# Effect of intravenous infusion of salbutamol on ventilatory response to carbon dioxide and hypoxia and on heart rate and plasma potassium in normal men

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## Summary

**Intravenous infusion of salbutamol 10 μg/min in seven healthy subjects significantly increased their ventilatory responses to inhaled $CO_2$ in both hypoxia and hyperoxia. These changes in chemical control of breathing are unlikely to be significant when the drug is used in severe asthma but may benefit patients with acute exacerbations of chronic ventilatory failure. The infusion also increased heart rate, which was most pronounced when hypoxia was combined with hypercapnia. The infusion produced an average fall in plasma potassium from 3·99 to 3·10 mmol/l, which was associated with an increase in plasma glucose and serum insulin, suggesting that this arose from a shift of potassium from the extracellular to the intracellular space. Routine monitoring of plasma potassium and the electrocardiogram is indicated when an intravenous salbutamol infusion is used to treat severe asthma as the drug may predispose to cardiac dysrhythmias.**


## Introduction

The mechanism by which catecholamines stimulate ventilation in animals[1] and man[2-4] is imperfectly understood. Noradrenaline stimulates ventilation in the cat by an action that depends on the integrity of the peripheral chemoreceptors.[5] In man the potentiating effect of noradrenaline on the ventilatory response to inhaled $CO_2$ depends on the presence of hypoxia,[6 7] suggesting a similar mechanism. Such effects on ventilation and its chemical control may be important when catecholamines are used to treat asthma and chronic bronchitis, when the mechanisms controlling breathing are already disordered.[8 9] The introduction of an intravenous preparation of salbutamol, a beta$_2$-adrenergic bronchodilator, for use in severe asthma has allowed us to study the effect of an intravenous infusion of this drug on the chemical control of ventilation in normal men. We also measured the effect of the drug on heart rate, and, since we have observed an association between hypokalaemia and changes in ventilatory control,[10] we measured the effect of salbutamol on plasma electrolytes, these results then leading us to study serum insulin and plasma glucose during infusion of salbutamol.

## Subjects and methods

Seven healthy male doctors aged 25-35 years and weighing 69-82 kg gave informed consent to the measurement of their ventilatory response to $CO_2$ and hypoxia during intravenous infusion of either salbutamol 10 μg/ml or a similar volume (40 ml) of 0·9% saline. Studies on each man were always separated by at least one week.

The isoxic steady-state ventilatory responses to inhaled $CO_2$ at an end tidal oxygen tension ($PETO_2$) of 6·67 kPa (50·0 mm Hg) (mean (± SE of mean) 6·54 ± 0·05 kPa (49·1 ± 0·38 mm Hg), n = 28) and 29-33 kPa (218-248 mm Hg) were determined 10 minutes after the infusion had been started. The comfortably seated subject breathed gas mixtures of 2% and 5% $CO_2$, the balance being composed of $O_2$ or $N_2$, adjusted to ensure a $PETO_2$ of 6·67 or 29-33 kPa. Humidified inspiratory mixtures were supplied by a Rotameter mixing device through a low resistance two-way valve, with expiration through a Parkinson-Cowan $CD_4$ dry gas meter to measure minute ventilation ($\dot{V}_E$), the mouth pressure measured on expiration being 0·05 kPa (0·38 mm Hg) at a flow of 1·5 l/s. A Varian M3 mass spectrometer continuously sampled $O_2$ and $CO_2$ tensions at the lips.

The relation between ventilation and $PETCO_2$ is linear and can be described by the equation $\dot{V}_E = S (PCO_2 - B)$,[11] where B is the intercept obtained by extrapolating the $\dot{V}_E/PCO_2$ line to the $PCO_2$ axis and S is the slope of the line. Values of S and B were derived from the straight line drawn through two points relating $\dot{V}_E$ and $PCO_2$ in hypoxia and hyperoxia. Heart rate was continuously monitored before and during the infusion and the electrocardiogram was displayed on an oscilloscope. Plasma electrolytes and total $CO_2$ content were measured in venous samples drawn without stasis immediately before and after the infusion.

As a result of the changes detected in plasma potassium in the main part of the study three of the subjects were studied again in the fasting state during the infusion of salbutamol 10 μg/min for one hour while they were breathing air. The venous plasma potassium, plasma glucose, and serum insulin were measured frequently before, during, and after the infusion. The serum insulin was assayed by a double antibody technique[12] using the reagents in the radioimmunoassay kit supplied by the Radiochemical Centre, Amersham, Bucks.

In one fasting subject urinary potassium excretion and venous plasma potassium were also measured after a water load at 20 minute intervals before, during, and after an infusion of salbutamol 10 μg/min while the subject was breathing air.

## Results

*Ventilatory response to $CO_2$ and hypoxia*—The mean slope of the line relating ventilation to $PETCO_2$ increased significantly by 48% in hyperoxia (29-33 kPa) and by 44% in hypoxia (mean $PO_2$ 6·54 ± 0·05

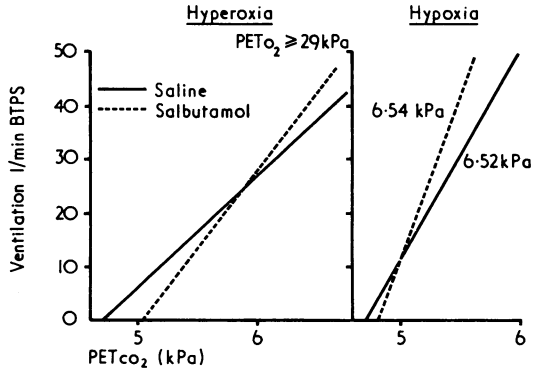


FIG 1—Mean relationship between steady state ventilation and $PCO_2$ during $CO_2$ inhalation in hyperoxia and hypoxia during saline or salbutamol (10 μg/min) infusions in seven men.

*Conversion: SI to traditional units:* 1 kPa ≈ 7·5 mm Hg.

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TABLE I—*Mean ventilatory and heart rate responses (± SD) during control (0·9% saline) and salbutamol (10 μg/min) infusions in seven men. (S is slope and B intercept of line relating steady state ventilation to $P_{CO_2}$ during inhalation)*

| | Control | Salbutamol |
|---|---|---|
| Ventilatory responses: | | |
| Hyperoxic S (l min$^{-1}$ kPa$^{-1}$) | 20·85 ± 7·28 | 30·75 ± 9·75* |
| Hyperoxic B (kPa) | 4·71 ± 0·46 | 5·11 ± 0·47 |
| Hypoxic S (l min$^{-1}$ kPa$^{-1}$) | 38·10 ± 14·7 | 54·83 ± 22·1* |
| Hypoxic B (kPa) | 4·65 ± 0·31 | 4·77 ± 0·4 |
| Heart rate (beats/min) breathing: | | |
| Air | 63 ± 12 | 79 ± 14† |
| 2% $CO_2$ in hyperoxia | 65 ± 9 | 87 ± 18† |
| 2% $CO_2$ in hypoxia | 71 ± 8 | 103 ± 16† |
| 5% $CO_2$ in hyperoxia | 67 ± 8 | 97 ± 14† |
| 5% $CO_2$ in hypoxia | 75 ± 9 | 113 ± 15† |

*P<0·05. †P<0·01.
*Conversion: SI to traditional units:* 1 kPa ≈ 7·5 mm Hg.

kPa (49·1 ± 0·38)) (fig 1). There was no significant change in the intercept of this line on the $P_{CO_2}$ axis in either hypoxia or hyperoxia (table I).

*Plasma biochemistry*—The control infusion produced no significant changes in the plasma sodium, potassium, or total $CO_2$ content in the five subjects in whom measurements were made. The salbutamol infusion had no effect on plasma sodium or total $CO_2$ content but did produce a highly significant fall in the plasma potassium from 3·99 to 3·10 mmol/l (3·99 to 3·10 mEq/l) (table II).

TABLE II—*Plasma sodium, potassium, and total $CO_2$ before and after infusion of salbutamol (10 μg/min) in seven men*

| Subject No | Sodium (mmol/l) | | Potassium (mmol/l) | | Total $CO_2$ (mmol/l) | |
|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After |
| 1 | 142 | 143 | 3·9 | 3·2 | 20 | 20 |
| 2 | 143 | 142 | 4·2 | 3·2 | 29 | 29 |
| 3 | 138 | 137 | 3·5 | 2·9 | 23 | 23 |
| 4 | 140 | 142 | 4·4 | 3·4 | 23 | 21 |
| 5 | 142 | 142 | 3·9 | 2·9 | 21 | 22 |
| 6 | 139 | 143 | 3·8 | 2·7 | 23 | 21 |
| 7 | 142 | 143 | 4·2 | 3·4 | 26 | 25 |
| Mean (± SD) | 140·9±1·9 | 141·7±2·1 | 3·99±0·30 | 3·10±0·27 | 23·6±3·0 | 23·0±3·1 |
| P | NS | | <0·01 | | NS | |

*Conversion: SI to traditional units*—Sodium, potassium, and $CO_2$: 1 mmol/l = 1 mEq/l.

*Heart rate*—The drug produced definite increases in heart rate, ranging from 25% when the subjects were breathing air to 50% in combined hypoxia and hypercapnia (table I). For a given inspired $CO_2$ concentration the heart rate was significantly higher (P = 0·05) in hypoxia than in hyperoxia.

*Plasma potassium and glucose and serum insulin*—Plasma potassium fell progressively after the start of the infusion, reaching minimum values at the end of the infusion, and began to return towards normal within 30 minutes of stopping the infusion (fig 2). The fall in plasma potassium was associated with increases in plasma glucose and serum insulin, which also returned towards normal after the end of the infusion.

*Urinary excretion of potassium*—Total urinary potassium excretion fell during the salbutamol infusion (fig 3). This fall was closely associated with the fall in plasma potassium in the one subject studied.

## Discussion

The dose of salbutamol which we used was in the middle of the dose range that causes significant bronchodilation in patients with asthma[13–15] and smaller than doses currently being evaluated in premature labour.[16] Our results show a significant increase in the slope of the line relating ventilation to $P_{CO_2}$ in our normal subjects inhaling $CO_2$-enriched mixtures in both hyperoxia and hypoxia, with no significant change in the intercept of this line. This increased sensitivity of the subjects to inhaled $CO_2$ as a ventilatory stimulus may partly explain the stimulant effect of catecholamines on ventilation,[1–4] but our

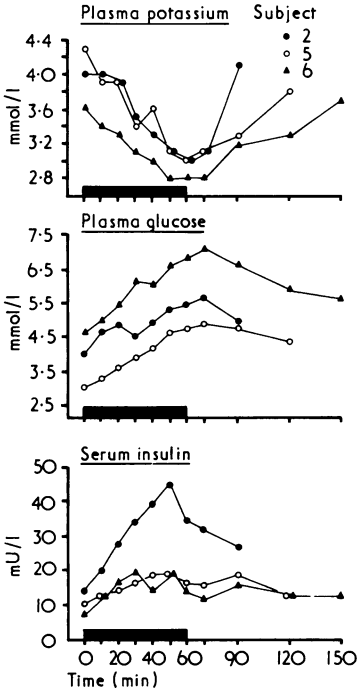


FIG 2—Plasma potassium, plasma glucose, and serum insulin in three men during and after intravenous infusion of salbutamol 10 μg/min.
*Conversion: SI to traditional units*—Potassium: 1 mmol/l = 1 mEq/l. Glucose: 1 mmol/l ≈ 18 mg/100 ml.

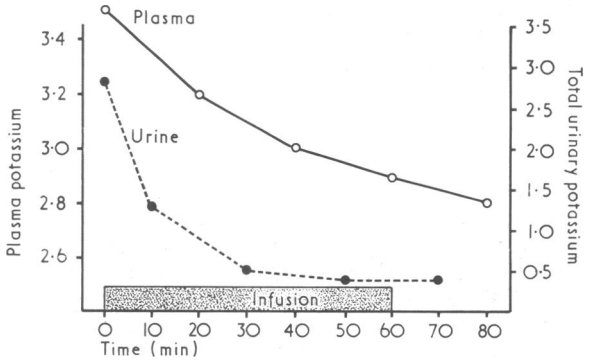


FIG 3—Total urinary potassium (mmol) and plasma potassium (mmol/l) measured at 20-minute intervals during and after intravenous infusion of salbutamol 10 μg/min in one man.

inability to inhibit this effect by hyperoxia argues against a role for the carotid body in mediating this response.[17] Alternatively, catecholamines may stimulate ventilation by metabolic[1 18] or central nervous system[3 19] actions. We suggest that the stimulation may result from a shift of potassium from the extracellular to the intracellular space, since hypokalaemia has been described in association with inappropriate stimulation of ventilation.[10 20] Further studies, using glucose and insulin infusion, are needed to investigate this possibility.

The pronounced fall in plasma potassium that we observed during salbutamol infusion was associated with rises in plasma glucose and serum insulin. Although the rise in serum insulin in two of the men was small, it was consistent and similar to the rise seen with a comparable infusion dose of isoprenaline.[21] Salbutamol, like other beta-adrenergic agents probably stimulates glycolysis[22] and insulin release,[21] resulting in a shift of potassium from the extracellular to the intracellular space. The fall in urinary potassium excretion observed in one man is consistent with such an action.

Beta-adrenergic agents increase the heart rate, but salbutamol is allegedly a $beta_2$-adrenergic agent with 10 times less effect on the heart rate than isoprenaline[14] when given by intravenous infusion to asthmatic patients. Nevertheless, the moderate

therapeutic dose that we used produced a striking increase in heart rate in our normal subjects that was maximal in combined hypoxia and hypercapnia. This increased heart rate was associated in all subjects with appreciable palpitations, flushing, and minimal tremor.

Undoubtedly intravenous infusions of salbutamol, in the dose which we have studied, may produce bronchodilatation in patients with stable[14] and severe[15] asthma. It is unlikely that the effects on the chemical control of ventilation which we have shown will be of much benefit when salbutamol is used in asthma, for in such patients the ventilatory drive is already considerably increased. The drug may be valuable in increasing ventilatory drive in bronchitic patients with the hypercapnia of chronic ventilatory failure.[9] We are concerned at the pronounced tachycardia that occurred during salbutamol infusion for serious cardiac dysrhythmias may result[23 24] when tachycardia, hypoxia, and acidosis are present, as they commonly are in status asthmaticus. The hypokalaemic effect of salbutamol is equally disturbing, for considerable falls in plasma potassium may also be associated with cardiac dysrhythmias in digitalised patients.[25] We therefore suggest that if intravenous infusion of salbutamol is used in the management of severe asthma both the plasma potassium and the electrocardiogram should be carefully monitored.

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# Deficiency of factor B of the complement system in sickle cell anaemia

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## Summary

**Factors B and D as well as the total activity of the alternative pathway of complement activation were measured using a functional assay in sera from 29 patients with sickle cell anaemia and 18 normal controls. Total alternative pathway activity was reduced in the patients compared with controls. In patients with abnormally low total alternative pathway activity factor D levels were normal, whereas factor B levels were significantly depressed to a mean level of about half of normal. Regression analysis in patients also showed a significant relation between total alternative pathway activity and factor B levels. A deficiency of factor B is the likely cause of the defect in the complement system in patients with sickle cell anaemia. Such a defect may contribute to the excessive proneness of such patients to severe infection.**

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## Introduction

Bacterial infection accounts for 30-40% of the mortality in patients with sickle cell anaemia,[1 2] the pneumococcus and Gram-negative pyogenic organisms being the commonest pathogens concerned.[1 3 4] A possible mechanism for this proneness to severe infection has been suggested by the report of a deficiency in the capacity of serum from patients with sickle cell anaemia to opsonify pneumococci.[5 6]

Alternative pathway function appears to be more critical than classical pathway function to the bactericidal effect of normal serum,[7] and the defect in sickle cell sera may result from a selective abnormality of the alternative pathway by which the third component of complement (C3), the essential opsonin, is activated; in these patients opsonification by the classical pathway is normal.[6] Although their precise interactions are not fully understood the main serum factors that interact to generate C3 convertase by the alternative pathway have been defined: they are properdin, factors B (C3 proactivator or glycine-rich β-glycoprotein) and D (C3 proactivator convertase), and $Mg^{++}$.[7-11] We assessed total alternative pathway function in patients with sickle cell anaemia and attempted to define the relative contributions of factors B and D to any defects observed.