in that a fall in resistance is only likely to be detected in a high but not a low resistance system.

Salbutamol did not stimulate the RAS as reflected by its lack of effect on PRA and ANG II levels. Thus, a direct pulmonary pressor effect of ANG II [15] cannot be invoked to explain the increase in MPAP in response to salbutamol. Our observations are consistent with the view that renin is stimulated primarily via β_1 -receptors [16] and agrees with other studies looking at the effect of high dose inhaled terbutaline (5 mg) [17] and i.v. salbutamol [18] which have shown no effect on plasma renin activity although a recent abstract report by Millar *et al.* [19] has suggested that ANG II levels may be slightly elevated after nebulised salbutamol. We have also demonstrated the hypokalaemic effect of salbutamol which is well documented [7].

It is important to comment on the use of Doppler-echocardiography to measure haemodynamic changes in the pulmonary circulation. These non-invasive techniques have been shown to be reproducible [10] and the close correlation between Doppler PAT and MPAP as measured by right heart catheter, is well established [11, 20, 21]. One possible limitation of this methodology is that the use of total PVR does not account for any changes in the post-capillary vascular bed, as assessed by pulmonary capillary wedge pressure (PCWP). In this respect we feel it is unethical to insert Swan-Ganz catheters into normal volunteers for research purposes particularly as volunteers would have to be recatheterised on different days. The extra information this would give us is however, not essential for the following reasons. It is known from previous work that hypoxaemia does not affect PCWP and so with respect to hypoxaemia effects on total PVR are reflective of changes in true

PVR in pre-capillary arterioles [22]. It is known that increases in MAP, at least those due to ANG II infusion, are associated with proportional increments in PCWP [23]. Although the effects of salbutamol on PCWP have not been evaluated by cardiac catheterisation we have shown that it has no significant effect on MAP compared with placebo either during normoxaemia or hypoxaemia and as such is unlikely to have any significant effects on PCWP. We believe therefore, that the observed changes in total PVR are a true reflection of changes in pre-capillary pulmonary vascular tone. With respect to our Doppler derived measurements of cardiac output a good correlation has been shown between these methods and those measured by thermodilution or Fick methods [24, 25]. In respect to the latter our method is likely to be more valid in the presence of hypoxaemia since the Fick equation cannot be accurately applied when oxygen uptake is changing [26].

Thus, we have shown for the first time that salbutamol does not appear to have a significant effect on the human pulmonary vasculature in health either during normoxaemia or acute hypoxaemia. It would be unjustified to extrapolate directly from this study to asthmatics receiving chronic β -adrenoceptor agonist therapy or older patients with COPD since we have given a single dose of salbutamol and have looked at acute rather than chronic hypoxia in a group of young subjects. However, we should be aware that this class of drug may potentially have deleterious cardiovascular and electrophysiological effects since even a single standard dose of nebulised salbutamol has combined chronotropic effects in the presence of hypoxaemia although it appears to have no pulmonary vasoconstrictor effects.

We would like to thank Gillian Pirie, Wendy Coutie and Lesley McFarlane for their expert technical assistance.

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(Received 20 March 1995,
accepted 20 June 1995)