

Imaging of skeletal muscle metabolism in heart failure

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Abstract

Heart failure (HF) is associated with exercise intolerance and insulin resistance. Imaging of skeletal muscle has shown that HF is accompanied by defects in muscle oxidative and glucose metabolism, together with a loss in muscle mass and remarkable intramuscular fat infiltration. These features are related to the degree of exercise intolerance and are partially restored by chronic exercise training. They are also typically present in conditions that predispose to the development of HF, indicating that skeletal muscle should be an early prevention target. ■ *Heart Metab.* 2014;64:13–17

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Heart failure (HF) is characterized by exercise intolerance that is already present in patients with preserved ejection fraction, and is related to a reduction in peak oxygen consumption (peak $\dot{V}O_2$). Patients with HF of ischemic and nonischemic origins typically manifest insulin resistance and an elevated prevalence of type 2 diabetes.^{1–5} Exercise intolerance and insulin resistance are reciprocally correlated and are both predictors of a worse prognosis. Skeletal muscle plays a dominant role in exercise performance and O_2 consumption during exercise. It is also the primary organ involved in insulin-mediated glucose disposal and in the pathogenesis of insulin resistance. This review will primarily address imaging studies of skeletal muscle perfusion, metabolism, whole-body lean/fat mass, or skeletal muscle mass and intramuscular fat, as conducted using positron emission tomography (PET) or ^{31}P magnetic resonance spectroscopy (^{31}P -MRS), and dual energy x-ray absorptiometry (DXA) or magnetic resonance imaging (MRI) in humans with HF.

Heart failure, skeletal muscle metabolism, and the response to insulin

PET imaging of perfusion and metabolism under euglycemic-insulin stimulation has documented that insulin-mediated glucose uptake in skeletal muscle declines with aging and with increasing body weight. Insulin-mediated glucose uptake was 61 ± 8 $\mu\text{mol}/\text{kg}$ muscle per minute in healthy 26-year-old subjects⁶ and 37 ± 17 $\mu\text{mol}/\text{kg}/\text{min}$ in healthy 50-year-old subjects.⁷ Skeletal muscle blood flow was on average 34 and 50 mL/kg/min, in young and older healthy subjects, respectively,^{6,7} and oxygen consumption was 1.6 mL/kg/min in the young group.⁶ We have shown that ischemic heart disease (ejection fraction [EF]=35%) was associated with skeletal muscle insulin resistance, independent of diabetes,⁷ with an average glucose uptake of 23 $\mu\text{mol}/\text{kg}/\text{min}$ (-40% vs age-matched controls) during insulin-stimulated conditions, and that glucose uptake was inversely related to the EF. Skeletal muscle blood flow at rest

Abbreviations

DXA: dual energy x-ray absorptiometry; **EF:** ejection fraction; **HF:** heart failure; **MRI:** magnetic resonance imaging; **MRS:** magnetic resonance spectroscopy; **O₂:** oxygen; **PCr:** phosphocreatine; **PET:** positron emission tomography; **Pi:** inorganic phosphorus; **$\dot{V}O_2$:** oxygen consumption

was 37 ± 14 mL/kg/min, which is not different from values observed in age-matched controls. In nondiabetic patients of similar age, but with nonischemic HF (EF=33%), Kempainen et al⁸ observed comparable values of insulin-mediated glucose uptake ($22 \mu\text{mol/kg/min}$) and blood flow (30 mL/kg/min) as well as normal values of oxygen consumption (1.7 mL/kg/min). In a subsequent study, the authors reported that insulin resistance in HF patients is not due to alterations in baseline or insulin-stimulated phosphorylation of the insulin receptor substrate (IRS)-1 and protein kinase B (Akt), or activation of phosphatidylinositol 3-kinase (PI3K), as measured in skeletal muscle biopsies.⁵ Therefore, neither the delivery of insulin, glucose, or oxygen through blood flow under resting conditions, nor the above listed insulin-signaling mediators could explain the lack of insulin action to stimulate glucose utilization in skeletal muscles. Possible mechanisms may involve the sympathetic nervous system and changes in skeletal muscle mass and composition, including adjacent fat masses, as addressed below.

Heart failure and the response of skeletal muscle metabolism to submaximal exercise

Skeletal muscle glucose utilization is potentially affected by exercise. PET studies have shown that an acute bout of submaximal isometric exercise can elevate skeletal muscle blood flow by >6-fold, oxygen uptake by >15-fold, and glucose uptake by 2.4-fold above the effect of insulin alone in young healthy individuals with peak $\dot{V}O_2$ of 44 mL/kg/min .⁶ By using a similar study set-up in patients with nonischemic HF (peak $\dot{V}O_2$ of 20 mL/kg/min), the same authors showed that skeletal muscle blood flow was stimulated by 4.4-fold, oxygen consumption by 7.6-fold, and glucose uptake by 2.4-fold during exercise+insulin vs insulin alone.⁸ Unfortunately, this study did not include a control group and comparison between the above

2 studies is limited by the marked age difference between study subjects.

Mitochondrial metabolism of skeletal muscle has been examined in HF by using ³¹P-MRS to measure the ratio of inorganic phosphate (Pi) and phosphocreatine (PCr), with higher values indicating ATP depletion, and to estimate pH, which decreases and may cause fatigue once anaerobic glycolysis and lactate production are stimulated.⁹ HF patients displayed normal Pi/PCr ratios and pH at rest, but an abnormal response during exercise with more severe fatigue, increased Pi/PCr at any given power output, and a more marked reduction in intracellular pH than observed in healthy controls. The findings suggested a depletion in PCr and impaired resynthesis of ATP, as seen in animal studies of primary HF.¹⁰ In a subsequent study, the authors used near-infrared spectroscopy to document that skeletal muscle oxygenation seemed normal under the submaximal exercise conditions of these studies.¹¹ The occurrence of normal oxygenation, even with the reduction in pH, was taken to suggest that lactate was produced despite the aerobic conditions, which may occur if mitochondrial inefficiency leads to cytosolic NADH accumulation, promoting the conversion of pyruvate into lactic acid to restore oxidation of NADH to NAD.¹¹ In support of this interpretation, the induction of HF in animal models resulted in similar changes in high-energy phosphate metabolism and was accompanied by an increase in the NADH/NAD ratio.¹⁰ In addition, creatine supplementation in patients with chronic HF increased skeletal muscle energy-rich phosphagens together with muscle strength and endurance.¹²

Heart failure and the response of skeletal muscle metabolism to chronic training

A 5-month training period, including supervised aerobic and resistance training in HF patients, resulted in a 27% improvement in peak $\dot{V}O_2$, a slight, but nonsignificant, reduction in NYHA functional class and heart rate, and a significant reduction in the percent body fat, but not body weight.⁸ Skeletal muscle glucose uptake under both insulin and insulin+submaximal isometric-exercise stimulation was significantly increased, but no change was seen in muscle blood flow and oxygen consumption.⁸ No change in muscle IRS-1 phosphorylation, Akt phosphorylation, or PI3K activation was found to explain the improvement in

insulin sensitivity.⁵ This was consistent with observations in healthy middle-aged men, in whom one-week of exercise training was not coupled with PI3K or Akt activity changes.¹³ This observation suggests the involvement of more distal pathways, including glucose transporter type 4 (GLUT4) membrane translocation, and/or the influence of the type of skeletal muscle fiber, as seen in insulin-resistant states¹⁴ or forced inactivity states due to disability,¹⁵ in which the proportion of type I fibers is reduced in parallel with insulin-mediated glucose uptake in skeletal muscle. A shift of type II glycolytic fibers into type I oxidative fibers was documented in biopsies from HF patients undergoing 6 months of exercise training.¹⁶ However, this shift was not observed in disabled subjects undergoing electrically stimulated leg cycling, in whom skeletal muscle insulin sensitivity and expression of GLUT4, hexokinase II, and glycogen synthase were increased despite no change in fiber composition.¹⁵

Studies conducted with arterial-venous (a-v) substrate differences and thermolilution assessed blood flow before and after 4 to 6 months of aerobic training in 12 patients with severe chronic HF (EF=24%). These studies showed an increased leg blood flow and a-v oxygen differences at peak exercise, but not at submaximal workloads, while circulating lactate levels were markedly reduced.¹⁷

Studies with ³¹P-MRS in HF patients before and after a one-month training period improved their responses to an incremental exercise test by increasing the intracellular pH, the PCr/(PCr+Pi) ratio, the PCr resynthesis rate, and the maximal rate of mitochondrial ATP synthesis in parallel with an improved contraction and duration of exercise.¹⁸ This is in accord with bioptic evidence of greater skeletal muscle mitochondrial volume density, which may reflect the oxidative capacity and increase in functional capacity after 6 months of physical exercise in HF failure patients.¹⁶

Altogether, the above findings suggest that skeletal muscle abnormalities accompanying HF may depend, in part, on physical inactivity, and can be partially restored with physical training.

Skeletal muscle mass and composition

HF patients are characterized by skeletal muscle atrophy, which relates to exercise intolerance in patients with reduced or preserved ejection fraction

where the percent of total and leg lean mass was reduced in parallel with peak $\dot{V}O_2$ compared with healthy controls.¹⁹ However, the relationship linking increments in peak $\dot{V}O_2$ with total or leg lean mass,¹⁹ calf muscle volume, or midarm area²⁰ was weak and poorly associated with ³¹P-MRS findings, implicating additional mechanisms. In fact, HF patients with and without a normal ejection fraction show a reduction in type-I oxidative muscle fibers and the capillary to fiber ratio.²¹ In addition, skeletal muscle in patients with HF was shown to be infiltrated by fat (Figure 1).²²

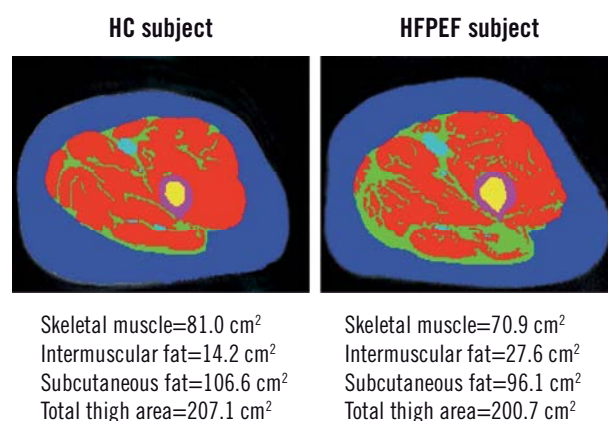


Fig. 1 MRI axial image of the mid thigh in a patient with HFPEF and in a HC subject. The red color indicates skeletal muscle, blue is subcutaneous fat, and green is intermuscular fat. The latter is substantially increased in the patient with HFPEF compared with the HC despite similar subcutaneous fat.

Abbreviations: HC, healthy control; HFPEF, heart failure with preserved ejection fraction; MRI, magnetic resonance imaging.

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These patients were mostly overweight and obese compared with controls, but their weight did not fully account for the difference. Intramuscular fat was suggested to limit oxygen diffusion or sequester blood flow during exercise, in accord with recent PET data documenting that a several-fold increase in perfusion occurs in leg adipose tissue while the adjacent muscle is exercising (Figure 2).²³ Adipocytes interspersed between muscle fibers could also lead to an underestimation of oxidative or glucose metabolism, as they may not always be dissected from muscle in image analysis. In addition, intramuscular fat may be a proximal source of fatty acids, provoking insulin resistance, and this mechanism may be exacerbated by an overactive sympathetic tone that is frequently seen in HF. Norepinephrine has been shown to correlate with fatty acid levels, and changes in norepinephrine levels during β -blockade were inversely correlated

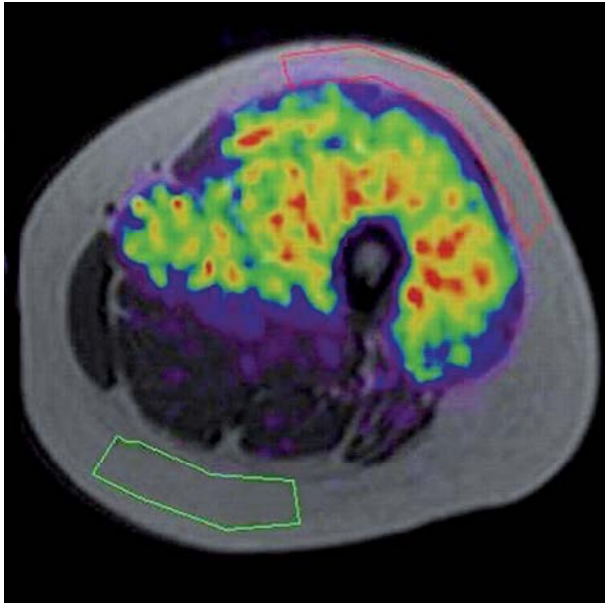


Fig. 2 Fusion image of PET and MRI of the midthigh region. The image shows the contrast between skeletal muscle blood flow (color scale bar) in exercising anterior and resting posterior muscle groups. Subcutaneous adipose tissue blood flow adjacent to the working knee extensors (region delineated by a red line) displayed increased blood flow compared with adipose tissue adjacent to the inactive posterior hamstring muscles (region delineated by a green line).

Abbreviations: MRI, magnetic resonance imaging; PET, positron emission tomography.

After reference 23: Heinonen et al. *J Appl Physiol* (1985). 2012;112(6):1059–1063. Copyright © 2012, the American Physiological Society.

with changes in the respiratory quotient.²⁴ Some, but not all, β -blockers have been shown to induce a lipid-to-glucose metabolic shift²⁴ and enhance insulin sensitivity.²⁵ However, other studies did not find a correlation between insulin resistance and plasma noradrenaline.^{3,26} Microneurography has been used to show that patients with ischemic cardiomyopathy had a higher resting muscle sympathetic nerve activity than patients with nonischemic dilated cardiomyopathy.²⁷ Sympathetic overtone and vasoconstriction may limit oxygenation and divert the available glucose into anaerobic glycolysis.

There is mutual influence between the mass and composition of skeletal muscle and HF/HF-symptoms, or between the mass and composition of skeletal muscle and skeletal muscle metabolism. Although muscle atrophy impairs exercise performance, studies on primary HF in dogs have shown that muscle atrophy can ensue as a complication.²⁸ Since muscles are prominent users of glucose, skeletal muscle atrophy will unavoidably reduce insulin sensitivity. On the other hand, when insulin resistance is primary due to the absence of skeletal muscle insulin receptors in

mice,²⁹ muscle mass and force production are lost due to decreased protein synthesis without fiber type abnormalities.

Conclusion

Imaging of skeletal muscle has shown that HF is accompanied by defects in oxidative and glucose metabolism in this organ, together with a loss in muscle mass and remarkable intramuscular fat infiltration. These features are related to the degree of exercise intolerance and are partially restored by chronic exercise training. The relationship between skeletal muscle and adjacent adipose tissue may explain several of the abnormalities observed and deserves a better understanding. Although the dissection of primary mechanisms is hampered by the mutually reinforcing nature of the pathways involved, we know that muscle fat infiltration, enhanced lipolysis, insulin resistance, impaired mitochondrial function, and sympathetic overtone can occur in a variety of conditions, from normal aging and sedentariness to obesity, diabetes, coronary artery disease with normal cardiac function and others. All of these conditions predispose patients to the development of HF and the subsequent exercise intolerance. Therefore, attention to skeletal muscle health should be carefully pursued in the management of these predisposing conditions. Imaging technologies can support the earliest detection and therapeutic monitoring of skeletal muscle morphology and functional changes. ■

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