β Agonists and ventilation

Acute treatment with a high dose of β agonist can cause an increase in oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$), and ventilation of the order of 20–50%.[1–4] In this issue of *Thorax* Amoroso *et al*[5] describe a dose dependent increase in oxygen uptake and CO_2 output with smaller doses of inhaled salbutamol (up to 1200 μg in 10 normal subjects). The changes were maximal at the time of the initial measurement five minutes after inhalation of salbutamol and the increase in CO_2 output of about 30% was then greater than the increase in oxygen uptake. This caused an increase in the ratio of $\dot{V}CO_2$ to $\dot{V}O_2$ (the respiratory exchange ratio (R)) from 0·85 to 0·93. Output of CO_2 subsequently fell more rapidly than oxygen uptake so that by 30 minutes the respiratory exchange ratio was marginally lower after salbutamol than after placebo. In a companion paper[6] the group compared the change in $\dot{V}O_2$ and $\dot{V}CO_2$ after 800 μg of salbutamol eight to 10 hours after completing 10 days of treatment with placebo or salbutamol (200 μg four times a day) in a crossover study. An acute increase in $\dot{V}O_2$ and $\dot{V}CO_2$ was seen after 800 μg salbutamol after 10 days of placebo but not after 10 days of regular salbutamol. These papers raise questions about the mechanisms underlying the change in oxygen uptake and CO_2 output with the acute administration of a β agonist, the clinical relevance of the findings, and, once again, the question of tolerance or tachyphylaxis.

Before discussing these questions some points about nomenclature need to be clarified. The group measured oxygen uptake, CO_2 output, and respiratory exchange ratio (R) at the mouth with indirect calorimetry. Subjects rested for 30 minutes before the first measurement so baseline values should reflect steady state conditions and hence CO_2 production and oxygen consumption in the tissues and the ratio of these, the respiratory quotient (RQ).[7] After salbutamol steady state conditions may not pertain and the increase in CO_2 output at the mouth, for example, may reflect a reduction in CO_2 stores rather than an increase in CO_2 production. Although described as a change in RQ in both papers the authors are in fact describing change in R, the respiratory exchange ratio—that is, change in the ratio of CO_2 output and oxygen intake at the mouth. The changes they describe with salbutamol could therefore be due to a change in metabolism (tissue production of CO_2 and consumption of oxygen) or the results of a perturbation that alters the relation between metabolic events and gas exchange at the mouth.

Underlying mechanism

Three mechanisms need to be considered to explain the increase in oxygen uptake and CO_2 output with β agonists—an increase in tremor, an increased drive to ventilation, and an increase in cardiac output and tissue perfusion. A fourth possibility—that the effects are due to an effect of β agonists on metabolic substrate—would be most unlikely to cause such rapid changes in $\dot{V}O_2$ and $\dot{V}CO_2$ in resting patients. β Agonists can cause a deterioration in matching of ventilation and perfusion in the lung but this too would not be expected to have any appreciable effect on resting $\dot{V}O_2$ and $\dot{V}CO_2$.

A β_2 mediated increase in tremor will increase metabolic rate and hence oxygen consumption and CO_2 production in the tissues. This may be contributing to the change at 30 minutes but is unlikely to be making a large contribution to the early changes and it would not explain the greater initial increase in $\dot{V}CO_2$ compared with $\dot{V}O_2$. There is evidence to suggest that respiratory drive is increased by β agonists[4 8] and depressed by lipophilic β blocking drugs such as propranolol.[9] Whether these effects are due to a central action or an effect on arterial chemoreceptors is uncertain.[4 8] Stimulation of respiration would increase CO_2 output initially to a greater extent than oxygen uptake and would cause arterial PCO_2 to fall as has occurred in some studies, although the effect has not been large.[3 4] The third and probably most important mechanism is that the changes are related to a β agonist induced increase in cardiac output and tissue perfusion. An increased venous return, whether due to a β agonist or cardiac pacing, increases CO_2 flux from peripheral tissues to the lungs and vice versa for oxygen. It thus uncouples gas exchange in the tissues from that in the lungs. Because CO_2 stores are greater than oxygen stores $\dot{V}CO_2$ will increase to a greater extent than $\dot{V}O_2$. The increased CO_2 flux to the lungs causes ventilation to increase, named cardiodynamic hyperpnoea by Wasserman and colleagues.[10] The opposite effect is seen with propranolol.[11] The fact that the time course of the increase in $\dot{V}CO_2$ and $\dot{V}O_2$ was mirrored closely by an increase in heart rate in the study by Amoroso *et al*[5] supports the suggestion that an increased cardiac output is the main mechanism underlying their changes in gas exchange. Measurement of $PaCO_2$ would have helped to determine which mechanism was predominant; all three may be contributing to some extent.

Clinical relevance

Is an increase in oxygen uptake or CO_2 output clinically important? The increase in CO_2 output will be associated with a small increase in ventilation and anything that increases ventilation in patients with moderate or severe asthma will increase the work of breathing and be unpleasant for the patient. It could conceivably contribute to their asthma by increasing heat loss across the airways, although a 25% increase in ventilation is very small in relation to the increase normally seen with exercise (up to 10-fold). Severe asthma is itself associated with an increase in ventilation and relief of bronchoconstriction in this situation can reduce ventilation and could more than offset any drug induced increase in ventilation. Patients with less severe asthma are less likely to take eight or 12 puffs of a β agonist over a short period. Patients with chronic asthma may take higher doses of β agonists regularly but they should be tolerant to these changes in gas exchange, according to the second paper.[6]

Tolerance

In the second paper Wilson *et al* show that there is pronounced tolerance to the acute effects of salbutamol on oxygen uptake and CO_2 output after regular treatment with a modest dose of 200 μg salbutamol four times a day for only 10 days.[6] The salbutamol challenge was made eight to 10 hours after the last dose of regular salbutamol or placebo. These data add to the substantial body of evidence showing that regular treatment with β_2 agonists causes tolerance to a wide range of β_2 agonist effects.[12] These include tremor,[13] increase in heart rate,[13] and metabolic effects such as fall in serum potassium and increase in insulin.[12 14 15] The surprising finding in some ways is that the bronchodilator response to β agonists has generally been maintained in patients with asthma,[12 16 17] although there are more subtle changes that represent tolerance. Firstly, there is a loss of the protective effect of β agonists against exercise[18] and exogenous stimuli such as inhaled histamine,[19] AMP,[20] and methacholine.[20 21] Secondly, after treatment with a β agonist

there is a rebound increase in bronchial responsiveness once the effect of the last dose of β agonist has worn off.[16 17 19 22-26] Some studies have shown a concomitant fall in forced expiratory volume in one second (FEV_1) of the order of 10%.[17 27-29] These changes in the airways are not trivial therefore and they could account for some of the adverse consequences associated with regular exposure to β agonists.[25 26]

How might all these findings be explained? Down regulation of β receptors is easily shown in human tissue in vitro and ex vivo after exposure to β agonists.[27-32] For example, six days of treatment with oral terbutaline causes an 85% reduction in the number of β receptors on circulating white cells within 6 days.[31] Such a phenomenon fits well with many of the findings described earlier except for the lack of tolerance to the bronchodilating effects of β agonists. β Receptors are found on several cells in the airways, including inflammatory cells. Down regulation of β receptors on inflammatory cells would cause the normal inhibitory effect of endogenous sympathetic stimulation to be attenuated once the effect of the β agonist wore off. The effects in essence would mimic the effects of a small dose of a β blocking drug.[33]

The tolerance seen by Wilson *et al*[6] could therefore be due to down regulation of β receptors in the heart and peripheral blood vessels, those responsible for tremor, or those involved in stimulation of respiration. If the first was correct the heart rate response to β agonists would be expected to be reduced after regular treatment with β agonists. Although this seems not to be the case in this study the findings are difficult to interpret as the heart rate response to 800 μg salbutamol was smaller in study 2 after placebo than in study 1 and the response after regular salbutamol in study 2 is close to the placebo effect in study 1. More detailed studies with larger numbers of subjects or a larger dose of salbutamol are needed to settle this point.

Another intriguing possibility to explain tolerance to the airway effects of β agonists is a negative interaction between β agonists and corticosteroids. In a recent study regular exposure to terbutaline negated the beneficial effect of regular budesonide on lung function and reduced the protection of budesonide against antigen challenge.[34] These data require confirmation but are in keeping with in vitro data showing a negative interaction between the activated glucocorticoid receptor and cyclic AMP related gene transcription factors.[35] Although such an effect could explain some of the airway effects it is difficult to see how it could explain many of the systemic manifestations of tolerance to β agonists.

These two papers in *Thorax* highlight an action of β agonists on metabolism that is not well known and where the underlying mechanism has not been fully clarified. The findings may not be of great clinical relevance but they again highlight the question of tolerance to the effects of β agonists, which is potentially of considerable clinical importance.

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