Assessment and Interpretation of Arterial Oxygen Saturation in Children with Cystic Fibrosis

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BACKGROUND

In CF, salt transport abnormalities at the airway surface lead to reduced volumes of airway surface liquid, thick mucous which traps bacteria, and recurrent respiratory infections. The resultant infection-inflammation cycle causes lung damage, and the subsequent lung function deterioration ultimately results in premature death. This process may be exacerbated by periods of low oxygen levels (hypoxia). Hypoxia may occur at times when the lungs are placed under stress in CF, namely sleep, exercise, air travel, and with CF chest exacerbations. This review attempts to summarise the impact of low oxygen levels in CF, in the current context of a lack of agreed guidelines on defining hypoxia in CF or on implementing oxygen therapy.

POTENTIAL EFFECTS OF LOW OXYGEN LEVELS IN CF

Low arterial oxygen blood content (saturations) occurring on a nightly basis during sleep, or to a lesser extent repeated periods of hypoxia occurring on exercise may be bad for the child with CF, stressing the heart and circulation, affecting quality of life, as well as having theoretical effects on lung inflammation.

Low oxygen levels are associated with higher lung blood pressure. Significant associations are reported between pulmonary artery blood pressures and average oxygen levels in the bloodstream (SaO₂) during sleep and exercise in adults with CF¹.

Quality of life in CF may be influenced by low blood oxygen levels (SaO₂). The only study of oxygen therapy undertaken in CF ² reported that, over a 12-month period, school and work attendance was maintained in 83% of the oxygen-treated group, compared with 20% in those randomised to air. There was a statistically significant
difference between the groups (p<0.01). Additionally, both sleep quality, and sleep duration correlate with sleep SaO$_2$.

There is also laboratory evidence to suggest that low oxygen levels may contribute to the decline in lung function by switching on inflammation, as well as encouraging growth of *Pseudomonas aeruginosa* (PA), the main bacteria associated with CF lung disease. Hypoxia is thought to activate several important blood proteins known as cytokines, which promote inflammation. Cytokines are part of the body’s response to infection, sending signals to recruit cells to the site of infection. One of these cytokines, known as interleukin-8, attracts a type of white blood cell, the neutrophil, which is important in the CF airway where ongoing neutrophilic inflammation is seen. The neutrophil releases enzymes including elastase, which destroy lung tissue.

*PA* also activates these same cytokines. Low oxygen levels may exert a role on this process, as under hypoxic conditions, *PA* biofilms prove virtually impenetrable to antibiotics, leading to an increased and prolonged immune response.

*If low oxygen levels might be bad, how do we detect them?*

**ASSESSING HYPOXIA IN THE CHILD WITH CF**

Pulse oximetry is the main assessment tool in children, where the oxygen concentrations are measured from the skin covering the finger. Traditional methods of assessing hypoxia in children with CF are to measure resting SaO$_2$ whilst awake in clinic, along with annual exercise testing, during which SaO$_2$ are measured.

**Exercise Hypoxia**

Exercise testing protocols depend upon the facilities and levels of expertise available in each CF centre. The gold-standard cardiopulmonary exercise test involves analysing the inhaled and exhaled gases with each breath to the point of maximal exertion. The volume of oxygen breathed in during exercise, as well as the volume of exhaled carbon dioxide, are monitored with increasing exercise workload, allowing maximal oxygen uptake (VO$_2$max) to be measured. Blood oxygen levels (SaO$_2$) are monitored throughout the test. More usual however, is that the six-minute walk test (distance walked in 6 minutes), or the three-minute step test (stepping up and down on a single step for 3 minutes) will be performed. During these tests, heart rate and SaO$_2$ are recorded, along with patient scores of breathlessness. The concern is that the latter tests are sub-maximal, except in those with severe CF lung disease. As such, potentially clinically significant desaturations may be missed.

**Nocturnal Hypoxia**

During sleep there is a change in breathing pattern and blood and air distribution in the lung, which may be associated with a reduction in SaO$_2$ in some circumstances. Sleep studies may be done in hospital, or undertaken at home, using a portable oximeter to measure pulse and SaO$_2$. Our own experience is with the latter method, whereby wristwatch-like oximeters are sent via the postal service with instructions for use. Patients record sleep data on consecutive nights, then return the oximeter to the sleep laboratory, where data is downloaded. Limitations of home oximetry are the inability to distinguish obstructive sleep apnoea from underventilation in the context of CF lung disease, and there is a need to offset these limitations against ease of use.
and the additional cost of in-patient studies. Overnight oximetry appears a useful screening test for sleep hypoxia.

**Fitness to Fly**

Flying increases the risk of hypoxia in CF. Barometric pressure and partial pressure of oxygen fall with altitude - airline passengers breathe air with an oxygen concentration of 15% instead of the usual sea-level 21%. Methods used to predict in-flight hypoxia have been to perform a pre-flight hypoxic challenge (exposing the patient to low oxygen concentrations for a given time-period), or to predict desaturation on the basis of baseline blood gas tests or lung function. Evidence is conflicting as to which method most usefully predicts in-flight hypoxia in children, and the British Thoracic Society guidelines suggest that children with CF undergo pre-flight assessment which may include “hypoxic challenge testing in addition to spirometric tests” ⁴.

**CF chest exacerbations**

Children with CF face challenges to their lung reserve at times of CF chest exacerbations, when ventilation to blood supply mismatching may be exaggerated, and hypoxia may ensue. Hospital admission provides an opportunity for SaO₂ monitoring.

_How do we interpret the meaning of tests used to assess oxygen levels in CF?_

**DEFINING HYPOXIA IN CF**

There is a lack of objective evidence for clear definition of hypoxia in CF, and some of the issues pertaining to this across given clinical scenarios are outlined below.

**Sleep Hypoxia in CF**

An e-mail survey of UK paediatric CF centres (K Southern, University of Liverpool – *Personal Communication*), concluded that less than a quarter of centres have a definition for sleep hypoxia in CF. Various definitions are used and published methods of quantifying sleep hypoxia in CF include measuring the minimum blood oxygen levels during sleep, the average sleep oxygen levels, percentage of time spent with oxygen levels below 90%, and the lowest hourly average oxygen level recorded during sleep. A lack of definition for nocturnal hypoxia hampers the description of the prevalence of CF hypoxia in clinical practice, and may have led to both under-recognition and under-treatment of this potentially important clinical entity.

**Exercise Hypoxia in CF**

Exercise hypoxia in CF is defined as a fall in blood oxygen levels (SaO₂) during exercise of 4% or more from the SaO₂ at the beginning of exercise. This is a definition also used in healthy subjects. Clearly, if this represents a fall in SaO₂ from 95% to 88%, one could deem this to represent a likely significant physiological drop in arterial blood oxygen concentration, though the definition holds less well in a very fit child whose SaO₂ fall from 99% to 95% at the end of exercise. Further work is needed to establish clinically significant parameters.
In-flight hypoxia in children with CF is defined as a fall in blood oxygen levels to below 90% at any time during the flight, necessitating the need for supplemental oxygen on long distance flights.\(^4\)

Clearly there are various methods for investigating hypoxia in children with CF, which probably all assess slightly different aspects. At present it is unknown which is the more relevant assessment with the greatest clinical impact. Given that most of us spend 8 hours or more asleep each day, then the most prolonged period of low oxygen levels is likely to occur at night.

*Is there any way of predicting likelihood of sleep hypoxia from routine clinical measures?*

**Predicting sleep hypoxia from daytime clinical measures**

**Daytime \(\text{SaO}_2\)**

Awake \(\text{SaO}_2 \leq 93\%\) in CF is reported to indicate a high risk of sleep hypoxia. Although highly specific, resting \(\text{SaO}_2 < 93\%\) is a poorly sensitive indicator of sleep hypoxia. A recent study reported 36% CF subjects with resting \(\text{SaO}_2 > 93\%\) became hypoxic at night\(^6\). All children participating in our study had resting \(\text{SaO}_2 \geq 95\%\), and resting \(\text{SaO}_2\) was not a useful predictor for sleep hypoxia in our study population.

**Lung Function (Forced Expiratory Volume in 1 second, FEV\(_1\))**

Two studies suggest that %predicted \(\text{FEV}_1\) below 65% might predict sleep hypoxia in CF\(^7,8\). This cut-off appears highly sensitive (most CF subjects with sleep hypoxia have \(\text{FEV}_1 < 65\%\)predicted), but poorly specific (a number of CF subjects with \(\text{FEV}_1 < 65\%\)predicted do not have sleep hypoxia). It may be useful in clinical practice however, to perform a sleep study in CF patients with a \(\text{FEV}_1\) below 65% predicted.

**Exercise \(\text{SaO}_2\)**

It is previously reported that hypoxia in CF occurs more frequently during sleep than exercise\(^8\), suggesting that sleep studies may be indicated for all CF patients with exercise hypoxia. The mechanisms of hypoxia during exercise are likely to differ from those during sleep, borne out by poor correlations between the fall in \(\text{SaO}_2\) during exercise and sleep \(\text{SaO}_2\) measurements\(^6\).

**How common is sleep hypoxia in the child with CF?**

**Prevalence of sleep hypoxia in CF**

At Great Ormond Street Hospital, we studied 41 children with CF aged 8 to 16 years (Median 12.7). All individuals underwent measures of resting \(\text{SaO}_2\), followed by home oximetry on consecutive nights. The definition of sleep hypoxia used was that of \(\text{SaO}_2 < 93\%\) for >25% of sleep time, as per the above paediatric definition used in Liverpool. Six of our 41 subjects (15%) met the criteria for sleep hypoxia using this definition. Bearing in mind that only 1-2% children with CF in the UK receive oxygen therapy\(^5\), then the possibility of under-recognition and undertreatment of sleep hypoxia in CF appears possible.
Does oxygen work as a treatment for low oxygen levels in CF?

OXYGEN THERAPY IN CF
In the only long-term oxygen trial in CF\(^2\), twenty-eight CF subjects were randomised to receive either air or oxygen therapy, and followed up for up to 3 years. Although no differences in mortality or hospitalisation were found, 83% of those in oxygen maintained school/work attendance at 12 months compared with only 20% of the air group (p<0.01). Of note in the study design is that night-time oxygen therapy flows were decided by the flow needed to normalise daytime blood gas tests. Since daytime measures may be poorly sensitive predictors of sleep hypoxia, it is possible that patients in the oxygen arm of the study may have remained hypoxic and treatment effect may have been underestimated.

Caveats exist to starting oxygen therapy in CF. Firstly; children with CF already carry a heavy burden of care. The only trial of long-term oxygen therapy in CF highlights this as, of 146 subjects approached to take part, only 28 entered the study\(^2\). Oxygen may be poorly tolerated, has household safety implications, and may be perceived as palliative rather than active therapy. Secondly, oxygen therapy may blunt respiratory drive, although no carbon dioxide retention was seen after one year of oxygen therapy in CF\(^2\). Finally, oxygen may itself cause toxicity and activate lung inflammation.

CONCLUSION
The lack of a clear definition of hypoxia in CF prevents a uniform approach of assessment for CF patients during sleep and exercise. It appears that daytime SaO\(_2\) are of little value in assessing sleep hypoxia. Hypoxia may occur during sleep in those with a normal exercise test, often because the type of exercise test undertaken or patient volition results in a sub-maximal effort. It appears therefore, that a sleep study is needed to confidently rule in/rule out sleep hypoxia in CF, and lung function may be the best daytime predictor of nocturnal desaturation. Limiting sleep studies to those with reduced FEV\(_1\) (i.e. FEV\(_1\)<65% predicted) may prove an effective screening tool in the detection of sleep hypoxia, but this remains to be confirmed.

The potential effects of hypoxia on the pulmonary circulation, sleep quality, quality of life and inflammation in CF, suggests that earlier use of oxygen therapy in those in whom low oxygen levels are demonstrated appears worthy of further exploration. Our prevalence data suggests that some children with CF and hypoxia may be undertreated. A uniform approach to defining hypoxia needs to be developed, along with guidelines for prescribing oxygen therapy in children with CF. Any change in practice must be evidence-based and the need for adequately-powered randomised, controlled trials of oxygen therapy in CF is apparent.


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