The Lung Clearance Index & Cystic Fibrosis

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Cystic Fibrosis (CF)

- Autosomal Recessive disease
- Cystic Fibrosis Transmembrane Conductance Regulator
  - Tsui, Riordan, Collins and colleagues in 1989
Cystic Fibrosis (CF)

- Altered salt regulation → Thick secretions
- Shortened life span
- Pulmonary Disease is the main source of morbidity and mortality
- Important to define lung function parameters that identify abnormalities as early in life as possible

Cystic Fibrosis Foundation 2008
Forced Expiratory Volume in 1 second

Main outcome measure in:
- therapeutic intervention studies
- clinical management

Rate of decline of FEV\textsubscript{1} is the best predictor of survival for CF

Corey et al. *Journal of Pediatrics* 1997
Limitations of FEV$_1$

- FEV$_1$ unreliable if < 6 yrs of age
- Many CF children have normal FEV$_1$ even though they have disease
  - Radiographic (CT)
  - Bronchoalveolar Lavage

Gibson et al. AJRCCM 2003
Konstan et al. Pediatric Pulmonology 1997
Lung Clearance Index (LCI) from Multiple Breath Washout (MBW)

- Ventilation inhomogeneity via washout of an inhaled gas mixture
- Done during tidal breathing
- Can be done from cradle to grave
Lung Clearance Index

- Two Phases
  - Washin Phase
  - Washout Phase
MBW – Washin phase

Gas supply:
4% SF₆, 4% He, 21% O₂, balance N

Pneumotach

Capillary to mass spectrometer
MBW – Washout phase

Pneumotach

SF$_6$

Capillary to mass spectrometer
Flowmeter

4 % SF₆

Air

Equilibration – end Washin

Flowmeter

Gas Concentration

Time
Air

Switch gas during expiration at end of washin

4 % SF$_6$

Flowmeter

Gas Concentration

Time
First Breath In - Washout

Air

4 % SF\textsubscript{6}

Flowmeter

Gas Concentration

Time
First breath out – Washout

Air

$4\% \text{ SF}_6$

Flowmeter

Gas Concentration

Time
Second breath out – Washout

Air

4 % SF₆

Flowmeter

Gas Concentration

Time
Parameters from MBW

FRC = \frac{\text{Cumulative Expired Volume (CEV) gas}^*}{(C_{\text{start}} - C_{\text{end}})}

LCI = \frac{\text{Cumulative Expired Volume}}{\text{Functional Residual Capacity}}

*Volume you exhale to completely wash the SF$_6$ out of your lungs
Lung Clearance Index (LCI) versus Age in CF Patients and Healthy Controls

LCI, FEV$_1$ and MEF$_{50}$ Across Ages

Kraemer et al. AJRCCM 2005
Lung Clearance Index

- Clear cut-offs between CF and controls
- LCI reference ranges same across all ages
- LCI increases with progression of disease

Aurora et al. *Thorax* 2004
Kraemer et al. *AJRCCM* 2005
Using the LCI to detect a treatment change over time?

- Hypertonic Saline
- DNAse
Normal Airway

- Airway
- Mucus
- Airway surface fluid
  - Mucociliary cell
  - Goblet cell
  - Basal cell

Normal mucociliary transport

Airway surface fluid

Na⁺, Cl⁻
CF & Hypertonic Saline

Ratjen F. New England Journal of Medicine 2006
CF and DNAse
Rationale

- HS & DNAse improve FEV$_1$ in CF patients with abnormal FEV$_1$
- HS & DNAse have never been studied in CF patients with normal FEV$_1$ because FEV$_1$ cannot be used as an outcome parameter in these patients
Study Hypotheses

- The LCI will detect a treatment effect from Inhaled Hypertonic Saline (7%) in pediatric CF patients with FEV$_1 \geq 80\%$ predicted.

- The LCI will detect a treatment effect from Inhaled DNAse in pediatric CF patients with FEV$_1 \geq 80\%$ predicted.
Study Design

- Two studies
- Single centre, randomized, placebo-controlled crossover study
- Two intervention periods of 28 days each
- Washout period of 28 days
Visit 1: Treatment (28 Days) → Placebo (28 Days)

Visit 2: Washout (28 Days)

Visit 3: Placebo (28 Days) → Treatment (28 Days)

Visit 4: STOP
Progress to Date

- 18 patients enrolled in each study
- Data collection should be complete by December 2008
Significance

- Non invasive tool
- Can be used in children < than 6 years old
- More sensitive than FEV$_1$
- Future role in assessing novel therapeutics
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