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EDITORIAL

Asthma, allergen challenge and gas exchange

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Until the late 1960's there was a remarkable lack of information on the consequences of asthma on arterial oxygenation [1, 2]. Since then, it has been known that arterial blood gas abnormalities can range from overt hypoxaemia, usually associated with hypocapnia and respiratory alkalosis, as shown in acute severe asthma, to mild increases in the alveolar-arterial O_2 tension difference ($AaPo_2$) alone, as seen in asymptomatic patients with mild asthma [3]. The identification of the features of gas exchange impairment and their impact on the guidelines for clinical management of the disease were progressively established during the 1970's [4, 5]. However, a full understanding of the underlying physiological mechanisms accounting for the abnormalities of arterial blood gases in asthma was only achieved after 1978 with the advent of early studies assessing the ventilation-perfusion ($\dot{V}A/\dot{Q}$) ratio distributions in patients with asthma [6].

Arterial Po_2 may not adequately reflect $\dot{V}A/\dot{Q}$ inequality

The application of the multiple inert gas elimination technique suggested that increased perfusion to poorly ventilated areas is the principal intrapulmonary mechanism causing arterial hypoxaemia in these patients. Subsequently, this notion has been confirmed with additional studies analyzing different clinical forms of asthma [6–9] and by the assessment of abnormalities of gas exchange induced after bronchial challenges [10–12]. One of the hallmarks of the inert gas measurements in asthma is that the percentage of bloodflow diverted to nonventilated lung units (shunt) is small or conspicuously absent, irrespective of the severity of the clinical manifestations.

A practical consequence is that arterial hypoxaemia in these patients can be rapidly corrected by moderate increases in inspired O_2 fraction. The lack of shunt has been explained by the beneficial compensatory effect of collateral ventilation in preventing collapse in alveolar units beyond the obstructed airways. Interestingly, different studies [7, 13] suggest a significant degree of hypoxic pulmonary vasoconstriction which play a role preventing further worsening of pulmonary gas exchange.

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The numerical analysis [14] of the interplay between intrapulmonary (essentially $\dot{V}A/\dot{Q}$ inequality) and extrapulmonary factors (namely, cardiac output, minute ventilation, and oxygen uptake) determining arterial oxygenation has been helpful for further assessment of the mechanisms of the "paradoxical hypoxaemia" (transient moderate Pao_2 fall following administration of some β-agonists) [6, 7, 14]. Alternatively, it is well established that patients with asthma exhibit compensatory increases in both minute ventilation and cardiac output which may prevent the fall in Pao_2 due to $\dot{V}A/\dot{Q}$ inequality. The effects of these extrapulmonary factors explain that, on an individual basis, the Pao_2 does not necessarily reflect the severity of pulmonary gas exchange impairment. However, a rough correlation between $AaPo_2$ and $\dot{V}A/\dot{Q}$ mismatching has been observed in most studies.

Dissociation between spirometric and gas exchange measurements

Since the earlier studies with inert gases in patients with asthma a lack of correlation between maximal expiratory flow rates and $\dot{V}A/\dot{Q}$ inequality in cross-sectional measurements has been consistently demonstrated either in acute severe asthma [7–9] or in milder forms of the disease [6]. Such a dissociation has also been found in patients with mild to moderate asthma following the administration of bronchodilators [6, 14].

Likewise, different time-courses between maximal expiratory flow rates and $\dot{V}A/\dot{Q}$ inequality have been observed both during the recovery period of acute severe asthma [9] and also after different types of bronchial challenges [10–12]. The study by LAGERSTRAND *et al.*, published in the present issue of the Journal [15], offers original data which are lacking in the literature on the gas exchange response of patients with asthma following allergen (a natural stimulus) challenge. In this study, both during the immediate phase reaction and the late phase reaction, the delay in the recovery of $\dot{V}A/\dot{Q}$ mismatch in comparison with that of maximal airflow rates gives further support to the hypothesis that inert gas measurements provide different and additional information to that obtained by means of spirometry. Accordingly, maximal expiratory flow rates, largely related to dyspnoea and wheezing, predominantly reflect bronchoconstriction of larger airways, while $\dot{V}A/\dot{Q}$ abnormalities would represent a

more silent manifestation of the disease, presumably related to uneven small airway narrowing. The latter is caused by a combination of phenomena, including bronchoconstriction, wall thickening, mucus plugging and, airway microvascular leakage. Although no direct evidence for this hypothesis has been provided so far, the post-mortem findings reported in patients who died from sudden fatal asthma [16] strengthen the notion that airway inflammatory changes constitute the morphologic basis for gas exchange abnormalities in asthma.

Interestingly, a different time-course of gas exchange response has been reported in exercise-induced asthma (EIA) [10]. Here, the mild-to-moderate degree of $\dot{V}A/\dot{Q}$ inequality induced by the challenge, reversed to baseline configuration before FEV_1 (and other maximal airflow rates) had returned to pre-challenge values. Whether or not this difference in the recovery of $\dot{V}A/\dot{Q}$ mismatch reflects specific physiologic pathways of EIA needs to be tested. In any case, the study by LAGERSTRAND *et al.* [15] represents the only available data in patients with asthma on the inert gas response during the late phase reaction after allergen bronchial challenge. Further investigations of the underlying phenomena explaining the different behaviour between immediate and late phase reaction may have relevant physiological and therapeutic implications.

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