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Body mass loss is a surrogate marker of frailty in heart failure

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Heart failure (HF) is a common cause of hospitalization and death in older adults. The prognosis of patients with HF remains unfavorable despite recent developments in medical treatment. Management of risk factors is a first-line strategy to improve the prognosis. Well-established risk factors for HF include hypertension, smoking, diabetes mellitus, and obesity. Since the prevalence of overweight has increased over the last decades, the role of obesity is the focus of intense research. Body mass index (BMI) is one of the most commonly-used practical parameters for obesity. An increased BMI is believed to be associated with a higher rate of cardiovascular disease. Prior studies have reported an increased risk of HF with a greater BMI over 30 kg/m² [1]. However, an optimal BMI level to improve prognosis of HF patients has been controversial, as BMI is not a perfect measure of body fatness and does not distinguish between body fat and muscle mass.

Observational studies now suggest “obesity paradox” in HF. Obesity paradox is a concept that in patients with HF, an increased BMI is expected to be associated with a lower quality of life. But, contrary to this expectation, an increased BMI is associated with improved outcomes in HF. A meta-analysis confirms a U-shaped relationship; low body weight and extreme obesity are both dangerous at the nadir of risk at a BMI of 32–33 kg/m² [2]. This indicates that a high BMI may be a marker of better nutrition. HF often results in undernourishment and muscle wasting, which can be a strong risk factor for death. The term “sarcopenia” has been used as progressive loss of “skeletal muscle” mass. Cachexia, on the other hand, is the loss of “body weight” and generally defined as 5% unintentional weight loss in the previous 12 months in the presence of a chronic illness. Cardiac cachexia is closely linked to frequent hospitalization and mortality in patients with chronic HF: 50% at 18 months follow-up [3]. Differential diagnosis between cachexia and sarcopenia requires the use of imaging techniques, which may not be easy to perform in a daily clinical practice.

In the current issue of *International Journal of Cardiology*, Nishikido et al. describe a simple surrogate way to stratify the risk of cardiovascular mortality and hospitalization in patients with HF [4]. In their cohort study, patients (baseline BMI; 21 ± 0.4 kg/m²) who showed a

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significant decrease in BMI values had a higher frequency of subsequent hospitalization and cardiac death. The majority of patients were elderly (73 ± 11 year-old), as overall life expectancy is longer in Asian countries. Although BMI generally correlates with nutritional status, a previous report demonstrates the lack of sensitivity of BMI in patients with HF aged over 65 years [5]. Consistently, the BMI itself was not predictive of the primary outcome of all-cause mortality or all-cause hospitalization in this study. Instead, measuring BMI over the time course of HF became a marker of frailty, which avoided potential bias from a single-baseline measurement. A simple hypothesis is that patients who lost weight during the time period had a worse prognosis due to the presence of active sarcopenia or cardiac cachexia. BMI does not take into account differences in the proportion of fat to lean body mass. But, a reduction of BMI may reflect changes in a prognostic indicator of wasting process. Explanations include that the lack of a functional reserve in underweight patients led to unfavorable hemodynamic changes, which could make patients vulnerable to adverse complications. Thus, BMI may be considered as a follow-up value to monitor the progression towards sarcopenia and ultimately cardiac cachexia (Fig. 1). There are several strengths and limitations in this study. First, average follow-up duration was four years, which is relatively longer than many of previous studies on the same topic. Second, the study includes both HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF), which showed a similar tendency for the effect of a BMI loss on survival. However, the sample size was relatively small. Ideally, their results should be validated in larger study populations. The study was also performed in a single ethnicity, which limits its generalizability to other multiple ethnic groups. Lastly, it would be more informative if the potential influence of specific inflammatory or adipokine activity was evaluated.

Chronic HF-related muscle wasting is normally attributed to multiple factors with metabolic, immune and neurohormonal consequences. Numerous hormone systems contribute to the wasting process by changing energy expenditure. An imbalance in these hormone systems can be triggered by pro-inflammatory cytokines, which are often activated systemically in patients with HF. During the last decade, a negative regulator of muscle growth, myostatin (also termed growth differentiation factor-8), has received much attention. Myostatin is a member of the transforming growth factor (TGF)- β family expressed in skeletal muscle. In HF, the myocardium produces myostatin, which is associated with the skeletal muscle atrophy [6]. Pharmacologic inhibition of myostatin signaling has currently under investigation as a promising treatment of skeletal muscle wasting associated with chronic illness. Thus, it would be interesting to see whether changes of BMI are related to any effects of a myostatin inhibitor in patients with cardiac cachexia in the future.

In conclusion, the mechanisms involved in a reduction of BMI may play a role in the development of sarcopenia and cachexia in HF. A better knowledge of these mechanisms will be the basis for the prevention of cardiac cachexic death.

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Fig. 1.

A possible mechanism of body mass loss in heart failure (HF). A reduction of body mass index is a sensitive marker of the severity of HF which represents the basis of outcome. Water imbalance, malnutrition, pro-inflammatory cytokines, metabolic imbalance, all play a role in muscle wasting (sarcopenia) that develops cardiac cachexia. Changes of BMI over the course of disease have a prognostic value in established HF patients.