

# Assessment of hypoxia in children with cystic fibrosis

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Hypoxia during sleep and exercise may occur in an important number of patients with cystic fibrosis (CF). Despite its recognition, no clear definition for hypoxia in CF exists, and nor do guidelines for commencing oxygen therapy. CF patients with hypoxia may have increased pulmonary artery pressure, reduced exercise ability, and skeletal muscle strength, and most importantly of all worse sleep quality, and a worse quality of life. Laboratory and rodent evidence exists to suggest that hypoxia may contribute to the decline in lung function in CF by upregulating lung inflammation, and encouraging growth of *Pseudomonas aeruginosa*, the most important pathogen associated with CF lung disease. The effects of hypoxia in childhood CF need to be fully studied, and a potential expanded role for oxygen as therapy in CF may be worthy of exploration.

Cystic fibrosis (CF) is the most common life threatening inherited disease in the UK, affecting over 7500 children and young adults. Average life expectancy is currently 31 years ([www.cftrust.org.uk](http://www.cftrust.org.uk)). Abnormal airway surface liquid results in recurrent lower respiratory tract infections and airway remodelling, leading to increased airway resistance, gas trapping, ventilation-perfusion mismatching, and increased work of breathing.

Episodic hypoxaemia may occur at times of physiological stress in CF, such as sleep,<sup>1,2</sup> exercise,<sup>3</sup> air travel,<sup>4</sup> and during infective exacerbations of CF. Hypoxia during sleep and exercise is reported to occur in stable adult CF patients who are not hypoxic during the day, when compared to healthy controls.<sup>1</sup> Furthermore, studies have shown significantly lower mean resting<sup>5</sup> and overnight<sup>2</sup> SaO<sub>2</sub> in stable CF children when compared to controls. During sleep, tidal volume falls due to reduced respiratory drive, precipitating hypoxia,<sup>1</sup> although upper airway obstructive pathology such as nasal polyps may also contribute, while exercise induced hypoxia may be related to airflow limitation,<sup>1</sup> or accentuation of V/Q mismatch.

This review aims to summarise the potential impact of hypoxia in childhood CF. At present, only 1–2% of childhood CF patients receive long term oxygen therapy at night,<sup>6</sup> and no guidelines exist on when to start oxygen, nor how to define hypoxaemia in childhood CF. There is a paucity of evidence to drive clinical practice in this area, and extensive literature searching identifies only one randomised, controlled trial (RCT) of long term oxygen therapy in CF.<sup>7</sup>

## DEFINING HYPOXIA IN CF

Children with CF may suffer reduced arterial oxygen saturation (SaO<sub>2</sub>) during sleep and while exercising. The failure of a clear definition of “significant hypoxaemia” hampers the description of its prevalence and severity. In adults, measurement of arterial PaO<sub>2</sub> is considered critical, but this is not always possible or practical in children. In paediatric practice, SaO<sub>2</sub> measured by pulse oximetry remains the main assessment tool. Arterial sampling from a crying (hypoxic) child is unreliable,<sup>6</sup> while capillary PaO<sub>2</sub> may not reflect arterial PaO<sub>2</sub>.<sup>8</sup> Although pulse oximetry is a freely available, non-invasive method of assessing oxygenation, correlation between SaO<sub>2</sub> and arterial PaO<sub>2</sub> may be poor,<sup>9</sup> and limits of accuracy for SaO<sub>2</sub> are ±2%.<sup>9</sup>

## Sleep hypoxaemia in CF

A study of stable CF children has shown significantly lower mean overnight SaO<sub>2</sub> when compared to controls,<sup>2</sup> but an e-mail survey of all UK paediatric CF centres found that less than a quarter have a clear definition of nocturnal hypoxia.<sup>10</sup> One such definition of sleep hypoxia is nocturnal SaO<sub>2</sub> <93% for >25% of the study.<sup>10</sup> However, various methods of quantifying nocturnal SaO<sub>2</sub> in CF studies of adults and children are reported, including percentage of time spent with SaO<sub>2</sub> below 90%,<sup>11</sup> minimum SaO<sub>2</sub>,<sup>12</sup> mean sleep SaO<sub>2</sub>,<sup>13,14</sup> and lowest hourly mean SaO<sub>2</sub>.<sup>15</sup> Normative data for nocturnal SaO<sub>2</sub> in children,<sup>16</sup> quote mean (Sat 50) and minimum (Sat min) SaO<sub>2</sub> values, as well as SaO<sub>2</sub> values below which 10% (Sat 10) and 5% (Sat 5) of the study were spent. Some studies cited above have chosen a cut-off for hypoxaemia (for example, mean SaO<sub>2</sub> <95%),<sup>13</sup> creating dichotomous results; whereas others record mean SaO<sub>2</sub> on a continuum using linear regression and correlation to explore relations with other variables.<sup>14</sup>

Currently it is unclear at what level oxygen desaturation becomes important during sleep, but clearly this may be a chronic, frequently repeated hypoxic insult and as such may impact on factors such as pulmonary circulation<sup>17</sup> and sleep quality,<sup>18</sup> as well as theoretical effects on lung inflammation,<sup>19</sup> and potentially *Pseudomonas aeruginosa* (PA) growth.<sup>20</sup>

## Exercise hypoxaemia in CF

Exercise induced arterial hypoxaemia (EIAH) in children with CF has been defined as a fall in SaO<sub>2</sub> during exercise of ≥4% from baseline,<sup>3</sup> and this definition has also been used in healthy children.<sup>21</sup> Our own (unpublished) data from 2004 showed that 8% have EIAH using these criteria when assessed using an incremental

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submaximal exercise test (3 minute step test). The UK CF Trust “Clinical guidelines for cystic fibrosis care”<sup>22</sup> recommend annual exercise testing, but no guidelines exist for managing exercise induced arterial hypoxaemia (EIAH). There seems little point in subjecting CF patients to a barrage of tests if we are to ignore the results, yet it is unclear as to how exercise testing should be used to inform treatment. In adolescent and adult CF patients, hypoxia is reported to occur more frequently during sleep than on exercise,<sup>1, 13</sup> suggesting a sleep study may be indicated for those with EIAH.

### Hypoxaemia and chest exacerbations of CF

Children may face challenges to their pulmonary reserve at times of infective exacerbations. At such times, ventilation-perfusion mismatching may be exaggerated and resultant hypoxaemia may ensue. Admission to hospital for intravenous antibiotics is an opportunity for monitoring SaO<sub>2</sub>. Appropriate antibiotic therapy, and aggressive physiotherapy may result in improvement in lung function over the course of an admission such that there is no longer a need for oxygen at the end of an antibiotic course. In adult CF patients, it is reported that minimum SaO<sub>2</sub> are lower and time spent with SaO<sub>2</sub> <90% is greater in patients with chest exacerbations than those with stable CF,<sup>23</sup> and treating the chest exacerbation significantly improves these indices.

### Hypoxaemia and fitness to fly

Flying heightens the risk of hypoxaemia in susceptible individuals, as both barometric pressure and partial pressure of oxygen fall with altitude, such that airline passengers breathe air with an inspired oxygen concentration (FiO<sub>2</sub>) of 15%. In-flight hypoxia is defined as a fall in SaO<sub>2</sub> to below 90% at some point during the flight.<sup>4</sup> The main methods used to predict hypoxia in “fitness to fly” assessments have been to undertake a pre-flight hypoxic challenge,<sup>4, 24</sup> or to predict in-flight hypoxaemia on the basis of baseline measures such as spirometry<sup>4</sup> or PaO<sub>2</sub>.<sup>25</sup> Buchdahl and colleagues suggest that %predicted FEV<sub>1</sub> below 50% correctly identifies 70% of those with in-flight hypoxia, and is also 96% specific, compared with 20% sensitivity for pre-flight hypoxic challenge. The British Thoracic Society guidelines suggest that children with CF should undergo pre-flight assessment which “may include hypoxic challenge testing in addition to spirometric tests”,<sup>26</sup> and the updated recommendations of Buchdahl and colleagues are that a hypoxic challenge be undertaken if FEV<sub>1</sub> is below 50% predicted.<sup>27</sup>

### Does daytime SaO<sub>2</sub> predict nocturnal and exercise desaturation in CF?

It is routine practice in CF clinics to record resting SaO<sub>2</sub>, and values ≤93% indicate a high risk of nocturnal hypoxaemia in CF.<sup>15</sup> There are no published childhood data on the predictive value of daytime oximetry in CF. However, in 70 CF adults, 40% of whom had significant nocturnal hypoxaemia,<sup>11</sup> all subjects with resting SaO<sub>2</sub> <93% had significant nocturnal desaturation, but 36% patients with resting SaO<sub>2</sub> >93% also became hypoxic at night. These data are supported by another study,<sup>14</sup> which reports that resting SaO<sub>2</sub> <94% correctly predicts 100% with nocturnal hypoxaemia, but misses 19% of patients with SaO<sub>2</sub> >94% who also become hypoxic at night. Therefore, although resting SaO<sub>2</sub> <93% may be specific for predicting nocturnal desaturation, a sleep study may be needed to confidently detect sleep hypoxia.

The only RCT of oxygen therapy in CF determined nocturnal oxygen flows by titrating the amount required to normalise daytime pO<sub>2</sub>.<sup>7</sup> Since daytime oxygenation is a poor predictor of overnight hypoxia,<sup>11, 14</sup> it may be that despite oxygen therapy, the oxygen treated group remained hypoxic at night. Further research may be required in order to more carefully define the

tissue effects of hypoxia in CF, and to carry out rigorous RCTs of oxygen therapy in CF in order to determine its efficacy, and the optimum point for intervention.

### IS HYPOXIA IMPORTANT IN CF?

Hypoxia in CF is potentially important for several reasons (table 1). Nocturnal and/or exercise hypoxia are chronic, frequently repeated insults which may affect the pulmonary circulation,<sup>17</sup> exercise ability (fig 1), and quality of life.<sup>7, 18</sup>, as well as exerting theoretical effects on lung inflammation,<sup>19</sup> and the bacterial profile in the CF lung.<sup>20, 28</sup> The effects of a hypoxia driven pro-inflammatory state on muscle wasting<sup>29</sup> may also be important in disease progression in CF.

### HYPOXIA AND THE PULMONARY CIRCULATION

The effects of chronic hypoxia on the pulmonary circulation are well documented, and the first case report of cor pulmonale in CF dates from 1946.<sup>33</sup> The pulmonary circulation responds to alveolar hypoxia by increasing systolic pulmonary artery pressure (sPAP) and pulmonary vascular resistance (PVR). Graded decreases in alveolar pO<sub>2</sub> (P<sub>A</sub>O<sub>2</sub>) produce similar increases in PVR.<sup>34</sup> Chronic hypoxia results in pulmonary arterial remodelling, with increased intimal thickness, which concurs with paediatric CF postmortem studies.<sup>35</sup>

Both sleep and exercise induced hypoxia are likely to be chronic, frequently occurring insults. A significant negative correlation between sPAP and mean SaO<sub>2</sub> during sleep ( $r = -0.56$ ,  $p < 0.008$ ), and exercise ( $r = -0.75$ ,  $p < 0.0001$ ) is reported in CF adults.<sup>17</sup> Therefore if pulmonary hypertension directly relates to degree of sleep and/or exercise hypoxaemia, then provision of oxygen at night and/or during exercise might be expected to result in beneficial effects on the right heart and pulmonary circulation.

### HYPOXIA AND EXERCISE ABILITY

Ability to exercise is important for preservation of lung function in CF, as well as having proven beneficial effects on quality of life.<sup>36</sup> Hypoxia may drive lung inflammation<sup>19</sup> and encourage *Pseudomonas aeruginosa* (PA) growth in the CF lung,<sup>28</sup> each worsening lung damage, and accelerating skeletal muscle dysfunction.<sup>29</sup> Deteriorating lung function, combined with reduced muscle mass,<sup>29</sup> limits exercise capacity and may instigate a vicious circle (fig 1) whereby decreased exercise ability reduces sputum clearance, encouraging bacterial growth within the CF lung. Inflammation may be perpetuated, causing further reductions in lung function and exercise ability. The effects of hypoxia on the heart and pulmonary circulation may further limit exercise.<sup>37</sup>

Oxygen therapy may down-regulate inflammation, halting the catabolic effects of a pro-inflammatory state.<sup>29</sup> The combination of reduced lung inflammation and improved skeletal muscle strength, as well as potential beneficial effects on the pulmonary circulation, may improve exercise ability.

Provision of oxygen during exercise in both CF,<sup>38, 39</sup> and adult chronic obstructive pulmonary disease (COPD)<sup>40</sup> is known to reduce work of breathing and breathlessness, as well as increasing exercise endurance. However, maximal oxygen uptake (VO<sub>2max</sub>) in CF changes little, suggesting that CF patients may have impaired utilisation of oxygen at skeletal muscle level,<sup>41</sup> which may reflect the catabolic effects of hypoxia on skeletal muscle.<sup>29</sup> A beneficial role for oxygen therapy alongside a pulmonary exercise rehabilitation programme has been reported in adult chronic obstructive pulmonary disease (COPD) patients,<sup>42</sup> and may be an area that warrants further investigation in patients with CF.

**Table 1** Potential adverse effects of hypoxia in CF

	Adverse effect
Pulmonary circulation Lung inflammation	Increased pulmonary artery pressures related to levels of sleep and exercise hypoxaemia <sup>17</sup> Up-regulated cytokine expression <sup>19</sup> with increased neutrophil chemoattraction, neutrophilic inflammation, and resultant parenchymal lung damage
Bacterial profile in the CF lung	Enhanced <i>P aeruginosa</i> growth in biofilms <sup>20</sup> with increased antibiotic resistance <sup>28</sup> Possible increased <i>S aureus</i> virulence <sup>30</sup>
Exercise ability	Limited exercise ability due to effects on pulmonary vasculature and also lung inflammation and bacterial colonisation. Reduced exercise ability sets up "vicious circle" (fig 1)
Muscle strength Quality of life	Reduced skeletal muscle mass <sup>29</sup> Potential adverse effects on quality of life, including maintenance of school or work attendance <sup>7</sup> Poor sleep quality <sup>18</sup>
Endothelium (CFTR trafficking)	Endothelial dysfunction <sup>31</sup> Reduced CFTR protein trafficking shown in vitro under hypoxic conditions in a non-CF cell line <sup>32</sup> Effects not documented in a CF cell line

## HYPOXIA AND QUALITY OF LIFE IN CF

In the only randomised, controlled trial (RCT) of LTOT in CF,<sup>7</sup> a cohort of 28 adults and children with severe CF lung disease received either oxygen or air at night. The double blind, placebo controlled trial lasted three years. Although no differences in mortality or hospitalisation rates were found between the two groups, school and/or work attendance continued in a significantly higher proportion of the oxygen group (80% versus 20%,  $p < 0.01$ ). This suggests that patients felt better in oxygen, although psychometric testing revealed no significant differences between groups. Sleep quality (Pittsburgh Sleep Quality Index,  $r = -0.4$ ,  $p < 0.05$ ) and sleep duration ( $r = -0.4$ ,  $p < 0.05$ ) in CF have been reported to negatively correlate with minimum SaO<sub>2</sub> during sleep.<sup>18</sup> It has also been reported that neurocognitive performance is impaired during chest exacerbations of CF, at a time when this group of subjects were hypoxic.<sup>23</sup> Therefore, the potential deleterious effects of hypoxia on sleep quality, sleep duration, neurobehavioural activity, and quality of life suggest that appropriate earlier use of oxygen therapy in those who are hypoxic is indicated.

## HYPOXIA AND LUNG INFLAMMATION IN CF

CF airway inflammation is typified by the presence of neutrophils, along with neutrophil enzyme products such as elastase which cause lung damage.<sup>43</sup> Neutrophils are attracted to the airway by interleukin-8 (IL-8),<sup>43</sup> a chemokine released by airway epithelial cells and macrophages as part of the innate immune response to infection. IL-8 levels, along

with other pro-inflammatory cytokines such as tumour necrosis factor  $\alpha$  (TNF $\alpha$ ), IL-1 $\beta$ , and IL-6 are increased in the CF airway,<sup>43</sup> and are regulated by transcription factors such as nuclear factor  $\kappa$ B (NF $\kappa$ B),<sup>44</sup> among others. The NF $\kappa$ B signalling pathway may be key to CF airway inflammation,<sup>44</sup> and is a potentially attractive target for anti-inflammatory therapy in CF.

NF $\kappa$ B is activated by factors including bacteria such as PA,<sup>45</sup> pro-inflammatory cytokines such as TNF $\alpha$ ,<sup>46</sup> and also possibly by hypoxia<sup>19</sup> and mutant CFTR protein.<sup>47</sup> Hence hypoxia driven NF $\kappa$ B activation may impact directly on lung inflammation in CF by increasing expression of cytokines which attract neutrophils and causing initiation then propagation of airway inflammation (fig 2). NF $\kappa$ B inhibitors used in the treatment of CF include corticosteroids,<sup>48</sup> and non-steroidal anti-inflammatory drugs.<sup>49</sup> Others such as cardiac glycosides are under investigation.<sup>50</sup> The effects of oxygen therapy on CF lung inflammation have yet to be studied.

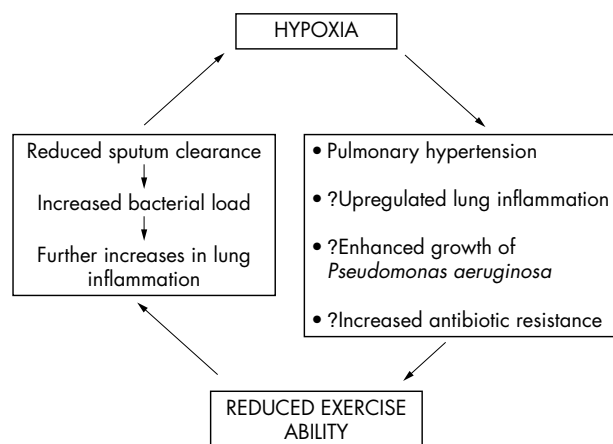
## HYPOXIA AND TISSUE EFFECTS OF INFLAMMATION

The effects of hypoxia on up-regulating lung inflammation in CF may have far reaching effects on tissues including endothelium<sup>31</sup> and skeletal muscle.<sup>29</sup> Pro-inflammatory states promote body wasting, due to the catabolic effect of cytokines including IL-6, and TNF $\alpha$ .<sup>29</sup> Therefore, if hypoxia activates NF $\kappa$ B mediated inflammation, and up-regulates pro-inflammatory cytokine expression, this may detrimentally affect nutritional status. Resultant muscle wasting may decrease respiratory muscle strength, thus promoting nocturnal hypoventilation, and impeding exercise capacity. The associated worsening of hypoxia could cause a "downward pathophysiological spiral".

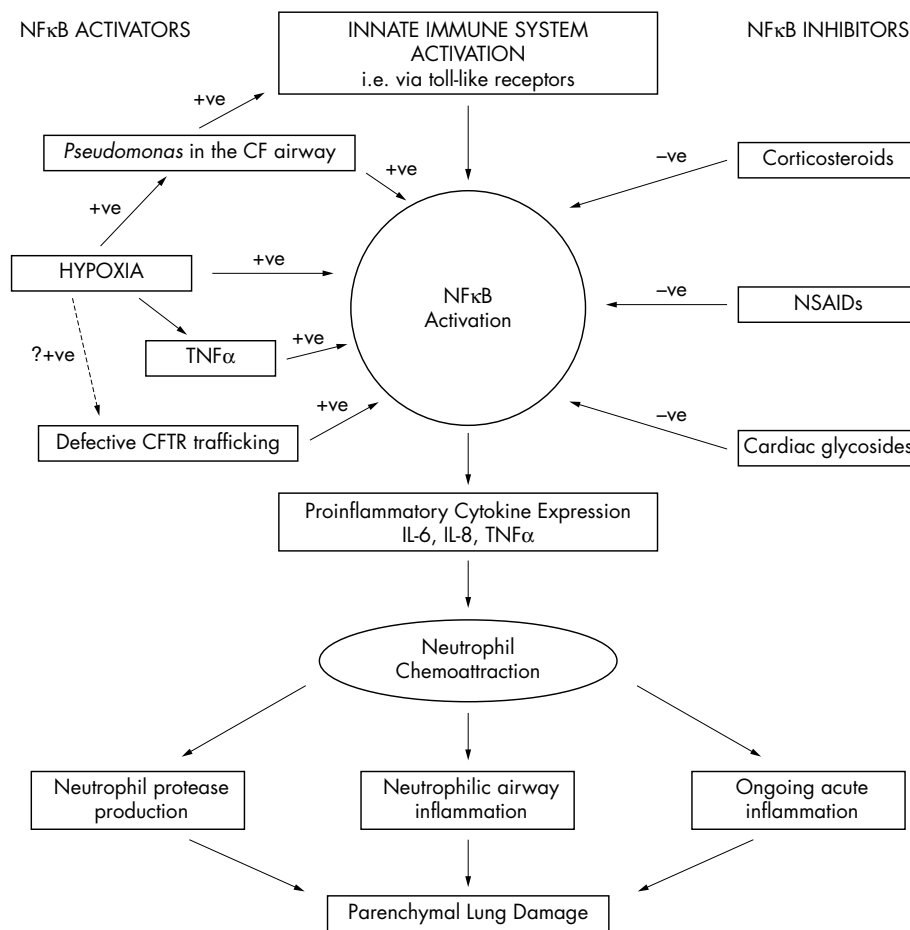
## SUPPORTING LABORATORY EVIDENCE OF A KEY ROLE FOR HYPOXIA IN MEDIATION OF CF LUNG INFLAMMATION

The effects of hypoxia on lung inflammation remain speculative, but a role for oxygen as a therapy in down-regulating lung inflammation in CF would be of great potential benefit.

In vitro evidence suggests that hypoxia up-regulates NF $\kappa$ B activation,<sup>19</sup> which is potentially important in CF. While NF $\kappa$ B activation due to hypoxia may be a direct effect, it is likely that other signalling pathways are involved to effect this action. Hypoxia enhances expression of TNF $\alpha$ ,<sup>29</sup> which in turn up-regulates NF $\kappa$ B.<sup>46</sup> Hypoxia also changes PA growth patterns in the CF lung,<sup>20</sup> increasing NF $\kappa$ B activation,<sup>51</sup> and the effects of hypoxia on intracellular trafficking of CFTR protein may also be important.<sup>32</sup>



**Figure 1** Hypoxia and its purported effects on exercise: "the vicious circle".



**Figure 2** Hypoxia, the innate immune system, and the CF lung.

### Hypoxia and bacterial profile in the CF airway

*Pseudomonas aeruginosa* (PA) produces bacterial lipopolysaccharide, which activates the innate immune system via Toll-like receptors (TLRs) on the airway epithelial cell surface.<sup>45</sup> TLR signalling up-regulates NFκB,<sup>45</sup> and the consequential pro-inflammatory cytokine response ensues. By age 3 years, 73% of CF patients have had a PA lung infection,<sup>52</sup> and the commonest cause of death in CF is unremitting lung disease associated with PA.<sup>53</sup>

PA changes phenotype under hypoxic conditions by forming biofilm-like macrocolonies.<sup>20</sup> Hypoxia and the resultant biofilm state of PA leads to antibiotic resistance,<sup>28</sup> and an increased<sup>51</sup> and prolonged<sup>54</sup> innate immune response. Hypoxia may therefore contribute to the persistence of PA infection in the CF lung and its associated chronic airways damage. The question of whether oxygen therapy might prevent a switch in PA phenotype remains unanswered, though the steep gradient that exists between airway lumen and the interior of CF airway mucus<sup>20</sup> means that oxygen must penetrate the mucus to exert an effect.

### Hypoxia and CFTR protein

Evidence exists that CF patients with the ΔF508 mutation (85% UK CF patients) have an ongoing process of NFκB driven inflammation, due to cell stress caused by overload of CFTR in the endoplasmic reticulum (ER).<sup>47</sup> This implies that neutrophilic inflammation in the CF airway may be associated with CFTR dysfunction as well as infection. Thus, if CFTR trafficking to the cell surface could be improved, inflammation might be reduced. In vitro work has shown increased NFκB activation and IL-8 expression in ΔF508 CF cell lines compared with non-CF cells,<sup>55</sup> while in

vivo studies report increased IL-8 levels and neutrophil numbers in bronchoalveolar lavage (BAL) fluid of young children<sup>56-57</sup> and infants<sup>58</sup> with CF in the absence of evidence of infection. A single study suggests that cell surface CFTR protein expression in a renal cell line is impaired under hypoxic conditions,<sup>32</sup> and reports that improved cellular oxygenation increases CFTR trafficking to the cell surface. In vivo work also suggests that hypoxia might inhibit CFTR function. In mountaineers with high altitude pulmonary oedema, CFTR mRNA levels fell by 60% at altitude,<sup>59</sup> and it is possible that a trafficking deficit may account for such CFTR dysfunction under hypoxic conditions.

Disease severity in CF correlates with the amount of functional CFTR protein expressed at the apical cell surface of airway epithelial cells,<sup>60</sup> and much research has focused on “molecular chaperoning”<sup>61</sup> to guide ΔF508 CFTR protein from the ER to the cell surface. Various compounds from curcumin<sup>62</sup> to sildenafil (Viagra)<sup>63</sup> have been touted as successful, but as yet, the trafficking effects of oxygen in a ΔF508 CF cell line remain undocumented, but represent a potential novel therapy.

### UNANSWERED QUESTIONS ABOUT OXYGEN THERAPY IN CF

#### When to start and how much?

In patients with evidence of chronic hypoxia, it appears that oxygen may be a therapy with exciting potential benefits in CF. Oxygen may improve quality of life, and beneficially modulate both heart and pulmonary circulatory responses, as well as exerting potential anti-inflammatory, antimicrobial, and anabolic effects.

The question of when to start oxygen remains unanswered. Previous UK consensus advocated consideration of oxygen therapy when resting SaO<sub>2</sub> is <90%.<sup>64</sup> However, although all patients with daytime SaO<sub>2</sub> <90% would be expected to have night-time hypoxia, many with night-time hypoxia would be missed were this the sole rationale for prescribing.<sup>11–14</sup> The American Consensus guidelines<sup>65</sup> recommend night-time oxygen in adults if SaO<sub>2</sub> is below 88–90% for ≥10% of sleep time, and oxygen during exercise if SaO<sub>2</sub> falls below 88–90% during exercise. It is not clear how best to manage children who desaturate during exercise, or who dip by 4% but do not reach this threshold. In adult COPD models, LTOT is known to decrease mortality in patients with severe hypoxaemia,<sup>66–67</sup> but in patients with night-time hypoxia only, no significant survival improvements were noted.<sup>68</sup> Further work in CF is required to answer the questions of when to start oxygen, how much oxygen should be given, and for how long.

### POTENTIAL HAZARDS OF OXYGEN THERAPY IN CF

It is important to recognise the potentially detrimental effects of oxygen for a child with CF. Such potential detrimental effects fall largely into three groups. Firstly, children with CF already carry a heavy burden of care.<sup>69</sup> Oxygen may be poorly tolerated, it has household safety implications, and space may be taken up by oxygen concentrators in bedrooms that already contain medical equipment. The presence of oxygen in the family home may necessitate behavioural change from parents, including the (beneficial) cessation of smoking. Advice must also be given about the risk of naked flames.<sup>70</sup> Meanwhile, oxygen therapy may be seen as palliative rather than active therapy, and the accompanying psych morbidity must not be underestimated. This is highlighted by the only trial of long term oxygen therapy in CF,<sup>7</sup> in which more than half of the 146 subjects approached refused to take part. Secondly, oxygen therapy may theoretically blunt respiratory drive. However, while short term studies have shown small rises in transcutaneous pCO<sub>2</sub> with oxygen therapy during sleep,<sup>71–72</sup> and exercise,<sup>38</sup> these rises are of doubtful clinical significance. The only paper to study long term oxygen therapy did not find a rise in arterial pCO<sub>2</sub> after one year.<sup>7</sup> Finally, hyperoxia itself may cause free radical damage, and may up-regulate NFκB.<sup>73</sup>

However, despite such caveats, the evidence reviewed suggests that earlier use of oxygen therapy in CF is worthy of exploration through the conduct of appropriately designed and powered randomised trials.

### SUMMARY

Cystic fibrosis may lead to reduced oxygen content in arterial blood. Studies of the impact of this phenomenon on disease progression and outcome have been hampered by the lack of a consensus definition of hypoxia—in terms of both its timing (during sleep, rest, or exercise) and magnitude. Indeed, less than a quarter of UK CF centres utilise a clinical definition of hypoxia in routine care.<sup>10</sup>

Even if uniform diagnostic criteria were to be available, proof that oxygen therapy impacts on disease progression and outcome is not strong. However, our review of the basic science and rodent literature suggests that lower arterial oxygenation does have the capacity to impact in this way. Although human data are sparse, such data as do exist would also support this conjecture: CF patients with periods of hypoxia may have increased pulmonary artery pressures, increased lung inflammation, greater levels of *Pseudomonas aeruginosa* burden, reduced exercise ability and skeletal muscle strength, and perhaps most importantly of all, worse sleep quality and quality of life.

Perhaps due to the lack of adequate definitions and subsequent appropriately powered trials, there is similarly

### Key points

- A consensus on definition of hypoxia in childhood CF is needed
- Daytime oximetry is a poor predictor of overnight oxygen saturations
- Overnight oximetry is needed to confidently detect nocturnal hypoxaemia in CF
- In those with exercise induced hypoxaemia, sleep and echocardiographic studies are recommended
- A fuller understanding of the effects of hypoxia in CF is needed
- A consensus on when to start oxygen therapy in children with CF is needed
- The question of whether oxygen ameliorates the adverse effects of CF hypoxia may need to be addressed by way of a randomised, controlled trial

no consensus as to when (and if) oxygen therapy should be initiated, nor for its mode or duration of delivery. The need for studies to document the prevalence and potential adverse effects of hypoxia in CF patients is thus apparent. For the time being, the need for overnight sleep studies to confidently detect nocturnal hypoxaemia in CF is reinforced by the poor sensitivity of daytime assessments,<sup>11–14</sup> and the presence of abnormal overnight oximetry in stable childhood CF.<sup>2</sup> It also seems sensible to seek evidence of exercise induced hypoxaemia. This occurs frequently in CF, and may indicate the need for a sleep study because of the association between sleep and exercise hypoxaemia.<sup>1–13</sup> An echocardiogram should also be considered as pulmonary artery pressure may correlate with exercise associated desaturation.<sup>17</sup>

The potential role of oxygen therapy improving disease progress or outcome also warrants further study: a theoretical case that earlier institution of oxygen therapy in CF may improve clinical phenotype by slowing lung function decline and enhancing quality of life is made. This is not a call for oxygen therapy in all CF patients, rather a recognition that some hypoxic CF patients may be under-treated. A uniform approach to defining hypoxia in CF needs to be developed, along with guidelines for oxygen prescribing in CF. We recommend that any change in practice must be evidence based, and needs to be prefaced by appropriately powered randomised controlled trials.

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