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Pressure-Flow-Volume Relationships in the Pulmonary Circulation of Normal Highlanders

Effects of Unilateral Pulmonary Artery Occlusion, Exercise, and Hypoxia

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A number of studies have now been published in which pressures and flow in the lesser circulation have been measured in normal highlanders (NHL) breathing ambient air [2, 20] and enriched oxygen mixtures [21–23, 26], as well as during infusion of vasodilator substances [19, 26], but we know of only one study involving the simultaneous determination of pulmonary blood volume at rest [22]. As a result of these studies pulmonary hypertension in resting NHL has been well documented, but the respective role of structural changes and vasoconstriction of small pulmonary arteries is still debatable, as well as the presence of pulmonary vasoconstriction during physical exercise [19, 26]. This prompted us to reevaluate the effects of oxygen breathing at rest and during exercise in NHL, and to investigate the effects of unilateral pulmonary artery occlusion (UPAO) in NHL a manoeuvre whose usefulness for our understanding of pressure flow-relationships in the lesser circulation of lowlanders has been well documented in normal subjects [7, 10, 14, 24] as well as in patients with chronic bronchitis complicated by hypoxaemia [7, 10]. Part of the work which I shall present today has already been published in preliminary form [14].

Pressure-Flow Relationships during UPAO and Exercise

In the first part of this presentation I shall outline comparative results of exercise and UPAO obtained in La Paz (3,750 m) in 10 recumbent

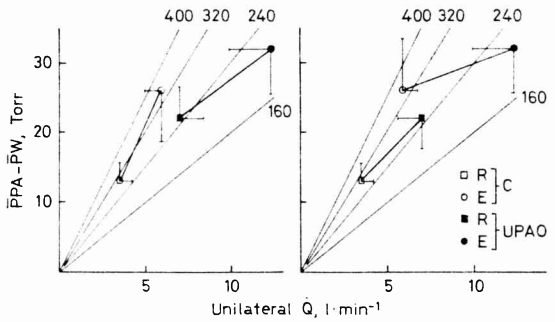


Fig. 1. Pressure-flow relationship during exercise and unilateral pulmonary occlusion (UPAO). In this figure as in subsequent ones, control values are represented by open symbols, experimental values by closed symbols. In both situations values at rest are represented by squares and exercise values by circles. Left: effects of UPAO; right: effects of exercise. Oblique lines fanning from the origin are isoresistance lines (CGS units).

male NHL from the Bolivian altiplano (aged 19–31 years). Cardiac output was measured by use of the direct Fick principle. Unilateral pulmonary blood flow through the non-occluded lung was equal to total cardiac output during UPAO and to half of it during the control period. The driving pressure was obtained by subtracting pulmonary wedge mean pressure obtained from a catheter wedged in the non-occluded lung from pulmonary arterial mean pressure. Pulmonary wedge pressure is actually equal to the lateral pressure in perilobular veins where blood velocity must be very low since overall dimensions of veins are similar to those of arteries [27], and velocity in arteries of comparable size is a few cm per second [5]. Pulmonary arterial pressure was measured through the proximal side opening of a regular Dotter-Lukas catheter. Henceforth, the kinetic energy component of both pressures was negligible and their difference provided a reliable estimate of the pressure drop across the lung circulation even in the presence of the fourfold increase in the flow rate of blood which obtained during exercise and UPAO. Measurements at rest and during leg pedalling were made during a control period and repeated during UPAO.

Group average values and standard deviations of driving pressure and unilateral pulmonary blood flow are shown in figure 1. Let us first consider the left panel of this figure. During the control period, blood flow through the non-occluded lung averaged 3.5 ± 0.7 l·min^{-1} at rest and

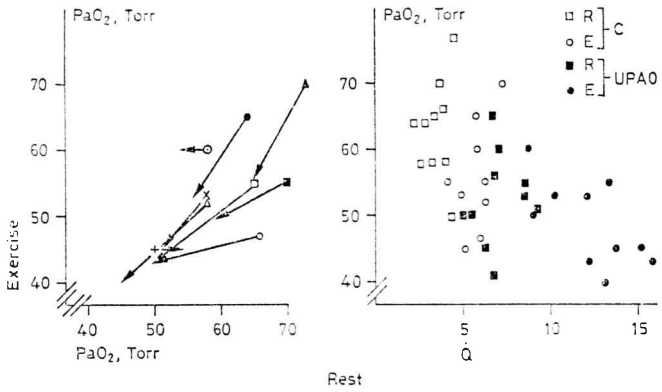


Fig. 2. Left: individual effects of exercise and UPAO on arterial partial pressure of oxygen (PaO_2). Each subject is represented by an arrow whose tail and head indicate control and UPAO values, respectively. Right: individual values of PaO_2 as a function of unilateral pulmonary blood flow ($\dot{Q}$). See text for discussion.

5.9 ± 0.9 l · min^{-1} during exercise. The rise in driving pressure (Δp) from 13 ± 2.5 to 26 ± 7.5 Torr was roughly proportional to blood flow. These driving pressures were far above those predicted for normal lowlanders of similar ages and cardiac outputs with the equation ΔP (Torr) $= 0.001 \times A \times \dot{Q} + 0.495 \times \dot{Q} + 0.004 \times A + 2.929$, where A and $\dot{Q}$ are the age in years and the cardiac output in litres per minute [25]. The pressure-flow relationship was strikingly modified by UPAO. At rest, when blood flow in the non-occluded lung was 7.0 ± 1.4 l · min^{-1}, the driving pressure was 22 ± 4.6 Torr a significantly lower value than during control exercise when blood flow was higher. Thus, the ratio of driving pressure to flow was significantly lower ($p < 0.05$) than during the control period. It did not fall significantly when flow rose to 12.4 ± 2.4 l · min^{-1} and driving pressure to 32 ± 6.4 Torr with exercise during UPAO. Let us now turn to the right panel of the figure where the same data points have been connected differently in order to illustrate the fact that during exercise the pressure-flow line is displaced upwards when compared to the resting one.

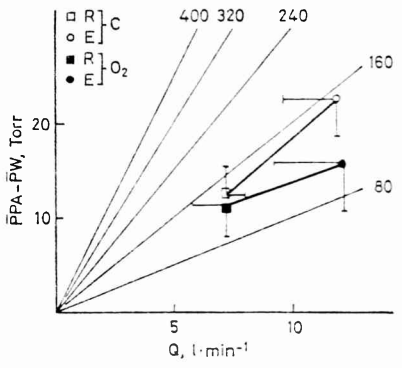
These results are strikingly different from those in normal lowlanders studied at sea level in whom driving pressure is directly proportional to blood flow during graded pulmonary arterial occlusion [7], physical exercise [2, 6, 15, 28], and exercise during UPAO [10, 24], and are not unlike those in chronic bronchitics at sea level in whom the pressure-flow relation-

ship also shifted upwards during exercise [10]. Indirect evidence suggests that this shift is best explained by pulmonary vasoconstriction during exercise, and that the similarity of pressure-flow curves in normal highlanders and chronic bronchitics at sea level is related to a common factor: (a) muscular hypertrophy of the media of the arterioles associated with chronic alveolar hypoxia is very similar in both conditions [1, 12] as well as in obese patients with alveolar hypoventilation [18], and represents a resistance varying with smooth muscle tone [8, 17]; and (b) vasoconstriction shifts the pressure-flow relationship upwards in isolated dog lung preparations when serotonin is added to the perfusate [13] as well as in lowlanders during acute hypoxia [7].

The mechanism of pulmonary vasoconstriction during exercise could not be elucidated in the present study. Individual values of PaO_2 are shown in figure 2. PaO_2 was lower during exercise than at rest as shown by the fact that most points are situated below the identity line (fig. 2, left). Since PaO_2 was also lower during UPAO at rest (53 ± 7 Torr) in the absence of pulmonary vasoconstriction than during exercise (56 ± 8 Torr) when vasoconstriction took place, the latter could not be attributed to arterial or alveolar hypoxia alone. The fall in PaO_2 with UPAO and/or exercise was probably due to a reduced contact time of blood with alveolar gas since there was a significant although loose correlation between PaO_2 and unilateral blood flow ($r = 0.560$) (fig. 2, right).

Pressure, Flow, and Volume in the Pulmonary Circulation during Acute Hypoxia and/or Exercise

The second part of this study was designed to confirm the existence of pulmonary vasoconstriction in exercising NHL and to investigate its mechanism. By use of a modified double injection, single sampling method for the determination of pulmonary blood volume [15, 16], we measured in La Paz in 6 male NHL from the Bolivian altiplano, cardiac output, pulmonary blood volume (PBV), and driving pressure across the pulmonary circulation. In all 6 subjects, measurements were obtained in the supine posture at rest and during moderate leg exercise while they breathed ambient air (PIO_2 approximately 100 Torr) or a gas mixture (PIO_2 approximately 150 Torr). Measurements at rest and during exercise were obtained on average 13 and 25 min after the onset of oxygen breathing.



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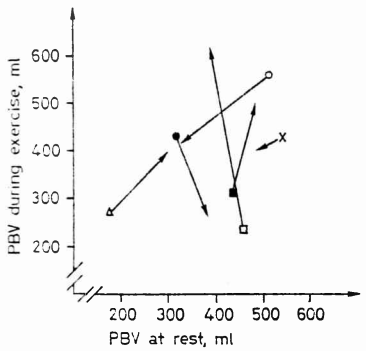

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Fig. 3. Pressure-flow relationship during exercise and acute hyperoxia. Note the lack of effects of oxygen breathing on cardiac output and the greater fall of driving pressure during exercise than at rest. C = Control; O_2 = hyperoxia; R and E = rest and exercise, respectively.

Fig. 4. Effects of exercise and acute hyperoxia on pulmonary blood volume (PBV). Abscissa = Resting values; ordinate = exercise values. Each subject is represented by an arrow connecting control values (symbol) and values during hyperoxia (arrow-head).

Group average values and standard deviations of driving pressure and pulmonary blood flow are shown in figure 3. At rest, hyperoxia caused no change in cardiac output and a slight fall in driving pressure. Conversely, during exercise hyperoxia caused a marked fall of driving pressure. Thus, as VOGEL *et al.* [26] and SPIELVOGEL *et al.* [23], we found that the effects of acute hyperoxia were more marked during exercise than at rest. This is consistent with the hypothesis that pulmonary vasoconstriction superimposed on structural changes of pulmonary vessels plays a minor role in NHL at rest, and is of paramount importance during exercise. Pulmonary blood volume determinations apparently failed to confirm these conclusions. Individual values of PBV are shown in figure 4. Exercise and oxygen breathing caused changes which were neither consistent nor significant. Group average values of PBV were comparable during air breathing ($R = 410 \pm 138$ ml; $E = 372 \pm 121$ ml), and were not modified during oxygen breathing ($R = 397 \pm 81$ ml; $E = 430 \pm 112$ ml). These values are comparable to those in normal lowlanders when the smaller body surface area of HL is taken into account (range 1.52–1.70 m^2). That PBV did not change significantly when vasomotor effects took place in the lung circu-

lation may seem paradoxical; in fact, it is not so. Resistance to blood flow is affected primarily by changes in vasomotor tone of small pulmonary arterioles which are in contact with alveoli from the respiratory bronchioles downwards [9] and have a muscularized media in NHL. Morphometric data from lungs of normal lowlanders suggest that the volume of blood in arteries ranging from 1,000 to 10 μm in diameter represents approximately 11% of total arterial blood volume, i.e. 10–12 ml [5]. Henceforth, it was predictable that a change in diameter of these vessels sufficient to affect pressure-flow relationships would cause no detectable changes in PBV.

Let us now turn to the mechanism of pulmonary vasoconstriction during exercise in NHL. Acidaemia could be ruled out since hydrogen ion concentration in the arterial blood changed with exercise neither during air breathing nor during hyperoxia. As already suggested by the UPAO experiments, alveolar hypoxia alone could be ruled out as well. In fact, during exercise breathing air PaO_2 did not change significantly ($R = 61 \pm 3$ Torr; $E = 59 \pm 5$ Torr) and mean alveolar PO_2 computed by use of the alveolar gas equation was maintained ($R = 63 \pm 7$ Torr; $E = 67 \pm 9$ Torr). Thus, neither hypoxia nor acidaemia, isolated or combined, were plausible mechanisms of exercise vasoconstriction in NHL. On the other hand, mixed venous PO_2 fell markedly ($p < 0.001$) during exercise breathing air ($R = 35 \pm 6$ Torr; $E = 24 \pm 6$ Torr) and was significantly higher ($p < 0.001$) during O_2 breathing at rest (42 ± 5 Torr) as well as during exercise (30 ± 5 Torr). Henceforth, it is an attractive hypothesis to attribute pulmonary vasoconstriction during exercise in NHL to severe mixed venous hypoxaemia superimposed upon alveolar hypoxia. This is in keeping with the occurrence of pulmonary vasoconstriction in anaesthetized dogs in whom $P\bar{v}O_2$ was reduced by administration of dinitrophenol or carbon monoxide [3], in isolated cat lungs perfused with hypoxaemic blood [4], and in isolated rat lungs when alveolar PO_2 was also reduced [11].

Summary

Pulmonary blood volume in NHL is comparable to that in sea level residents. In resting NHL, pulmonary hypertension is best explained by structural changes in pulmonary vessels. In NHL, exercise elicits a pulmonary vasoconstriction which is probably due to mixed venous hypoxaemia superimposed upon alveolar hypoxia.

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