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ORIGINAL ARTICLE

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Effects of hyperoxia on oxygen uptake kinetics in cystic fibrosis patients as determined by pseudo-random binary sequence exercise

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Abstract Patients with cystic fibrosis (CF) have been shown to exhibit impaired oxygen uptake ($\dot{V}O_2$) kinetics independent of their physical fitness. This study investigated whether oxygen supplementation improves $\dot{V}O_2$ kinetics in CF as determined by cycle ergometry at submaximal exercise intensities using a pseudo-random binary sequence exercise test i.e. a simultaneous application of different frequencies of sinusoidal work. The subjects were 9 CF patients and 13 healthy controls (HC) and they exercised while breathing humidified and heated air with a fractional concentration of oxygen in inspired air (F_IO_2) of either 0.21 or 0.40. With a F_IO_2 of 0.21 the respiratory exchange ratio (R) was higher in CF than in HC both at rest (0.91 vs 0.81) and during exercise (0.97 vs 0.89). Oxygen saturation (SO_2) was slightly lower in CF, but remained above 90% during exercise (92.7% vs 95.2%). Spectrum analysis revealed that in CF, the amplitude ratio (AR) between $\dot{V}O_2$ and exercise intensity was lower over a wide frequency range ($P < 0.05$). In addition, CF showed a larger negative phase shift (PS) at lower frequencies ($P < 0.005$). With a F_IO_2 of 0.40, SO_2 increased to about 97% in both groups; while R remained higher in CF (0.92) compared to HC (0.81). In the control group, the O_2 supplement raised AR but the $\dot{V}O_2$ kinetics of the CF patients were not significantly affected. In HC the enhanced AR during oxygen supplementation would suggest a cardiopulmonary limitation of $\dot{V}O_2$ at the onset of submaximal exercise. In CF patients low AR and PS would indicate an attenuated $\dot{V}O_2$ response attributable to an impaired oxygen utilization in the muscles because the oxygen supplement normalised SO_2 but failed to improve R and $\dot{V}O_2$ kinetics.

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Introduction

Exercise has been used to evaluate and follow-up patients with chronic diseases (Casaburi 1993; Godfrey 1974). In patients with cystic fibrosis (CF) exercise has been employed for diagnostic purposes, for the evaluation of treatment and for the adjustment of rehabilitation programmes (Friedrichs et al. 1992; Orenstein 1988) with various exercise protocols (Bar Or 1986; Jones and Campbell 1982). The use of submaximal exercise tests is preferable in respect of children and severely ill patients because of fewer adverse events and a smaller influence of the degree of motivation. It has been found that protocols for exercise intensities below the anaerobic threshold allow the determination of oxygen uptake ($\dot{V}O_2$) kinetics (Wasserman et al. 1987). At the onset of exercise the dynamic response of gas exchange demonstrates slow $\dot{V}O_2$ kinetics in cardiac (Sietsema et al. 1984) or pulmonary (Casaburi et al. 1997) disease, in hypoxia (Hughson and Morrissey 1983) and in subjects with a low degree of physical fitness (Hickson et al. 1978). The different authors applied repeated step changes between sustained exercise intensities or repeated sinusoidal exercise intensities. The clinical applicability of both approaches has been found to be limited because they are time consuming.

Exercise tests using pseudo-random binary sequences (PRBS) of exercise intensity have been shown to be another way of measuring $\dot{V}O_2$ kinetics (Hughson et al. 1990a; Stegemann et al. 1985). It requires a randomized switching between two levels of power in the aerobic range and can be interpreted as the simultaneous application of different frequencies of sinusoidal power output. The capability of a subject to follow the changing demand for oxygen by $\dot{V}O_2$ is analysed for a relevant frequency range and described by the ratio between amplitudes of $\dot{V}O_2$ and power and the time lag

between $\dot{V}O_2$ and power. It has been shown that the higher the ratio and the shorter the time lag the better is the aerobic performance (Eßfeld et al. 1987). The PRBS exercise has been demonstrated to be well tolerated by children and patients with CF and to provide reliable information on $\dot{V}O_2$ kinetics (Kusenbach et al. 1994; Wieching 1996).

In CF cardiopulmonary oxygen transport limits maximal aerobic working capacity ($\dot{V}O_{2max}$) only in the advanced disease state and it can be improved by oxygen supplementation (Cropp et al. 1982; Marcotte et al. 1986). Independent of physical fitness ($\dot{V}O_{2max}$/body mass), $\dot{V}O_2$ kinetics have been shown to be impaired in CF patients with mild to moderate lung disease (Kusenbach et al. 1994; Wieching 1996). This study was designed to investigate whether this is due to a disturbance of muscle oxygen utilization or to an insufficient cardiopulmonary oxygen delivery that can be improved by oxygen supplementation during submaximal PRBS exercise.

Methods

Subjects

Groups of 9 CF patients and 13 healthy controls (HC) matched for age, height and sex gave their informed consent to participate in the study.

Protocol

The subjects completed one exercise test breathing room air and another with supplemental oxygen on the same day at least 1 h apart. After the patient's history had been obtained, physical examination, including assessment of leg muscle volume (Jones and Pearson 1970), forced spirometry and an electrocardiogram (ECG), was carried out (Table 1). Leg muscle volume was used to estimate maximal exercise capacity (Davies et al. 1972). The subjects then sat on a cycle ergometer (ER 900, Jaeger, Germany) adjusted for height and crank length. Via a mouthpiece, they breathed through a pneumotachograph and were connected by a sample line to a gas analyser (CPX, MedGraphics, USA) which determined breath-by-breath data for ventilation ($\dot{V}_E$), $\dot{V}O_2$ and carbon dioxide production ($\dot{V}CO_2$). The respiratory exchange ratio ($R = \dot{V}CO_2/\dot{V}O_2$) was calculated breath-by-breath. The subjects were allowed to habituate until cardiopulmonary data were stable at rest. Data from the last 2 min before exercise were averaged to calculate R. The subjects then exercised at 60 rpm. After 4 min at 20 W, the exercise intensity was changed between this value and 40% of the predicted maximal intensity in a PRBS with two identical cycles of 5 min each (Fig. 1). A second 4-min period of sustained exercise at the upper intensity concluded the test. The subjects breathed water vapour saturated and heated (34–36°C) air or a mixture of air and oxygen from a flow-through reservoir. For hyperoxic conditions, compressed oxygen and air were mixed by adjustable valves to keep the fractional concentration of oxygen in inspired air (F_IO_2) between 0.39 and 0.41. Gas concentration and temperature were monitored close to the inspiratory port of the mouthpiece. The order of high and low F_IO_2 was random and not known to the subjects. Heart rate (HR) (eliXR, Mortara Instruments, USA) and oxygen saturation (SO_2) (Biox 3700 E, Ohmeda, USA) were displayed.

Breath-by-breath data of gas exchange were smoothed by a moving average of three breaths using a method that has been described by Eßfeld et al. (1987) and Wieching (1996). The autocorrelation function of the PRBS exercise intensity (P) and the cross-correlation function between $\dot{V}O_2$ (output) and P (input) were calculated. After Fourier transformation, amplitude ratio (AR), i.e. the ratio between $\dot{V}O_2$ and P, and phase shift (PS), i.e. the time lag between $\dot{V}O_2$ and P, were computed for the first six harmonic frequencies (0.0033–0,020 Hz, Fig. 2). The duration of the PRBS cycle (300 s) determined the basic frequency and the following harmonics could be calculated by multiplication of the basic frequency by 2, 3, 4, 5 and 6. The influence of CF, F_IO_2 and of the order of high and low F_IO_2 on AR and PS was assessed by multivariate analysis of variance (MANOVA). Average data for the PRBS period were compared by paired student's t-test. An error probability below 5% was considered significant.

Table 1 Anthropometric and respiratory data of cystic fibrosis patients (*CF*) and controls at rest. FEV_1 Forced expiratory volume in 1 s *FVC*, forced vital capacity, SO_2 oxygen saturation, R respiratory exchange ratio

	CF		Controls	
Sex (male/female)	5/4		8/5	
	mean	range	mean	range
Age (years)	19	13–31	21	9–29
Height (cm)	168	148–181	170	141–196
Body mass (kg)	55	32–72	62	29–91
FEV_1 (%pred.)	61	42–88	107	84–143
FVC (l)	3.2	1.4–4.5	4.3	2.1–6.2
SO_2 (%)	93	92–95	95	94–97
R	0.91	0.71–0.97	0.81	0.71–0.91

Results

In the CF patients lung function tests gave results ranging from normal to severely impaired, while SO_2 was near to normal and HR at rest was high (Table 1). The HC had normal pulmonary function. The ECG was normal in all the subjects.

During exercise breathing room air, SO_2 was low but did not fall below 90% in CF. Oxygen supplementation increased SO_2 to about 97% in both groups (Table 2). The R was higher in CF than in HC during both normoxia and hyperoxia. The HR decreased with increasing F_IO_2 only in the CF patients. The following

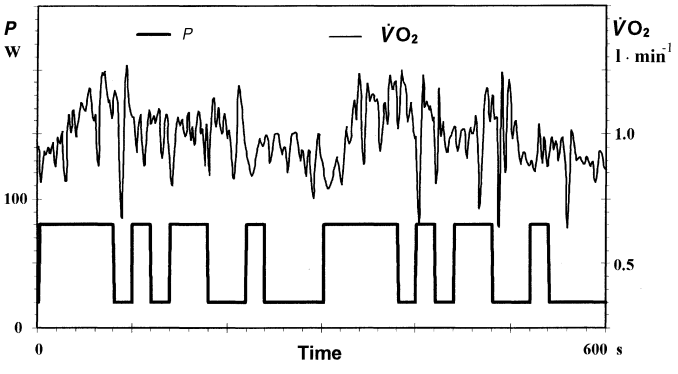

Fig. 1 Exercise protocol. Two pseudo-random sequences of binary exercise intensity (P) were used and the corresponding oxygen uptake ($\dot{V}O_2$) measured breath-by-breath for 600 s. The lower exercise intensity was 20 W and the upper exercise intensity adjusted to 40% of the predicted individual working capacity or to 80 W

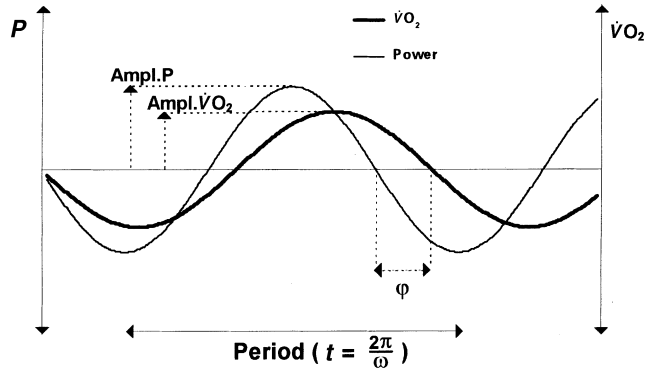

Fig. 2 Frequency analysis illustrated for a single sine wave. The period (t) of the sine wave is determined by the frequency expressed in terms of angle speed (ϖ). The ratio between the amplitudes of oxygen uptake $\dot{V}O_2$ (*Ampl.* $\dot{V}O_2$) and power (P)(*Ampl.P*) and the phase shift (φ) between $\dot{V}O_2$ (output) and power (input) provide information about the ability of the subject to meet the oxygen demand caused by a change in exercise intensity

parameters showed no significant differences between the groups and were not influenced by the F_IO_2 in either group: breathing frequency, tidal volume, end-tidal partial pressure of carbondioxide, $\dot{V}_E$, $\dot{V}O_2$, $\dot{V}_E/\dot{V}O_2$, and $\dot{V}_E/\dot{V}CO_2$.

During exercise in normoxia, spectrum analysis revealed a lower AR in CF than in HC (Fig. 2). At the two lower frequencies CF also displayed a larger negative PS. During hyperoxia, AR increased over the entire frequency range in HC but not in CF. The PS did not change significantly in either group. Both the presence of disease ($P < 0.001$) and F_IO_2 had an influence on AR but not on PS over the whole frequency range. These results were confirmed when MANOVA was performed with forced expiratory volume in 1s (FEV_1) as a cofactor to control for the state of disease. The order of low or high F_IO_2 did not significantly affect any of the parameters (Fig. 3).

Table 2 Average cardiopulmonary data during pseudo-random binary sequences of exercise. *CF* Cystic fibrosis patients, *HC* healthy controls, F_IO_2 fractional concentration of oxygen in inspired air, *HR* heart rate, SO_2 transcutaneous oxygen saturation, $\dot{V}CO_2$, carbon dioxide production, $\dot{V}O_2$ oxygen consumption, *R* respiratory exchange ratio

F_IO_2		0.21		0.40		*P*
		mean	SD	mean	SD	
CF	HR (min^{-1})	117	17	113	18	< 0.01
	SO_2 (%)	92.7	1.4	96.9	1.7	< 0.001
	$\dot{V}CO_2$ ($l \cdot min^{-1}$)	0.75	0.07	0.69	0.12	< 0.05
	$\dot{V}O_2$ ($l \cdot min^{-1}$)	0.78	0.10	0.77	0.19	> 0.10
	R	0.97	0.05	0.92	0.10	< 0.05
HC	HR (min^{-1})	114	12	111	13	> 0.10
	SO_2 (%)	95.2	1.4	97.0	1.4	< 0.01
	$\dot{V}CO_2$ ($l \cdot min^{-1}$)	0.77	0.12	0.72	0.12	0.06
	$\dot{V}O_2$ ($l \cdot min^{-1}$)	0.87	0.05	0.91	0.19	> 0.10
	R	0.89	0.05	0.81	0.06	< 0.001

P = Error probability of student's *t*-test

Discussion

It has been shown that during exercise, instantaneous $\dot{V}O_2$ is influenced by pulmonary gas exchange, cardiovascular oxygen transport and muscle oxygen utilisation (Wasserman et al. 1987). The limiting factor for $\dot{V}O_2$ kinetics during transients of exercise has been the subject of debate (Eßfeld et al. 1991; Hughson et al. 1990a). Using pseudo-random sequences of exercise intensities it has been found that $\dot{V}O_2$ kinetics differ between CF patients and HC (Kusenbach et al. 1994; Wieching 1996). These patients had a lower AR between $\dot{V}O_2$ and exercise intensity than HC; disease, physical fitness and age have been identified as independent factors of influence.

The CF patients and HC performed identical PRBS exercise tests with or without oxygen supplementation. During exercise in normoxia, PRBS results supported the suggestion that CF patients exhibit impaired $\dot{V}O_2$ kinetics as has been indicated by a reduced AR (Kusenbach et al. 1994; Wieching 1996). In contrast, Braggion et al. (1989) have reported $\dot{V}O_2$ kinetics in CF patients similar to those of HC. They have used multiple step transitions from rest to 1.7 $W \cdot kg$ body $mass^{-1}$. Using this approach nonlinear cardiovascular reactions such as central nervous stimulation of HR and venous admixture from non-exercising parts of the body have been suggested to contribute to the early $\dot{V}O_2$ kinetics (Leyk et al. 1992). Moreover, additional energy expenditure is necessary for the acceleration of the flywheel at the onset of exercise.

Oxygen supply increased SO_2 and AR during PRBS exercise in HC. This observation would support the hypothesis that has been made that oxygen transport limits $\dot{V}O_2$ kinetics in healthy subjects breathing room air (Linnarson et al. 1974; Gaultier et al. 1978; Hughson et al. 1990b). In contrast, F_IO_2 did not affect $\dot{V}O_2$ kinetics significantly in CF patients, although the initially low SO_2 increased to the level of HC and HR decreased during oxygen supplementation. These results would suggest that muscle oxygen utilisation rather than cardiopulmonary oxygen supply limited $\dot{V}O_2$ kinetics in CF. Differences in physical fitness, which were not allowed for in this study, might be one explanation. The effect of disease on $\dot{V}O_2$ kinetics did not depend on the disease state as defined by FEV_1. Moreover, the influence of disease on $\dot{V}O_2$ kinetics has been shown to be independent of fitness ($\dot{V}O_{2\,max} \cdot kg$ body $mass^{-1}$) in CF (Wieching 1996).

During exercise with oxygen supplementation, a decrease of $\dot{V}CO_2$ was observed in both groups. This has been explained by a smaller oxygen deficit and less lactate production at the onset of exercise in HC (Gaultier et al. 1978; Palange et al. 1995). In CF a decrease of $\dot{V}CO_2$ has also been observed by Nixon et al. (1990)

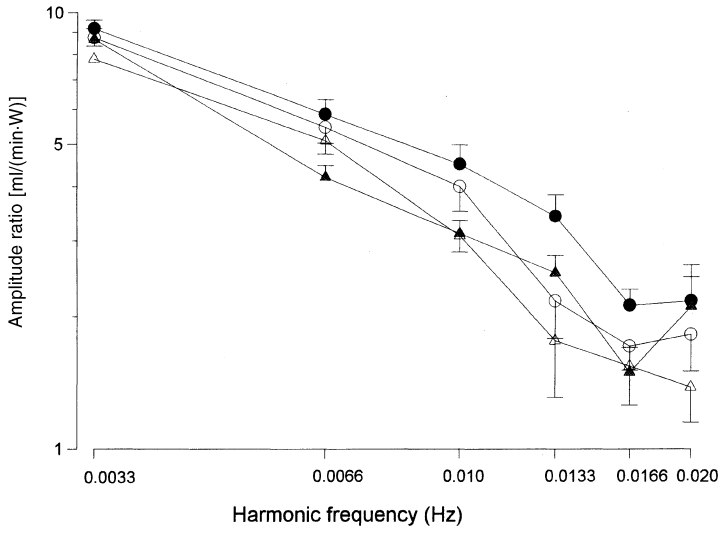

Fig. 3 Amplitude ratio between exercise intensity and oxygen uptake for the first six harmonic frequencies of exercise applied during pseudo-random binary sequence exercise. Breathing room air the amplitude ratio was lower in the cystic fibrosis patients. With supplemental oxygen an increase was observed in the control group only. ○ Control group, fractional concentration of oxygen in inspired air (F_IO_2) 0.21 ● control group, F_IO_2 0.40, △ cystic fibrosis group, F_IO_2 0.21, ▲ cystic fibrosis group F_IO_2 0.40

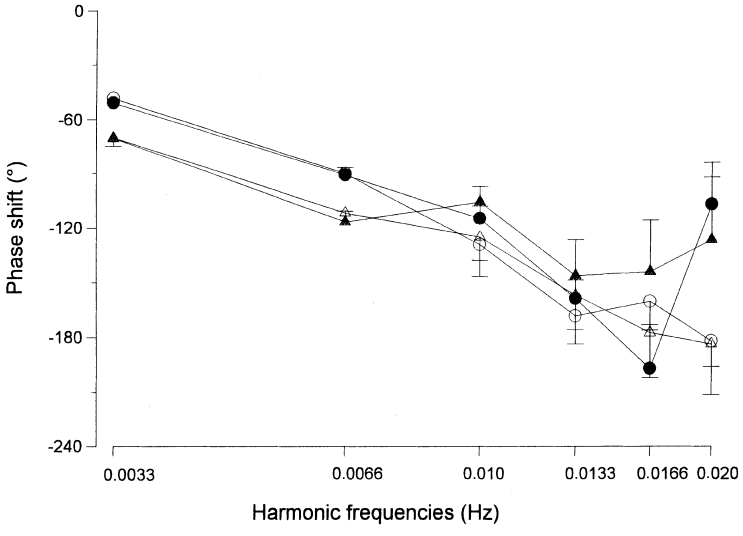

Fig. 4 Phase shift between oxygen uptake ($\dot{V}O_2$) and exercise intensity for the first six harmonic frequencies during pseudo-random binary sequence exercise. The phase shift was smaller in the control group at lower frequencies irrespective of the fractional concentration of oxygen in inspired air (F_IO_2). Oxygen supplementation ($F_IO_2 = 0.40$) prompted no significant effect. ○ Control group, F_IO_2 0.21 ● control group F_IO_2 0.40, △ cystic fibrosis group F_IO_2 0.21, ▲ cystic fibrosis group, F_IO_2 0.40

during submaximal exercise with an oxygen supply. As in healthy humans, this may be due as has been suggested by Cooper et al. (1986) to a smaller contribution of carbohydrate metabolism.

During both normoxia and hyperoxia R was elevated in CF. During PRBS this may be explained by the delay of $\dot{V}O_2$ in relation to $\dot{V}CO_2$ kinetics. However, an increased R in CF at rest has also been observed by others (Spicher et al. 1991). Independent of pulmonary inflammation, a disturbed energy metabolism has been shown to be related to certain CF genotypes including the most common mutation ΔF508 (O'Rawe et al. 1992; Shapiro 1989; Thompson et al. 1996). The defect of membrane chloride permeability has been found to affect not only the cell surface but also the intracellular vesicular membranes, thereby altering substrate metabolism and oxygen utilisation in CF (Barasch et al. 1991; Bradbury et al. 1992; Shapiro 1989).

Our data would support the hypothesis that during aerobic exercise in healthy subjects $\dot{V}O_2$ kinetics is influenced by cardiopulmonary oxygen supply. By contrast, in CF patients with mild to moderate lung disease, it is limited predominantly by muscle oxygen consumption. This may be explained by a reduced physical fitness and/or a primary disorder of energy metabolism in CF.

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