Exercise Physiology in Health and Disease

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Physiologic Requirements to Perform Exercise

Metabolic Pathways for Energy Production
Major Chronic Illnesses Featuring Exercise Intolerance

- Chronic Obstructive Pulmonary Disease
- Chronic Renal Failure on Hemodialysis
- Peripheral Arterial Disease
- Congestive Heart Failure

Exercise Intolerance in COPD - The Bad Old Days -

- Airflow limitation dictates exercise tolerance
- Airflow limitation is largely irreversible
- Exercise intolerance is irremediable
Exercise Intolerance in COPD
- The Modern Approach -

- Airflow limitation has a useful reversible component in most COPD patients
- Strategies aimed at reducing the effect of airflow limitation have been developed
- Peripheral muscle dysfunction has been shown to contribute to exercise intolerance

Mechanisms of Exercise Intolerance in COPD

- Ventilatory limitation to exercise
- Peripheral muscle dysfunction

Ventilatory Limitation to Exercise Tolerance
Excessive Ventilatory Requirement and Limited Ventilatory Capacity

Dynamic Hyperinflation with Exercise in COPD

Healthy vs. COPD}

Level of exercise

Ventilation

COPD

Normal
Dynamic Hyperinflation with Exercise in COPD

Relieving Ventilatory Limitation

- Increasing Ventilatory Capacity
  - Bronchodilation
  - Respiratory Muscle Training
  - Lung Volume Reduction Surgery
  - Helium Breathing
- Reducing Ventilatory Requirement
  - Exercise Training
  - Oxygen Breathing

Mechanisms of Exercise Intolerance in COPD

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Skeletal Muscle Dysfunction in COPD

- Low Muscle Mass
- Poor Capillarity
- Low Aerobic Enzyme Concentration
- Low Fraction of Type I Fibers
- Muscle Inflammation
- Corticosteroid Myopathy
- Low Levels of Anabolic Hormones
- Vasoregulatory Abnormalities
CT Cross-Section of Healthy and COPD Thigh Muscle

Bernard et al., 1998

Skeletal Muscle Dysfunction in COPD -Mechanisms-

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Capillarity of Vastus Lateralis Muscle

Jobin, 1998

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Aerobic Enzyme Concentrations in Leg Muscles of Normal and COPD Subjects

Skeletal Muscle Dysfunction in COPD -Mechanisms-

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Vastus Lateralis Fiber-Type Proportions in Healthy and COPD Subjects

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Testosterone Levels in Men with COPD

Healthy Young Men

Casaburi, et al., AJRCCM, 2004

Skeletal Muscle Dysfunction in COPD
-Mechanisms-

• Low Muscle Mass

To What Extent is Dysfunction Due to Deconditioning?

• Corticosteroid Myopathy
• Low Levels of Anabolic Hormones
• Vasoregulatory Abnormalities

Peripheral Muscle Dysfunction
-why it matters-

• Subjectively, many COPD patients complain of muscle fatigue during exercise
• Objective evidence for muscle fatigue has been obtained
• There is evidence that muscle fatigue, not ventilatory limitation, is the limiting factor for exercise tolerance in a substantial fraction of patients

Mechanisms of Exercise Intolerance in COPD

• Ventilatory limitation to exercise

• Peripheral muscle dysfunction

Physiologically-based strategies to address one or both of these mechanisms are sought
Major Chronic Illnesses
Featuring Exercise Intolerance

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- Congestive Heart Failure

Exercise Intolerance in End-Stage Renal Disease
- Johansen, 1999

Exercise Intolerance in End-Stage Renal Disease
- Painter, 1994
Causes of Exercise Intolerance in Chronic Renal Failure

- Deconditioning
- Decreased muscle mass
- Anemia
- Cardiovascular dysfunction
- Myopathy
- Low levels of anabolic hormones
- Other abnormalities impairing muscle function

Deconditioning in the Dialysis Population

- Very sedentary lifestyle and poor quality of life
- 40% of hemodialysis patients perform only self-care activities (Gutman et al., 1981)
- However, morphologic changes in muscle not characteristic of deconditioning alone

Decreased Muscle Mass in the Dialysis Population

- In 180 stable male hemodialysis patients, 50% had muscle mass below the 10th percentile for healthy men (Williams et al., 1999).
- Lean mass loss is most pronounced in the limbs.
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Anemia as a Cause of Exercise Intolerance in the Dialysis Patient

- Hematocrit values average 26%.
- Low hematocrit levels result from decreased erythropoietin secretion by the kidneys.
- For a given blood flow level, oxygen delivery is reduced in proportion to hematocrit reduction

Erythropoetin Supplementation in Dialysis Patients

Summarizing 11 trials, including 196 patients: 61% male, average 41 years old, 2.5-12 month trial duration

- Hemoglobin level rose 6.9 → 11.2 g/dl (63%)
- VO₂max increase averaged 29% (in 8 studies)
- Lactic acidosis threshold increase averaged 22% (in 5 studies)
Effect of Erythropoetin on Muscle Oxygen Transport in Chronic Renal Failure
- Marrades et al. J Clin Inv, 1996 -

- 8 patients studied before and after EPO therapy
- Arterial and femoral venous blood sampled during incremental exercise
- EPO yielded 68% increase in [Hb] and 33% increase in VO2max
- Peak leg blood flow was lower after EPO; leg O2 delivery increased 37%
- Peak O2 extraction was low; O2 conductance from muscle capillary to mitochondria was reduced

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Impaired Cardiovascular Function in Dialysis Patients
- Common Findings -

- Left ventricular hypertrophy
- Coronary artery disease
- Impaired chronotropic response
- Congestive heart failure
- Hypertension
- Peripheral vascular disease
- Impaired baroreceptor function

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Myopathy in the Dialysis Patient

- Uremic myopathy - a syndrome of proximal muscle weakness
- Muscle biopsy characteristics
  - fiber atrophy (particularly IIb)
  - morphologic abnormalities include irregular fiber size, whorling and inclusion bodies
  - mitochondrial damage
  - low aerobic enzyme concentrations
  - loss of capillaries
- EMG shows denervation

Potential Causes of Dialysis-Associated Myopathy

- “Uremic toxins”
- Insulin resistance
- Abnormal vitamin D metabolism
- Peripheral neuropathy
- Impaired amino acid metabolism
- Deconditioning
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Androgen Deficiency in Men with Chronic Renal Failure

- Gynecomastia, impotence, testicular atrophy and infertility are common
- Majority of men with CRF have testosterone levels in the hypogonadal range
- LH and FSH levels are only moderately elevated, consistent with both 1º testicular failure and inadequate hypothalamic-pituitary response

Growth Hormone Axis Abnormalities in Chronic Renal Failure

- Muscle resistance to actions of GH and IGF1
- Increased GH production
- High serum IGF binding protein concentrations reduce bioavailability of IGF1

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Other Abnormalities Impairing Muscle Function

- Carnitine insufficiency
- Amino acid deficiencies
- Electrolyte imbalance
- Uremic toxins
- Fluid overload

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