# The interplay between heart failure, metabolism and body composition

**A complex interplay exists between heart failure, metabolic status and body composition. The idiosyncrasies of these relationships are poorly understood, but they offer prognostic value and potential clinical utility. Current understanding of this relationship and known clinical value are discussed in this article.**

Heart failure is a common and disabling condition, defined as an abnormality in cardiac structure and/or function that is unable to meet the metabolic demands of the body. Heart failure affects 800 000 people in the UK and ultimately carries a high mortality (McMurray et al, 2012). There is strong evidence of the impact of obesity and overall body composition on the development and progression of heart failure. Understanding of this complex interplay is limited, but has clinical value given the recognized impact of adiposity and weight loss on predicting heart failure outcomes. This article summarizes the current evidence and importance of this interplay between heart failure, metabolism and body composition.

## Heart failure metabolism

Under normal physiological circumstances there is a balance between anabolic and catabolic metabolism and its regulation. The development and progression of heart failure is associated with activation of neurohormonal systems, the development of a pro-inflammatory state and endothelial dysfunction (McMurray et al, 2012; Melenovsky et al, 2013; Christensen et al, 2014). The imbalance in metabolism that favours a pro-catabolic state is associated with progression of heart failure and alters skeletal and adipose tissue metabolism (Christensen et al, 2014).

Natriuretic peptides (e.g. N-terminal prohormone of brain natriuretic peptide; NT-pro-BNP) are released in response to the haemodynamic changes in heart failure and convey diagnostic and prognostic value (McMurray et al, 2012). An inverse relationship is well established between levels of natriuretic peptides and body mass index (Christensen et al, 2013). In a small cross-sectional study, Christensen et al (2014) observed that high levels of NT-pro-BNP were associated with low total fat mass (ß=-0.3, $P<0.05$).

Adipocytes are sensitive to natriuretic peptides, activating lipolysis and enhancing the expression of brown adipocyte genes; increasing energy use and thermogenesis (Christensen et al, 2014). Natriuretic peptides stimulate the release of adipokines, specifically adiponectin and leptin, which increase energy use and weight reduction (Christensen et al, 2014). Adipokines are involved in whole body energy metabolism, and adiponectin is particularly involved in the regulation of skeletal muscle metabolism and weight loss in patients with heart failure. In a cross-sectional study of elderly males with stable heart failure and no cardiac cachexia, Loncar et al (2013) observed that adiponectin was independently associated with muscle mass and strength. In a pivotal prospective observational study of right ventricular dysfunction and cardiac cachexia ($n$=408), Melenovsky et al (2013) identified that adiponectin levels were significantly raised in both patients with right ventricular dysfunction who were cachectic. Furthermore, adiponectin was one of the few variables (alongside NT-pro-BNP, right ventricular dysfunction and neurohormonal antagonist therapy) to independently predict cardiac cachexia (Melenovsky et al, 2013).

Serum adiponectin levels are associated with severity of heart failure and adverse outcomes (Loncar et al, 2013). Paradoxically, adiponectin has been observed to have beneficial effects on lipid and glucose metabolism, alongside myocardial inflammation, hypertrophy and

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fibrosis (Okamoto, 2009). It has been identified as a well-placed potential biomarker for the cross-talk in heart failure metabolism (Okamoto, 2009).

Pro-inflammatory signals from cytokines and interleukin-6 (IL-6) are increased in patients with heart failure (Christensen et al, 2014). Proteolysis in muscle occurs predominantly via the ubiquitin–proteasome system, which has increased activation in patients with heart failure as a result of stimulation from these increased pro-inflammatory signals (Fülster et al, 2013). Christensen et al (2014) described a trend towards an association between high IL-6 levels and fat free mass. Adiponectin and leptin have receptors in skeletal muscle which have acute and chronic effects on local metabolism (Loncar et al, 2013).

## Adiposity and heart failure

Obesity, defined as a raised body mass index (>30.0 kg/m$^2$), is recognized as a risk factor for heart failure. The risk of developing heart failure increases for men and women by 5% and 7% respectively for every one unit rise in body mass index, independent of other important co-variables (Clark et al, 2014). A graded increase in risk of developing heart failure is recognized for increasing body mass index in both males and females in different population groups (Clark et al, 2014). Furthermore, Clark et al (2014) describe the increased risk of heart failure from other raised adiposity surrogate metrics, for example waist circumference and waist–hip ratio.

Counterintuitively, those with a raised body mass index and established heart failure have been observed to have improved outcomes (Oreopoulos et al, 2008; Pocock et al, 2008; Futter et al, 2011; Clark et al, 2014). In a large meta-analysis of 28 209 patients with heart failure who were obese or overweight (25.0–29.9 kg/m$^2$), Oreopoulos et al (2008) found an all-cause mortality of -19.0% and -40.0% and cardiovascular mortality of -16.0% and -33.0% respectively compared to those without a raised body mass index (<24.9 kg/m$^2$) at >2years follow-up. The relationship between body mass index and mortality has a U-shaped curve with the lowest rates associated with those overweight and obese and the higher rates associated with leanness and severe obesity (>35.0 kg/m$^2$) (Pocock et al, 2008), although not all datasets have replicated this finding (Futter et al, 2011).

The inverse relationship of NT-pro-BNP and adiponectin with body mass index and total percentage body fat suggests that a higher fat content protects against the catabolic activity of these neurohormonal signalling pathways, and supports the observation that fat mass is preserved in patients with cardiac cachexia (Christensen et al, 2013; Loncar et al, 2013). In a retrospective cohort study of 219 Chinese patients with severe left ventricular systolic dysfunction (ejection fraction <35%), Cai et al (2014) demonstrated that overweight (24.0–28.0 kg/m$^2$) and obese (>28.0 kg/m$^2$) predicted response to cardiac resynchronization therapy and improved survival at

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6 months. Notably in this study the defined body mass index ranges were lower than those used in other studies because the Chinese population has a lower average body mass index than western populations. Furthermore, this study demonstrated that the obese population better tolerated optimal medical therapy, an observation noted in other studies (Melenovsky et al, 2013; Cai et al, 2014).

The paradoxical observations that an overweight or obese body mass index predicts development of heart failure but offers improved survival once established is referred to as the ‘obesity paradox’ (Pocock et al, 2008; Clark et al, 2014). Several explanations and hypotheses have been offered to explain the obesity paradox. First, lower levels of natriuretic peptides are seen in obese patients, therefore symptoms may present earlier (Clark et al, 2014). Second, patients with lower levels of circulating natriuretic peptides are thought to have a more attenuated renin–angiotensin–aldosterone system (Clark et al, 2014). Despite this, obesity also contributes to maintaining systemic blood pressure, preserving renal function, which allows patients to better tolerate anti-heart failure medication (Clark et al, 2014). Third, body mass index is a crude metric of body composition, with some patients classified as overweight or obese actually containing a high proportion of muscle; body mass index does not account for the different body composition components (Clark et al, 2014). Finally, obesity is a heterogeneous condition with various fat mass distributions. These can include visceral fat deposits or subcutaneous or gluteofemoral obesity, each of which have differing metabolic profiles (Clark et al, 2014).

## Body composition and heart failure

Muscle wasting is common in patients with heart failure. Sarcopenia, defined as reduced muscle mass and limited mobility, occurs naturally with aging at a rate of 1–2% per annum over 50 years of age. Fülster et al (2013) recruited 200 patients with heart failure at a single centre and observed that 19.5% of the cohort had sarcopenia, a higher proportion than would be expected through natural aging. Significantly patients with heart failure with both reduced (68.8%) and preserved (31.2%) ejection failure were recruited to this study (Fülster et al, 2013). Heart failure patients with sarcopenia had a higher incidence of reduced left ventricular ejection fractions, reduced muscle strength, worse functional capacity and significantly higher IL-6 levels (Fülster et al, 2013). Elevated levels of pro-inflammatory signals in patients with heart failure, including cytokines and IL-6, stimulate catabolic pathways, for example the ubiquitine-protease pathway, and cause sarcopenia (Fülster et al,

## KEY POINTS

- Interplay between heart failure, altered metabolism and body composition remains poorly understood, but has high clinical value in predicting adverse outcomes.
- Heart failure alters systemic metabolic processes towards a catabolic imbalance, and is driven by neurohormonal and pro-inflammatory signalling pathways.
- Adiposity is cardio-protective in patients with established heart failure.
- Presence of cardiac cachexia (unintentional, non-oedematous weight loss >5% over 6 months) is a poor prognostic sign in heart failure.
- Presence of right ventricular dysfunction and cardiac cachexia in patients in heart failure is a powerful predictor of adverse outcomes.

2013). Neurohormonal signalling cross-talk is associated with muscle wasting (Loncar et al, 2013).

On the other hand, cardiac cachexia is defined as unintentional non-oedematous ≥5% weight loss over ≥6 months, although higher levels of weight loss have been set in the literature (Pocock et al, 2008; Christensen et al, 2013). The imbalance of metabolic systems progressing towards a catabolic state in heart failure results in cardiac cachexia. One of the strongest and most reproducible signs of poor prognosis in heart failure is development of cardiac cachexia (Oreopoulos et al, 2008; Pocock et al, 2008; Melenovsky et al, 2013; Clark et al, 2014). Pocock et al (2008), in a sub-study of the CHARM programme which involved 6933 patients, demonstrated that together leanness (<22.5 kg/m$^2$) and cardiac cachexia increased mortality rate by 150% at 37.7 months. Melenovsky et al (2013) observed cardiac cachexia with right ventricular dysfunction *vs* non-cardiac cachexia with a normal right ventricle was a powerful predictor of adverse events in patients with heart failure (hazard ratio 6.7, 95% confidence interval 4.1–10.9, $P$<0.0001).

The prevalence of cardiac cachexia has improved with the introduction of new treatments and now is estimated to be 10.5% in stable heart failure patients (Christensen et al, 2013). Cardiac cachexia represents wasting across all body tissues although sarcopenia was initially described as being the critical trigger (Christensen et al, 2013). Fat mass loss has also been associated with cardiac cachexia (Melenovsky et al, 2013). Neurohormonal and inflammatory signals are also elevated in cardiac cachexia and have their own prognostic value in heart failure (Christensen et al, 2013, 2014; Melenovsky et al, 2013; Clark et al, 2014). Cardiac cachexia represents the critical step in the pro-catabolic transition of the body's metabolism in advancing heart failure, although the cross-talk of signalling demonstrates a heterogeneous picture of triggers and regulation. Further understanding is required.

## Conclusions

There is clear interplay between heart failure development and progression, and metabolism and body composition. The literature in this field is limited to small cohort or cross-sectional studies. The complexity of the interplay is clear and full understanding of development, regulation, progression and ultimately clinical value has yet to be achieved. The prognostic value of certain biomarkers and especially cardiac cachexia is critical in predicting adverse outcomes. The obesity paradox remains poorly understood and what it specifically represents is challenging. Further research within this field is needed to progress understanding, but the importance of this interplay cannot not be underestimated. **BJHM**

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