

Pulmonary gas exchange in cystic fibrosis: basal status and the effect of *i.v.* antibiotics and inhaled amiloride

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Pulmonary gas exchange in cystic fibrosis: basal status and the effect of i.v. antibiotics and inhaled amiloride. L. Lagerstrand, L. Hjelte, H. Jorulf. ©ERS Journals Ltd 1999.

ABSTRACT: In order to evaluate the degree and type of gas exchange impairment in cystic fibrosis, ventilation/perfusion relationships in ten patients (mean age 26 yrs, mean Shwachman score 86) were examined.

Pulmonary gas exchange was studied using the multiple inert gas elimination technique. High-resolution computed tomography (HRCT) and spirometry, including diffusing capacity, were performed after each gas exchange study for comparison. Examinations were done before and after home *i.v.* antibiotic treatment (HIVAT, 14 days) and after inhaled amiloride and placebo (14 days), in crossover fashion, clinical status after HIVAT serving as the baseline for the crossover study.

Before HIVAT, the mean residual volume was 182% of the predicted value, the mean vital capacity 72% pred and the mean forced expiratory volume in one second 53% pred ($p < 0.001$). The dispersion of pulmonary blood flow at different ventilation/perfusion ratios (V'/Q') (logarithmic sd of the perfusion distribution (log SDQ)), used as an index for gas exchange impairment, was increased to a mean of 0.72. No linear correlation was seen between ventilation/perfusion inequality, spirometry and HRCT ($p > 0.05$). After HIVAT, log SDQ was significantly improved to 0.66 ($p < 0.05$). After placebo, but not after amiloride, log SDQ, arterial oxygen tension, alveolar-arterial oxygen tension difference and maximal expiratory flows when 50% and 25% of the forced vital capacity tension remain to be exhaled were significantly worse ($p < 0.05$, respectively). Areas with a low V'/Q' were significantly lower after amiloride compared to after the placebo period ($p < 0.05$).

Moderate ventilation/perfusion inequality was present in the majority of the studied cystic fibrosis patients. The degree of ventilation/perfusion inequality cannot be estimated from spirometry or high-resolution computed tomography. The low proportion of low ventilation/perfusion ratios indicates that the regular treatment directed towards mucus plugging of small airways is beneficial. An improvement in the ventilation/perfusion relationship was seen after home *i.v.* antibiotic treatment and inhaled amiloride may possibly have a further positive effect on gas exchange.

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Cystic fibrosis (CF) is the most common autosomal recessive hereditary lethal disease among the Caucasian population. It is associated with increased sodium absorption, reduced chloride conductance and an increased potential difference across the respiratory epithelium [1, 2]. These abnormalities may contribute to the pathogenesis of the disease by reducing the water content of the airway surface liquid [3], thus impairing mucociliary clearance and predisposing to chronic bacterial infection.

Current therapies for CF lung disease target the overt clinical manifestations. These therapies include antibacterial agents and mechanical clearance of airway secretions. Amiloride, a Na^+ channel blocker, inhibits Na^+ absorption across normal and CF airway epithelia in a dose-dependent fashion [1, 4, 5]. Inhibition of the excessive absorption of sodium in the airway epithelium by use of aerosolized amiloride four times daily for 1 yr has been shown to slow the loss of forced vital capacity (FVC) and to improve sputum viscosity and elasticity [6], rendering this agent a drug of interest.

Since airway secretion is one of the main factors in the development of ventilation/perfusion inequality, evaluation

of the ventilation/perfusion relationship ought to be of special interest in cystic fibrosis, in which airway secretion is impaired as described above. So far only one study using the multiple inert gas elimination technique to describe the ventilation/perfusion ratio (V'/Q') in patients with CF [7] has been published. That study from 1982 showed, in six hypoxaemic patients, a considerable ventilation/perfusion mismatch dominated by rather high levels of shunt.

The aim of the present study was to examine the ventilation/perfusion inequality in patients with CF and to compare the V'/Q' with standard measures of pulmonary function. A second aim was to evaluate intravenous antibiotic treatment performed at home [8] together with intensified physiotherapy as well as to evaluate treatment with inhaled amiloride.

Material and methods

Patients

Ten patients (four males and six females) with CF regularly attending Stockholm CF centre were investigated.

Inclusion criteria were CF, age ≥ 16 yrs, and FVC $>70\%$ of the predicted value. The diagnosis of CF was based on clinical symptoms together with a positive sweat test (chloride >80 mmol·L⁻¹). Their mean age was 26 yrs (range 17–32 yrs) and their mean Shwachman score 86 (range 77–90) [9]. Six patients were homozygous and two heterozygous for the most common mutation $\Delta F508$ ($\Delta 508/394$ del TT, $\Delta 508/3659$ del C). Of the remaining two, one had the mutations 3659 del C/394 del TT. The other patient had still unknown mutations. All patients were sputum producers and were all colonized with *Pseudomonas aeruginosa* in their lower airways. All were treated with oral mucolytics (bromhexine and acetylcysteine) as well as with inhalation of acetylcysteine, salbutamol and sodium chloride (9 mg·mL⁻¹). None were on steroids. Pancreatic supplementation (enteric coated microspheres containing lipase, amylase and trypsin) as well as fat-soluble vitamins were given to all.

Informed consent was obtained in each case and the study was approved by the human ethics committee at Huddinge Hospital.

Study design

The study was initiated when *i.v.* antibiotics were indicated. Measurements were performed immediately before and after 14 days of home *i.v.* antibiotic treatment (HIVAT) together with intensified physiotherapy [8] and again after 14 days of inhalation of each of placebo (sodium chloride 9 mg·mL⁻¹; 3.5 mL four times daily) and amiloride (5 mM, pH 7.0; 3.5 mL four times daily [6, 10]) in a single-blind crossover manner. The clinical status after HIVAT served as the baseline for the crossover study. The patients were studied for a total of 6 weeks. For inhalation, nebulizers (Aiolos; Medicinsk Teknik, Karlstad, Sweden) were used. Indications for antibiotic treatment were at least two of the following symptoms of low-grade infection: change in volume, appearance and/or colour of sputum, increased respiratory frequency or dyspnoea, progressive worsening of physical findings on chest auscultation, increased cough, decreased appetite, loss of weight or deterioration in the results of standard biochemical tests. Two antibiotics (tobramycin and a β -lactam) were given as rapid infusions three times daily. Five of the 10 patients were randomly assigned to amiloride and five to sodium chloride for the first period. Before inhaling amiloride or sodium chloride, the patients inhaled their mucolytics and performed their physiotherapy (morning and evening). All patients met a physiotherapist before the start of the study and then every other week to make sure that there were no significant changes to the physiotherapy programme.

Spirometry

The spirometry was always performed immediately after the gas exchange study. Functional residual capacity (FRC) was determined by means of body plethysmography. Total lung capacity (TLC) and residual volume (RV) were calculated. Vital capacity (VC), forced expiratory volume in one second (FEV₁), FEV₁ as a percentage of VC (FEV₁/VC, %), peak expiratory flow (PEF), and maximal

expiratory flow at 50% and at 25% of FVC (MEF₅₀ and MEF₂₅) were measured separately. FEV₁, FVC and PEF were taken as the highest value from the first two technically satisfactory forced expirations. The highest values of the measured flow indices (MEF₅₀ and MEF₂₅) were chosen, unless the FVC from that measurement was $<95\%$ of the highest measured FVC [11]. The diffusing capacity of the lung for carbon monoxide (DL_{CO}) was determined by means of the single breath CO method. None of the patients were anaemic and consequently no correction for haemoglobin concentration was performed. The mean of two technically acceptable measurements was used. All measurements were performed using a Sensor Medics pulmonary function laboratory (Sensor Medics, Biltoven, the Netherlands).

Ventilation/perfusion relationships

The distributions of V'/Q' were measured using the multiple inert gas elimination technique [12]. A modified technique was used in which mixed expired inert gas levels were measured, whereas arterial levels were estimated from samples of peripheral venous blood from the hand 90 min after the inert gas infusion began [13, 14].

The inert gas samples were analysed by means of gas chromatography (Varian 3300; Varian Associates, Inc., Sunnyvale, CA, USA). Retention and excretion ratios were computed and the solubility of each inert gas was determined using a two-step procedure and, finally, the V'/Q' distribution was estimated. Cardiac output (L·min⁻¹) was assumed to be 2% of oxygen uptake (mL·min⁻¹) which was measured, together with the carbon dioxide production ($V'\text{CO}_2$), at the time of inert gas sampling by using and analysing a Douglas bag for O₂ and CO₂ (Ametek, Pittsburgh, PA, USA). Theoretical work has shown that the V'/Q' dispersion indices are very insensitive to the estimate of cardiac output [13]. Alveolar oxygen tension for the calculation of alveolar-arterial oxygen tension difference (P_{A-a,O_2}) was estimated from arterial carbon dioxide tension (P_{a,CO_2}), oxygen uptake and $V'\text{CO}_2$. Minute ventilation was measured by analysing the volume of the content in the Douglas bag. The dispersion of the perfusion and ventilation on different V'/Q' were expressed as the log-arithmetic standard deviation of the perfusion distribution (log SDQ) and of the ventilation distribution (log SDV). Log SDQ and log SDV thus express the degree of overall ventilation/perfusion mismatch. The mean values from three runs were used to obtain a low SEM [14]. When the peripheral venous sampling technique is used, log SDQ and log SDV are underestimated by $\sim 6\%$ [14]. From the V'/Q' distributions, data were also derived for shunt (perfusion of lung regions with V'/Q' ratios <0.005), "low V'/Q' " (perfusion of lung regions with V'/Q' ratios 0.005–0.1), "high V'/Q' " (ventilation of lung regions with V'/Q' ratios 10–100) and dead space (ventilation of lung regions with V'/Q' ratios >100). However, when cardiac output is assumed, no exact data on shunt and low V'/Q' can be calculated. Shunt and low V'/Q' are therefore considered as estimated.

The requirements for the multiple inert gas elimination technique, as defined by WAGNER and WEST [15], are that the fit of the derived V'/Q' distributions to the measured

Table 1. – Clinical data from cystic fibrosis patients

	Weight kg	Haemoglobin g·L ⁻¹	WBCs 10 ⁹ cells·L ⁻¹	Albumin g·L ⁻¹	Haptoglobin g·L ⁻¹	Orosomucoid g·L ⁻¹	ESR mm·h ⁻¹	CRP mg·L ⁻¹
Before HIVAT	61.3±8.3	132±12.7	7.3±2.1	32.5±3.9	2.26±0.60	1.19±0.38	22.1±16	15.8±9.4
After HIVAT	61.9±8.7	131±14.0	6.0±2.2	33.6±2.6*	1.80±0.66*	1.03±0.40	15.5±9.1	16.4±15.2
After placebo	61.7±8.4	129±9.5	7.5±3.6	32.8±2.6	2.53±1.33	1.20±0.38	31.6±26.6 [#]	26.4±36.3
After amiloride	61.9±8.6	132±9.4	7.1±2.3	35.3±3.5* ⁺	1.89±0.48	0.99±0.22	21.3±12.1	22.3±19.3

HIVAT: home *i.v.* antibiotic treatment; WBC: white blood cell; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein. *: $p < 0.05$ versus before HIVAT; [#]: $p < 0.05$ versus after HIVAT; ⁺: $p < 0.05$ versus after placebo.

data, expressed as the remaining sum of squares (RSS), should not exceed 6.0 in >50% of measurements. The mean RSS from all data in the present study was 1.67 and the range was 0.04–10.5. No significant differences were found when the mean values of log SDQ and log SDV from the first, second and third run were compared. The uncertainty of the calculation of shunt when using an assumed and thereby uncertain cardiac output was estimated by recalculating the shunt using a 50% higher and a 50% lower cardiac output. When a 50% lower cardiac output compared to the original was used, the fraction of shunt was decreased by a mean of 46% (range 31–56%), and, when a 50% higher cardiac output was used, the fraction of shunt was increased by a mean of 50% (range 43–69%).

Blood gas analyses

Immediately after the inert gas sampling 2 mL of arterial blood was drawn from the radial artery for duplicate determination of arterial oxygen tension (P_{a,O_2}), P_{a,CO_2} and pH. Standard electrode techniques (ABL 520; Radiometer, Copenhagen, Denmark) were used.

Biochemical analyses

Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) concentration, white blood cell (WBC) count and serum electrophoresis results (albumin, haptoglobin, orosomucoid) were measured using standard methods.

Thin-section high-resolution computed tomography

HRCT was performed using a somatotome (Philips, Eindhoven, the Netherlands) DHR unit with 1.5-mm sections at 10-mm intervals. The scanning time was 1 s. Eight patients underwent scanning at 120 kV and 150 mA. All HRCT scans were evaluated by an experienced radiologist

(H. Jorulf), who was blinded as to which treatment the patients were receiving. The HRCT findings were scored according to BHALLA *et al.* [16], with a maximal score of 25. All the patients were awake and collaborating, holding their breath at deep end-inspiration, and were examined in the supine position.

Statistics

All data are presented as mean±SD. The measurements before and after HIVAT were compared using the paired Student's t-test or Wilcoxon's signed-rank test (shunt, low V'/Q' , high V'/Q' and dead space). For assessing the significance of a difference between the measurements after HIVAT, after placebo and after amiloride, analyses of variance (ANOVA) were used. Differences between the measurements were localized using Fisher's protected least significant difference test. A p -value < 0.05 was considered significant. The relationship between spirometric findings, gas exchange variables and HRCT were evaluated using linear regression analysis.

Results

Before treatment

Clinical examination. At the time the patients were included into the study, clinical examination revealed signs of low grade infection, indicating the need for antibiotic treatment and extended physiotherapy, the most frequent indications being larger amounts of sputum and increased cough. One patient had a slight basal infiltrate, which was revealed on HRCT but not suspected clinically. *Pseudomonas aeruginosa* was present in the sputum of all patients. No patient revealed any multiresistant strains. Inflammatory parameters were slightly increased in all patients (table 1).

Table 2. – Spirometry data from cystic fibrosis patients

	TLC L	FRC L	VC L	RV L	DL_{CO} mmol·kPa ⁻¹ ·min ⁻¹	FEV ₁ L	FEV ₁ /VC %	PEF L·s ⁻¹	MEF ₅₀ L·s ⁻¹	MEF ₂₅ L·s ⁻¹
Before treatment	5.8±1.4	3.5±1.2	3.2±0.7 [#]	2.6±0.9	8.2±2.9	1.9±0.4	62±9	5.1±1.4	1.5±0.6	0.43±0.15
After HIVAT	5.9±1.4	3.5±1.0	3.3±0.8*	2.6±1.0	8.5±2.7	2.0±0.6	61±12	5.2±1.4	1.6±0.9 ⁺	0.44±0.21 ⁺
After placebo	6.1±1.6	3.6±1.1	3.2±0.7	2.8±1.2	7.9±2.1	1.9±0.4	50±10	4.9±1.3	1.4±0.8 [#]	0.37±0.16 [#]
After amiloride	6.0±1.5	3.5±1.2	3.3±0.8	2.7±1.1	8.3±2.7	2.0±0.5	60±9	5.2±1.5	1.5±0.9	0.40±0.15

Vital capacity (VC), forced expiratory volume in one second (FEV₁), FEV₁/VC, peak expiratory flow (PEF), maximal expiratory flow at 50% and at 25% of forced vital capacity (MEF₅₀ and MEF₂₅) and diffusing capacity of the lung for carbon monoxide (DL_{CO}) were significantly lower and residual volume (RV) significantly higher than their reference values. TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; HIVAT: home *i.v.* antibiotic treatment. *: $p < 0.05$ versus before treatment; [#]: $p < 0.05$ versus after HIVAT; ⁺: $p < 0.05$ versus after placebo.

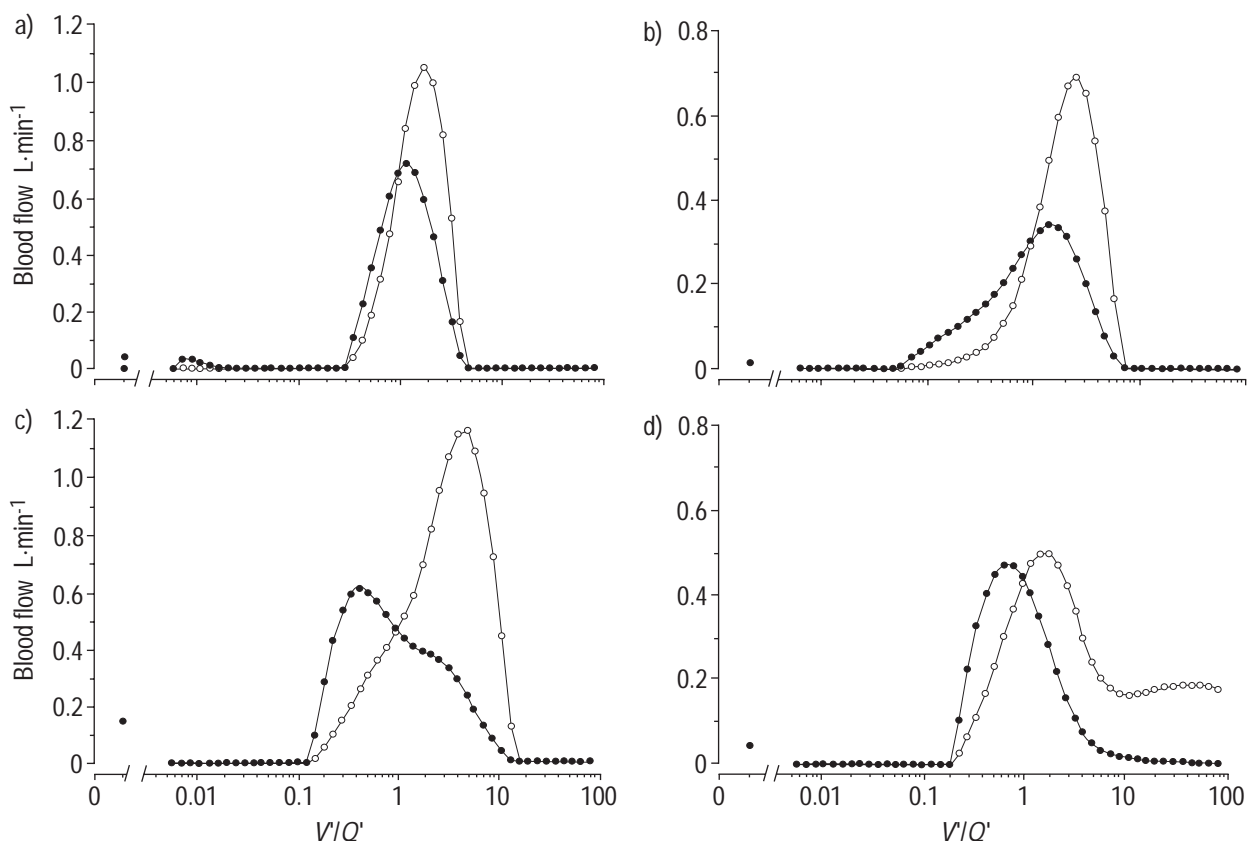


Fig. 1. – a) Ventilation/perfusion ratio (V'/Q') distribution of patient 6 before any treatment was given. Note the small mode at low V'/Q' . b) Deviation toward low V'/Q' (patient 7). c) Patient 2 before treatment. Note the deviation toward high V'/Q' . d) Patient 10 shows a significant additional mode at high V'/Q' . The points before the break on the V'/Q' axis correspond to a value of ≤ 0.005 (shunt). \circ : ventilation; \bullet : perfusion.

Spirometry. The spirometry data are shown in table 2. The mean RV was 182% pred and the mean VC 72% pred ($p < 0.001$), in comparison to normal individuals [11]. TLC did not differ from the predicted value (99.8%). The mean FRC was slightly high (121% pred), however, not significantly increased compared to predicted values. The mean FEV₁, FEV₁/VC, PEF, MEF₅₀ and MEF₂₅ were 53, 74, 64, 30 and 18% pred ($p < 0.001$), respectively. The mean DL_{CO} was 78% pred ($p < 0.01$). The individual differences were, however, considerable, *i.e.* the range of FEV₁ was 40–67% pred and of MEF₅₀ 15–64% pred.

Gas exchange. All perfusion distributions were unimodal except for a very small additional mode at low V'/Q' ratios in one patient (0.5% of the perfusion). However, eight perfusion distributions were broad, one with a deviation towards low V'/Q' . Two patients had a ventilation distribution with a deviation towards high V'/Q' and two patients had a bimodal ventilation distribution with an additional mode at high V'/Q' (fig. 1). The mean log SDQ was 0.72 ± 0.16 , (table 3), which should be compared with the upper 95% confidence interval of 0.6 [17]. That interval ought to be decreased to 0.56 when using peripheral venous sampling [14]. Even 0.6 is a rather high value in a young person and a mean value of ~ 0.4 would be expected in healthy individuals in the age group of the patients studied [18]. Only two patients had a log SDQ of < 0.56 . The mean log SDV was 0.80 ± 0.34 . Only minor shunt was measured ($1.4 \pm 0.4\%$), a result that would not substantially be changed even if the cardiac

output were $\pm 50\%$ of the assumed value. Perfusion to areas with low V'/Q' was seen in only two patients and the degree was low: 0.5 and 0.3% of the perfusion in these two patients. Ventilation to areas with high V'/Q' was seen in three patients: 1.6, 12.6 and 15.6% of the total ventilation in each respective patient.

The mean P_{a,O_2} was slightly decreased (10.2 ± 1.0 kPa) and P_{A-a,O_2} was increased (3.7 ± 1.5 kPa). Mean P_{a,CO_2} (5.2 ± 0.4 kPa) was within the normal range, as was pH (7.43 ± 0.02).

Thin section, high-resolution computed tomography. Owing to technical difficulties, only eight of the ten patients were examined. These eight patients showed bronchiectases and peribronchial thickening. Five patients showed some atelectases/consolidations. Seven of the patients showed mucus plugging (score 1–2).

Effects of home i.v. antibiotic treatment and intensified physiotherapy

Clinical examination. The clinical and biochemical results of the 14 days of HIVAT together with intensified physiotherapy are shown in table 1. All patients improved clinically as expected and were considered to be in an optimal condition when they had finished the antibiotic course. The inflammatory parameters of three patients, however, were not normalized at the end of the antibiotic course.

Table 3. – Ventilation/perfusion relationships in cystic fibrosis patients

	Ventilation L·min ⁻¹	Cardiac output L·min ⁻¹	P_{a,O_2} kPa	P_{a,CO_2} kPa	pH	$V'O_2$ mL·min ⁻¹	$V'CO_2$ mL·min ⁻¹
Before treatment	9.30±2.97	5.21±1.34	10.2±1.0	5.2±0.4	7.43±0.02 [§]	260±67	230±48
After HIVAT	9.54±2.41	4.97±0.88	10.7±0.9 ⁺	5.4±0.4	7.42±0.03	249±44	209±74 ⁺
After placebo	9.68±2.24	5.31±1.24	9.8±0.8 [#]	5.4±0.4	7.42±0.03	264±63	240±48 [#]
After amiloride	9.58±2.51	5.11±1.59	10.3±0.7	5.4±0.3	7.41±0.02*	256±79	233±54
	Log SDQ	Log SDV	Shunt % of perfusion	Low V'/Q' % of perfusion	High V'/Q' % of ventilation	VD % of ventilation	$PA-a,O_2$ kPa
Before treatment	0.72±0.16 [#]	0.80±0.34	1.4±0.4	0.08±0.18	3.3±6.2	26.6±6.0	3.7±1.5
After HIVAT	0.66±0.17 ^{*,+}	0.81±0.32	0.9±0.3	0.06±0.16	2.3±4.8	32.9±9.4	3.3±1.0 ⁺
After placebo	0.77±0.15 [#]	0.70±0.19	1.1±0.8	0.50±0.76 [§]	1.8±5.1	30.6±8.0	4.2±0.9 [#]
After amiloride	0.69±0.16	0.72±0.20	0.9±0.5	0.19±0.50 ⁺	2.0±5.4	30.3±8.6	3.7±0.5

P_{a,O_2} : arterial oxygen tension; P_{a,CO_2} : arterial carbon dioxide tension; $V'O_2$: oxygen consumption; $V'CO_2$: carbon dioxide production; log SDQ: logarithmic standard deviation of the perfusion distribution; log SDV: logarithmic standard deviation of the ventilation distribution; V'/Q' : ventilation/perfusion ratio; VD : dead space; $PA-a,O_2$: alveolar-arterial oxygen tension difference; HIVAT: home *i.v.* antibiotic treatment. *: $p < 0.05$ versus before treatment; #: $p < 0.05$ versus after HIVAT; +: $p < 0.05$ versus after placebo; §: $p < 0.05$ versus after amiloride.

Spirometry. VC was slightly but significantly improved, otherwise only a tendency to an overall improvement was seen in the spirometric measurements when compared to values obtained before treatment (table 2). Two patients showed a clear improvement in all spirometric indices of forced expiratory flow.

Gas exchange. A small but significant improvement was seen in the V'/Q' , as measured by mean log SDQ (table 3). Log SDQ decreased from 0.72 to 0.66. The low degree of shunt, perfusion of areas with low V'/Q' , dead space ventilation, arterial blood gas levels (P_{a,O_2} , P_{a,CO_2} , and pH), $PA-a,O_2$ and total ventilation were unchanged.

Thin section, high-resolution computed tomography. The mean Bhalla score was 12.6 before and 12.4 after treatment, *i.e.* no significant difference. Three of the eight patients investigated using HRCT showed a reduction in the extent of mucus plugging after treatment with HIVAT and intensified physiotherapy. The other findings, *i.e.* bronchiectases and peribronchial thickening, were unchanged.

Effects of amiloride

Clinical evaluation. Clinically there were no significant differences between the period of inhalation of amiloride and of sodium chloride, except that inflammatory parameters were slightly more elevated during the period of placebo treatment (table 1). The inhalation of amiloride produced no pulmonary or systemic side effects. No change in blood pressure was noted in any patient.

Spirometry. Significant reductions in flow rates (MEF50 and MEF25) were seen after the placebo period compared to measurements after HIVAT. No other significant differences were seen in the spirometry results when comparing the periods after HIVAT, the placebo period and the period after inhalation of amiloride (table 2).

Gas exchange. Log SDQ, $PA-a,O_2$ and P_{a,O_2} were significantly less favourable after the placebo period when compared to measurements before the inhalations (table 3). The degree of perfusion of areas with low V'/Q' was significantly lower after the amiloride than after the placebo period. One individual patient (No. 5) showed a substantial improvement in gas exchange after amiloride (fig. 2).

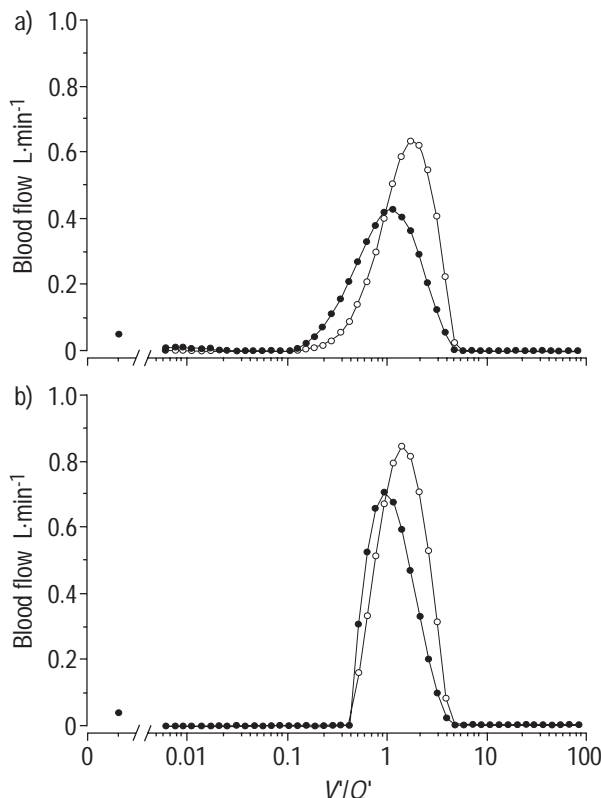


Fig. 2. – Patient 5. a) A broad ventilation/perfusion (V'/Q') distribution with a small additional mode within low V'/Q' areas was seen after 2 weeks of placebo treatment. b) After 2 weeks of amiloride inhalations, a normal V'/Q' distribution was seen. The points before the break on the V'/Q' axis correspond to a value of ≤ 0.005 (shunt). ○: ventilation; ●: perfusion.

Computed tomography, high-resolution computed tomography. There were no significant changes in HRCT after treatment with sodium chloride or with amiloride, except for mucus plugging.

Correlation between spirometry, gas exchange and computed tomography

When the indices of gas exchange impairment (log SDQ and log SDV) were compared with spirometry results (volumes, flows and DL_{CO}) and P_{a,O_2} , no significant correlations were found. Nor were the scores of HRCT (total score, mucus plugging and emphysema according to BHALLA *et al.* [16]) correlated to the spirometry results or the gas exchange variables mentioned above.

Discussion

Ventilation/perfusion relationships in cystic fibrosis

In order to evaluate gas exchange impairment that could be secondary to secretion and oedema in the distal airways, the multiple inert gas elimination technique was used. Arterial blood gas concentrations are also dependent on other factors, such as cardiac output and metabolic rate, as was shown by the absence of significant correlation between log SDQ and P_{a,O_2} . There have been several reports on an increased resting energy expenditure in patients with CF, which may be intrinsic and related to genotype and degree of essential fatty acid deficiency [19, 20].

Clear-cut spirometric signs of significant airway obstruction were found in all the patients studied, indicating major obstructive changes in their larger airways. The increased RV and somewhat high FRC together with the reduced VC are compatible with increased compliance and hyperinflation. The low estimated level of areas of low V'/Q' and the absence of a clear bimodal distribution of the perfusion even before HIVAT indicates a very low degree of complete obstruction of airways by mucus. One important conclusion would therefore be that the currently used standard treatment against mucus is successful. However, all patients were clearly impaired in gas exchange, indicating small airways disease. One likely cause of the gas exchange impairment in CF is mucus that gives incomplete airway obstruction and uneven ventilation. This is of special interest since this kind of obstruction is potentially reversible and treatable.

The gas exchange impairment, as shown by log SDQ, was similar to that found in patients with moderate stable asthma [21] and allergic asthmatics, after antigen provocation [22]. Thus, moderate ventilation/perfusion inequality seems to be present in the majority of well-treated CF patients. In an earlier study from 1982 by DANTZKER *et al.* [7] on six hypoxaemic patients with CF (mean age 24 yrs), a considerable V'/Q' impairment with a rather high level of shunt was found. The considerable difference between the gas exchange impairment noted in that study and the results presented here is probably due to the different stage of the disease in the two patient groups and to the intensified treatment practised during the last decade [23].

The cause of a broad ventilation distribution with a deviation towards high V'/Q' or a mode of ventilation in areas

of high V'/Q' is not clear. A probable reason is local hypoperfusion, caused by hyperinflation in obstructed areas. Studies of asthmatic children have shown areas of high V'/Q' [24]; the mechanism was proposed to be hyperinflation and secondary hypoperfusion. Also patients with increased compliance (emphysema) show areas of high V'/Q' [25]. The abnormalities in lung volumes shown in the present study also indicate increased compliance and hyperinflation.

The absence of correlation between spirometric, gas exchange analysis and computed tomography results indicates that the different methods show the results of different pathophysiological events. In asthmatics, the spirometric abnormalities are assumed to be caused by bronchoconstriction in larger airways, and the gas exchange impairments by secretion and oedema in small airways [21]. The present results indicate that the same mechanisms may be active in CF. The degree of ventilation/perfusion inequality cannot be estimated in a CF patient from the results of spirometry or HRCT, and not even measurement of arterial blood gas concentrations is sufficient. A CF patient's clinical status could thus deteriorate without this leading to any significant decrease in the results of spirometry.

Implications of spirometry, ventilation/perfusion relationships and computed tomography after initial treatment with home i.v. antibiotic treatment and physiotherapy

HIVAT together with intensified physiotherapy initiated at mild symptoms of low grade infection has previously been shown to improve the somatic status of CF patients, including forced expiratory flows and inflammatory parameters [8]. In the present study, the patients improved clinically, with eight of the 10 showing decreased inflammatory parameters at the end of treatment. After 14 days of HIVAT and intensified physiotherapy, significant improvements were seen in the V'/Q' . A probable explanation for the latter result is that small airway function was increased by at least partial elimination of reversible changes. Reversible changes in small airways may be mucus and inflammatory products. However, the changes were small, probably due to the fact that CF patients nowadays are treated at very early signs of exacerbations, *i.e.* before any considerable reversible changes develop.

Implication of spirometry, ventilation/perfusion relationships and computed tomography after inhaled amiloride

As mucus is assumed to be one of the main factors giving rise to ventilation/perfusion inequality, it was of interest to evaluate gas exchange after the patients had received a drug supposed to improve mucus mobilization [26]. After the placebo period, log SDQ, P_{a,O_2} and P_{A-a,O_2} were significantly less favourable than after HIVAT, observations which would be in agreement with a deterioration in small airways function. After inhalation of amiloride, however, no significant deterioration was seen, and areas of low V'/Q' were even significantly decreased compared to placebo. This result is compatible with the normal course of events in CF being a gradual deterioration in gas exchange and small airways function with

time, a process that amiloride might delay. It was also in the placebo situation that the main indices of airflow were mainly (significantly) decreased, indicating that some deterioration had also taken place in somewhat larger airways during the placebo period, which was counteracted by amiloride.

Conclusions

The multiple inert gas elimination technique can be a valuable research tool in the evaluation of cystic fibrosis and of its treatment. Moderate ventilation/perfusion inequality of the same degree as that found in moderate stable asthma is present in the majority of cystic fibrosis patients despite modern treatment. The low proportion of areas of low ventilation/perfusion ratio also found before home intravenous antibiotic treatment indicates, however, that complete mucus plugging of the airways is rare. Home intravenous antibiotic treatment could partially improve the ventilation/perfusion relationship. The degree of ventilation/perfusion inequality does not correlate with spirometric or high-resolution computed tomographic results. Thus, the degree of ventilation/perfusion inequality in cystic fibrosis cannot be estimated from spirometry, high-resolution computed tomography or even arterial blood gas concentrations. The deterioration in gas exchange seen after placebo but not after amiloride inhalation indicates that inhaled amiloride may influence the development of the pathophysiological changes in small airways.

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