

# Cardiac cachexia

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## KEYWORDS

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Cachexia is a multifactorial disease characterized by a pathologic shift of metabolism towards a more catabolic state. It frequently occurs in patients with chronic diseases such as chronic heart failure and is especially common in the elderly. In patients at risk, cardiac cachexia is found in about 10% of heart failure patients. The negative impact of cardiac cachexia on mortality, morbidity, and quality of life demonstrates the urgent need to find new effective therapies against cardiac cachexia. Furthermore, exercise training and nutritional support can help patients with cardiac cachexia. Despite ongoing efforts to find new therapies for cachexia treatment, also new preventive strategies are needed.

Chronic heart failure (CHF) is a complex multifactorial disease affecting >20 million people worldwide.<sup>1,2</sup> It is associated with high hospitalization<sup>3</sup> and mortality rates.<sup>4</sup> Today, each CHF hospitalization on average costs 8000 US dollars.<sup>5</sup> Despite multiple effective therapies,<sup>6–10</sup> CHF patients still have a poor long-term prognosis.<sup>11,12</sup> Therefore, CHF represents one of the major challenges for the global healthcare and socioeconomic systems.<sup>1</sup> Besides many different cardiovascular<sup>13</sup> and non-cardiovascular comorbidities,<sup>14,15</sup> metabolic disturbances such as metabolic syndrome,<sup>16</sup> anorexia, sarcopaenia, frailty<sup>17</sup> and cachexia<sup>18,19</sup> negatively affect survival,<sup>20</sup> physical performance,<sup>21</sup> and quality of life in CHF patients.<sup>22</sup> Cachexia itself is characterized by an imbalance between catabolic and anabolic mechanisms.<sup>23</sup> Such alterations are frequently seen in patients with chronic diseases such as CHF.<sup>24</sup>

In general, cachexia is clinically defined as unintentional weight loss, with or without skeletal muscle wasting, of at least 5% of baseline weight during the previous year.<sup>25</sup> For the diagnosis, three of the following factors are also

required: anorexia, fatigue, reduced muscle strength, reduced fat-free mass index, and abnormalities in blood biomarkers (haemoglobin  $\leq 12$  g/dL, serum albumin  $< 3.2$  g/dL, elevated IL-6, or increased C-reactive protein).<sup>22</sup> In patients with established heart failure, it is estimated that cardiac cachexia is present in about 10% of patients.<sup>26</sup> The pathophysiology of cardiac cachexia is characterized by diverse mechanisms such as: systemic inflammatory activity,<sup>27</sup> autonomic dysfunction,<sup>28,29</sup> up-regulation of the renin-angiotensin axis,<sup>30</sup> dysregulation of the immune system,<sup>31</sup> and catabolic/anabolic imbalance. Consequently, skeletal musculature is also frequently negatively affected, resulting in relative and absolute sarcopaenia.<sup>32,33</sup> These morphologic and metabolic changes seem to occur not only in skeletal muscle but also in cardiac tissue: myocardial fibrosis has been observed in patients affected by heart failure with preserved ejection fraction,<sup>34,35</sup> while an increased cardiac muscle depletion was found in cancer patients affected by cachexia.<sup>36,37</sup>

Hence, it is important to screen patients with heart failure for muscular wasting and cardiac cachexia.<sup>38</sup> Different diagnostic tools are available to detect muscle wasting, but all carry advantages and disadvantages. Despite

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some limitations regarding inter- and intra-individual variability,<sup>39</sup> some authors consider dual-energy X-ray absorptiometry (DXA) as the standard reference tool for body composition and lean mass measurement.<sup>40</sup> For the purpose of muscle mass monitoring, other imaging techniques such as computer tomography (CT),<sup>41</sup> magnetic resonance imaging (MRI),<sup>42</sup> bioelectric impedance analysis,<sup>43,44</sup> and ultrasound<sup>45</sup> may also be helpful. However, DXA, CT, and MRI are infrequently utilized in daily practice to diagnose metabolic abnormalities, since they are only available in large medical centres and are expensive. A new experimental approach, liquid chromatography-tandem mass spectrometry applied on methyl-d3 (D3)-creatinine dilution, may represent a future diagnostic method.<sup>46</sup> It has been shown, that through the repetitive and non-invasive measurement of urinary excretion of enriched creatinine it is possible to indirectly obtain information about muscular mass changes.<sup>47</sup>

Recently, the role of serological biomarkers has grown in importance in the early detection and prognosis of cardiac cachexia: abnormal serum concentration of sarcomeric proteins (e.g. actin, myosin, troponin, tropomyosin) released after protein breakdown, are associated with muscle wasting.<sup>48</sup> Moreover, an overexpression of myostatin, known as a negative modulator of myocytes proliferation, has been found in female patients affected by CHF.<sup>49</sup> Increased inflammatory cytokines [e.g. interleukin (IL)-1, IL-6, tumour necrosis factor- $\alpha$ ] have been associated with an augmented systemic inflammatory status in CHF patients suffering from cachexia.<sup>50</sup> In cachectic CHF patients, impairments in hormonal factors (e.g. leptin, ghrelin, adiponectin) have been documented in some studies, suggesting that neurohormonal dysregulation may precede metabolic changes in CHF.<sup>51-53</sup>

Regarding possible treatment strategies, exercise training programmes have shown beneficial effects in limiting muscle loss<sup>54</sup> while nutritional supplements may also be helpful.<sup>55</sup> Numerous experimental drugs have been recently tested: acylated ghrelin demonstrated positive results in counteracting catabolic disturbances present in CHF pre-clinical models.<sup>56</sup> Also enobosarm (selective androgen receptor modulators)<sup>57</sup> and megestrol acetate<sup>58</sup> showed some benefits but were tested in patients with cancer cachexia and results in patients with CHF are needed. In addition, ongoing research is focusing on protein synthesis and degradation processes in order to identify novel therapeutic targets.<sup>59,60</sup> In a retrospective analysis from the SOLVD trial, randomizing enalapril vs. placebo in 1929 CHF patients, angiotensin conversion enzyme inhibitors reduced the risk of weight loss in patients with heart failure.<sup>61</sup> A similar cachexia preventing effect within the heart failure population has been shown with beta-blockers,<sup>62</sup> suggesting neurohormonal blockade may have useful cachexia preventing effects. More studies are therefore needed to better understand the underlying mechanisms.

In conclusion, cardiac cachexia is a frequent problem that needs special attention by clinicians. Many researchers are currently trying to find new treatment strategies.<sup>63-66</sup> For better understanding of cardiac cachexia, more research in preclinical and clinical models is urgently needed.

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