

# Skeletal muscle wasting in chronic heart failure

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## Abstract

Patients suffering from chronic heart failure (CHF) show an increased prevalence (~20% in elderly CHF patients) of loss of muscle mass and muscle function (i.e. sarcopenia) compared with healthy elderly people. Sarcopenia, which can also occur in obese patients, is considered a strong predictor of frailty, disability, and mortality in older persons and is present in 5–13% of elderly persons aged 60–70 years and up to 50% of all octogenarians. In a CHF study, sarcopenia was associated with lower strength, reduced peak oxygen consumption (peak  $\text{VO}_2$ ,  $1173 \pm 433$  vs.  $1622 \pm 456$  mL/min), and lower exercise time ( $7.7 \pm 3.8$  vs.  $10.22 \pm 3.0$  min, both  $P < 0.001$ ). Unfortunately, there are only very limited therapy options. Currently, the main intervention remains resistance exercise. Specialized nutritional support may aid the effects of resistance training. Testosterone has significant positive effects on muscle mass and function, and low endogenous testosterone has been described as an independent risk factor in CHF in a study with 618 men (hazard ratio 0.929,  $P = 0.042$ ). However, the use of testosterone is controversial because of possible side effects. Selective androgen receptor modulators have been developed to overcome these side effects but are not yet available on the market. Further investigational drugs include growth hormone, insulin-like growth factor 1, and several compounds that target the myostatin pathway. The continuing development of new treatment strategies and compounds for sarcopenia, muscle wasting regardless of CHF, and cardiac cachexia makes this a stimulating research area.

**Keywords** Muscle wasting; Cardiac cachexia; Sarcopenia; Heart failure

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## Introduction

In the elderly population, cardiovascular diseases represent a highly prevalent group of disorders that include chronic heart failure (CHF), which leads to high morbidity and mortality.<sup>1</sup> The overall prevalence of cardiovascular disease in patients is ~2% of the population.<sup>2</sup> After 55 years of age, the rates of CHF increase strongly and double approximately every 10 years in male and every 7 years in female patients; thus, this patient population can be considered elderly to very old. With the rise in life expectancy, a rise in CHF patients' numbers will follow.<sup>3–5</sup> The symptom burden of patients is high, and it has been reported that 55–95% of patients experience shortness of breath and 63–93% experience tiredness.<sup>6</sup> However, public awareness about CHF aetiology and symptoms is unsatisfactory; particularly, knowledge about management, severity, and prognosis is

lacking, which is critical for good self-care and adherence of patients.<sup>7</sup>

The CHF population can be divided into heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction, and of the two, HFpEF is the most common form.<sup>8</sup> The impaired myocardial relaxation in HFpEF is a robust and independent predictor of aerobic exercise capability,<sup>9</sup> and these patients also show a high prevalence of sarcopenic obesity.<sup>10–12</sup> Sarcopenia is mainly associated with the age-related loss of skeletal muscle<sup>13</sup> but is commonly observed in advanced stages of CHF leading to reduced exercise capacity and frailty,<sup>14,15</sup> which may represent a risk marker for adverse outcomes in CHF.<sup>16</sup> Cardiac troponin T contributes to the functional decline of the neuromuscular junction with ageing by interfering with protein kinase A signalling, which primarily affects the fast-twitch skeletal muscle.<sup>17</sup> Sarcopenia itself is a common

manifestation in the aged population<sup>18–20</sup> and is associated with increased mortality independently of age or other clinical and functional variables.<sup>21–24</sup> Low body mass index may be a risk factor for both current and future sarcopenia in the very old aged 85 and above, of whom 74.3% displayed either slow gait speed or weak grip strength.<sup>25</sup>

A large retrospective study showed that the prevalence of sarcopenia in the general population ranged from 12.6% (Poland) to 17.5% (India), and that of sarcopenic obesity ranged from 1.3% (India) to 11.0% (Spain).<sup>13</sup> Despite the high prevalence and profound negative impact, sarcopenia was given an ICD-10-code only recently.<sup>26</sup> Interestingly, in non-obese men, sarcopenia can be considered a risk factor for cardiovascular disease<sup>27</sup> and may predict adverse outcome in CHF.<sup>16</sup> However, using a combined lean mass and gait speed approach, sarcopenia was found in 36.5% subjects in a cohort of ~4400 with a mean age of 70 years, which was associated with an increased risk of cardiovascular-specific death for women, but not men.<sup>22</sup> Sarcopenia is also associated with standard R-CHOP chemotherapy intolerance in patients with malignancies<sup>28</sup> and worse survival of patients with ovarian cancer receiving neoadjuvant chemotherapy,<sup>29</sup> as well as rectal cancer<sup>30</sup> and haemodialysis patients.<sup>31</sup> Moreover, sarcopenia and myosteatosis are independently associated with a higher long-term mortality in liver cirrhosis.<sup>32</sup>

## Chronic heart failure and muscle maintenance

Sarcopenia is considered to be a largely age-dependent syndrome, was originally defined as the age-related loss of skeletal muscle of the limbs two standard deviations below the mean of a healthy young reference group, and has been linked with to a range of adverse outcomes.<sup>25,33</sup> In contrast to cachexia, sarcopenia and muscle wasting cannot be identified by simply longitudinally determining the patients' body weight to detect involuntary weight loss.<sup>34,35</sup>

Sarcopenia affects 5–13% of elderly persons aged 60–70 years and up to 50% of all octogenarians.<sup>36</sup> The prevalence of sarcopenia in Asia ranges from 4.1% to 11.5% of the general older population.<sup>37</sup> The effects of sarcopenia are not only restricted to the loss of skeletal muscle mass but are also associated with muscle dysfunction and impaired physical performance, which may be exacerbated by chronic diseases.<sup>38</sup> In acute care wards, sarcopenia was an independent predictor of 3 year mortality (adjusted hazard ratio: 2.49; 95% confidential interval: 1.25–4.95) and readmission (adjusted hazard ratio: 1.81; 95% confidential interval: 1.17–2.80) after adjustment for age, sex, and other confounders.<sup>39</sup> Therefore, patients are in dire needs for a specialized sarcopenia therapy. Unfortunately, because of a lack of consensus on the definition of sarcopenia, there are problems

with its definite detection.<sup>35,40</sup> This fact is exacerbated by the fact that no clinically validated biomarkers have been identified despite enormous research efforts both by academia and industry.<sup>41–43</sup> As a result, the definition of sarcopenia (two standard deviations of normal muscle mass) has been modified to contain measurements of impaired physical function, such as slow walking speed and low grip strength.<sup>34</sup> In addition, a sarcopenia-specific Quality of Life questionnaire has recently been introduced.<sup>44</sup> Despite this, there are still several definitions of sarcopenia with diverse cut-off values<sup>45,46</sup> that were all confirmed to be independent predictors of adverse outcomes.<sup>47</sup>

The prevalence of sarcopenia in CHF patients is higher at 20% compared with control subjects of the same age.<sup>48</sup> An even higher prevalence of sarcopenia (47%) has recently been suggested in patients below the age of 55 years suffering from dilated cardiomyopathy.<sup>49</sup> This particularly high incidence may be due to mitochondrial dysfunction combined with an abnormal energy metabolism and a transition of type I to type II myofibres.<sup>50,51</sup>

In CHF, divergent anti-oxidative and metabolic but similar catabolic responses, i.e. wasting of myofibrillar proteins, of the diaphragm and quadriceps muscles have been observed.<sup>52</sup> The increased catabolic stress in the skeletal muscle of CHF patients results in exercise intolerance, ventilatory inefficiency, and chronotropic incompetence, as well as insulin resistance, suggesting a significant contributing of the catabolic status mechanism to the patients' limited functional status.<sup>53,54</sup> Skeletal muscle density has been suggested to be an independent marker of clinical outcome.<sup>55</sup>

Continuous treatment with acetylated ghrelin was shown to normalize CHF-induced skeletal muscle mitochondrial dysfunction, pro-inflammatory changes, and reduced insulin signalling in a rat model.<sup>34</sup> Another contributing factor to sarcopenia is a variable degree of malnutrition<sup>56</sup> that may be caused by inflammatory cytokines,<sup>57–59</sup> which have been known to contribute to anorexia in chronic disease.<sup>60–63</sup> Malnutrition and sarcopenia are also common features of rehabilitation patients in whom the prevalence of malnutrition was 49–67% and that of sarcopenia 40–46.5%.<sup>64</sup> Malnutrition and sarcopenia have also been shown to be associated with early post-liver transplant morbidity/mortality, yet allocation indices do not include nutritional status.<sup>65</sup> Interestingly, premorbid obesity, but not exogenous macronutrients, attenuated muscle wasting in critical illness.<sup>66</sup> Low levels of testosterone or vitamin D were not prognostic for muscle mass and function in middle-aged and elderly men, while low insulin-like growth factor 1 (IGF-1) levels were found to predict alterations in gait speed in men aged ≥70 years.<sup>67</sup> A recent study has identified low testosterone in men as an independent risk factor in CHF.<sup>68</sup>

However, testosterone deprivation therapy due to prostate cancer selectively impairs lower-limb muscle function, primarily affecting muscles that support body weight,

mediate the forward movement the body during walking, and mediate balance.<sup>69</sup> On the other hand, supplementation of androgens such as dihydrotestosterone in mice reversed the reduction in protein synthesis and amino acid transporter expression observed in ageing animals.<sup>70</sup> In contrast to Gielen *et al.*,<sup>67</sup> a strong association between high vitamin D deficiency and an increased risk of heart failure in the elderly has been described.<sup>71</sup> Targeted medical nutrition including vitamin D supplementation has positive effects on blood pressure and plasma lipids.<sup>72</sup> In a Korean study, high serum vitamin D levels in mid-life and late-life were linked to reduced odds of various adverse effects on body composition, particularly in osteosarcopenic obesity, stressing the importance of maintaining adequate levels of vitamin D.<sup>73</sup> Vitamin D supplementation has also proven beneficial in improvement of muscle weakness in prostate cancer patients.<sup>74</sup> However, a recent systematic review finds not enough solid evidence for the use of minerals, vitamins, proteins, or other supplements in cancer.<sup>74</sup> Currently, there are only few therapy options for patients suffering from sarcopenia, which include (resistance) exercise,<sup>75–77</sup> nutritional approaches to increase consumption of proteins and micronutrients,<sup>78,79</sup> and finally, drug treatment, including testosterone,<sup>80,81</sup> growth hormone (GH), and IGF-1.<sup>82</sup> Resistance exercise is often used in combination with nutrition support, which increases muscle mass and muscle strength more than exercise alone.<sup>46,83–85</sup> Supplementation of a low-dose creatine in combination with resistance training improved lean mass in elderly over a period of 12 weeks.<sup>86</sup> A patient-centred exercise approach in frail elderly and older adults with mobility limitations physical activity was considered to improve effective quality of life and reduce frailty, while also being cost-effective.<sup>87</sup> An accelerometer-determined physical activity showed an independent, dose–response relationship with lean mass percentage and lower limb strength.<sup>88</sup> High-intensity training over a period of 6 months resulted in greater improvements of frailty and sarcopenia status among community-dwelling elders.<sup>89</sup> Interestingly, a significant plasticity of ageing skeletal muscle to adapt to resistance-type exercise training has been shown by transcriptomics after a 6 month training period including partial reversal of age-related changes in skeletal muscle gene expression.<sup>90</sup> Exercise training has been acknowledged as an evidence-based therapeutic approach with prognostic benefits in cardiovascular illness including CHF, as it improves risk factors such as hyperlipidaemia, hypertension, and coronary endothelial function.<sup>91</sup> Exercise training not only has cardio-protective effects and thereby attenuates the progression from cardiac dysfunction to CHF but also induces anti-catabolic signalling in skeletal muscle, possibly by stimulation of PGC1 $\alpha$ .<sup>92</sup> In breast cancer patients undergoing adjuvant chemotherapy, a favourable effect of resistance exercise training was seen on sarcopenia and dynapenia.<sup>93</sup> However, in a meta-analysis on the effects of exercise, rehabilitation

after intensive care unit discharge found no overall effect on functional exercise capacity and health-related quality of life.<sup>94</sup> A novel treatment option in CHF patients is neuromuscular electrical stimulation, which has been deemed safe to use. It has been shown to increase functional capacity, muscle strength, and quality of life more compared with conventional aerobic exercise.<sup>95</sup> However, in type II muscle fibres, baseline capillarization of the muscle may be a critical factor for permitting any muscle fibre hypertrophy in resistance exercise training in older men.<sup>96</sup>

Testosterone levels decline at the rate of 1% per year from 30 years of age leading to a reduction in muscle mass and strength.<sup>97</sup> The waning of testosterone appears to primarily decrease lower-limb muscle function,<sup>69</sup> making replacing it a seemingly perfect choice to treat sarcopenia. However, there is a fear that it will result in disproportionate side effects, predominantly an increased risk of prostate malignancies and cardiovascular events.<sup>82</sup> Interestingly, the administration method of testosterone appears to impact the cardiovascular risk. In a meta-analysis, oral testosterone significantly increased the risk of cardiovascular events, while no significant undesirable effects were observed, when testosterone was applied transdermally or by intramuscular injections.<sup>98</sup> Hence, studies focused on the testosterone application route are desirable, particularly in CHF patients. To circumvent the potential severe side effects of testosterone, selective androgen receptor modulators like enobosarm have been developed, which have similar anabolic effects to testosterone, but are believed to have fewer severe side effects.<sup>99,100</sup> However, a trial using the 4-aza steroidal drug MK0773 that has androgen gene selectivity and has been shown to increase IGF-1 levels and improve muscle function in women was terminated because of increased cardiovascular risk.<sup>101</sup> Recently, urolithin B, an ellagitannin-derived metabolite, has been observed to have beneficial effects on skeletal muscle growth by involving the androgen receptor in C2C12 myotubes and a mouse model of denervation.<sup>102</sup> Alternatives to stimulating the androgen receptor to induce muscle growth and strength are the use of GH and IGF-1, but of which are important in maintaining and building muscle mass.<sup>103</sup> However, a large meta-analysis showed that patients receiving GH were significantly more likely to experience side effects such as soft tissue oedema, arthralgias, carpal tunnel syndrome, and gynecomastia.<sup>104</sup> The GH/IGF-1 axis is controlled by several GH secretagogues that have been the subject of experimental therapies. Nasal application of growth hormone-releasing peptide-2, which is already in use for detection of GH secretion deficiency, has proven successful in anorexia.<sup>105</sup> Ghrelin, which is primarily produced in the fundus of the stomach, has been used in disease-related anorexia and conditions of muscle loss like sarcopenia and cachexia. In cancer cachexia patients, ghrelin improves food intake,<sup>106,107</sup> possibly by modulation of the central control of appetite dysregulation during cancer anorexia.<sup>63</sup> The small

molecule ghrelin-analogue anamorelin also increased muscle mass but had no effect on muscle strength.<sup>108</sup> However, ghrelin attenuated tumour-induced and cisplatin-induced muscle wasting in cancer cachexia mouse model.<sup>109</sup> A comparable effect was observed in a rat model of cisplatin-induced cachexia where the GH secretagogues hexarelin and JMV2894 improved calcium homeostasis in skeletal muscle.<sup>110</sup> Acetylated ghrelin normalized skeletal muscle mitochondrial oxidative capacity and Akt activation in rat CHF model.<sup>34</sup>

Myostatin (also known as GDF-8) is a negative regulator of muscle mass, which binds primarily to the activin II B receptor. A suppression of myostatin expression in knockout mice has shown significant increased muscle mass, an effect that can also be found in spontaneous, natural gene deletions in Belgian Blue cattle, whippets, and in a rare case, humans.<sup>111</sup> Human myocardium expressed myostatin in end-stage heart failure and the related signalling pathways in the myocardium seen to have a gender effect.<sup>112</sup> Myostatin released from the myocardium has been reported to be causal for skeletal muscle atrophy in a CHF mouse model.<sup>113</sup> In patients with liver cirrhosis, higher serum myostatin levels were associated with muscle mass loss, hyperammonemia, and impaired protein synthesis, as well as impaired survival.<sup>114</sup> Activation of activin II B receptor by activin A in the muscle has been described to induce muscle catabolism, which was dependent on p38beta MAPK-activated signalling pathway and resulted in the up-regulation of ubiquitin ligases MAFbx and UBR2 (E3alpha-II), as well as increases in LC3-II, a marker of autophagosome formation.<sup>115</sup> Circulating activin A levels have also been shown to be an independent predictor of survival in cancer patients.<sup>116</sup> Doxorubicin-induced cachexia was prevented by ACVR2B ligand blocking. Pretreatment with soluble ACVR2B-Fc had only minor impact in the heart while it had major effects in skeletal muscle at the transcriptome level.<sup>117</sup>

However, while neutralizing antibodies such as MYO-029, AMG 74, and LY2495655 or soluble receptor decoys such as ACE-11 and ACE-031 has significant beneficial effects on muscle mass and strength, they also exhibit several side effects including urticarial, aseptic meningitis, diarrhoea, confusion, fatigue, and unintentional muscle contractions.<sup>82</sup>

Other possibilities to induce muscle mass include  $\beta_2$ -adren-ergic receptor agonists like salbutamol, clenbuterol, and formoterol. These compounds have beneficial effects on muscle mass and induction of protein synthesis in myocytes and simultaneously increased blood flow.<sup>118</sup> While clenbuterol has been observed to increase lean mass and maximal strength, the endurance and exercise duration was decreased.<sup>119</sup> Treatment of CHF patients with salbutamol resulted in detrimental ventricular arrhythmias.<sup>120</sup> However, formoterol treatment was cardio-protective aside from attenuating cachexia and improving survival in experimental cancer cachexia.<sup>121</sup> A combination treatment with formoterol and megestrol acetate has proven to be more effective in

preventing muscle wasting than formoterol alone in the Yoshida hepatoma rat cancer cachexia model.<sup>122</sup> Megestrol acetate alone reduced autophagy in the heart and improved cardiac function in experimental cancer.<sup>123</sup>

Espindolol, the *s*-enantiomer of pindolol, is another multifactorial drug. It is a beta-1 receptor antagonist thereby reducing cellular stress and a partial beta-2 receptor agonist inducing muscle mass and also has 5-HT1A receptor activities leading to improvements in appetite and mood. Espindolol treatment in aged rats over the period of 1 month increased muscle mass considerably, while decreasing fat mass without negatively affecting cardiac function, making it an interesting candidate for sarcopenic obesity.<sup>124</sup> Importantly, espindolol lead to an increase in muscle mass and hand grip strength in Phase IIa cancer cachexia trial.<sup>125,126</sup> The beta blocker carvedilol has recently been shown to attenuate the development of cardiac cachexia and stimulate a partial reversal of cachexia in patients with severe CHF.<sup>127</sup>

## Transition to cardiac cachexia

Sarcopenia in CHF may ultimately progress to cardiac cachexia,<sup>128,129</sup> which is associated with an exceptionally poor prognosis.<sup>130</sup> Earlier numbers showed a rate of up to 40% of CHF patients progressing to cardiac cachexia, which has significantly improved because of improved treatment of heart failure itself and is currently estimated to have a prevalence of 10%.<sup>131</sup> Other studies estimate a prevalence of cardiac cachexia of 5–15% in CHF. Mortality rates of cachectic patients range from 10–15% per year in chronic obstructive pulmonary disease to 20–30% per year in CHF and chronic kidney disease.<sup>4</sup> Cardiac cachexia has a dramatic prognostic impact with an 18 month mortality rate of up to 50%,<sup>132</sup> mortality is particularly high in obese cachectic CHF patients.<sup>133</sup> Patients with cardiac cachexia show higher rates of atrial fibrillation,<sup>134</sup> possibly contributing to the increased mortality.

Standard heart failure medication not only has remarkable beneficial effects on attenuating the progression to cardiac cachexia but also has shown to reduce cachexia and improve survival in experimental cancer cachexia, without affecting the tumour.<sup>135</sup>

While the majority of CHF patients has benefitted from heart failure medication, a subgroup of CHF patients seem to be unprotected from developing cachexia despite standard medication. Recently, several small molecule inhibitors of the E3-ligase muscle ring finger 1 have shown great potential in experimental cardiac cachexia by reducing muscle wasting and contractile dysfunction by inhibiting apoptosis and ubiquitin-proteasome-dependent proteolysis.<sup>136</sup> Additionally, microRNAs may also represent promising novel targets as potential biomarkers and as an interventions strategy in cardiac cachexia.<sup>137</sup>

In conclusion, while there have been stimulating and encouraging improvements in the field of muscle wasting, there are a number of crucial points that still have to be addressed in muscle wasting, sarcopenia, and cachexia in CHF: (i) the definition and discrimination of the different diseases states, (ii) robust biomarkers that aid tailor the anti-wasting therapy and allow monitoring of treatment success, and (iii) more research into exercise training in combination with existing drugs and/or investigational compounds.

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None declared.

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