The complex pathophysiology of cardiac cachexia: A review of current pathophysiology and implications for clinical practice

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ABSTRACT
Cardiac cachexia is a muscle wasting process that often develops in those with chronic heart failure resulting in weight loss, low levels of physical activity, reduced quality of life, and is associated with a poor prognosis. The pathology of cardiac cachexia is complex with new evidence emerging that implicates several body systems. This review describes the pathophysiology associated with cardiac cachexia and addresses: 1) hormonal changes - neurohormonal abnormalities and metabolic hormone imbalance; 2) mechanisms of muscle wasting in cardiac cachexia, and the integral mechanisms between changed hormones due to cardiac cachexia and muscle wasting processes, and 3) associated abnormalities of gastrointestinal system that contribute to cardiac cachexia. These pleiotropic mechanisms demonstrate the intricate interplay between the affected systems and account for why cardiac cachexia is difficult to manage clinically. This review summarises current pathophysiology of cardiac cachexia and highlights symptoms of cardiac cachexia, implications for clinical practice and research gaps.

Keywords: Cardiac cachexia; Heart failure; Muscle wasting; Weight loss; Malnutrition.

INTRODUCTION
There are multiple terms that identify nutritional status or diseases, such as malnutrition, sarcopenia, cachexia and muscle wasting. Malnutrition is the state of unmet nutritional needs leading to reduced fat free mass and body cell mass as a result of declined physical performance and mental ability, including worsening clinical profile from disease while sarcopenia develops with aging (primary sarcopenia) and factors in addition to ageing (secondary sarcopenia), such as organ failure,1 resulting in losing skeletal muscle mass combined with losing muscle strength and/or decreased physical performance.2 However, the definition of sarcopenia remains controversial as it is used for healthy ageing while sarcopenia in chronic disease leads to muscle wasting without the accompanying weight loss.3 Cachexia is defined as unintentional weight loss due to loss of any tissue caused by chronic disease4,5 that results in altered body compositions and imbalances of several body systems.6 It is worth noting that the term muscle wasting is recommended in conjunction with sarcopenia and cachexia.1

Cachexia develops in the advanced stages of chronic diseases, primarily in cancer and chronic heart failure (CHF), chronic kidney disease, and chronic obstructive pulmonary disease.7 When CHF related cachexia develops, it is known as cardiac cachexia (CC).1 It is estimated that 5-15% of advanced CHF patients have CC, and it is considered a serious complication with a poor prognosis.7 In addition, associated co-morbidities or sequelae of CHF, such as atrial fibrillation, lead to an increased risk of developing CC.8 The mortality rate of patients with CC has been reported to increase by 50% within 18 months of diagnosis and therefore is a major mortality risk.9

There are variations in reported prevalence of CC in the literature, reflecting a lack of consensus on the CC diagnostic criteria, with some studies applying 5% as a cut-off point of unintentional weight loss in a previous year as a main criteria,10 whereas others have employed ranges of 6%-7.5% as a cut-off points in 6 months.11 Interestingly, the retrospective study using results from studies that compared enalapril versus (vs) placebo (SOLVD)12 or enalapril vs the combination of hydralazine...
and isosorbide dinitrate (V-HeFTII) suggested that 6% weight loss within 1 year was the strongest predictor of reduced survival when compared to 5%, 7.5%, 10% and 15% weight loss and therefore 6% weight loss should be used as a cut-off point to identify CC. Indeed, the different treatments provided in SOLVD and V-HeFTII might affect the finding on the cut-off points of weight loss on mortality rates, and the study was underpowered to examine the differences between both groups.

Hence, although various cut-off points have been suggested, according to cachexia consensus, the former cut-off point of 5% weight loss within 12 months is recommended, and a person having two major and three minor criteria can be diagnosed cachexia (Table 1).

Therefore, CC is diagnosed by applying Evans et al (2008) diagnostic criteria. To date, there are no specific criteria for diagnosing CC.

### CHRONIC HEART FAILURE PATHOPHYSIOLOGY AND RELATIONSHIP TO CARDIAC CACHEXIA

CHF is caused by numerous pathologies due to abnormal structures and/or functions of the heart leading to increased intracardiac pressures and/or insufficient cardiac output at resting stage and/or during exercise causing poor perfusion to the vital organs including the kidneys, intestine and skeletal muscle. This in turn triggers neurohormonal abnormalities and immunological activation giving rise to an inflammatory process that leads to muscle wasting. There are several theories on how CC develops and manifests clinically, including poor gastrointestinal absorption, loss of nutrients in gastrointestinal tracts and imbalances of anabolism and catabolism.

The aim is to provide an evidence-based review of the pathology related to CC (in particular in relation to neural and metabolic hormones), how this relates to symptoms experienced by those with CC, and the implication for clinical practice, including the current gaps in research.

#### Table 1. Criteria for diagnosing Cardiac Cachexia major and minor criteria.

| Diagnostic Criteria for Cachexia | Major criteria | Minor criteria |
|---------------------------------|---------------|---------------|
| Chronic diseases, such as chronic heart failure, chronic kidney disease, etc. | Fatigue, anorexia | Decreased low fat-free mass index |
| Oedema-free body weight loss > 5% in the past 12 months or BMI < 20kg/m² | Haemoglobin ≤ 12 g/dl | Serum albumin ≤ 3.2 g/dl |
|                                 | Elevate C-reactive protein > 5.0 mg/l | Increase in interleukin-6 > 4.0 pg/ml |

Reference: Evans et al. (2008)

#### Table 2. Role of hormones and changes due to cardiac cachexia.

| Hormones | General roles | Changes of hormone levels due to cardiac cachexia | Conflicting findings |
|----------|---------------|-------------------------------------------------|---------------------|
| Neuropeptides | 1) Regulating blood volume and systemic vascular resistance. | Significantly increased levels of noradrenaline, adrenaline, AngII, aldosterone | N/A |
|            | 2) Increasing a release of catecholamines. | | |
| Glucocorticoids | 1) Maintaining physical functions under homeostasis; 2) Adjusting to changes of environments. | Significantly raised levels of cortisol were seen in patients with CC than without (p < 0.002). | N/A |
| Renin-Angiotensin system | | | |

(continued on next page)
Table 2. (continued)

| Hormones | General roles | Changes of hormone levels due to cardiac cachexia | Physiological Effects | Conflicting findings |
|----------|---------------|--------------------------------------------------|----------------------|---------------------|
| **Testosterone** | 1) Elevating protein synthesis; 2) Decreasing protein breakdown; 3) Stimulating cell regeneration in skeletal muscles. | Among CHF patients, low baseline levels of testosterone were reported. | A reduction in general metabolism linked to energy expenditure, fatigue, dyspnoea and cachexia in particular. | N/A |
| **Metabolite hormones** | | | |
| **Growth hormone** | 1) Anabolism and regulating energy stores; 2) GH mostly mediated to act by IGF-1, directly or indirectly. | - Low IGF-1 levels with raised GH level was reported in CHF. | A low anabolic rate and possibly a high catabolic rate results in muscle depletion. | N/A |
| | 1) Increasing appetite and GH; 2) Acting as vasodilation; 3) Cardio-protective; 4) Anti-inflammatory; 5) Increase gastric and intestinal motility. | - The ghrelin levels found to be significantly higher in CC patients than patients without CC. | Ghrelin potentially leads to muscle wasting in CC. | N/A |
| **Leptin** | 1) Decreasing appetite and lipid synthesis; 2) Increases in energy imbalance and thermogenesis. | In CC patients, levels of leptin have been reported lower than non-cachectic CHF patients. | Leptin impairs appetite and increases energy expenditure. | High leptin levels might be due to elevated energy expenditure, protective mechanism of leptin to the released TNF-alpha, and increased activation of SNS. |
| **Adiponectin** | 1) An anti-inflammatory, insulin-sensitising, and anti-atherogenic adipocytokine; 2) Acting on skeletal muscle by controlling glucose and lipid metabolism. | Adiponectin levels were significantly higher in patients with CC than without, and the level remained significant after adjusting for fat mass and BMI. | Increased energy expenditure leads to energy deficits resulting in weight loss in CC. | Low level of adiponectin recorded in diabetic patients with CHF regardless of heart failure stage. |
| **Myostatin** | Acting as a potent inhibitor of muscle growth. | Rising myostatin level from both myocardium of advanced heart failure patients and skeletal muscles due to prolonged cardiac stress contributing to rising circulating serum myostatin. | High levels of myostatin lead to skeletal muscle wasting. | Myostatin serum was reported lower in patients with CC than without and the reason behind this is that myostatin is mostly found in skeletal muscle rather than serum. |
| **Follistatin** | Increase muscle mass and strength. | No evidence directly linking CC to follistatin, however, follistatin is likely to relate to CC due to its antagonist of myostatin. | Inhibiting myostatin signalling in skeletal muscle. | N/A |

CC=cardiac cachexia, CHF=chronic heart failure, BMI=body mass index, TNF=tumour necrosis factor, SNS=sympathetic nervous system, AngII=angiotensin II, RAAS=renin-aldosterone-angiotensin system, GH= growth hormone, IGF-1=insulin growth factor 1, N/A= not available
THE CHANGES OF NEURAL AND METABOLIC HORMONES IN CHRONIC HEART FAILURE WITH CARDIAC CACHEXIA

There are two main categories of hormones that involve in the pathophysiology of CC; 1) neurohormones-renin-aldosterone-angiotensin system (RAAS), glucocorticoid hormones, testosterone (Table 2); 2) metabolic hormones- growth hormone, ghrelin, leptin, adiponectin, myostatin and follistatin. The changes of these hormones and their interactions lead to catabolic and anabolic imbalances that subsequently reduce muscle mass as a result in CC (Figure 1). The effects and levels of each hormone due to CC, including the conflicting findings have been reported in the literature.

MECHANISMS OF MUSCLE WASTING IN CARDIAC CACHEXIA

Protein degradation pathways

There are at least five main pathways of proteolysis: ubiquitin-proteasome pathway (UPP); Ca2+-dependent; lysosomal autophagy; caspase dependent; matrix metalloproteinases51 and mitochondrial dysfunction that can contribute to muscles wasting. This muscle wasting in CHF patients significantly impairs physical exercise tolerance52 and limits daily activities53 affecting quality of life. It is associated with frailty, and this in turn leads to an increased risk of falls and associated risk of fractures and as a consequence hospitalisation.54

UPP is activated by various models that results in muscle wasting.55 The nuclear factor-κB (NF-κB) transcription factor family facilitates the activation of UPP as a major process of muscle catabolism is reported with a recent model highlighting muscle wasting due to cytokines55 and the presence of reactive oxygen species (ROS).56 The muscle-specific E3 ligase; the components of the UPP, which has muscle ring finger 1 (MuRF-1) as a component,57 can also be stimulated by NF-κB.58 Although, they act via different pathways, activation of NF-κB increase MuRF-1 which mediates UPP, results in muscle wasting.56 A study reported that increases in MuRF-1 in skeletal muscle of CHF patients was significantly higher than in a healthy control group.59 Additionally, the activation of NF-κB can also be stimulated by activation of neurohormones: AngII,56 and aldosterone,51 and metabolic hormones: glucocorticoids51 and myostatin, including pro-inflammatory cytokines, such as IL-1β60 and in particular TNF-α,61 and high levels of these hormones and cytokines were observed among CHF with CC. Thus, together these mechanisms cause muscle depletion and atrophy seen in CC via activation of UPP, and CHF patients are highly likely to develop muscle loss.

Another important protein degradation pathway is lysosomal autophagy.57 Autophagy is a process that preserves protein homeostasis via lysosomal-dependent degradation, that breaks down long-lived protein, preventing accumulation of redundant or defective proteins.63 It has been suggested that the autophagy process might occur simultaneously with cachexia, resulting in muscle wasting.64

It was evident that mitochondrial dysfunction has a negative impact on both myocardium and skeletal muscles in CC. This might be due to decreased mitochondrial oxidative capacity as a result of reduced adenosine triphosphate (ATP)-energy carrier in cell and increased production of ROS as a consequence of the activation of the inflammatory process.65 In CHF, mitochondrial dysfunction plays an important role as its reduced function decreases the energy to support cardiac contraction and relaxation.66 Similarly, reduced mitochondrial oxidative capacity has been reported resulting in a decline of energy production in skeletal muscles in CHF.67 This process might be the reason behind HF-related to exercise intolerance due to mitochondria dysfunction,68 resulting in muscle wasting.

Apoptosis is identified as unwanted cells or damaged cells, such as cellular shrinkage, formation of apoptosis body.69 These are caused by caspase, a family of cysteine proteases, in other words, caspase-mediated apoptosis.69 Apoptosis and caspase-mediated apoptosis might be seen in CC due to its association with mitochondrial dysfunction.65 However, there were no differences in apoptosis between those with CC or without.70 Indeed, the collagen-causing fibrosis was significantly found in patients with CC compared to those without. Collagen accumulation leads to fibrosis in skeletal muscles resulting in muscle wasting related to exercise intolerance.70 Thus, protein degradation pathways appear to play a significant role in the muscle wasting process via several mechanisms.

Immunological activation

Cytokines, such as tumour necrosis factor (TNF) α, interleukin (IL)-1; IL-1α and IL-1β,71 IL-6, and interferon-γ which augments catabolism in the body are mainly produced by monocytes and macrophages.72 Endothelial cells and myocardium are also reported to release inflammatory cytokines, and the myocardial response leads to the hypothesis that hypoxia might lead to increased pro-inflammatory cytokine secretion in CHF, with the failing heart might be the major source of TNF-α.72 The release of these cytokines due to CHF can be as a result of homeostatic imbalance, activation of neurohormones; catecholamines, aldosterone, AngII73; and increasing levels of endotoxin such as lipopolysaccharides (LPS), resulting from bowel wall oedema and bacterial translocation.74 Interestingly, IL-1β increases levels of the adrenocorticotropic hormone and cortisol75 which may facilitate catabolism in cachexia (Table 2).76 TNF-α, IL-1 and IL-6 signal NF-κB76,77, and activation of NF-κB itself can also produce IL-1, TNF-α,78 IL-6 that can establish an autoregulatory feedback loop.78 IL-
6 could also be secreted by IL-1. All these cytokines trigger upregulation of the UPP increasing protein degradation and increased resting energy expenditure in CHF patients contributing to muscle wasting (which is seen in CC) as indicated in the protein degradation pathway section. TNF-α and other types of cytokines; IL-1, IL-6, also reduce appetite through the activation of anorexigenic agents; such as corticotropin-releasing factor, and inhibition of orexigenic neuropeptide-Y in hypothalamus. This means that a raise in TNF-α may cause an imbalance between energy consumption and expenditure. TNF-α is a fundamental cytokine that was found to significantly correlate with weight loss in CC patients (r = 0.78, p = .0003). The levels of TNF-α were significantly higher in CHF patients with CC compared to non-cachectic CHF patients, suggesting that TNF-α plays a role in inducing cachexia. As well as the effect of TNF-α on the muscles, it also increases gut permeability. In addition to TNF-α, the level of cytokines; IL-6, in the circulation increases significantly in CHF patients, with even greater levels noted in CC patients compared to non-cachectic CHF patients. Also, the elevation of IL-6 causes hypoferremia triggered by hepcidin-liver peptides that primarily control systemic iron balance produced by hepatocytes possibly leading to iron deficiency.

In conclusion, immunological activation in CC due to CHF can worsen muscle wasting through the protein degradation pathway and lead to an imbalance of catabolism and anabolism.

ABNORMALITIES OF GASTROINTESTINAL TRACT

CHF reduces cardiac output stimulating the SNS which results in a diversion of blood from the gastrointestinal tract to the core circulation. The reduction in systolic blood supply of 58%, 55% and 57% respectively to the celiac trunk, superior mesenteric artery, and inferior mesenteric artery in CC were reported compared to the control group. Reduced blood flow perfusion in the bowel causes mucosal ischaemia, acidosis, and elevated epithelial permeability or a 'leaky gut'. These physiological responses in the gastrointestinal tract may be responsible for bacterial translocation leading to endotoxin release and immune activation. Gram negative LPS-endotoxin is a strong inducer of pro-inflammatory cytokines, particularly TNF-α, and antibody Immunoglobulin A (IgA). In addition, the release of IgA; activation of immunological defence, was found to be responsible for an increase in juxtamucosal bacterial concentration with bacterial attachment to biofilm. This might further augment systemic inflammation in CHF.

Besides the rise in LPS, increased venous congestion due to CHF also causes bowel wall oedema. This bowel wall oedema is found between the intestinal epithelium and mesenteric capillary that increases the gap between capillary wall and enterocyte membrane in all parts of the intestine in heart failure. The greatest distance between the basal wall of the enterocyte and the capillary wall and highest collagen content of the mucosal wall in small intestines were seen in CC patients

FIG. 1. The diagram illustrates the complex pathophysiology of cardiac cachexia.
pared to CHF patients without CC and healthy control.\textsuperscript{90} These physical bowel changes are thought to be the causes of reduced iron absorption\textsuperscript{16} leading to ID,\textsuperscript{91} protein, fat and possibly medicine absorption in patients CC than without.\textsuperscript{90}

The occurrence of paracellular passive permeability together with altered intestinal bacteria further deteriorates gut permeability.\textsuperscript{92} Increased gut permeability results in poor absorption of carbohydrates in the form of lactulose/mannitol and sucralose.\textsuperscript{92} These findings support the presence of bowel wall oedema and increased gut permeability resulting in CC due to impaired nutrient absorption, contributing to accelerated catabolic process.

CARDIAC-CACHECTIC SYMPTOMS AND MANAGEMENT

Clinically, changes in the gastrointestinal system cause abdominal discomfort\textsuperscript{15} together with the changes in numerous hormones as mentioned above (growth hormone, leptin, ghrelin, and alterations of smell and taste perception),\textsuperscript{15} increases the likelihood of heart failure patients experiencing lack of appetite or worsening appetite in CC.\textsuperscript{85} Gastrointestinal symptoms such as severe nausea or vomiting and burping, have been observed in CHF with CC.\textsuperscript{93} The worsening of these symptoms have a negative impact on nutrient intake, adding to the catabolic and anabolic imbalance.\textsuperscript{93} ID due to CHF results in reduced physical activity as seen with 6-minute walking test compared to non-ID group (p<0.001).\textsuperscript{95} This impaired physical activity together with the activation of chronic inflammatory process in HF\textsuperscript{16} and protein degradation pathway might worsen exercise tolerance among CC patients causing fatigue and muscle depletion.

IMPLICATION FOR CLINICAL PRACTICE AND FUTURE RESEARCH DEVELOPMENT

The literature review has highlighted the variance in reported diagnostic cut off points leading to conflicting prevalence and survival rates. This variance has led to a lack of consensus on the severity of CC and treatments. The recent consensus on the cachexia diagnostic criteria\textsuperscript{15} needs to be adapted so that early detection can be optimised which has the potential to reduce mortality.\textsuperscript{54}

There is an under-diagnosis and under-assessment for cachexia or muscle wasting in patients with cardiovascular disease.\textsuperscript{55} This is likely due to oedema masking true body compositions. Expensive anthropometric measurements such as DEXA and MRI are also not always available.\textsuperscript{1} Cancer services have addressed this with a simplification for diagnosis, but this has not been validated in HF patients.\textsuperscript{96}

Muscle wasting can be accelerated via SNS activation along with increasing levels of catecholamines and RAAS that are evident in HF and therefore early medication initiation with ACEIs\textsuperscript{97} and beta-blockers\textsuperscript{98} have the potential to slow down the muscle wasting process.

Parenteral ghrelin administration shows promising results in CC patients with positive effects on lean body mass, muscle strength, improvement of cardiac structure and function, reducing norepinephrine, epinephrine and BNP.\textsuperscript{99} Similarly, in a meta-analysis study of cancer-related cachexia, the oral form of ghrelin agonist; anamorelin, demonstrated statistically significant increases in body lean mass (and total body weight).\textsuperscript{100} Currently, anamorelin is in clinical trial phase III with results expected.\textsuperscript{101}

Iron deficiency in CHF and CC should be treated with intravenous iron showing significant improvements in exercise tolerance using the 6 minute walk test (p<0.0001).\textsuperscript{102} Although the European Society of Cardiology (ESC) Guidelines recommend ferric carboxymaltose in acute and chronic HF to improve symptoms, physical performance and quality of life in patients with HF and LVEF ≤ 45%,\textsuperscript{16} evidence is lacking for its use in CC.

The pharmacological target to treat cachexia is now the Act-R ligands due to its effect on activated muscle wasting.\textsuperscript{101} In the RCT study, bimagrumab; the inhibitor of ActRIIA and ActRIIB, was tested in elderly with sarcopenia which reported bimagrumab significantly increasing lean muscle mass (P<0.001) but no significant changes in physical performance (P > 0.05) when compared to control group.\textsuperscript{103} Further studies on bimagrumab in CC patients are required.

IL-1 signal blockade may be a reasonable target for muscles wasting caused by chronic disease\textsuperscript{104} with evidence of decreased levels of CRP and IL-6 with IL-1 blockade-anakinra.\textsuperscript{105} This is in line with the recent conference presentations suggesting that IL-1 signalling pathway blockade may reduce inflammatory markers.\textsuperscript{101}

Bowel wall oedema can cause poor nutrient absorption due to bacterial translocation, and elevating bowel movement (using metoclopramide) or curbing bacteria overgrowth (using lactobacilli) could indirectly decrease bowel wall oedema as a result in improved food absorption.\textsuperscript{11} Prescribing antibiotics to reduce intestinal bacterial translocation is not advised with the adverse effects on the gut microflora.\textsuperscript{106} Undoubtedly, this area of research will continue as we understand more about the gut microbiome.

Testosterone can be used to improve muscle strength and exercise capacity but its associated increase in cardiovascular adverse effects cannot be ignored, especially when orally administered.\textsuperscript{107}

The combination of nutritional support and aerobic exercise should be provided as it might be appropriate to manage CC symptoms. This is because dietary support; high calories and protein supplements, help to compensate excessive catabolism and build the muscle\textsuperscript{108} while the latter restores the proteasome overactivation and protect the oxidation stress and UPS overactivation\textsuperscript{109}.
as bowel oedema can be decreased with improved food absorption, and as a consequence a reduction in muscle wastage. Likewise, exercise-based cardiac rehabilitation is recommended in the ESC heart failure Guidelines. Branched-chain amino acids (BCAA) with provided resistance exercise training have shown significant improvement of HF symptoms- dypnone and fatigue when compared to the group with exercise alone while another study by Azhar et al. (2020) reports a significant reduction of pulse pressure and heart rates and improved exercise tolerance using whey protein with exercise training compared to whey protein alone and (p < 0.05). This approach of nutritional and physical training support has potential but larger randomised control-trial studies are needed.

Fish oil-omega-3 polyunsaturated fatty acids; PUFA-, containing rich protein, rich calories, nutritional supplements and important amino acid have been used in CC patients and shown to reduce TNF-α. PUFA together with BCAA have potential benefits but extensive evidence is currently lacking.

There is a need to involve the multidisciplinary team with the cardiologist, physiotherapist, dietician, pharmacologist and cardiac nurse, to provide comprehensive care and treatment to HF patients with CC and has the potential to improve self-management as seen in HF.

CONCLUSIONS

This review has demonstrated the complexity of the pathophysiology of CC in relation to heart failure that is primarily driven by neural and metabolic hormonal changes, the activation of inflammatory process due to cytokines, protein degradation and abnormal gastrointestinal systems leading to a multitude of symptoms. The understanding of pathophysiology of CC can play a role in developing beneficial treatments and this review highlights the lack of robust evidence to support any one treatment.

The immediate priority is to improve the assessment and diagnosis of CC as early detection allows for early treatment and optimisation of medications etc as well as promoting a multidisciplinary approach to managing this complex condition. The development of effective evidenced-based CC treatments is urgently needed.

AUTHORS CONTRIBUTIONS STATEMENT

Jeniratchaya Thanapholsart, Dr Ehsan Khan, Dr Teflik F. Ismail and Dr Geraldine A. Lee desinged the concept of the work, methodology and the diagram of pathophysiology of CC; Jeniratchaya Thanapholsart wrote the original draft, drew the orginal diagram, performed data curation and formal analysis. Dr Ehsan Khan, Dr Teflik F. Ismail and Dr Geraldine A. Lee supervised and substantially reviewed and edited the work and the diagram.
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