Exercise as a bronchodilator

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INTRODUCTION

Exercise is usually thought of as a bronchoconstrictor stimulus in asthmatic patients. This inference is drawn from the very many studies which have demonstrated a fall in maximum expiratory flow rate or an increase in airway resistance after exercise. There are very few studies in which measurements of airway resistance have been made during exercise, and comparatively few in which simpler techniques, such as measurement of maximum expiratory flow rate, have been employed, but from these a different picture emerges—that of exercise as a potent protector against bronchoconstriction in normal subjects and as a bronchodilator in asthmatic patients. The reason why comparatively few measurements have been made during exercise is that it is technically difficult to measure airway resistance in these circumstances, while maximum expiratory flow rate suffers from the drawback that the necessary respiratory manoeuvres, chiefly the need to take a maximal inspiration, may themselves affect the resulting measurement. Before reviewing the results of available studies, I will discuss the measurement of airway resistance and the difficulties which may arise in the interpretation of the data due to the increased ventilation caused by exercise.

MEASUREMENT OF AIRWAY RESISTANCE

Calculation of airway resistance requires knowledge of flow rate at the mouth, which is easily measured, and the pressure drop along the airways, from mouth to alveoli. It is the measurement of alveolar pressure which requires technical sophistication, such as the use of the body plethysmograph [1]. This is clearly not very practicable during exercise, chiefly because of the problems of temperature control but this has been achieved for short periods [2]. Stubbington et al. [3] achieved longer spells of exercise in a body plethysmograph, but their measurements did not use the ‘plethysmographic’ method but the chief alternative, an oesophageal balloon.

It has long been established that alveolar pressure, and hence pulmonary resistance, of which airway resistance is overwhelmingly the major component, can be derived from pleural pressure [4], and the use of a balloon-tipped catheter in the lower oesophagus offers a comparatively easy way of measuring this [5]. The method is tedious when the calculations are done manually, but Mead & Whittenberger [6] described a way of circumventing this by using an electrical analogue, and their method has been widely adopted for experimental purposes.

Its use during exercise is, however, difficult. This may be illustrated by reference to Fig. 1. This shows two traces from an oscilloscope screen derived using the method of Mead & Whittenberger [6]. Fig. 1(a) is taken from the record of a normal subject at rest, after the inhalation of some methacholine to increase airway resistance. The pressure–flow trace is almost linear and the slope is fairly constant over most of the breath. Resistance, as the slope of the line, can with some confidence be expressed as a single number for the whole breath. This is in contrast with Fig. 1(b) taken from the same subject in the same session but during bicycle exercise at 150 W. The pressure–flow relationship is now much more sigmoid and varies continuously throughout the breath for several reasons. First, tidal volumes increase, and airway resistance varies inversely with lung volume. Second, with the increased flows, air flow becomes turbulent, requiring greater driving pressures, and hence increased pleural pressures during exercise. The increased pressures also cause dynamic compression of the airways, so that resistance increases towards maximum expiration. In patients with airflow obstruction, the dynamic compression may cause flow-limitation over a large portion of the lung volume during expiration, which means that pressures may increase without a cor-
Fig. 1. Relationship of alveolar pressure (P_{alv}, abscissa) with flow (ordinate) in two individual breaths from one normal subject after methacholine challenge. (a) At rest. (b) During exercise. Traces were derived using the method of Mead & Whittenberger [6] (see the text for a full description). Abbreviations: Insp, inspiration; Exp, expiration.

responding increase in flow [7] (although this is not an invariable finding [7, 8]).

In normal subjects, at maximum exercise levels, flow-limitation is rarely encountered, and then only over a limited range of lung volume, close to functional residual capacity [9], although it has been reported that a group of trained athletes at very high work loads (ventilations of 128–195 litres/min) all had expiratory flow rates which coincided with their maximum expiratory flow-volume curves over most of the breath [10].

Looking at Fig. 1(b), resistance clearly cannot be expressed as a single number for the whole breath but the flow rate at which the slope is measured must be specified. It is conventional to make the measurement at a flow rate close to zero, say between zero and 0.5 litre/s on the inspiratory side. From a purely technical point of view this imposes severe requirements on the fidelity of the transducers and recording equipment, as the flow trace becomes much more like a square wave during exercise, and the exact point at which the zero line is crossed becomes more difficult to determine. It also begs the question as to which measurement of resistance is most relevant, and the answer to this depends on the purpose of the experiment. If it is to make some deductions about airway size, then a measurement close to zero flow, as described above, will be appropriate because at these low flows, there will not be any dynamic compression of the airways and resistance will closely reflect airway diameter. This measurement is comparable with measurements made while panting in the body plethysmograph (although strictly the balloon method is measuring total pulmonary resistance, including flow resistance of lung tissue, rather than purely airway resistance as in the plethysmograph). If, on the other hand, the required information is the total load opposing the respiratory muscles, then perhaps a number derived at a higher flow rate might be more appropriate. Alternative methods exist of calculating pulmonary resistance from oesophageal pressure and flow which give more weight to values at higher flow rates [11, 12].

Total pulmonary resistance can also be measured without the use of an oesophageal balloon in spontaneously breathing subjects, by the use of an imposed oscillating pressure wave of small amplitude at the mouthpiece of the apparatus [13], but the method has the problem of distinguishing between signal and noise, and with current methodology it is difficult to obtain readings of resistance at low imposed frequencies at ventilations much above 20 litres/min, although it should be possible to collect data at higher imposed frequencies. This method has been used in children during exercise [14].

There is also a method by which acoustic reflections are analysed, and this provides the only available direct measurements of bronchial dimensions after exercise [15].

**AIRWAY AND PULMONARY RESISTANCE DURING EXERCISE**

**Normal subjects**

The earliest measurement of pulmonary resistance during exercise in normal subjects was that of Granath et al. [16], who studied five men at workloads up to 200 W, measuring oesophageal pressure and calculating resistance using a method based on that of Neergaard & Wirz [4]. They partitioned resistance into inspiratory and expiratory components and found no change in either, nor in dynamic lung compliance, whether the subjects were sitting or supine. Similar results, using the same method of calculation or that of Mead & Whittenberger [6], were obtained by two other
groups in the 1960s [17, 18], neither of whom provide adequate data about the response times and other characteristics of their equipment, and it is therefore reassuring that more modern studies using the same techniques and with adequate response times of their equipment give similar results [19, 20].

In the most complete study [3], a specially adapted constant-pressure body plethysmograph was used, fitted with the cranks of a cycle ergometer for the subject to pedal, and cooled so that exercise could be continued comfortably at a steady state. The advantage of using the plethysmograph was that the authors could monitor lung volume, which is such an important determinant of pulmonary resistance, which was measured by the method of Mead & Whittenberger [6]. They concluded that there was no significant change in pulmonary resistance or in maximum expiratory flow at mid lung volume. There was a small fall in static pulmonary compliance at the highest workloads (100–130 W). Thus, the consensus is that pulmonary resistance does not change during exercise in normal subjects, although there are two studies which suggest that bronchodilatation occurs. In the first of these, Kagawa & Kerr [2] exercised four subjects for 5 min periods at several workloads in a non-air-conditioned constant-volume plethysmograph and found an average 20% increase in specific conductance, a change which is at the margins of detectable magnitude. In the second, Warren et al. [21] used an ingenious methodology in which they imposed a set pattern of breathing on their subjects, with constant peak flow rates, and measured the peak-to-peak oesophageal pressure swings. They too found a decrease in pressures as exercise progressed with a maximum fall of 36% in what they termed ‘transpulmonary index’, but which is probably better characterized as total pulmonary impedance.

There are, surprisingly, many fewer studies in normal subjects in which the simpler indices derived from forced expiration have been measured. Lefcoe [22] found an increase of 0.4 litre in forced expiratory volume in 1 s (FEV$_1$) and of 1.2 litre/s in maximum mid-expiratory flow rate during exercise, and similar increases in peak expiratory flow rate have been measured [23]. However, the majority of authors have again found no change [3, 19]. The biggest study was that of Irnell & Swartling [24], who measured peak flow rates in 58 normal subjects as controls for a larger series of asthmatic patients (see below). They found no significant changes during exercise at workloads of 200–900 kpm/min (32–144 W).

It therefore seems that there is little change in airway resistance in normal subjects during exercise in the absence of any pharmacological intervention, with a suggestion of a slight decrease from some studies using less direct methods. A different picture emerges if the airways are constricted by pharmacological agents before exercise.

**Normal subjects after bronchoconstriction**

Kagawa & Kerr [2] gave their subjects propranolol before exercise. This induced an increase in resting airway resistance, but they still found a fall on exercise. Atropine produced a fall in resting resistance and no further fall on exercise. Similar findings were reported using propranolol and a different anticholinergic drug, ipratropium, and with a method which measured total respiratory impedance at imposed flow rates [21], and with a different β-adrenoceptor blocker using FEV$_1$ [23]. These three studies are slightly unusual, most studies finding that propranolol does not alter resting airway resistance in normal subjects (e.g. [25]).

In our laboratory, we have found that bronchoconstriction induced by methacholine in normal subjects is abolished within 2 min of the start of exercise [26]. The same effect was produced by isocapnic hyperventilation without any exercise. We tested a variety of bronchoconstrictor agents, including histamine, propranolol, prostaglandin F$_2$α and methacholine after pretreatment with an anticholinesterase, but none of them produced bronchoconstriction which survived exercise or hyperventilation (S. Freedman et al., unpublished work).

**Asthma**

In 1956, McIlroy & Marshall [27] reported their measurements of airway resistance in three asthmatic patients at rest and during exercise. They measured oesophageal pressure but calculated resistance by a ‘simplified method’. Two of the three patients showed a fall in resistance during exercise. There appears to be only one published study of the changes in pulmonary resistance during exercise in asthmatic patients using modern, adequate technology: that of Stirling et al. [19], using the method of Mead & Whittenberger [6]. They found, on average, a low starting value of 2.9 cmH$_2$O litre$^{-1}$ s$^{-1}$ at rest, but this fell significantly to an average of 2.4 cmH$_2$O litre$^{-1}$ s$^{-1}$ on exercise, without any significant change in lung volume. They also found that histamine was less effective as a bronchoconstrictor during exercise than at rest, and that isocapnic hyperventilation was as effective a bronchodilator as exercise. We have recently measured pulmonary resistance continuously during exercise in five asthmatic patients using a method involving direct calculation of resistance from oesophageal pressure and flow by an analogue computer using the Neergaard–Wirz approach [28] and found falls in resistance of up to 30% (Fig. 2). None of the five patients showed any increase in resistance during exercise lasting 10 min, but they all had increases above their resting values several minutes after the end of exercise. In 10 asthmatic children, Engstrom et al. [29] found, on average, a fall in resistance from 7.1 to 6.3 cmH$_2$O litre$^{-1}$ s$^{-1}$ on exercise, using oesophageal pressure measurements. A further study
in normal and asthmatic children [14] using imposed oscillations reported falls of about 2 cmH₂O litre⁻¹s⁻¹ in the asthmatic patients during exercise and twice that in normal subjects. No validation of the methodology is given, however, and doubts are cast on its validity by the control pre-exercise values of resistance which were 7 cmH₂O litre⁻¹s⁻¹ in both groups.

Simpler measurements, such as peak expiratory flow rate, frequently show an increase in asthmatic patients during exercise, even when followed by a subsequent fall below the resting level (e.g. Godfrey [30]). Indeed, the increase during exercise is incorporated into some of the various indices of bronchial lability (reviewed by König & Godfrey [31]). Ironell & Swartling [24] studied 101 asthmatic patients, using peak flow measurements. They do not give results as percentages of predicted normal, but their asthmatic population started exercise at an average peak flow which was 53% of that of the normal control subjects. This rose to an average of 67% of the baseline value of the normal subjects at peak exercise loads (400 kpm/min in women and 600 kpm/min in men), falling to 45% 10 min after completion of the exercise.

The only experiments which attempted a more direct measurement of bronchial dimensions than can be inferred from changes in resistance or maximum flow rates, are those of Rubinstein et al. [15], who used the acoustic reflection technique. They reported a significant increase in the diameter of both the extra- and intra-thoracic portions of the trachea of about 25% in 14 asthmatic patients after exercise at a time when FEV₁ had fallen by an average of 37%. Normal subjects, whose FEV₁ did not change significantly after exercise, also had increases in tracheal diameter, of greater magnitude than the asthmatic patients. The technique has been well validated in vitro and against radiological measurements [32, 33], certainly as far as the main carina, but the biological significance of these findings is not clear.

**Chronic airflow obstruction**

Stubbing et al. [7], using the same techniques as previously described for normal subjects [3], found no change during exercise in pulmonary resistance or maximum flow rate at 60% of vital capacity despite a significant increase in end-expiratory lung volume. However, a subsequent abstract [34] reports an increase in FEV₁ during exercise in a similar group of patients even when apparently maximally bronchodilated by isoprenaline.

**MECHANISM OF EXERCISE-INDUCED BRONCHODILATATION**

Changes in the partial pressure of CO₂ (PCO₂) are not the cause of changes in airway resistance during or after exercise. Although, as is well known, a fall in PCO₂ may increase airway resistance [35] (in approximate terms, a halving of PCO₂ will double resistance), PCO₂ has been shown not to change very much during exercise either in asthmatic patients [36] or in normal subjects [37], and certainly not to the extent or in the direction which could account for the observed changes. Circulating catecholamine concentrations increase during exercise in normal subjects [38] and this would seem to be an obvious cause of exercise-induced bronchodilatation. It was suggested that asthmatic patients had a reduced sympathoadrenal response to exercise, which was responsible for their exercise-induced bronchoconstriction [39]. However, a study in which the exercise intensities were carefully matched showed no differences in plasma adrenaline or noradrenaline concentrations between asthmatic patients and normal subjects [40]. However, it must be added, as a qualification, that in both asthmatic patients and normal subjects, the increases occurred quite late in the course of a progressive exercise test, when the subjects were close to their maxima.

The abolition of drug-induced bronchoconstriction in normal subjects and asthmatic patients can be caused by hyperventilation quite independently of exercise [19, 26], and hyperventilation does not cause an increase in circulating catecholamine levels.
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[38]. Further support for the idea that hormonal or reflex mechanisms are unlikely to be responsible for exercise-induced bronchodilatation comes from studies in patients with diabetic autonomic neuropathy, who have a normal bronchodilator response to deep inspirations after induced bronchoconstriction [41].

It is probably the mechanical effect of repeated deep inspirations which is responsible for changes in airway resistance on exercise. Melville & Caplan [42] first showed that, in dogs given histamine, bronchoconstriction could be reversed by a deep inflation of the lungs, and also that adrenaline would only counteract the effects of histamine when administered after a deep inflation. Subsequently, Nadel & Tierney [43], using the body plethysmograph to measure airway resistance, showed that in normal subjects a deep inspiration would temporarily reverse the bronchoconstrictor effects of inhaled cigarette smoke, sulphur dioxide or histamine. In asthmatic patients, the response to a deep inspiration is very variable, and may provoke either bronchoconstriction or dilatation [44, 45]. This wide variability in response persists after drug-induced bronchoconstriction. In some patients, a deep inspiration will reverse the constriction, and in others, not [46, 47], and this depends, at least in part, on sensitivity to the drugs. Patients with the greater sensitivity to inhaled carbachol (measured in terms of the fall in FEV<sub>1</sub> after a fixed dose) had the smaller falls in airway resistance after a deep inspiration [47]. Similarly, the size of the bronchodilator response to a deep inspiration is inversely related to FEV<sub>1</sub> in asthmatic patients [48].

The mechanism of action of a deep inspiration on the airways has been extensively studied in the last few years by Ingram and co-workers, and they have recently reviewed the topic [49]. The most likely explanation lies in there being a difference in the hysteresis shown by lung parenchyma and airways, an idea originally advanced by Froeb & Mead [50] to explain how changes in anatomical dead volume curve of the airways shows than that of the surrounding lung parenchyma, after a deep inspiration, looking at the expiratory limb of the respective pressure–volume curves, the airways will show a relatively greater increase in volume at any given pressure than the parenchyma, and so would appear to have dilated (Fig. 3). Conversely, if the parenchyma had greater hysteresis than the airways, the reverse would apply and a deep inspiration would lead to an increase in airway resistance. Burns et al. [51] found some direct experimental evidence to support this theory by measuring specific airway conductance and anatomical dead space as indicators of airway size, and lung pressure–volume curves to quantify parenchymal hysteresis, in asthmatic patients before and after inhalation of methacholine. All patients had a bronchoconstrictor response to a deep inspiration before methacholine. After methacholine, those who dilated with a deep inspiration had the biggest increases in specific conductance and those who did not, the biggest increases in hysteresis of their lung pressure–volume curves. The bronchodilator effect of a deep inspiration lasts about 0.5–1 min [43]. A recent study which suggested that the effect is due to a myometric reflex is probably invalid because measurements were not made until at least 30 s afterwards when the changes may well have been resolving [52].

Similarly, measurements of FEV<sub>1</sub> made 1 min or more after the end of a period of exercise in asthmatic patients may lead incorrectly to the conclusion that induced bronchoconstriction had necessarily been well-maintained during the exercise period [53].

Whatever the mechanism of action of a deep inspiration, an important practical implication of its effects is that it severely limits the usefulness of tests based on a forced expiration, which, apart from partial expiratory flow–volume curves, all demand a full inspiration to total lung capacity before the expiratory effort. Such tests are of little use for monitoring interventions which produce small changes in airway dimensions, of which exercise is one.

The implications of more direct measurements of bronchial dimensions [15] is that, at least after exercise, different parts of the tracheo-bronchial tree may behave differently in response to the same influences. Further, detailed, investigation of the effects of exercise on the airways may well uncover some important fundamental mechanisms.

Fig. 3. Schematic drawing showing how differences in hysteresis between two systems (e.g. airways and lung parenchyma) exposed to the same cycle of pressure changes (abscissa) can result in different volume changes (ordinate). From Froeb & Mead [50].
CONCLUSIONS

In normal subjects, under basal conditions, exercise is either a very mild bronchodilator or has no effect. In asthmatic patients, it appears to bronchodilate or at least to protect against exercise-induced bronchoconstriction as long as the exercise continues, but the end of exercise is followed by the bronchoconstriction which we recognize as 'exercise-induced asthma'. Exercise appears to have little effect in patients with chronic airflow obstruction. In both normal subjects and asthmatic patients, drug-induced bronchoconstriction is rapidly reversed by exercise. All these effects of exercise can just as readily be produced by isocapnic hyper ventilation and the mechanism is probably the repetitive deep inspirations consequent upon increased pulmonary ventilation. The effect of deep inspirations is, in turn, probably due to a difference in the elastic properties of airways and lung parenchyma, producing a greater hysteresis in the pressure–volume characteristics of the airways than in that of the lung parenchyma.

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