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Review Article

# Aerobic exercise training as therapy for cardiac and cancer cachexia

Christiano Robles Rodrigues Alves, Telma Fátima da Cunha, Nathalie Alves da Paixão, Patricia Chakur Brum *

*School of Physical Education and Sport, University of São Paulo, São Paulo, Brazil*

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ABSTRACT

Aerobic exercise training (AET) induces several skeletal muscle changes, improving aerobic exercise capacity and health. Conversely, to the positive effects of AET, the cachexia syndrome is characterized by skeletal muscle wasting. Cachexia is a multifactorial disorderassociated with other chronic diseases such as heart failure and cancer. In these diseases, an overactivation of ubiquitin–proteasome and autophagy systems associated with a reduction in protein synthesis culminates in severe skeletal muscle wasting and, in the last instance, patient's death. In contrast, AET may recycle and enhance many protein expression and enzyme activities, counteracting metabolism impairment and muscle atrophy. Therefore, the aim of the current review was to discuss the supposed therapeutic effects of AET on skeletal muscle wasting in both cardiac and cancer cachexia.



**Contents**



## Introduction

Aerobic exercise capacity is a strong indicator of early death for both healthy individuals and those with cardiovascular diseases [46,54,69]. Moreover, rats artificially selected to display intrinsic high aerobic capacity present superior life expectancy (~45%) when compared to low aerobic capacity rats [53]. In fact, the enrollment in aerobic physical activity reduces major mobility disability in elderly individuals [70] and it is associated with a prevention of a large spectrum of disorders and diseases over the adult lifespan [13,36,37,48].

Aerobic exercise training (AET) (*i.e.* regular aerobic exercise characterized by high repetition and low resistance demands during skeletal muscular contraction) is a well-established approach to improving aerobic exercise capacity and health. AET has a homeostatic role regulating the rate of energy production, blood flow, and substrate utilization in response to locomotion. Importantly, the skeletal muscle is highly responsive to AET. Bioenergetic and contractile protein remodeling contribute to AET-induced adaptations in the skeletal muscle, such as protein turnover, mitochondrial biogenesis and antioxidant capacity improvement. Additionally, AET modulates several oxidative and glycolitic gene expression and enzyme activities (for a complete review, see: [31]).

In this sense, recent findings have demonstrated that acute aerobic exercise increases proteolysis in the skeletal muscle through ubiquitin–proteasome and autophagy systems [23,47]. Both systems maintain cellular quality control mechanisms, recycling damaged organelles (mainly via autophagy) or myofibrillar proteins (mainly via proteasome degradation) and allowing new synthesis. In fact, AET enhances many protein expression and enzyme activities, resulting in higher myofibrillar proteins and mitochondrial content and function [31]. Fig. 1 illustrates these mechanisms.

* Corresponding author at: Avenue Mello de Moraes, 65, Butantã, 05508-030 Sao Paulo, SP, Brazil. Tel.: +55 11 3091 2149; fax: +55 11 3813 5921.
*E-mail address:* pcbrum@usp.br (P.C. Brum).

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Conversely, to the positive effects of AET on skeletal muscle function and bioenergetics, the cachexia syndrome (*i.e.* "bad condition" from the Greek *kakos hexis*) induces a serious metabolic impairment that, in the last instance, results in skeletal muscle atrophy and dystrophy [1,33]. Cachexia is a multifactorial disorder associated with other chronic diseases such as heart failure (HF) (known as cardiac cachexia) and cancer. Importantly, both HF and cancer are still the main causes of death worldwide [43,50]. While other muscle wasting conditions have characterized causes, such as skeletal muscle atrophy induced by disuse, glucocorticoid treatment, nerve injury, genetic muscular dystrophies and aging, the molecular basis of cachexia is still poorly understood and the lack of therapies is obvious [33,52].

Over the last years, our group has been studying the effects of AET on cardiac cachexia. Currently, our laboratory is also developing studies regarding the effects of AET on cancer cachexia. Therefore, the aim of the present review was to briefly discuss the supposed therapeutic effects of AET upon skeletal muscle wasting in cardiac and cancer cachexia, emphasizing the recent findings of our group.

## AET on cardiac cachexia

In spite of remarkable improvement in the HF treatment over the past decades, the number of hospitalizations and mortality rates is still high, keeping HF as a serious public health problem worldwide [28,43]. Significant changes in the interactions between central and peripheral organs have been observed in HF patients [20] following several abnormalities in the skeletal muscle such as capillary rarefaction, type I (*i.e.* oxidative) to II (*i.e.* glycolytic) fiber switch, impaired metabolism and excitation–contraction coupling, and atrophy [29,87]. Taken together, these modifications implicated in skeletal myopathy are associated with early and continuous fatigue, dyspnea and exercise intolerance [61]. Notably, skeletal muscle wasting is associated with poor prognosis in HF, worsening quality of life and survival [3].

Among all known therapeutic strategies, AET is the most effective to mitigate skeletal muscle wasting [15,16,93]. Conversely, to the HF-induced effects, AET promotes muscle capillarization and a switch from type II to I fibers, and increases oxidative enzyme activity and antioxidant defense [2,41,58]. In this respect, our group has dedicated efforts in order to understand the mechanisms underlying such benefits [8,15,16,18,22,23,65]. Bacurau et al. [8] submitted to AET a sympathetic hyperactivity-induced HF mice model (*i.e.* $\alpha_{2A}/\alpha_{2C}$-adrenergic receptor knockout mice), which displays exercise intolerance, capillary rarefaction, exacerbated oxidative stress and skeletal muscle atrophy at 7 months of age [17,78]. AET reestablished exercise tolerance into control mice levels and prevented muscular atrophy and capillary rarefaction associated with reduced oxidative stress in this HF mice model [8].

Among several the skeletal muscle abnormalities detected in HF patients, alterations in excitation–contraction coupling have been proposed to explain the early muscle fatigue. In fact, depressed sarcoplasmic $Ca^{2+}$ levels and diminished rate of sarcoplasmic reticulum $Ca^{2+}$ release and reuptake have been observed in HF rat models [61,74]. AET reestablished the expression profile of proteins involved in sarcoplasmic $Ca^{2+}$ handling toward control mice levels, rearranging the network of these proteins in the skeletal muscle [18].

Briefly, skeletal muscle atrophy is a consequence of protein synthesis and degradation imbalance [42]. Recent studies in cardiac cachexia research have focused on the ubiquitin–proteasome and autophagy/lysosomal proteolytic pathways to better understand the process of muscle wasting in HF [22,49,56,81]. The ubiquitin–proteasome system plays a predominant role in the breakdown of myofibrillar proteins [6,60]. Importantly, the overactivation of the ubiquitin–proteasome system in the skeletal muscle during chronic disease, including HF, has been attributed to increased oxidative stress [10,68,72,75,89]. In fact, it has been demonstrated that oxidized proteins are selectively degraded by proteasome at faster rates than their native counterparts. The free 20S particle degrades these proteins in a process independent of ubiquitin conjugation, while the 26S proteasome operates in an ubiquitin-dependent manner due to the preferential ubiquitination for certain oxidized proteins [84,98]. Therefore, we evaluated the effects of AET on redox balance and ubiquitin–proteasome system activation in the sympathetic hyperactivity-induced HF mice model [22]. HF mice presented oxidative stress damage associated with overactivation of chymotrypsin-like proteasome activity and upregulation of atrogin-1 mRNA levels in the plantaris muscle. AET restored lipid hydroperoxides and carbonylated protein content paralleled by reduced E3 ligases mRNA levels. Moreover, AET reestablished chymotrypsin-like proteasome activity and skeletal muscle mass. In order to verify the clinical relevance of our findings, we evaluated chymotrypsin-like proteasome activity in HF patients submitted to AET

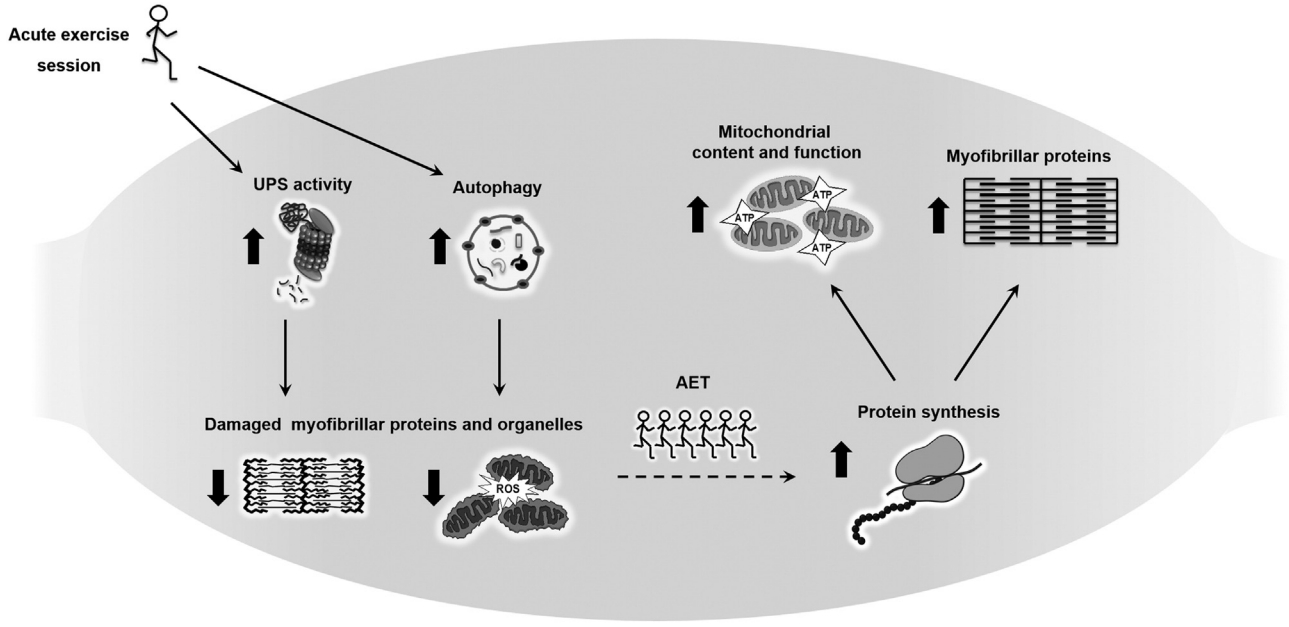


**Fig. 1.** Acute aerobic exercise induces proteolysis in the skeletal muscle through the ubiquitin–proteasome and autophagy systems. Both systems maintain cellular quality control mechanisms, recycling damaged organelles or myofibrillar proteins. Chronically, the AET allows new protein synthesis, resulting in higher myofibrillar proteins, and mitochondrial content and function. UPS = ubiquitin–proteasome system; AET = Aerobic exercise training.

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