Cachexia: Common, Deadly, With an Urgent Need for Precise Definition and New Therapies

Mitja Lainscak, MD, PhD,[a,b,*] Gerasimos S. Filippatos, MD,[c] Mihai Gheorghiade, MD,[d] Gregg C. Fonarow, MD,[e] and Stefan D. Anker, MD, PhD[a,f]

Cachexia—sometimes also referred to as wasting disease, malnutrition, or hypercatabolism—has been described for centuries and has always raised ominous thoughts that "the end is near." The disease is encountered in many malignant and nonmalignant chronic, ultimately fatal, illnesses. Yet, although cachexia is a deadly syndrome, little is known about its pathophysiology, and the debate regarding its definition is ongoing. Thus, the data on epidemiology can be contested, but a few things are certain: Cachexia is associated with exceedingly high mortality once the syndrome has fully developed, irrespective of the definition we apply, and it is associated with weakness, weight loss, muscle wasting, and inflammation. It is not simply an ancillary event, and it may contribute to the death of the patient either through effects on neuroendocrine and immune defense mechanisms or through protein calorie malnutrition. The therapeutic standard of care for cachexia remains undefined to date, with a few exceptions. Among the recognized approaches, exogenous oral amino acid supplementation appears very promising. Further research efforts are needed and they are ongoing. **(Am J Cardiol 2008;101[suppl]:8E–10E)**

Over the course of a lifetime, many individuals experience reductions of body weight and/or a change of body composition, which in healthy people is mainly deliberate and motivated by aesthetic impulses. The goal to significantly lose weight, however, frequently is not reached. Although remaining in a healthy weight category is associated with longevity in middle-aged adults, this equation is altered when applied to the elderly and chronically ill.[1] Chronic illness, particularly in advanced stages, frequently results in reductions in body weight and alterations in body composition, and this can lead to a syndrome known as cachexia.[2–4] Although described for centuries, clinical science continues to have many questions and few answers regarding cachexia.

Currently it is acknowledged that cachexia is a complex syndrome, frequently present in various chronic diseases. It is estimated that >5 million persons in the United States are affected by this syndrome.[5] There is no single cause of cachexia, and most of the current knowledge is derived from the advanced stages of various chronic illnesses, including chronic heart failure (CHF), chronic obstructive pulmonary disease, and chronic kidney disease.[6–9] Although completely different at first sight, these diseases actually share many pathophysiologic mechanisms, including neuroendocrine abnormalities, inflammatory system activation, increased lipolysis, and muscle wasting.[10,11] Additionally, lack of appetite and malabsorption also play a role, but the importance of individual pathways and the exact interplay between them remains unknown. Over time, however, a process of weight loss with pathologic wasting of muscle or muscle and fat tissue ensues. Finally, in CHF, cachexia (ie, cardiac cachexia) develops, reaching a prevalence of approximately 10% to 15% in patients with New York Heart Association (NYHA) class II–III CHF with a left ventricular ejection fraction <0.35.[12] These patients frequently die within months or years; indeed, the 18-month mortality rate in patients with cardiac cachexia reaches up to 50% compared with 17% in patients with CHF without cachexia.[13] Interestingly, treatment with β-blockers and angiotensin-converting enzyme inhibitors in heart failure (HF) not only improves outcomes[14] but also protects against tissue wasting.[15]

At this stage, the vital question to be answered is the basic one: How should we define cachexia? Diversity of weight and body composition changes makes it difficult to adopt a single universal definition. Furthermore, some con-

[a]Division of Applied Cachexia Research, Department of Cardiology, Campus Virchow Clinic, Charité–Universitätsmedizin Berlin, Berlin, Germany; [b]Department of Internal Medicine, General Hospital Murska Sobota, Murska Sobota, Slovenia; [c]Department of Cardiology, Heart Failure Unit, Athens University Hospital Attikon, Athens, Greece; [d]Division of Cardiology, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA; [e]Ahamanson-UCLA Cardiomyopathy Center, UCLA Medical Center, University of California-Los Angeles, Los Angeles, California, USA; and [f]Department of Clinical Cardiology, National Heart and Lung Institute, Imperial College School of Medicine, London, United Kingdom.

Statement of author disclosure: Please see the Author Disclosures section at the end of this article.

*Address for reprints: Mitja Lainscak, MD, PhD, Department of Internal Medicine, General Hospital Murska Sobota, Dr. Vrbnjaka 6, SI-9000 Murska Sobota, Slovenia.

E-mail address: mitja.lainscak@guest.arnes.si.

0002-9149/08/$ – see front matter
doi:10.1016/j.amjcard.2008.02.065

fusion is caused by lack of agreement on the terms used to describe wasting. The scientific community frequently (mis) uses the terms "cachexia," "anorexia," "sarcopenia," "malnutrition," and even "hypercatabolism" as synonyms. *Sarcopenia* (aging-associated "normal" muscle wasting),[16] for instance, may not be associated with significant weight change because the loss of muscle mass is counterbalanced by gains in fatty tissue. In *anorexia* (the term describes the loss of appetite, ie, a symptom), the bulk of the weight loss may be owing to consumption of fat for energy yield rather than muscle tissue loss. The term malnutrition is even more problematic because it is often used when cachexia is meant. *Malnutrition* suggests that the disease is associated with nutritional problems or failure, and it implies that it can be cured by adequate nutrition. It is a characteristic of cachexia that it cannot be cured by nutrition alone.[17] The term *hypercatabolism*, finally, is difficult for a practicing clinician to apply for 2 reasons. First, it generally nonidentifiable by clinical examination. Second, it neglects the other side of the equation in cachexia pathophysiology, namely lack of anabolism, which itself recently was shown to be related to poor outcomes in CHF[18] and is a key component of catabolic/anabolic imbalance in HF, which seems to be a key issue for the development of body wasting in cardiovascular illness.[19,20]

We are proponents of a clinical definition of cachexia that can be implemented in clinical practice to readily identify patients with this syndrome. The definition thus should not rely on the use of complicated tests or devices. Yet, it should be evidence based and the criteria should be validated as having prognostic significance. Indeed, the documentation of nonedematous weight loss of >6% of total body weight over a period of ≥6 months was the best predictor of mortality in a large cohort of patients with HF[12]; this study supports 2 core issues of cachexia: the weight loss itself, and, even more important, the dynamics of weight change. The latter was frequently neglected in earlier studies, leading to underestimation of cachexia prevalence and severity.[1,3,4] However, besides weight changes, low body mass index can predict poor outcome in patients after myocardial infarction[21] or in acute HF as well as in CHF.[22] An interesting approach for cancer cachexia was recently reported. Fearon and colleagues[23] evaluated a 3-factor profile of weight loss (≥10%), low food intake (≤1500 kcal/day [1 kcal = 4.2 kJ]), and systemic inflammation (C-reactive protein ≥10 mg/dL), and showed a better prognostic yield than for weight loss alone. These findings, which are in accordance with a previous report using a score of clinical and laboratory parameters in patients with HF,[24] probably set the stage for an agreement on the basic criteria for a global cachexia definition. Efforts to reach a consensus on the definition of cachexia are underway (see www.cachexia.org).

Cachexia in cardiovascular illness unfortunately remains without specific treatment. Once the global definition for cachexia (ie, wasting disease) in cardiovascular illness and beyond is adopted, intensified therapeutic efforts will be urgently needed. We hope that future therapies will be able to stop or even reverse the deadly cascade of events leading to full-blown cachexia and improve the quality of life and clinical outcomes for our patients. Currently, no approved therapies for cachexia exist, apart from growth hormone and some appetite stimulants in acquired immunodeficiency syndrome–induced cachexia. Nonetheless, causative therapy is still not available, although some potential candidates have been tested.[20,25,26] Among them, exogenous oral amino acid (AA) supplementation appears very promising. AAs stimulate muscular protein synthesis and mitochondrial biogenesis and improve energy performance in wasting syndromes. Intriguing clinical and basic science results are summarized elsewhere in this supplement. We hope to stimulate new developments in the field, including evidence-based treatments for cachexia. Great efforts in basic and clinical science are underway, and the results are eagerly awaited.

Author Disclosures

The authors who contributed to this article have disclosed the following industry relationships:

Mitja Lainscak, MD, PhD, has no financial arrangement or affiliation with a corporate organization or a manufacturer of a product discussed in this supplement.

Gerasimos S. Filippatos, MD, has received research/grant support from GlaxoSmithKline, Medtronic, Inc., Otsuka Pharmaceutical Co., and Vifor International Inc.

Mihai Gheorghiade, MD, serves as a consultant to Debbio Pharm, ErreKappa Euroterapici, GlaxoSmithKline, Medtronic, Inc., and PDL BioPharma; has received research/grant support from Merck & Co., Inc., the National Institutes of Health (NIH), Otsuka Pharmaceutical Co., SCIOS Inc., and Sigma-Tau Pharmaceuticals; and has received honoraria from Abbott Laboratories, AstraZeneca Pharmaceuticals, GlaxoSmithKline, Medtronic, Inc., Otsuka Pharmaceutical Co., PDL BioPharma, SCIOS Inc., and Sigma-Tau Pharmaceuticals.

Gregg C. Fonarow, MD, has worked as a consultant for Amgen Inc., AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, GlaxoSmithKline, Medtronic, Inc., Merck & Co., Inc., NitroMed, Inc., Otsuka Pharmaceutical Co., Pfizer Inc, sanofi-aventis, Schering-Plough, and Scios, Inc.; has received research/grant support from Amgen Inc., GlaxoSmithKline, Medtronic, Inc., the National Institutes of Health (NIH), Pfizer Inc, and Scios. Inc.; and has received honoraria from Abbott Laboratories, Amgen Inc., AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, GlaxoSmithKline, King, Inc., Merck & Co., Inc., NitroMed, Inc., Pfizer Inc, sanofi-aventis, Schering-Plough, and Scios, Inc.

Stefan D. Anker, MD, PhD, has worked as a consultant for Amgen Inc., Biomeasure Inc., Brahms Diagnostica, and Vifor International Inc.; has received research/grant support

from Amgen Inc., Brahms Diagnostica, Vasogen Inc., and Vifor International Inc.; and has received honoraria from Amgen Inc., Berlin-Chemie, Brahms Diagnostica, Merck & Co., Inc., Otsuka, sanofi-aventis, Vasogen Inc., and Vifor International Inc.

1. Anker SD, Steinborn W, Strassburg S. Cardiac cachexia. *Ann Med* 2004;36:518–529.
2. Filippatos GS, Anker SD, Kremastinos DT. Pathophysiology of peripheral muscle wasting in cardiac cachexia. *Curr Opin Clin Nutr Metab Care* 2005;8:249–254.
3. Schols AM. Pulmonary cachexia. *Int J Cardiol* 2002;85:101–110.
4. Fearon KC, Moses AG. Cancer cachexia. *Int J Cardiol* 2002;85: 73–81.
5. Morley JE, Thomas DR, Wilson MM. Cachexia: pathophysiology and clinical relevance. *Am J Clin Nutr* 2006;83:735–743.
6. von Haehling S, Doehner W, Anker SD. Nutrition, metabolism and the complex pathophysiology of cachexia in chronic heart failure. *Cardiovasc Res* 2007;73:298–309.
7. Anker SD, John M, Pedersen PU, Raguso C, Cicoira M, Dardai E, Laviano A, Ponikowski P, Schols AM, DGEM (German Society for Nutritional Medicine), Becker HF, Böhm M, Brunkhorst FM, Vogelmeier C, for ESPEN (European Society for Parenteral and Enteral Nutrition). ESPEN guidelines on enteral nutrition: cardiology and pulmonology. *Clin Nutr* 2006;25:311–318.
8. Koehler F, Doehner W, Hoernig S, Witt C, Anker SD, John M. Anorexia in chronic obstructive pulmonary disease—association to cachexia and hormonal derangement. *Int J Cardiol* 2007;119:83–89.
9. Kalantar-Zadeh K, Abbott KC, Kronenberg F, Anker SD, Horwich TB, Fonarow GC. Epidemiology of dialysis patients and heart failure patients. *Semin Nephrol* 2006;26:118–133.
10. Kalantar-Zadeh K, Kuwae N, Wu DY, Shantouf RS, Fouque D, Anker SD, Block G, Kopple JD. Associations of body fat and its changes over time with quality of life and prospective mortality in hemodialysis patients. *Am J Clin Nutr* 2006;83:202–210.
11. Strassburg S, Springer J, Anker SD. Muscle wasting in cardiac cachexia. *Int J Biochem Cell Biol* 2005;37:1938–1947.
12. Anker SD, Negassa A, Coats AJ, Afzal R, Poole-Wilson PA, Cohn JN, Yusuf S. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. *Lancet* 2003;361:1077–1083.
13. Anker SD, Ponikowski P, Varney S, Chua TP, Clark AL, Webb-Peploe KM, Harrington D, Kox WJ, Poole-Wilson PA, Coats AJ. Wasting as independent risk factor for mortality in chronic heart failure. *Lancet* 1997;349:1050–1053.
14. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'Connor CM, Pieper K, Sun JL, Yancy C, Young JB, for the OPTIMIZE-HF Investigators and Hospitals. Association between performance measures and clinical outcomes for patients hospitalized with heart failure. *JAMA* 2007;297:61–70.
15. Lainscak M, Keber I, Anker SD. Body composition changes in patients with systolic heart failure treated with beta blockers: a pilot study. *Int J Cardiol* 2006;106:319–322.
16. Evans WJ. What is sarcopenia? *J Gerontol A Biol Sci Med Sci* 1995;50 (Spec No):5–8.
17. Springer J, von Haehling S, Anker SD. The need for a standardized definition for cachexia in chronic illness. *Nat Clin Pract Endocrinol Metab* 2006;2:416–417.
18. Jankowska EA, Biel B, Majda J, Szklarska A, Lopuszanska M, Medras M, Anker SD, Banasiak W, Poole-Wilson PA, Ponikowski P. Anabolic deficiency in men with chronic heart failure: prevalence and detrimental impact on survival. *Circulation* 2006;114:1829–1837.
19. Lainscak M, Doehner W, Anker SD. Metabolic disturbances in chronic heart failure: a case for the "macho" approach with testosterone?! *Eur J Heart Fail* 2007;9:2–3.
20. Springer J, Filippatos G, Akashi YJ, Anker SD. Prognosis and therapy approaches of cardiac cachexia. *Curr Opin Cardiol* 2006;21:229–233.
21. Kennedy LM, Dickstein K, Anker SD, Kristianson K, Willenheimer R, for the OPTIMAAL Study Group. The prognostic importance of body mass index after complicated myocardial infarction. *J Am Coll Cardiol* 2005;45:156–158.
22. Fonarow GC, Srikanthan P, Costanzo MR, Cintron GB, Lopatin M, for the ADHERE Scientific Advisory Committee and Investigators. An obesity paradox in acute heart failure: analysis of body mass index and inhospital mortality for 108,927 patients in the Acute Decompensated Heart Failure National Registry. *Am Heart J* 2007;153:74–81.
23. Fearon KC, Voss AC, Hustead DS, for the Cancer Cachexia Study Group. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. *Am J Clin Nutr* 2006;83:1345–1350.
24. Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, Knosalla C, Davos CH, Cicoira M, Shamim W, Kemp M, et al. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. *Circulation* 2003;107: 1991–1997.
25. Muscaritoli M, Bossola M, Aversa Z, Bellantone R, Rossi Fanelli F. Prevention and treatment of cancer cachexia: new insights into an old problem. *Eur J Cancer* 2006;42:31–41.
26. Filippatos G, Rauchhaus M, Anker SD. Decompensated heart failure and cachexia: is it time to legalize anabolics? *Int J Cardiol* 2006;111: 185–186.