Does Pharmacological Exercise Mimetics Exist?

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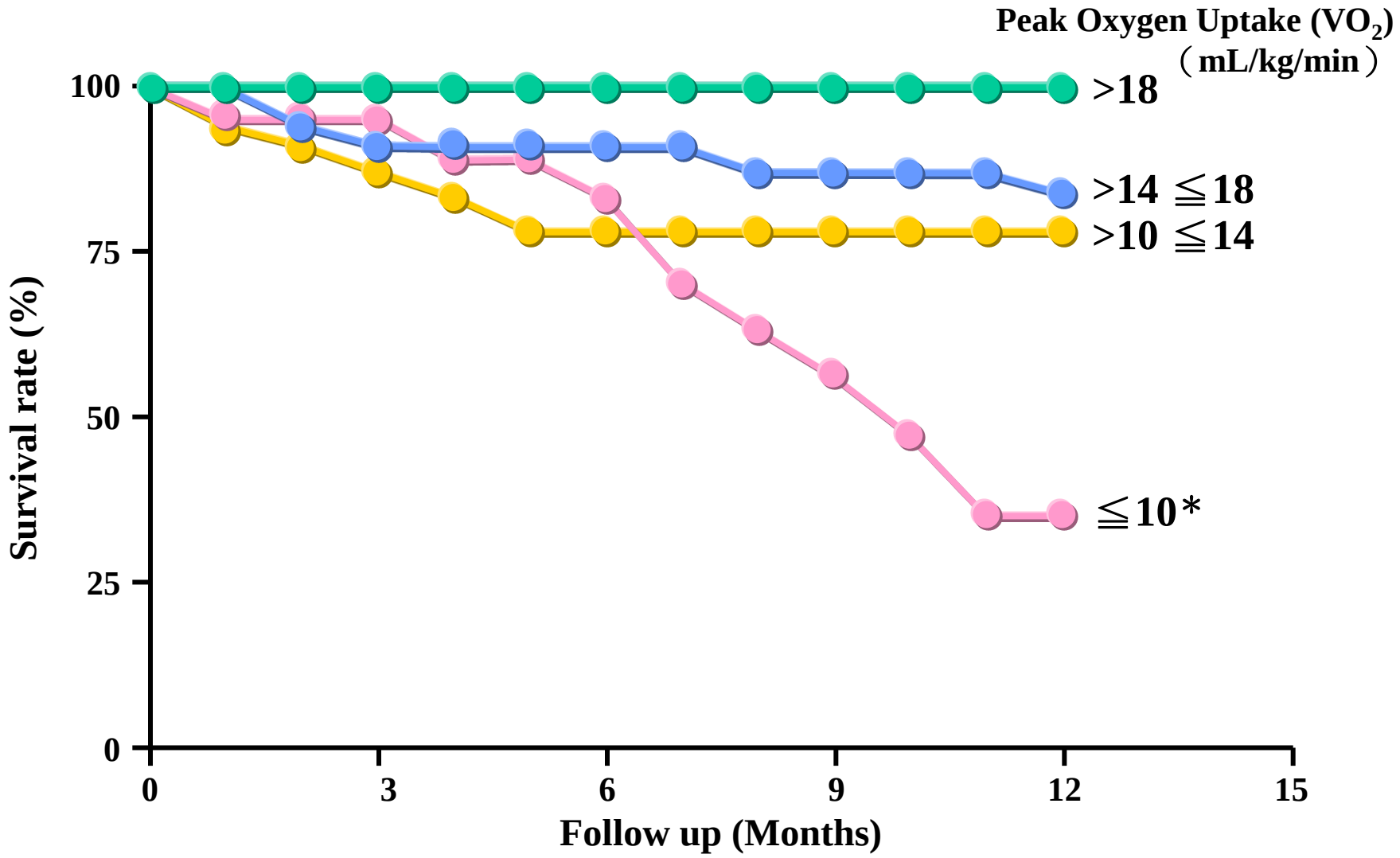
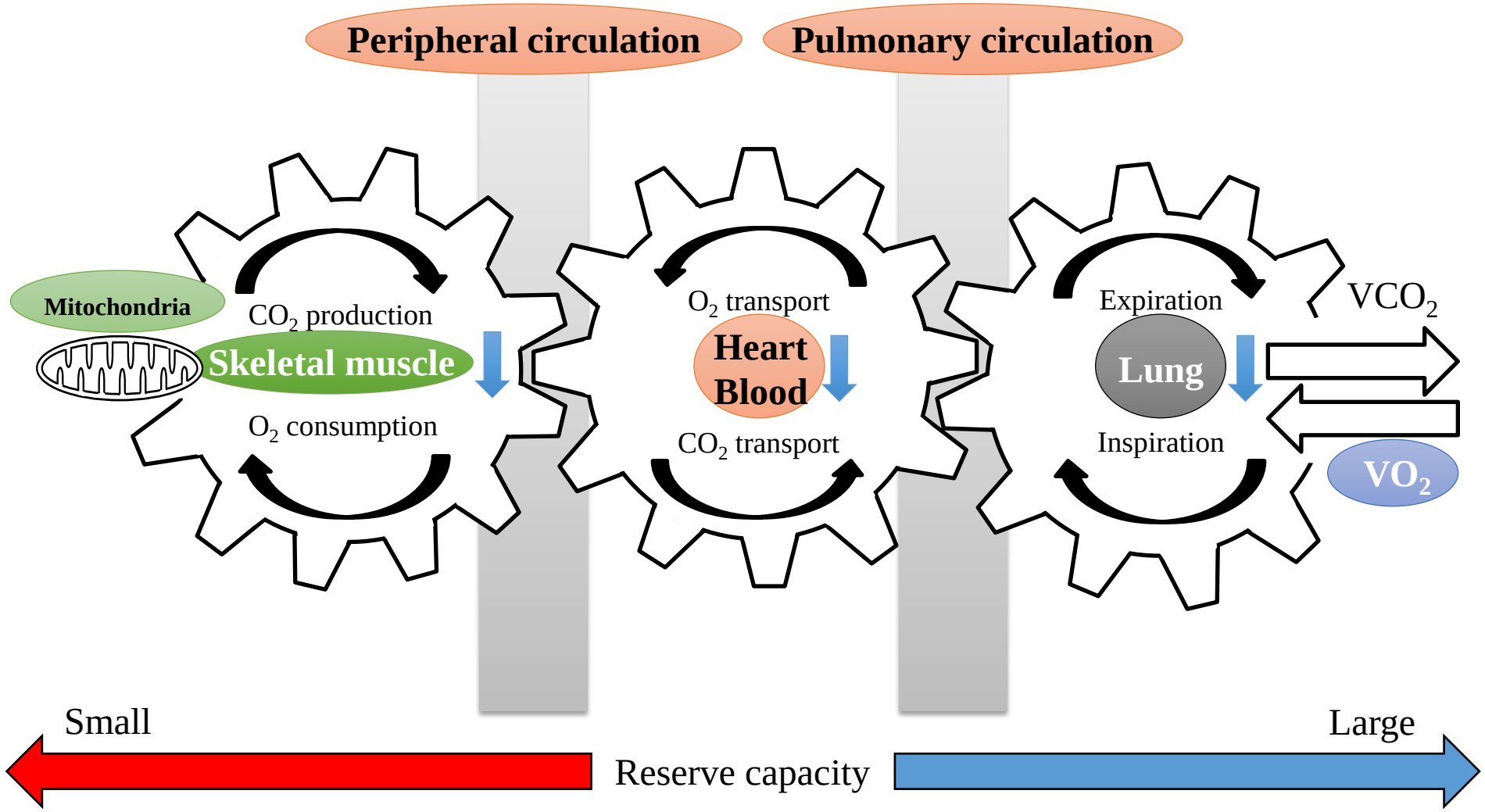
Peak oxygen uptake and prognosis in patients with heart failure (HF)

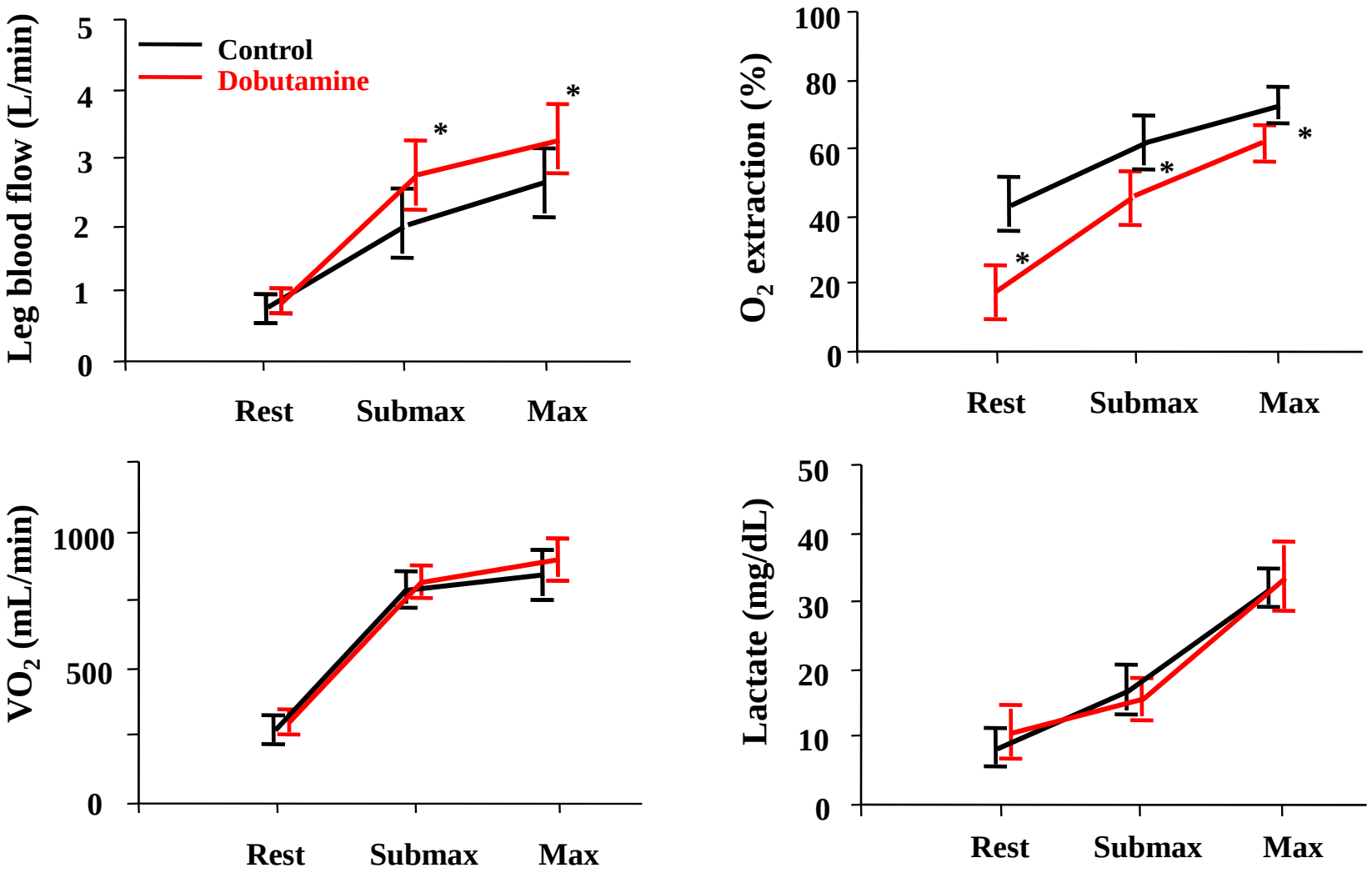


Mancini DM, et al. Circulation 1991; 83: 778-786

Factors regulating exercise capacity



Dobutamine does not increase exercise capacity



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

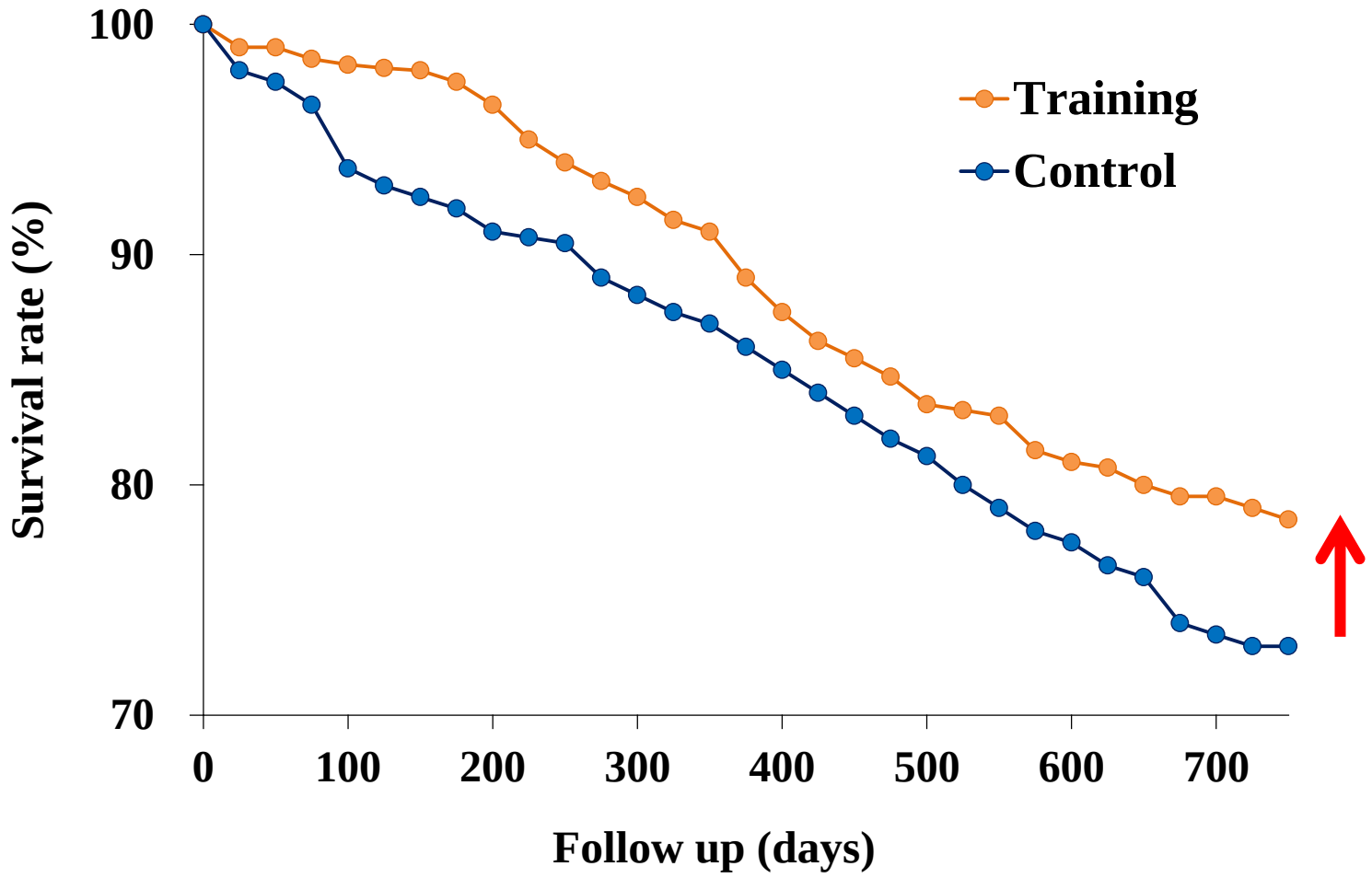
Skeletal muscle abnormalities in HF

Morphology	Histology	Biochemistry	Others
Muscle wasting Muscle fiber atrophy (IIb)↓→	Type I fibers ↓ Type II fibers↑ Shift from type IIa to IIb	Oxidative enzymes ↓ Glycolytic enzymes ↑→	Impaired energy metabolism 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.

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

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**

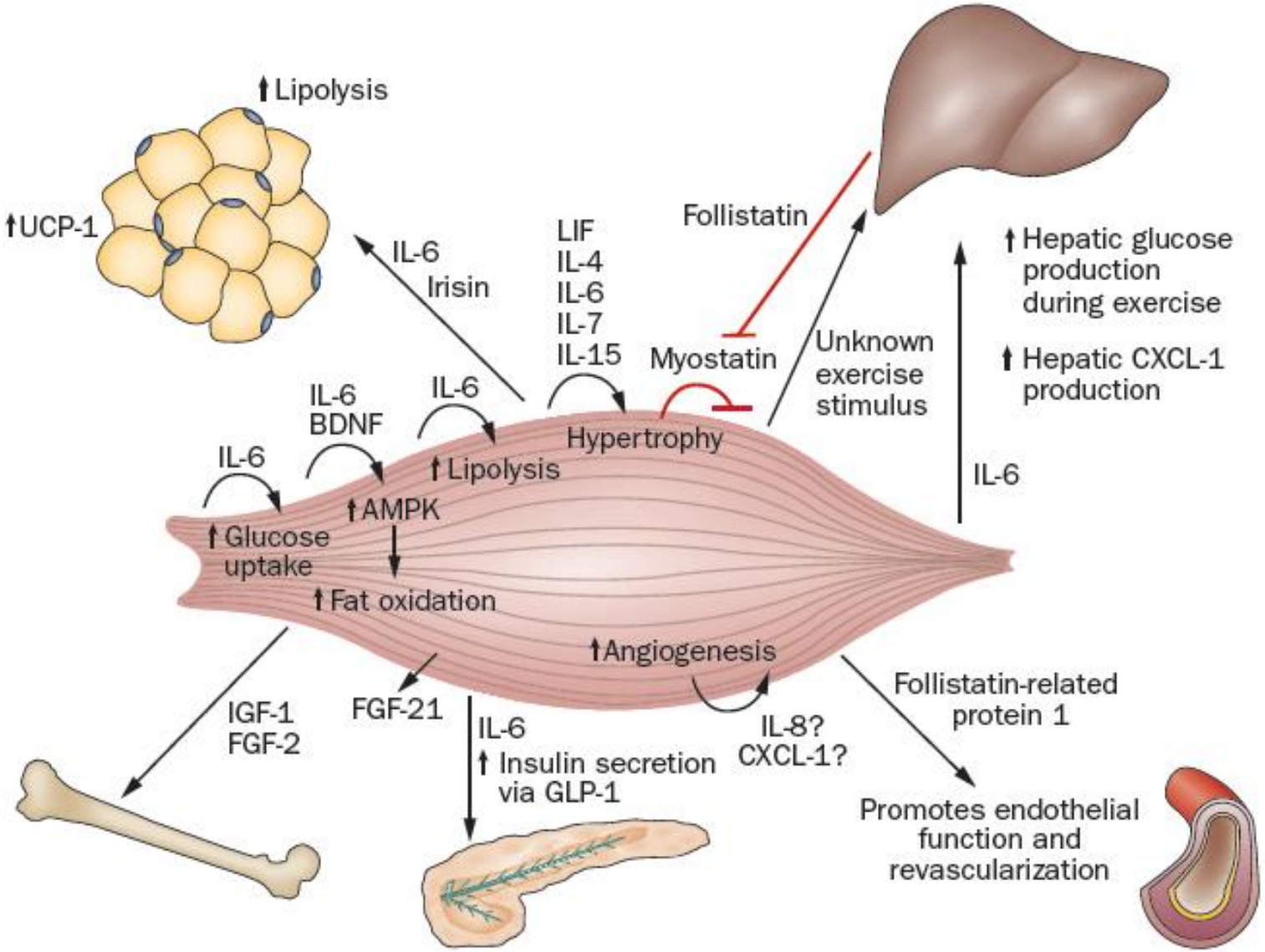
The greatest effect is to improve skeletal muscle abnormalities.

Treatment targeting skeletal muscle abnormalities

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’t perform aerobic exercise.

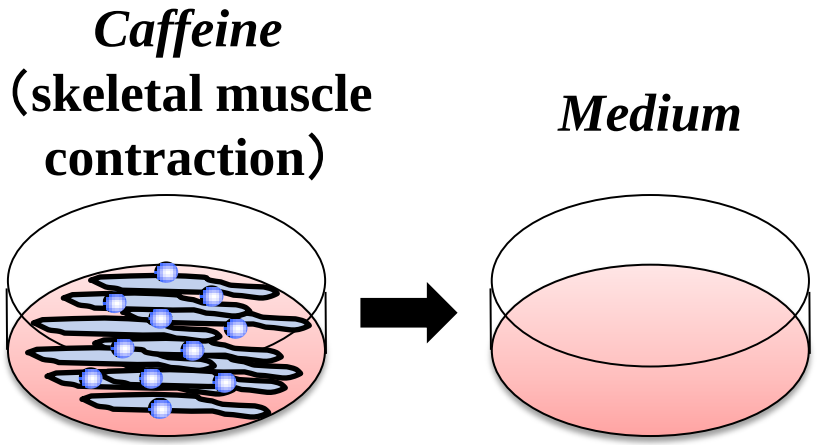
We focused on myokine secreted from skeletal muscle and performed studies.

Skeletal muscle is a huge endocrine organ

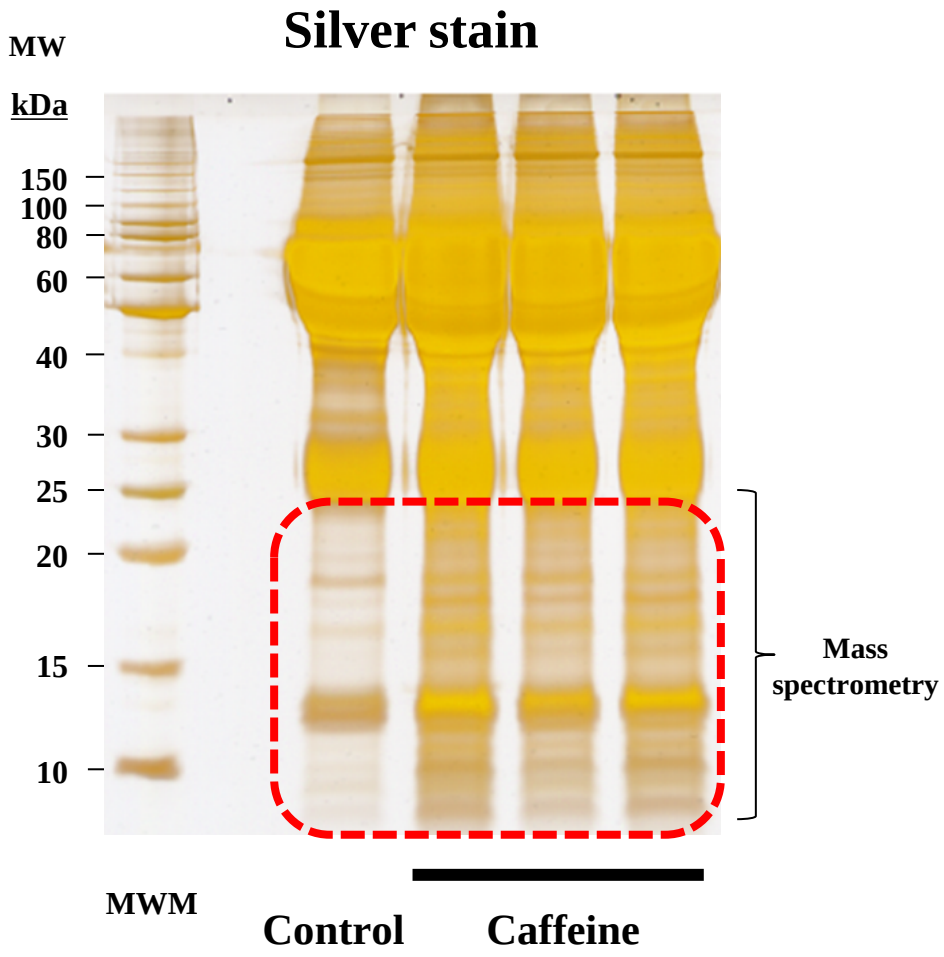


Pedersen BK, et al. Nat Rev Endocrinol 2012; 8: 457-65

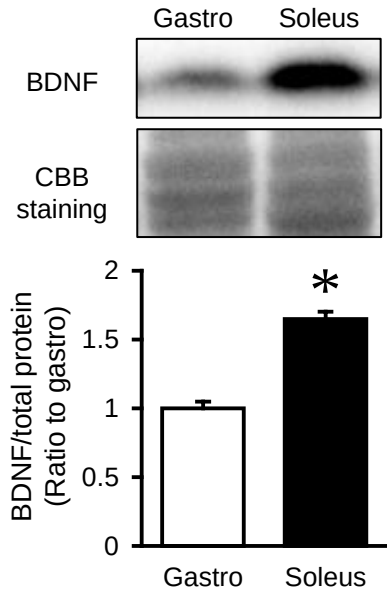
Search for proteins secreted by skeletal muscle contraction

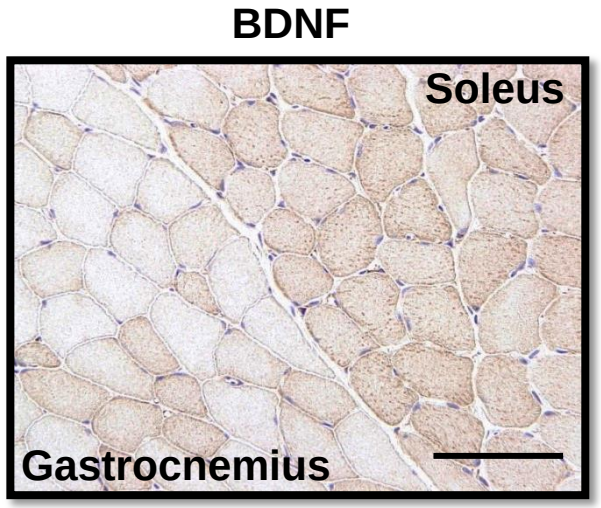


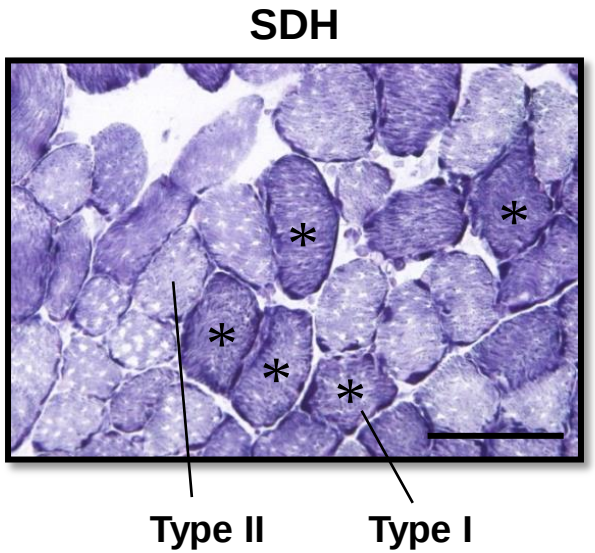
Cultured medium					
Without caffeine			With caffeine		
Name	Cover (%)	MASCOT score	Name	Cover (%)	MASCOT score
MIF	21	317	MIF	21	115
VEGF	6	38	VEGF	14	89
SPARC	5	36	**BDNF**	**8**	**71**
FSTL	3	44	FSTL	3	30

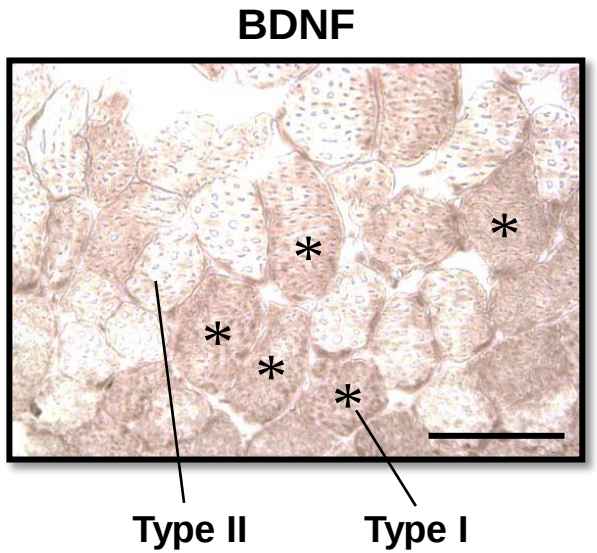


BDNF is preferentially present in the slow twitch fiber

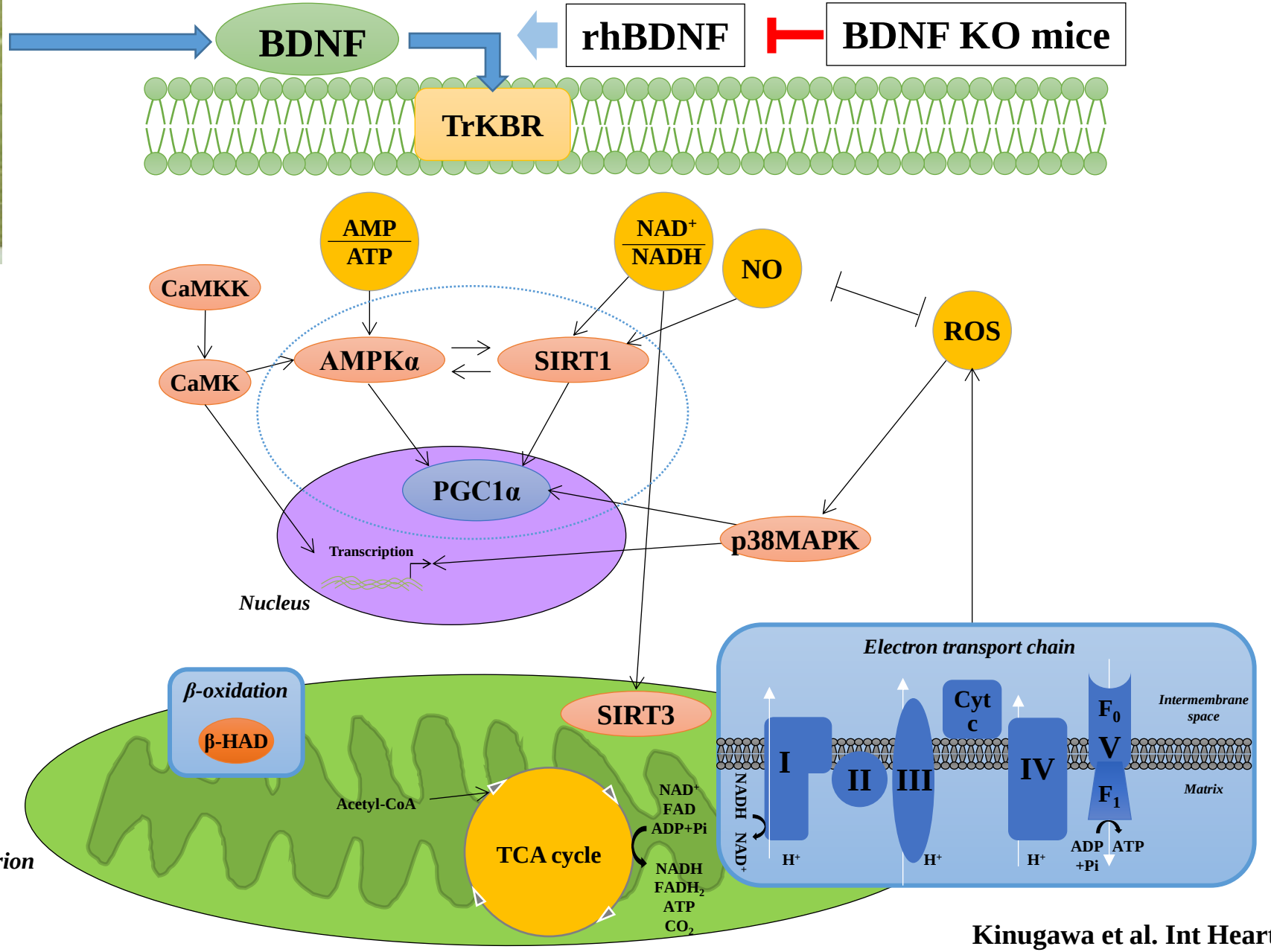






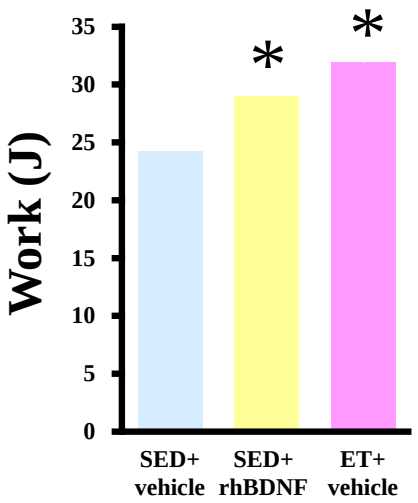


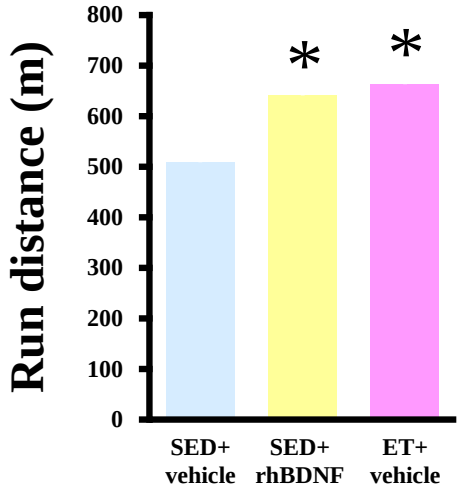
Signal regulating mitochondrial biogenesis

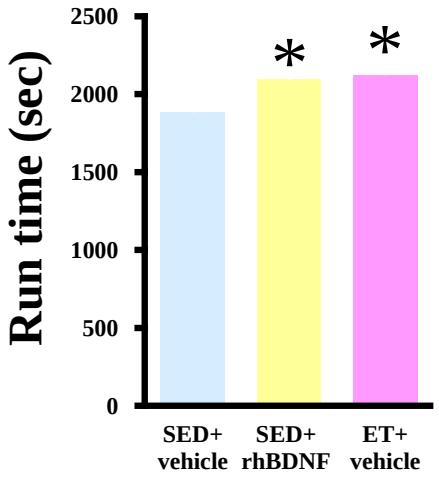


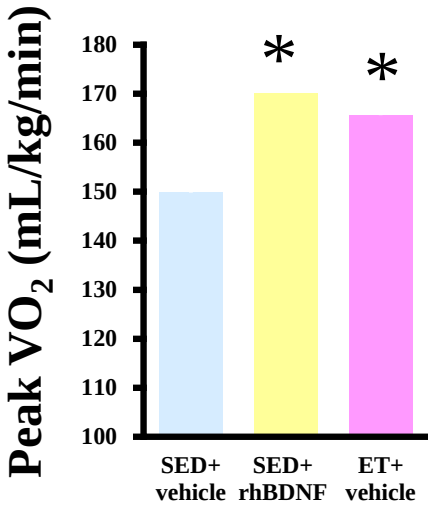
Kinugawa et al. Int Heart J 2015; 56:475-84

BDNF mimics exercise training





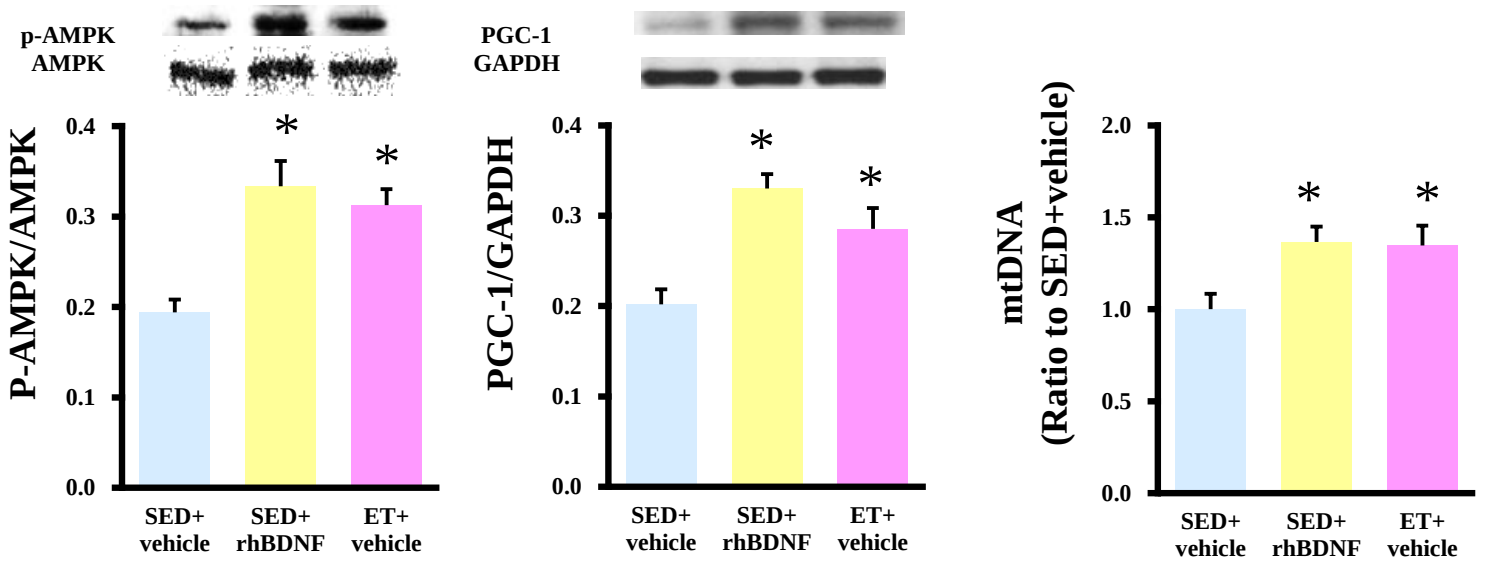


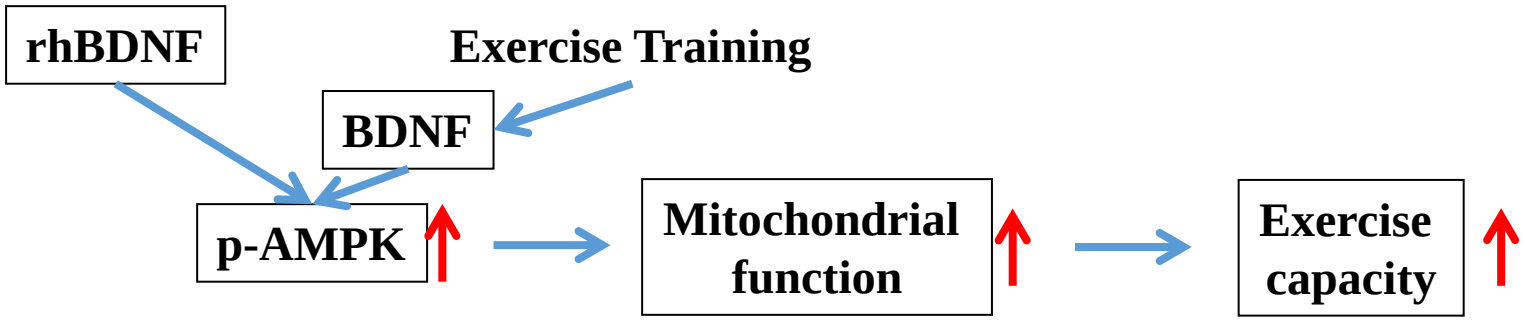


\+ **rhBDNF** =

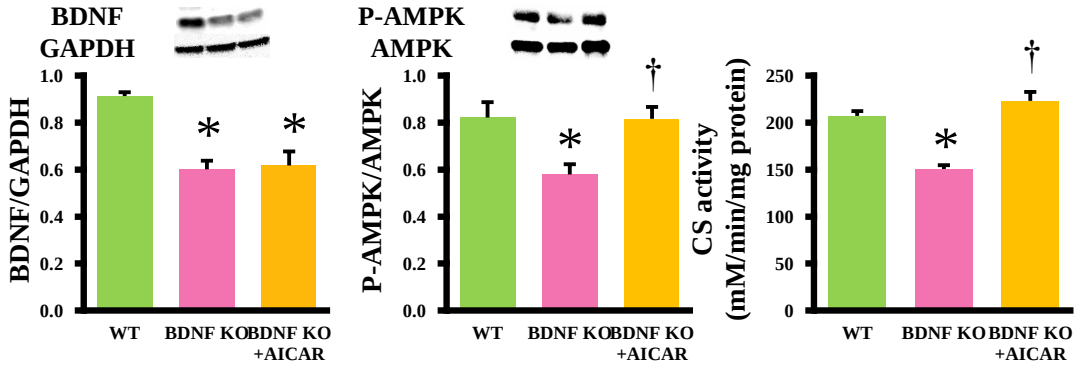
What a wonderful thing if this happen!!

Signaling regulating mitochondrial function





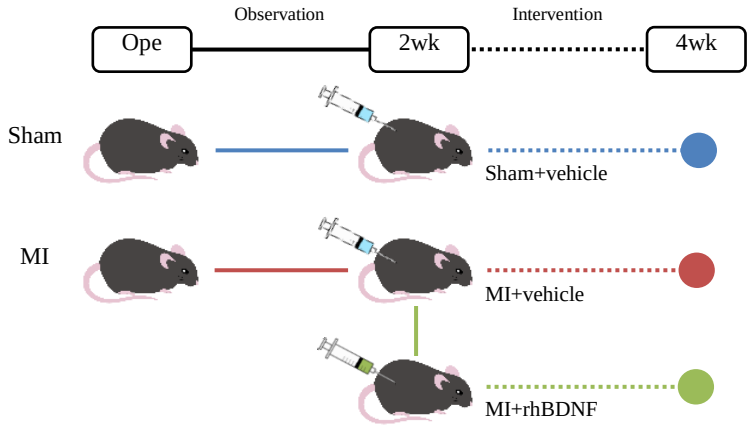
Effects of AMPK activator in BDNF KO mice

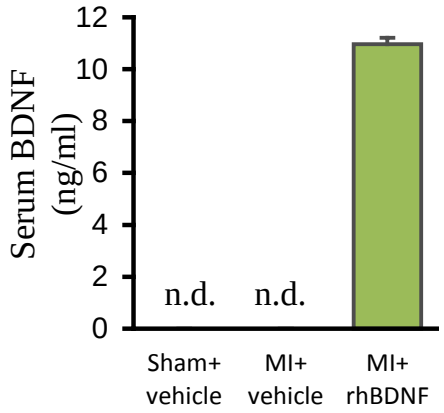


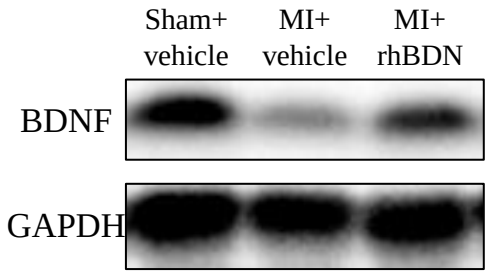
BDNF KO mice ＋ **AICAR（AMPK activator）**

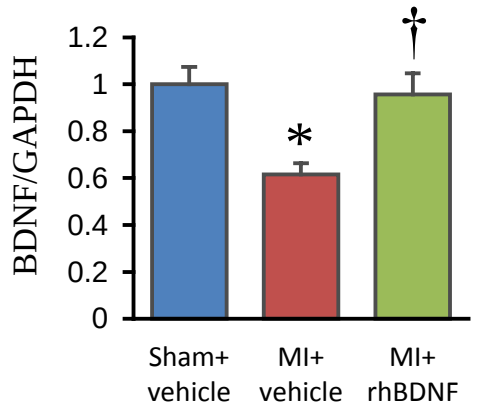
p-AMPK ↑ → **Mitochondrial function** ↑ → **Exercise capacity** ↑

BDNF expression is decreased in the skeletal muscle from mice with HF after myocardial infarction



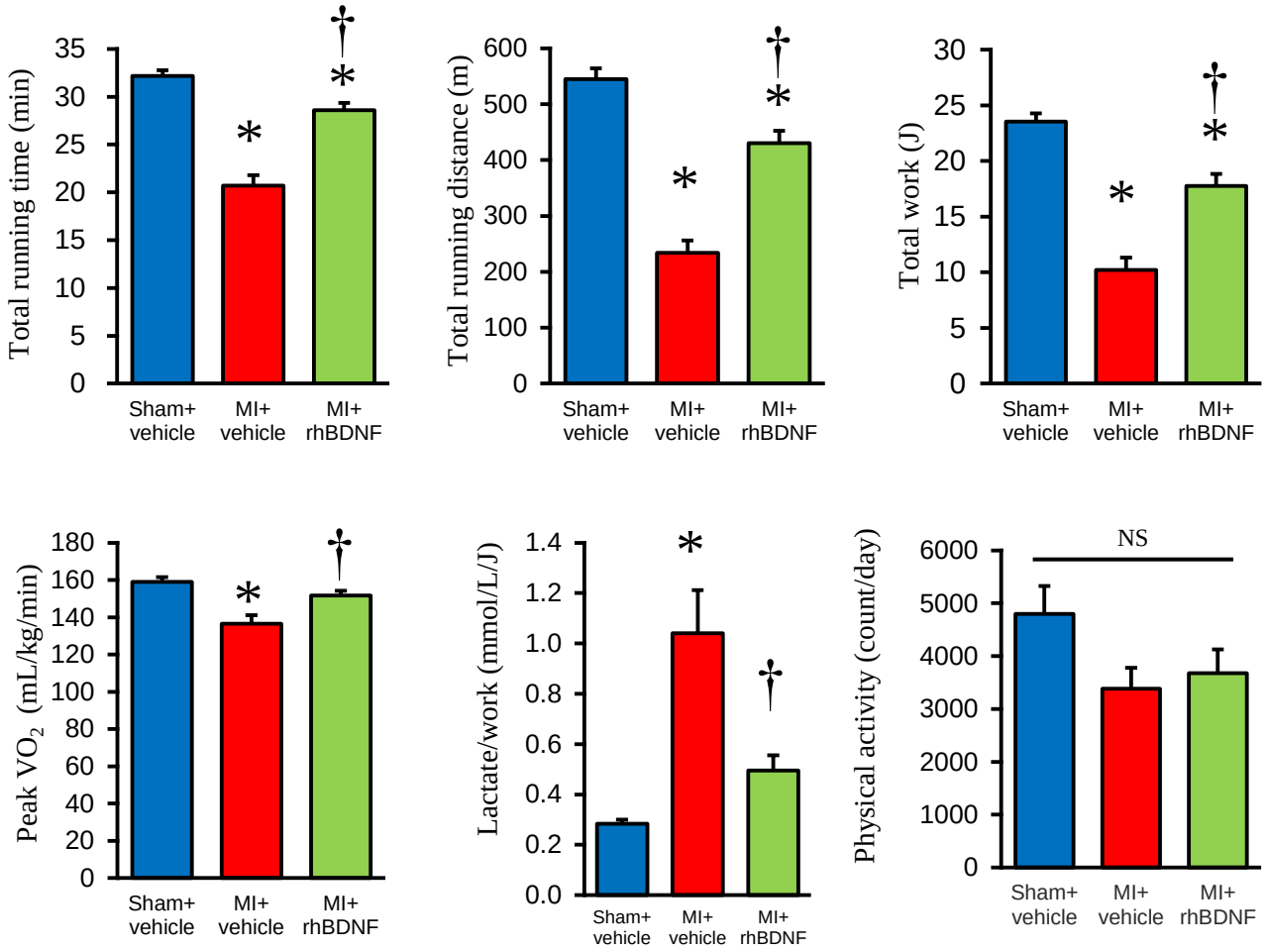






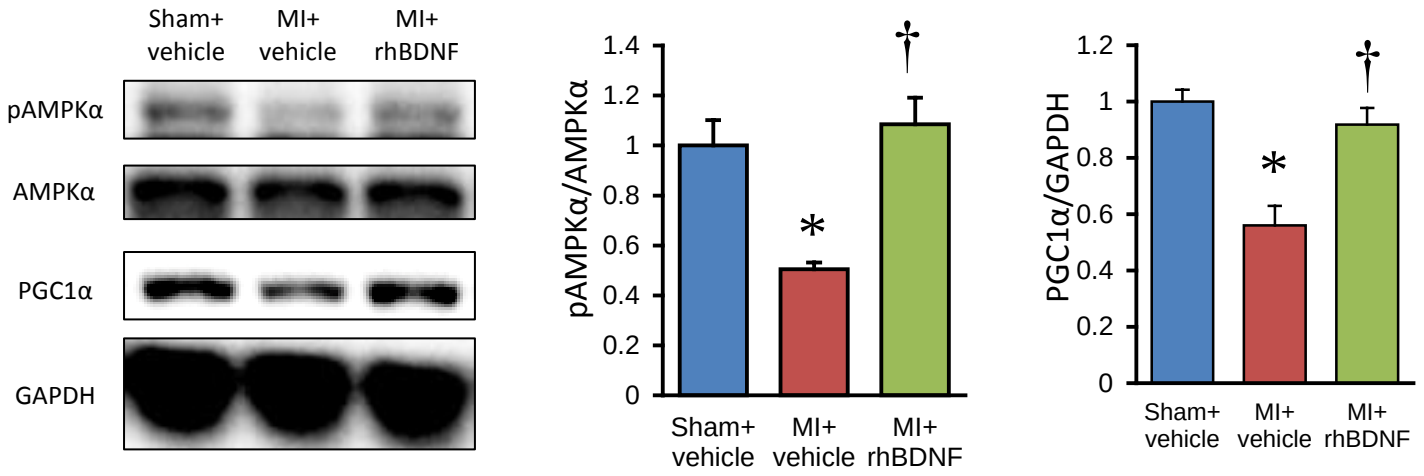
Matsumoto J, et al. Circulation 2018; 138:2064-6

BDNF improves exercise capacity in HF mice

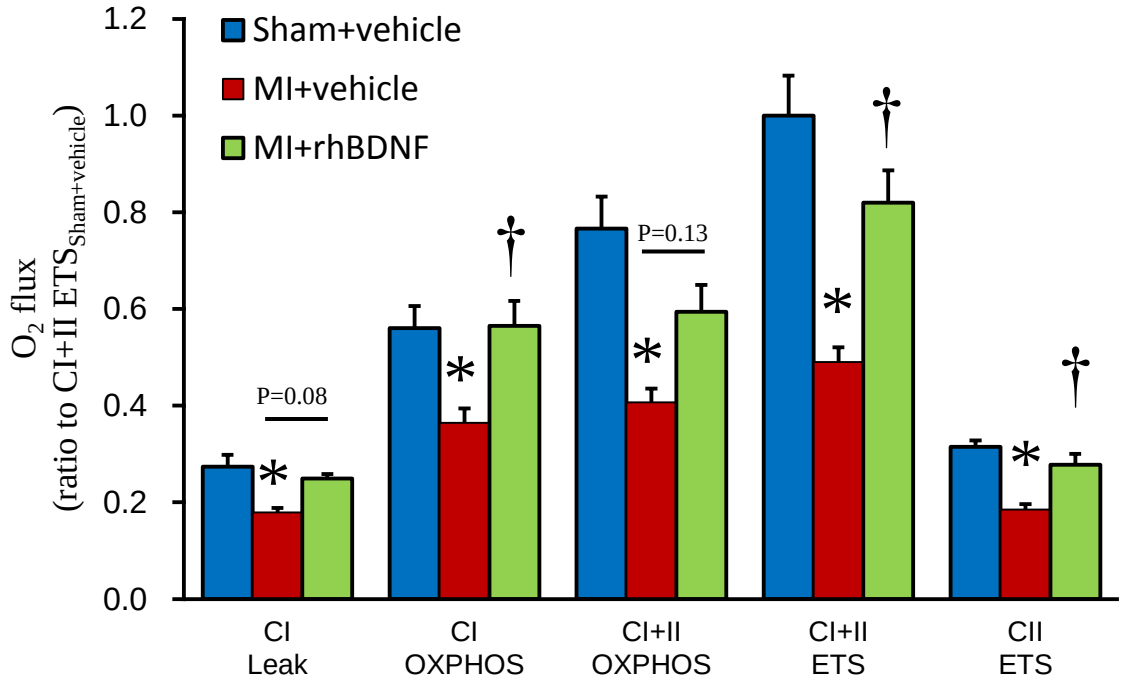


Matsumoto J, et al. Circulation 2018; 138:2064-6

BDNF activates AMPKα-PGC1α signal in the skeletal muscle

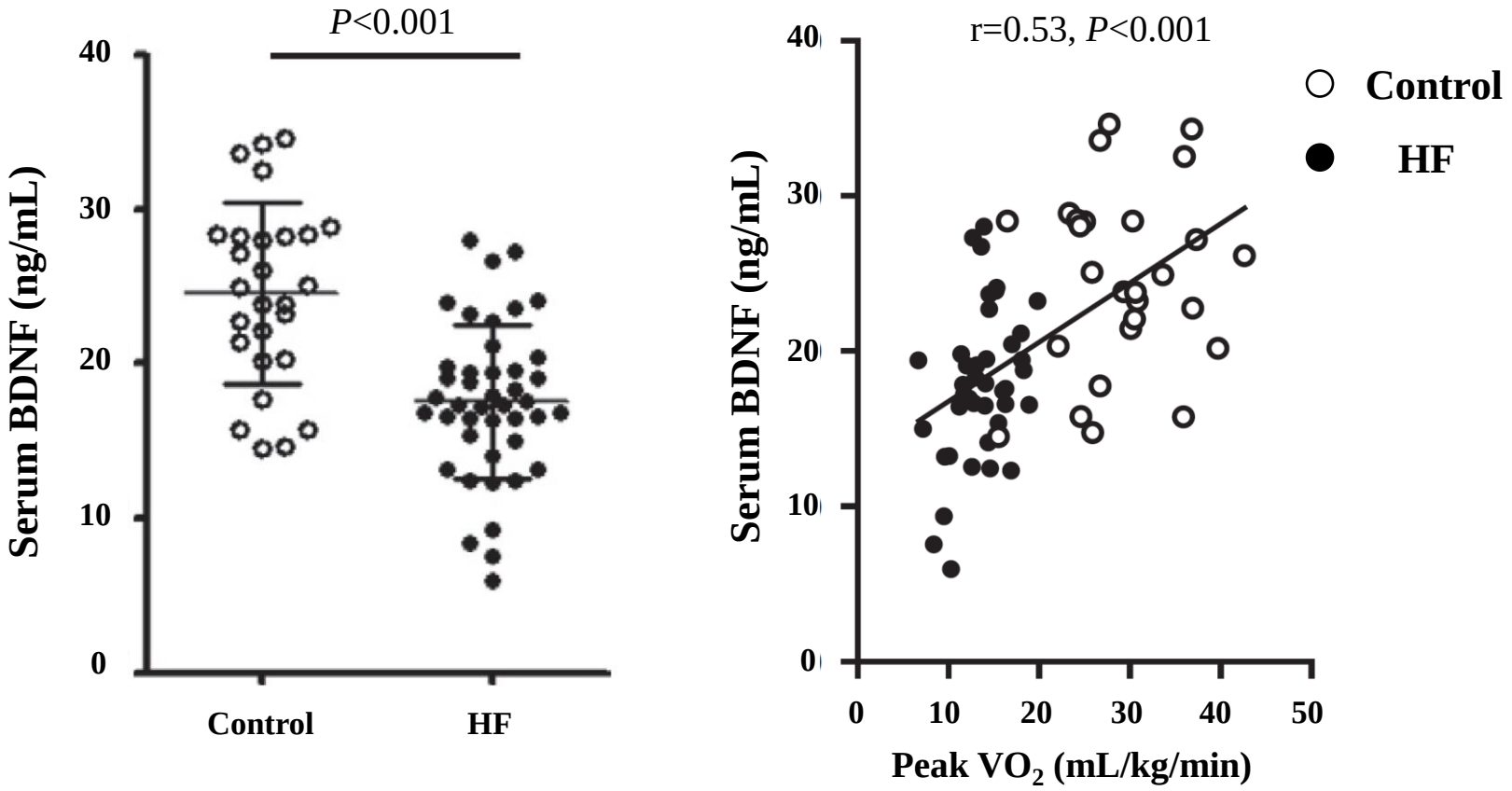


BDNF improves mitochondrial respiration in the skeletal muscle



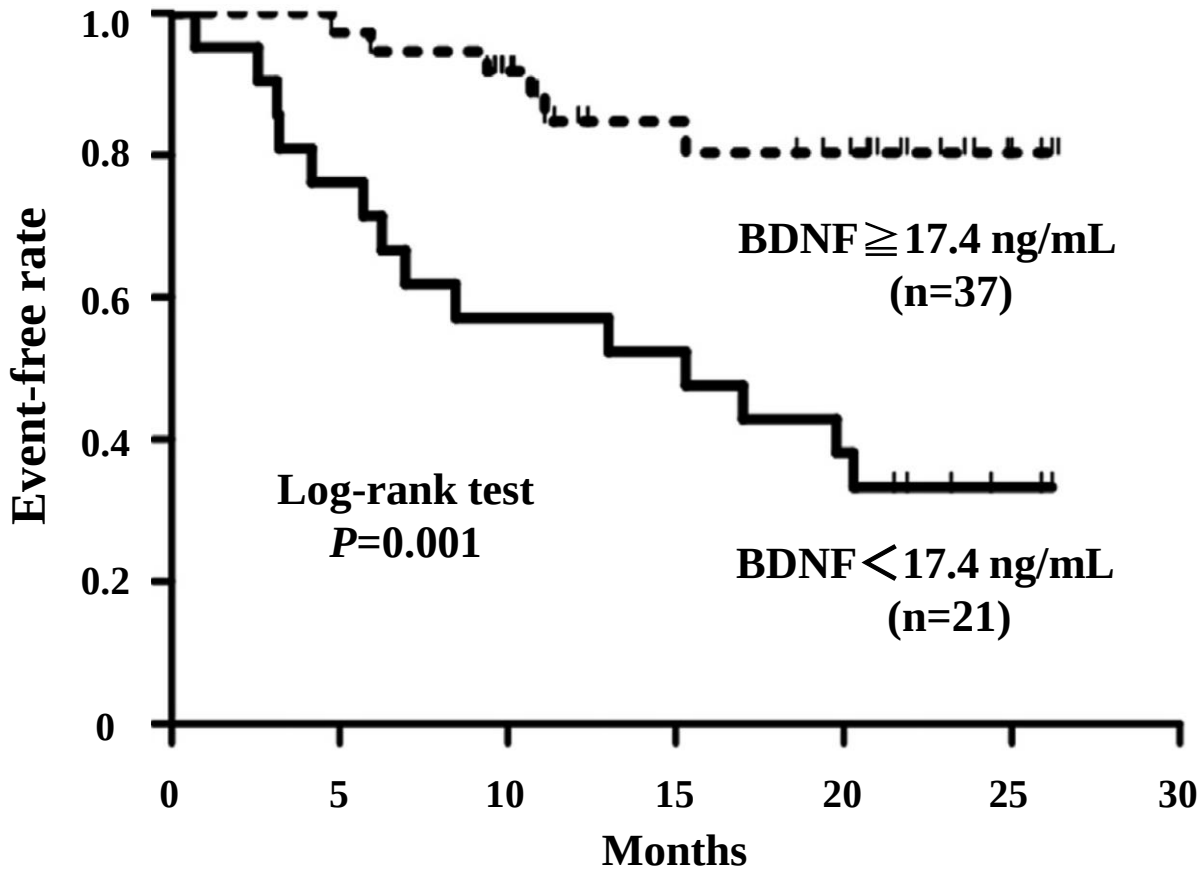
Matsumoto J, et al. Circulation 2018; 138:2064-6

BDNF and exercise capacity in patients with HF



Fukushima A, et al. Int J Cardiol 2013; 168: e142-4

BDNF is an independent predictor for clinical events



Fukushima A, et al. J Cardiac Fail 2015; 21: 300-6

Conclusion

BDNF may be a new treatment aiming at improvement in exercise capacity and targeting skeletal muscle.