Exercise in Cystic Fibrosis

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Objectives

- Why is exercise capacity abnormal in CF?
- Can exercise be used to predict outcomes in CF?
- What are the benefits of exercise in CF?
- Do exercise programs improve outcomes in patients with CF?
- What are potential negative impacts of exercise in CF?

Why is exercise capacity abnormal in CF?
Components of Physical Fitness

- Morphologic component
  - Body mass for height
  - Body composition
  - Subcutaneous fat distribution
  - Abdominal visceral fat
  - Bone density
- Flexibility
- Muscular component
  - Power
  - Strength
  - Endurance
- Motor component
  - Agility
  - Balance
  - Coordination
  - Speed of movement
- Cardiorespiratory component
  - Submaximal exercise capacity
  - Maximal aerobic power
  - Heart functions
  - Lung function
- Metabolic component
  - Glucose tolerance
  - Insulin sensitivity
  - Lipid and lipoprotein metabolism
  - Substrate oxidation characteristics

Exercise Response in CF

- Abnormal exercise capacity in CF
  - Associated with very mild disease
  - Worsens with disease progression
  - Decreases maximum work
  - Diminished rate of response to exercise
  - Why?

Abnormal Muscle Function

- Comparison of exercise capacity for lean body mass (muscle mass) between subjects with and without CF
- Subjects with CF able to:
  - Produce less work per kilogram of LBM
  - Had less efficient work
  - Abnormal use of substrate (fuel) by muscle
  - Indicates abnormal use of fuel by muscles
Decreased Muscle Mass
- Chronic infection/inflammation
- Poor nutrition
- Deconditioning
- ? Abnormal anabolic steroid response
- Treatment → steroids

Abnormal Breathing Response
- Breathing response to exercise in CF
  - Small breaths
  - Rapid breathing
- Ideal response to exercise
  - Large breaths
  - Less rapid breathing
- Small breaths less efficient for gas exchange

Lung Disease
- CF associated with:
  - Areas of lung that don’t exchange gas
    - Requires more breathing for less gas exchange
  - Inflamed airways
    - ↑ work of breathing
  - Propensity to trap gas in lungs
    - Air trapping may worsen with exercise and limit capacity
Less Resting Work Capacity

- Work limited by maximal oxygen consumption
- CF associated with:
  - Higher resting oxygen consumption
  - ↑ work by respiratory muscles at rest
  - Closer to maximal oxygen consumption at rest
  - Improves after antibiotics

Abnormal Pulmonary Blood Vessels

- Pulmonary blood vessels damaged by progression of lung disease
- ↑ CO2 and ↓ O2 constrict pulmonary blood vessels
- Combination → right heart strain
- Normal exercise:
  - ↑ pulmonary blood flow with ↓ resistance

Abnormal Heart Function

- Studies have shown ↓ left heart function in CF
- Secondary to chronic inflammation
- Function worsens with ↑ inflammatory markers
- Improves with ↓ inflammatory markers
Can exercise be used to predict outcomes in CF?

Exercise as a Biomarker

- Nixon PA et al. NEJM. 1992
  - Followed 109 CF pts for 8 yrs after undergoing cardiopulmonary exercise testing (CPET)
  - Survival assessed based on peak VO2
    - 83% in highest group
    - 52% in middle group
    - 28% in lowest group
  - Age, sex, BMI, FEV1, and end-tidal PCO2 at peak exercise - NOT independently correlated with mortality

Exercise as a Biomarker

  - Followed 77 children with CF 3 yrs after CPETs
  - Lung function, anthropometric data and muscle strength not predictive of time to hospitalization
  - Peak VO2-only variable associated with time to hospitalization
What are the benefits of exercise in CF?

Exercise in CF

- Physical training regimen in CF may:
  - Improve shortness of breath (dyspnea)
  - Improve exercise tolerance – independent risk factor for mortality in CF
  - Help manage CFRD
  - Improve appetite
  - Give more positive body image
  - Improve mucus clearance Salh W et al. 1989
  - Reduce residual volume (trapped gas in lung) Andreasson B et al. 1987
  - Delay osteoporosis by improving bone mineral density (BMD)
  - Decrease anxiety and depression
  - Enhance feelings of well-being
  - Enhance performance at work, recreation, and sports

Exercise Training in CF

- Multiple studies have shown training may:
  - Improved fitness
  - ↓ decline in lung function Schneiderman B et al. 2014
  - Possible ↑ quality of life
  - ↑ longevity of life
- Studies have assessed response of CF patients to:
  - Long and short programs of aerobic exercise
  - Anaerobic training programs
  - Combination exercise programs
  - Inspiratory muscle training (IMT)
- Studies looking for changes in:
  - Lung function
  - Quality of life
  - Exercise capacity
Exercise – The First Potentiator

- Exercise is associated with a significant decrease in nasal potential difference in CF patients and controls.
- Response more exuberant in CF pts.
- No significant difference in PD at end of exercise.
- Response in PD to amiloride is decreased after exercise in CF and control patients.
- Exercise may inhibit amiloride sensitive Na channels.
- PD response to solution of amiloride and low chloride and isoprenaline unchanged by exercise.
- PD change likely not due to Cl channel.

Hebestreit A et al. AJRCCM. 2001

Fig. 1. Nasal PD at rest and during exercise in nine patients with CF and nine healthy control subjects. PD was measured with the exploring electrode perfused with isotonic saline solution. Data are means ± SEM.

Hebestreit A et al. AJRCCM. 2001

Normal Cell  CF Cell

Ashlock CF Conf 2003
Exercise and ASL

- Airway surface liquid (ASL) is necessary for ciliary action and mucus clearance
- Primarily regulated through apical membrane trafficking of Na and Cl which regulate water flow.
- Na is primarily regulated by ENaC
- Cl is primarily regulated by CFTR and to a lesser extent the CaCC

Exercise and ASL

- Exercise may regulate ASL in 2 ways
- Moderate exercise releases catecholamines (epinephrine and norepinephrine) that stimulate adrenergic receptors (ADBR2) in airway epithelium
  - Results in activation of protein kinase A (PKA)
    - PKA activates CFTR and ENaC
    - CFTR (if present) activation inhibits ENaC
      - Results in ↑ Cl secretion and ↓ Na absorption across airway lumen
    - If CFTR is absent, ENaC is activated
      - Results in ↑ Na absorption across airway lumen
Exercise and ASL

- ↑ ventilation causes mechanical stress of airway epithelium
- Stimulates ATP release
- ATP and adenosine (ADO) stimulate purinergic receptors (P2Y) on cell membrane
- P2Y: activation causes ↓ in phosphatidylinositol 4,5-bisphosphate (PIP2)
  - PIP2 is necessary for ENaC activation
  - ↓ Na+ absorption across airway lumen
- P2Y: activation also stimulates Ca release from endoplasmic reticulum
  - Stimulates CaCC
  - ↓ Cl secretion across airway lumen
Do exercise programs improve outcomes in patients with CF?

Assessing Exercise in CF

- Six minute walk test (6MWT)
  - Walk as far and as fast as comfortable in 6 min
  - Monitor oxygen saturation
  - Rough estimation of exercise capacity
- Shuttle test
  - Back and forth between two points
  - Time allowed for trip continues to shorten
  - Estimation of exercise capacity
  - Incorporates more "components" of physical fitness
- Cardiopulmonary exercise test
  - Gold standard for assessing exercise function
  - Measures maximum exercise capacity
  - Able to interpret physiologic limitations to exercise
- Anaerobic exercise test
  - Estimates anaerobic power and capacity
  - Allows for assessment of different metabolic pathways

Aerobic Training in CF

- Turchetta et al.
  - 12 weeks of treadmill exercise
  - ↑ fitness
  - No change in lung function
- Moorcroft et al.
  - 12 months of unsupervised aerobic training of various types
  - Improved exercise response
  - Trend towards maintenance of lung function
- Schneiderman et al.
  - 3 yr program of aerobic training
  - ↓ rate of decline in lung function
  - Most subjects:
    - ↑ feeling better about themselves
    - ↑ energy
    - ↓ chest congestion
Anaerobic Training in CF

- Orenstein et al.
  - 12 months of anaerobic and aerobic training
    - ↑ exercise capacity
    - ↑ strength
- Klijn et al.
  - 3 month program of anaerobic training
    - ↑ anaerobic performance
    - ↑ aerobic performance
    - ↑ wellbeing scores
- Selvadurai et al.
  - Anaerobic training program
    - ↑ strength
    - ↑ lung function compared to controls

Inspiratory Muscle Training

- Training program – patients breath against resistance
- Enright et al.
  - 3 groups
    - High resistance
    - Low resistance
    - Control
  - High resistance group
    - ↑ inspiratory muscle function
    - ↑ work capacity
    - ↓ diaphragm thickness
    - Improved lung volumes
    - ↓ anxiety and depression
- Large review of all literature unable to give recommendation

What’s Best?

- Bradley J and Moran F. Cochrane Database Syst Rev. 2008
  - Likely benefit from training programs
  - Not clear best choice between:
    - Aerobic
    - Anaerobic
    - Both
- Most studies:
  - Too short
  - Not well designed
  - Not good follow-up
- van Doorn N. Disabil Rehabil. 2010.
  - Review of randomized controlled trials of exercise programs in children with CF
  - Only 4 studies met inclusion criteria
  - Evidence to support strength and aerobic training programs
  - Positive impact on pulmonary function, strength and aerobic fitness
Long Term Program for Long Term Benefit

- Recent review of studies to improve physical activity in CF patients
- No programs less than 6 months promoted continued physical activity
- Programs longer than 12 months showed best ongoing adherence
- No program showed significant improvement in quality of life

Cox NS et al. Cochrane Database Syst Rev. 2013

What are potential negative impacts of exercise in CF?

Heat acclimation

- Athletes acclimate to heat by:
  - Improved thermoregulation
  - Lower body temperature
  - Faster onset of sweating
  - Vasodilation of skin vasculature
  - Improved cardiovascular response
  - Diminished heart rate response
  - Diminished sweat electrolyte concentration
Hypohydration

- ↑ physiologic strain
- ↓ exercise performance
- Negates advantages of aerobic fitness
- Negates advantages of heat acclimation

Mechanism of Dehydration

- ↑ sweat
  - 1.0-2.5 L/hr with ↑ exercise in heat
- ↓ intake
  - Thirst not perceived until ~2% body weight loss
    - 1.4 L in 70 kg man
- ↓ bioavailability
  - ↓ gastric emptying with hypohydration (20-25%)

Normal Outcome

![Image of a graph showing the relationship between two variables, likely from Sawka MN and Montain SJ, 2000]
Consequences

Minor
- Tiredness
- Decreased urine output
- Muscle weakness
- Headache
- Lightheadedness

Major
- Heat injury (heat exhaustion, heat stroke)
- Delirium
- Seizures
- Hypovolemic shock
- End organ failure
- Coma and death

Exercise Response to Hypohydration

- Temperature ↑ 0.1-0.23 °C (0.18-0.41 °F) for every % BWL
- Hypohydration impairs both:
  - Dry (radiant) heat loss
    - ↓ skin blood flow with volume loss
  - Evaporative heat loss
    - Sweat production ↓ % with ↑ % BWL
- Hypohydration negates fitness and heat acclimatization

Heat Retention

- Normal subambient work output (%)
- Temperature (°C)
- Flat line

FIGURE 5: Effects of hydration level and climate temperature on subambient work output (%); BWL, body weight loss due to dehydration

Sawka MN and Montain SJ, 2000
Electrolyte Imbalance

- Sweat Na and Cl concentrations 3-4x > in CF (Kriemler S et al., 1999; Orenstein D et al., 1984)
- Volume of sweat equal to controls
- Leads to ↓ Na and Cl serum concentrations
- Serum osmolality dependent on Na and Cl concentrations
  - ↓ serum osmolality
Abnormal Acclimation in CF

- Orenstein D et al., 1984
- 70 minutes of exercise on 8 consecutive days
- CF subjects and control subjects showed:
  - ↓ temperature response to exercise by day 8
  - ↓ HR response to exercise by day 8
  - Control able to ↓ sweat Na and Cl by day 8
  - No change in CF group

Electrolyte Loss

<table>
<thead>
<tr>
<th>TABLE 3. Sweat responses</th>
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<tbody>
<tr>
<td>CF</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Day 1</td>
</tr>
<tr>
<td>Sweat Na⁺ (mmol/L)</td>
</tr>
<tr>
<td>Sweat Cl⁻ (mmol/L)</td>
</tr>
<tr>
<td>Sweat volume (ml/kg)</td>
</tr>
</tbody>
</table>

Values are means ± SD. Sweat responses in 15 cystic fibrosis (CF) patients and 15 normal controls. Same format as Table 1. * CF significantly different from control P < 0.05. ↓ Too loss expressed as mmol lost per m² of body surface area.

Electrolyte Loss

<table>
<thead>
<tr>
<th>TABLE 4. Solute electrolyte concentrations</th>
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<tbody>
<tr>
<td>Day 1</td>
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<tr>
<td>---</td>
</tr>
<tr>
<td>CF</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
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<tr>
<td>F (mg/day)</td>
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</tbody>
</table>

Values are means ± SD. Sodium, potassium, and F (molecular weight 31) values before and after exercise were shown in Table 1. F is a significant change from before to after exercise (day 8). There was no difference between groups in sodium or potassium. F was significantly lower in the CF group compared to controls.

(Orenstein D et al., 1984)
Decreased Osmolality

Normal Exercise Response:
↑Osmolality → ↑Thirst

<table>
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<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>F</th>
<th>Pre</th>
<th>Post</th>
<th>P</th>
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<tr>
<td>Serum</td>
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<tr>
<td>CF</td>
<td>301.7</td>
<td>310.7</td>
<td>&lt;0.035</td>
<td>301.7</td>
<td>309.1</td>
<td>&lt;0.01</td>
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<tr>
<td>Control</td>
<td>319</td>
<td>314</td>
<td>&lt;0.004</td>
<td>319</td>
<td>318.6</td>
<td>NS</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
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<td>NS</td>
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</tbody>
</table>

CF Exercise Response:
↓Osmolality → ↓Thirst

*Values are mean ± SE; CF, cystic fibrosis; serum osmolality; Zn, calcium; K, potassium; F, P<0.05. Please mean activity in log unit. V̇ E: minute at 55% VO2max in Table 5.*
Decreased Water Intake in CF

- Bar-Or O et al., 1992
- 8 children with CF and 8 control children
  - 2 exercise sessions for each child
  - ~ 90 °F and 45% humidity
  - Session 1: forced to drink every 15-20 min
  - Session 2: drink only when thirsty

- Forced drinking
  - Equal water intake in both groups
  - Normal hydration status throughout in both groups
- Thirst guided
  - CF subjects drank half as much as controls
  - CF subjects lost 2x as much weight as controls
  - No difference in urine or sweat volume

Consequences

- CF patients at ↑ risk of all dehydration related illnesses
- Special concerns include:
  - Hypochloremic metabolic alkalosis
  - Cerebral edema
  - Seizures
Prevention

- NaCl and carbohydrates with water shown to ↑ thirst drive in normal subjects
- Kriemler S et al., 1999
- 11 CF subjects
  - 3 separate exercise sessions
  - Given different drinks with each session and allowed to drink when thirsty
  - Water
  - Flavored water
  - Flavored water with 30 mmol/L NaCl and 6% carbohydrate

Prevention

- Similar fluid intake with all 3 drinks
- Similar degree of hypohydration
  - ~ 1% BWL
- Serum Na, Cl, and osmolality dropped with all 3 sessions

Hypohydration
Prevention

- 6 subjects repeated test
  - Flavored water with 50 mmol/L NaCl and 6% carbohydrate
- 50 mmol/L NaCl group
  - Drank 56% more fluid than when offered water
  - Despite preferring water
  - No evidence of hypohydration
  - No change in serum electrolytes or osmolality
  - 3x ↓ in negative fluid balance

Euhydration

Recipe for Prevention

- Gatorade
  - ~ 20 mmol/L Na
  - 6% carbohydrate
- 32 oz Gatorade + ¼ tsp table salt
  - ~ 45 mmol/L Na
  - 6% carbohydrate
- Prehydrate
- Frequent breaks for hydration
Conclusions

- CF associated with ↓ exercise capacity
  - Inherent defects
  - Disease progression
- Multiple psychological and physiologic benefits to exercise in CF
- Exercise programs
  - Improved exercise capacity
  - Improved lung function
  - May or may not improve quality of life
- Studies on exercise in CF exist, but better studies needed
- Exercise recommended for patients with CF as part of their treatment regimen

Recommendations

- Training program
  - Start light and gradually increase
  - Exercise at least 4-5 times per week
  - Combination of:
    - Aerobic
      - Biking
      - Running
      - Swimming
      - Treadmill or other aerobic machine
    - Anaerobic
      - Circuit training
      - Weight lifting
      - Sprinting
  - Vary regimen
    - More fun
    - Less likely to fail
Recommendations

- Young children – be creative
  - Children with CF as active as kids without
  - Play tends to be less vigorous
- Encourage frequent activity
- Encourage vigorous activity
- Encourage parents/siblings to be involved
- Sports!!!
- Hiking
- Biking
- Outdoor activities
  - Active video games shown to provide light-moderate activity

QUESTIONS?