Exercise Intolerance in Heart Failure: Significance of Skeletal Muscle Abnormalities

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Peak oxygen uptake and prognosis in patients with heart failure (HF)

Factors regulating exercise capacity

Peripheral circulation

Pulmonary circulation

Skeletal muscle

Mitochondria

CO₂ production

O₂ consumption

Heart

Blood

CO₂ transport

O₂ transport

Expiration

Inspiration

Lung

VCO₂

VO₂

Reserve capacity

Small

Large
HF is a systemic disorder
Exercise capacity and pathology of HF

Heart failure
- Depression
- Anemia
- Cardiac dysfunction
- Activation of neurohumoral factors
- CKD
- Immunological disorder
- Sleep disordered breathing
- Metabolic disorder
- Skeletal muscle abnormalities
- Endothelial dysfunction

Peripheral circulation
- Mitochondria
- CO₂ production
- Skeletal muscle
- O₂ consumption

Pulmonary circulation
- Heart
- Blood
- O₂ transport
- CO₂ transport
- Expiration
- Inspiration
- VCO₂
- VO₂
Aerobic exercise training improves survival rate in patients with HF (ExTraMATCH)
Effects of exercise therapy for heart failure

1. Improve exercise capacity (peak VO₂, AT)
2. Minor change in cardiac function (LV systolic function and remodeling)
3. Improve endothelial function (Coronary and peripheral circulation)
4. Improve ventilation
5. Improve autonomic nerves function
6. Improve skeletal muscle abnormalities

Exercise therapy is a highly ideal treatment for HF and is a standard of care.
Dobutamine does not increase exercise capacity

Does heart regulate peak whole body exercise capacity?

Leg bicycle ergometer

Arm bicycle ergometer

Increase in VO$_2$

The heart is not reaching the limit at the limit of exercise (peak VO$_2$) as severe heart failure

Skeletal muscle is impaired in patients with HF

- Decreased mitochondrial enzyme (cyto C)

- Decreased slow twitch fiber and capillary

- Impaired metabolism independent on blood flow
Energy metabolism in the skeletal muscle during exercise in HF patients

- Skeletal muscle cells
  - Fatty acid
  - Mitochondria
  - O$_2$ → H$_2$O → ATP
  - IMCL
  - β-oxidation
  - PCr ↔ Cr + Pi
  - ¹H-MRS
  - ³¹P-MRS

PCr, phosphocreatine; Pi, inorganic phosphate; Cr, creatine; IMCL, intramyocellular lipid
What is happening in skeletal muscle during whole body exercise?

Whole body MR system

Rapid inflator
PCr depletion at peak exercise

Normal subject

CHF patient

Rest

Peak Exercise

Decreases in phosphocreatine and pH are larger in patients with HF.
Intramyocellular lipid (IMCL)

**Control**

**HF**

**IMCL (mmol/kg wet weight)**

Association between IMCL and exercise capacity

- **Peak VO$_2$ (mL/kg/min)**
  - Control (n=12)
  - HF (n=18)
  - $r=-0.589$, $p<0.01$

- **AT (mL/kg/min)**
  - Control (n=12)
  - HF (n=18)
  - $r=-0.602$, $p<0.01$

- **PCr loss (%)**
  - Control (n=12)
  - HF (n=18)
  - $r=0.630$, $p<0.01$

IMCL content (mmol/kg wet weight)

Survival rate is lower in low knee flexors strength group (<68NmX100/kg) than in high group.
Skeletal muscle mass and muscle strength/endurance capacity

**Muscle strength**

- Handgrip (kg)
  - Muscle atrophy
  - 
  - +

- Quadriceps (kg)
  - Muscle atrophy
  - *
  - *

**Endurance capacity**

- Peak VO₂ (mL/kg)
  - Muscle atrophy
  - *
  - *

- Exercise time (min)
  - Muscle atrophy
  - *
  - *

Sarcopenia and HF

- Elderly people aged 60 to 70 years with sarcopenia are 5 to 13%.
  

- HF patients (mean age of 66.9) with sarcopenia are 19.5%.
  

Cardiac event free (%) vs. follow up (day)
## Skeletal muscle abnormalities in HF

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Histology</th>
<th>Biochemistry</th>
<th>Others</th>
</tr>
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<tbody>
<tr>
<td>Muscle wasting</td>
<td>Type I fibers ↓</td>
<td>Oxidative enzymes ↓</td>
<td>Impaired energy metabolism</td>
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<td>Glycolytic enzymes ↑</td>
<td>Ergoreflex ↑</td>
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<td>Capillary density ↓ →</td>
<td>Shift from MHC1 to MHC2</td>
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**Skeletal muscle abnormalities** are largely associated with the limited exercise capacity in patients with HF and are the target of exercise therapy.

- Impaired mitochondrial function and decrease in mitochondrial volume
- Muscle atrophy and decrease in muscle strength

Signal regulating mitochondrial biogenesis

Mitochondrion

- AdipoR1
- CaMKK
- CaMK
- AMPKα
- SIRT1
- PGC1α
- eNOS
- ATIR
- Nox
- AMP/ATP
- NAD+/NADH
- NO
- ROS
- β-oxidation
- NAD+/NADH
- FADH2
- ATP
- ADP+Pi
- Acetyl-CoA
- TCA cycle
- Electron transport chain
- F0 F1
- H+ H+ H+ ATP
- Intermembrane space
- Matrix

Signal regulating mitochondrial biogenesis

Kinugawa et al. Int Heart J 2015; 56:475-84
Signal regulating protein synthesis and degradation

Translation

Protein synthesis

Protein degradation

Kinugawa et al. Int Heart J 2015; 56:475-84
Ang II induces muscle atrophy in mice

Ang II induces mitochondrial dysfunction in skeletal muscle and transition of fiber type

Ang II induces apoptotic cell death in skeletal muscle

Ang II enhances ROS by activated NAD(P)H oxidase in skeletal muscle

Ang II induces all skeletal muscle abnormalities clinically observed in HF

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Ang II → ROS → Skeletal muscle abnormalities

Skeletal muscle is a huge endocrine organ

Conclusion

Skeletal muscle abnormalities play an important role in the pathogenesis of HF. However, no therapy targeting skeletal muscle abnormalities has been developed. Developing new drug therapy may be useful for treatment of patients with severe HF who can not perform exercise.

We need to clarify the mechanism for skeletal muscle abnormalities in HF and to develop new treatment targeting them.