Relationship between airway obstruction, desaturation during exercise and nocturnal hypoxaemia in cystic fibrosis patients

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ABSTRACT: We measured pulmonary function, responses to exercise and oxygen saturation (So_2) at rest, and also before and during sleep in 24 patients with cystic fibrosis in a varying degree of severity. The pulmonary function indices analysed were forced expiratory volume in one second (FEV_1), total lung capacity (TLC), measured by body plethysmography (TLC box) and Helium dilution (TLC He), residual volume measured by body plethysmography (RV) and the amount of trapped air (TA=TLC box-TLC He). The exercise variables included symptom limited maximal oxygen uptake ($\dot{V}o_2max$), maximum minute ventilation ($\dot{V}Emax$) and So_2, at rest in sitting position and during maximal exercise. So_2 was measured by ear oximetry. The lowest mean So_2 obtained in two consecutive nights over a period of 1 hour was taken as the indicator of nocturnal oxygen saturation. A high correlation existed between resting supine and sitting So_2, and the degree of nocturnal hypoxaemia (0.84 and 0.76, respectively). Highly significant correlations existed also for the indices of airway obstruction, $\dot{V}o_2max$ and lowest So_2 at exercise *versus* the nocturnal lowest hourly mean So_2. From all variables a resting So_2 in the sitting position lower than 94% appeared to be most predictive of nocturnal desaturation and indicates a risk of nocturnal hypoxaemia in patients with cystic fibrosis.
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Cystic fibrosis (CF) is a multisystem disorder in which infection and impairment of ventilation are the predominant features. There is progressive lung damage from an early age onwards, resulting in respiratory insufficiency after a variable number of years [1].

The pulmonary pathophysiology of CF is complex. The main feature is airway obstruction and an increase in residual volume and amount of trapped air [1]. The resulting unequal ventilation is associated with a ventilation-perfusion mismatch due to both underperfused lung regions and relatively underventilated regions, leading to an increased venous admixture [2]. In order to maintain alveolar ventilation, minute ventilation ($\dot{V}E$) is high and consequently the ventilatory equivalent for oxygen ($\dot{V}E$ divided by oxygen uptake, Vo_2) is also high. The work of breathing at rest is increased.

In the early stages of the disease, oxygen saturation (So_2) is normal or only slightly decreased. During exercise So_2 remains normal or may even increase [3]. CROPP *et al.* [4], LEBECQUE *et al.* [5] and HENKE and ORENSTEIN

[3] found a significant decrease in So_2 during exercise to be more likely in patients with severe obstruction, *i.e.* when forced expiratory volume in one second (FEV_1) was less than 60% of predicted.

In patients with CF, nocturnal hypoxaemia is rare [6]. In severely affected subjects So_2 may decrease in rest with a further drop during exercise. Hypoxaemia may then also occur during sleep, predominantly in rapid eye movement (REM) periods [7].

As yet no studies have been published comparing So_2 and cardiopulmonary variables during exercise and sleep in CF patients. The relevance of such a study is given by the possibility of predicting nocturnal hypoxaemia from a standard laboratory procedure as lung function or exercise testing. The rationale is given by earlier investigations in which it was shown that in advanced stages of the disease exercise tolerance and cardiorespiratory reserve are decreased and nocturnal hypoxaemia is more likely to occur [2–8]. We therefore performed sleep studies, measurements of

pulmonary function and exercise testing in a group of CF patients with varying disease severity. During sleep and exercise transcutaneous So_2 was also measured.

Patients and methods

Patients

Twenty four CF patients under the care of the Department of Paediatric Pulmonary Medicine of the Sophia Children's Hospital Rotterdam, The Netherlands, participated. The patients included 12 males and 12 females with a mean age of 16 yrs (range 10–22). The diagnosis of CF was based on characteristic clinical findings [1] and a sweat chloride concentration of >70 $mmol \cdot l^{-1}$. All patients were in a stable condition at the time of the study. There was a wide range in disease severity; 4 patients died with clinical symptoms of cor pulmonale and 1 patient died during an acute exacerbation of the disease within 6 months after the measurements were completed.

All patients and/or parents gave their informed consent. The study was approved by the Medical Ethics Committee of the University Hospital, Rotterdam.

Pulmonary function

Standard spirometric (Mijnhardt volumograph 2000) and plethysmographic (Siemens Siregnost FD 40) techniques [9] were used.

Parameters measured were forced expiratory volume in one second (FEV_1), total lung capacity (TLC) measured by body plethysmography (TLC box) and TLC measured by Helium dilution (TLC He), residual volume measured by body plethysmography (RV) and trapped air (TA=TLC box-TLC He). FEV_1 and TLC box are presented as % predicted. RV and TA are expressed as percentage of TLC box. Reference values were taken from QUANJER [9].

Nocturnal oxygen saturation

So_2 was monitored continuously with a Biox III ear oximeter (Bioximetry Technology Inc., Boulder Co. USA) and stored by computer over two consecutive nights. The patients were observed regularly by the nursing staff. The following calculations were made:
a) mean So_2 (mean nocturnal So_2).
b) mean values of So_2 for periods of one hour (hourly means) and
c) the total number of minutes during sleep in which the So_2 was equal to or lower than 90%.
Nocturnal hypoxaemia was considered to be present if at least one hourly mean So_2 value equal to or lower than 90% was observed in each of the two nights. This level of 90% was chosen on the basis of results from investigations on sleep desaturation in obstructive lung disease [10].

Exercise tests

Progressive exercise tests were carried out using an electronically braked cycle ergometer (LODE L 77). Subjects started pedalling with a workload of 20 W which increased by 20 W every 4 min in order to reach a steady state in the fourth minute. Pedalling continued until the subject indicated exhaustion.

The following data were continuously recorded on a Hewlett-Packard 7758 A eight channel recorder: work load; CO_2 and O_2 in mixed expiratory air (Jaeger infrared CO_2 analyser, and Mijnhard paramagnetic O_2 Oxylyzer, respectively); minute ventilation ($\dot{V}E$) (Jaeger; Lilly type pneumotachometer); transcutaneous So_2 (Biox III oximeter) and pulse rate from the electrocardiogram (Kontron type 108). Data were taken at rest, from the last 30 s of each work load and directly at the end of the test.

Blood pressure was measured manually by cuff sphygmomanometer at the times given above. Minute ventilation was expressed as percentage of maximum voluntary ventilation at a frequency of $30 \cdot min^{-1}$ (MVV_{30}). MVV_{30} was calculated indirectly as: $30 \times FEV_1 /1.2$. This was considered to be an accurate approximation, as has been shown in subjects without impairment of pulmonary mechanics [11]. Oxygen uptake ($\dot{V}o_2$) was calculated according to the Haldane transformation, in which the inspired volume is derived from the expired minute volume via a nitrogen balance [12]. In order to estimate the degree of lactic acidosis at the end of the test the increase in lactate concentration compared to the resting condition was measured from venous blood (vena brachialis) from a non–exercising muscle. The venous concentration has shown to be a reliable measure of lactate concentration in arterial blood [13]. Results used were the maximum oxygen uptake ($\dot{V}o_2$max % pred.) and So_2. A So_2 value of equal to or less than 90% was defined as hypoxaemia. In each subject all tests were completed within 48 h.

Statistical methods

Results are presented as median and range because of the skew distribution of most data. Spearman rank correlation was used to analyse the relationship between pulmonary function, exercise variables and So_2 during sleep. Predictive indices for hypoxaemia during sleep were defined from discriminant analysis with stepwise logistic regression, for which we applied the programme as given in the BMDP package [14]. This method was taken because logistic discriminant analysis does not assume normally distributed variables. The likelihood ratio test [14] was used to analyse the discriminatory value of resting So_2 combined with indices of lung function and exercise.

Results

In the two consecutive nights both the mean nocturnal So_2 and the lowest hourly mean So_2 correlated highly

(Spearman rank correlation, r=0.83 and r=0.84, respectively). The same was true for the lowest hourly mean and the number of minutes during sleep in which the So_2 was equal to or less than 90% (r =0.89). For the calculations of the relationship between airway obstruction, exercise indices and oxygenation during sleep, the lowest hourly mean value of So_2 obtained in the two nights was taken.

During exercise testing at maximum workload, the median heart rate was 91% of the predicted maximum (range 78–101), the median respiratory quotient (RQ) 1.04 (range 0.85–1.39), the median $\dot{V}E$ 94% of MVV_{30} (range 61–163), and the median increase in blood lactate concentration 6.4 $mmol \cdot l^{-1}$ (range 1.8–11.1), indictating that in general patients performed maximally. Pulmonary function, results from exercise testing and So_2 during sleep are summarized in table 1.

Table 1. – Pulmonary function, indices of exercise testing, and So_2 during sleep in 24 CF patients

	Median	Range
Pulmonary function		
FEV_1 % pred.	57	24–111
RV/TLC %	45	21–80
TA/TLC %	21	0–56
Exercise test		
$\dot{V}o_2$max % pred.	60	26–92
Resting So_2 % sitting	94	81–99
Lowest So_2 %	91	59–96
Change in So_2 %	5	1–22
So_2 during sleep		
Resting So_2 % supine	94	80–98
Means of 2 nights %	94	85–97
Lowest hourly mean %	92	80–96
Mean number of minutes with So_2<90%	10	0–545

Because of skewness of distributions, median and range of the variables are shown. So_2: oxygen saturation; FEV_1: forced expiratory volume in one second; RV: residual volume; TLC: total lung capacity; TA: trapped air; $\dot{V}o_2$ max : maximal oxygen uptake; CF : cystic fibrosis

The lowest hourly mean So_2 in relation to FEV_1, RV and TA is shown in fig. 1a–c. Hypoxaemia began to show at a FEV_1 below 65% of predicted, a RV/TLC box over 35% and a TA higher than 15% TLC box. The lowest hourly mean So_2 during sleep correlated very highly with FEV_1, but the correlation with the other indices of airway obstruction was also significant (table 2). In fig. 1a and b the data of STOKES *et al.* [6], who correlated pulmonary function with the largest fall in So_2 in one night, are also shown.

The lowest So_2 and the $\dot{V}o_2$ max (% pred.) during exercise were significantly correlated with the lowest
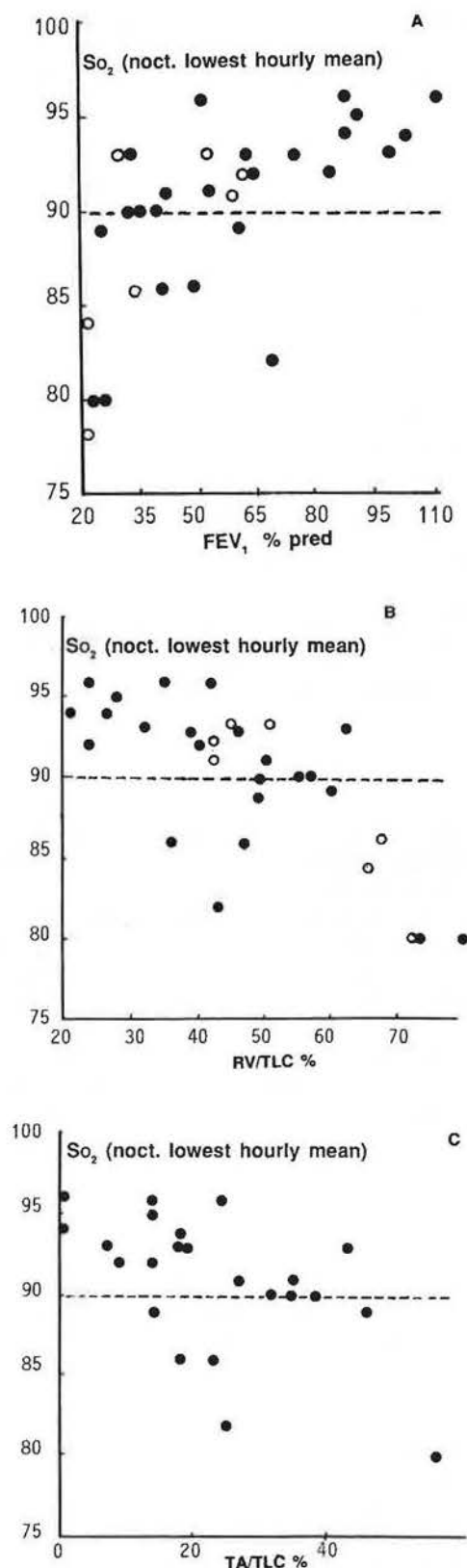

Fig. 1. – Lowest hourly mean nocturnal So_2 (%), as a function of a) FEV_1 (% predicted), b) RV/TLC (%) and c) TA/TLC (%). Open dots (o) are data from STOKES *et al.* [6]. So_2: oxygen saturation; FEV_1: forced expiratory volume in one second; RV: residual volume; TLC: total lung capacity; TA: trapped air.

Table 2. – Spearman rank correlation coefficients between pulmonary function, indices of exercise testing and nocturnal So_2

Pulmonary function indices and exercise variables	Lowest hourly mean value of So_2 during sleep
Pulmonary function	
FEV$_1$ % pred	0.70
RV/TLC %	-0.66
TA/TLC %	-0.61
Exercise test	
$\dot{V}o_2$max % pred	0.70
Resting So_2 % sitting	0.76
Lowest So_2 %	0.71
Sleep study	
Resting So_2 % supine	0.84

All correlations are significant at p=0.001 level. For abbreviations see legend table 1.
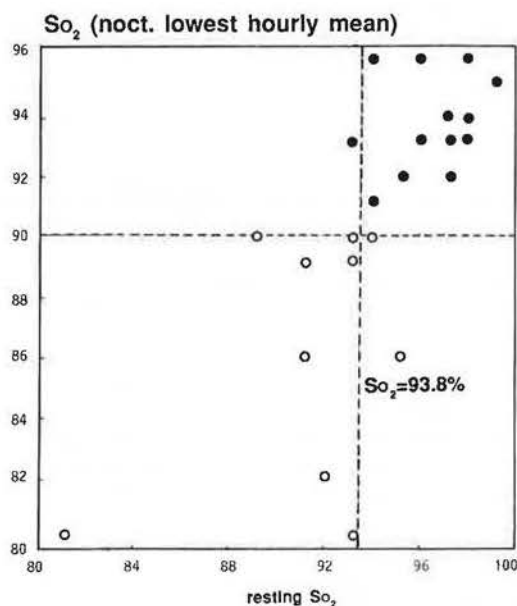
So$_2$ (noct. lowest hourly mean)

Fig. 2. – Relationship between the lowest hourly mean value of nocturnal So_2 (%) and resting So_2 at the beginning of exercise in sitting position. The vertical line represents the threshold following from discriminant analysis in order to separate desaturation (o) and normal saturation during sleep(•). So_2: oxygen saturation.

hourly mean So_2 during sleep (table 2). However, the correlation with So_2 at the start of exercise (sitting) and at the beginning of sleep (supine) was even better. These resting values for So_2 were also mutually significantly correlated (r=0.69, p<0.001).

Logistic discriminant analysis was performed in order to predict the risk of nocturnal hypoxaemia using the indices of airway obstruction, exercise variables and resting So_2. Patients were divided into subjects in whom the nocturnal lowest hourly mean So_2 dropped to 90% or

less and subjects in whom this value remained higher than 90%. From the indices of airway obstruction FEV$_1$ appeared to be the best predictor. However, considering all variables, resting So_2 at the start of exercise (sitting) was superior in this respect. Fig. 2 shows this variable, plotted against the nocturnal lowest hourly mean So_2. Resting So_2 turned out to be most discriminatory, giving three misclassifications for the patients (fig. 2). The value of So_2, for which the probability of nocturnal hypoxaemia is equal to 50% was 93.8%. The same analysis, carried out for the resting So_2 at the beginning of sleep (supine), yielded nearly the same threshold value of So_2 (93.6%) but the number of misclassifications was four.

Addition of other variables to the resting So_2 at the start of exercise (sitting) did not significantly improve the discriminatory power, as expressed in the log–likelihood. Although the likelihood ratio test was not significant (p=0.11), $\dot{V}o_2$max turned out to be the best additional variable (table 3).

Table 3. – Probability values of the log likelihood ratio test and the log likelihood after addition of one extra variable in stepwise discriminant analysis when a constant term and resting So_2 in sitting position were already entered (log likelihood=7.05)

Variable	p value	log likelihood
FEV$_1$	0.53	-6.85
TA/TLC	0.80	-7.02
RV	0.69	-6.97
$\dot{V}o_2$ max (% pred)	0.11	-5.76
Lowest So_2 at exercise (sitting)	0.20	-6.24

For abbreviation see legend table 1.

Discussion

In this study we investigated whether indices of airway obstruction, oxygen metabolism during exercise or resting So_2 have a predictive value for nocturnal hypoxaemia. We found that resting So_2 either supine before sleep or sitting at the start of exercise, correlated best with nocturnal hypoxaemia. Resting So_2 at the start of exercise appeared to be most discriminatory with a resting So_2 of 93.8%. Using this point as a threshold led to three misclassifications. Addition of other variables did not add significantly to the discriminatory power.

So_2 measurements with the Biox ear oximeter have been shown to give reliable and highly reproducible results [15], which was confirmed in this study. SMYTH et al. [16] showed that So_2 is overestimated with the Biox ear oximeter when it falls appreciably below 85% in arterial blood. It seems unlikely that this will have affected our conclusions since So_2 fell below 85% during exercise in only 4 patients. The various methods we used to express nocturnal hypoxaemia were highly correlated. The lowest hourly mean value of So_2 during sleep was taken because it was considered to be the most practical indicator.

Values for heart rate, $\dot{V}E$, lactate concentrations and RQ, indicate that the majority of patients exercised up to their maximal capacity. $\dot{V}o_2$max can therefore be considered as a symptom-limited maximum. The mean increase in workload during exercise testing which we applied (20 W per 4 min) is lower than the increase used by MALMBERG *et al.* [17] in adults (50 W per 6 min). This may have resulted in slightly lower values of $\dot{V}o_2$max than in tests of shorter duration because of the greater time dependent lactate accumulation [18].

Desaturation during exercise and sleep was only found in patients with a FEV_1 less than 65% of predicted. With respect to nocturnal desaturation these findings are in agreement with those of STOKES et al. [6] in a smaller number of patients (fig. 1). Looking at desaturation during exercise our results are in agreement with those of HENKE and ORENSTEIN [3], MARCOTTE *et al.* [8] and LEBECQUE *et al.* [5]. Henke and Orenstein found that only 1 out of 62 patients with a FEV_1/FVC ratio greater than 50% showed a drop of more than 5% in So_2 at maximal exercise, whereas this occurred in 8 out of 29 patients with a lower FEV_1/FVC ratio. A larger fall in So_2 than 5% in a group of 50 CF patients was only found in patients with a FEV_1 smaller than 60% of predicted by Marcotte *et al.*, while Lebecque *et al.* found a fall in So_2 of less than 90% a subgroup of his patients in whom FEV_1/VC ranged from 40–54%.

Impaired pulmonary mechanics with airway obstruction, air trapping (increased TA/TLC) and hyperinflation (increased RV/TLC) but also a deranged ventilation-perfusion relationship with increased physiological dead-space and increased venous admixture are characteristic features in an advanced stage of CF [1]. The decrease in cardiorespiratory reserves, exercise-induced deterioration of ventilation-perfusion abnormalities and alveolar hypoventilation explain the desaturation at exercise [3, 5, 8].

During sleep the relative hypoventilation and increase in venous admixture contribute in a complex way to arterial desaturation. Particularly during REM sleep in which intercostal muscle tone is reduced, alveolar ventilation will diminish further. This results in a more pronounced deterioration of the ventilation-perfusion balance. Furthermore, the diminishment of functional residual capacity in the supine position will increase venous admixture and hence contribute to the ventilation-perfusion inequality [19]. Most investigators found that the FEV_1 or the FEV_1 related maximal voluntary ventilation (MVV) correlated most closely with the oxygen desaturation during exercise in CF patients [2–4, 8]. We confirmed this with respect to nocturnal hypoxaemia. Analysis of the data published by STOKES *et al.* [6] in 8 patients gives the same correlation coefficient (r=0.84) as we found for the relation between resting So_2 in sitting position and nocturnal hypoxaemia.

With HENKE and ORENSTEIN [3] we conclude that the FEV_1 can be considered as a marker of the complex pathophysiological disturbances in advanced stages of CF. With FRANCIS *et al.* [7] we find that resting So_2 either sitting or supine, is more closely associated with the degree of nocturnal hypoxaemia than exercise variables.

The most reasonable explanation is that the more the resting So_2 approaches the steep portion of the O_2 dissociation curve, the higher the risk is of passing the limit of 90% So_2 during sleep and the larger the expected fall in So_2. Furthermore, some patients with low resting So_2 may increase their saturation during exercise by improving ventilation in already perfused areas of the lung [3]. This is in contrast to what happens during hypoventilation in sleep and explains why the relationship between resting So_2 and hypoxaemia in sleep and exercise differ.

We found a slightly better predictive power of So_2 in the sitting compared to the supine position but taking into account the high correlation of So_2 (supine) and nocturnal hypoxaemia we think that So_2 measured in both positions is equally useful.

We conclude that a resting So_2 in sitting position lower than 94%, as measured by ear oximetry, indicates a risk of nocturnal hypoxaemia in patients with CF.

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Relations entre l'obstruction des voies aériennes, la désaturation à l'effort et l'hypoxémie nocturne, chez les patients atteints de fibrose kystique. F.G.A. Versteegh, J.M. Bogaard, J.W. Raatgever, H. Stam, H.J. Neijens, K.F. Kerrebijn.

RÉSUMÉ: Nous avons mesuré la fonction pulmonaire, les réponses à l'effort et la saturation au repos (So$_2$), ainsi qu'avant et pendant le sommeil, chez 24 patients atteints de fibrose kystique de degré variable. Les indices de la fonction pulmonaire analysés ont été le VEMS, la capacité pulmonaire totale mesurée par pléthysmographie corporelle (CPT box) et par dilution de l'hélium (CPT He), le volume résiduel mesuré par pléthysmographie corporelle (VR), et l'air trappé (TA = CPT box – CPT He). Les variables d'effort ont compris la consommation maximale d'oxygène limitée par les symptômes (Vo$_2$ max), la ventilation maximale minute (VE max) ainsi que So$_2$, au repos en position assise ou pendant l'effort maximal. So$_2$ a été mesurée par oxymétrie à l'oreille. La So$_2$ minimale moyenne obtenue au cours de deux nuits consécutives pendant une période d'une heure, a été considérée comme l'indicateur de la saturation d'oxygène nocturne. Il existe une corrélation élevée entre la So$_2$ au repos en position couchée et assise, et le degré d'hypoxémie nocturne (respectivement 0.84 et 0.76). Des corrélations hautement significatives existent également pour les indices d'obstruction des voies aériennes, le Vo$_2$ max et la So$_2$ minimale à l'effort, par rapport à la So$_2$ moyenne horaire minimale nocturne. De toutes les variables, une So$_2$ au repos en position assise inférieure à 94% est la plus prédictive de la désaturation nocturne et indique un risque d'hypoxémie nocturne chez les patients atteints de fibrose kystique.