Eur Respir J, 1996, 9, 1278–1282
DOI: 10.1183/09031936.96.09061278
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European Respiratory Journal
ISSN 0903 - 1936

POINT OF VIEW

Gas exchange, expiratory flow obstruction and the clinical spectrum of asthma

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Gas exchange, expiratory flow obstruction and the clinical spectrum of asthma. P.D. Wagner, G. Hedenstierna, R. Rodriguez-Roisin. ©ERS Journals 1996.

ABSTRACT: More than any other chronic respiratory disease, asthma is characterized by functional and clinical variability: expiratory flow obstruction, dyspnoea and wheezing may be absent, mild, or severe. Moreover, pulmonary gas exchange often does not closely relate to measured airway obstruction. Accordingly, the correlation between arterial oxygen tension and airflow (P_{a,O_2}) rate indices of obstruction is poor, both in a single patient over time, and within groups of clinically similar patients. Here, these concepts are extended by examining relationships between airflow obstruction and gas exchange across the clinical spectrum of asthma (from asymptomatic to acute severe).

Six individual studies encompassing 86 patients are analysed together, focusing on: 1) airways obstruction; 2) arterial blood gas data; and 3) the distribution of alveolar ventilation/perfusion (V'_A/Q') ratios, measured by the multiple inert gas elimination technique.

V'_A/Q' mismatching was greater than normal even when forced expiratory volume in one second (FEV_1) was normal, but with increasing severity of airways obstruction there was essentially no further deterioration in gas exchange until FEV_1 reached about 40% of predicted normal values. Then, with little further airways obstruction, gas exchange rapidly worsened, P_{a,O_2} falling to about 50 torr.

This study emphasizes that what has been observed in individual patients and within clinically similar patient groups can be extended across the spectrum of asthma severity: airways obstruction and gas exchange are poorly correlated. Furthermore, these results suggest that spirometric data alone may not adequately define remission, nor clearly identify those patients liable to serious gas exchange deterioration.
Eur Respir J., 1996, 9, 1278–1282.

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Keywords: Airways obstruction
asthma
gas exchange
hypoxaemia
ventilation/perfusion distribution

Received: January 18 1996
Accepted for publication January 20 1996

This study was funded by NIH grant HL 17731 and by #91/0290 from the Fondo de Investigacion Sanataria (Fis), Spain.

Asthma is characterized by episodic airways obstruction. Both between and within subjects there is great variability in clinical state and in spirometric indices of obstruction. Gas exchange disturbances are expected in asthma, and this is widely recognized to occur on the basis of alveolar ventilation/perfusion (V'_A/Q') inequality, a phenomenon whereby a considerable range of local airways obstruction occurs leading to reduced ventilation and, hence, to regions of low V'_A/Q' ratio.

It may, thus, come as some surprise that studies of physiological derangement in asthma have repeatedly found a poor correlation between the degree of airways obstruction and the severity of hypoxaemia [1–3]. An extreme example of this dissociation between spirometric and gas exchange properties is the well-documented and not uncommon consequence of β-sympathetic agonist administration: simultaneous worsening of gas exchange in the face of reduced airways obstruction [4–6]. Spirometric and clinical abnormalities (shortness of breath and wheezing) are readily documented without specialized equipment, but gas exchange disturbances require arterial puncture to establish their presence - a procedure not often employed, especially in the out-patient setting. If one takes the reasonable position that gas exchange abnormalities are just as much a reflection of dysfunction in asthma as are spirometric changes, this poses a therapeutic dilemma in that patients without symptoms and showing near normal spirometry may have significant gas exchange defects [4]. The dissociation between spirometry and gas exchange is evident not only across the broad groups of clinical severity from the asymptomatic state to acute severe asthma [1–3], but also within individual patients over time [2]. Not only does it have the clinical implications noted above, it suggests that either different pathophysiological processes or possibly similar processes acting at different locations within the tracheobronchial tree are responsible for the alterations in spirometry and gas exchange. If so, this would open up the possibility of a more precise understanding of the disease process in individual patients, and ultimately to more targeted therapy according to the physiological changes seen.

Whilst individual, rather homogeneous patient groups have been examined with respect to both spirometry and gas exchange [7–9], there is no overview analysis available of the relationships between spirometry and gas exchange over the clinical spectrum from asymptomatic patients in remission to those with status asthmaticus, who occasionally require assisted ventilation in the intensive

Table 1. – Spirometry and gas exchange

Group	Description	Pts n	[Ref.]	FEV1 % pred	FEF25–75 % pred	Log SD$_Q$	Log SD$_V$	P_{a,O_2} torr	$P_{(A\text{-}a),O_2}$ torr
A	Mild asthma	16	[10]	92±5	71±7	0.71±0.09	0.57±0.04	88.1±2.7	22.9±3.4
B	Asymptomatic asthma	6	[1]	81±7	49±10	0.88±0.12	0.55±0.05	85.0±5.7	23.7±4.4
C	Chronically symptomatic out-patients, moderately severe	26	[2]	72±5	43±4	0.74±0.05	0.58±0.03	89.8±2.3	19.1±3.0
D	Chronically symptomatic out-patients, severe	9	[11]	39±3	21±4	0.77±0.03	0.72±0.02	77.3±2.4	25.9±2.2
E	Acute, severe asthma (hospitalized)	19	[12]	41±3	21±4	1.18±0.08	0.77±0.03	70.7±2.9	35.6±3.0
F	Acute, severe asthma (hospitalized)	10	[3]	33±5	16±4	1.41±0.12	0.78±0.04	50.5±2.6	53.8±3.0

Values are presented as mean±SEM. Pts: patients; [Ref.]: reference number; FEV1: forced expiratory volume in one second; FEF25–75: flow rate in the middle half of expiration; Log SD$_Q$: dispersion of the distribution of blood flow; Log SD$_V$: dispersion of ventilation; P_{a,O_2}: arterial oxygen tension; $P_{(A\text{-}a),O_2}$: alveolar-arterial pressure difference for oxygen; % pred: percentage of predicted value.

care unit. This paper provides such an overview by collecting and analysing data from six previously published studies that have never before been considered as a group.

The six papers are listed in table 1. They are united by a common author group, and more importantly for gas exchange analyses, by common methodology. Specifically, analysis of gas exchange only by arterial oxygen tension (P_{a,O_2}) and arterial carbon dioxide tension (P_{a,CO_2}) is problematical in asthma. This is because of the generally high cardiac output noted in this setting due to a combination of anxiety and therapeutic use of sympathetic agonist drugs aimed at bronchodilation [1]. Thus, P_{a,O_2} can reach the normal clinical range despite considerable V'_A/Q' inequality, as a result of the elevated cardiac output. Consequently, in these six studies, we have employed a technique that directly estimates the degree of V'_A/Q' inequality [13, 14]. This has become known as the multiple inert gas elimination technique (MIGET) and its basis is the steady-state elimination by the lungs of a continuously infused solution of six inert gases dissolved in 5% dextrose. The gases are chosen so that their blood solubilities range from very low to very high. The quantitative degree of pulmonary elimination of the six gases is determined by the V'_A/Q' distribution so that, by mathematical inversion techniques, it is possible to estimate theV'_A/Q' distribution showing how capillary blood flow in the lung is distributed to lung units of particular V'_A/Q' ratios over the entire physiological V'_A/Q' range. There are several ways of quantifying the degree of V'_A/Q' inequality from such data, and the most common is to compute the 2nd moment of the distribution about its mean, a parameter that has come to be labelled "log SD". This term reflects the fact that the 2nd moment expresses the variance of the distribution and is, thus, a useful index of dispersion of V'_A/Q' ratios about the mean. The "log" term reflects a longstanding practice to express those moments on a logarithmic rather than linear axis of V'_A/Q' ratios. Since the MIGET yields dispersion indices for blood flow distribution as well as for ventilation distribution, we use both log SD$_Q$ (blood flow) and log SD$_V$ (ventilation) to characterize in parametric form the amount of V'_A/Q' dispersion. Log SD$_Q$ is sensitive to areas of normal and low V'_A/Q' ratio, whilst log SD$_V$ mostly reflects areas of normal and high V'_A/Q' ratio. A completely homogeneous lung would produce log SD$_Q$ and log SD$_V$ values of zero, but such does not exist. The normal degree of V'_A/Q' inequality produces log SD$_Q$ and log SD$_V$ values that average 0.3–0.5 in young, normal seated subjects [2]. The 95% upper confidence limit is 0.6 for both indices [2]. In contrast, severe V'_A/Q' inequality, sufficient to produce arterial hypoxaemia that is barely tolerable (P_{a,O_2} ≤40 torr on room air), leads to log SD$_Q$ and log SD$_V$ values of 2–2.5 [15].

Spirometric abnormalities in the six papers analysed herein are based on conventional forced expiratory manoeuvres and are expressed by forced expiratory volume in the first second of a maximal expiratory effort (FEV1) and average flow rate in the middle half of expiration (FEF25–75). Both indices in the present report are given as a percentage of predicted normal values, taking into account the well-known factors of age, body size, gender and race.

For the most part, mean spirometric and gas exchange data obtained simultaneously in the six studies are compared graphically. Further analysis of individual patient data is presented as appropriate. Error bars for all data indicate SEM.

Spectrum of severity

Table 1 describes the physiological state of the subject groups indicating a wide range of function. This is

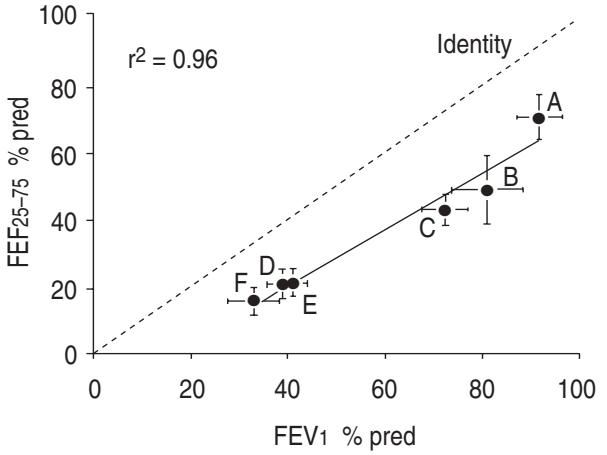

Fig. 1. – Reduction both in forced expiratory volume in one second (FEV1) and forced expiratory flow rate in the middle half of expiration (FEF25–75) across the clinical spectrum of asthma. Values are present as mean±SEM. As clinical severity increases from Group A to F, both indicies fall, essentially in proportion. FEF25–75 is always reduced to a greater extent than FEV1. % pred: percentage of predicted value. For description of Groups A–F see table 1.

reflected in figure 1 by a corresponding range in FEV1 from 90% of predicted (Group A) to about 30% (group F) and similar reductions in FEF25–75. Note the systematically lower FEF25-75 than FEV1 across the entire range, a common clinical observation. Hypercapnia was observed in only one patient, who was in the most severely affected group, *i.e.* Group F.

V'A/Q' inequality

Figure 2 shows the principal findings of the present paper 1) abnormally elevated degrees of V'_A/Q' mismatch even in subjects with relatively well-preserved spirometry (groups A–C); in these groups, log SDQ is about twice the normal average at around 0.9; 2) no further worsening of V'_A/Q' relationships until FEV1 is ≤40% of predicted; and 3) V'_A/Q' mismatch that worsens rapidly with decreasing FEV1 below 40% of predicted reaching moder-ately, but not extremely, severe levels (*i.e.* log SDQ ~1.4, Group F). Note, in particular, that on average no group showed V'_A/Q' dispersion indices in the normal range. In contrast, dispersion of the ventilation distribution characterized by log SDV remained within normal limits in groups A–C and barely exceeded the upper 95% confidence limit of normal subjects even in the most obstructed patients. Since log SDQ reflects primarily normal and low V'_A/Q' lung regions, figure 2 suggests that the main physiological form of altered V'_A/Q' distribution in asthma is the development of low V'_A/Q' areas, not unexpected from a process that principally causes airways narrowing.

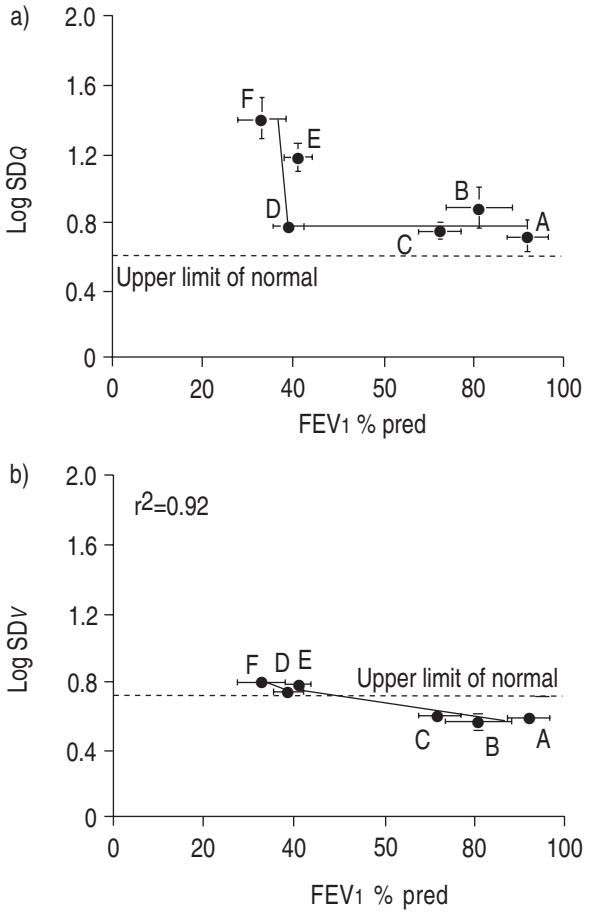

Fig. 2. – Relationship between ventilation/perfusion inequality and forced expiratory flow rates as asthma becomes more severe. a) Log SDQ represents the 2nd moment of the perfusion distribution about its mean on a logarithmic scale, and b) log SDV is the corresponding variable for the ventilation distribution. Inequality in the perfusion distribution is present even in asymptomatic patients (Groups A and B), changes little until forced expiratory volume in one second (FEV1) reaches 40 % of predicted normal values, and then worsens markedly. The ventilation distribution is at the upper limits of normal over the clinical spectrum of asthma. For description of Groups A–F see legend to table 1.

Arterial oxygenation

Simultaneous but methodologically independent measurements of P_{a,O_2} show a pattern of change with FEV1 that mirrors the development of V'_A/Q' mismatch (fig. 3). Note, however, that absolute values of P_{a,O_2} considerably exceed 80 torr in Groups A–C despite their abnormal V'_A/Q' relationships, a finding explained by the relatively high cardiac output in these subjects. Even Groups D and E demonstrate P_{a,O_2} levels that could only be described as mild hypoxaemia, and it is only Group F in whom hypoxaemia is severe. Figure 3 also presents corresponding changes in the alveolar-arterial pressure difference for oxygen (P_{a,O_2}) which, as expected, reflects predominantly the nonlinear behaviour of P_{a,O_2} in figure 3. Note, however, that even in Group A, $P_{(A\text{-}a),O_2}$ is

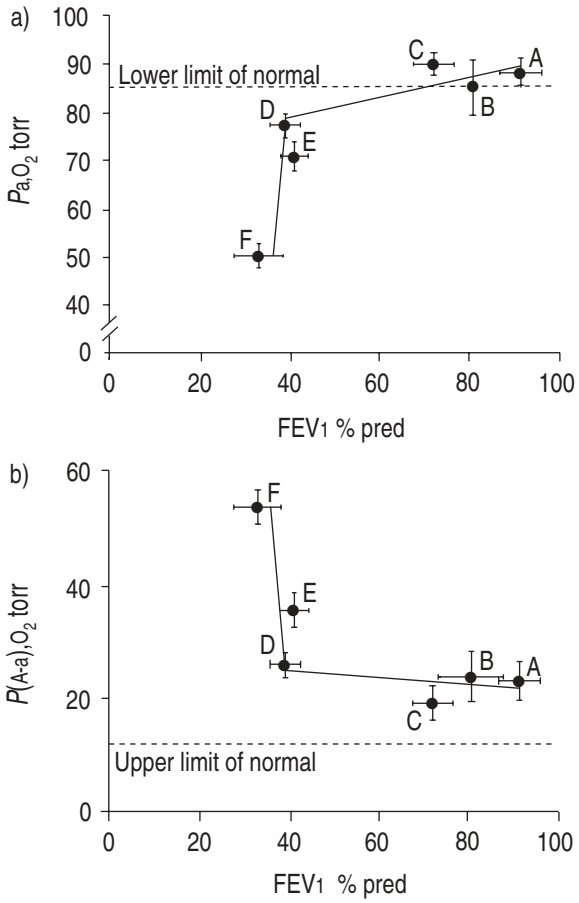

Fig. 3. – a) Arterial oxygen tension (P_{a,O_2}) and b) the alveolar-arterial pressure difference in oxygen ($P_{(A\text{-}a),O_2}$) as a function of expiratory flow rates. Using conventional values for normal limits of subjects in the 30–40 years age range, P_{a,O_2} is essentially normal in Groups A–C and well-compensated until asthma is clinically severe. The $P_{(A\text{-}a),O_2}$ mirrors these changes, but is abnormal across the entire spectrum. For description of Groups A–F see legend to table 1.

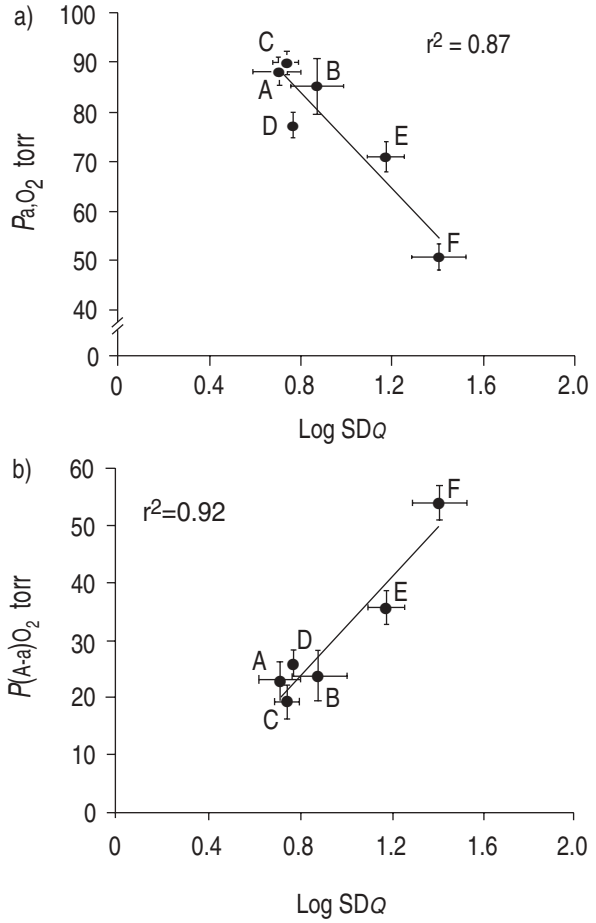

Fig. 4. – a) Relationship between arterial oxygen tension (P_{a,O_2}) and inequality of the blood flow distribution. b) Relationship between alveolar-arterial pressure difference in oxygen ($P_{(A-a,O_2}$). The tightness of these relationships indicate not only that ventilation/perfusion mismatch explains approximately 90% of the gas exchange abnormalities for oxygen, but that measurements of blood gases and calculation of the $P_{(A-a),O_2}$ difference broadly identifies ventilation/perfusion mismatch over the clinical range. For further abbreviations see legend to figure 2. For description of Groups A–F see table 1.

abnormally high at about 20 torr, consistent with the abnormal degree of V'_A/Q' mismatch present (fig. 2). Figure 4 relates arterial blood gas data to those of V'_A/Q' mismatch (log SDQ) and a strong relationship is seen with some 90% of the variation in P_{a,O_2} or $P_{(A-a),O_2}$ accountable by V'_A/Q' mismatch.

Thus, Figures 2–4 indicate that while independent indices of gas exchange are internally consistent over a broad range of severity, those of gas exchange and of airways obstruction are not closely related. Such a pattern is seen not only across groups of patients, but within a group over time. Figure 5 shows for Group F the pattern of recovery both of V'_A/Q' inequality (log SDQ) and spirometry over a 5 week period. With close following and aggressive therapy [3], log SDQ improves eventually to within normal limits, but this takes some 2 weeks from admission to occur. In contrast, spirometry is maximal by discharge, with no further improvement over the next month. In particular, 5 days of in-patient treatment considerably improve airways obstruction, but have little effect on gas exchange.

Finally, it is important to point out that despite the clear-cut pattern of group mean responses in figure 2,

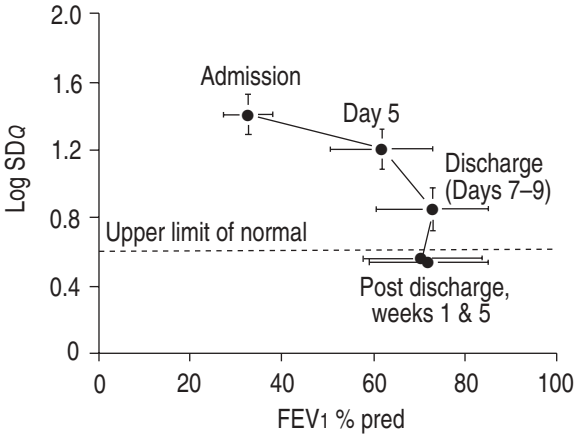

Fig. 5. – Relationship between perfusion distribution inequality and expiratory flow rates during recovery from acute, severe asthma (Group F) requiring admission to hospital. Ventilation/perfusion relationships remain abnormal despite return of flow rates to stable out-patient levels over the first week. For definitions see legends to figures 1 and 2.

there is great variability within a group. Figure 6 exemplifies this by comparing the six subjects of Group B to the nine of Group F, two groups at opposite ends of the spectrum of severity and also essentially distinct by spirometry as shown in figure 6. Thus, in this figure, four patients of Group F show less V'_A/Q' mismatch than the patient of Group B having the greatest mismatch.

The rationale for this paper is that it brings out patterns of respiratory dysfunction across the spectrum of severity in asthma that no single study has provided. The implications would seem to be of two kinds - those for understanding pathophysiology and those of direct clinical significance.

Pathophysiological implications

This paper shows, both between groups (fig. 2) and within (fig. 6) groups identified by clinical severity, very little association between spirometric evidence of airways obstruction and abnormal gas exchange. Whilst there is a

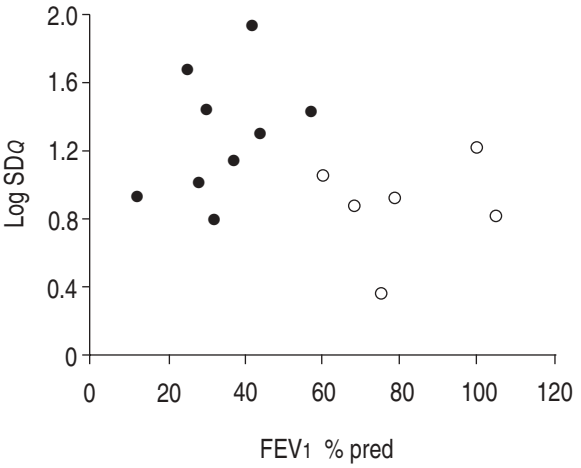

Fig. 6. – Individual data relating perfusion distribution inequality to expiratory flow rates. In two studies of markedly different clinical severity, considerable overlap in perfusion distribution inequality is seen between the two groups, with marked variation within a group. ●: Group F (acute severe); ○: Group B (asymptomatic). For definitions see legends to figures 1 and 2.

very broad correlation (Group A has the most well-preserved indices of both gas exchange and obstruction; Group F the worst of both), figures 2 and 6 show, for example, that over the FEV_1 range 40–100% of predicted, log SD_Q is on average completely unrelated to FEV_1. Both on theoretical [16] and experimental grounds, it is well-known that such spirometric indices are dominated by large airways calibre. Unless large airways become completely obstructed (a rare event), gas exchange disturbances have traditionally been considered to reflect more peripheral airway obstruction. In asthma, it is known that airway obstruction results from a combination of: 1) bronchoconstriction; 2) airway wall thickening due to inflammatory changes; and 3) presence of luminal secretions in airways. Our findings are consistent with the hypothesis that the severity of large airway obstruction is poorly related to the severity of small airway obstruction. This in turn could reflect corresponding differences in bronchoconstriction in large and small airways, but more likely [17] the effect of inflammatory oedema and/or luminal mucus in small airways that may not relate closely to the severity of large airways bronchoconstriction. Certainly, it is common clinical knowledge that the most severely affected asthmatics (those in status asthmaticus) have quite abnormal gas exchange and are characteristically found to have extensive mucous plugging at postmortem examination. However, true cause and effect relationships will be very difficult to establish in man.

Clinical implications

The poor relationship between gas exchange (whether measured by $P_{(A\text{-}a),O_2}$ difference or by V'_A/Q' inequality) and spirometry suggests that the concepts of remission and of the criteria for optimal treatment require further discussion. It is easy to imagine that peripheral airway mucous plugging may be present, perturbing gas exchange, despite relative freedom from the classic symptoms of asthma and despite relatively normal spirometric indices. Should criteria for adequate treatment of asthma episodes go beyond resolution of symptoms and of spirometric abnormalities to demonstrate resolution of gas exchange defect? Although not presented here, earlier work [1] suggests that continuing presence of poorly ventilated regions of low V'_A/Q' ratio underlie the well-known tendency for P_{a,O_2} to fall (rather than rise) acutely after β-sympathetic bronchodilator therapy [4]. There have been suggestions that this phenomenon may be important as one factor contributing to the recent apparent upswing in asthma deaths.

If it should transpire that closer attention to gas exchange is warranted in the clinical care of asthma, the findings of this paper (and thus of the six studies that forms its basis) would suggest that two important points might be made. Firstly, reliance on P_{a,O_2} *per se* for gas exchange evaluation is likely to fail to identify a significant number of patients who, when their $P_{(A\text{-}a),O_2}$ is calculated, are clearly abnormal. This is due to the buffering effect that high cardiac output (characteristic of many asthmatics) has on arterial P_{a,O_2} [12]. It is, however, not necessary to use MIGET to follow individual patients as figure 4 shows, as long as the $P_{(A\text{-}a),O_2}$ is computed. Secondly, it would be valuable to improve understanding of the relative importance of bronchoconstriction, inflammatory oedema and luminal airway mucus on gas exchange because the pharmacological approach to these three abnormalities would be clearly different.

Acknowledgements: The authors wish to thank T. Davisson and C Murphy for secretarial assistance in preparation of this manuscript.

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