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EXERCISE CAPACITY, PHYSICAL ACTIVITY AND MORBIDITY

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INTRODUCTION

By 2050, 20% of the US population will be over the age of 65 years, with muscle weakness and atrophy as the key characteristic traits for the aging adult (1). A similar trend can be seen in patients with heart failure (HF) with an accelerated level of muscle dysfunction (2). The absence of physical activity greatly increases muscle loss and decreases quality of life in both the aging and HF populations (3, 4). The purpose of this review is to provide an overview of the effects of aging and HF on skeletal muscle function and how exercise training can improve long-term outcomes associated with skeletal muscle dysfunction.

Effects of Aging on Skeletal Muscle

Sarcopenia, a geriatric syndrome (5), is an age-related loss of muscle mass associated with senescence and begins in the fourth decade of adult life, with an approximate loss of muscle mass of 0.4% per year while living a sedentary lifestyle (6). Sarcopenia has to be distinguished from cachexia, which describes the syndrome of loss of skeletal muscle with and underlying pathological correlate such as cancer cachexia or cardiac cachexia. Sarcopenia implies quantitative as well as qualitative changes in skeletal muscle with strength lost most rapidly, indicating derangements in skeletal muscle composition and functioning. In the aging muscle, changes in muscle fiber composition such as a change in the myosin heavy chain ratio can be observed with an increase of a co-expression of myosin heavy chain (MHC) I and MHC IIA in muscle fibers (7). Furthermore, metabolic derangements have been described in the sarcopenic muscle and have been linked to mitochondrial dysfunction (8). A recent study by Porter et al., comparing mitochondrial respiratory capacity in young versus elderly adults, found that mitochondrial respiratory capacity and coupling control declines with age. This indicates a decreased ATP production capacity in the aging muscle of elderly adults (9). However, while a large body of research supports the importance of mitochondrial senescence in sarcopenia, contradictory theories emphasize on the detrimental effects of inactivity for muscle homeostasis, attributing changes in muscle energy capacity to a sedentary lifestyle of the elderly (10). Recently, Johnson et al. compared the effects of endurance training on muscular mitochondrial health in the elderly (11). Interpreting changes of mitochondrial function on a transcriptional level, they concluded that in sarcopenia there is a decrease of mitochondrial genes and pathways

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involved in oxidative phosphorylation, which was compensated by endurance training in the older cohort compared to the sedentary cohort. Interestingly, however, physical activity had a more profound effect on the transcriptional profile in the younger cohort than in the elderly (11).

Skeletal muscle, which contributes 30–50% of the total body mass, influences a plethora of other organs and physiological processes (12) and muscle mass as well as strength can be correlated with longevity (13, 14). Skeletal muscle tissue is pivotal for insulin-mediated glucose turnover and has signaling function through cytokine secretion. Since insulin is a major anabolic stimulus for skeletal muscle homeostasis, age-related insulin resistance can contribute to the development of sarcopenia (15, 16). Of note, physically active older adults have better insulin sensitivity which coincides with a reduced rate of sarcopenia (17).

Another proposed mechanism contributing to sarcopenia are systemic inflammatory processes (18, 19). In a large study including over 900 elderly study participants, Schaap et al. could correlate higher circulating pro-inflammatory cytokine levels with loss of muscle strength (20). Proposed pathomechanisms describe the inhibitory effect of circulating cytokines such as TNFα and interleukins on insulin signaling (21, 22) and through the PI3K-Akt signaling pathway (23). It is important to note that physically active older adults have decreased levels of chronic inflammation compared to sedentary controls (24).

Effects of Heart Failure on Skeletal Muscle

While mortality from coronary artery disease, sudden cardiac death and other cardiovascular illnesses has declined, those that survive become predisposed to develop heart failure (HF) (25). Exercise intolerance is a common complaint expressed by HF patients and functional decline compounds HF risks (26, 27). As well-established in the literature (28), peak exercise capacity is not the only determinant of exercise performance in HF patients. Reduced cardiac output, inflammation, and insulin resistance are all contributing factors leading to skeletal muscle abnormalities seen in advanced HF (28). Patients with chronic HF subsequently have reduced physical activity, leading to low-grade systemic inflammation. Thus, these mechanisms promote further loss of muscle mass and exacerbation of local inflammation (29, 30). Skeletal muscle undergoes extensive changes in patients with HF, independent of tissue perfusion or hemodynamic instability, contributing to intrinsic muscle weakening and fatigability as well as to functional declines (3).

Phenotypic and metabolic changes in skeletal muscle of HF patients have been well described (3, 31). Changes in fiber composition include reduced type I oxidative fibers (slow twitch) with increases in less aerobic type II fibers (fast twitch) and altered myofibrillar protein isoform expression (with shifts in distribution from MHC I slow oxidative towards MHC IIA fast oxidative and MHC IIB fast glycolytic forms) (32). Histomorphometric analyses demonstrate decreased fiber sizes (both type I and II) as well as reduced number and altered structure of mitochondria (33, 34). Decreased levels of mitochondrial creatine kinase and downregulation of the sarcoplasmatic reticulum Ca^{2+}-ATPase-1 (SERCA-1) are also seen, signifying a shift away from aerobic metabolism (35, 36). While progressive muscle wasting develops in HF, metabolic and functional derangements typically precede the loss of muscle mass, with subsequent muscle atrophy then exacerbating functional

decline. HF skeletal myopathy is omnipresent, independent from disuse, refuting the hypothesis that skeletal muscle changes arise from disuse rather than direct HF effects (37).

Muscle protein breakdown is regulated by several cellular systems, including the ATP-dependent ubiquitin (Ub)-proteasome system (UPS). The UPS regulates skeletal muscle protein breakdown in a number of disease models including diabetes mellitus, cancer, renal failure, starvation (38) and HF (39). Through transcriptional profiling, a set of ~120 response genes, or atrogenes, has previously been identified in atrophying muscles (38). Dysregulation of atrogenes occurs in muscle atrophy, including genes required for ATP production and transcripts for extracellular matrix proteins. Further, protein quality control mechanisms in the cell are closely controlled by cellular autophagy and dysregulation of autophagy has been linked to abnormal protein turnover and overall cellular dysfunction (40) in the failing myocardium (41) and skeletal muscle (42). Suppression of PGC-1α, a central regulator of metabolism and mitochondrial biogenesis, was found in the setting of muscle atrophy (43). Induction of PGC-1α prevents muscle atrophy and transcription of atrogenes (44).

These changes in skeletal muscle lead to progressive muscle wasting and atrophy, causing further impairments in the exercise capacity of HF patients. Severe exercise intolerance is primarily due to reductions in peak cardiac output (CO) and peripheral arterial-venous oxygen difference (A-VO_2 Diff) (26, 45), as well as a proposed impairment of skeletal muscle oxidative metabolism (46). HF therapeutic advances have centered on central cardiac pathophysiology, i.e., improving ventricular contractility, improving cardiac pre- and afterload and reducing remodeling and arrhythmias (47), which only yield marginal improvements in functional capacity. In contrast, therapies oriented towards skeletal muscle functional improvement (e.g. exercise training) have led to greater functional gains in patients with HF (31, 48).

Comparison of Skeletal Muscle Changes in HF and Normal Aging

Clinically, both sarcopenia and cachexia overlap and in principal, similar factors have been described to lead to the induction of muscle mass loss, with changes in muscle fiber composition along with mitochondrial derangements, insulin-resistance (or reduced sensitivity to other hormones) and chronic inflammation among them. The pathophysiological substrate of sarcopenia and cachexia is similar: Circulating proinflammatory cytokines, such as TNFα, IL-1 and others have been found to be pivotal especially in cachectic muscle wasting. The ill-fated combination of disease-related bed rest, decreased food intake and systemic inflammation caused by the underlying pathology such as a neoplasm or a chronic proinflammatory state in severe HF are thought to be the major underlying processes in cachexia.

However, in recent years, sophisticated studies focusing on protein turnover and anabolic-catabolic balances have unveiled pathomechanistic differences between these two syndromes. While cachexia is characterized by massive protein degradation, in sarcopenia, mainly a decrease in the rate of protein synthesis can be observed (49). In cachexia, protein degrading machineries such as the ubiquitin-proteasome system along with the suppression

of the muscle anabolic PI3K-Akt-system, have been identified to be important mechanisms in this complex system of skeletal muscle turnover (50).

Age-related sarcopenia can also be linked to a decrease in regenerative capacity of injured muscle tissue. Satellite cells, which are characterized as myogenic stem cells are reduced and have a decreased regenerative potential (50, 51) in the aging muscle. Hence, repair mechanisms for cumulative muscle tissue injury decrease in the aging muscle with the myogenic stem cells likely converting from activatable quiescentic state to a senescence state (52).

Clinical Testing Methodology for Exercise Capacity

Regardless of how muscle mass is lost, sarcopenia or cachexia, there are a variety of methods used for measuring physical activity and exercise capacity. The gold standard method for measuring exercise capacity is the treadmill or bike exercise testing in association with air-gas-exchange, also known as cardiopulmonary exercise testing (CPET). This is considered to be an optimal gauge of functional capacity (53). Often older adults and HF subjects may perform incremental biking exercise on an electronically braked cycle ergometer as previously described by the American Thoracic Society (54), instead of on a treadmill due to issues with balance and stability on a treadmill. However, treadmill testing is recommended for optimal peak VO_2 levels (55). Peak oxygen consumption (VO_2peak), VO_2 at anaerobic threshold, VO_2/VCO_2, and respiratory exchange ratio (RER) are measured using online computer-assisted open-circuit spirometry. Rate of perceived exertion, blood pressure and heart rate should be measured throughout exercise. Beyond a CPET, the six minute walk test is a commonly used clinical tool, which allows for the assessment of the functional capacity in HF patients in a “real-life” setting. Using standard methodology (56), patients will be asked to walk as quickly as possible on a 25 meter course for 6 minutes.

For the specific assessment of skeletal muscle function and fatigue, measures of isolated muscle group strength and fatigability can be analyzed using a dynamometer. The Biodex System 4 Pro can be used for measuring isometric and isokinetic measurements on the extremities. Isometric data will be collected to measure peak torque to body weight (PKTQ/BW). Isokinetic data will be collected to measure PKTQ/BW, work to body weight (WK/BW), average power, fatigability, time to peak torque, acceleration time and deceleration time. Muscle strength can be further analyzed through the use of hand grip strength (57), repeated three times on both dominant and non-dominant hands.

Obtaining skeletal muscle tissue provides researchers with information about local changes in skeletal muscle of older adults or patients with HF. This procedure should be done at least one week after the cardiopulmonary stress test or other strenuous activity. Aspirin should be held for two days (the day prior to the muscle biopsy and the day of the muscle biopsy) and study subjects should not be taking any blood thinning medication. The patients will lie comfortably in the supine position for biopsy of the vastus lateralis muscle. One fragment of the biopsied muscle should be frozen in liquid nitrogen cooled isopentane for histomorphological and enzymatic analysis. A second fragment can be cut and placed in cryotubes containing RNA preservation solution (RNAlater) and immediately frozen in liquid nitrogen (58).

In addition to muscle biopsies, a whole body dual-energy x-ray absorptiometry (DXA) scan characterizes the different compartments of soft tissue in the body. Analysis for specific compartments is only possible with an imaging method, which is beneficial because as stated earlier, both aged and patients with advanced HF develop metabolic abnormalities that include muscle wasting (1, 59).

Clinical Implications of Skeletal Muscle Dysfunction

Similarly to cachexia, sarcopenia, as a geriatric syndrome, but not attributable to an underlying disease, has important clinical implications. Sarcopenia has been defined as “a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death” (60). Clinically relevant sarcopenia has been associated with mobility impairment (61) and increased mortality, especially in female patients (62) and in the very old, where it has been shown that sarcopenia is associated with mortality, independently of age or other clinical factors (63). Mobility impairment is a major risk in this context implying an increased risk of falls and fractures with hospitalization and immobilization. Sarcopenia has been termed a “societal burden” (64), reflecting on the consequential individual and socio-economical risk of physical disability, nursing home admission, depression, hospitalization and death (64).

Cachexia is a serious complication of many diseases and is associated with poor outcome. The diagnosis of cachexia against the background of an underlying disease is associated with a high mortality (65, 66). For example, cardiac cachexia mortality rates doubled in the cachectic cohort when compared to non-cachectic patients with the same underlying condition (67). After cachexia is diagnosed, yearly mortality rates are reported to range from 10% to 15% per year for COPD and 20% to 30% per year in HF (68). It is believed that several pathomechanisms occur in the cachectic patient that lead to the observed increase of mortality independently of the primary condition (69). Fatal consequences are cardiac arrhythmia, thromboembolism, compromised immune system and multi organ failure due to complex systemic derangements (69).

Unfortunately. treatment options for muscle wasting are limited with aerobic exercise being the best proven and most effective therapeutic approach (70). Many studies have been undertaken to find a pharmacological approach to tackle wasting syndromes, including appetite stimulants, anti-inflammatory agents or anabolic drugs. Promising candidates are the appetite stimulant megestrol acetate, anabolics such as the selective androgen receptor modulator enobosarm and the hormone ghrelin (71). Currently, larger clinical trials are under way to assess for the usefulness of these approaches to treat muscle wasting. Nutritional supplementation, another often studied approach to countervail muscle wasting, shows inconclusive results in many studies with a large variety of supplements (72).

Effects of Exercise Training

It is important to note that lower exercise capacity in heart failure and aging are associated with worse outcomes (73). Exercise training has been associated with reductions in both mortality and hospitalizations for HF patients with New York Heart Association class III or

IV symptoms (74). Regardless of advanced age or disease state, exercise training is recommend for all age groups and patients with CVD, including HF by both the American Heart Association, American College of Cardiology Foundation and American College of Sports Medicine among other organizations (75). The Physical Activity Federal Guidelines recommend a minimum of 150 minutes per week of moderate aerobic exercise, but there are substantial evidence that shows benefits can be attained at much lower levels of weekly aerobic exercise (75, 76). There is a 14% reduction in mortality with just 15 minutes of exercise per day (77) and exercise training provides important improvements in health–related quality of life (78). Aerobic exercise training provides many beneficial improvements to the cardiovascular system, such as reduced resting HR (79), improved vascular endothelial function and parasympathetic tone, and myocardial improvements that result in improved tolerance for reperfusion injuries and ischemia (80). These improvements not only affect the cardiovascular system, but also the musculoskeletal system which aides in decreasing morbidity and increasing quality of life.

Continuous moderate intensity training has been the standard program choice for the elderly and patients with HF, but recent studies have demonstrated that high intensity interval training (HIIT) can be performed safely and provides greater improvements in VO_2 peak and quality of life (81, 82). Wisloff et. al. showed that compared to moderate intensity training, patients with stable HF had a 46% increase in VO_2max compared to a 14% increase in patients exercising at a moderate intensity (83). While HIIT training may show the greatest improvements for older adults and HF patients, not everyone is able to deal with its high demands and moderate aerobic intensity may be a better alternative with proven benefits (84).

Resistance training has become more popular over the last decade for both the elderly and patients with stable HF due to a decreased cardiac load requirement making resistance training well tolerated (84). Furthermore, the benefits of aerobic exercise training may not be enough to increase muscle mass and combat sarcopenia and cardiac cachexia (85). The use of resistance training in individual muscle groups has shown to improve. In a study by Esposito et al., knee extension training for 8 weeks in patients with HF showed total body improvements oxygen transport and metabolism (86).

SUMMARY and CONCLUSIONS

Sarcopenia and a decrease in quality of life are often associated with aging and HF, which can be attributed to the absence of physical activity. Exercise intolerance is a common problem for both the aging and HF population, and it is important to note that poor functional capacity increases HF risk. Throughout this review we have examined the skeletal physiological changes associated with aging and HF, as well as provide an overview of how exercise training can improve outcomes associated with skeletal muscle dysfunction. The benefits of exercise training are widely accepted for all ages and various disease states, and exercise programs and interventions have become the standard of care for patients with stable HF. Unfortunately, while the benefits of exercise training is shown in numerous studies for both aging adults and HF patients, the greatest setback is compliance.

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