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Letter to the Editor: ***Beyond Protein Intake – The Critical Role of Amino Acid Profiles in Cardiac Malnutrition***

Giovanni Corsetti

Institution: Università di Brescia

Disclosures:

Speakers' Bureau/Honoraria: Mytho s.r.l (Cagliari - Italy)*

Evasio Pasini

Institution: Università di Brescia

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Beyond Protein Intake – The Critical Role of Amino Acid Profiles in Cardiac Malnutrition

Dear Editor

We read with great interest the recent American Heart Association Scientific Statement, "Malnutrition and Cachexia in Patients With Acute Cardiac Illness," published in *Circulation* (2026;153:e00–e00. DOI: 10.1161/CIR.0000000000001405).

As researchers who have dedicated their efforts to studying malnutrition in cardiac patients, we are pleased that this crucial topic is receiving such high-level attention.

Complementing the authors' valuable considerations, we would like to emphasize the importance of distinguishing between "whole proteins" and their specific amino acids (AAs) composition physiologically important to understand nutritional impact. Indeed, there is a substantial metabolic difference between the ingestion of whole proteins and the administration of individual AAs. In this context, it is essential to consider several aspects:

1. Diet vs. Nutrition: In acute/chronic cardiac diseases, the distinction between "diet" (food intake, particularly enteral) and "nutrition" (actual cellular absorption and utilization) is of primary importance. The presence of fluid retention alters protein metabolism. In fact, the resulting intestinal and splanchnic oedema, as well as the alteration of the intestinal microbiome, evident in these diseases, often cause incomplete protein digestion and intestinal dysfunction with poor assimilation of the resulting AAs. Furthermore, ingested proteins are digested by specific enzymes produced primarily by the pancreas, requiring a large amount of AAs and energy for their synthesis.

Conversely, mixtures of individual AAs in specific stoichiometric ratios do not require digesting and can be immediately absorbed by intestine.

2. Metabolic specificity: many papers indicate that there is a difference in the metabolic activities and signalling pathways (such as mTOR activation) triggered by essential amino acids (EAAs) compared to Non-EAAs (NEAAs). It is therefore important to consider the quality of ingested proteins, defined by the presence of EAAs. Notably, the ratio of EAAs to NEAAs, even in high-quality dietary proteins, is always biased toward NEAAs.

Protein metabolism is highly complex phenomena, and all AAs are required for protein synthesis. Stimulating synthesis with a single AA supplement without providing the other molecules necessary for the anabolic response has limited effects on protein synthesis. Evidence indicates that mixtures of EAAs in stoichiometric ratios based on metabolic human's needs are more effective than single AA.

3. Monitoring efficacy: we believe it would be useful for physicians to have indications (e.g., prealbumin measurement) to assess the long-term effects of ongoing nutritional therapy and make therapeutic adjustments based on the patient's metabolic response.

We believe that recognizing the bioavailability and specific role of amino acids is a necessary step to optimize the recovery of "fragile" cardiac patients. We hope these considerations will contribute to the continued evolution of nutritional strategies for cardiovascular health and further enrich the debate initiated by this excellent article.

Best regards,

Giovanni Corsetti, Evasio Pasini (MD, PhD)
Department of Clinical & Experimental Sciences
Università di Brescia
Brescia, Italy

477 words

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Response authors:

Amanda R. Vest

Institution: Cleveland Clinic

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Carlos L. Alvear

Institution: New York University

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Robert J. DiDomenico

Institution: University of Illinois at Chicago

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We thank Drs Corsetti and Pasini for their thoughtful comments regarding the next research steps and appreciate their contributions to the understanding of hypercatabolic states. We agree with their very salient points that an integrated treatment paradigm that accounts for personalized energy needs, protein quality, amino acid availability, inflammatory state, and anabolic resistance – rather than simply total protein delivery – is highly applicable to patients with acute and chronic cardiovascular conditions. Experimental nutritional interventions directed at loss of skeletal muscle mass or strength have often focused on leucine-enriched protein sources or essential amino acid formulations, reflecting the role of leucine as a stimulator of mechanistic target of rapamycin complex 1 signaling, which regulates skeletal muscle protein synthesis. In aging populations, such nutritional interventions may be most effective when paired with exercise or other anabolic stimuli;¹ in hospitalized or critically ill patients, neuromuscular electrical stimulation may represent one potential adjunctive anabolic strategy, although further study is needed.²

Within cardiovascular populations, we agree with the importance of testing the hypothesis that free essential amino acids may be more rapidly absorbed and assimilated than intact dietary proteins and, when provided in balanced proportions, may more effectively stimulate muscle protein synthesis. The complexity of amino acid biology also raises the possibility of tissue-specific therapeutic responses. Whereas branched-chain amino acid (BCAA) supplementation may promote skeletal muscle synthesis in select contexts, impaired myocardial BCAA catabolism has been implicated in maladaptive cardiac remodeling during heart failure;³ enhanced BCAA catabolism is even being therapeutically evaluated (NCT06991257). Such intricacies reinforce the need for mechanistic and clinical studies that define which patients, tissues, disease stages, and outcomes are most likely to benefit from specific protein, amino acid, or metabolic interventions.

At present, nutritional care for patients with acute cardiovascular conditions should be individualized and multidisciplinary. The goal is to incorporate validated malnutrition screening and diagnostic criteria with assessment of dietary intake, gastrointestinal tolerance, perfusion and hemodynamic status, inflammation, renal function, body composition, physical function, and patient-centered goals. We agree that validated, clinically accessible biomarkers of protein turnover would be highly valuable for guiding patient care. We appreciate the authors' contribution to this important discussion and look forward to future trials that address protein dose and quality, amino acid composition, bioavailability, co-interventions, and clinically meaningful functional outcomes for patients with cardiac conditions and malnutrition or cachexia. [384 words]

Amanda R. Vest MBBS, MPH, Robert J. DiDomenico PharmD, Carlos L Alviar, MD

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