Does a reduction in anabolic signaling contribute to muscle wasting in chronic heart failure?

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CHRONIC HEART FAILURE (CHF) is a complex and prevalent disease affecting 2% of adults in developed countries. This number increases to 6–10% in adults over the age of 65 (3, 8), and on diagnosis, half of all CHF patients die within 4 years (11). In addition to the significant increase in mortality risk, CHF patients experience substantial declines in physical and mental health, the ability to perform activities of daily living, and, subsequently, have a decreased quality of life (6). A common comorbidity of CHF is the loss of metabolically active lean tissue, known as cardiac cachexia. Cachexia is not unique to CHF. Loss of skeletal muscle occurs with aging and is prevalent in AIDS, cancer, sepsis, and other chronic diseases. Depending on how cachexia is defined, this condition has been found in up to 50% of CHF patients, which is an important concern as the development of cardiac cachexia significantly increases risk of mortality (2, 6). Skeletal muscle mass increases or decreases depending on the balance between anabolic and catabolic stimuli, and the net muscle protein balance is influenced by a number of extrinsic and intrinsic factors, including Akt-mediated mammalian target of rapamycin (mTOR) signaling. For instance, phosphorylation of Akt (Ser473) is an upstream positive regulator of mTOR (an important pathway in the regulation of translation initiation and overall muscle size), but it also controls muscle protein breakdown by preventing the nuclear translocation of forkhead box O (FOXO) transcription factors, which facilitates ubiquitin ligase-mediated proteolysis (12). However, while CHF is not associated with any alterations in the FOXO-regulated genes atrogin and MuRF1 (9), it has previously been reported that CHF is associated with decreased expression of insulin-like growth factor-1 (IGF-1), a key upstream regulator of Akt signaling (1). Thus it is plausible that altered Akt/mTOR signaling may underlie CHF-related muscle loss, and by extension, the development of cardiac cachexia.

In this issue of the Journal of Applied Physiology, Toth and colleagues (17) provide novel data showing that basal Akt phosphorylation is decreased in CHF patients compared with healthy age- and physical activity-matched controls. Specifically, phosphorylation of Akt at Ser473 relative to total Akt protein expression (pAkt/Akt) was lower in CHF patients compared with control subjects, and positively correlated with myosin protein content. However, IGF-1 mRNA expression was not different between groups. The decreased phosphorylation of the Akt Ser473 site is indicative of decreased Akt activation, which the authors speculate may influence the downstream regulation of translation initiation and the rate of muscle protein synthesis. Unfortunately, the authors were unable to detect a signal for Akt phosphorylation at Thr308, but the authors did measure a number of downstream targets of this phosphorylation site, including mTOR and glycogen synthase kinase-3\(\beta\) (GSK-3\(\beta\)). Phosphorylation of mTOR stimulates protein translation via the downstream regulation of p70 ribosomal S6 kinase 1 (S6K1) and eukaryotic translation initiation factor 4E binding protein-1 (4E-BP1), while GSK-3\(\beta\) activates translation via the inhibition of eukaryotic translation initiation factor 2B (eIF2B). mTOR, S6K1, and 4E-BP1 phosphorylation tended to be lower in CHF patients but did not reach statistical significance. There was no difference between groups for GSK-3\(\beta\) phosphorylation. One likely explanation for why the authors report a significant reduction in Akt Ser473 phosphorylation (but only a nonsignificant trend for lower mTOR and S6K1 phosphorylation and no differences in IGF-1 expression) is the careful matching of the control subjects for age, muscle mass,
and physical activity. Previous studies did not account for muscle disuse (a common trait in CHF patients), but this is essential, as conditions associated with physical inactivity can reduce total Akt content and mTOR signaling in skeletal muscle (4). Another possibility is that the present study is insufficiently powered to detect group differences in a number of the variables measured. However, detecting differences in protein phosphorylation can be difficult in the basal, fasting condition. On the other hand, it may be more likely to detect group differences under anabolic conditions such as feeding and exercise. Overall, the findings of this study are essentially limited to the group difference reported in Akt (Ser473) phosphorylation. The difference in basal Akt phosphorylation between CHF patients and healthy controls is interesting and does provide preliminary evidence that muscle anabolic signaling appears to be reduced in CHF. However, given the absence of significant group differences in the phosphorylation of Akt-associated signaling proteins, it will be important for future studies to establish the precise role of reduced basal Akt signaling in the development of cardiac cachexia.

The loss of lean mass concomitant with CHF significantly worsens quality of life and mortality risk in CHF patients (2, 6), and uncovering the mechanisms underlying the development of cardiac cachexia is an important area of future research. The study by Toth et al. (17) represents an important first step toward identifying the cellular mechanisms that may contribute to, or serve as molecular biomarkers for the onset of this condition. It should be pointed out that in the fasted state (as the subjects were in the present study) muscle protein breakdown exceeds muscle protein synthesis, resulting in overall catabolism (i.e., net negative protein balance). This, however, is only half of the story, as skeletal muscle fluctuates between periods of positive and negative net balance throughout the day depending primarily on feeding and activity status. A molecular “next step” toward increasing our understanding of the molecular events that may influence CHF-related muscle loss is to focus on the influence of anabolic stimuli (e.g., feeding) in CHF patients as this may improve the ability to detect differences in anabolic signaling. For instance, when comparing healthy elderly and young subjects, basal muscle protein synthesis and Akt-mTOR signaling are essentially equivalent (5). However, recent studies have shown age-related differences in the response to anabolic stimuli such as exercise (5, 13), nutrition (7, 18), and insulin administration (10, 14, 15). Consequently, it has been proposed that an inadequate response to anabolic stimuli, rather than any intrinsic basal differences, may significantly contribute to age-related muscle loss (sarcopenia). It is reasonable to speculate that a reduced ability to respond to anabolic stimuli may also play a key role in CHF-related muscle loss (Fig. 1). Toth et al. (17) have provided good evidence of reduced anabolic signaling in skeletal muscle from fasted CHF patients, and it will be interesting to see if future studies in CHF patients also demonstrate an inability to respond to anabolic stimuli as detected in age-related sarcopenia.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES