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Taegtmeyer, and Mihai Gheorghiade  
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## Micronutrient Deficiencies

### An Unmet Need in Heart Failure

Victor Soukoulis, MD, PhD,\* Jamil B. DiHu, DO,‡ Michael Sole, MD,§  
Stefan D. Anker, MD, PhD,||¶ John Cleland, MD,# Gregg C. Fonarow, MD,\*\*  
Marco Metra, MD,†† Evasio Pasini, MD,‡‡ Theresa Strzelczyk, APN, CNS,\*  
Heinrich Taegtmeyer, MD, DPHIL,§§ Mihai Gheorghiadu, MD†

*Chicago, Illinois; Toronto, Ontario, Canada; Berlin, Germany; Roma and Brescia, Italy;  
Kingston upon Hull, United Kingdom; Los Angeles, California; and Houston, Texas*

Heart failure (HF) is a common, disabling, and costly disease. Despite major advances in medical therapy, morbidity and mortality remain high, in part because current pharmacological regimens may not fully address some unique requirements of the heart for energy. The heart requires a continuous supply of energy-providing substrates and amino acids in order to maintain its function. In HF, defects in substrate metabolism and cardiac energy and substrate utilization may contribute to contractile dysfunction. HF is often accompanied by a deficiency in key micronutrients required for unimpeded energy transfer. Correcting these deficits has been proposed as a method to limit or even reverse the progressive myocyte dysfunction and/or necrosis in HF. This review summarizes the existing HF literature with respect to supplementation trials of key micronutrients involved in cardiac metabolism: coenzyme Q10, L-carnitine, thiamine, and amino acids, including taurine. Studies using a broader approach to supplementation are also considered. Although some of the results are promising, none are conclusive. There is a need for a prospective trial to examine the effects of micronutrient supplementation on morbidity and mortality in patients with HF. (J Am Coll Cardiol 2009;54:1660-73) © 2009 by the American College of Cardiology Foundation

Heart failure (HF) is a common, disabling, and costly disease throughout the world (1,2). Annual costs related to

From the \*Department of Medicine and †Center for Cardiovascular Quality and Outcomes, Northwestern University Feinberg School of Medicine, Chicago, Illinois; ‡Department of Medicine, University of Chicago (North Shore), Pritzker School of Medicine, Chicago, Illinois; §Division of Cardiology, University Health Network, Toronto, Ontario, Canada; ||Department of Cardiology, Charite, Campus Virchow-Klinikum, Berlin, Germany; ¶Centre for Clinical and Basic Research, IRCCS San Raffaele, Roma, Italy; #Department of Cardiology, Castle Hill Hospital, Hull York Medical School, Kingston upon Hull, United Kingdom; \*\*Division of Cardiology, David Geffen School of Medicine at UCLA, Los Angeles, California; ††Section of Cardiovascular Diseases, Department of Experimental and Applied Sciences, University of Brescia, and ‡‡Fondazione "S Maugeri," Medical Centre of Lumezzane, Brescia, Italy; and the §§Department of Medicine/Cardiology, University of Texas Houston Medical School, Houston, Texas. Dr. Sole has a share in patents on a nutritional supplement for heart failure (containing any effective combination of coenzyme Q10, L-carnitine or its derivatives, and taurine) issued by the U.S., Canada, and most Western European countries. He has licensed a supplement in Canada to Seaford Pharmaceuticals. Dr. Anker receives research grants and honoraria for speaking and consultancy from Fresenius (Germany) as well as honoraria for consultancy from Professional Dietetics (Italy). Dr. Cleland has a consultancy with NUMICO (recently taken over by DANONE). Dr. Fonarow receives research funding from the National Heart, Lung, and Blood Institute, GlaxoSmithKline, and Pfizer, and is a consultant for or receives honoraria from GlaxoSmithKline, Debiopharm, Novartis, Merck, and Scios. Dr. Taegtmeyer receives research funding from the National Heart, Lung, and Blood Institute and the American Heart Association. Dr. Gheorghiadu performs consultant work with Otsuka, Solvay Pharma, Novartis, Bayer, Sigma-Tau, Debiopharm, Medtronic, Merck, Astellas Pharma, Cytokinetics, Corthera, PeriCor Therapeutics, GlaxoSmithKline, Johnson & Johnson, Abbott, Errekappa Therapeutics, PDL: BioPharma, AstraZeneca, and Sanofi-Aventis.

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the treatment of HF in the U.S. are estimated at \$38 billion, and account for 5.4% of the health care budget (3). The treatment of HF is based on medical guidelines published by the professional societies (4-7). The recommended pharmacological therapy includes the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, beta-blockers, and aldosterone antagonists. Additional nonpharmacologic measures, such as cardiac resynchronization therapy, implantable cardioverter-defibrillators, and exercise training, have shown beneficial outcomes in quality of life, morbidity, and/or mortality of HF patients (7).

Despite improvements in mortality, HF hospitalizations continue to rise (8). Hospitalization for HF is a strong predictor of poor prognosis and is associated with post-discharge mortality and readmission rates that can be as high as 15% and 30%, respectively, within 60 to 90 days (9,10). Although new therapeutic options have undoubtedly improved morbidity and mortality, additional interventions are needed to prevent progression of HF and improve outcomes (10,11).

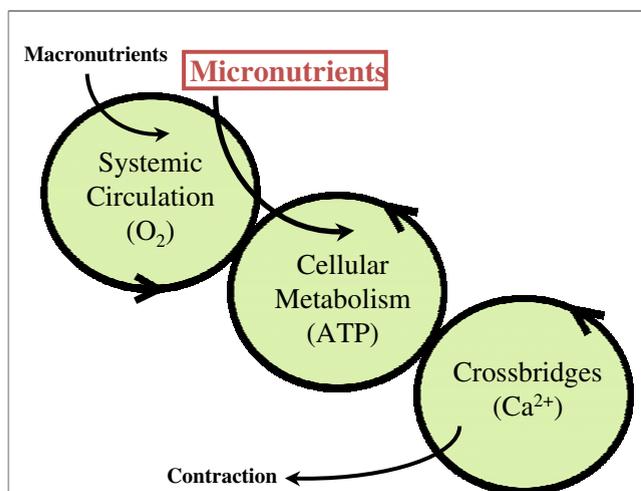
Although current therapies have addressed hemodynamics, neurohormonal modulation, and electrophysiological aspects of HF, these therapies have not targeted the metabolic needs of the failing heart (12).

## Normal Cardiac Metabolism

The adult human heart, which weighs between 200 and 425 g, is a highly efficient converter of chemical energy to mechanical energy (13). This relatively small mass uses more energy, in the form of adenosine triphosphate (ATP), than any other organ as it pumps 5 l of blood per minute, 7,200 l per day, and over 2.6 million liters per year (14). It is estimated that over 6 kg of ATP is hydrolyzed by the heart daily for this pumping function (15). To maintain this essential level of efficiency, the enzymes, membranes, and structural elements of the heart undergo constant turnover and rebuilding. Every 30 days, an entire heart is reconstructed with brand-new protein components, using a steady supply of nutritional building blocks in the form of amino acids, lipids, and carbohydrates (16,17).

Energy transfer in the beating heart can be visualized as a system of interconnected cycles that receives nutrients through the circulation and that transfers energy from nutrients to ATP, which, in turn, is used to support cyclic contractions (Fig. 1). Under normal conditions, the system readily responds to environmental changes by either increasing or decreasing the rate of energy turnover. The schematic refers to yet another biological principle: cycles consist of moieties (e.g., blood in the circulation, enzymes in cells) that provide the necessary machinery for energy transfer.

The heart has also been described as a metabolic omnivore, because it has the capacity to oxidize fat and carbohydrates simultaneously or interchangeably for its energy needs (18,19). *Macronutrients* are defined here as fats and carbohydrates that constitute the main sources of ATP for contraction of the mammalian heart. *Micronutrients*, such as coenzyme Q10 (CoQ10), L-carnitine, thiamine, amino acids, including taurine, and other small molecules are



**Figure 1** Cycles of Energy Transfer and the Place of Micronutrients

Energy transfer in the heart as a system of interconnected cycles. Micronutrients are essential components of moiety-conserved cycles in the cell. See the Normal Cardiac Metabolism section for further discussion.

defined as essential cofactors for energy transfer, biochemical maintenance, and physiological heart function (20,21).

## Metabolism in HF

Deficiencies in CoQ10, L-carnitine, thiamine and other B vitamins, and taurine are all well documented in the failing myocardium (22,23). Deficiencies of L-carnitine, thiamine, and taurine alone are well-established causes of cardiomyopathy (23). Animal models have similarly revealed that micronutrient deficiencies are present in HF, that genetically induced deficiencies lead to HF, and that correction of these deficits can improve heart function (24–30).

Thus, in HF, it has been proposed that the human heart is deficient in adequate amounts of key nutrient cofactors or micronutrients (Fig. 1) (23,31–36). However, the heart is “not out of fuel” as it has been suggested (34), because the coronary circulation provides substrates in excess of their rate of utilization. Indeed, a large part of the morbidity of HF appears to be the result of impaired energy substrate metabolism (37). ATP turnover in the failing myocardium may be reduced by as much as 30%, although it is not clear whether the reduced rate of ATP turnover is the cause or the consequence of HF (38).

When the heart is stressed, as seen in HF, it returns to the fetal gene program, switching from the dominant fatty acid metabolism to a more efficient use of carbohydrates in an attempt to limit further damage (39–44). It is also of interest that infants have a reduced ability to biosynthesize L-carnitine and taurine. Hence, these nutrients are mandated for inclusion in infant formulas. Whether the fetal gene program contributes to the deficiencies of L-carnitine and taurine seen in HF is unknown. In any case, the early adaptation of the heart eventually becomes maladaptive as HF progresses (17,45). The evolution of HF usually occurs over a number of years; therefore, only a very small percentage of cardiomyocytes at a given time may be irreversibly injured. These myocytes retain a relatively preserved structure and are in a “vegetative state” equal to viable, but dysfunctional, myocardium as a result of metabolic imbalance, in part related to excessive and continuous activation of the neuroendocrine system (31,32,46,47). Therapy with micronutrients when deficiencies exist has the potential to prevent myocyte death and restore function.

In HF, maladaptive changes appear to occur at all steps of energy production and transfer: substrate utilization, oxidative phosphorylation, and ATP utilization (37). Inadequate energy conversion in already overworked cardiomyocytes may potentially result in cell damage or death mediated by oxidative stress, resulting in mitochondrial damage and

### Abbreviations and Acronyms

|              |                                         |
|--------------|-----------------------------------------|
| <b>ATP</b>   | = adenosine triphosphate                |
| <b>CoQ10</b> | = coenzyme Q10                          |
| <b>EF</b>    | = ejection fraction                     |
| <b>HF</b>    | = heart failure                         |
| <b>LV</b>    | = left ventricle/ventricular            |
| <b>LVEDV</b> | = left ventricular end-diastolic volume |
| <b>LVESV</b> | = left ventricular end-systolic volume  |
| <b>MRI</b>   | = magnetic resonance imaging            |
| <b>NYHA</b>  | = New York Heart Association            |

**Table 1** Guideline Recommendations for Nutritional Support in HF

| Guideline   | Recommendation                                                                                                                                                                                                                   | Level of Evidence               |
|-------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| ACC/AHA (7) | Routine use of nutritional supplements of unproved value and not recommended                                                                                                                                                     | Class III, Level of Evidence: C |
| HFSA (5)    | Patients with HF, especially those on diuretic therapy and restricted diets, should be considered for daily multivitamin-mineral supplementation to ensure adequate intake of the recommended daily value of essential nutrients | Level of Evidence: C            |
| ESC (4)     | Omitted in 2008 guidelines                                                                                                                                                                                                       | N/A                             |
| CCS (6)     | CoQ10, vitamin and herbal supplements are not recommended as HF therapy                                                                                                                                                          | Class III, Level of Evidence: C |

ACC = American College of Cardiology; AHA = American Heart Association; CCS = Canadian Cardiovascular Society; CoQ10 = coenzyme Q10; ESC = European Society of Cardiology; HF = heart failure; HFSA = Heart Failure Society of America; N/A = not available.

cytochrome c release (23,48). Decreased capacity for energy conversion makes the damaged heart more susceptible to ischemia, accelerating the process of HF. In Figure 1, it is proposed that micronutrients allow for the efficient and appropriate utilization of fuel for the preservation of normal structure and function of the heart. It should also be recognized that plasma levels of compounds such as L-carnitine, taurine, and CoQ10 may not reflect tissue levels because of large transmembrane cellular gradients (23,49-53).

The lack of sufficient micronutrients may be intensified by medical interventions. Commonly prescribed medications, such as the cholesterol-lowering HMG-CoA reductase inhibitors, have been shown to cause reductions in serum CoQ10 levels, thus potentially exacerbating already-present nutritional deficiencies and limiting long-term treatment success (54-59). Similarly, loop diuretics have been shown to substantially lower thiamine levels in patients with HF (60-63).

### Micronutrient Supplementation

Micronutrients may work synergistically with standard therapies in patients with HF by correcting defects in energy metabolism and providing the failing heart with deficient cofactors that are limiting cellular energy transfer (Fig. 1). Despite the appeal of such a strategy, large clinical trials evaluating therapy with micronutrients are lacking (Table 1). However, this is a potentially promising new paradigm for the treatment of HF therapy, deserving further investigation. Micronutrient supplementation offers the opportunity to correct deficiencies in critical myocyte pathways, including those associated with the provision of ATP (CoQ10, L-carnitine, thiamine and the B vitamins, amino acids), protein production (amino acids), intracellular calcium balance (taurine), and the reduction of oxidative stress (CoQ10 and taurine).

To date, clinical research of a single micronutrient in the treatment of HF has been the usual investigative approach. However, this method may potentially shift the rate-limiting step to another pathway of the energy cascade. There are only a few studies evaluating a broader, multiple-micronutrient approach. Such an approach may be a more comprehensive method of supplementation and overcome some of the limitations with a single-supplement method. As described below, nutritional studies to date as a whole

have significant design drawbacks, indicating an important need for larger, more comprehensive micronutrient trials in HF.

### The Need for More Clinical Trials

The subsequent sections will summarize the existing data in this supplementation field, identify the limitations of current studies, and propose how to move forward with research to fill critical gaps in knowledge. Here, the focus is primarily on CoQ10, L-carnitine, thiamine, and taurine. These nutrients were chosen because: 1) they are known essential components for metabolic pathways that participate in energy production, myocardial calcium balance, and oxidative defenses; 2) there is evidence for a reduction in the level of each in HF; 3) there is evidence that a deficiency in each of them, alone, may result in cardiac or skeletal muscle pathology; and 4) there is possibly pathological reversal (27,64,65).

### CoQ10

CoQ10, or ubiquinone, is an obligatory component of the respiratory chain in mitochondria. It serves as a carrier for electrons flowing through complexes I, II, and III. As such, CoQ10 plays an essential role in ATP formation in most tissues, including the heart, skeletal muscle, brain, kidney, and liver. CoQ10 is localized in the inner mitochondrial (and other intracellular) membrane, where it serves to stabilize these structures, control electron flow, and regulate the flow of reducing equivalents (66,67). In addition to its role in energy transfer, CoQ10 also functions as an antioxidant and protects circulating low-density lipoprotein particles from oxidation (68). Its inhibition of the mitochondrial permeability transition pore prevents the activation of apoptotic cascades and the oxidative inactivation of key proteins involved in ATP production (69,70). The diverse roles of CoQ10 in energy metabolism are important in the failing heart, where oxidation of energy-providing substrates becomes inadequate (54). Deficiency of CoQ10 can be caused by inhibition of its synthesis. Mevalonate, a precursor of CoQ10, is formed in a pathway dependent on HMG-CoA reductase. Not surprisingly, statins, which inhibit HMG-CoA reductase, have been shown to reduce the production of CoQ10 (54-58).

CoQ10 is widely available in dietary sources such as meat, poultry, and oils, which together provide an average daily intake of 5 mg (71). However, the majority of CoQ10 is produced by the human body from tyrosine and mevalonate through endogenous pathways. Trials involving CoQ10 supplementation in HF have primarily used dosage ranges from 60 to 300 mg/day. No significant toxicity has been observed in human studies, although there have been adverse side effects, including diarrhea, nausea, epigastric discomfort, and elevated liver enzyme levels. Gastrointestinal side effects are decreased by administration in divided doses no greater than 100 mg (55,72).

The first study on the role of CoQ10 in HF was published in 1976 (73). Serum and tissue levels of CoQ10 are lower in HF patients compared with normal control subjects (74,75). Additionally, the degree of CoQ10 deficiency may correlate with New York Heart Association (NYHA) functional class, left ventricular (LV) function, and mortality (76–79). This apparent deficiency of CoQ10 in HF has led to numerous trials seeking to establish the efficacy of CoQ10 supplementation in varying etiologies of HF (Table 2). These trials are promising because they have shown statistically significant improvement in a variety of functional, structural, and hemodynamic parameters, including ejection fraction (EF), stroke volume, cardiac output, pulmonary artery pressure, exercise capacity, and quality of life (72,75,80–86). Additionally, decreases in end-diastolic volume, NYHA functional class, hospital admissions, dyspnea, and fatigue have also been documented. However, results have been mixed (87,88). The largest trial conducted with CoQ10 in an HF population was not a double-blind, placebo-controlled study (72). Conversely, several of the studies showing no effect have been criticized for not achieving adequate CoQ10 serum levels, in addition to being too short in duration (87–89). Meta-analyses to evaluate the overall findings of CoQ10 trials appear to support many of the aforementioned benefits of CoQ10 in HF (90–92). In short, CoQ10 appears to be a safe and potentially effective nutritional supplement for the treatment of HF, based primarily, however, on small studies and meta-analyses. Larger trials of CoQ10 in combination with other micronutrients are needed to show a reduction in morbidity and mortality for HF patients already receiving standard therapy.

### L-Carnitine

L-carnitine is an amino acid derivative synthesized primarily from the amino acids lysine and methionine (93). It plays a critical role in fatty acid transport into the mitochondria (94). Additionally, L-carnitine reverses the inhibition of pyruvate dehydrogenase, allowing for improved coupling between glycolysis and glucose oxidation (95). Genetic carnitine deficiency, secondary to a plasma membrane transporter defect, results in a cardiomyopathy (28). Lastly, an alternate form of the molecule, propionyl-L-carnitine, has a

high penetration rate into myocytes, and its products can serve as a substrate of the Krebs cycle (93). Propionyl-L-carnitine has been shown to improve contractile function in the isolated working rat heart (96) and also to reduce the lactate and hydrogen burden in the hypertrophied human heart by increasing glucose oxidation (95).

L-carnitine is either supplied in the diet or produced endogenously, although daily consumption far exceeds endogenous production (97). L-carnitine deficiency in the failing heart has been well documented (36,98–100). As noted previously, infants have a reduced ability to biosynthesize L-carnitine; whether the fetal gene program contributes to the deficiency of L-carnitine seen in HF is unknown. Studies have also shown that plasma levels of L-carnitine often do not reflect the tissue level of L-carnitine because a significant intracellular-to-extracellular gradient is maintained by sodium-dependent pumps (23,100). Most trials conducted with L-carnitine supplements in HF have used doses of 1.5 to 3 g/day, which seem to be well tolerated (101–105).

There have been several promising studies evaluating the role of L-carnitine in cardiac diseases, including HF (Table 3). However, their value has been limited by their design and inconsistent results. Although multicenter trials, such as the CEDIM (L-Carnitine Ecocardiografia Digitalizzata Infarto Miocardico) study, have shown a benefit of L-carnitine on cardiac remodeling after myocardial infarction (106), less is known about L-carnitine in the treatment of HF of non-ischemic causes. Supplementation of L-carnitine or its analog, propionyl-L-carnitine, in HF has led to statistically significant increases in exercise capacity, maximum exercise time, peak heart rate, and peak oxygen consumption (101–104). Small studies on hemodynamic and echocardiographic effects of supplementation also have shown promising results, reducing pulmonary artery pressure, as well as LV systolic, diastolic, left atrial, and end-diastolic dimensions (102). Improvements in EF have also been observed, albeit not consistently (102,104). Interpretation has been limited due to lack of control groups and high dropout rates in certain trials (102,103). A larger European study relied on subgroup analyses to observe an effect (101). One trial revealed a potentially interesting benefit of L-carnitine on mortality by demonstrating a significantly improved 3-year survival in patients with dilated cardiomyopathy and NYHA functional class III to IV HF (105). It is therefore proposed that both carnitine and propionyl-L-carnitine warrant further study in patients with HF.

### Thiamine (Vitamin B<sub>1</sub>) and Other B Vitamins

Thiamine (vitamin B<sub>1</sub>) is a water-soluble B vitamin that plays an important role as a coenzyme in carbohydrate metabolism. Through the addition of magnesium and ATP, thiamine is converted to thiamine pyrophosphate by the enzyme thiamine pyrophosphokinase (107). As the metabolically active form of thiamine, thiamine pyrophosphate

**Table 2** Selected Trials With CoQ10 Supplementation in HF

| Study Author (Ref. #)    | Year | No. of Patients | Study Design                               | Primary End Point                                                                                                                   | NYHA Functional Class | Results                                                                                                                              | Dose          | Side Effects Related to CoQ10 | Remarks                                                                                                                                      |
|--------------------------|------|-----------------|--------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|-----------------------|--------------------------------------------------------------------------------------------------------------------------------------|---------------|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| Baggio et al. (72)       | 1994 | 2,664           | Post-marketing surveillance study          | Assessment of clinical signs and symptoms using a 7-point scale                                                                     | II-III                | Improvement of at least 3 symptoms seen in 54% of patients                                                                           | 50-150 mg/day | None                          | Not a double-blind, placebo-controlled study. Doses varied. Before modern therapy was available. Used point system for clinical improvement. |
| Langsjoen et al. (75)    | 1985 | 19              | Double-blind, placebo double-crossover     | Evaluation of EF, SV, CoQ10 serum level, weight, and clinical status over 28 weeks                                                  | III-IV                | ↑ EF and SV, ↑ CoQ10 serum level                                                                                                     | 33.3 mg BID   | None                          | Small size and before modern therapy                                                                                                         |
| Belardinelli et al. (80) | 2006 | 23              | Double-blind, placebo-controlled crossover | At 4 weeks effects of CoQ10 and exercise training on V <sub>o2</sub> max, EF, and endothelium-dependent dilation of brachial artery | II-III                | Increase in V <sub>o2</sub> max, increase in LVEF at rest and peak, improvement in endothelium-dependent dilation of brachial artery | 100 mg TID    | None                          | Small study size. Also evaluated patients in exercise training regimen.                                                                      |
| Morisco et al. (81)      | 1993 | 191             | Double-blind placebo-controlled            | Incidence of hospitalization and life-threatening pulmonary edema                                                                   | III-IV                | ↓ Hospitalization and pulmonary edema                                                                                                | 2 mg/kg/day   | NA                            | Small size and before modern therapy                                                                                                         |
| Munkholm et al. (85)     | 1999 | 22              | Double-blind, placebo-controlled           | Right heart catheterization for RAP, RVSP, EDP, PAP, and PCWP at rest, 1, or 3 min of work done at 12 weeks                         | II-III                | ↑ Stroke index at rest and work, ↓ PAWP at rest. ↓ PCWP at work. Otherwise no changes.                                               | 100 mg BID    | NA                            | Small study size                                                                                                                             |
| Keogh et al. (86)        | 2003 | 39              | Double-blind, placebo-controlled           | Physician-assessed NYHA symptom functional class at 3 months                                                                        | II-III                | Small but statistically significant improvement in NYHA functional class                                                             | 150 mg/day    | NA                            | Small study size. Treated with ACEI but not beta-blockers.                                                                                   |
| Khatta et al. (87)       | 2000 | 46              | Double-blind, placebo-controlled           | At 6 months change in EF, as assessed by nuclear ventriculography, and change in peak O <sub>2</sub> consumption                    | III-IV                | No effect on EF, peak O <sub>2</sub> consumption                                                                                     | 200 mg/day    | None                          | Small study size, lower CoQ10 serum levels attained                                                                                          |
| Watson et al. (88)       | 1999 | 30              | Double-blind, placebo-controlled crossover | At 3 months evaluation of LVEDV, LVESV, and EF. Right heart catheterization for CO and PCWP.                                        | Not reported; EF <35% | No significant change                                                                                                                | 33 mg TID     | None                          | Small size, used lower dose of CoQ10                                                                                                         |

ACEI = angiotensin-converting enzyme inhibitor; BID = twice daily; CO = cardiac output; EDP = end-diastolic pressure; EF = ejection fraction; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; RVSP = right ventricular systolic pressure; SV = stroke volume; TID = three times daily; other abbreviations as in Table 1.

**Table 3 Selected Trials With Carnitine in HF**

| Study Author (Ref. #)     | Year | No. of Patients | Study Design                     | Primary End Point                                                                                                                            | NYHA Functional Class         | Results                                                                                                                                                                                                            | Dose                                              | Side Effects Related to Carnitine           | Remarks                                                                                                             |
|---------------------------|------|-----------------|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|---------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| Study investigators (101) | 1999 | 353             | Double-blind, placebo-controlled | At 6 months and evaluation of exercise capacity using bicycle exercise                                                                       | II-III                        | No difference in maximum exercise duration                                                                                                                                                                         | 1 g BID                                           | None                                        | No BB used (only ACEI and diuretic), non-a priori subgroup analysis. ↑ Max HR in patients with higher EF (30%-40%). |
| Anand et al. (102)        | 1998 | 30              | Single-blind, placebo-controlled | At days 1, 15, and 30 measurement of LV function, hemodynamics, hormone levels, exercise capacity, and peak O <sub>2</sub> consumption       | II-III                        | No change in LV function. ↓ End-diastolic dimensions and end point septal separation. ↓ PAP and PAWP on days 1 and 30. No change in hormone levels. ↑ Peak O <sub>2</sub> consumption, exercise time, exercise HR. | Initial bolus 30 mg/kg, then 500 mg TID           | None                                        | Single blind and small study size                                                                                   |
| Loster et al. (103)       | 1999 | 41              | Double-blind, placebo-controlled | Bicycle ergometer test to determine maximum performance, systolic and diastolic pressure, HR, and ST changes at up to 180 days               | II-III                        | Improved performance. Trend toward improved hemodynamic parameters.                                                                                                                                                | 1 g TID                                           | NA                                          | Small size and limited end point assessments, high dropout rate                                                     |
| Mancini et al. (104)      | 1992 | 60              | Double-blind, placebo-controlled | LVEF and maximum exercise time on ergometer bicycle at up to 180 days                                                                        | II-III                        | ↑ Maximum exercise time and EF                                                                                                                                                                                     | 500 mg TID                                        | NA                                          | Small size, before current treatments available                                                                     |
| Rizos (105)               | 2000 | 80              | Double-blind, placebo-controlled | Measurement of LVEF, maximum exercise time, peak V <sub>O<sub>2</sub></sub> consumption, arterial and pulmonary BP, CO, and 3-year mortality | III-IV dilated cardiomyopathy | ↑ 3-yr survival. Improved maximum exercise time, peak O <sub>2</sub> consumption, CO, arterial/pulmonary BP                                                                                                        | 2 g/day                                           | GI discomfort in 3 patients (all completed) | Limited to dilated cardiomyopathy                                                                                   |
| Iliceto et al. (106)      | 1995 | 472             | Double-blind, placebo-controlled | LV volume and EF at 12 months after MI                                                                                                       | NA                            | ↓ LVEDV and LVESV. No difference in LVEF.                                                                                                                                                                          | 9 g/day IV for 5 d, then 6 g/day PO for 12 months | NA                                          | Evaluated results after acute MI. Not in HF.                                                                        |

BB = beta-blocker; BP = blood pressure; EDV = end-diastolic volume; ESV = end-systolic volume; GI = gastrointestinal; HR = heart rate; IV = intravenous; LV = left ventricular; MI = myocardial infarction; PO = by mouth; other abbreviations as in Tables 1 and 2.

serves as a cofactor for the pyruvate dehydrogenase complex and for transketolase, both key mediators of energy substrate metabolism. Thiamine deficiency results in decreased ATP production and increased cellular acidosis on a metabolic level (108).

Thiamine itself is stored in the body in only small amounts and cannot be produced endogenously (23). Adequate nutritional intake through diet (whole grains, legumes, nuts) or supplements is therefore critical in preventing deficiency. Doses used in trials have ranged from 1.5 to 200 mg/day.

The cardiac effects of severe thiamine deficiency are clinically referred to as wet beriberi (109). A chronic disease develops consisting of a peripherally vasodilated state that leads to fluid retention through activation of the renin-angiotensin system. The end result of thiamine deficiency is high-output HF (110). In the Western world, however, wet beriberi is rarely encountered. Instead, concern focuses on moderate thiamine deficiency in patients with HF. Animal models have shown that thiamine deficiency can lead to cardiac dysfunction, hypertrophy, and arrhythmias without the presence of beriberi (111–121). In patients with HF, the incidence of thiamine deficiency ranges from 13% to 93% (60–62,122–125). Patients with NYHA functional class III/IV HF appear to have more severe deficiency than their class I/II counterparts (60). Furosemide, commonly used in such patients, may exacerbate this problem through urinary excretion of thiamine (60–63). There also appears to be an increased need for thiamine in the setting of HF, as similar nutritional amounts are inadequate in HF patients compared with controls (60).

Given the proposed role of thiamine deficiency in HF, several small studies have been conducted to examine the clinical utility of supplementation. Thiamine deficiency appears to respond to oral supplements as small as 1.5 mg/day, as shown in 1 study of 100 hospitalized HF patients (60). In one of the most promising trials, 30 patients with HF receiving furosemide were given either thiamine (200 mg/day) or placebo (126). After only 1 week, thiamine levels had increased, with statistically significant improvements in diuresis and EF noted. By the end of the 7-week study, improvement in cardiac function was observed with a 22% increase in EF. Although results from other trials have been mixed (124,127), the known effects of thiamine deficiency on the heart suggest that supplementation may be of therapeutic benefit if examined in larger HF trials.

Riboflavin (vitamin B<sub>2</sub>) and pyridoxine (vitamin B<sub>6</sub>) play critical roles in carbohydrate energy metabolism and the production of red blood cells. These B vitamins, like thiamine, are water soluble, are subject to renal excretion, have limited tissue storage, and are dependent on intake. Therefore, their status may also be adversely affected by the use of loop diuretics. Indeed, similar deficiencies in HF have been reported (22). The prevalence of having a deficiency of

any one B vitamin in HF was recently reported to be 68% (35). Vitamin B<sub>12</sub> and folate have also been shown to be deficient in a small subset of HF patients (128). Although these vitamins have been postulated to play a role in endothelial dysfunction through homocysteine action, studies to support an effect in HF are currently lacking.

## Amino Acids

Amino acids play a dual role in cardiac metabolism. First, they are the “building blocks” of proteins. Second, they are intermediary metabolites in energy substrate metabolism (16,33). A relevant role is played by taurine, which comprises 25% of the cardiomyocyte amino acid pool in humans. Taurine is not a substrate for protein synthesis or intermediary metabolism, but rather functions both as an antioxidant and as an important endogenous regulator of intracellular calcium homeostasis (129–132). Taurine modulates voltage-dependent calcium channels, sodium-calcium exchange, and sodium-aurine cotransport. The net effect is to protect heart muscle cells from calcium overload, on the one hand, and low calcium states on the other. Since myocyte calcium levels increase in HF and contribute to cellular injury, maintenance of appropriate taurine levels would seem to be critical. Taurine, like CoQ<sub>10</sub>, is also a potent antioxidant and reacts with a variety of potentially toxic intracellular aldehydes (133). Cytokine activity, particularly TNF- $\alpha$ , is increased in HF; TNF- $\alpha$  has been shown to decrease taurine levels (134). Lastly, the adverse actions of angiotensin II are potentiated in taurine-deficient cardiomyocytes (135).

Although taurine can be synthesized from methionine or cysteine, and as such is not an essential amino acid, the majority is obtained from dietary sources such as fish and milk (136,137). The heart extracts its supply through active transport by a taurine transporter (138). In infants and the elderly, taurine biosynthesis is reduced; thus, there was an increasing dependence on dietary sources (137). It is an essential ingredient in infant formulas, as taurine deficiency can produce HF. Taurine, dosed at up to 1 g 3 times per day, appears to be well tolerated (137). Indeed, large doses of taurine are a central component of many popular caffeine energy drinks.

Taurine levels are reduced in ischemic cardiomyopathy (137,139,140). Animal studies have shown that supplemental amino acids, including taurine, are beneficial in several cardiac injury and HF models (24,25,30,141,142). In humans with HF, amino acid mixtures have resulted in improvements in exercise capacity (143–145). There is only 1 small study examining taurine supplementation specifically (129). After 6 weeks, a significant improvement in EF was observed in the taurine-treated group. Additional studies are needed to confirm any beneficial effects of amino acid supplementation in HF.

## Other Micronutrients

There are many other micronutrients of potential interest with respect to HF. Although the evidence surrounding them is not as robust as for the molecules we have mentioned above, and some may not play a role in energy metabolism, it is worthwhile to briefly mention them to provide a complete picture of the field.

Creatine is a key regulator of energy metabolism in all muscle tissues of the body, including the heart. Mitochondrial energy stored in the phosphate bond of ATP is transferred to phosphocreatine by creatine kinase (146). In the failing myocardium, there is evidence that this system becomes dysfunctional and that the level of deficiency may correlate with the severity of HF (147–150). There are few studies specifically examining creatine supplementation in HF, however, and analysis is complicated by its effects on skeletal muscle and the alterations in creatinine levels that occur with supplementation that confuse monitoring of renal function (151–153).

Vitamin D is a molecule that plays an important role in the homeostasis of calcium, a key player in cardiac contractility. It is also an inhibitor of renin production (154). Low vitamin D levels have been observed in HF patients (155). Early experiments have suggested that low vitamin D levels may contribute to cardiac dysfunction through both calcium-dependent and calcium-independent processes (156,157).

Multiple cations, such as magnesium, potassium, zinc, and selenium, have been associated with HF to varying degrees (158). Magnesium and potassium deficiencies have been primarily related to arrhythmias in HF, although the prognostic significance of this finding is unclear (159–161). Zinc is an antioxidant that has been found to be deficient in HF patients, although the exact importance of this finding remains unclear (162). Finally, selenium is a component of glutathione peroxidase, an antioxidant enzyme that protects against endothelial dysfunction (163). Dietary deficiency in China has been associated with a cardiomyopathy in children, and there are case reports suggesting a role of severe selenium deficiency in the development of HF after bariatric surgery in the U.S. (164).

## Multiple-Micronutrient Supplementation

A limitation of many of the clinical trials reviewed here has been the use of only a single supplement. Although this allows researchers to focus on the effects of each micronutrient individually, it may potentially lead to minimal clinical outcomes if it simply shifts rate-limiting steps from one to another component of the complex energy-providing pathways. Correcting 1 deficiency thus, in theory, would unmask 1 of the many other deficiencies present. Also, the need for a given nutrient may not be apparent, as blood levels do not always reflect a deficiency or increased requirements in the diseased myocardium (e.g., L-carnitine).

Therefore, given the multiple-nutrient deficits in HF patients, an alternative strategy is to use a combination of supplements to attempt to maximize clinical effects, as performed in animal experiments (27,36,165).

One study showed that cardiomyopathic hamsters had deficiencies in CoQ10, L-carnitine, and taurine at the myocardial level during the late stages of their disease (27). Supplementation for 3 months versus a placebo diet improved the actual structure of myocyte sarcomeres and mitochondria, contractility, and cardiac function. In a more recent study, rats pre-treated with this combination before coronary artery ligation exhibited markedly improved survival, cardiac function, and reduced infarct size when compared with placebo (165).

Few studies have included multiple-nutrient supplementation in human HF (Table 4). One study (79) examined the effects of a nutrient drink. Although this supplement contains many nutrients, the ones relevant to this review include CoQ10, carnitine, thiamine, and taurine. Forty-one patients with ischemic cardiomyopathy (EF <40%) scheduled for elective bypass surgery were randomized to either the nutrient supplement or a similar-tasting placebo. The groups were relatively well matched except for a slightly higher age and lower digoxin use in the control group. The patients were then followed for 40 to 45 days until their surgery, at which point LV biopsies were obtained. These tissue samples were used to confirm the primary end points: increases in myocardial levels of taurine, carnitine, and CoQ10. Indeed, tissue samples revealed 40% to 144% higher levels of each of these nutrients in the treated group. Secondary end point analysis showed a decrease in left ventricular end-diastolic volume (LVEDV) when compared with placebo and a trend toward reduced left ventricular end-systolic volume (LVESV). However, EF was unaffected. Adverse effects of the supplement were minimal. The primary complaint was gastrointestinal, possibly due to the large undivided dose of CoQ10 administered. An isolated increase in creatinine, not blood urea nitrogen, was felt to likely be secondary to the breakdown of creatine consumed through the supplement. Overall, whereas the results were promising, the study did face several limitations. The small sample size and short duration of the trial made detecting significant differences more difficult. Additionally, many patients in the study did not have clinical symptoms of HF at the onset of the trial. Thus, no comment could be made on symptom improvement with supplementation. The confirmation, however, of increased levels of certain key nutrients in the myocardium with oral administration did reaffirm the validity of such a delivery method for future trials.

Another study evaluating the role of multiple-micronutrient supplementation in elderly HF patients has also showed promising results (166). In this trial, patients with stable, ischemic HF (EF <35%) were randomized to either capsules containing multiple nutrients or placebo. Although many vitamins and minerals were administered,

**Table 4** Selected Trials Utilizing Multiple-Micronutrient Supplementation in HF

| Study Author (Ref. #)  | Year | No. of Patients | Study Design                     | Primary End Point                                                                        | Patient Population                                | Results                                                                             | Dose                                                                     | Side Effects Related to Supplement     | Remarks                                                                                                                          |
|------------------------|------|-----------------|----------------------------------|------------------------------------------------------------------------------------------|---------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------|----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Jeejeebhoy et al. (79) | 2002 | 41              | Double-blind, placebo-controlled | Comparison of the myocardial levels of taurine, carnitine, and CoQ10 for 30–45 days      | HF with CAD (EF ≤40%)                             | ↑ Myocardial levels of carnitine, CoQ10, and taurine                                | CoQ10 150 mg/day, carnitine 3 g/day, thiamine 25 mg/day, taurine 3 g/day | 1 patient exited study due to diarrhea | Short study duration and small size. No assessment of symptoms. Secondary end point improvement in LVED volume. No change in EF. |
| Witte et al. (166)     | 2005 | 30              | Double-blind, placebo-controlled | Evaluation of LV function, pro-inflammatory cytokines, and QoL at end of therapy (~1 yr) | HF with CAD (EF ≤35% + fatigue or breathlessness) | ↑ EF, ↓ LVEDV, LIVESV. No difference in cytokine levels. Improvement in QoL scores. | CoQ10 150 mg/day, thiamine 200 mg/day                                    | None                                   | Small study size. Limited supplement cocktail.                                                                                   |

CAD = coronary artery disease; QoL = quality of life; other abbreviations as in Tables 1 and 2.

the substances relevant to this review were CoQ10 and thiamine. No significant adverse effects were noted during the study. Patients were followed for 9 months, at which point the primary end point, a change in EF, was evaluated by cardiac magnetic resonance imaging (MRI). The active compound, but not placebo, significantly improved EF, with a significant decrease in LVESV and LVEDV. There was an improvement in quality-of-life scores at 6 months, reaffirming the need for long-term observation to witness improvement from supplementation. However, there were no changes in NYHA functional class or exercise capacity, which the authors attributed to the small sample size. Overall, this study did show improvement in cardiac function parameters on MRI, which is highly promising. Yet again, a larger study population would have been helpful for detecting more subtle differences, as noted by the authors. Also, the inclusion of key missing nutrients, such as carnitine and amino acids, would have minimized the chance of unmasking these deficiencies when administering a more limited supplement cocktail.

Both of the trials described here, in their own way, illustrate the promise for long-term improvement of cardiac function in HF patients when key nutrients are administered simultaneously. Future studies are needed to first confirm these results and to then lead to a better definition of the ideal regimen to maximize cardiac benefits.

### Outlook and Challenges

The optimal treatment of HF remains a formidable challenge, as suggested by the disappointing outcomes of recent trials (10,59,167–169). There is a clear need for new therapies that can work synergistically with standard treatments to reverse the progression of the disease. This calls for a more detailed examination of the role of nutrition in the treatment of HF. The recent GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio-Heart Failure) trial, for example, has shown the promise of such a complementary approach with respect to fatty acids (170).

In the failing heart, the presence of viable, but dysfunctional, myocardium is relatively common and is an important predictor of improvement of systolic function (reverse remodeling) in response to medical and revascularization therapies (171–174). Certain causes of dysfunctional myocardium are known, such as stunning hibernation due to chronic ischemia (175). Perturbed energetics due to micronutrient deficiencies may also be responsible for dysfunctional myocardium. The chronic improvement or normalization of contractility of dysfunctional myocardium may be used as a surrogate end point to assess the effects of micronutrients in HF (171,173,174,176).

An underexplored therapeutic field involves micronutrients and their effects on the energy dynamics of the heart. The nutritional studies summarized here show interesting results in the treatment of HF. It is well known that the

**Table 5** Limitations of Existing Trials and Suggested Improvements in Methodology

| Pitfalls in Previous Study Methodologies                              | Suggested Improvements                                                                                                             |
|-----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| Supplementation of only a single nutrient                             | Supplementation of multiple nutrients previously studied individually                                                              |
| Small sample size (largest multinutrient trial has 41 patients)       | Large patient population in a double-blind, placebo-controlled trial                                                               |
| No pre-trial assessment of viable, but dysfunctional, myocardium      | Use of MRI or other modalities to assess for viable, but dysfunctional, myocardium pre-trial and at specified intervals thereafter |
| Conducted prior to the use of current standard-of-care therapy for HF | Use of current guideline-directed standard-of-care therapy, including ACEI and BB                                                  |
| Short duration of study                                               | Long-term outcome trial (>1 yr)                                                                                                    |
| Evaluation of limited end points                                      | Evaluation of symptom improvement, cardiac structure/function (e.g., reverse remodeling, EF), and survival                         |

MRI = magnetic resonance imaging; other abbreviations as in Tables 1, 2, and 3.

heart has unique and significant energy requirements due to its mechanical pumping function and that a failing heart is in a perpetual state of increased stress due to neurohormonal activation. Defects in complex pathways, such as those involved in ATP production and driving calcium cycling, result in further energy imbalances and lead to additional contractile impairment in HF. Results from animal models and small human trials suggest a potential cardiac benefit to correcting micronutrient deficiencies. To varying degrees, CoQ10, L-carnitine, thiamine, taurine, and amino acids have all been shown to improve functional, structural, and hemodynamic parameters in HF patients, mostly by improving flux through the cycles of energy transfer in the heart (Fig. 1). Micronutrients have been shown to improve EF (90,91,104,126,129). However, there are substantial limitations to the research in its current state. First, studies have often been small, with inconsistent end points, and short in duration. A few trials were not randomized, and most did not examine key end points such as improvement in pump function and clinical outcomes. Lastly, the focus on replenishment of only a single nutrient has possibly masked therapeutic effects by simply shifting rate-limiting steps to other energy pathways. Given the complex nature of myocardial energy metabolism (19), it is not likely that a single substance alone will be able to reverse the widespread deficits present in HF, similar to a starving individual requiring diverse nutrition from multiple food groups for survival. These design limitations have together contributed to the often inconsistent results evident in the existing literature (Table 5). Animal and human studies that have attempted to overcome the single-nutrient restriction have yielded interesting, but not conclusive, results (79,166). Current advances in imaging technology (e.g., MRI, echocardiography) have also not yet been adequately utilized in this field (171). No single trial conducted to date has met the necessary criteria to demonstrate a significant clinical benefit when 1 or more micronutrients were added to standard therapy for HF (Table 5). Such a study should show conclusive improvement in important outcomes such as hospitalizations and mortality in HF when micronutrients are added to standard therapy. Compared with the landmark multicenter trials of existing HF therapies, the studies of nutritional supplementation are in a relative state of infancy (177–179). If proven to be beneficial, the wide-

spread availability of these individual nutritional compounds from generic manufacturers may offer patients a lower-cost therapy not burdened by development and marketing expenses.

In summary, the potential importance of any novel therapy in a disease with increasing prevalence, such as HF, necessitates a timely and detailed examination of efficacy in a clinical trial population. The unmet energy requirements of the failing heart have been carefully detailed, and the molecules controlling energy and substrate utilization are equally recognized from extensive laboratory work. Unfortunately, the effort dedicated up to now to testing the theoretical benefits of these micronutrients in a scientifically rigorous clinical trial fashion has been insufficient to yield any conclusions that can be applied to widespread practice.

**Reprint requests and correspondence:** Dr. Heinrich Taegtmeier, Department of Internal Medicine, Division of Cardiology, University of Texas Houston Medical School, 6431 Fannin, MSB 1.246, Houston, Texas 77030. E-mail: Heinrich.Taegtmeier@uth.tmc.edu.

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**Key Words:** heart failure ■ nutrition ■ energy ■ micronutrients ■ metabolism.

## Micronutrient Deficiencies: An Unmet Need in Heart Failure

Victor Soukoulis, Jamil B. DiHu, Michael Sole, Stefan D. Anker, John Cleland, Gregg C. Fonarow, Marco Metra, Evasio Pasini, Theresa Strzelczyk, Heinrich Taegtmeyer, and Mihai Gheorghiad

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