Cystic Fibrosis and Sleep Disordered Breathing

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Cystic Fibrosis and Sleep Disordered Breathing

Utah Sleep Society Conference

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Sleep Specialists Should Partner With Local Cystic Fibrosis Centers

- (Very) brief review of cystic fibrosis (CF)
  - Pathophysiology
  - Diagnosis
  - Treatments
  - Changing epidemiology *
- Nocturnal hypoxemia in CF
- Sleep disordered breathing in CF
  - Children
  - Adults
CYSTIC FIBROSIS

- Complex, multi-system, genetic (autosomal recessive) disease
- Primarily affects Caucasians in the United States
- Still no cure but survival is steadily improving
- Broad and varied phenotypic expression within the population and even within a family

Genetics of CF

- Autosomal recessive
- Defect in the CF transmembrane conductance regulator (CFTR) gene on chromosome 7
  - Absence of normal CFTR protein in multiple organs
  - Lungs, intestines, pancreas, sweat gland, hepatobiliary tract, etc
  - CFTR is a cAMP-regulated epithelial ion transporter of chloride and bicarbonate
    - Dysregulated electrolyte and fluid content on surface of various epithelia
- Nearly 2000 known disease causing mutations
  - Grouped into 6 classes based on effect on protein expression and/or function
# Descriptive Statistics

## Incidence

<table>
<thead>
<tr>
<th>Country</th>
<th>Carrier Frequency</th>
<th>Two Carrier Couples</th>
<th>Live births of CF patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>1/25</td>
<td>1/625</td>
<td>1/2500</td>
</tr>
<tr>
<td>Ireland</td>
<td>1/14</td>
<td>1/196</td>
<td>1/784</td>
</tr>
</tbody>
</table>

## Prevalence

- Depends on survival
- Depends on treatment - country specific
CFTR Mutation Classes

Pathogenesis of cystic fibrosis lung disease is characterized by absent or dysfunctional cystic fibrosis transmembrane conductance regulator (CFTR) at the epithelial surface (1), resulting in impaired ion transport and a depleted airway surface liquid layer (2). This contributes to delayed mucociliary clearance (3), setting the stage for colonization and chronic infection with bacterial pathogens (4) and a robust inflammatory response (5). Therapeutic approaches to each feature are indicated: ASL, airway surface liquid; PMN, polymorphonuclear cell.
CFTR Mutation Classes

• I. Absence of synthesis
• II. Defective protein maturation and premature degradation
• III. Disordered regulation
• IV. Defective chloride conductance
• V. Promoter or splicing abnormalities reducing number of transcripts
• VI. Accelerated turnover from cell surface

Progression of Lung Disease

- Altered CFTR activity
- Abnormal sputum
  - Thick, dehydrated, tenacious, hyperviscous mucus
- Impaired mucociliary clearance
- Chronic cough and sputum production
- Chronic airway infection and inflammation
- Airway obstruction and cystic bronchiectasis
  - Hypoxia, hypercarbia, increased work of breathing
- Recurrent pulmonary exacerbations
- Lung destruction and respiratory failure

Age of Onset of Manifestations

**Sinopulmonary**
- Infection
- ABPA
- Sinusitis
- Polyposis
- ABPA
- Haemoptysis, pneumothorax
- Respiratory failure
- Sinusitis, polyposis, anosmia

**Gastrointestinal**
- Fetal echogenic bowel
- Meconium ileus
- Pancreatic insufficiency
- Rectal prolapse
- DIOS
- Intussusception
- Hepatic steatosis, biliary fibrosis
- Rectal prolapse
- DIOS
- Intussusception
- Biliary fibrosis, cirrhosis
- Digestive tract cancer (adenocarcinoma)

**Infancy**
- Dehydration
- Hyponatraemic hypochloraemic metabolic alkalosis
- Renal calculi
- Hyponatraemic hypochloraemic metabolic alkalosis
- Delayed puberty, osteoporosis, CFRD
- Renal calculi, renal failure
- CBAVD, HPOA
- Arthritis, vasculitis
- Hyponatraemic hypochloraemic metabolic alkalosis

**Childhood**

**Adolescence/adulthood**
Making a Diagnosis of CF

I. Clinical Syndrome
   - Unexplained chronic purulent lung disease
   - Malabsorption syndrome

II. Laboratory Demonstration of CFTR Defect
   - Sweat chloride test
   - Nasal potential difference

III. Identification of Genetic Mutation

   - Neonatal Screening
     - Immunoreactive trypsinogen; DNA screen; sweat chloride test
Acute Exacerbations of CF

- **Symptoms**
  - Increased dyspnea
  - Increased cough
  - Increased sputum
  - Fever
  - Hemoptysis
  - Weight loss

- **Physical Findings**
  - Crackles
  - Rhonchi

- **CXR changes**

- **PFT changes**
  - Significant drop in FEV1

- **Trigger**
  - Viral infections
  - *P. aeruginosa*
    - Treatment often effective even if culture negative

References:

Treatment

- Antibiotics
- Chest physiotherapy
- Mucolytics
- Airway surface rehydration
- Macrolides
- Nutrition
- Treat metabolic complications
- CFTR modulators
- Anti-inflammatory
Simplified Pathophysiology of CF

CF Mutation

Infection

Thick Mucus

Inflammation

Malabsorption Malnutrition

Tissue Destruction Bronchiectasis
Treatment of CF

CF Mutation → Thick Mucus → Malabsorption

Infection → Inflammation → Tissue Destruction

Malnutrition → Bronchiectasis
CF Mutation

Infection

Inflammation

Thick Mucus

Malabsorption

Malnutrition

Pancreatic Enzymes

Dietary supplements

Tissue Destruction

Bronchiectasis
CF Mutation → Thick Mucus
Infection → Inflammation
Inflammation → Tissue Destruction
Malabsorption → Malnutrition
Malnutrition → CPT/airway clearance
rhDNase
Hypertonic saline
Inhaled mannitol
Albuterol
Tissue Destruction → Bronchiectasis
CF Mutation

Infection

CPT/airway clearance
Antibiotics
Vaccines

Inflammation

Malabsorption
Malnutrition

Thick Mucus

Tissue Destruction
Bronchiectasis
CF Mutation

Malabsorption
Malnutrition

Thick Mucus

Infection

Inflammation
Steroids
Azithromycin
Ibuprofen

Tissue Destruction
Bronchiectasis
CF Mutation

- CFTR potentiators (Ivacaftor, VX-661, Lumacaftor)
- Transcription/translation modifiers
- Gene therapy

Infection

- Thick Mucus
- Inflammation

Malabsorption

- Malnutrition
- Tissue Destruction
- Bronchiectasis
Burden of Disease

- Constant sputum, cough, and dyspnea
- Malnutrition, malabsorption, bulky diarrhea
- Decreased or absent fertility
- Sinusitis, anosmia
- Decreased social opportunity
- Social isolation
- Early death
Burden of Treatment

- Hours of therapy per day
  - Airway clearance
  - Inhaled medications
- Eating as work
- Frequent clinic visits
- Frequent prolonged hospitalizations
- High costs
Table 1. Characteristics of Patients in the Cystic Fibrosis Foundation Patient Registry

<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>22240</td>
<td>23149</td>
<td>26298</td>
<td>34547</td>
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<tr>
<td>Deaths, n</td>
<td>421</td>
<td>358</td>
<td>407</td>
<td>4402</td>
</tr>
<tr>
<td>Median age (IQR), y (range)</td>
<td>14.3 (7.7–22.5)</td>
<td>15.3 (8.1–23.7)</td>
<td>16.7 (8.5–26.1)</td>
<td>NA</td>
</tr>
<tr>
<td>Age, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–9 y</td>
<td>7041  (31.8)</td>
<td>6833  (29.5)</td>
<td>7370  (28.0)</td>
<td>NA</td>
</tr>
<tr>
<td>10–17 y</td>
<td>7041  (29.5)</td>
<td>6422  (27.7)</td>
<td>6423  (24.4)</td>
<td>NA</td>
</tr>
<tr>
<td>18–29 y</td>
<td>6570  (24.6)</td>
<td>6299  (27.2)</td>
<td>7536  (28.7)</td>
<td>NA</td>
</tr>
<tr>
<td>30–39 y</td>
<td>2119  (9.5)</td>
<td>2173  (9.4)</td>
<td>2733  (10.4)</td>
<td>NA</td>
</tr>
<tr>
<td>≥40 y</td>
<td>1034  (4.6)</td>
<td>1422  (6.1)</td>
<td>2236  (8.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>10464 (47.1)</td>
<td>11097 (47.9)</td>
<td>12498 (48.3)</td>
<td>16972 (47.7)</td>
</tr>
<tr>
<td>Median age at diagnosis among patients with incident disease* (IQR), y</td>
<td>0.5 (0.2–2.6)</td>
<td>0.5 (0.0–4.9)</td>
<td>0.1 (0.0–6.2)</td>
<td>0.5 (0.1–3.2)</td>
</tr>
<tr>
<td>Race/ethnicity, n (%)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>20072 (90.3)</td>
<td>20656 (89.2)</td>
<td>23141 (88.0)</td>
<td>31222 (87.8)</td>
</tr>
<tr>
<td>Nonblack Hispanic</td>
<td>1156  (5.2)</td>
<td>1383  (6.0)</td>
<td>1744  (6.6)</td>
<td>2267 (6.6)</td>
</tr>
<tr>
<td>Other</td>
<td>1012  (4.6)</td>
<td>1110  (4.8)</td>
<td>1413  (5.4)</td>
<td>1962 (5.5)</td>
</tr>
<tr>
<td>F508del mutation, n (%)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 copies</td>
<td>9820  (51.0)</td>
<td>10480 (50.1)</td>
<td>11484 (47.6)</td>
<td>14525 (46.4)</td>
</tr>
<tr>
<td>1 copy</td>
<td>7279  (37.8)</td>
<td>7952 (38.0)</td>
<td>9531 (39.5)</td>
<td>12309 (39.3)</td>
</tr>
<tr>
<td>0 copies</td>
<td>2166  (11.2)</td>
<td>2506 (12.0)</td>
<td>3110 (12.9)</td>
<td>4477 (14.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2875  (13.4)</td>
<td>2211 (9.6)</td>
<td>2173 (8.3)</td>
<td>4236 (11.9)</td>
</tr>
<tr>
<td>Ever received lung transplant, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with incident disease* who were asymptomatic at diagnosis, n (%)</td>
<td>136 (13.9)</td>
<td>242 (26.0)</td>
<td>507 (57.1)</td>
<td>7327 (28.8)</td>
</tr>
</tbody>
</table>

IQR = interquartile range; NA = not applicable.
* For the purpose of these analyses, patients were considered to have incident disease the year they were diagnosed.
Table 2. Mortality Rate Ratios Observed in the Cystic Fibrosis Foundation Patient Registry From 2000 to 2010

<table>
<thead>
<tr>
<th>Variable</th>
<th>Person-Years</th>
<th>Hazard Ratio (95% CI)</th>
<th>Adjusted Hazard Ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 y</td>
<td>163 947</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1–4 y</td>
<td>63 798</td>
<td>0.84 (0.78–0.91)</td>
<td>0.81 (0.74–0.89)</td>
</tr>
<tr>
<td>5–9 y</td>
<td>17 722</td>
<td>0.77 (0.68–0.86)</td>
<td>0.79 (0.69–0.91)</td>
</tr>
<tr>
<td>10–25 y</td>
<td>17 892</td>
<td>0.57 (0.51–0.64)</td>
<td>0.57 (0.50–0.65)</td>
</tr>
<tr>
<td>≥25 y</td>
<td>83 566</td>
<td>0.39 (0.32–0.46)</td>
<td>0.38 (0.31–0.47)</td>
</tr>
<tr>
<td><strong>Symptomatic at diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>232 563</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>No</td>
<td>29 285</td>
<td>0.71 (0.62–0.82)</td>
<td>0.65 (0.55–0.76)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>125 354</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Male</td>
<td>136 503</td>
<td>0.85 (0.80–0.90)</td>
<td>0.81 (0.76–0.87)</td>
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<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>233 584</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Nonblack Hispanic</td>
<td>15 471</td>
<td>1.42 (1.24–1.63)</td>
<td>1.61 (1.37–1.87)</td>
</tr>
<tr>
<td>Other</td>
<td>12 802</td>
<td>1.09 (0.94–1.26)</td>
<td>1.31 (1.10–1.55)</td>
</tr>
<tr>
<td><strong>F508del mutation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 copies</td>
<td>116 648</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1 copy</td>
<td>90 713</td>
<td>0.82 (0.76–0.88)</td>
<td>0.86 (0.80–0.93)</td>
</tr>
<tr>
<td>0 copies</td>
<td>28 563</td>
<td>0.69 (0.61–0.77)</td>
<td>0.75 (0.66–0.85)</td>
</tr>
<tr>
<td><strong>Calendar year</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>–</td>
<td></td>
<td>0.965 (0.956–0.974)</td>
<td>0.982 (0.972–0.993)</td>
</tr>
<tr>
<td><strong>10-y change</strong></td>
<td></td>
<td></td>
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<tr>
<td>–</td>
<td></td>
<td>0.70 (0.64–0.77)</td>
<td>0.83 (0.75–0.93)</td>
</tr>
</tbody>
</table>

* Adjusted for age at diagnosis, presentation at diagnosis, gender, race/ethnicity, and F508del mutation status.
† 1.8% improvement in survival during 2000 to 2010.
‡ Cumulative 17% adjusted reduction in mortality during the decade, which can be derived from the calendar year mortality ratio of 0.982 (i.e., 1.8% improvement in survival) as follows: (0.982)^10 = 0.83.
The most optimistic projection (dotted line) assumes that mortality will continue to decrease indefinitely at the rate observed between 2000 and 2010 (1.8% per year). The solid line represents survival if mortality does not decrease further (i.e., stays at 2010 levels). The other projection (dashed line) assumes that mortality decreases at half the rate seen from 2000 to 2010 (0.9% per year).
Table 3. Projections of Median Survival of Children Born and Diagnosed With Cystic Fibrosis in 2010 Under 3 Scenarios of Rate of Improvement in Survival*

<table>
<thead>
<tr>
<th>Group</th>
<th>Median Survival (95% CI), y</th>
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<tr>
<td></td>
<td>No Further Improvement</td>
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<tr>
<td>Overall</td>
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<tr>
<td>2 copies of F508del mutation</td>
<td>39 (38–40)</td>
</tr>
<tr>
<td>1 copy of F508del mutation</td>
<td>40 (39–42)</td>
</tr>
<tr>
<td>No F508del mutation</td>
<td>46 (41–53)</td>
</tr>
<tr>
<td>Females</td>
<td></td>
</tr>
<tr>
<td>2 copies of F508del mutation</td>
<td>37 (35–39)</td>
</tr>
<tr>
<td>1 copy of F508del mutation</td>
<td>38 (36–41)</td>
</tr>
<tr>
<td>No F508del mutation</td>
<td>44 (38–57)</td>
</tr>
<tr>
<td>Males</td>
<td></td>
</tr>
<tr>
<td>2 copies of F508del mutation</td>
<td>40 (39–42)</td>
</tr>
<tr>
<td>1 copy of F508del mutation</td>
<td>42 (39–45)</td>
</tr>
<tr>
<td>No F508del mutation</td>
<td>49 (40–70)</td>
</tr>
</tbody>
</table>

* Data were used for Figure 3.
† 0.9%/y.
‡ 1.8%/y.
Who is Providing Routine Care?

- Cross-disciplinary care
  - Clinicians
  - Respiratory therapists
  - Pharmacists
  - Dietician
- Psychosocial support
  - Patients
  - Families
  - Health Care Systems
Limitations of CF Sleep Literature

- Age range
- Disease stability at time of testing
- Small numbers
- Different lung baseline function at enrollment
- Methods for assessing sleep
- Different definitions of nighttime hypoxia
- Year of study
- Sea level bias (all but 1 study < 1000 ft elevation)
- Variability of results limit ability to generalize
CF Features Potentially Impacting Sleep

- Chronic cough
- Upper airway obstruction
- Musculoskeletal pain
- GERD
- Abdominal discomfort and urgency
- Overnight enteral nutrition
- Medications
- Depression

Subjective Sleep Complaints

- Sleep-onset insomnia
- Frequent awakenings
  - Underestimated as most studies done in stable patients
- Night cough
- Snoring
  - Obstructive sleep apnea more of an issue for children
- Excessive daytime sleepiness
- Headaches
- Anxiety
- Frequent defecation and reflux
- Restless legs syndrome
Subjective and Objective Data Relationship is Modest

- Healthy individuals cough < 1/hr and rarely during sleep
- Patients with lung disease often have nocturnal cough
  - Nocturnal coughing is more typically observed during wakefulness than as a cause of arousal
- 80% of children with CF can display nocturnal cough, however, in the stable state (FEV1 72% predicted) it is present 0.6 to 0.9 seconds per hour
  - Cough more than healthy children but duration of cough is relatively brief
  - Yet questionnaire studies often report high rates of cough-associated sleep disruption

Clin Chest Med 2014; 35:495
Objective Sleep Data

- Despite subjective complaints most adult studies have shown modest abnormalities
  - Reduced efficiency, reduced REM sleep
  - Sleep architecture otherwise preserved
  - Arousals not typically increased
  - Sleep apnea not typically present in adults
- Desaturation is usually present
  - No consensus on definition of nocturnal hypoxia that warrants therapy
    - SpO2 < 90% for 10% of recording time? SpO2 nadir < 85%?
    - Lung function not a consistent predictor of nocturnal hypoxia
      - Resting SaO2 may be best clue
      - Drop in ventilation with sleep may explain the hypoxia

Sleep in CF Patients vs Controls

• Study Aim
  • Compare sleep parameters between patients with CF (severe airflow limitation) and healthy controls
  • CF patients with severe airflow obstruction (FEV1 < 40% predicted) compared with healthy age matched controls
• Studies
  • Sleep diaries and ESS
  • Polysomnography, MSLT*
    • 4 naps and awaken once fallen asleep
  • 6MWT, spiro, ABGs

Eur Respir J 2002; 19:504
## Demographics and PFT Data

<table>
<thead>
<tr>
<th></th>
<th>CF (n=19)</th>
<th>Con (n=10)</th>
<th>p-value</th>
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<tr>
<td>Age, y</td>
<td>30</td>
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</tr>
<tr>
<td>M/F</td>
<td>15/4</td>
<td>5/5</td>
<td></td>
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<tr>
<td>BMI</td>
<td>21.8</td>
<td>25.5</td>
<td>0.006</td>
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<td>FEV1 %pred</td>
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<tr>
<td>pH</td>
<td>7.4</td>
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<tr>
<td>PaCO2</td>
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<tr>
<td>PaO2</td>
<td>65.6</td>
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<tr>
<td>SaO2</td>
<td>92.1</td>
<td></td>
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<tr>
<td>SaO2 supine awake</td>
<td>87</td>
<td>95</td>
<td>.001</td>
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<td>6MWT, meters</td>
<td>407</td>
<td>534</td>
<td>.012</td>
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<td>6MWT, minSaO2</td>
<td>86.6</td>
<td>93.5</td>
<td>.008</td>
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## Diary and ESS

<table>
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<th>CF (n=15)</th>
<th>Con (n=8)</th>
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<tr>
<td>Diary report days</td>
<td>12.3</td>
<td>13.9</td>
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<tr>
<td>Awakenings/h</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td>TST, h</td>
<td>8.1</td>
<td>7.3</td>
</tr>
<tr>
<td>Caffeine drinks/day</td>
<td>1.5</td>
<td>1.3</td>
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<tr>
<td>Alcohol drinks/day</td>
<td>0.3</td>
<td>0.3</td>
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<tr>
<td>ESS</td>
<td>7.3</td>
<td>5.6</td>
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</table>
MSLT

6.7 minutes

4.6 minutes
## Polysomnography Data

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<th>Con</th>
<th>p-value</th>
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<tr>
<td>TST, h</td>
<td>4.7</td>
<td>5.9</td>
<td>.048</td>
</tr>
<tr>
<td>SE, %</td>
<td>71</td>
<td>93</td>
<td>.004</td>
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<tr>
<td>Sleep latency, m</td>
<td>36</td>
<td>4.8</td>
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<tr>
<td>WASO, m</td>
<td>69.6</td>
<td>20.4</td>
<td>.002</td>
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<tr>
<td>Stage 1, % TST</td>
<td>16.8</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>Stage 2, % TST</td>
<td>46.7</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>SWS, % TST</td>
<td>22.7</td>
<td>24.2</td>
<td></td>
</tr>
<tr>
<td>REM, % TST</td>
<td>13.8</td>
<td>19.5</td>
<td></td>
</tr>
<tr>
<td>PLM/h</td>
<td>3.6</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>AHI</td>
<td>1.5</td>
<td>3.5</td>
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<tr>
<td>TST SaO2%</td>
<td>84.4</td>
<td>94.3</td>
<td>.0001</td>
</tr>
<tr>
<td>REM SaO2%</td>
<td>83.5</td>
<td>94.6</td>
<td>.0001</td>
</tr>
</tbody>
</table>
Correlation Between Mean $\text{SaO}_2$ and Sleep Efficiency
Conclusions

- Adult CF patients with severe airflow obstruction have sleep restriction and sleep disruption
  - Cough, hypoxia, medications, pain, WOB?
    - Techs reported coughing in 4 patients
    - Neither obstructive nor central apneas are described
- CF patients had daytime hypoxemia which worsened during sleep
  - Nocturnal oxygenation was associated with sleep efficiency
- Unclear why there is prolonged latency at night and short sleep latency during the MSLT
  - Beta-agonists?
Effects of NREM Sleep on Ventilation and Respiratory Mechanics in CF

- **Study Aim**
  - Quantify effect of sleep on ventilation, airflow resistance, and FRC in patients with CF (at altitude)

- **5 adult CF patients (4M,1F) in stable state**

- **Studies**
  - Lung function tests, ABG, polysomnography
  - Esophagoal balloon, supraglottic catheter
  - Horizontal volume displacement plethysmograph
    - Tightly fitting face mask (measure FRC)
  - 36 h

# Demographics and PFTs

<table>
<thead>
<tr>
<th>Upright</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>29.6</td>
</tr>
<tr>
<td>PaO₂, mm Hg (room air)</td>
<td>54.2</td>
</tr>
<tr>
<td>PaCO₂, mm Hg (room air)</td>
<td>43.8</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>42.2</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>54.7</td>
</tr>
<tr>
<td>TGV at FRC, % predicted</td>
<td>139.0</td>
</tr>
<tr>
<td>RV, % predicted</td>
<td>255.8</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>95.8</td>
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</table>
## Polysomnography Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep duration, min</td>
<td>280.4 (4.7 h)</td>
</tr>
<tr>
<td>Sleep latency, min</td>
<td>6.7</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>68.3</td>
</tr>
<tr>
<td>Stage 1, % TST</td>
<td>15.5</td>
</tr>
<tr>
<td>Stage 2, % TST</td>
<td>45.9</td>
</tr>
<tr>
<td>Stage 3, % TST</td>
<td>38.6</td>
</tr>
<tr>
<td>REM</td>
<td>0</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td></td>
</tr>
<tr>
<td>Pre-sleep</td>
<td>40.4</td>
</tr>
<tr>
<td>Post-sleep</td>
<td>38.6</td>
</tr>
<tr>
<td>FRC, pre-sleep supine, L</td>
<td></td>
</tr>
<tr>
<td>Plethysmograph</td>
<td>4.33</td>
</tr>
<tr>
<td>Helium dilution</td>
<td>2.48</td>
</tr>
</tbody>
</table>
Changes in SaO2 With Sleep
Ventilatory Pattern in Sleep

- Tidal volume decreases 0.48L to 0.38L to 0.37L
- Respiratory rate does not significantly change
- Minute ventilation drops 11.1L to 9.32L to 9.17L
Ventilatory Pattern in Sleep

- Po.1 decreases during sleep compared with wakefulness
  - 3.33 to 1.79 to 1.99 cm H2O
  - Suggests sleep-associated reduction in respiratory neuromuscular output
Resistance and FRC

A

B

FRC (liters)

SLEEP STAGE

W 2 3-4
People will agree to anything
Hypoxia worsens with sleep
NREM sleep is associated with a decline in the minute ventilation due to a drop in the tidal volume
- Change in airway resistance?
- No obvious change in FRC
Reduction in respiratory neuromuscular output during sleep likely contributes to the reduced ventilation
Unfortunately no REM sleep
Subjective Sleep Quality in CF

- **Study Aim**
  - Compare subjective sleep quality as determined by the Pittsburgh Sleep Quality Index with polysomnography

- **Study Population**
  - 37 adult patients clinically stable
  - Moderate or severe lung disease (based on FEV1 % predicted)

- **Studies**
  - Lung function measurements
  - ABG
  - Pittsburgh Sleep Quality Index
    - ≤ 5 = “good” sleeper
  - Polysomnography

Sleep Med 2002; 3:205
Pittsburgh Sleep Quality Index

- Self-rated questionnaire
- Assesses sleep quality and disturbances over a 1 month time interval
- 19 self-rated questions grouped into 7 component scores, each weighted 0-3
  - Sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, daytime dysfunction
- Seven components are summed to yield a global score
- Score > 5 considered poor sleep quality
Study Results

- **N = 37**
- **Lung function and ABGs**
  - FEV1 18% to 70% predicted
  - 12/37 hypercapnic (PaCO₂ > 44 mm Hg)
  - 4/37 hypoxemic (PaO₂ < 60 mm Hg on room air)
- **PSQI**
  - 14/37 (38%) “poor” sleepers
## Demographics, ABGs, Lung Function

<table>
<thead>
<tr>
<th>Component</th>
<th>PSQI ≤ 5 (n=23)</th>
<th>PSQI &gt; 5 (n=14)</th>
<th>Component score differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>14 M, 9 F</td>
<td>6M, 8F</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>26</td>
<td>29</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>FEV1 (% pred)</td>
<td>38</td>
<td>33</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>43</td>
<td>45</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>BMI</td>
<td>19</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>69</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>RV (% pred)</td>
<td>236</td>
<td>230</td>
<td></td>
</tr>
<tr>
<td>TLC (% pred)</td>
<td>106</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>MIP/MEP</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Relationship Between $\text{PaCO}_2$ (mmHg) and Global PSQI.
Polysomnography Results

33 of 37 undergo room air polysomnography
TST 352 minutes (5.9 hr), Sleep latency 11.4 minutes
PSQI estimates TST 456, Sleep latency 22.7 min
Sleep architecture and arousal index normal
Sleep efficiency 87%
Significant correlation between SpO₂ nadir and PQSI

<table>
<thead>
<tr>
<th>N=33</th>
<th>TST RDI</th>
<th>REM RDI</th>
<th>NREM RDI</th>
<th>REM %TST</th>
<th>TST min avg SpO₂%</th>
<th>SpO₂% Nadir</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean</td>
<td>3.1</td>
<td>11.9</td>
<td>0.7</td>
<td>20.7</td>
<td>90.1</td>
<td>82.5*</td>
</tr>
</tbody>
</table>
Sleep efficiency and REM as a percent of TST: differences between patients when grouped according to PSQI score, * $P < 0.05$.

No difference between “good” and “poor” sleepers in TST, sleep latency, sleep oxygenation, RDI or arousal index
Conclusions

• Subjective poor sleep quality is common in CF patients
• Subjective complaints centered around sleep quality, sleep latency, and sleep disturbance
• Subjective poor sleep quality associated with hypercarbia and SpO₂ nadir
• Subjective poor sleep quality associated with sleep efficiency and REM as a % TST but not RDI or arousal index
• This study is “exploratory”
Treatment

• Limited data on impact of supplemental oxygen on sleep in CF patients with hypoxia
  • 4 studies evaluated effect of oxygen during sleep with polysomnography
    • Improved SpO2 during REM and NREM
    • Mild hypercapnia but data inconsistent
    • Shorter sleep latency
    • Reduced REM as % of TST
    • No effect on TST or arousal index
    • No impact on mood, cognitive function, medical compliance
    • Long term study by Zinman reported improved attendance at school/work without other disease modifying factors

Treatment

- Even less data on non-invasive ventilation and sleep
- Improves oxygenation and hypercarbia
- No impact on sleep architecture
- May prevent fall in tidal volume seen during sleep
- Long-term impact on lung function not clear
- Inconsistent subjective improvement
- Remember non-invasive ventilation risks
  - Pneumothorax
  - Reduced airway clearance

Thorax 2008; 63:72; Sleep Med Rev 2004; 8:295; Cochrane Database Sys Rev 2013 (7)