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Muscle wasting in heart failure: An overview☆

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ABSTRACT

Patients with heart failure are frequently limited in their exercise capacity. Although this clinical phenomenon is mostly attributed to the failing myocardium, the effects of skeletal muscle wasting should not be underestimated. Muscle wasting may present in the form of loss of muscle mass and function, termed sarcopenia in healthy aging, or in the form of cachexia. Only cachexia is associated with loss. The mechanisms involved embrace an anabolic-/catabolic imbalance with increased degradation of myofibrils and myocyte apoptosis. Clinical effects include reduced muscle mass, strength and consequently reduced exercise capacity. This article describes the terminology, molecular pathways, prevalence, clinical implications and possible treatment approaches to muscle wasting in patients with heart failure.

This article is part of a Directed Issue entitled: Muscle wasting.

1. Introduction

Body composition has been a matter of ongoing debate across a vast array of chronic diseases in recent years. General understanding holds that involuntary loss of body weight is always a *signum mali ominis*. Cachexia has recently been defined as loss of more than 5% of body weight over 12 months or less in the presence of a chronic illness such as heart failure (HF), chronic obstructive pulmonary disease, chronic kidney disease, or cancer (Evans et al., 2008). Cachexia in all of these illnesses has been discussed in detail elsewhere (Mak et al., 2011; Vaughan et al., 2012; Schols and Gosker, 2009). Sarcopenia, on the other hand, is not usually associated with weight loss but rather with loss of muscle mass and muscle function (von Haehling et al., 2012). The loss of muscle mass may be compensated for by adipose tissue or other non-functional tissue inside of skeletal muscles, making its detection difficult in daily clinical life, because not only a pair of scales but sophisticated techniques such as dual-energy X-ray absorptiometry (DEXA), computed tomography, or magnetic resonance imaging are required for reaching a correct diagnosis.

For clinicians not actively involved in ongoing debates, it is usually difficult to decipher the complex terminology of body wasting. In fact, cachexia does imply weight loss and its presence is a *conditio sine qua non* for the diagnosis. However, the diagnosis requires not only the presence of a chronic illness, but also altertations in several biochemical and clinical parameters (Evans et al., 2008). This means that patients with severe obesity may at the same time be cachectic, however, the image of "cachectic obesity" does not translate well into physicians' daily lifes. Sarcopenia, on the other hand, requires the loss of muscle mass (von Haehling et al., 2012), but the presence of cachexia and sarcopenia may overlap and may be present in the same subject at the same time. These considerations become even more confusing considering that a debate exists as to whether or not the term sarcopenia should be restricted to healthy elderly subjects only (Fearon et al., 2011; von Haehling, 2012). In fact, the term myopenia was recently suggested to describe muscle wasting that fulfills the criteria of sarcopenia in patients with chronic disease (Fearon et al., 2011). Although this debate may appear academic, it implies important considerations for the development of future treatments.

This article aims to provide an overview of muscle wasting that fulfills the criteria of sarcopenia in patients with HF. We will discuss the terminology, molecular pathways of muscle wasting, its prevalence, clinical implications and possible treatment approaches.

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2. From muscle wasting to sarcopenia

The term sarcopenia, literally meaning poverty of flesh, was originally suggested in 1989 by Irwin H. Rosenberg at a meeting in Albuquerque, NM, that was aimed at collecting information about the population distribution of conditions associated with aging (Rosenberg, 2011). The original implication of sarcopenia was the presence of "involuntary loss of skeletal muscle mass and consequently of strength" (Roubenoff et al., 1997). A recently published consensus statement defines "sarcopenia with limited mobility" as being present in "a person with muscle loss whose walking speed is equal to or less than 1 m/s or who walks less than 400 m during a 6-min walk, and who has a lean appendicular mass corrected for height squared of 2 standard deviations or more below the mean of healthy persons between 20 and 30 years of age of the same ethnic group (Morley et al., 2011)." No consensus was reached with regards to the question of applying an age-range to the use of the term sarcopenia, for example, to use the term only in persons aged 60 years and above (Morley et al., 2011). No consensus was reached also with regards to using the term sarcopenia only in healthy elderly subjects or additionally in patients with underlying chronic disease. However, it was acknowledged that sarcopenia is a syndrome, not a disease (Morley et al., 2011).

Although the proposed definition is very helpful in answering research questions, it is rather cumbersome in daily clinical practice, and therefore it is not surprising that in the real world a diagnosis of sarcopenia remains a rarity (von Haehling et al., 2012). Appendicular skeletal muscle mass means muscle mass of the arms and legs combined, and this value is corrected for the subject's height. The diagnostic gold standard is computed tomography or magnetic resonance imaging, as only these techniques are able to directly assess skeletal muscle mass. Unfortunately, both are time-consuming and costly. Many researchers have therefore relied on DEXA scanning that was originally developed for the diagnosis of osteoporosis (Mazess et al., 1990). Using minimal radiation exposure, DEXA assesses fat-free mass that serves as a proxy for skeletal muscle mass. Several factors may influence the results, because fat-free mass is heterogenous with components including total body water, protein, and bone mineral, and particularly changes in hydration are reflected as changes in lean tissue (Woodrow, 2007). This may be an important clinical problem in patients with edema, particularly in HF or chronic kidney disease.

In the absence of alternatives, many researchers have used the term sarcopenia also in the presence of chronic disease. We prefer to use the term muscle wasting to highlight the fact that the discussion is ongoing and far from finished.

3. Endocrine and molecular mechanisms of wasting

An understanding of the pathophysiology of muscle wasting in health and disease is paramount in order to develop an understanding of potential therapeutic targets. The muscle hypothesis (Coats, 1996) holds that many different factors are involved in the development of reduced peak oxygen uptake (peak VO_2) in patients with chronic HF including histological abnormalities, alterations in mitochondrial structure and function, oxidative stress, and a shift in fiber distribution (Sullivan et al., 1990) inside skeletal muscles. It is believed that these findings are independent of alterations in blood flow, and an augmented blood flow does not increase exercise capacity or delay the onset of anaerobic metabolism. Histological abnormalities include changes in the ultrastructure of muscles. Since skeletal muscle structure is a matter of permanent changes, an anabolic-/catabolic-imbalance is required for increased degradation of myofibrils and myocyte apoptosis. Looking at this imbalance, muscle wasting may be a consequence of reduced muscle anabolism, increased muscle catabolism, or both. The maintenance of balance depends largely on the balance between the anabolic players (Table 1) growth hormone and insulin-like growth factor-1 and the catabolic factors (Table 2) tumor necrosis factor (TNF), interleukin-1β, interferon-γ, myostatin, and glucocorticoids (Fig. 1) (Schulze and Späte, 2005). Some studies suggest that increased muscle degradation predominates in HF, and the main mechanism involved in myofibril degradation appears to be the adenosine triphosphate-dependent ubiquitin–proteasome pathway, which is present both in the nucleus and the cytosol. The proteasome, a multisubunit protease that specifically degrades ubiquitin-conjugated proteins, is responsible for the degradation of proteins from the intracellular compartment (Von Haehling et al., 2002). Its involvement in muscle degradation has been demonstrated in patients with cancer (Williams et al., 1999), chronic kidney disease (Bailey et al., 1996), sepsis (Garcia-Martinez et al., 1995), and AIDS (Llovera et al., 1998), as well as HF.

The local expression of the anabolic insulin-like growth factor-1 in skeletal muscle has been shown to be reduced in patients with HF (Hambrecht et al., 2002) with peripheral deficiency and an impaired response to its upstream regulator growth hormone (Douglas et al., 1991). Insulin-like growth factor-1 is a key regulator of protein kinase B, also known as Akt, whose downstream target is called mammalian target of rapamycin (mTOR), a pivotal regulator of translation initiation and overall muscle size (Fig. 1). Recent data have shown that basal Akt phosphorylation is decreased in patients with HF compared to controls who were matched for age and physical activity-level (Toth et al., 2011). In this setting, no differences were found in total Akt protein content or protein content of mTOR. In addition, pro-inflammatory cytokines like TNF can induce a state of growth hormone resistance (Cicoira et al., 2003) with high levels of this hormone and normal or low levels of insulin-like growth factor-1 (Schulze and Späte, 2005). Such pro-inflammatory mediators have long been known to be overexpressed in patients with HF (Anker and von Haehling, 2004), and increased levels are associated with poor short- and long-term survival (Ferrari et al., 1995; Rauchhaus et al., 2000). Transcription of pro-inflammatory cytokines is regulated in large part by the transcription factor nuclear factor-κB (Fig. 1). Together with forkhead box O (FoxO), NF-κB also activates the proteasome pathway by increasing the expression of the E3 ubiquitin-ligases muscle ring-finger protein-1 (MuRF-1) and muscle atrophy F-box-1 (MAFbx-1) (Fig. 1). These two ligases are involved in muscle wasting of many different origins (Bodine et al., 2001; Gomes et al., 2001). Another negative regulator of muscle bulk is myostatin, also known as growth differentiation factor-8, which is expressed predominantly in skeletal muscle (Fig. 1) (Springer et al., 2010; Elkina et al., 2011). Interruption of myostatin's gene expression leads to muscle hypertrophy and hyperplasia (McPherron et al., 1997). It is interesting to note that the baseline expression of myostatin mRNA was about 50% higher in vastus lateralis muscle biopsies from patients with HF than in those from healthy age-matched controls (Gielen et al., 2012). Recently, it was proposed that myostatin released from the failing myocardium may be involved in muscle wasting in patients with HF as well (Heineke et al., 2010). Therefore, myostatin inhibition may be a potential therapeutic target in the future (Busquets et al., 2012).

Besides over-activity of the ubiquitin–proteasome system, lysosomal proteases and the calcium-dependent calpain system are involved in muscle protein breakdown (Fig. 1). Skeletal muscle atrophy, however, is eventually the result of a combination of increased protein breakdown and apoptosis. The fact that each muscle fiber contains more than 100 nuclei makes it difficult to understand the effects of apoptosis of a single nucleus (Schulze and Späte, 2005). However, it has been suggested that every nucleus controls a certain territory of the muscle fiber implicating that the

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