Malnutrition, muscle wasting and cachexia in chronic heart failure: the nutritional approach

Evasio Pasini, Roberto Aquilani*, Mihai Gheorghiade**, Francesco Saverio Dioguardi***

*Cardiovascular Pathophysiology Research Center, S. Maugeri Foundation, IRCCS, Gussago (BS), *Service of Metabolic and Nutritional Pathophysiology, S. Maugeri Foundation, IRCCS, Medical Center of Montescano, Montescano (PV), Italy, **Division of Cardiology, Northwestern University Medical School, Chicago, IL, USA, ***Department of Internal Medicine, University of Milan, Milan, Italy*

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Malnutrition, muscle wasting and cachexia are often present in chronic heart failure (CHF). However, malnutrition in CHF patients is not always as severe as muscle wasting. Data in the literature show that 24% of CHF patients have malnutrition (albumin < 3.5 mg/dl) but 68% have muscle atrophy. This apparent discrepancy can be explained by considering the metabolic role of the striate muscle. In fact, the striate muscle maintains the body metabolic performance by continuous exchanges of fuels (amino acids) with the liver. This happens in case of malnutrition or starvation. In such situations, glucose is produced by gluconeogenesis when amino acids are metabolized in the liver. Malnutrition, muscle wasting and the frequent progression through cachexia can be reduced by specific therapy such as cytokine and/or catabolic hormone antagonists. This is because cytokines and catabolic hormones, with consequent insulin resistance, cause muscle wasting. An alternative and/or complementary therapy may be exogenous amino acid supplementation. In fact, amino acids: a) are rapidly absorbed regardless of pancreatic activity, b) reduce insulin resistance, c) induce the hepatic synthesis of anabolic molecules such as growth hormone and insulin-like growth factor, and d) modulate the catabolic hormonal-mediated effects on adipocytes. Research on the best suitable qualitative and quantitative amino acid composition for an alternative and/or complementary therapy is still being studied in different research centers.

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Address:

Dr. Evasio Pasini

Centro di Fisiopatologia Cardiovascolare Fondazione S. Maugeri, IRCCS Via Pinidolo, 23 25064 Gussago (BS) E-mail: evpasini@libero.it

The problem

Malnutrition, muscle wasting and cachexia are often present in chronic heart failure (CHF)[1,2]. Malnutrition is caused by a reduced caloric (amino acids, carbohydrates and lipids) intake. Malnutrition can be estimated on the basis of the serum albumin concentration. Values of albumin < 3 mg/dl are considered the main marker of a poor nutritional status, because they constitute a significant predictor of morbidity and mortality in several pathological conditions such as cardiovascular surgery[3] or strokes[4]. However, it is interesting to note that malnutrition in CHF patients is not always as severe as muscle wasting, and protein synthesis is often conserved. In a recent survey, skeletal muscle atrophy (documented at magnetic resonance spectroscopy) was found in 68% of the patients studied, although up to 24% of patients had albumin levels < 3.5 mg/dl[1].

This apparent discrepancy can be explained considering the metabolic role of the amino acids of striate muscles. Striate muscles comprise about 45% of the average human adult body weight. As a whole, they should be considered as the pivotal organ for the maintenance of the body metabolic performance by continuous exchange of fuels with the liver. Striate muscle protein degradation with consequent amino acid muscle release is a predominant feature of malnutrition or starving. In these cases, the amino acids released from striate muscle are essential to maintain either global protein synthesis or plasma glucose levels.

The role of skeletal muscles as storage sites of amino acids in health and disease was fully recognized at the end of 70's[5]. Amino acids contain carbon, oxygen, hydrogen and nitrogen. Thus, they can be metabolized into either carbohydrates (such as glucose) or directly into lipids depending on the thermodynamic status of the cell. Lipids cannot be transformed into carbohydrates by mammals. Indeed, lipids are metabolically a dead-end suitable only for energy production. Neither lipids nor carbohydrates can be transformed into essen-

tial amino acids. In addition, amino acids are fundamental intermediates for the tricarboxylic acid cycle. In view of this, from a metabolic standpoint, we can consider amino acids as totipotent molecules[6]. Figure 1 illustrates the interrelationships of macronutrient metabolism, and helps us to understand why amino acids are so indispensable for life.

Clinically, the presence of muscle wasting is not only related to exercise intolerance, typical of CHF patients, but it is also an independent risk factor for mortality. In addition, progression through cachexia (defined as progression of wasting, when the non-edematous, non-intentional weight loss reaches more than 7.5% of the premorbid normal weight, which happens after more than 6 months) is frequent (about 16%), as recently demonstrated by Anker et al.[7,8]. This phenomenon is related to a dramatic increase in mortality. In fact, 50% of cachectic patients died within 18 months.

The pathogenesis of striate muscle wasting

The genesis of muscle wasting in CHF is not yet totally understood. The more accredited hypotheses indicate the inflammatory cytokines (tumor necrosis factor, interleukin family) and neuroendocrine activation as responsible for muscle wasting[9-11].

Cytokines are soluble peptides involved primarily in the inflammatory process modulating the function, activation, growth and death of immune cells. Recent experimental data show that cytokines can play a role in the progression of CHF. In fact, cytokines can: 1) cause deleterious myocardial hypertrophy, 2) influence the vascular tone, and 3) cause muscle wasting and cachexia[12].

However, recent clinical trials which examined the effects of antitumor necrosis factor agents on the morbidity and mortality in CHF were discontinued because of their futility and because of the higher mortality in the active-therapy group. Given that tumor necrosis factor plays a role in CHF, we can explain these negative results by formulating different hypotheses.

Firstly, the anticytokine molecules are used incorrectly. Secondly, the patients were chosen in an inappropriate manner. Thirdly, the study design was not adequate.

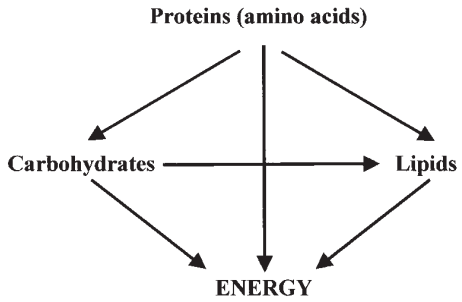

Figure 1. *Amino acids are biochemical totipotent molecules which can be transformed into both carbohydrates and lipids. All molecules produce energy.*

In addition, we have to bear in mind that cytokines are a complex network of molecules, receptors and intracellular signals which cross-talk among themselves. The clinical results depend on the balance between different reactions. In this context, an individual patient's response due to his own genes cannot be excluded[13].

We think that further work is necessary to clarify the role of the cytokine system in the evolution of CHF. The role of neuroendocrine activation in CHF has been known since the 80's[11]. Neuroendocrine activation is characterized by an increase in catabolic hormones and by a decrease in anabolic hormones. The increase in plasma catabolic hormones such as catecholamines, cortisol and renin has been well documented in patients with CHF. Recently, even the impairment of anabolic hormones, such as insulin, has been found in CHF. Indeed, Swan et al.[14] have documented that insulin resistance is present in most CHF patients. This abnormality is found even in the presence of normal glucose fasting concentrations. In fact, in these patients the serum levels of insulin were doubled (67 vs 29 pmol/l, $p < 0.002$) and insulin resistance (measured by the intravenous glucose tolerance test) was halved (58%).

The phenomenon of insulin resistance is extremely important for the general metabolism. It can significantly affect the metabolism of the whole body including the biochemistry of peripheral muscle and of adipose tissue.

In the muscles, the lack of anabolic stimulation due to insulin resistance causes protein degradation and amino acid release. These amino acids are used in the liver to produce glucose by gluconeogenesis. In addition, insulin resistance inhibits the mRNA synthesis of phosphoenolpyruvate carboxykinase (the key enzyme of the gluconeogenetic pathway) in the liver. This contributes to further reduce gluconeogenesis via pyruvate synthesized from lactate. This condition generates a vicious circle in which, owing to the malnutrition status, exogenous nutrients are not available, the liver produces low quantities of carbohydrate from alternative metabolic pathways and the muscular amino acids are used to produce glucose essential to maintain the glucose-dependent metabolism of fundamental structures such as the brain and erythrocytes.

Moreover, in these conditions the muscle glycogen reserve is depleted and free fatty acids become the principal fuel for the muscle. However, the use of free fatty acids is a limiting factor for energy production[15]. In fact, their accumulation in myocytes reduces energy production during exercise with consequent skeletal muscle fatigue[16].

Insulin plays an important role also in regulating adipose metabolism. Biochemistry teaches that even slight plasma insulin increases (5-10 μU/l) significantly reduce lipolysis in adipose tissue. This insulin increase reduces the free fatty acid availability for acetylcoenzyme A production, fundamental to maintain cel-

lular energy production. Under these conditions, cell energy production via the anaerobic metabolic pathway is maintained by acetate which derives predominantly from amino acid breakdown and oxidation.

In summary, insulin resistance has well established effects on the overall metabolism. It facilitates protein catabolism and activates gluconeogenesis from amino acids and lipid anabolism. This metabolic condition generates and maintains muscle wasting. Indeed, amino acids are shuttled mostly to energetic purposes instead of to the synthesis of proteins.

Our hypothesis is illustrated in figure 2.

The nutritional approach

It is clear that the availability of amino acids is a key factor for the overall metabolism of mammals. Thus, exogenous supplementation could be a valid therapeutic strategy to use in combination with conventional therapy in CHF patients.

We think that for various reasons the supplementation of exogenous amino acids can avoid malnutrition, muscle wasting and maybe cachexia.

First, amino acids could resolve the malnutrition related to a reduced nutrient absorption for CHF, aging or disease-related pancreatic exocrine exhaustion.

It is well known that the pancreas is the major consuming organ of amino acids of the whole body. In addition, the pancreas plays a fundamental role in food digestion. However, digestion and food absorption require that various enzymes be adequately synthesized and secreted. This process consumes enormous quantities of amino acids and energy at any meal. In CHF patients the pancreatic exocrine efficiency is progressively reduced. This results in a vicious circle: the lower the digestion of proteins, the less the availability of amino acids for the synthesis of digestive enzymes. This condition leads to impaired digestion and consequently to reduced serum levels of plasma amino acids which are insufficient for promoting proteins synthesis. Interestingly, amino acids are not digested. They are rapidly absorbed and immediately available in the blood for protein synthesis[17].

Second, amino acids act as specific positive signals for the maintenance of muscular protein stores by several mechanisms.

One of the most interesting mechanisms is that amino acids may antagonize the negative influence of insulin resistance. Indeed, amino acids inhibit the alteration in glucose transport and in gluconeogenesis mediated by insulin resistance. In addition, at high physiologic concentrations amino acids activate different important steps of protein synthesis[18]. These assertions are supported by some recent observations. In animals and humans, the acute intravenous infusion of an amino acid mixture stimulated skeletal muscle, but not liver, protein synthesis[19,20]. It has been suggested that protein synthesis can occur through an additional metabolic pathway involving the hormonal profile. Amino acid flow through the

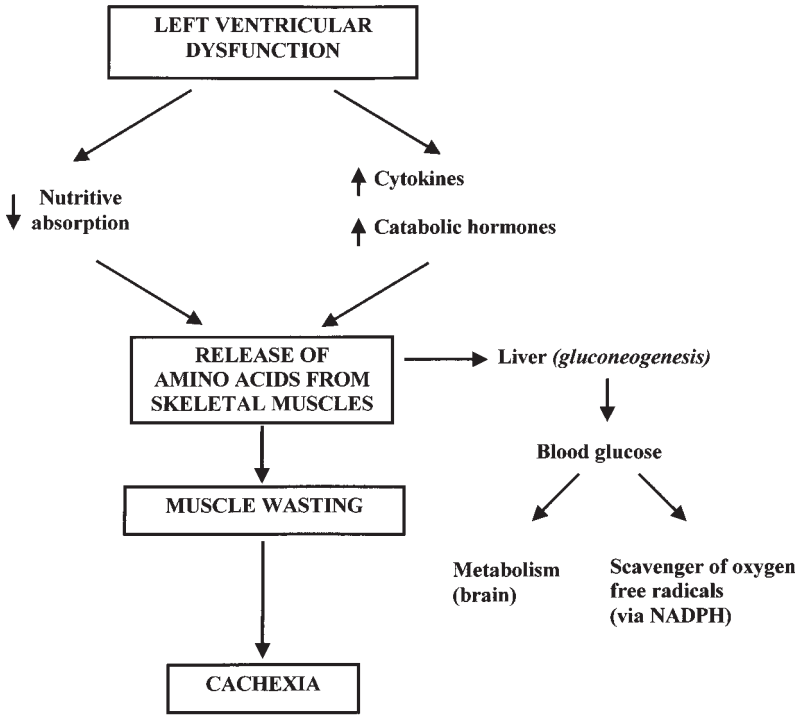

Figure 2. *Left ventricular dysfunction impairs the mesenteric blood flow with a consequent reduction in nutrient absorption and the release of cytokines and catabolic hormones. Malabsorption and catabolic molecules induce muscle wasting and amino acid release. Amino acids are used in the liver to produce glucose (by gluconeogenesis). Glucose is the fundamental molecule for the maintenance of both aerobic metabolism (i.e. in brain and red blood cells) and of the antioxidant cell potential via NADPH (by the pentose phosphate pathway).*

portal vein is the signal for insulin-like growth factor (IGF)-1 and 2 secretion[21]. IGF-1 is the main somatomedin responsible for the activation of growth hormone. The serum concentrations of the latter are inversely related to those of the former. Growth hormone is a family of immunologically similar anabolic hormones which promotes protein synthesis and counteracts insulin resistance. In all states of severe malnutrition growth hormone plasma levels are very high. It has also been shown that IGF-1 overexpression protects cardiomyocytes from infarction and reduces ventricular dilation, myocardial loading, and hypertrophy[22]. In addition, IGF-1 seems to reduce skeletal muscle protein degradation under stressful conditions. Moreover, recent data suggest that nutrients, including amino acids, directly influence protein synthesis through regulatory signals in the untranslated regions of mRNA. This results in enhanced mRNA stability. This effect is particularly relevant for the skeletal muscle where the post-transcriptional control of the site of synthesis of specific proteins may channel amino acids towards protein synthesis instead of energy consumption use[23].

Third, amino acids can modulate the effects of insulin on adipocytes. Amino acids enhance the glucose-induced desensitization of insulin-stimulated glucose transport. Thus they modulate the synthesis of free fatty acids in adipose tissue with a consequent improvement in adipose metabolism. The modulation of the effects of insulin on adipocytes is mediated peculiarly by glutamine[24].

On the basis of these speculations we can conclude that supplementation of amino acids can be used in CHF patients to contrast malnutrition, muscle wasting and cachexia. However, the best suitable qualitative and quantitative amino acid composition to use still needs to be certified[25-28]. Therefore, some peculiar amino acid mixtures are being studied in different research centers.

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