# Exercise Intolerance in Heart Failure: Significance of Skeletal Muscle Abnormalities

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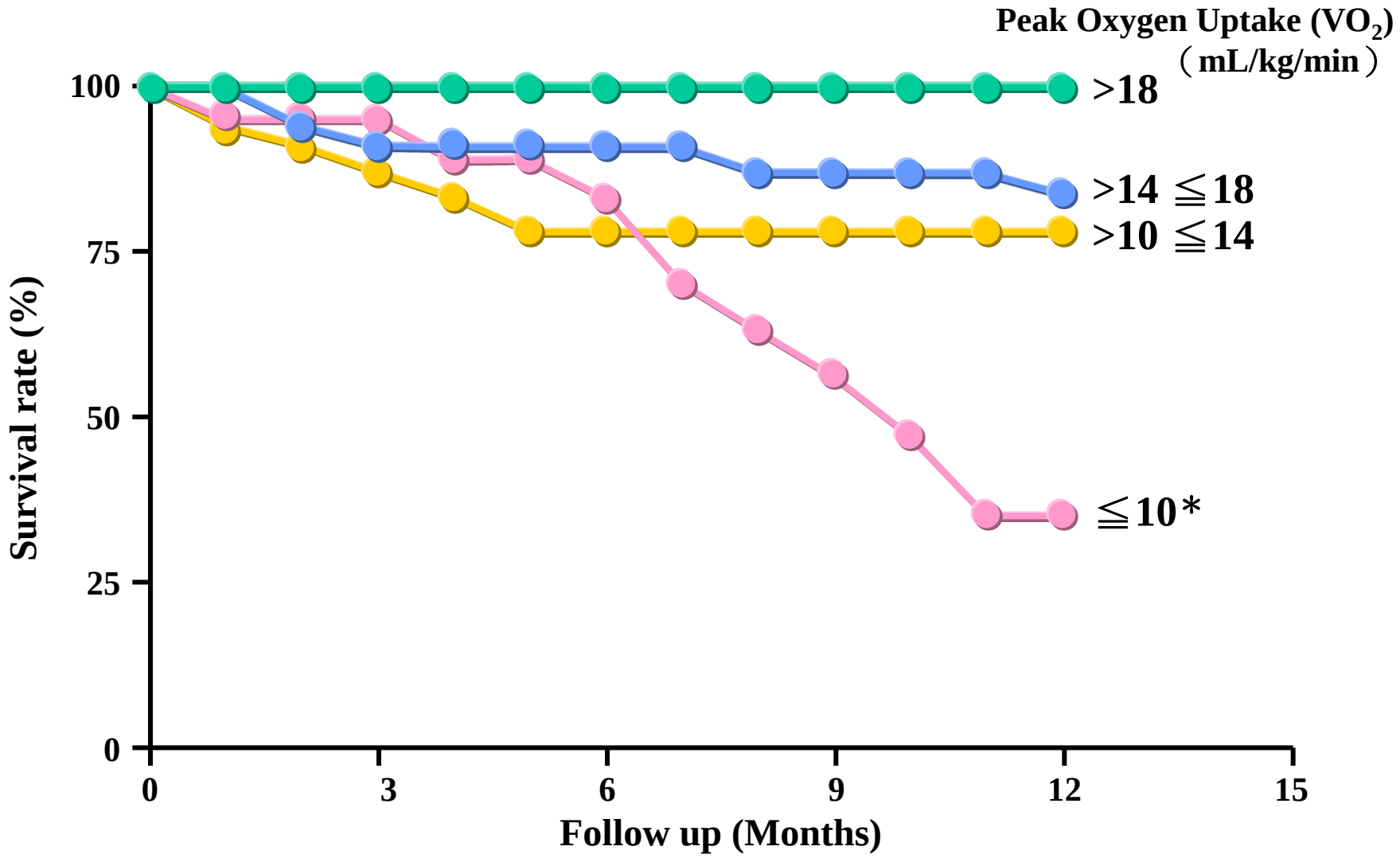
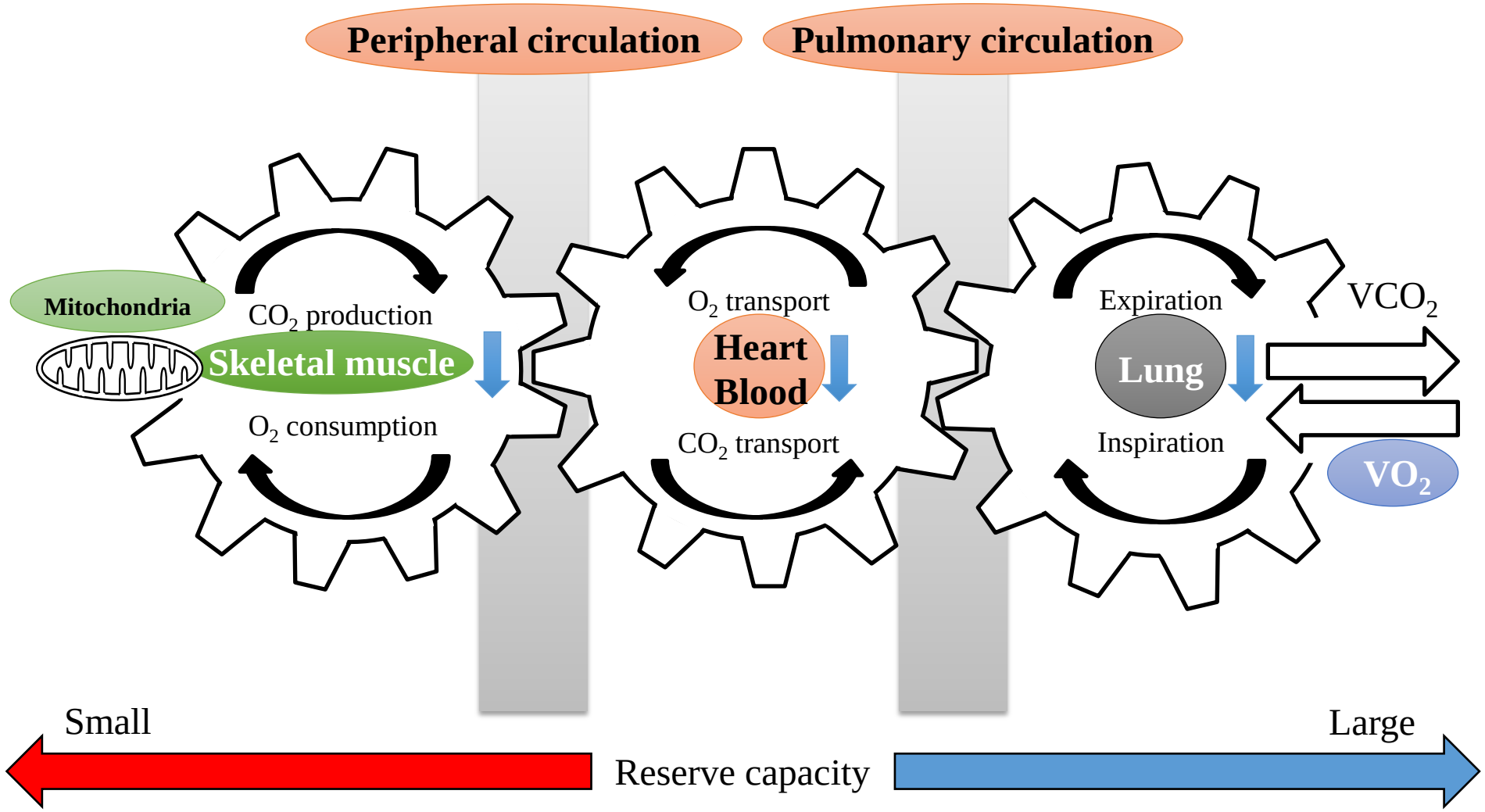
# Peak oxygen uptake and prognosis in patients with heart failure (HF)

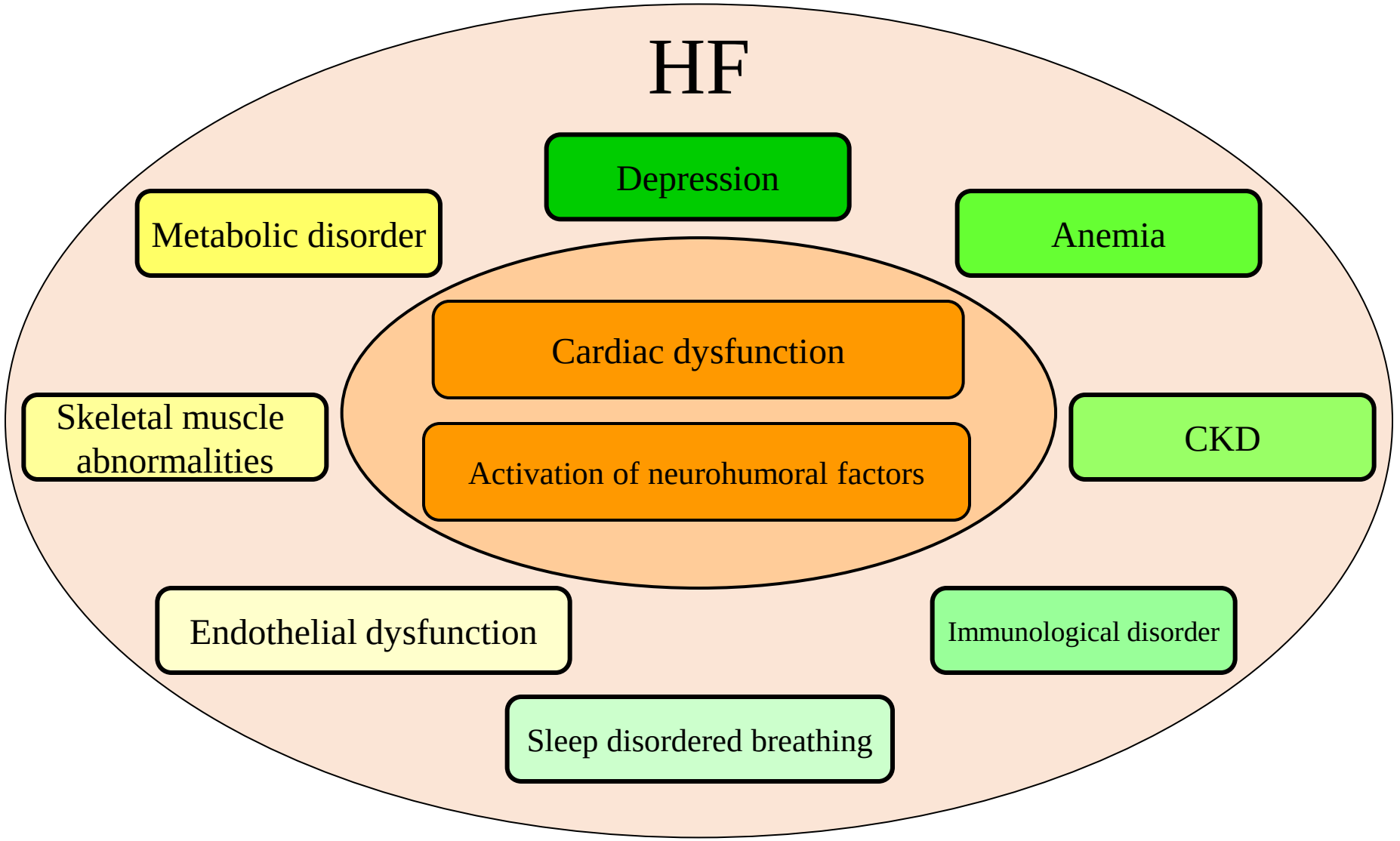



Mancini DM, et al. Circulation 1991; 83: 778-786

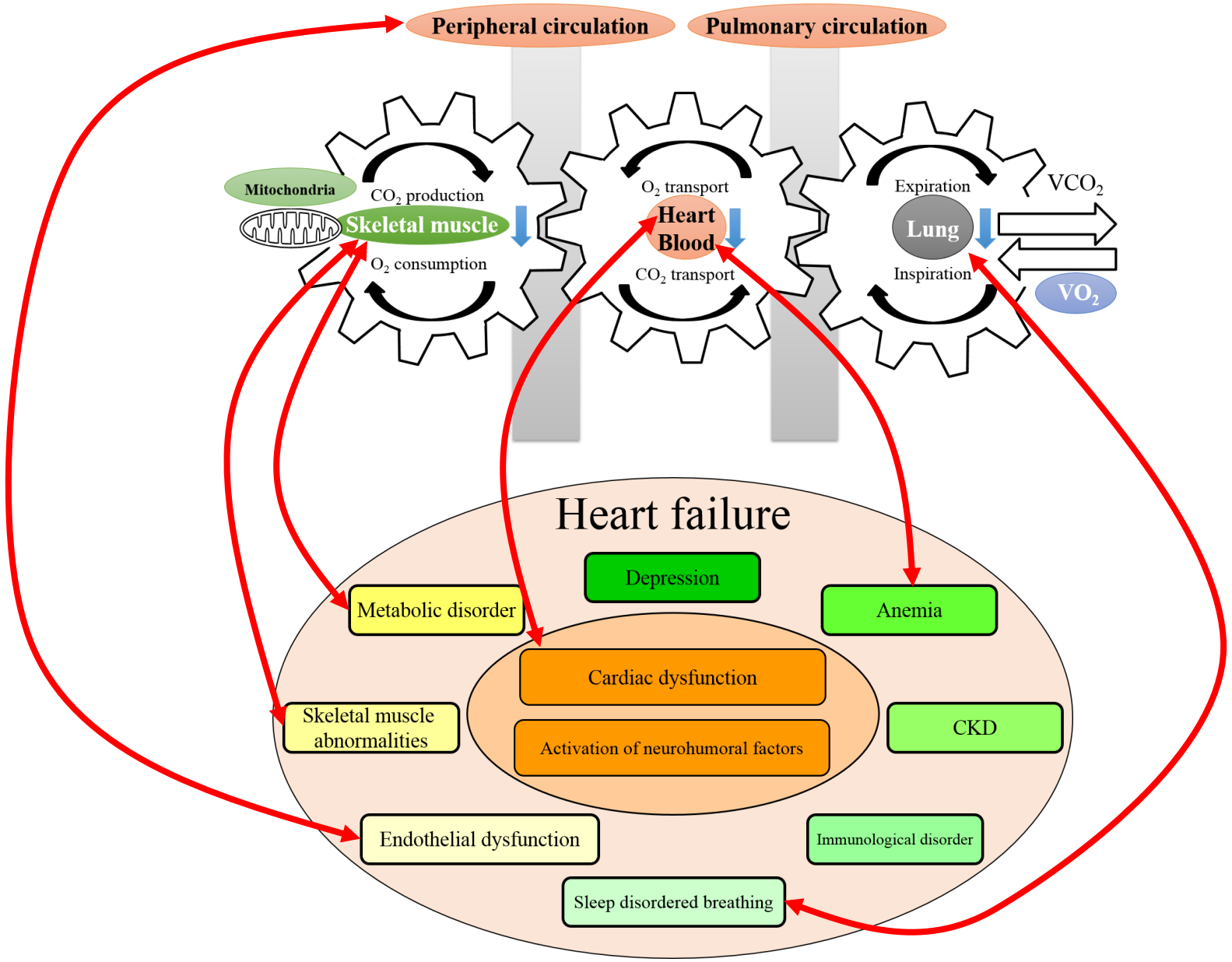
# Factors regulating exercise capacity



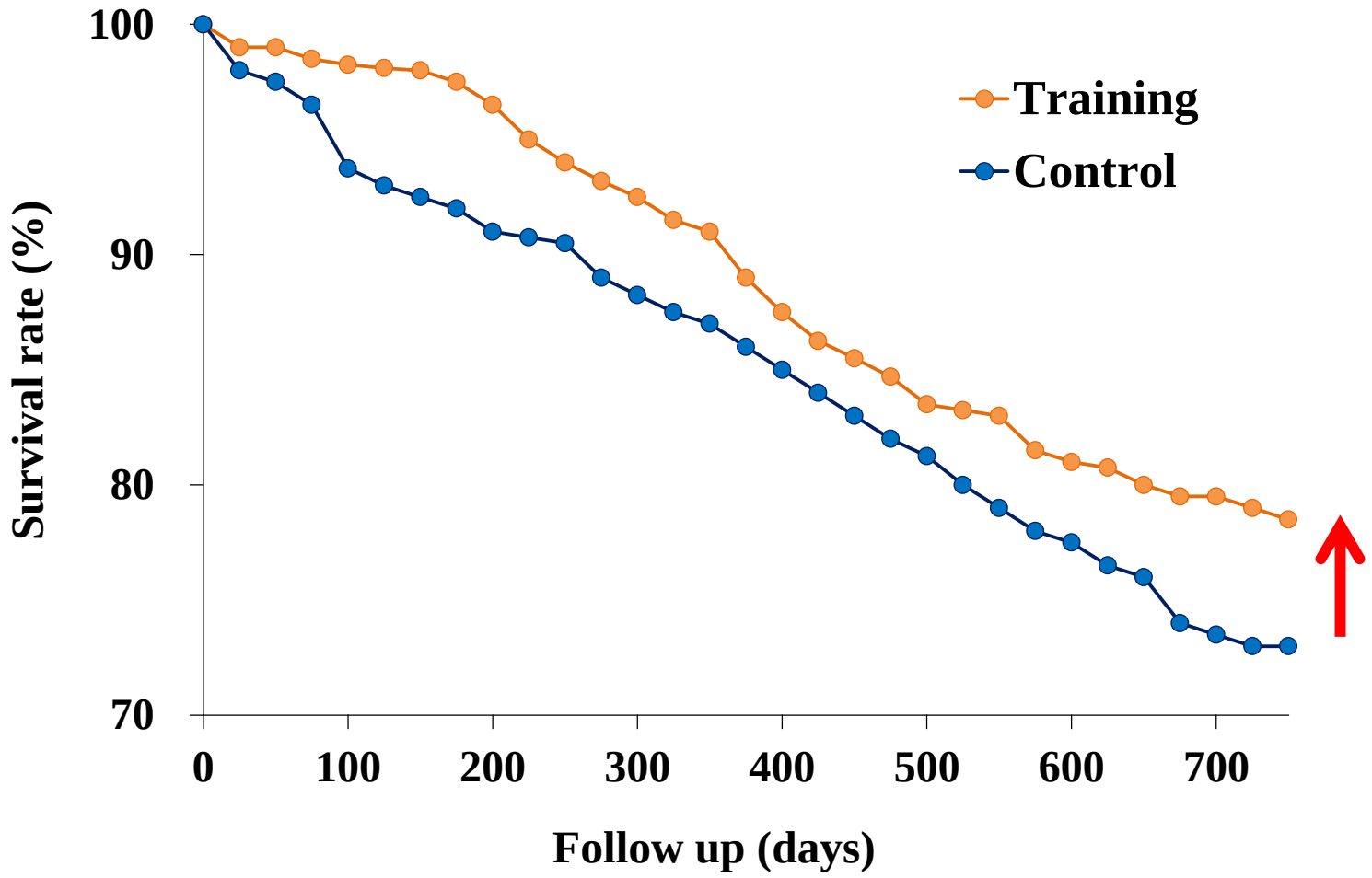
# HF is a systemic disorder



# Exercise capacity and pathology of HF



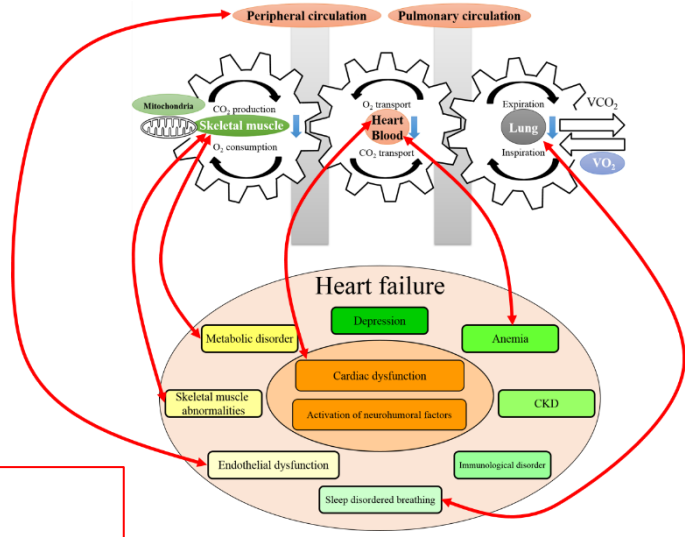
# Aerobic exercise training improves survival rate in patients with HF (ExTraMATCH)




Modified, Piepoli MF. BMJ 2004; 328: 189

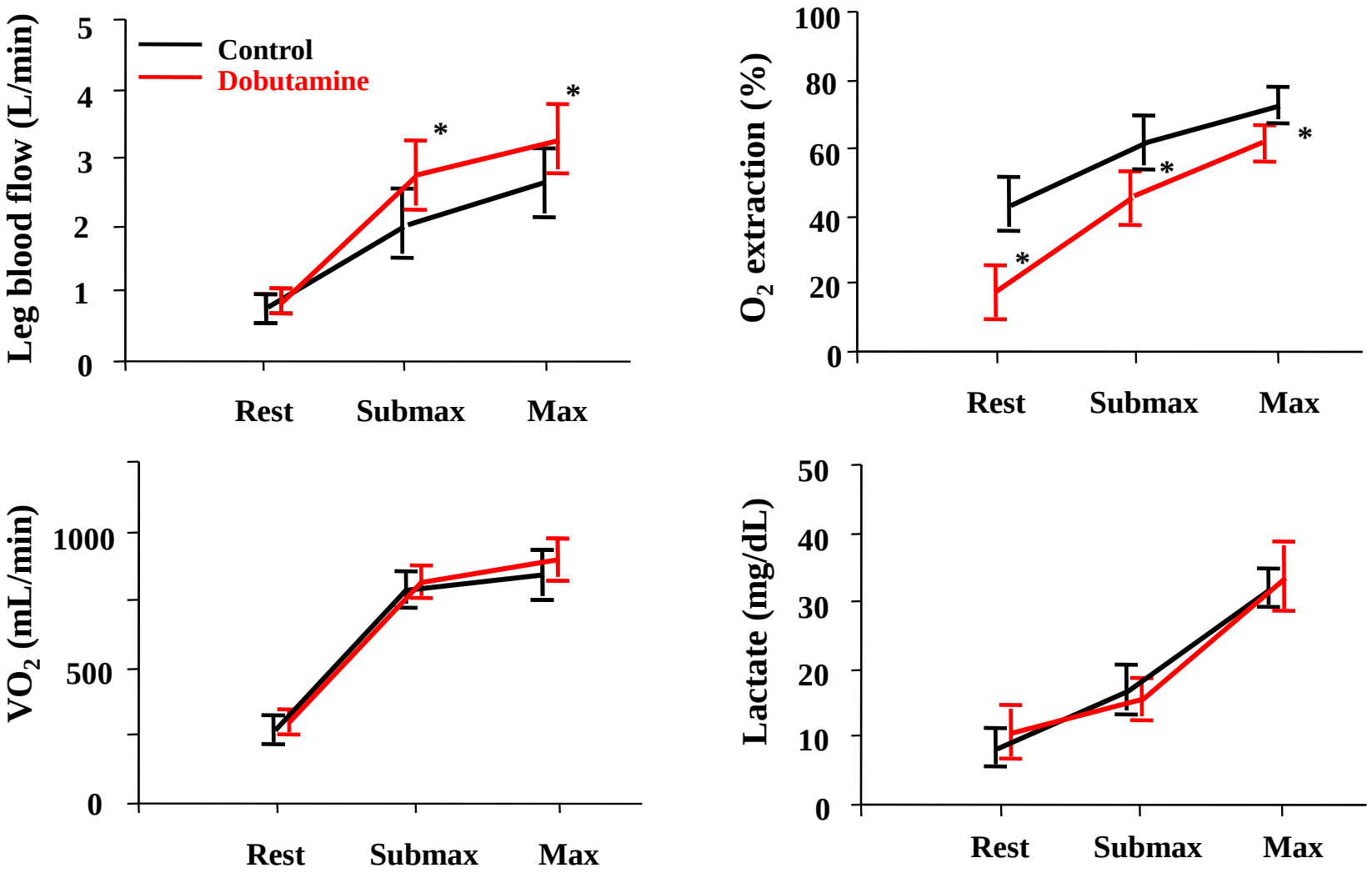
# Effects of exercise therapy for heart failure

1. Improve exercise capacity (peak $VO_2$, 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




Wilson JR, et al. Am J Cardiol. 1984; 53: 1308-15

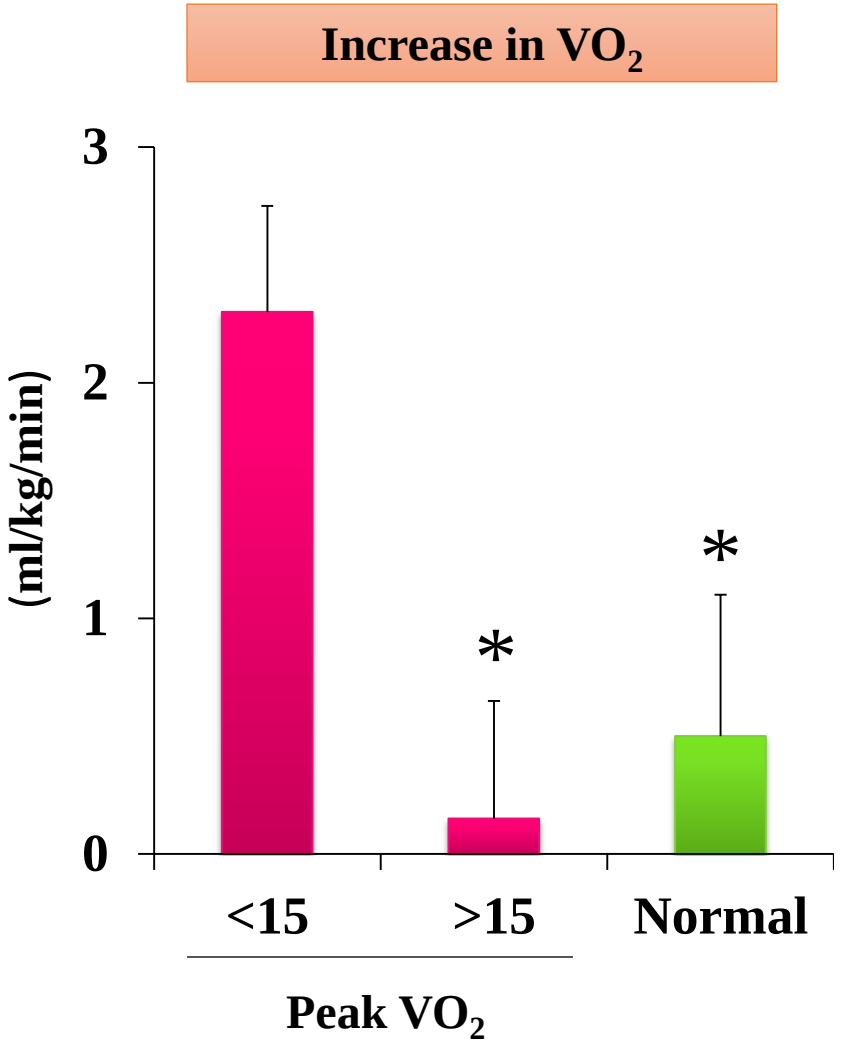
# Does heart regulate peak whole body exercise capacity?

**Leg bicycle ergometer**

**Arm bicycle ergometer**


Added arm bicycle ergometer when AT is exceeded

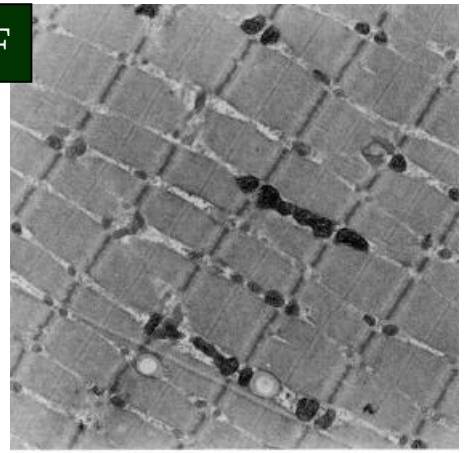
The heart is not reaching the limit at the limit of exercise (peak $VO_2$) as severe heart failure



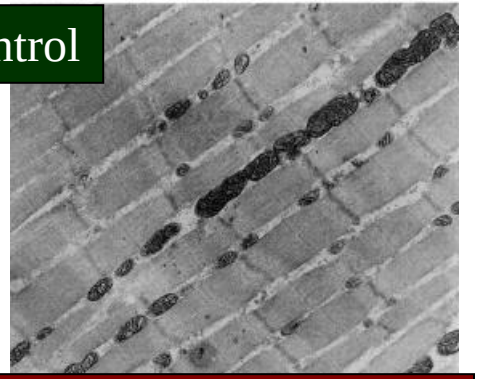

Jondeau G, et al. Circulation 1992; 101: 219S-222S

# Skeletal muscle is impaired in patients with HF

HF



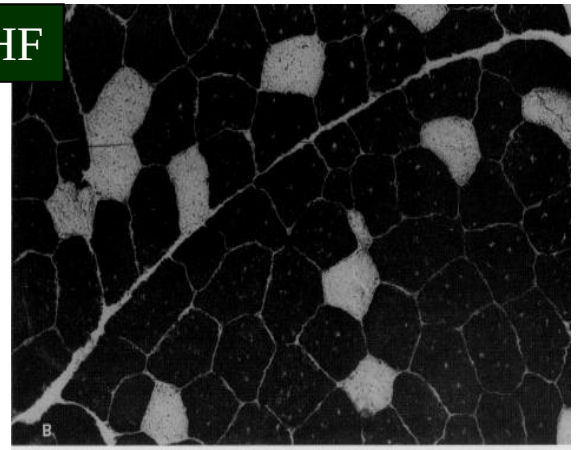
Control



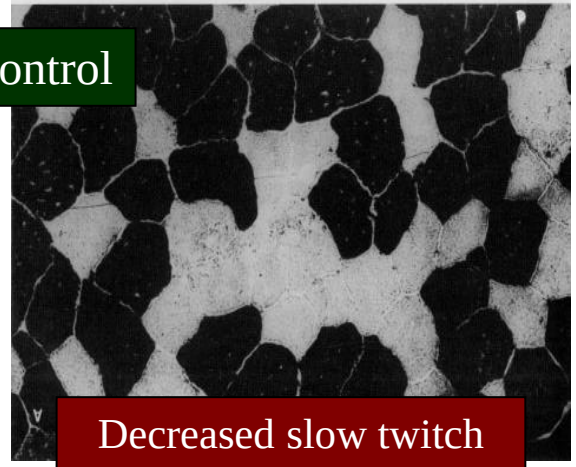
Decreased mitochondrial enzyme (cyto C)

**Drexler H, et al. Circulation 1992; 85: 1751-9**

HF



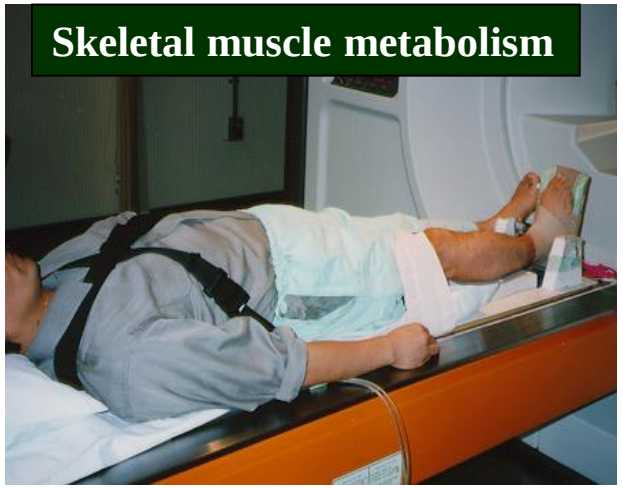
Control



Decreased slow twitch fiber and capillary

**Sabbah HN, et al. Circulation 1993; 87: 1729-37**

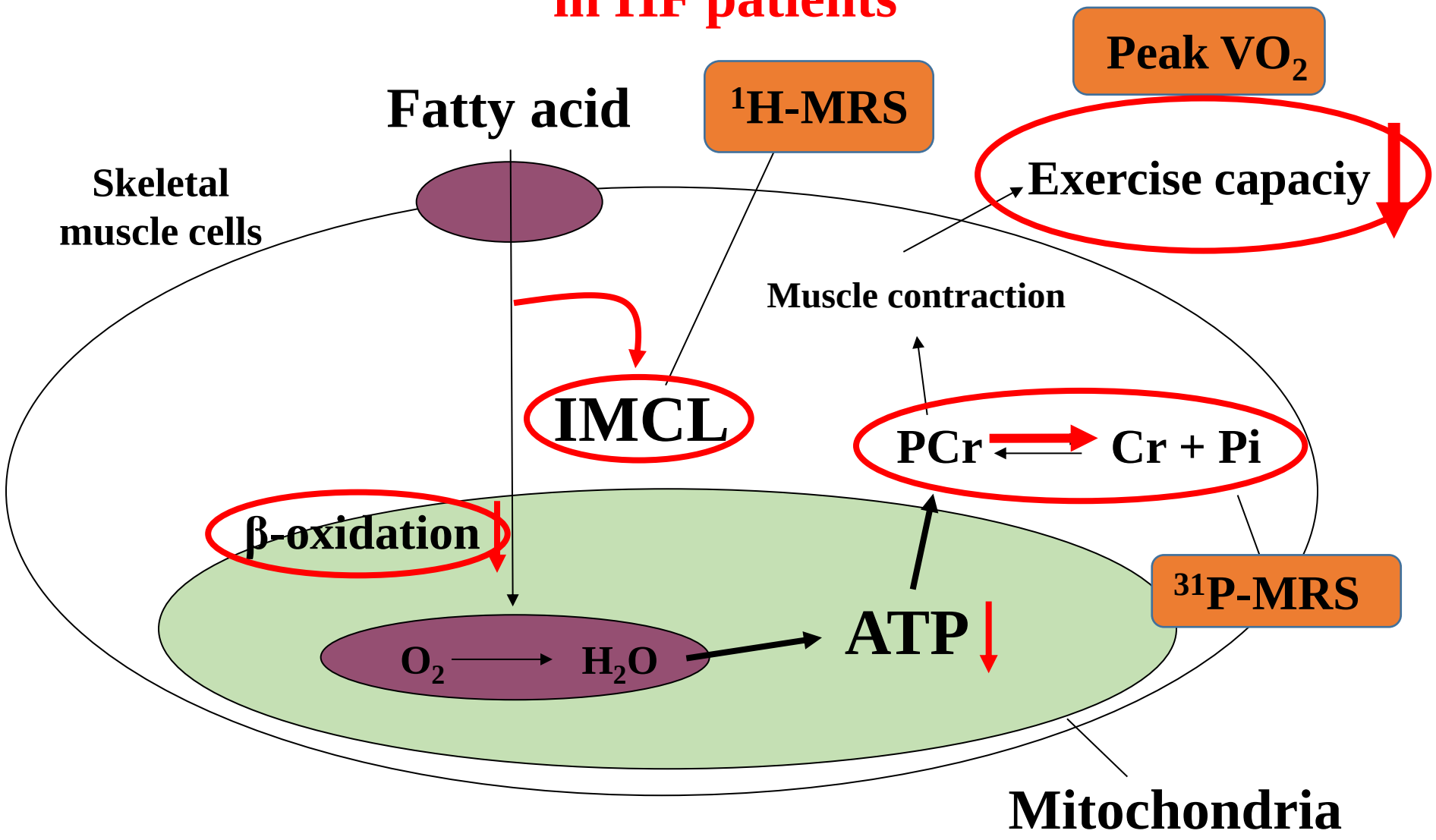
**Skeletal muscle metabolism**



Impaired metabolism independent on blood flow

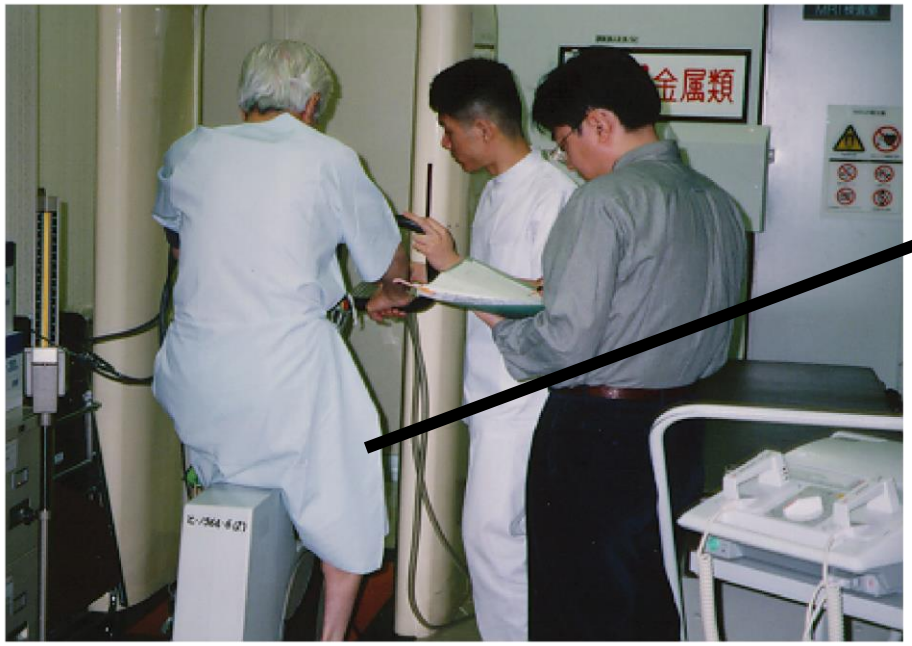
**Okita K, et al. Circulation 1998; 98: 1886-91**

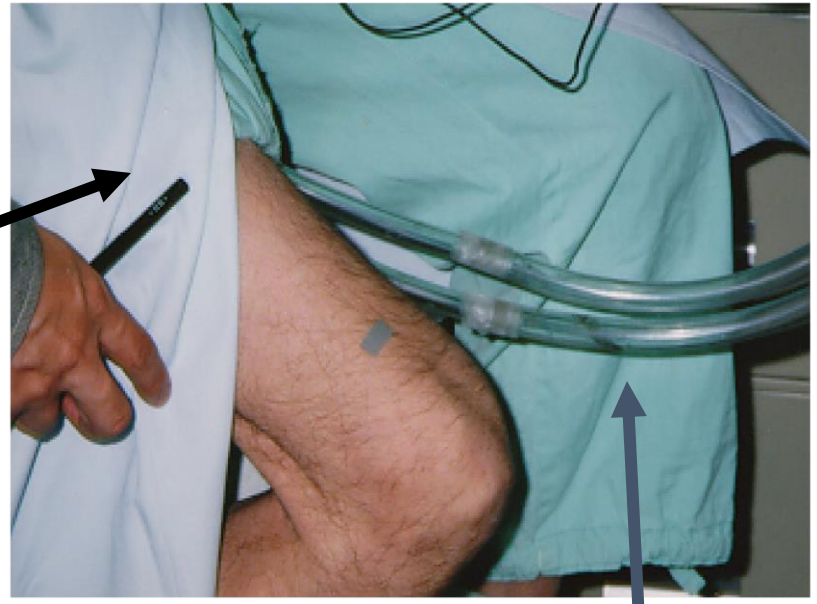
# Energy metabolism in the skeletal muscle during exercise in HF patients



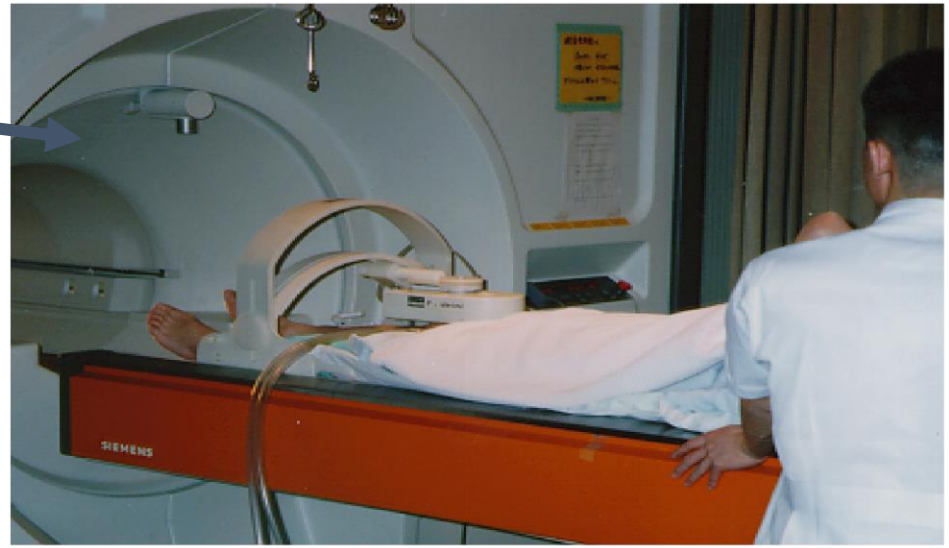

PCr, phosphocreatine; Pi, inorganic phosphate; Cr, creatine; IMCL, intramyocellular lipid

# What is **happening** in skeletal muscle during whole body exercise?



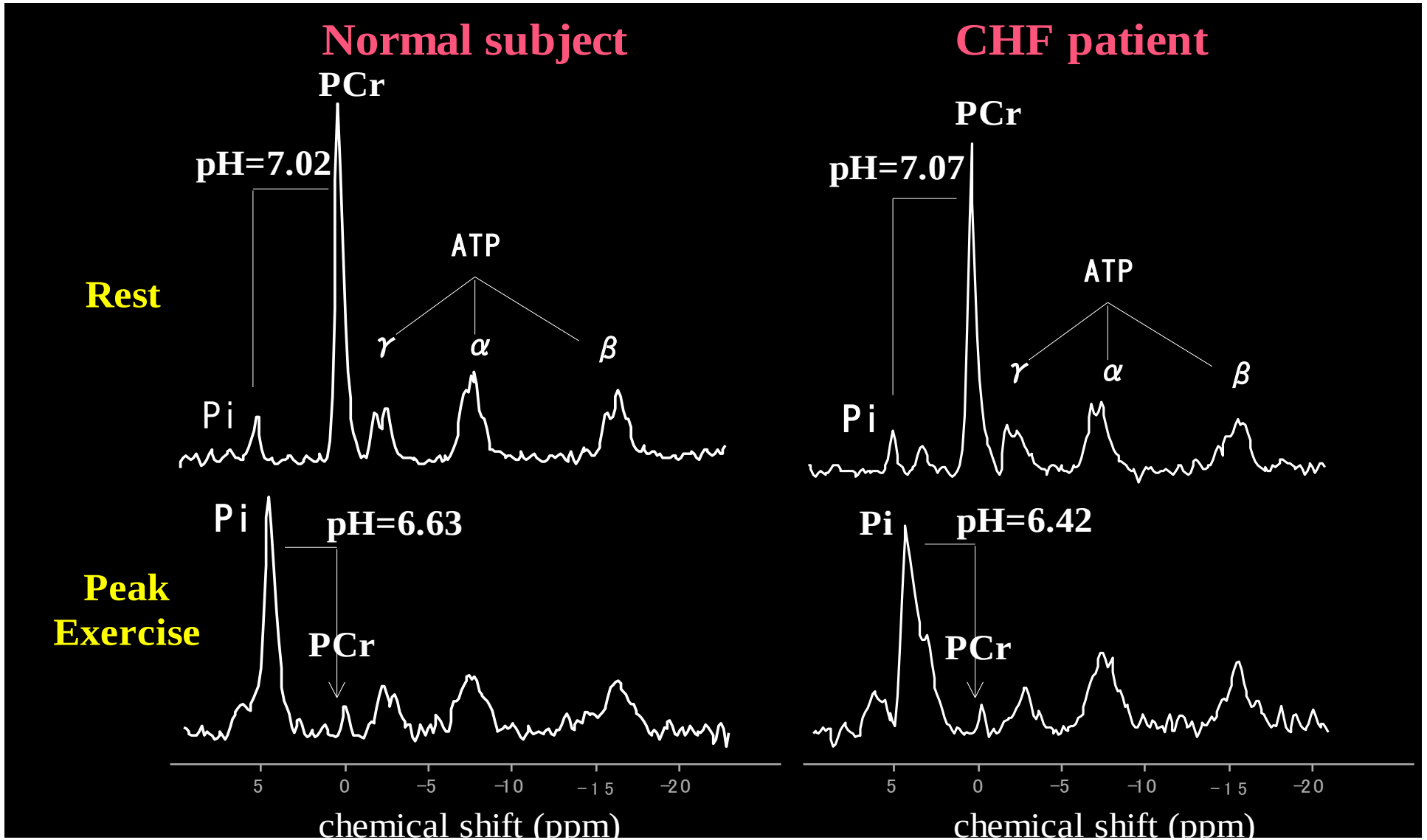


Whole body MR system



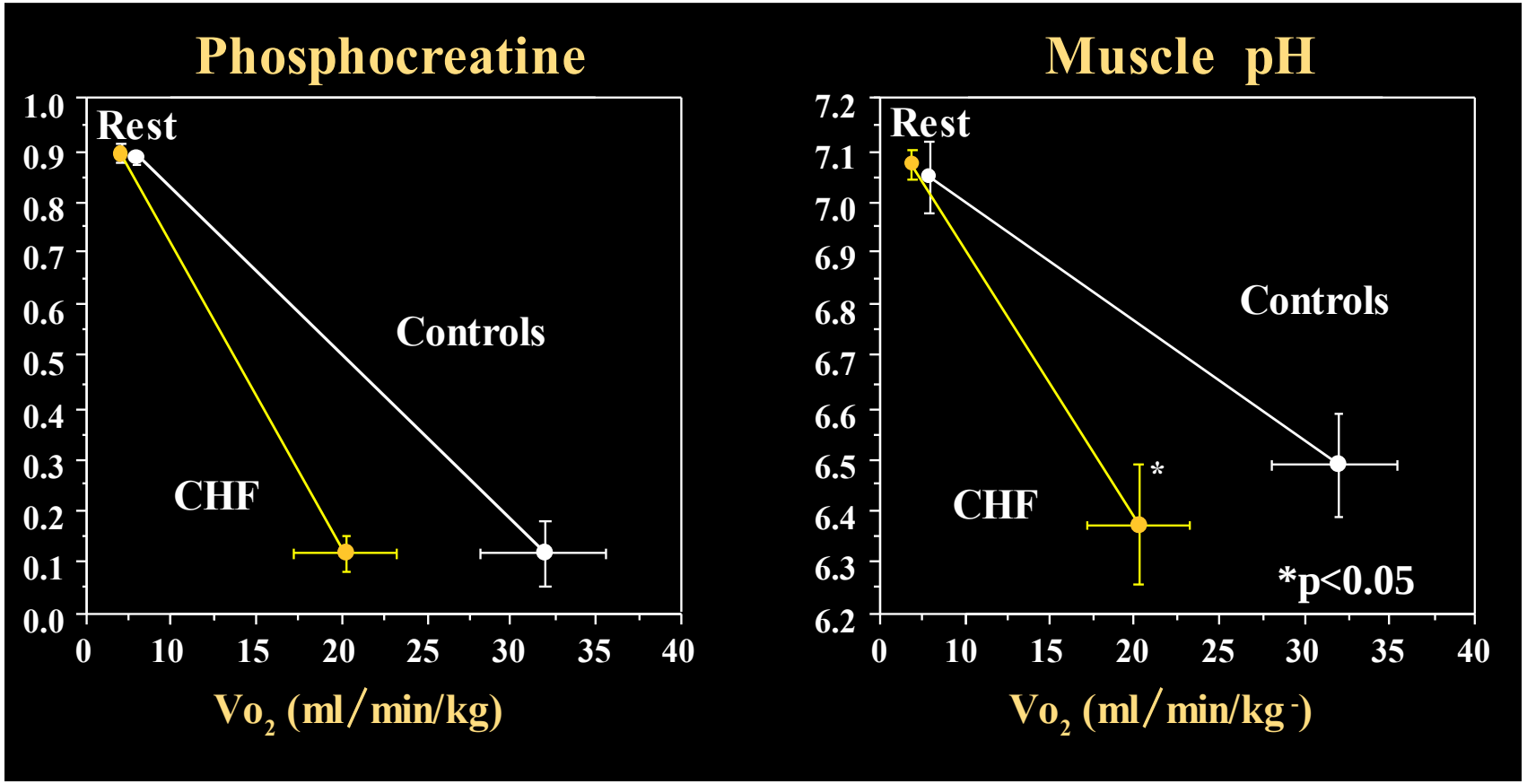

Rapid inflator

# PCr depletion at peak exercise




Okita K, et al. Circulation 1998; 98: 1886-91

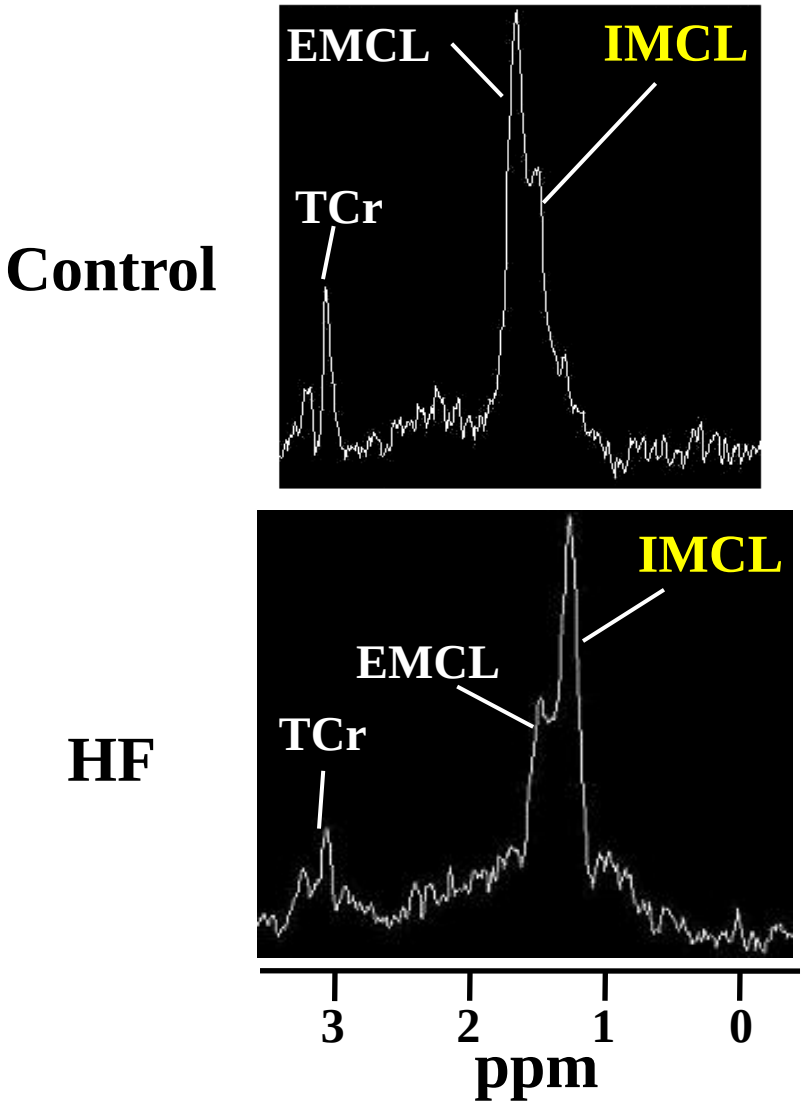
# Impaired skeletal muscle metabolism

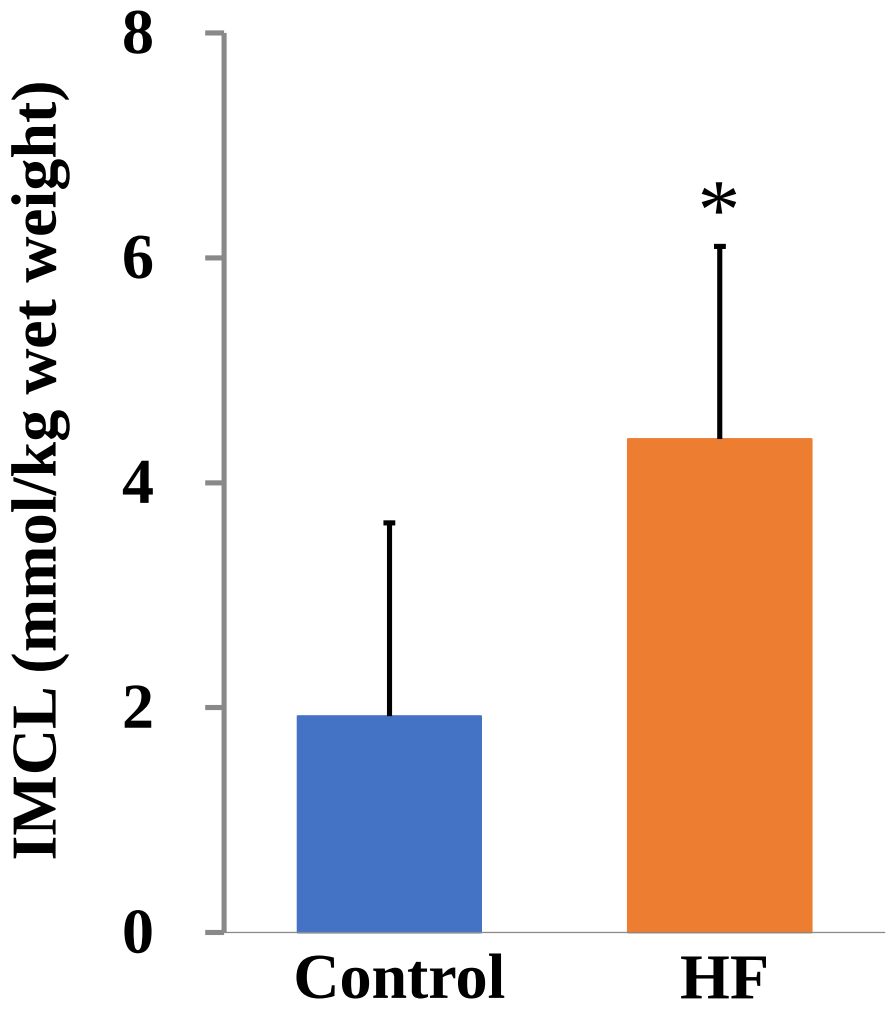



**Decreases in phosphocreatine and pH are larger in patients with HF.**

Okita K, et al. Circulation 1998; 98: 1886-91

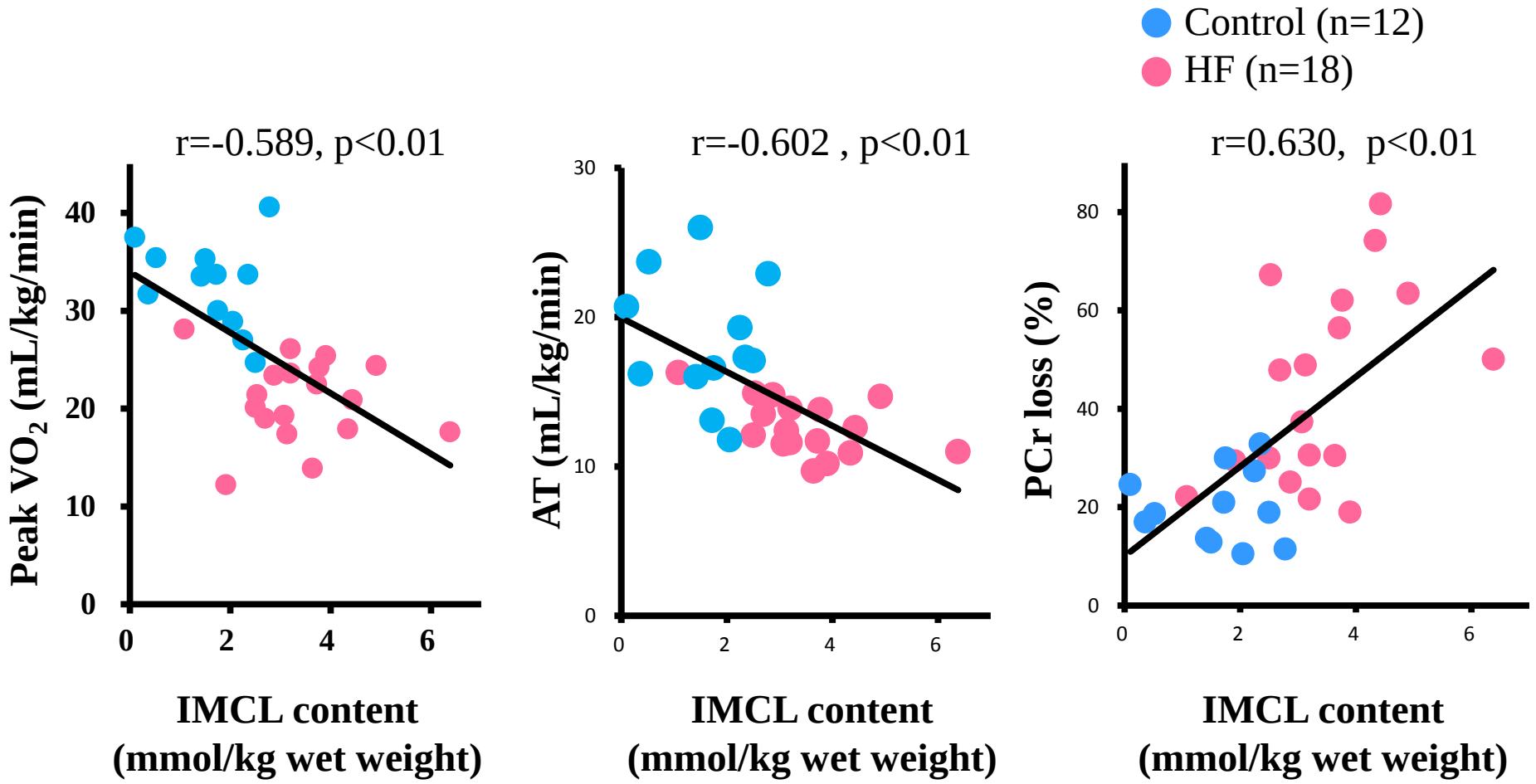
# Intramyocellular lipid (IMCL)



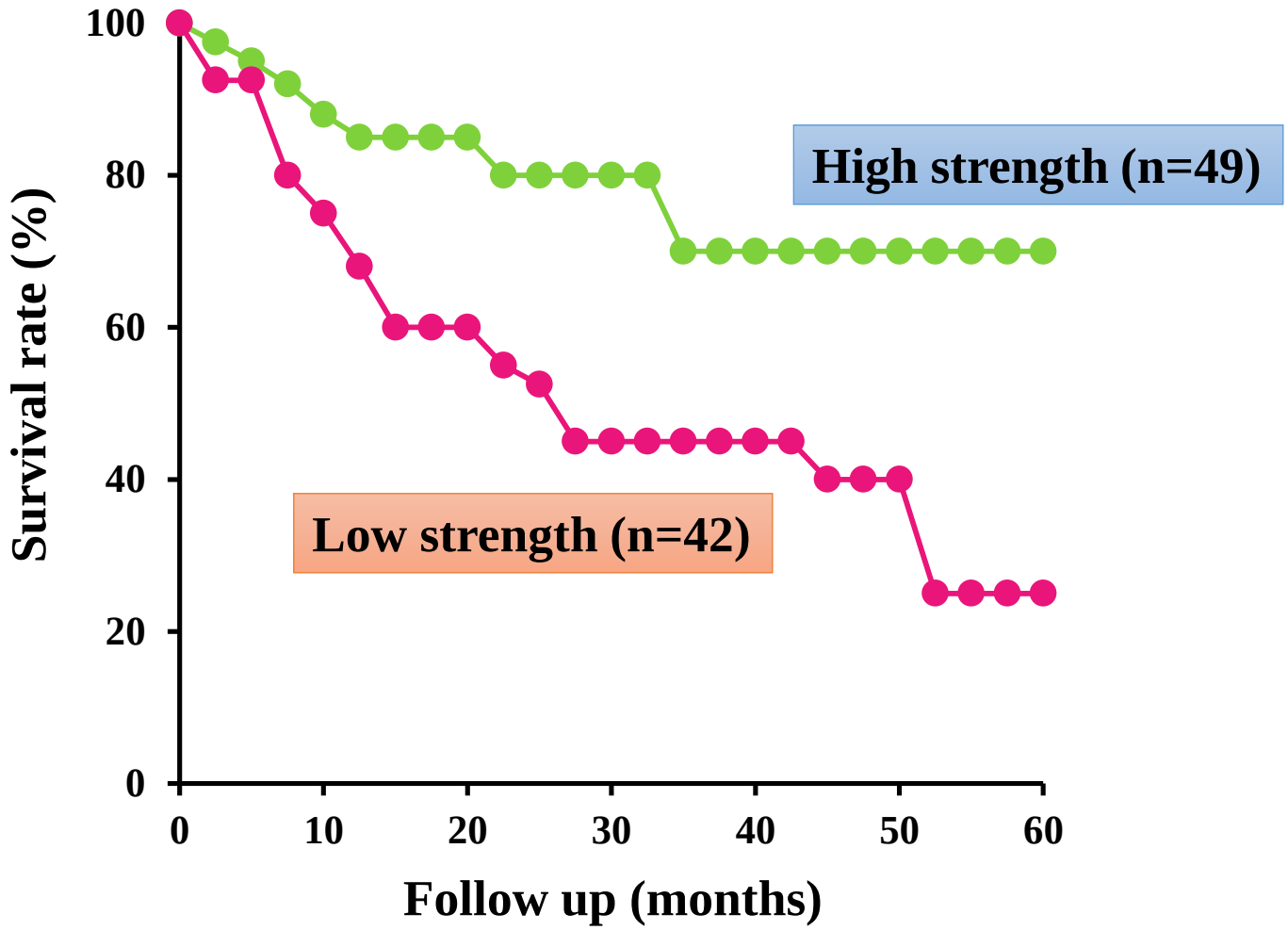

Hirabayashi K, et al. Int J Cardiol 2014;176:1110-2

# Association between IMCL and exercise capacity




Hirabayashi K, et al. Int J Cardiol 2014;176:1110-2

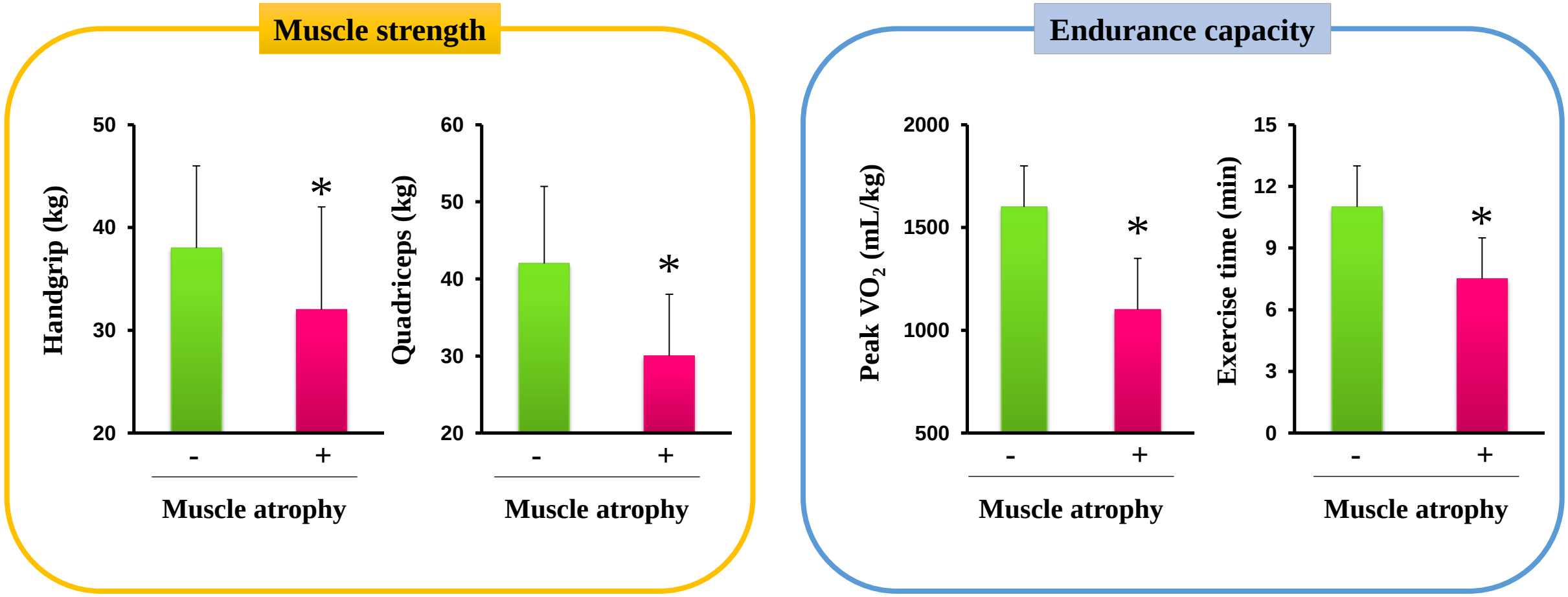
# Muscle strength and survival rate




**Survival rate is lower in low knee flexors strength group (<68NmX100/kg) than in high group.**

Hülsmann M, et al. Eur J Heart Fail 2004; 6: 101-7

# Skeletal muscle mass and muscle strength/endurance capacity




Fulster S, et al. *Eur Heart J*. 2013;34:512-9

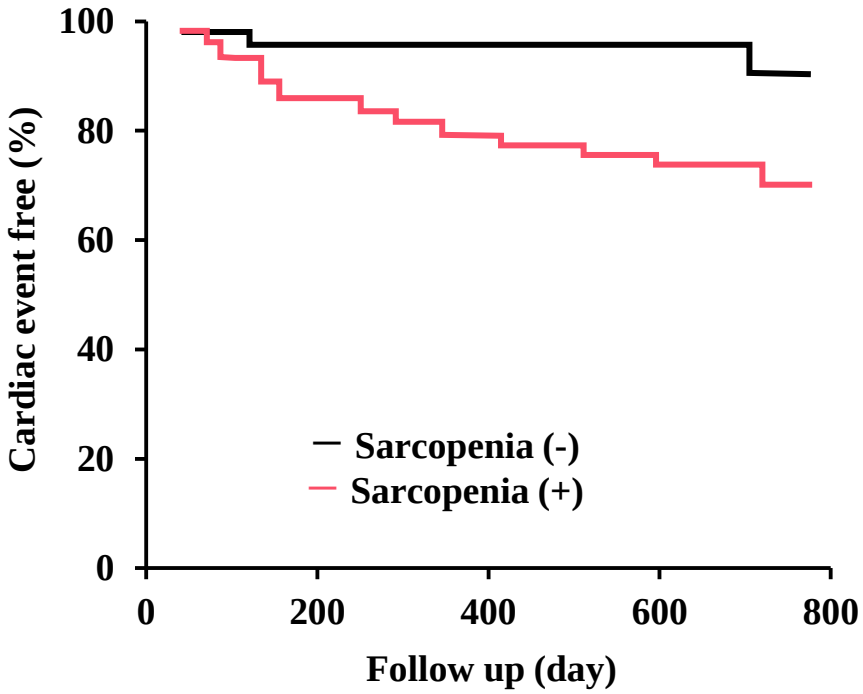
# Sarcopenia and HF

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

**von Haehling S. et al. Int J Biochem Cell Biol. 2013; 45: 2257-65**

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

**Fulster S, et al. *Eur Heart J*. 2013;34:512-9**




**Onoue Y, et al. Int J Cardiol. 2016; 215: 301-6**

# Skeletal muscle abnormalities in HF

| Morphology | Histology | Biochemistry | Others |
|---|---|---|---|
| Muscle wasting<br>Muscle fiber atrophy<br>（IIb）↓→ | Type I fibers ↓<br>Type II fibers ↑<br>Shift from type IIa to IIb | Oxidative enzymes ↓<br>Glycolytic enzymes ↑→ | Impaired energy metabolism<br>Ergoreflex ↑ |
| | Capillary density ↓→ | Shift from MHC1 to MHC2 | |
| | Mitochondrial volume ↓ | eNOS ↓ | |
| | Apoptosis ↑ | | |

**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**

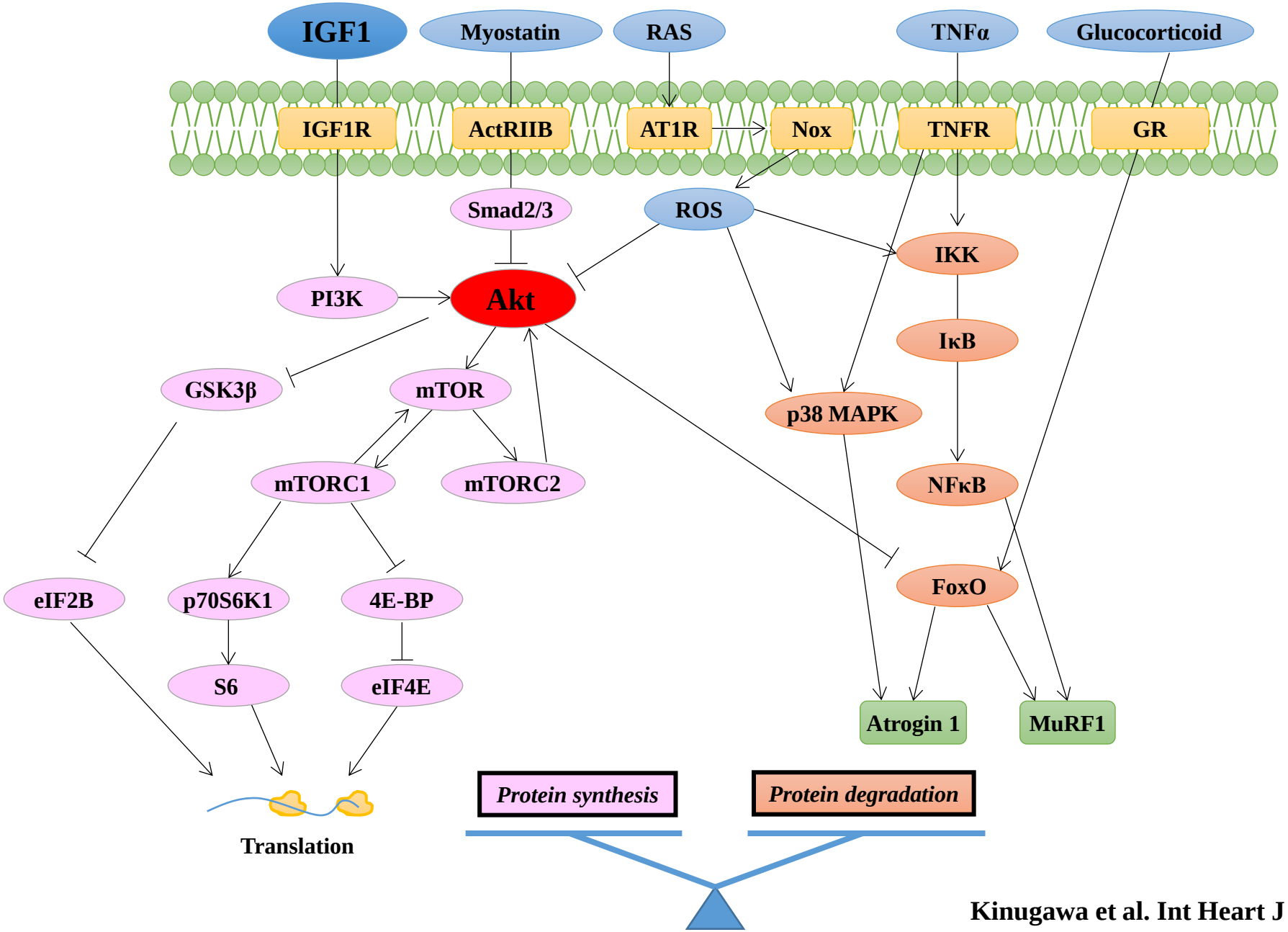
Okita K, et al. Circ J 2013; 77: 293-300

# Signal regulating mitochondrial biogenesis

RAS
AdipoR1
eNOS
AT1R
Nox
[Ca2+]
AMP / ATP
NAD+ / NADH
NO
ROS
CaMKK
CaMK
AMPKα
SIRT1
PGC1α
Transcription
Nucleus
p38MAPK
Electron transport chain
I
II
III
IV
Cyt c
F0
V
F1
Intermembrane space
Matrix
NADH NAD+
H+
ADP +Pi
ATP
β-oxidation
β-HAD
SIRT3
Acetyl-CoA
TCA cycle
NAD+ FAD ADP+Pi
NADH FADH2 ATP CO2
Mitochondrion

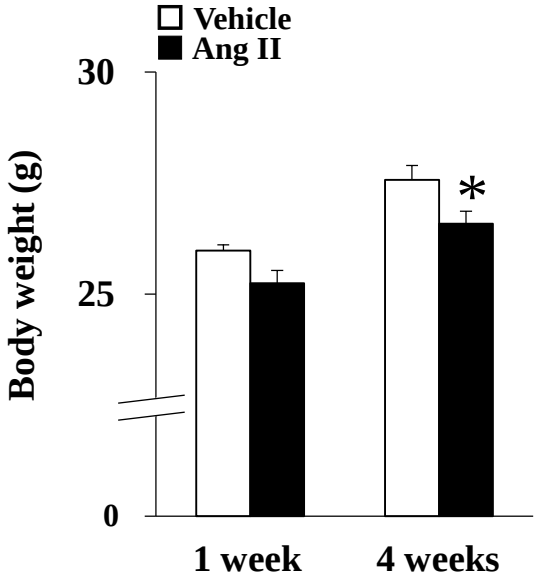
Kinugawa et al. Int Heart J 2015; 56:475-84

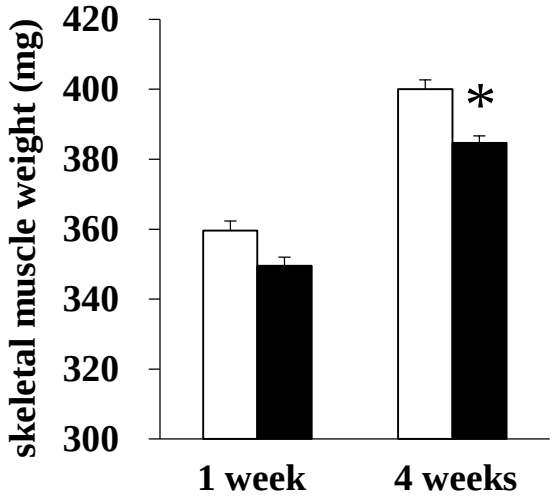
# Signal regulating protein synthesis and degradation

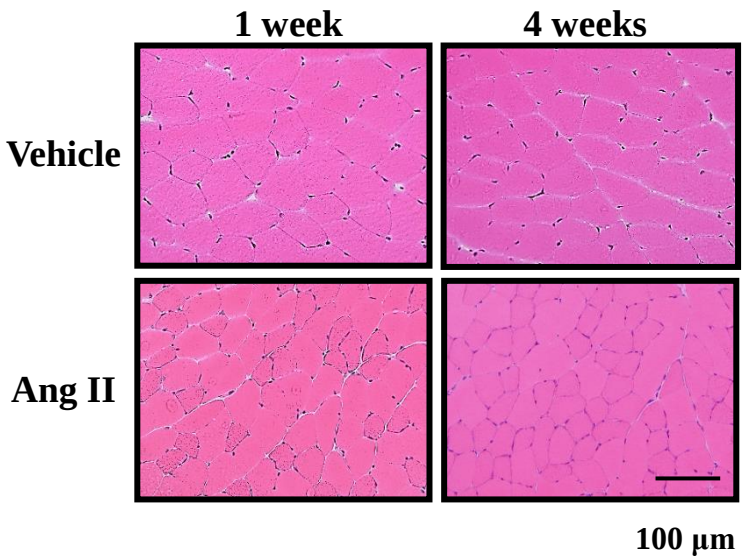


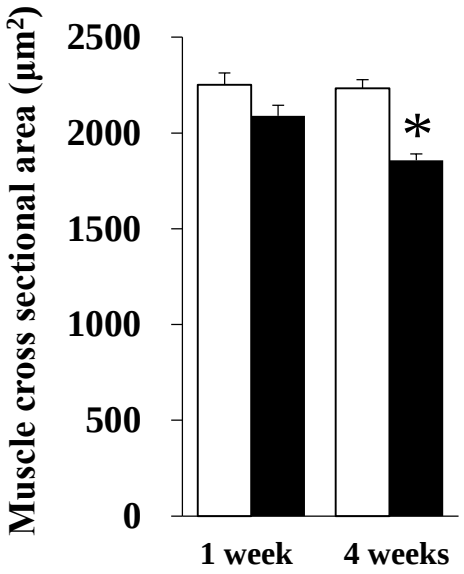

Kinugawa et al. Int Heart J 2015; 56:475-84

# Ang II induces muscle atrophy in mice



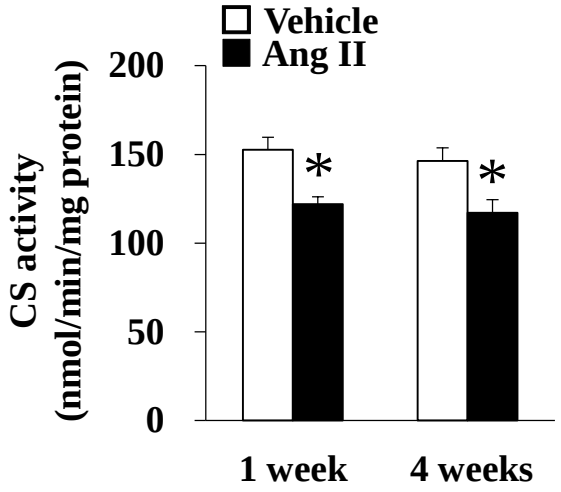



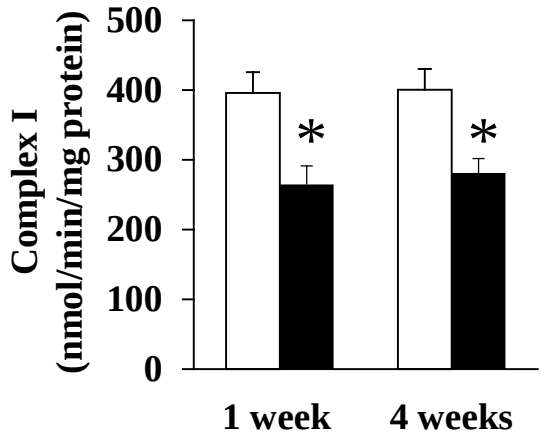



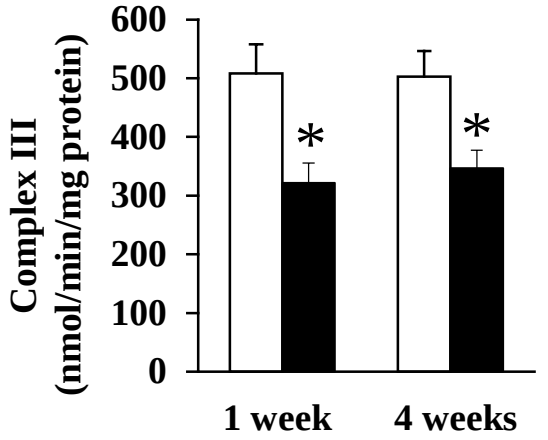



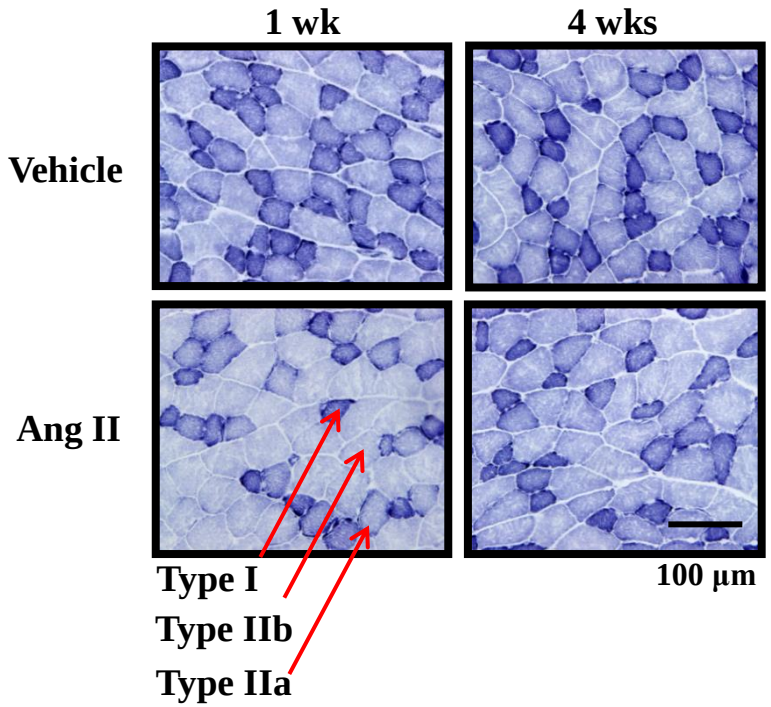

Kadoguchi T, et al. Exp Physiol 2015; 100: 312-22

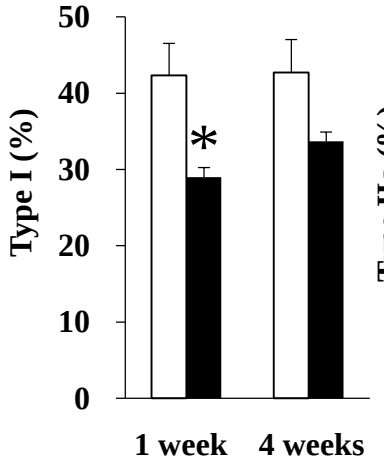
# Ang II induces mitochondrial dysfunction in skeletal muscle and transition of fiber type

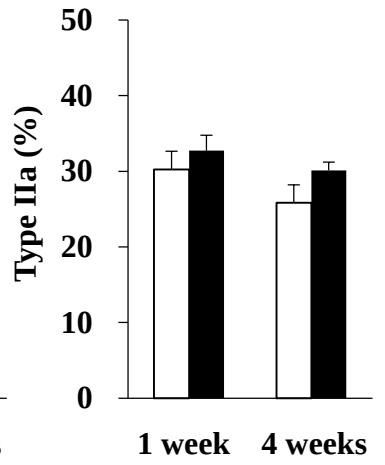


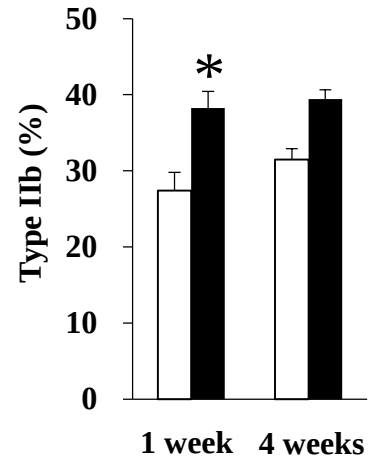



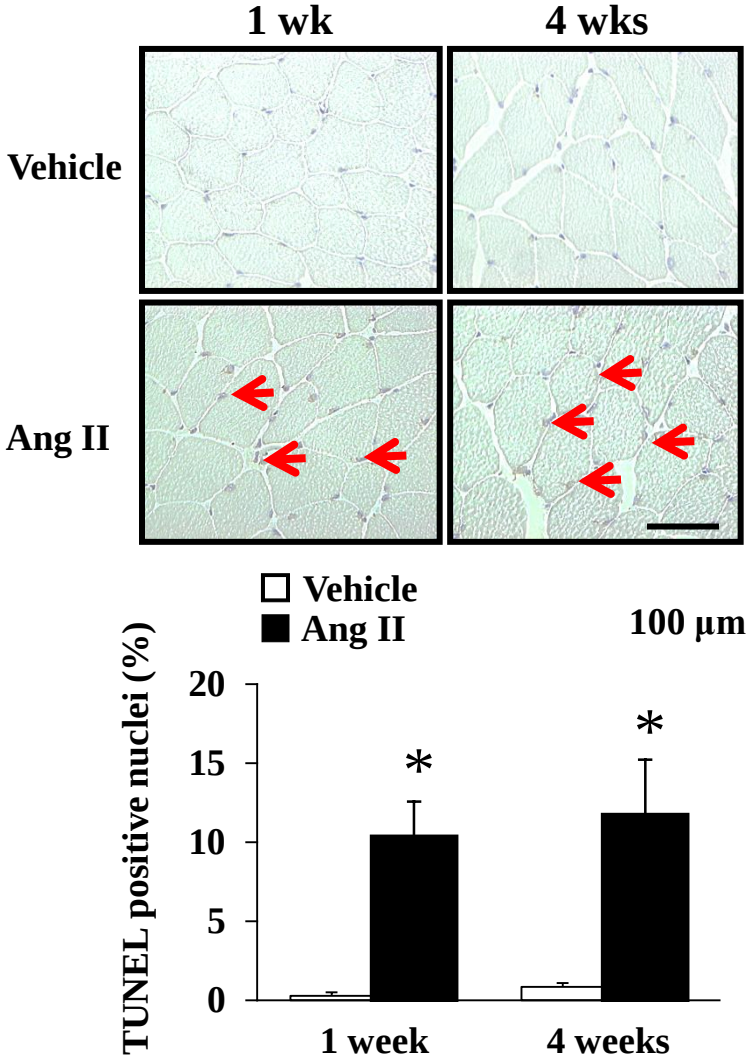



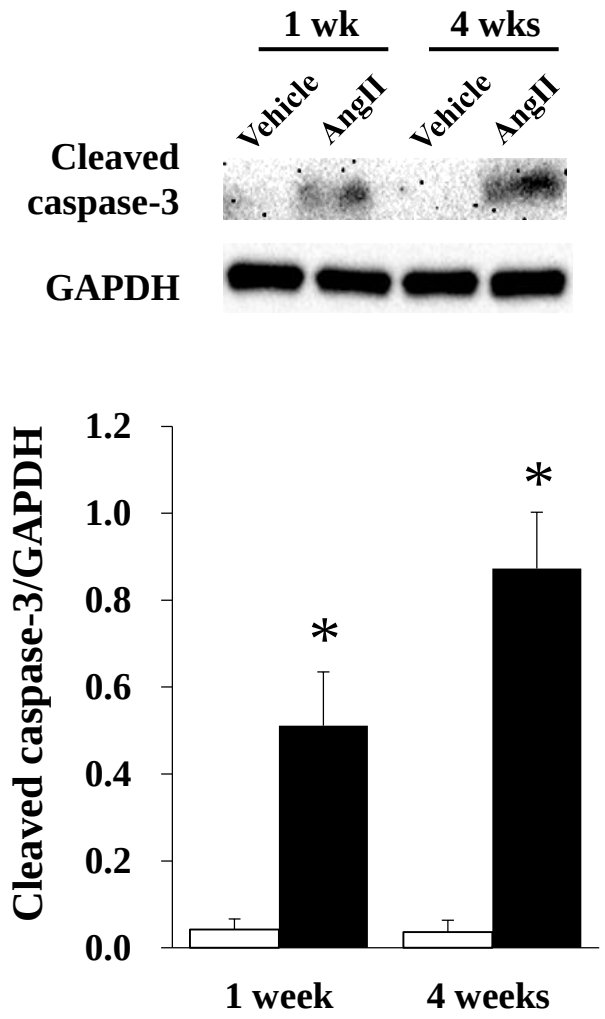




Kadoguchi T, et al. Exp Physiol 2015; 100: 312-22

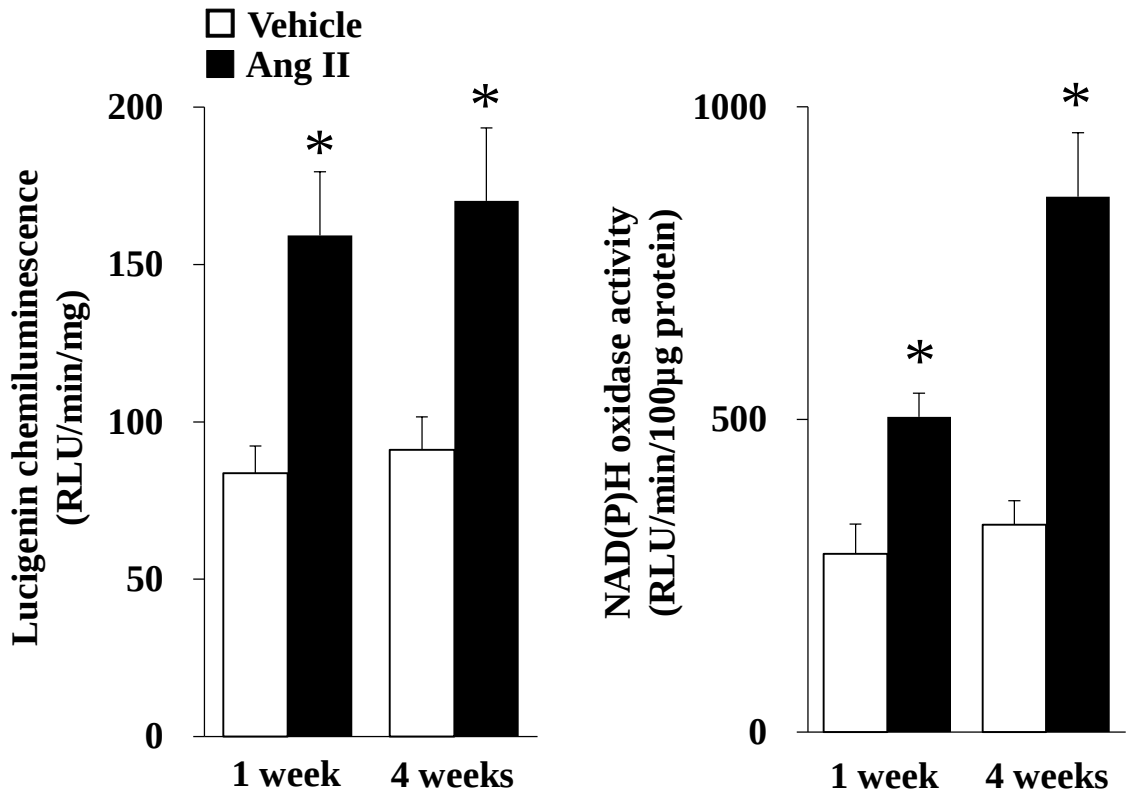
# Ang II induces apoptotic cell death in skeletal muscle




Kadoguchi T, et al. Exp Physiol 2015; 100: 312-22

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



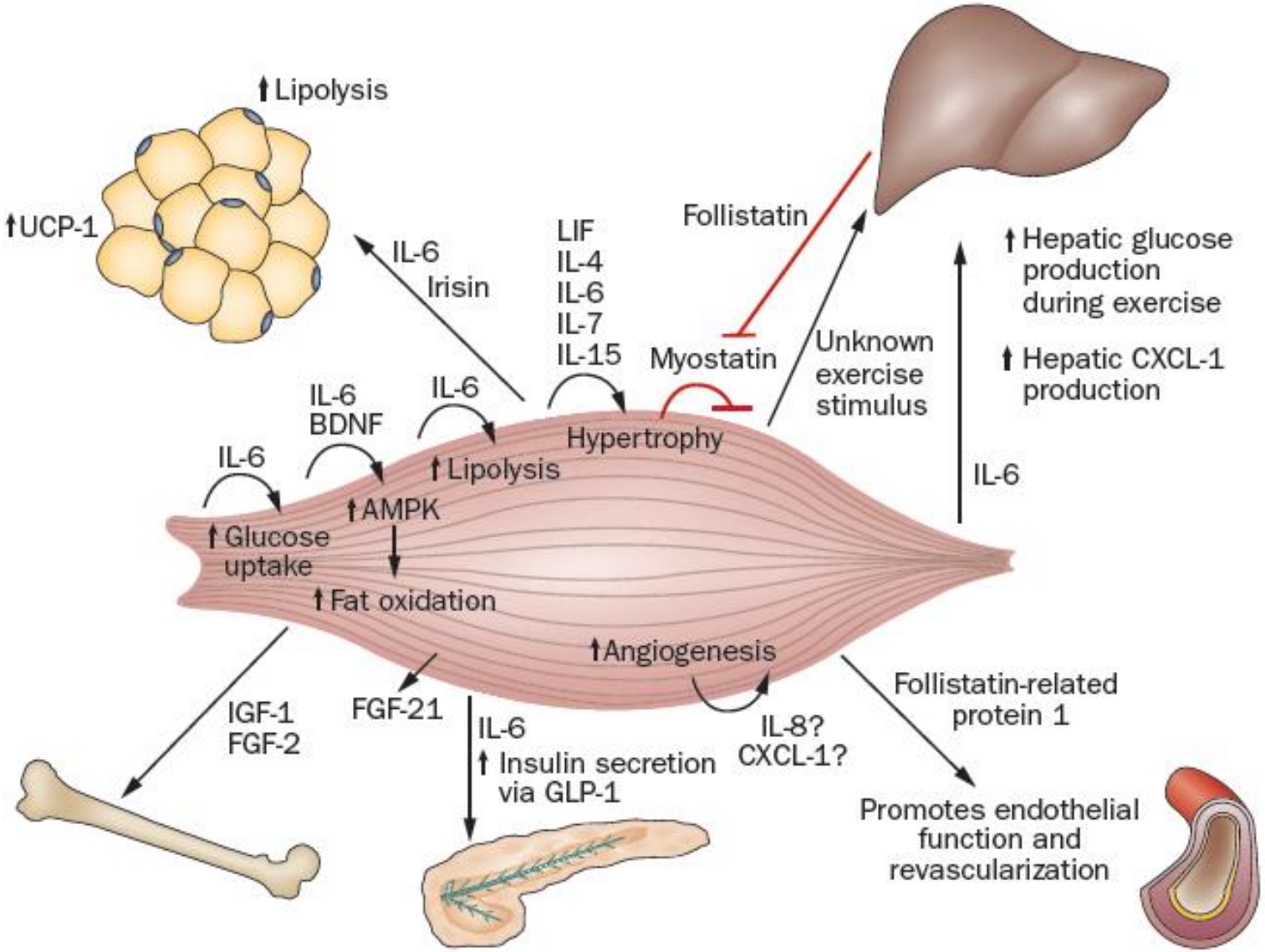

Kadoguchi T, et al. Exp Physiol 2015; 100: 312-22

# Ang II induces all skeletal muscle abnormalities clinically observed in HF

| Morphology | Histology | Biochemistry | Others |
|---|---|---|---|
| Muscle wasting<br>Muscle fiber atrophy<br>（IIb）↓→ | Type I fibers ↓<br>Type II fibers ↑<br>Shift from type IIa to IIb | Oxidative enzymes ↓<br>Glycolytic enzymes ↑→ | Impaired energy metabolism<br>Ergoreflex ↑ |
| | Capillary density ↓→ | Shift from MHC1 to MHC2 | |
| | Mitochondrial volume ↓ | eNOS ↓ | |
| | Apoptosis ↑ | | |


Okita K, et al. Circ J 2013; 77: 293-300

# Skeletal muscle is a huge endocrine organ




Pedersen BK, et al. Nat Rev Endocrinol 2012; 8: 457-65

# 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.**