Catecholamines contribute to exertional dyspnoea and to the ventilatory response to exercise in normal humans

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Background Exogenous catecholamine administration in humans stimulates ventilation. The present study was designed to investigate whether increased endogenous catecholamine release influences objective measures of ventilation and subjective measures of breathlessness in normal subjects.

Methods Yohimbine, a pre-synaptic α2 adrenoceptor antagonist, or placebo was administered to 10 normal male subjects in a double-blind cross-over fashion. Ventilation and metabolic gas exchange were measured during steady state exercise at 60% of previously determined maximal oxygen consumption. Venous lactate and noradrenaline were measured during exercise. Subjects' sensation of breathlessness and fatigue were recorded using visual analogue scales.

Results Plasma noradrenaline was higher following yohimbine administration (at 6 min exercise; 4.58 ± 0.56 nmol l⁻¹ vs 8.74 ± 1.53; P<0.05). Oxygen consumption was unchanged, but ventilation was greater throughout exercise following yohimbine. The sensation of exertion was greater following yohimbine, and at any given level of ventilation, the sensation of exertion was greater.

Conclusions Yohimbine administration causes increased noradrenaline release. This is associated with an increased ventilatory response and an increase in the sensation of exertion during steady state exercise. An increase in circulating noradrenaline might be a mechanism for both increased ventilation and pathological conditions of breathlessness such as chronic heart failure.

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Introduction

Experimental work in resting animals suggests that catecholamines stimulate ventilation[10]. Infused catecholamines have a similar effect in resting humans[2-11]. This may be of relevance to pathological conditions such as chronic heart failure where excessive adrenergic drive is associated with an excessive ventilatory response to exercise and dyspnoea. The present study was designed to investigate whether increased endogenous catecholamine release influences objective measures of ventilation and subjective measures of breathlessness in normal subjects. Catecholamine release was increased by pre-treatment with yohimbine. Yohimbine is a pre-synaptic α2 adrenoceptor antagonist and thus removes the normal negative feedback of noradrenaline on its own release at adrenergic synapses.

Method

The study protocol was approved by the local ethics committee. All subjects gave fully informed, signed consent to the study. Ten male subjects aged 20–44 years were recruited from hospital staff. None was known to have any past medical history, and none was receiving current medication, nor had ever taken a- or β-adrenoceptor blockers.

Subjects were asked to attend on three occasions. At the first visit, subjects undertook an incremental treadmill exercise test to exhaustion with metabolic gas exchange measurements to derive peak VO₂. This also allowed the subjects to become familiar with the
apparatus and with the subjective symptom scaling systems (see below).

Subjects attended at the same time of day on two further occasions, separated by at least 72 h. The subjects rested supine, and an intravenous cannula was placed in an antecubital vein. Fifteen milligrammes of yohimbine or matching placebo was administered orally in a double-blind fashion. This dose was chosen to allow peripheral increases in noradrenaline without inducing central nervous system effects[5,6]. After a further 45 min resting supine, subjects then undertook fixed-rate submaximal treadmill exercise, consisting of a 2 min warm-up period followed by 6 min at 70% of the predetermined peak Vo2. Heart rate was measured at 1 min intervals.

Metabolic gas exchange

During the exercise tests, patients breathed through a one-way valve connected to a metabolic measurements cart (Beckman NMC, Horizon Sensor Medics System, Anaheim, CA, U.S.A.). Every 30 s, minute ventilation (Ve), oxygen consumption (Vo2), carbon dioxide production (Vco2) and respiratory frequency (f) were measured. Tidal volume (Vt; Ve/f) and respiratory exchange ratio (Vco2/Vo2) were derived.

Subjective symptom scaling

The subjects were asked to indicate their sensation of breathlessness using a visual analogue scale and a modified Borg (CR10) scale using the method described by Adams et al.[7] A similar visual analogue scale was used to determine subjects' feelings of exertion or effort. Symptoms were recorded at the end of the 2 min warm-up period and at the end of the 3rd and 6th min of submaximal exercise.

Blood sampling

Blood was sampled from the indwelling venous cannula. Peripheral venous whole blood lactate concentration was measured with the subjects erect before the onset of treadmill exercise and at the end of the 6th min of constant rate exercise. Lactate was measured by an enzymatic fluorometric analyser (Analox GM7 Analyser, Analox Instruments, London, U.K.).

Noradrenaline was measured before administration of treatment (placebo or yohimbine), 45 min post-treatment both supine and erect, and at the end of the 3rd and 6th min of constant rate exercise. Noradrenaline was measured by a radioenzymatic method[8].

Statistical methods

Statistical analysis of ventilatory data was performed by repeated measures analysis of variance, examining for time effect and treatment-time interactions. All other analyses were by paired t-test with appropriate correction for multiple comparisons. The null hypothesis was rejected when the P value was <0.05. Results are quoted as means (SEM).

Results

Noradrenaline

Plasma noradrenaline increased during exercise. This increase was greater after yohimbine than after placebo, reaching statistical significance at peak exercise (Fig. 1). Heart rate was significantly higher following yohimbine at 3 min (146±9 (4) vs 156±7 (5); P<0.05) and 6 min (167±4 (4.9) vs 175±6 (5.7); P<0.05), suggesting an adrenergic effect of yohimbine. Lactate levels were unchanged by yohimbine administration.

Metabolic gas exchange

There were no differences between pre-exercise and baseline (end of 2 min warm-up) values for any of these variables between the two exercise tests. No treatment-time interactions were demonstrated, but all variables showed a significant time effect.

Oxygen consumption

A plateau of oxygen consumption was reached at 3 min of exercise. Mean Vo2 at 6 min of steady state exercise after placebo was 36±5 ml·kg⁻¹·min⁻¹ (68% of predetermined peak Vo2). There was no difference between the yohimbine and placebo periods.

Minute ventilation

Ventilation was significantly greater during exercise with yohimbine compared with placebo (see Fig. 2). There was a trend to an increase in both Vt and f after yohimbine, but neither of these changes reached statistical significance. As a consequence of the greater minute ventilation and unchanged Vo2 the ventilatory equivalent for oxygen (Ve/Vo2) was greater following yohimbine administration.

Carbon dioxide production

Vco2 increased more following yohimbine than with placebo (P=0.05). As a consequence, the respiratory exchange ratio rose more following yohimbine than during the control period.

Subjective symptom scaling

The modified Borg score was significantly higher at 3 min exercise after yohimbine than after placebo (2.17 (0.41) vs 2.65 (0.41); P=0.05). The visual analogue scale score for breathlessness tended to be higher after
yohimbine, but this difference was not statistically significant. The visual analogue scale score for exertion was significantly greater following yohimbine at 3 min (36.6 (6.6) vs 41.9 (6.6); P<0.05) and 6 min exercise (45.0 (6.0) vs 51.8 (5.5); P<0.05). Figure 3 shows the relationship between visual analogue scale exertion score and minute ventilation; these results suggest that at any given minute ventilation, the subjective sensation of exertion is greater following yohimbine.

Discussion

In normal humans, infusion of noradrenaline causes an increase in minute ventilation due to an increase in both minute ventilation and respiratory rate. This action is short lived as hyperventilation relative to arterial blood gases is induced. The consequent fall in arterial carbon dioxide (Paco₂) results in a reduction in ventilatory stimulus. If Paco₂ is prevented from falling, prolonged stimulation of ventilation is seen. The ventilatory effects of noradrenaline are mediated by peripheral chemoreceptor stimulation, probably via β₁-adrenoceptors. Clonidine, an α₂ adrenoceptor agonist, seems to have depressive effects on ventilation. The effects of increased noradrenaline release on ventilation and the sensations of fatigue and breathlessness during exercise are not known.

We have previously shown that during exercise in normal humans, a sustained rise in ventilation during
exercise can be maintained, presumably because the fall in Pco2 is buffered by the continued production of CO2 by the exercising muscle. The results of the present study show that yohimbine causes an increase in minute ventilation, which is sustained during continued exercise. Yohimbine treatment was associated with an increase in carbon dioxide production and the ventilatory equivalent for O2. There was no change in VO2 and no change in blood lactate, which suggests that yohimbine is causing hyperventilation by an increase in sympathetic stimulation, rather than by any alteration in muscle metabolism.

The hyperventilation is accompanied by an increase in the sensations of dyspnoea and effort. Kjaer et al. found that curarised normal subjects at matched workloads had increased plasma noradrenaline levels and perceived exertion scores compared to control. It may be that the increased central command to ventilation due to curarisation causes the increased noradrenaline release, but it is possible that increase in catecholamines modulate central perception of exertion.

**Time course of effect**

The greatest effect of yohimbine was seen before steady state metabolic gas exchange was reached (see Fig. 2), and yet the yohimbine effect on circulating noradrenaline was seen only towards the end of steady state exercise (Fig. 1), by which time the incremental effect of yohimbine on ventilation was wearing off. Yohimbine has its effects at the level of the synapse, and circulating catecholamines will lag behind release from synapse.

There are a number of possible explanations for the time course of the yohimbine effect on ventilation. (1) It may be that catecholamines stimulate ventilation predominantly early in exercise before steady state has been reached. This effect may be mediated predominantly via the carotid chemoreceptors which are known to be particularly influential during this phase of exercise. (2) As exercise proceeds and more noradrenaline is released at nerve terminals, levels may rise high enough locally to compete with yohimbine for a2-adrenoceptors, preventing further augmentation of catecholamine release. (3) Hyperventilation with a fall in Pco2 may negate the effect of increased sympathetic drive.

**Pathophysiological implications**

The mechanism underlying the dyspnoea and increased ventilatory response to exercise seen in patients with chronic heart failure is unclear. There is sympathetic activation in chronic heart failure and there are raised levels of circulating noradrenaline. The levels we induced in normal subjects are similar to those reported from patients with heart failure in some studies, although others have reported somewhat higher levels in heart failure patients on exercise. Chemoreceptor activity is increased in chronic heart failure. The present findings allow speculation that increased circulating noradrenaline is a possible mechanism for both increased ventilation and breathlessness, possibly mediated through increased chemoreceptor activity.

**Limitations**

Yohimbine in larger doses than used in this study has been reported to have mood-altering effects.
which may influence the perception of dyspnoea and effort. By augmenting heart rate, yohimbine could be causing 'cardiodynamic dyspnoea' \(^2\), although exogenous catecholamines have been associated with increase ventilation in the absence of any heart rate increase.\(^3\)

We did not measure either end-tidal or arterial \(\text{Paco}_2\), which could have contributed data to support the concept of yohimbine-induced hyperventilation with respect to blood gases. Nevertheless, this study shows that an increase in plasma noradrenaline using yohimbine results in increased ventilation during exercise and an increase in the subjective sensation of dyspnoea. Catecholamines may contribute to the increased ventilation and dyspnoea of disease states.

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References