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GLOBAL CARDIOLOGY
Global Cardiology 2024; **4**
Published online 30 December 2024 | **DOI**: 10.4081/cardio.2024.57

ARTICLE

The muscle hypothesis of shortness of breath in patients with cachexia

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Abstract

Cachexia is a major contributor to dyspnea (shortness of breath), particularly in conditions like heart failure and chronic obstructive pulmonary disease (COPD) with a prevalence of up to 100%, but also develops frequently in patients with chronic kidney disease (circa 60%) as well as in advanced cancer with an estimated prevalence of about 50% in patients in palliative care settings. In all conditions muscle wasting impacts respiratory function and exercise capacity. The muscle hypothesis of the development of shortness of breath in cachexia presented here provides a pathophysiological framework for understanding muscle wasting induced dyspnea. Persistent systemic inflammation, elevated cytokines such as tumor necrosis factor-alpha and interleukin-6, and hormonal imbalances like insulin resistance drive a catabolic state, resulting in skeletal muscle myopathy and respiratory muscle fatigue. This contributes to hyperactivation of the metabo-ergoreflex, a cardiorespiratory reflex involving mechanoreceptors and metaboreceptors. The hyperactive reflex increases ventilatory drive, exacerbating dyspnea, and triggers sympathetic excitation, leading to vasoconstriction and reduced peripheral blood flow. These mechanisms create a feedback loop of worsening myopathy, reduced exercise tolerance, and heightened breathlessness. In specific diseases, cachexia-related muscle wasting amplifies dyspnea through disease-specific mechanisms. In advanced cancer, dyspnea affects up to 80% of patients and is often caused by respiratory muscle fatigue, independent of cardiopulmonary pathology in 24% of cases. In heart failure, muscle wasting worsens dyspnea beyond reduced cardiac output and pulmonary congestion, with mortality increasing by 50% within 18 months in cardiac cachexia. COPD cachexia impairs respiratory muscles, independently predicting mortality beyond airflow obstruction. Current management of cachexia includes nutritional support, physical activity, pharmacological agents, and experimental therapies targeting inflammation, cytokines, and anabolic pathways. Despite these efforts, cachexia remains largely irreversible. Future directions include precision diagnostics leveraging artificial intelligence and interdisciplinary therapeutic strategies aimed at mitigating its devastating impacts on morbidity, mortality, and quality of life.

Key words: heart failure; cachexia; dyspnea.

Received: 16 December 2024; Accepted: 17 December 2024.
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Cachexia epidemiology and presentation

With a prevalence of 9 million patients globally and an annual death rate of 2 million patients worldwide, cachexia is a significant contributor of morbidity and mortality.[1,2] Cachexia is a common complication across nearly all advanced-stage chronic diseases, with its occurrence and mortality rates varying by condition.[3] The prevalence rises to 50% in chronic kidney disease (CKD) and is highest in advanced malignancies, where it impacts 50% to 80% of patients. Cachexia also carries

significant prognostic implications, with one-year mortality rates of 15–25% in COPD, 20–40% in advanced HF, and 20% in CKD.[3] In cancer, mortality ranges widely from 20% to 80% depending on the type and stage, while severe RA with cachexia has a comparatively lower one-year mortality rate of 5%.[3]

The diagnostic criteria for cachexia vary from general to disease specific and include relevant weight loss in individuals with chronic illness (e.g. 5% or more within the past 12 months), accompanied by at least three of the following five criteria: fatigue, reduced muscle strength, a low fat-free mass index, anorexia, and/or abnormal biochemical markers, such as hemoglobin levels below 12 g/dL, serum albumin below 3.2 g/dL, elevated interleukin-6, or increased C-reactive protein.[4] Clinical presentation of cachexia, including impaired exercise capacity, shortness of breath, malaise, fatigue and depression very closely mimic the symptoms of heart failure (HF) patients. Dyspnea, in particular, is a prevalent problem in both cancer (~50%) and HF (up to 100%) patients.[5] With the established predominance of cachexia in these patient populations, it is important discussing the pathophysiology of how cachexia causes or worsens shortness of breath.

Muscle hypothesis of shortness of breath

Cachexia is a complex syndrome resulting from systemic inflammation, neurohormonal dysregulation, and metabolic disturbances. Key pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF) and interleukin-6 (IL-6), are central to driving skeletal muscle atrophy and fat loss.[6] Several metabolic alterations are seen in cachexia, such as insulin resistance, increased cortisol, and hormone resistance syndromes; lack of anabolism; and iron deficiency.[7,8] These result in anabolic-catabolic imbalance, resulting in a persistent catabolic state. Muscle wasting results in physical frailty, inactivity and further exacerbates skeletal muscle myopathy. This muscle hypothesis of persistent catabolism and lean mass myopathy can result in metabo-ergoreflex.[5] The ergoreflex is compromised of the mechanoreflex, activated by muscle contraction and metaboreflex, which is stimulated by metabolites which accumulate during physical activity in skeletal muscle. Skeletal myopathy observed in cachexia results in metabo-ergoreflex hyperactivity.[9] The marked peripheral muscle mass depletion seen in cachexia is directly correlated to ergoreflex overactivity and exercise intolerance.[10] This results in both increased ventilatory drive, which directly causes shortness of breath, and also leads to excitation of the sympathetic nervous system.[11] The resulting vasoconstriction, coupled with endothelial dysfunction that is often seen in chronic inflammatory states, results in decreased peripheral blood flow to already myopathic muscles, resulting in a positive feedback loop and worsened exercise capacity and shortness of breath.[12] This is further evidenced by the correlation of dyspnea with loss of quadriceps strength and function, evidenced by an increased likelihood of moderate-to-severe exertional dyspnea in patients with poor performance on a single chair stand.[13] The muscle hypothesis is summarized in Figure 1.

Dyspnea in specific diseases

Shortness of breath in cachectic patients with advanced chronic diseases can thus, in part, be explained by the muscle wasting and resulting derangements. Dyspnea is a frequent and devastating complication in cancer, with a prevalence of 21-79% of advanced cancer patients.[14] The primary causes of dyspnea in cancer include an increased chemical or neurological drive to breathe due to stimulation of chemoreceptors; increased work of breathing, due to concomitant cardiac failure or pleural effusions from lung metastases; and reduced neuromuscular strength, often resulting from muscle wasting that affects the respiratory musculature.[15] Respiratory muscle fatigue is the predominant driver of dyspnea in cancer cachexia. This is supported by the absence of any cardiopulmonary disease in 24% of cancer patients exhibiting shortness of breath.[16]

Cardiopulmonary exercise testing is a vital assessment tool in monitoring disease progress in heart failure. Measures of physical capacity such as peak oxygen consumption (peak VO_2) are prognostic indicators of the disease.[17] With muscle wasting seen in cardiac cachexia, the resulting dyspnea is contributed not only by the underlying HF, reduced cardiac output, and pulmonary congestion, but is also largely enhanced by respiratory fatigue and skeletal myopathy.[16] Interestingly, in patients with cachexia and cardiac cachexia, fat accumulation provides benefit and obesity plays a protective role.[18] The mortality rate of patients with cardiac cachexia may increase by 50% within 18 months of diagnosis and therefore is a major mortality risk.[19]

Although COPD patients have primary pulmonary disease resulting in poor ventilation and resulting dyspnea, COPD patients with cachexia have concomitant muscle fiber atrophy which can involve respiratory muscles and the diaphragm.[20] Muscle wasting is common in COPD and significantly impacts patients by impairing skeletal muscle function, reducing exercise capacity, and lowering overall health status.[21] Furthermore, muscle wasting serves as an independent predictor of mortality in COPD, separate from the degree of airflow obstruction.[22]

Dyspnea significantly impacts patients with CKD, with a prevalence as high as 60%, which only partially improves with renal replacement therapy.[23,24] Studies suggest that protein-energy wasting seen in CKD, and a strong predictor of mortality, is part of a continuous process that leads to cachexia in these patients.[25] Patients with CKD and high levels of high sensitivity C-reactive protein, depicting systemic inflammation, also have lower muscle mass and impaired pulmonary function.[26] Similarly, dyspnea prevalence can be as high as 88% in end-stage liver disease, and closely correlates with respiratory muscle strength.[27]

Clinical implications and future direction

Due to the high prevalence and mortality of cachexia and due to its significant role in driving shortness of breath in chronic illness, it is imperative to have early recognition and timely interventions to improve outcomes. Although the diagnostic criteria has been discussed earlier, nutritional and body assessments are not common in clinical practice. In recent years, many chronic diseases are being targeted for the development of artificial intelligence in enhancing early diagnosis.[28] Early machine learning models for detecting cachexia and pre-cachexia show promise, though more research is needed to assess their external validity.[29]

Effective management of cachexia involves multimodal strategies targeting its multifactorial nature. Several papers have summarized current modalities and ongoing areas of research, including nutritional support, physical activity and exercise regimens, pharmacological agents targeting cytokines, appetite stimulators, anabolic hormones and immunological agents.[30,31] Despite the various therapeutic strategies, cachexia remains largely irreversible. Due to the complexity of cachexia, its prevalence, high mortality and significant contribution to shortness of breath, research towards multi-disciplinary therapeutic strategies is needed to mitigate the disease.

Contributions

All authors made a substantive intellectual contribution, s read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

SDA reports grants and personal fees from Vifor and Abbott Laboratories, and personal fees for consultancies, trial committee work and/or lectures from Actimed, Astra Zeneca, Bayer, Boehringer Ingelheim, Brahms, Cardiac Dimensions, Cardior, Cordio, CVRx, Cytokinetics, Edwards, Farraday Pharmaceuticals, GSK, Impulse Dynamics, Lilly, Mankind Pharma, Medtronic, Novartis, Novo Nordisk, Occlutech, Pfizer, Regeneron, Relaxera, Repairon, Scirent, Sensible Medical, Vectorious, and V-Wave. Named co-inventor of two patent

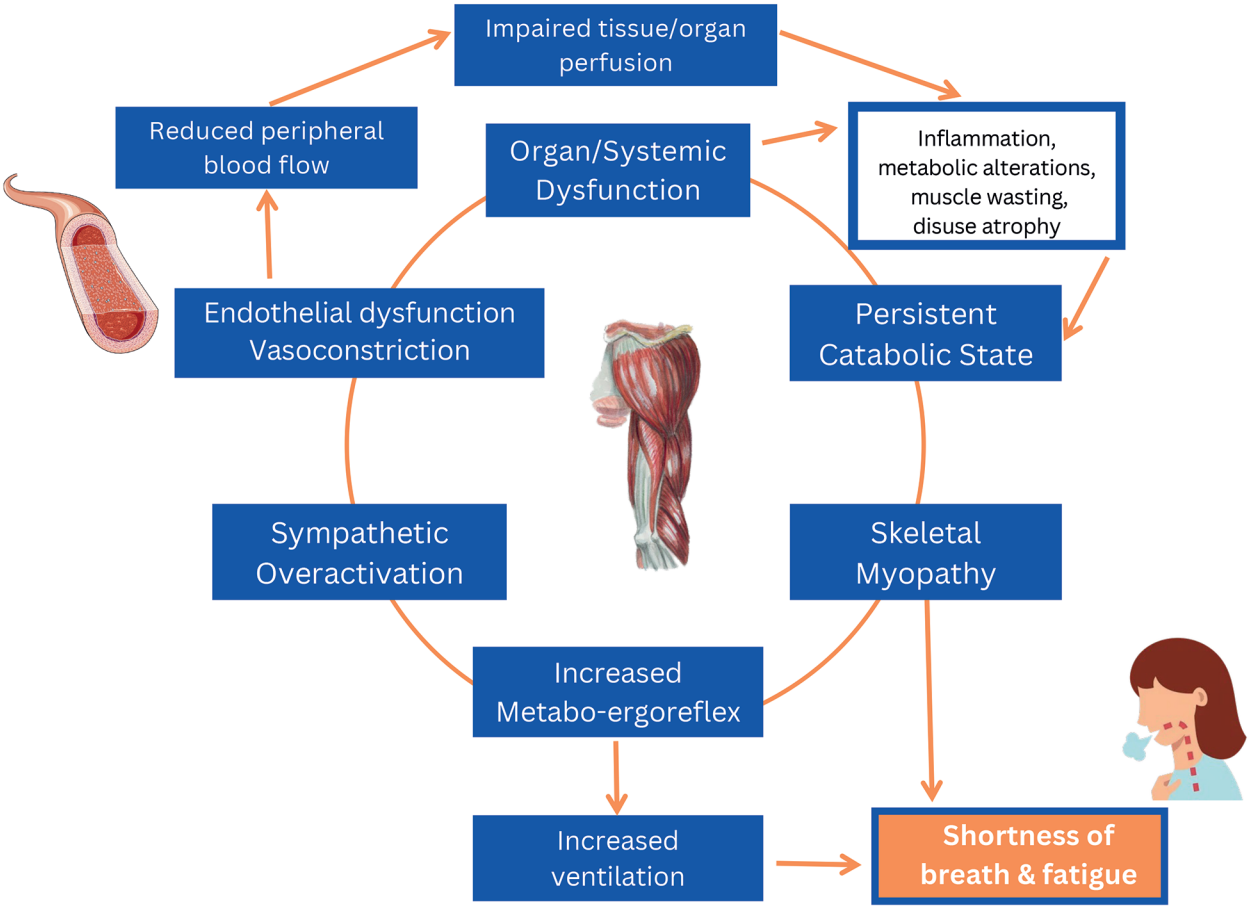

Figure 1. Muscle hypothesis of shortness of breath in cachexia.

applications regarding MR-proANP (DE 102007010834 & DE 102007022367), but he does not benefit personally from the related issued patents. MSK received fees from Bayer and Novartis. LAK and GMCR have no disclosures to report. ML reports grants from Slovenian Research Agency and honoraria from Novartis, Boehringer Ingelheim and AstraZeneca. MV reports no conflict of interest. PP reports grant from Vifor Pharma and consulting fees and/or honoraria from Boehringer Ingelheim, AstraZeneca, Vifor Pharma, Servier, Novartis, Berlin Chemie, Bayer, Abbott Vascular, NovoNordisk, Pharmacosmos, Moderna, Pfizer and Abbott Vascular and fees for trial committee work from Boehringer Ingelheim, Vifor Pharma, NovoNordisk, Pharmacosmos and Moderna. AJSC reported honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Menarini, Novartis, Nutricia, Servier, Vifor, Abbott, Actimed, Arena, Cardiac Dimensions, Corvia, CVRx, Enopace, ESN Cleer, Faraday, Gore, Impulse Dynamics, Respicardia, and Viatris.

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