

Effects on diffusing capacity and ventilation–perfusion relationships of budesonide inhalations for 2 months in chronic obstructive pulmonary disease (COPD)

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Abstract Forced expiratory volumes are reduced in chronic obstructive pulmonary disease (COPD), mainly as a result of inflammatory and morphological changes in the small airways (with a diameter < 2 mm) and in the alveoli. However, it is difficult to detect minor changes in small airways by spirometry measurements. To study the effects on small airways of inhaled corticosteroids (ICS), 19 stable COPD patients were investigated; 15 were evaluated by ventilation–perfusion (V_A/Q) relationships, assessed by the multiple inert gas elimination technique, and by diffusing capacity for carbon monoxide (DL_{CO}), assessed by the single breath technique. Measurements were repeated after 2 months of budesonide inhalations (800 μ g) twice daily. Before ICS treatment: mean forced expiratory volume in 1 sec (FEV_1) as a percentage of predicted (%P) was 40.1 (± 16.0), DL_{CO} %P was 45.7 (± 25.0) and 6.0 (± 6.4)% of the ventilation was directed at high V_A/Q areas. The mean of the V_A/Q ratio for ventilation (V -mean) was 2.7 times higher than normal. After 2 months of ICS: the mean of DL_{CO} %P increased by 8.6 (± 19.4)%, and FEV_1 /vital capacity decreased by 6.9 (± 11.3)%. Basal morning and ACTH-stimulated S-cortisol levels were significantly reduced. All the V_A/Q relationships remained unchanged. In conclusion, a significant increase in diffusing capacity for carbon monoxide levels after treatment with corticosteroid inhalations for 2 months was shown, but no significant improvements were found in forced expiratory airflow, lung volumes, or V_A/Q relationships. © 2001 Harcourt Publishers Ltd

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INTRODUCTION

Airflow limitation in chronic obstructive pulmonary disease (COPD) frequently develops as a result of inflammatory processes in pulmonary bronchioli and alveolar walls (1–4). It has previously been shown that after the use of inhaled corticosteroids (ICS) for 2 months, the number of neutrophil granulocytes and the proteinase–anti-proteinase ratio in induced sputum may become reduced (5,6).

COPD patients using high doses of ICS for 1–2 years show a decrease in symptom score (7,8). Forced expiratory volumes in stable COPD patients may increase dur-

ing the first 3–6 months after initiating ICS treatment. This effect is most apparent in young patients with increased bronchial reactivity and reversibility (8). Other researchers have found that 6 months of ICS therapy do not reduce symptoms or improve lung function (9). It has also been found that continuous use of ICS treatment over a period of 2–3 years does not prevent long-term decline in forced expiratory volume among COPD patients with irreversible airflow obstruction (7,10,11). Thus, long-term treatment with ICS remains controversial in COPD patients. Previous long-term studies of COPD have only assessed the effects of ICS on lung function by measurements of forced expiratory volumes (7,9–11). In the case of severe COPD, physiological and morphological studies (1,2) imply that forced expiratory volumes are reduced mainly as a result of inflammatory processes and functional impairments of both small airways (less than 2 mm in diameter) and pulmonary parenchyma (2).

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Diffusing capacity for carbon monoxide (DL_{CO}) is a sensitive method to assess emphysema in patients with mild to moderate airway obstruction (12,13). In severe COPD, impaired DL_{CO} reflects abnormal alveolar and bronchial attachments, and also other typical emphysematous changes (14). DL_{CO} is a more important prognostic parameter than degree of airflow obstruction in hypoxaemic COPD patients given long-term oxygen therapy (15), and it may reflect minor changes in small airway function and in the pulmonary parenchymal function not apparent from dynamic spirometry in emphysematous patients (16). In COPD patients with mild airway obstruction, changes within the small airways and the severity of emphysema are reflected by inequality in ventilation–perfusion (V_A/Q) relationships and be assessed by the multiple inert gas technique (MIGET) (13). By measuring diffusing capacity and V_A/Q ratios it should therefore be possible to show minor functional impairments of the small airways and pulmonary parenchyma that cannot be revealed by dynamic spirometry tests.

The aim of the study was to establish whether 2 months of treatment with inhaled corticosteroids (budesonide) improves small airway function in COPD patients with moderate to severe irreversible airway obstruction. Small airway function was assessed by measurements of diffusing capacity and ventilation–perfusion ratios.

Since a slow progressive reduction of forced expiratory airflow (7,10,11) is characteristic of stable COPD patients, any improvement in pulmonary function should be regarded as a treatment effect. This investigation was performed as an open pilot study and the patients were used as their own controls.

METHODS

Subjects

Nineteen stable COPD patients with irreversible airflow obstruction were initially enrolled for the study. Inclusion criteria were a forced expiratory volume in 1 sec as per cent of predicted ($FEV_1\%$ P) <70%, an increase in $FEV_1\%$ P of <10% 15 min after inhalation of 2.5 mg nebulized salbutamol (17), and typical signs of generalized emphysema on X-ray images. The possibility of a history of atopy and/or asthma was excluded by administration of a questionnaire. None of the patients had congestive heart failure or any pulmonary disease other than COPD. Two patients were excluded because of oropharyngeal candida infections, and two more because of poor medication compliance (not using the recommended dosages of budesonide). Fifteen patients, with a mean age of 58.9 (± 7.8) years, seven men and eight women, completed the study. All were observed for several months at our outpatient clinic, from where they had been randomly selected. Nine were ex-smokers (smoking cessation having taken place at least 4 months prior to the measure-

ments) and six were active smokers. One of the 15 patients could not repeat the diffusing capacity measurement procedure because of pronounced breathlessness.

No patient had suffered from respiratory exacerbation for at least 4 weeks before entering the study, and no oral or inhaled steroids had been used for at least 2 months. All patients continued their ordinary medication. Nasal or ophthalmic corticosteroids were not used in our COPD group. Seven patients used oral theophylline, and all used inhalations of (short- or long-acting) β_2 -adrenergic stimulating drugs and/or ipratropium bromide.

The study was approved by the Research Ethical Committee of Huddinge University Hospital and all subjects gave their informed consent.

Measurement of ventilation–perfusion (V_A/Q) ratios

Ventilation–perfusion ratios were measured using MIGET (18). A modified technique was employed in which six mixed expired inert gas levels were measured, while arterial levels were estimated from samples of peripheral venous blood 90 min after starting infusion of inert gas (19,20).

The inert gas samples were analysed by gas chromatography (Varian 3300, Varian Associates Inc., CA, U.S.A.). Retention and excretion ratios were computed, and the solubility of each inert gas was determined by a two-step procedure, thereby enabling estimation of the V_A/Q distribution. Mean values from three runs were used to achieve a low standard error (20).

The dispersion of perfusion and ventilation for different V_A/Q ratios were expressed as the logarithmic standard deviation of the perfusion distribution (log SDQ) and of the ventilation distribution (log SDV) respectively. When the peripheral venous sampling technique is used, log SDQ and log SDV are under-estimated by about 6% (20), and the upper limits of log SDQ and log SDV are 0.70 and 0.75 respectively (21). The mean V_A/Q ratio for the ventilation distribution is denoted as 'V-mean' and the mean V_A/Q ratio for the perfusion distribution as 'Q-mean'. These mean values are describing the average levels of ventilation and perfusion respectively within the distribution of the V_A/Q ratios.

From the V_A/Q distributions, information was also obtained regarding shunt (perfusion of lung regions with V_A/Q ratios <0.005), 'low V_A/Q ' level (perfusion of lung regions with $0.005 < V_A/Q < 0.1$); 'inferior V_A/Q ' (perfusion of lung regions with $0.1 < V_A/Q < 0.3$), 'high V_A/Q ' level (ventilation of lung regions with $10 < V_A/Q < 100$), and dead space (ventilation of lung regions with V_A/Q ratios > 100). Perfusion of lung regions of $V_A/Q < 0.3$ is unusual in healthy individuals (22). Significant effects of treatment in COPD and asthma may be described by different

V_A/Q patterns although the V_A/Q parameters are inter-related (23,24).

Oxygen uptake ($V'O_2$), CO_2 production ($V'CO_2$) and minute ventilation were measured by analysing the O_2 and CO_2 contents of a Douglas bag (Ametek, Pittsburgh, PA, U.S.A.). Cardiac output was assumed to be 1/50 of oxygen uptake ($V'O_2$). Previous simultaneous assessments of CO by thermodilution — during right heart catheterization in 21 stable resting patients with severe and moderate hypoxaemia - and $V'O_2$ measurements in our laboratory showed similar results (23,25). There was a significant correlation between the two kinds of assessments ($r=0.72$, $P=0.001$) (23,25). In another study at our laboratory of cystic fibrosis, it was found that changes in CO of a magnitude 50% are required to significantly influence CO derived parameters, such as shunt (26). In the present study, estimated shunt, and low and inferior V_A/Q (derived from CO assessments) can be considered as reasonably accurate (based on $V'O_2$ measurements) in our stable COPD patients. The fit of the derived V_A/Q distributions to the measured data, expressed as the remaining sum of squares (RSS), should not exceed 6.0 (18,22). Mean RSS in the present study was 1.4 (± 1.5).

Blood gas analyses

Blood gas analyses (ABL 520, Radiometer, Copenhagen, Denmark) were performed on radial arterial samples, following V_A/Q measurements, during air breathing.

Lung function tests

Forced vital capacity (FVC), vital capacity (VC) and FEV_1 were measured by dynamic spirometry. The best FEV_1 value of three was accepted. Residual volume (RV) and total lung capacity (TLC) were measured by body plethysmography. The spirometry measurements were carried out with a Pulmonary Function Laboratory 2400 (Sensor Medics BV, Bilthoven, The Netherlands). Predicted values for the lung function tests were selected from equations provided by the European Coal and Steel Community (27).

DL_{CO} was measured using the single breath method (28) (Sensor Medics BV 2400). The mean value of two technically acceptable measurements was employed. None of the patients were anaemic and the mean post-ICS treatment haemoglobin (Hb) value decreased by 3.2 g l^{-1} and therefore no correction for Hb was needed. Predicted values for the diffusing capacity tests were selected from equations provided by the European Coal and Steel Community (27).

Procedure

All subjects received new, unopened canisters of budesonide, and were given oral and written instructions on how to use the powder metered dose inhaler (Turbuhaler Pulmicort $400 \mu\text{g dose}^{-1}$; Draco, Sweden). Instruction took place on the same day ventilation–perfusion measurements and spirometry tests were to be performed. The next day all patients started corticosteroid therapy. Compliance with treatment was checked by telephone calls and by a colour indicator on the canister, indicating when 90% of the full dose inside the Turbuhaler device had been exhausted. The effect of budesonide on the hypothalamic–pituitary–adrenal (HPA) axis was assessed by a short adrenocorticotropin (ACTH) stimulation test (29). Serum cortisol was measured (Autodelphia, Wallac OY, Finland) before and 30 min after an i.v. ACTH ($0.25 \text{ mg Synachten}$, Novartis, Sweden) injection was given.

Ventilation–perfusion measurements, spirometry tests and the ACTH stimulation test were repeated after two inhalations of $400 \mu\text{g}$ budesonide twice daily for 2 months. Tests for all patients were carried out at the same time of the day and in the same order.

STATISTICS

Results are presented in the form of means and standard deviations ($\pm \text{SD}$) unless otherwise stated. Changes over time were assessed by paired Student's *t*-test. Correlations between variables were assessed by simple regression. Significance of difference between groups was determined by Student's unpaired *t*-test. For changes in V_A/Q parameters and S-cortisol values the difference between the final and initial value was employed. Regarding change in lung function volume, the difference between final and initial value was divided by the initial value.

RESULTS

2 months before ICS treatment ($n = 10$)

Dynamic, static spirometry and diffusing capacity were measured in 10 patients about 8 weeks before inclusion in the study. In four of these patients ICS had been discontinued. Two months later (the day before the ICS therapy started) mean VC% P and $FEV_1\%$ P levels were significantly reduced, whereas mean RV% P level was significantly increased. However, the mean $DL_{CO}\%$ P level remained unaltered in this subgroup of patients [Fig. 1(a–d)]. Increments in VC% P levels correlated with decrements in RV% P ($r = -0.74$, $P < 0.05$), but change in $FEV_1\%$ P level did not correlate with change in any spirometric parameter.

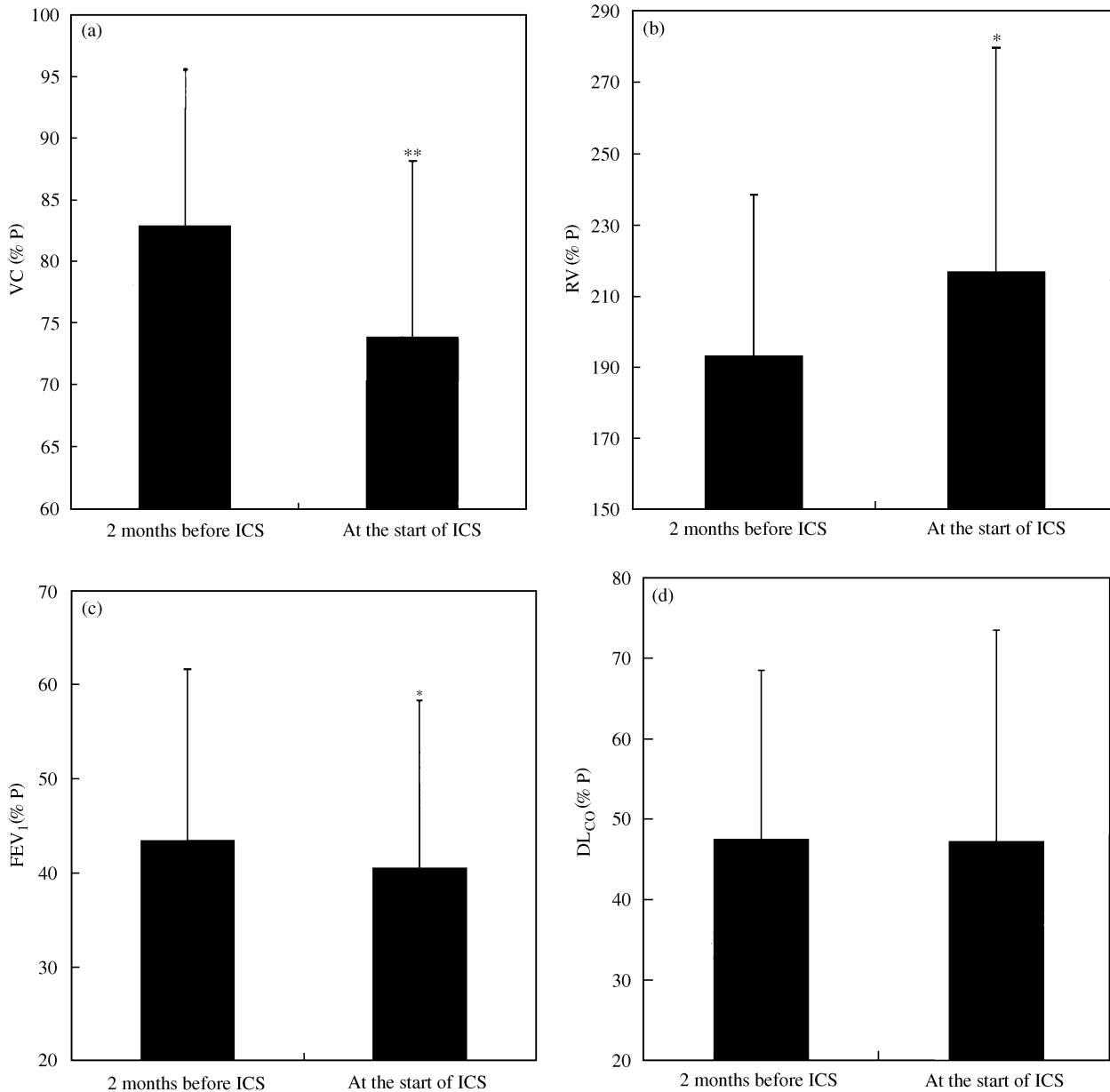


FIG. 1. (a) Vital capacity (VC) as a percentage of predicted (% P); (b) residual volume (RV) as a % P; (c) forced expiratory volume in 1 sec (FEV₁) as a % P; (d) diffusing capacity for carbon monoxide (DL_{CO}) as a % P. All measurements were performed 2 months before and the day before the start of inhaled corticosteroid treatment (ICS) (n=10). *P < 0.05; **P < 0.01 regarding differences in time.

The day before ICS treatment (n = 15)

At the beginning of the study the 15 patients who completed the trial had a mean FEV₁% P of 40.1 (± 16.0)% [which increased to 42.9 (± 14.6)% after β₂-adrenergic stimulation] and a mean DL_{CO}% P of 45.7 (± 25.0)%. Their PaO₂ value was 9.8 (± 1.4) kPa and no secondary polycythaemia or anaemia was observed (Table 1).

A substantial ventilation towards high V_A/Q regions, 6.0 (± 6.4)% of minute ventilation and a significant increase in V-mean level (22), 2.7 (± 0.8), were noted

(Table 2). Dead space was within normal range. Only minor shunt and scarce perfusion were found for low V_A/Q regions (Table 2). About 30% of the patients showed detectable perfusion of inferior V_A/Q areas. The Q-mean level was 1.3 (± 0.3), which is close to normal (22). Log SDV was significantly higher than normal, and log SDQ was at the upper limit of normality (21). No significant correlations between V_A/Q parameters and spirometry values were found. DL_{CO}% P correlated with forced expiratory volumes, and was inversely correlated with RV% P (Table 3).

TABLE 1. Spirometric data, blood gas and S-cortisol levels for 15 COPD patients the day before and 2 months after inhaled corticosteroids (ICS)

		The day before ICS	After 2 months of ICS
VC	(% P)	75.6 ± 15.4	77.9 ± 12.3
FVC	(% P)	77.7 ± 16.9	74.5 ± 14.7
FEV ₁	(% P)	40.1 ± 15.9	38.2 ± 16.3
FEV ₁ /VC	(%)	40.6 ± 12.1	37.9 ± 13.1*
RV	(% P)	213.5 ± 55.8	201.9 ± 50.3
TLC	(% P)	122.8 ± 18.1	122.9 ± 15.6
DL _{CO}	(% P)	45.7 ± 25.0	52.9 ± 30.1*
PaO ₂	(kPa)	9.8 ± 1.4	9.7 ± 1.3
PaCO ₂	(Kpa)	5.1 ± 0.6	5.0 ± 0.5
EVF	(%)	45.9 ± 2.7	44.9 ± 2.7
S-cortisol (nmol l ⁻¹):			
Before ACTH		242.2 ± 95.5	147.2 ± 57.7**
After ACTH		610.5 ± 78.9	492.8 ± 106.1**
ΔS-cortisol		368.3 ± 104.2	345.6 ± 89.0

ACTH: adrenocorticotropin hormone; DL_{CO}: diffusion capacity for carbon monoxide; ΔS-cortisol: the change in cortisol level after the ACTH challenge test; EVF: haematocrit value; FEV₁: forced expiratory volume in 1 sec; FEV₁/VC: forced expiratory volume; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; VC: vital capacity. **P* < 0.05 and ***P* ≤ 0.01, regarding significant differences in values between the day before and 2 months after ICS treatment.

TABLE 2. Ventilation-perfusion relationships in 15 COPD patients the day before and 2 months after inhaled corticosteroids (ICS)

	The day before ICS	After 2 months of ICS
V-mean	2.7 ± 0.8	3.0 ± 0.3
Q-mean	1.3 ± 0.3	1.4 ± 0.3
Log SDV	0.90 ± 0.30	0.76 ± 0.40
Log SDQ	0.74 ± 0.20	0.72 ± 0.14
Shunt	1.4 ± 1.0	1.5 ± 1.0
Inferior V _A /Q	3.0 ± 4.3	1.1 ± 2.4
Low V _A /Q	0.2 ± 0.6	0.1 ± 0.4
High V _A /Q	6.0 ± 6.4	7.2 ± 9.4
Dead space	26.9 ± 8.1	26.0 ± 7.5
V _E (l min ⁻¹)	9.9 ± 3.1	10.0 ± 3.4

V-mean: the mean V_A/Q ratio for ventilation; Q-mean: the mean V_A/Q ratio for perfusion; Log SDV: the dispersion of ventilation; Log SDQ: the dispersion of perfusion; Shunt: V_A/Q < 0.005 in % of cardiac output; Inferior V_A/Q: 0.1 < V_A/Q < 0.3 in % of cardiac output; Low V_A/Q: 0.005 < V_A/Q < 1 in % of cardiac output; High V_A/Q: 10 < V_A/Q < 100 in % of minute ventilation; Dead space: V_A/Q > 100 in % of minute ventilation; V_E: Minute ventilation.

TABLE 3. Linear correlations between spirometric values and diffusion capacity in percentage of predicted values (DL_{CO}% P) the day before inhaled corticosteroid (ICS) treatment started

DL _{CO} % P	r-value
FVC (% P)	0.52*
FEV ₁ (% P)	0.71**
FEV (% P)	0.61*
RV (% P)	-0.55*

P* < 0.05 and *P* ≤ 0.01, regarding significant correlations before ICS treatment.

TABLE 4. Differences between COPD patients with an increase in DL_{CO} level (ΔDL_{CO} level > 0, n=8) as compared with COPD patients with reduced or unchanged DL_{CO} level (ΔDL_{CO} level ≤ 0, n=6) after 2 months of ICS

	ΔDL _{CO} level ≤ 0	ΔDL _{CO} level > 0
S-cortisol (nmol l ⁻¹)	189 ± 20	112 ± 56*
Q-mean	1.6 ± 0.3	1.3 ± 0.2*
V-mean	3.6 ± 1.1	2.5 ± 0.8†

For abbreviations see previous tables and text. **P* ≤ 0.05, †*P* = 0.06, regarding significant differences between the two subgroups of COPD patients.

Baseline level of serum cortisol and response to the ACTH-challenge test were within normal limits (29) (Table 1).

After 2 months of ICS treatment (n = 15)

There was a non-significant trend for VC to increase and for FEV₁ to decrease, resulting in a FEV₁/VC decrease of 6.9 (± 11.3%) (Table 1). A non-significant trend towards reduced RV% P level was noted. No other significant change in any dynamic or static spirometric parameter was found. The mean DL_{CO}% P for the entire group significantly increased by 8.6 (± 19.4)%. Four patients had unchanged DL_{CO}% P levels while two patients had decreased levels. Eight patients (57%) showed an average increase in DL_{CO}% P level of 20.1 (± 13.4)%. The same pretreatment DL_{CO}% P levels were found in patients for whom DL_{CO}% P levels increased after treatment as for those with DL_{CO}% P levels remaining unchanged. V-mean and Q-mean were closer to normal, and a significantly lower basal s-cortisol level was shown for the patients with an increase in DL_{CO}% P levels than for those with an unchanged or decreased level of DL_{CO}% P (Table 4).

All the V_A/Q relationships remained unchanged (Table 2). V-mean and Q-mean values were inversely correlated with post-treatment $DL_{CO}\%P$ (Fig. 2). The non-significant changes in log SDV correlated significantly with changes of high V_A/Q ($r=0.83, P<0.001$), log SDQ ($r=0.62, P<0.05$) and changes of V-mean ($r=0.59, P<0.05$), and were inversely related to changes of Q-mean ($r=-0.54, P<0.05$). Less mismatch between V-mean and Q-mean was found in patients with reduced log SDV (Fig. 3). Q-mean was found to be inversely correlated with FEV_1/VC ($r=-0.57, P<0.05$). No other significant correlations were found between V_A/Q ratios and spirometry parameters.

Both the average baseline serum cortisol level and the average level after ACTH-challenge decreased significantly from pre-treatment levels (Table I). Mean cortisol level after the ACTH challenge test was lower than normal after two months of ICS (501 nmol l^{-1}) (29). However, the post-ACTH cortisol rate of rise (Δ cortisol) remained unchanged after ICS treatment (Table I). Current smokers showed an increased level of post-treatment V-mean of $3.6 (\pm 1.1)$, as opposed to $2.5 (\pm 0.8)$ among ex-smokers and also a wider log SDV $1.1 (\pm 0.4)$ as opposed to $0.8 (\pm 0.2)$ ($P<0.05$ for both groups).

DISCUSSION

No improvements in forced expiratory volumes after 2 months of ICS treatment were shown, in line with previous studies of COPD patients with moderate to severe airflow obstruction (5–79). However, a slight reduction in the ratio between FEV_1 and VC was noted in association with a significant increase in diffusing capacity.

In the ISOLDE trial of moderate COPD patients (11), discontinued ICS treatment or administration of oral corticoids was followed by a rather steep decrease in

FEV_1 . In our group of 10 patients, based on measurements of lung function about 2 months before the start of ICS, the median fall in FEV_1 was found to be 210 ml year^{-1} . This is more than three times the fall in FEV_1 value found in the ISOLDE trial. Our group of COPD patients either belonged to the group of ‘rapid decliners’ (30), with a typically steep decline in FEV_1 (which is most likely), or the rapid FEV_1 fall was caused by the discontinuation of previous ICS treatment. In line with previous studies (10,11) the rate of decline in FEV_1 was found to fall when ICS treatment was given. However, the reduction in fall of FEV_1 due to ICS seems to last for only the first 3–6 months of treatment in mild to moderate COPD. Accordingly, ICS offers no protection against progressive fall in FEV_1 over a longer period of time (7,10,11).

The lack of association between changes in FEV_1 and changes in hyperinflation in our study may support the notion that forced expiratory volume in COPD mainly depends on peripheral airway obstruction (2).

In agreement with a previous study (12,16), forced expiratory volumes were found to be related to the level of DL_{CO} before ICS treatment. This correlation may be due to the reduced alveoli–capillary area associated with chronic airway obstruction (12,16). The increased level of V-mean (2.7 times higher than normal) in our patients indicate that a substantial part of the ventilation was wasted to poorly perfused areas (31). There was also a significant correlation between low DL_{CO} and post-treatment increases in V-mean, supporting the hypothesis that uneven distribution of inspired gas influences DL_{CO} level as measured by the single breath technique (16). The increase in $DL_{CO}\%P$ of about 20% in more than 50% of our patients was found mainly among those with moderate V_A/Q inequality (Table 3). Patients with less severe V_A/Q disturbances probably suffer from less pronounced bronchiolar distortion and inflammation (13), which might mean that inhaled corticoid steroids are more abundantly deposited in the small airways (as compared with COPD patients with more severe V_A/Q inequality). It is unlikely that the change in $DL_{CO}\%P$ was due simply to chance, since no significant change in $DL_{CO}\%P$ level was shown before ICS treatment was started. $DL_{CO}\%P$ may also increase because of enlarged alveolar volume (V_A), and thus augmented diffusion area (32). V_A is usually measured by the helium dilution technique. But such measurements are also influenced by V_A/Q inequalities, and are often spuriously low in COPD with considerable V_A/Q mismatch, as in our patients, especially when the single breath method is used (33). For the purposes of the current study, an increase in V_A is not of major importance, since the change in lung volume was always two to three times smaller than the change in $DL_{CO}\%P$ in our subgroup of patients showing a post-treatment increase in diffusing capacity.

Two months of ICS treatment were not accompanied by any significant changes in V_A/Q relationships in our

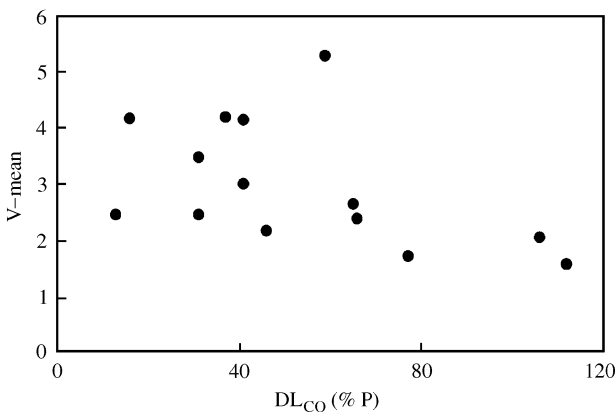


Fig. 2. Spearman-Rank correlation between post-treatment diffusing capacity for carbon monoxide as a percentage of predicted value ($DL_{CO}\%P$) and mean of V_A/Q ratios for ventilation (V-mean): $r_s=-0.59, P<0.05$ ($n=14$).

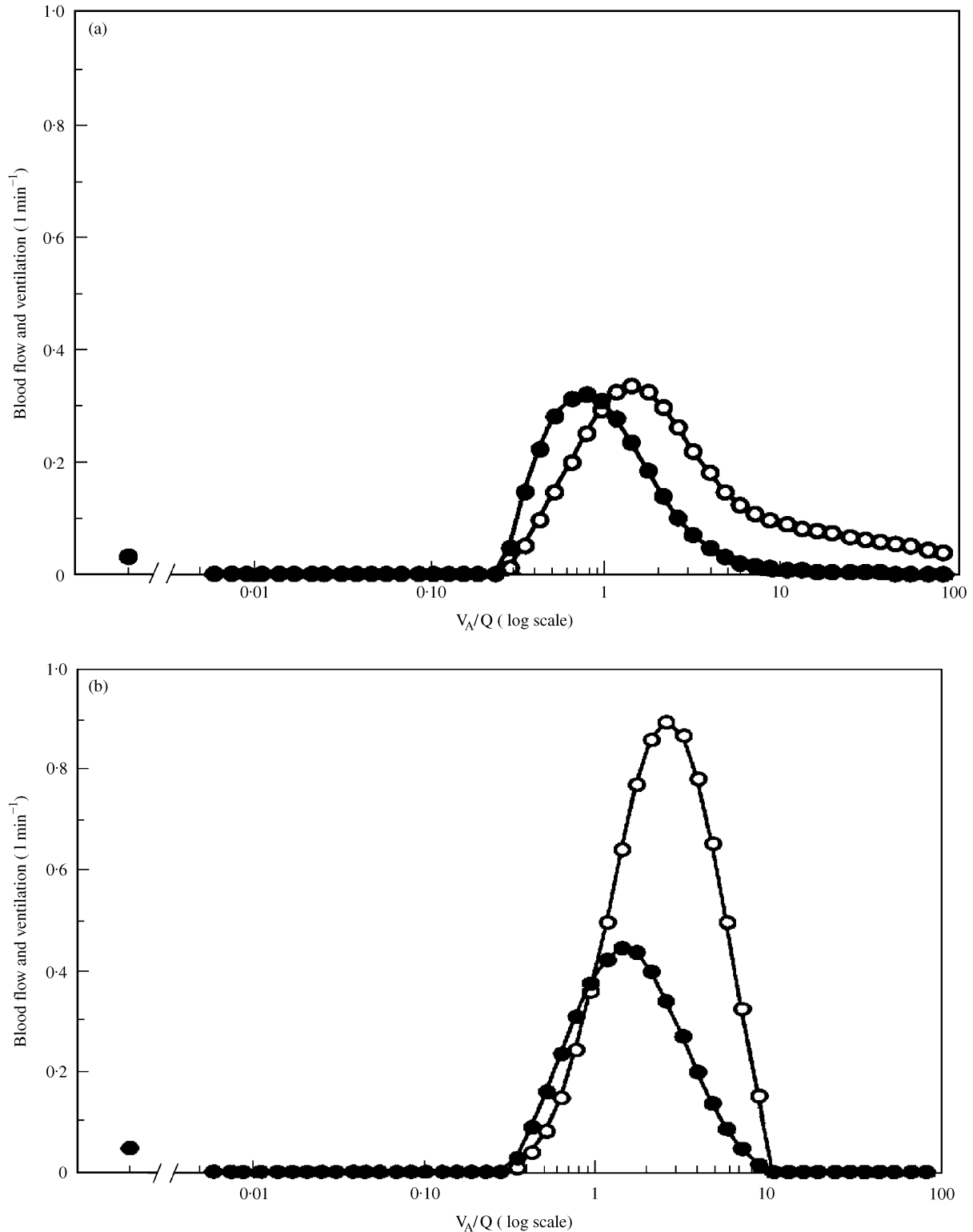


FIG. 3. (a) V_A/Q ratios the day before inhaled corticosteroids (ICS) treatment and (b) V_A/Q ratios after ICS treatment for 2 months (lower frame) in one patient. Note the reduced dispersion of ventilation and the reduced ventilation to high V_A/Q areas, and the improvement of ventilation and perfusion inequality after 2 months of ICS treatment. V_A (-○-), Q (-●-), shunt (●).

entire study population. However, log SDV was reduced in a subgroup of our patients, and this reduction was accompanied by improvements in other indices of V_A/Q inequality.

The single breath method performed as a single inspiration of carbon monoxide-enriched gas mixture measures the rate of carbon monoxide transport from the alveolar gas to the haemoglobin in the capillary

during 10 sec of breath-hold. The MIGET test performed during normal tidal breathing (in steady state) for 90 min represents the overall gas exchange and ability of gas transport inside the lung. For all our COPD patients, no relationships were found between change in $DL_{CO}\%$ P and post-treatment change in any V_A/Q or spirometry parameter. It is possible that the ICS post-treatment improvement in $DL_{CO}\%$ P reflects an increase in volume of inspired air inside the alveoli without measurable changes of V_A/Q ratios or lung volumes.

In line with an earlier study of severe asthmatic patients (24), it was shown that V_A/Q relationships may be altered without concomitant changes in forced expiratory volumes.

In mild (mean $FEV_1\%$ P of 68%) COPD an inverse correlation was found between $FEV_1\%$ P and severity of $CD8^+$ T-lymphocytic inflammation within the alveolar wall and arterioli adjacent to the bronchioli (4). We believe that the post-treatment increase in $DL_{CO}\%$ P found in the present study represents reduced inflammation inside the small airways due to inhaled corticosteroids, followed by remodelling of bronchioli and alveoli. How long such remodelling would require is unknown. Since previous studies have shown reduced airway inflammation after 2 months of ICS treatment in COPD (5,6) the effects of ICS were also assessed after 2 months in the current study. However, it should be emphasised that further studies are needed to describe the morphological and physiological mechanisms to explain an increase in $DL_{CO}\%$ P after continuous use of ICS in COPD. Those of our patients who were active smokers showed worse post-treatment V_A/Q inequality than ex-smokers, this providing corroborating evidence that smokers often suffer from progressive small airway disease (34).

The patients in this study used a fairly high dose of budesonide, 1600 μ g daily, similar to that used in previous studies of COPD patients (7,17). Even half of this ICS dosage may result in dermal thinning and bruises (10). In the case of moderate COPD, 2 years of treatment with 1600 μ g budesonide daily have not been found to result in any significant changes in morning cortisol levels (7). By contrast, in the ISOLDE trial (11), a small decrease in S-cortisol was noted after 6 months of ICS treatment. Two months of treatment of our patients with severe COPD produced a significant reduction in basal serum cortisol before and after the ACTH-challenge test. This reduction in basal cortisol was particularly large in the subgroup with increased $DL_{CO}\%$ P. This finding suggests that higher amounts of budesonide may have reached the blood circulation by the respiratory and/or the gastrointestinal routes, thereby suppressing the HPA-axis. The increment in S-cortisol after the ACTH-challenge test was not altered by the ICS treatment given to our patients, and thus adrenal reactivity and cortisol reserve were not affected.

CONCLUSION

Inhaled corticosteroid treatment for 2 months was found to be accompanied by a significant increase in diffusion capacity for carbon monoxide, but not by any significant improvements in forced expiratory airflow measurements, lung volume tests or ventilation-perfusion relationships. The increase found in $DL_{CO}\%$ P probably reflects improvement in small airway function, possibly depending on reduced inflammation of bronchioli and alveoli.

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