Review Article

Aerobic exercise training as therapy for cardiac and cancer cachexia

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A B S T R A C T

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 disorder associated 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, countering metabolic 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.

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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 glycolytic 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.
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 [8,15,16,18,21,23,65]. Bacurau et al. [8] submitted to AET a sympathetic hyperactivity-induced HF mouse model (i.e. α2AR/α2C-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 mouse 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 Ca2+ levels and diminished rate of sarcoplasmic reticulum Ca2+ release and reuptake have been observed in HF rat models [61,74]. AET reestablished the expression profile of proteins involved in sarcoplasmic Ca2+ 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 [64,98]. 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
protocol. As expected, AET restored chymotrypsin-like proteasome activity toward healthy control subjects’ levels [22].

While the ubiquitin–proteasome system is responsible for selective removal of short-living cytosolic and nuclear proteins, the autophagy–lysosome system accounts for the engulfment of long-living proteins, glycolytes, protein aggregates, and organelles [11,63]. For instance, we provide direct evidence that autophagy signaling is increased in a cardiac cachexia rat model induced by myocardial infarction. Cathespin L activity and autophagy-related genes and protein levels were upregulated in the plantaris muscle. Interestingly, the same increased autophagy–lysosome system activation was not observed in the soleus muscle (i.e. a highly oxidative muscle) [49]. Therefore, the response of the skeletal muscle to cachetic stimulus differs according to muscle fiber type composition, the glycolytic muscles being more affected. In this context, further studies verifying the impact of AET in cachexia-induced autophagy–lysosome system activation in muscles comprised of different fiber types are still necessary.

The protein synthesis is also essential to maintain muscle mass [42, 71] and it seems to be decreased in HF [82]. Further to the hypothesis that AET increases protein synthesis pathways in the skeletal muscle, our group is currently studying the effects of AET on cardiac cachexia animal model and humans. It is known that the PI3K/Akt pathway can be stimulated by insulin or insulin-like growth factor 1 (IGF1), leading to increase downstream effectors, such as the mammalian target of rapamycin (mTOR). This pathway was first described in cancer, in which it reduces apoptosis and increases cell proliferation [66]. Specifically for skeletal muscle physiology, IGF1/PI3K/Akt/mTOR is the main signaling pathway known to control protein synthesis [12,81]. Akt induces activation of protein synthesis by blocking repression of mTOR and, hence, allowing TORC1 and TORC2 complex signals. TORC1 signals to the p70S6 kinase and 4E-BP pathways, which induces ribosome formation, while TORC2 controls the autophagy process mentioned above [81,99]. Our preliminary data indicate that AET increases IGF-1 and Akt protein content in the skeletal muscle of sympathetic hyperactivity-induced HF mice model (Bacurau et al. – unpublished observations). Further data will be helpful in order to understand the impact of HF and AET in the whole machinery.

As observed, moderate-intensity AET is recommended for HF patients as part of non-pharmacological management [19,24,39,79,96]. However, recent studies including HF patients have suggested that high-intensity AET promotes superior effects in maximal oxygen consumption (VO2max) when compared to moderate-intensity AET [64, 97]. Considering these findings, Moreira et al. [65] compared the effects of high-intensity AET with those of a moderate-intensity protocol on the skeletal muscle of myocardial-infarcted rats. In fact, the superior effects of high-intensity AET were verified on VO2max. Surprisingly, the benefits of AET on skeletal muscle mass, metabolic capacity and proteasome activity changes were remarkably similar between protocols [65]. These results highlight the importance to continue exploring the AET protocols (e.g. different intensities, durations, frequencies and types) in order to optimize the effects of AET on cardiac cachexia.

In conclusion, AET is recommended for clinically stable HF patients due to its beneficial skeletal muscle adaptations. Despite the AET efficacy, the risks of major cardiac events during an acute session of aerobic exercise are low (i.e. one occurrence per 50 to 150,000 h of summed exercise time) [77,88], also indicating the safety of AET to cardiac cachexia patients.

**AET on cancer cachexia**

Cancer occupies the first position in the leading causes of death in developed countries and the second position worldwide [50,85]. Importantly, cachexia is associated with approximately 80% of severe cancer cases and it is responsible for more than 30% of deaths [90]. Similarly to cardiac cachexia, cancer cachexia is a complex multifactorial syndrome characterized by loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Most (but not all) mediators of cachexia are similar in HF and cancer. In contrast, while cardiac cachexia tends to implicate gradual skeletal muscle wasting [93], cancer cachexia usually displays a faster progression and the most severe wasting scenario leads to early death (less than 3 months for refractory cancer cachexia) [32]. Furthermore, given the current epidemic of obesity, including in cancer patients, the inhibition of lipolysis is probably not a priority. However, skeletal muscle wasting remains as the key problem [33].

Over the last two decades, several authors have dedicated efforts in order to understand the mechanisms behind the cancer cachexia syndrome [33,34,90]. Smith and Tisdale [86] demonstrated a significant depression in a protein synthesis rate associated with a significant increase in protein degradation in MAC-16 tumor-bearing mice presenting a 15% to 30% reduction in body mass [86]. Since this pioneer study, several other evidences have indicated that skeletal muscle atrophy occurs as a result of an imbalance between protein synthesis and degradation. As observed in HF models, cancer research has focused on the ubiquitin–proteasome and autophagy/lysosomal proteolytic pathways as being important contributors of protein degradation (for a review, see [51]). In this sense, researchers are searching for novel catabolic mediators that control the expression of E3 ligases during the syndrome progression. So far, the main proposed mediators are elevated cytokines, such as the tumor necrosis factor alpha [76], the interleukin-1β [5] and the interleukin-6 [55,67], characterizing a chronic inflammation [4,5,33,45,91]. However, anti-cytokine therapies are ineffective and poorly understood [34,52,73]. Additionally, hormonal treatments used to stimulate protein synthesis have to be avoided, since they may stimulate cancer growth [33]. Altogether, these issues point to the importance of discovering an effective and safe treatment to counteract catabolic mediators or downstream signaling pathway changes on the skeletal muscle in cancer cachexia.

In fact, recent advances in molecular and cell biology have provided a high spectrum of novel drug targets, such as the ActRIIB pathway [100], the adipose triglyceride lipase or hormone-sensitive lipase [25], the HMGBl protein [62] and the tumor-derived parathyroid-hormone-related protein [52]. However, the current lack of success for a single therapy indicates that cancer cachexia intervention may include different approaches, including non-pharmacological strategies, such as AET [(32); [5,90]]. During cachexia progression, skeletal muscle endurance capacity is severely reduced [21,35,92,95]. The oxidative metabolism dysfunction, insulin resistance and increased glycolysis have been attributed to skeletal muscle mitochondrial dysfunction and the hypoxic environment of the tumor, mainly due to hypoxia-inducible transcription factors [33]. On the other hand, AET is able to stimulate the skeletal muscle oxidative metabolism and antioxidant capacity, to lower chronic inflammation and to improve insulin sensitivity [26,44]. Additionally, evidences indicate that AET prevents metabolic changes induced in immune cells and decreases tumor metabolism, slowing down tumor growth in rats [9].

Deuster et al. [27] reported that AET retarded tumor growth and skeletal muscle degradation in Walker 256 tumor-bearing rats [27]. Walker 256 tumor-bearing rats mimic many of the alterations induced by human tumors and has been used in several studies due to easily manipulation and injection [14,27,30,38,40,59,83]. AET effects in this model also include 1) an increase in aerobic consumption of substrates and prevention of glucose and glutamine metabolism impairment in immune cells (i.e. lymphocytes and macrophages) associated with an increased survival [79, 2] a decrease in tumor growth [79,59], 3) a prevention of body mass losses [7] and 4) a decrease in skeletal muscle degradation process associated with an increase in skeletal muscle myosin content [80].

All of the studies cited above have injected Walker 256 tumor cells in rat’s subcutaneous flank. Recently, our group has standardized the bone marrow injection of Walker 256 tumor cells as a more interesting cancer...
cachexia animal model due to higher homogeneous mortality rate and skeletal muscle atrophy progression than the subcutaneous flank injection. Collectively, our results suggest that bone marrow injection of Walker 256 tumor cells in rats is a new model of severe cancer-induced muscle atrophy selective to glycolytic fibers (Alves et al. — unpublished observations). After an extensive characterization, we have submitted this new model to different AET protocols (i.e. moderate-intensity or high-intensity interval training). Although no differences were observed in tumor growth, our ongoing studies indicate that both AET protocols partially restore exercise intolerance and increase rat’s survival when compared to sedentary injected animals. The next steps will help to understand the role of AET on skeletal muscle mass and metabolism in this and other cancer cachexia models.

Despite the mentioned benefits of AET, some limitations have to be taken into consideration before an AET intervention in cancer patients. First, it is common to observe chronic fatigue in many patients, mainly due to oxidative metabolism impairment [5]. Thus, it is not expected that cachectic patients be able to conclude a long-term AET protocol as healthy people usually perform. In this respect, other AET protocols should be considered in clinical practice. In spite of the putative superior effects, it is possible to speculate that interval AET may be more tolerable in cancer patients than long term continuous AET. On the whole, clinical trials are still necessary to investigate different AET protocols in cancer patients, including acute session safety measurements. Second, Argilés et al. [5] highlighted that any acute physical effort has to be avoided in cancer patients presenting anemia. Therefore, it is mandatory to correct anemia and rescue tolerance to acute physical efforts before any exercise approach. Finally, a recent study of Wang et al. [94] indicated that mice with increased mitochondrial biogenesis specific in the skeletal muscle tissue (i.e. MCK-PGC-1α transgenic mice) [57] do not prevent skeletal muscle loss after Lewis lung tumor cell injection. Surprisingly, MCK-PGC-1α transgenic mice also led to the development of larger tumors [94]. Therefore, further experiments are absolutely necessary in order to elucidate the potential therapeutic effect of increased mitochondrial biogenesis in different models of cancer cachexia.

**Conclusion**

The expertise and main purpose of our group have been to understand the effects of AET on cardiovascular disease, including cardiac cachexia syndrome. Recently, our laboratory also started studies regarding the effects of AET on cancer cachexia, presenting some preliminary data. Although HF and cancer are completely different diseases and present distinct primary outcomes, both result in cachexia. As illustrated in Fig. 2, overactivation of ubiquitin–proteasome and autophagy systems associated with a reduction in protein synthesis culminates in skeletal muscle wasting. On the other hand, AET may recycle and enhance many protein expression and enzyme activities, counteracting metabolism impairment and muscle atrophy. Moreover, AET acts in several cachexia mediators, attenuating the whole scenario.

In summary, AET is an adjuvant therapy with sufficient evidence for counteracting skeletal muscle wasting in HF. Additionally, AET is recommended (although with restrictions under study) to most of cancer patients. Recent studies have addressed the mechanisms underlying the benefits of AET on cachetic muscle and further experiments will help to better clarify the mediator’s network behind the AET counteracting ubiquitin–proteasome and autophagy/lysosomal system overactivities in both cardiac and cancer cachexia.

**Conflict of interest statement**

The authors declare that there are no conflicts of interest.

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