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EDITORIAL COMMENT

Paradoxical Effect of Caloric Restriction on Overload-Induced Muscle Growth in Diastolic Heart Failure*

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Physical exercise is as an efficient method for maintaining health and ameliorating the pathology of a number of diseases. There are two extremes of muscle activities: strengthening and endurance exercises. Each has a different spectrum of benefits. Not long ago endurance exercise has been considered more beneficial for cardiovascular and lung function, whereas strengthening exercise has been considered more beneficial for increasing muscle size. However, strengthening exercise has gained more attention recently because it produces more myokines than endurance exercise does.[1] Myokines are mainly peptides secreted by muscle and acting also on other organs, for example, on the heart in pathology. Maintaining muscle mass, therefore, is important in cardiovascular diseases for health benefits and retaining life quality. One way to do this is to apply increased load (resistance exercise with intervention), which belongs to the strengthening type of exercises. To work with optimal overload for cardiovascular patients it might be just as "easy" as doing moderate endurance exercise. Considering the systemic connection between skeletal and cardiac muscle function, it is a relevant question if pharmacologic drugs used in heart diseases may also improve skeletal muscle pathology.

In this issue of *JACC: Basic to Translational Science*, Espino-Gonzalez et al[2] report on a study using obese male ZSF1 rats that develop heart failure with preserved ejection fraction (HFpEF). In this syndrome the left ventricle is stiff and unable to fill properly and the skeletal muscle becomes dysfunctional and atrophies. In the article by Espino-Gonzalez et al,[2] HFpEF rats were compared with healthy lean male controls of the same strain. A clinically approved drug, Sacubitril/Valsartan, improved cardiac structure and function in HFpEF rats but neither rescued skeletal muscle atrophy as measured by fiber size, nor changed fiber type, capillarity, fibrosis, and muscle mass. There was a 15%-30% reduction in gross wet-mass in the predominantly type II fiber containing extensor digitorum longus (EDL) and in the type I fiber-enriched soleus both in treated and untreated HFpEF rats. Next, mechanical overload was applied by synergist ablation of tibialis anterior in 1 leg. This is an accepted way to mimic resistance exercise and to induce hypertrophy in the neighboring muscles like EDL. The changes in muscle size have been compared in the loaded and unloaded legs of the same rat. The lean control animals have responded to 14 days of physical overload with a 30% increase in fiber size (preferentially type II) and a higher absolute twitch and maximal tetanic force of EDL muscle. However, no such change was measured in HFpEF rats showing impairment in load-induced myofiber growth. No fiber type change or a difference in force normalized to muscle mass and in relative fatigue was associated with this pathology.

Peripheral vascular dysfunction is one of the problems of HFpEF that might be important for pressure overload-induced hypertrophy. However, the capillarity-to-fiber ratio increased in both control and HFpEF rats in overload, whereas the capillary

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density was elevated only in HFpEF in a type IIa and type IIx/b fiber-dependent manner. In silico simulated PO_2 and muscle blood flow was not different in control and HFpEF rats. Meanwhile the increase in blood flow relative to muscle mass in stimulated contraction after overload was about 40% lower in the control group but unchanged in the HFpEF group. Therefore, none of these parameters would explain the impairment in load-induced myofiber growth in HFpEF.

Mitochondrial metabolism and energetics are important for myofiber growth and HFpEF was associated with muscle mitochondrial defects. High-resolution respiratory analysis of permeabilized EDL muscles revealed that complex I-dependent respiration was increased in controls but not in HFpEF rats in overload. However, citrate synthase activity, a marker of mitochondrial content (rather than function), was not changed. This was further supported by a 51% increase of mitochondrial coupling efficiency in overload of controls but not in that of HFpEF, indicating a deficit that might limit the load-induced growth of myofibers. Detailed analysis of pro-fusion and -fission proteins of mitochondria revealed no difference in dynamics of this pivotal organ between groups. However, the basal phosphorylation of adenosine tryphosphate citrate lyase (ACL) was lower in HFpEF than in the control and after overload it was increased only in HFpEF. The activity of ACL is initiated by self-phosphorylation and it is an important cytosolic enzyme that produces oxaloacetate and acetyl coenzyme A from citrate. The citrate derives from mitochondria by transport when the tricarboxylic acid cycle is inhibited in energy overload by adenosine tryphosphate and reduced coenzyme. Acetyl coenzyme A can be used for biosynthesis of fatty acids, which are necessary for cardiolipins, the essential compounds of the inner membrane of mitochondria. Therefore, ACL is coupled to anabolic metabolism and mitochondrial function and also a target of IGFI-Akt signaling. The decrease of IGF-ACL-cardiolipin pathway is associated with fiber atrophy.[3] Therefore, the decreased load-induced myofiber growth in HFpEF might be at least partly due to dysfunction of this mitochondrial anabolic pathway.

Caloric restriction (CR) increases catabolism in the body but paradoxically it also supports anabolic processes in muscle such as load-induced fiber growth. CR in combination with exercise has been shown to improve muscle health also in patients with HFpEF.[4] So the investigation proceeded with applying stepwise caloric reduction for 4 weeks in combination with muscle overload. Remarkably, this treatment restored overload-induced hypertrophy in type I and IIa fibers of EDL of HFpEF rats without a change in fiber type and overt atrophy in other investigated muscles. The in vitro peak contractile power also showed improvement toward the control. This indicated that CR had a positive effect on overload-induced myofiber growth and on basal function and structure of skeletal muscle in HFpEF. In addition, hyperglycemia was reduced and ventricular hypertrophy also showed improvement.

The rates of protein synthesis and degradation were investigated to provide further insights into the mechanism of CR restored muscle fiber growth in HFpEF rats. None of these processes showed differences between groups, neither did the IGF1 expression, a main upstream regulator of Akt-mTORC1 signaling. Anabolic signals can be transient, therefore, soleus muscles have been subjected to repeated isometric contractions in vitro and analyzed but no difference in phosphorylation or acute expression of marker proteins was found. Neither the ubiquitin-proteasome-dependent factors (MuRF1 and MAFBx) nor the myostatin-transforming growth factor-β signaling pathway and the autophagy-dependent p62 showed differences between groups.

In spite of the comparable levels in the above markers, the muscle fiber growth was reflected by differential gene expression in transcriptomic profiling. Interestingly the largest effect was seen after CR treatment. The Hedgehog and Apelin signal pathways have been depicted as critical for myogenesis and muscle satellite cells (MuSCs), subsequently. Only the Hedgehog-dependent transcription factor Gli2 was lower in HFpEF than in the control or HFpEF + CR groups. Although the myogenic transcripts have not been increased, the transcript of the fusion protein Myomaker was higher in overload of control and HFpEF + CR rats, indicating disruption of myonuclear fusion in HFpEF. Indeed, the myonuclear number increased by 90% in overload of control and HFpEF + CR but not in that of HFpEF rats. Pathway interrogation of transcriptomic analysis with another method revealed many terms of cell cycle regulators involved in G1/S transition (cyclins, mitotic DNA damage checkpoints, stabilization of p53) in control and HFpEF + CR but not in HFpEF. This confirmed that MuSC homeostasis and myonuclear accretion have a deficit in HFpEF, which can limit myofiber growth but be restored by acute CR. Biopsy analysis of vastus lateralis from patients with HFpEF indeed showed lower levels of myogenic Pax7 and MyoD

compared with age-matched controls further supporting the disturbance in MuSC homeostasis as a major limit of adaptive myofiber growth.

In summary, the study by Espino-Gonzales et al[2] hints at a possible therapy to improve skeletal muscle mass and function in HFpEF. The authors note the limitations because the majority of their study has been done in a rat model where muscle fiber types are not entirely identical with those of human. The biopsy specimens taken from the vastus lateralis of female patients raise the questions how the other muscles behave and would there be any sex-specific differences? Other questions that remain unanswered include what factors mediate pathogenicity from heart to muscle and how CR can improve anabolic adaptation of overload muscle in HFpEF? However, the present study highlights several important details that might help to resolve the paradox of anabolic effect of CR on skeletal muscle adaptation in HFpEF.

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