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New Approaches to Treating Cardiac Cachexia in the Older Patient

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Abstract

Congestive heart failure (CHF) is a leading cause of morbidity and mortality in the elderly, accounting for more hospitalizations than any other condition. Advanced stages of congestive heart failure can be associated with serious complications such as cardiac cachexia (defined here as unintentional weight loss of more than 6% in 6 months). Cardiac cachexia and the associated progressive weight loss are sometimes overlooked by older patients, their families and care providers. A delay in the diagnosis can result in further loss of vital organ tissue, progressive weakness, fall-related injuries and even long-term care institutionalization and/or death. During the past several years, researchers have begun to broaden their understanding of this common, morbid and often fatal condition, and these findings will help to characterize the features that assist in its diagnosis, minimize its exacerbation, delay the progressive decline, and educate clinicians about the potential management options.

Keywords

congestive heart failure; weight loss; inflammation; muscle wasting; weakness; decline; catabolic state; sarcopenia; cytokines

Introduction

In the first reported observational study of cachexia on the island of Cos, Hippocrates (460–377 BC) observed that in patients with advanced CHF ‘the flesh is consumed and becomes water, ...the abdomen fills with water, the feet and legs swell, the shoulders, clavicles, chest and thighs melt away. ...This illness is fatal’. It has been proposed that in patients with CHF without signs of other cachectic states (e.g. cancer, thyroid disease, or severe liver disease), that clinical cardiac cachexia be defined as unintentional weight loss of more than 6% of the previous normal weight over 6 months. Heart failure is a condition in which the heart is unable to fill with or eject blood at a rate commensurate with the requirements of the body's metabolizing tissues (1-5). CHF impacts multiple body systems, including the vascular, musculoskeletal, neuroendocrine, renal, gastrointestinal, CNS and immune systems. The condition of cardiac cachexia usually occurs in the setting of chronic CHF, especially when

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Conflict of Interest
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there is right heart failure with tricuspid regurgitation and/or in severe, advanced stages of heart failure (5-7).

Epidemiology and Natural History

Severe CHF has been observed to be associated with progressive weight loss and emaciation in approximately 10–15% of the heart failure patients. CHF is a common problem and afflicts over 10% of older persons (1-8). The prevalence of CHF rises nearly exponentially with age, and from about age 55 years onward it doubles approximately every 10 years in men and every 7 years in women (1-3). Neuroendocrine and acute-phase reactant activation are associated with CHF progression and certain circulating proteins such as catecholamines, atrial natriuretic peptide, adiponectin and/or heat-shock protein levels are elevated in cardiac cachexia (1-14). The prognostic indicators of outcome in CHF include age, gender, CHF functional class, cardiac ejection fraction, duration of disease, VO_2 max, and/or low serum sodium. However, cardiac cachexia itself is a significant mortality risk in all patients with CHF, independently of the other prognostic indicators, and cachexia is usually an ominous sign in CHF patients, with an 18-month mortality of up to 50% (8, 15). Therefore, it would be helpful to identify factors that will help to reduce cardiac cachexia and the attendant mortality in seniors.

Pathophysiology

Although the exact mechanisms of how heart failure causes cardiac cachexia remain incompletely established, recent research has shed light on the potential etiologies. Possible contributing factors include (1) dietary deficiency, (2) malabsorption, (3) metabolic dysfunction, (4) loss of nutrients via urinary and/or gastrointestinal tract, and (5) imbalance between energy intake and expenditure, or anabolism and catabolism. It is thought that chronic CHF, especially in the presence of tricuspid regurgitation, may cause blood to back up from the right side of the heart into the liver and intestines. This passive congestion in turn would cause interstitial edema, hepatomegaly and ascites, which would then lead to decreased gastric volume with feelings of abdominal fullness, early satiety, nausea and decreased appetite.

In persons with severe heart failure, activation of the neuroendocrine factors such as catecholamines and of the proinflammatory cytokines such as TNF and other cytokines can further increase the metabolic rate of the tissues, thus burning more calories. The catabolic state associated with increased resting energy expenditure would then predispose some CHF patients to develop cachexia. Working to find ways to break this sequence is one of the research goals of a number of researchers. The findings will in the future help practioners and caregivers to better manage this condition in older persons.

Cytokine and neuroendocrine activation

Cachectic CHF patients tend to have increased blood levels of TNFα, interleukins 1 and 6, norepinephrine, epinephrine, cortisol, angiotensin II, renin and aldosterone (6-18). Growth hormone is often elevated but insulin-like growth factor 1 is usually inappropriately low in cachectic patients(20). The effects of the proinflammatory cytokines such as TNFα and interleukins 1 and 6 include proteolysis, apoptosis, muscle wasting and weight loss. The angiotensin II and aldosterone could also contribute to muscle wasting, apoptosis and fibrosis, through many mechanisms of activating the ubiquitin-proteasome system pathway. Angiotensin also increases TNF-α, IL-6, serum amyloid-A, glucocorticoids and myostatin, all of which regulate muscle protein synthesis and degradation (21). In addition, angiotensin inhibits IGF-1, which is the anabolic hormone that inhibits apoptosis (21). Researchers have

observed that IGF-1 is significantly correlated with muscle mass, and its local expression in muscle is very low in CHF patients with cardiac cachexia (7-21).

Muscle wasting and loss of muscle protein

Fatigue and muscle weakness are two of the most common complaints of CHF patients, and muscle atrophy is present in approximately two-thirds of patients with CHF (11-12). The exact stimulus for activation of protein degradation in cardiac cachexia is a current focus of interest. In other catabolic states or in cancer cachexia, ubiquitin levels in skeletal muscle have been reported to be increased. It is likely that the muscle wasting associated with cardiac cachexia may also be due to increased protein degradation, likely in part from activation of the ubiquitin–proteasome proteolytic pathways, as well as reduced protein synthesis (13-22). A central point of the molecular signalling associated with muscle breakdown occurs via inhibition of Akt which then causes dysrgeulation of Foxo and increased atrogin transcription (23-25). Another mechanism is via elevation of NF-κB which has been found particularly in cachectic muscles and is induced by any stimulus producing reactive oxygen species (23). The increased TNF-α or NF-κB results in downstream increased expression of ubiquitin ligases such as atrogin1 and MuRF-1 or MuRF2 (23-24). In a rat model of CHF, siRNAs against MuRF-1 resulted in reduced degradation of troponin 1 (24). Lysosomal degradation of muscle and autophagy which is generally employed by cells as a homeostatic mechanism for the degradation and recycling of proteins and organelles might be enhanced during the stress of cachexia (25). Other methods of muscle and protein degradation include mitophagy, which denotes autophagy of mitochondria, and is under Foxo control, is still being investigated in cardiac cachexia.

The gastrointestinal system in cardiac cachexia

The small and large intestines are highly vascularized, and receive their blood supply via the superior and inferior mesenteric arteries. The splanchnic circulation receives 25% of the total cardiac output, therefore the gut is the most intensively perfused organ at rest. The gut mucosa is the metabolically active part of the gut, and receives over 50% of the total resting organ blood flow. Impaired bowel perfusion could cause mucosal ischemia, acidosis, and increased permeability, or a ‘leaky gut’. The presence of mucosal injury resulting from ischemia in one of the extremities has been observed clinically, especially in those patients with diabetes and/or peripheral artery disease. In addition, gut mucosal ischemia and edema can reciprocally cause multiple-organ system failure (15-18).

Potential Therapeutic options

Improvement of bowel perfusion with agents such as inhibitors of angiotensin-converting enzyme or angiotensin receptor blockers could help to stabilize systemic hemodynamics and can also help to minimize or prevent mucosal injury. Bowel-wall ischemia and edema in CHF can often result in bacterial translocation, endotoxemia and immune activation. It is anticipated that therapeutic reduction of bacterial translocation might be achieved by increasing gut motility (e.g. metoclopramide or Reglan) or treating bacterial overgrowth (e.g. lactobacilli). It has been shown that in CHF patients with peripheral edema, the endotoxin levels were elevated, but that these levels could be normalized after intensive diuretic therapy. Lipoproteins such as cholesterol can bind to endotoxins and can potentially ameliorate some of the toxic effects of endotoxins. This could partly explain why low serum cholesterol is an independent prognostic factor for a poor outcome in CHF (17-20).

The influence of heart failure on the gastrointestinal system also includes protein loss from the gut (protein-losing enteropathy) and anorexia, especially in veterans with right heart failure. Attention must also be paid to ensure that the treatment of peripheral edema does not

result in salt depletion, electrolyte imbalance and/or dehydration. One must guard against hyponatremia as well as hypokalemia from diuretics, especially in the elderly, because of the age-related impairment in salt retention by the kidneys. Other possible therapies to treat cardiac cachexia may include agents that inhibit TNFα (such as pentoxyfylline), reduce C-reactive protein (such as statins in low doses), alter adiponectin or leptin levels, and/or bind endotoxin (such as lipoproteins). In addition, mental and flexibility exercises, such as yoga and/or meditation, may be helpful. Physical activity is associated with lower fasting insulin levels. The cardiac natriuretic peptides are known to regulate salt and water excretion by the kidneys, thereby playing an important role in blood-pressure control and volume homeostasis. Interestingly, overweight CHF patients have a better prognosis than underweight CHF patients, and the obese patients also have lower natriuretic peptide levels compared with underweight patients. The natriuretic peptides are also involved in fat-cell metabolism; they reduce leptin production, increase circulating free fatty acids and also increase insulin resistance (7-19).

Importance of Nutrition in Cardiac Cachexia

Some research teams have proposed that it would be extremely important to ensure that, in addition to the usual food intake, that the diet of the older adult with cardiac cachexia contains ample amounts of high caloric, high protein supplements, plus adequate sodium, potassium, calcium and magnesium as well as other micronutrients. Increased intake of fresh vegetables and fruits would also be helpful (10-19, 26-31).

Those dietary and lifestyle factors that are pro-inflammatory (i.e. raise C-reactive protein) should be avoided: for example, sugars, saturated fats, excess alcohol, cigarette smoking, sedentary lifestyle, and periodontal or gum disease. Trans-fats found in partially hydrogenated oils (e.g. margarine, vegetable shortening) should also be avoided (16-17, 26-31).

Those dietary and lifestyle factors that are anti-inflammatory (i.e. reduce C-reactive protein) should be recommended: for example, oily fish and fish oil supplements, olive, walnut or flaxseed oil, fruits and vegetables, garlic, ginger and turmeric (curcumin), sunflower seeds, eggs, herring, nuts or zinc tablets, pineapple or bromelain supplements, grape juice or red wine (small amounts), antioxidant supplements (e.g. vitamins C and E), *S*-adenosyl-methionine, α-lipoic acid, coenzyme Q10, mild to moderate exercise, abdominal fat reduction, stress reduction and regular teeth flossing. Green Tea (a strong natural anti-oxidant) may also be helpful. Foods and supplements that are rich in omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) tend to have a synergistic effect with drugs used for treating the major risk factors of CHF including hypertension and atherosclerosis, as well as coronary restenosis, stroke and CHF (16-17, 26-31).

Conclusions

Congestive heart failure is a complicated, dynamic disorder of many organ systems, including the myocardial, neurohormonal, immune, vascular, gastrointestinal, renal, CNS and musculoskeletal systems. It is the deterioration of this interactive, multisystem, network complex that results in the systemic inflammation and progressive wasting and atrophy of muscle and multiple other organ tissues, which is the hallmark of cardiac cachexia.

Cardiac cachexia may be associated with a low level of physical activity in the elderly with congestive heart failure. A high systemic inflammatory state is another marker of cardiac cachexia. Prudent anti-inflammatory nutrition in addition to the usual food intake, including ample protein and other supplements, active lifestyle and regular exercise can serve to

ameliorate and/or potentially prevent the progressive tissue wasting. In counselling older patients with CHF and cardiac cachexia, it is important to include the family and available community resources. The older person's caregivers need to appreciate the importance of 1) a high caloric, high protein diet plus supplements and 2) regular activity (both physical and mental) as significant parts of the patient's overall treatment plan for cardiac cachexia. Of equal importance is the maintenance of social involvement and psychological well-being. Micronutrient and vitamin supplements are also helpful, especially in patients with malabsorption secondary to CHF. Finally, the cornerstone in the prevention of cardiac cachexia remains the early diagnosis and prompt treatment of heart disease and the prevention of its progression to severe CHF.

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