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Abstract Patients suffering from congestive heart failure exhibit impaired myocardial energy production, myocyte calcium overload and increased oxidative stress. Nutritional factors known to be important for myocardial energy production, calcium homeostasis and the reduction of oxidative stress, such as thiamine, riboflavin, pyridoxine, L-carnitine, coenzyme Q10, creatine and taurine are reduced in this patient population. Furthermore, deficiencies of taurine, carnitine, and thiamine are established primary causes of dilated cardiomyopathy.

Studies in animals and limited trials in humans have shown that dietary replacement of some of these compounds in heart failure can significantly restore depleted levels and may result in improvement in myocardial structure and function as well as exercise capacity. Larger scale studies examining micronutrient depletion in heart failure patients, and the benefits of dietary replacement need to be performed. At the present time, it is our belief that these conditioned nutritional requirements, if unsatisfied, contribute to myocyte dysfunction and loss; thus, restoration of nutritional deficiencies should be part of the overall therapeutic strategy for patients with congestive heart failure.

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1. Introduction

Congestive heart failure (CHF) has emerged as a major health problem during the last four decades [1]. With an aging population and the prolongation of lives of cardiac patients, the incidence of CHF is increasing steadily in most countries [2]. Despite a better understanding of the pathophysiology of this disease and recent advances in pharmacotherapy, myocardial dysfunction is usually a relentless, progressive process resulting in an unacceptably high 5 year mortality of 59% and 45% in men and women, respectively [3].

In the past, much of the research in this field has been focused on pharmacotherapy targeting fluid overload, hemodynamic abnormalities and neurohormonal stimulation. More recently, another growing field of research has been resynchronization therapy and defibrillation with implantable devices. Perhaps overshadowed by this, there is also a growing interest in the role that metabolic abnormalities contribute to the progressive long term myocyte damage seen in heart failure. Factors which reduce myocyte energy production as well as myocardial injury result in accumulation of calcium in myocytes of the failing heart, which in turn causes mitochondrial injury. This further decreases myocyte energy production and increases in oxidative stress, resulting in free radical damage, myocyte dysfunction and death [4, 5, 6]. These metabolic processes also affect skeletal muscle in patients with congestive heart failure, and contribute to fatigue and disability [7, 8, 9]. With high protein-calorie feeding and a marked positive energy balance, these metabolic derangements do not appear to improve [10]. This suggests that this

is not a problem with negative protein-calorie balance, but due to specific nutritional deficiencies that are not met by standard dietary therapy.

There is growing evidence that patients with congestive heart failure are deficient in many micronutrients that play important roles in the maintenance of calcium homeostasis, the control of oxidative stress and the metabolism of protein-energy foods [11, 12]. Similar to the need for increased folic acid in pregnancy, patients with heart failure may have nutritional requirements that are different than those in individuals in a normal physiologic state. That is, the nutritional demands of a given pathologic process, such as heart failure, may result in "conditioned nutritional requirements" for the affected organ–the failing myocardium has different nutritional needs than the normal myocardium and these needs may not be satisfied by the usual nutritional guidelines published by government agencies. Furthermore, the need for a given nutrient may not be readily evident in the blood but only be reflected by direct tissue sampling. In some cases, even normal levels may be insufficient to maintain full functional status in the face of pathologic metabolic demands.

Biochemical alterations do not occur across the myocardium in a uniform manner; the failing heart is heterogeneous in both composition and structure. Only a small minority of myocytes at any given time can be irreversibly injured–cells can not remain irreversibly injured over the multi-year course of heart failure–the vast majority must be capable of recovery under appropriate conditions. The contemporary treatment of heart failure has focused on myocardial survival by normalizing environment through correcting hemodynamic and neurohormonal stress. We believe that addressing the conditioned nutritional requirements of the patient with congestive heart failure is also important.

This paper will review the different nutritional deficiencies that have been identified in patients with heart failure and whether nutritional supplementation aimed at correcting these deficiencies results in improved patient outcomes. We will focus on factors integral to myocyte energetics, intracellular calcium homeostasis and the control of oxidative stress. We will exclude a review of vitamin D and abnormal mineral calcium homeostasis in heart failure as these are dealt with fully elsewhere in this focused issue of *Heart Failure Reviews.*

2. Nutrient factors important in myocardial energetics

Normal myocardial energy production is dependent on the continual and adequate flow of nutrients. Several important cofactors that are needed to assist in aerobic metabolism have been found to be deficient in patients with congestive heart failure. These include B vitamins, carnitine, coenzyme Q10 and creatine.

2.1. B Vitamins

Thiamine is a water soluble B complex vitamin that is synthesized by a wide variety of plants and microorganisms, but not animals. It is an important coenzyme required in carbohydrate energy metabolism. Because thiamine is stored in only small amounts (20–30 mg) in skeletal muscles, heart, liver, kidney and brain [13], individuals are dependent on daily gastrointestinal absorption to maintain thiamine stores.

In patients with heart failure, the reported incidence of thiamine deficiency ranges from 13% to 93% [14–19]. There are numerous factors that have been found to be associated with thiamine deficiency in patients with heart failure including loop diuretic use [14, 15], malnutrition [16, 17], severe heart failure [16], advanced age and frequent hospitalizations [15, 18, 20, 21]. In a recent prospective study of 100 hospitalized patients with CHF, the prevalence of thiamine deficiency was found to be 33% [22]. In this population, spirinolactone use, preserved renal function and non-use of thiamine supplements were associated with thiamine deficiency. In addition, multivitamin vitamin supplementation was found to be somewhat protective against deficiency.

Patients with thiamine deficient heart disease exhibit sodium and water retention, vasodilatation and reduced ejection fraction. These features can be reversed in patients with thiamine administration [23]. There is little prospective data examining the role of thiamine repletion in patients with CHF. Shimon *et al.* reported a 22% increase in ejection fraction with seven weeks of thiamine replacement in 27 patients with severe CHF [24].

Riboflavin (vitamin B2) and pyridoxine (vitamin B6) play critical roles in the production of red blood cells and in carbohydrate mediated energy production. These B vitamins, like thiamine, are water soluble, subject to renal excretion and have limited tissue storage. In contrast to the studies with thiamine, there has been little investigation of these B vitamins. We (Keith et al. in preparation), recently evaluated the prevalence of riboflavin (B2) and pyridoxine (B6) deficiency in 100 diverse patients hospitalized with heart failure compared to 50 age and sex matched healthy controls. In patients with heart failure the prevalence of riboflavin deficiency was 27% and that of pyridoxine 38% as compared to 2% and 19% respectively in the controls. A remarkable 65% of patients were deficient in at least one of thiamine, riboflavin or pyridoxine compared to only 19% of controls. There was no relationship between deficiency and the use of diuretics or the presence of renal disease; however, B6 deficiency was associated with anemia–an important concomitant of the heart failure state. The status of both vitamins did reflect

multivitamin supplement intake – 42% and 30% of unsupplemented patients were deficient in B2 and B6 respectively as compared to 22% and 18% respectively in those who took multivitamin supplements.

Given vitamin B deficiency has been found to be prevalent in this patient population, consideration for vitamin B supplementation to patients with CHF should be made, particularly if they have features that have been associated with increased risk of deficiency.

2.2. L-Carnitine

L-Carnitine and its derivatives, acetyl- and propionyl-L-carnitine, are organic amines that play an important role in myocardial energy production. This amino acid derivative is essential for the transport of long-chain fatty acids from the cytoplasm into sites of beta-oxidation in the mitochondria [25]. In addition, carnitine binds acyl groups and facilitates the free diffusion of toxic short chain acylcarnitines out of the cell. This process leads to an increase of free coenzyme A, which activates pyruvate dehydrogenase, allowing for improved coupling between glycolysis and glucose oxidation. The end result of this is a reduction in lactate and hydrogen burden on the cardiac myocyte [25, 26].

Carnitine stores can be replenished from endogenous synthesis from lysine and methionine, as 10–20 mg a day is produced in liver and kidney tissue [27]. As well, the average dietary intake ranges from 100–300 mg of carnitine, of which the bioavailability is 54–87% [28]. Patients with genetically determined deficiency develop both cardiac and skeletal dysfunction, which can be improved by carnitine administration [29].

Carnitine deficiency can also be an acquired state in individuals with established CHF, with levels reported to be depleted by as much as 50% [26, 30]. The effect of carnitine supplementation in patients with heart failure has been examined in a few small studies. Chronic replacement has been reported to increase peak oxygen consumption, increase exercise time and decrease cardiac dimensions [31]. A randomized study of 70 patients with dilated cardiomyopathy and NYHA class III–IV symptoms found an improved 3 year survival for patients given daily oral supplementation of 2 g/day of carnitine, compared to placebo [32]. A larger multicenter, double-blind, placebo controlled, randomized trial in patients with high risk myocardial infarction found that administration of L-carnitine for 12 months attenuated left ventricular dilatation [33]. Somewhat disappointing in this study was that L-carnitine supplementation did not appear to improve left ventricular function or survival [34]. More studies are needed to better understand the importance of L-carnitine supplementation in heart failure.

2.3. Coenzyme Q10 (Ubiquinone)

Coenzyme Q10 (CoQ10) is a micronutrient that is an obligatory component of the mitochondrial electron transport chain. It plays a vital role as the rate limiting carrier for the flow of electrons through the early portion of the mitochondrial respiratory chain [35]. CoQ10 also serves as an intracellular antioxidant and inhibits the oxidation of LDL cholesterol [27].

Body stores of CoQ10 are dependent on both endogenous synthesis through the enzyme hydroxyl-methylglutaryl coenzyme A reductase (HMGCoA reductase) and the acetylCoA-mevalonate pathway and tyrosine [28]; CoQ10 is also provided by diet through a wide range of food sources including fish and meat. Although its bioavailability is less than 5% due to a large hepatic first pass effect [36], dietary supplementation with a 100 mg three times a day results in a 4 fold increase in plasma CoQ10 [37]. "Statin" drugs, used to decrease cholesterol in patients with cardiovascular disease, inhibit HMGCoA reductase, and thus decrease plasma and tissue levels of CoQ10 [38, 39].

Myocardial CoQ10 levels have been found to be reduced by up to 50% in both animal and human models of CHF [11, 40]. The effect of oral replacement of CoQ10 in patients with heart failure is unclear, as only small clinical trials have been performed, and these have had mixed results. A meta-analysis of 8 randomized, placebo controlled trials conducted between 1984–1994 found that oral CoQ10 supplementation improved stroke volume and cardiac output, with a trend towards reducing end-diastolic volumes [41]. More recently, Morisco et al. randomized 319 patients with NYHA III–IV symptoms to CoQ10 at 2 mg/kg versus for placebo for the duration of one year. Individuals in the active treatment arm had fewer hospitalizations and exacerbations of pulmonary edema [42]. Other studies have reported improvement in exercise capacity [43, 44, 45], functional status [45] and quality of life [44,45]. Not all studies have found CoQ10 to be beneficial in addition to standard medical therapy [46, 47]. Nonetheless, at doses of 50–150 mg it has been shown to be safe and well tolerated with few side effects [48].

2.4. Creatine

Creatine phosphate is a phosphorylated creatine molecule that is an important energy store in the heart in skeletal muscle. In the mitochondria, high-energy phosphate is transferred from creatine phosphate to adenosine diphosphate to form adenosine triphosphate through catalysis by creatine kinase.

Muscle stores of creatine are maintained by endogenous production and from dietary intake. Creatine is biosynthesized in the liver and spleen from the precursors arginine, glycine and methionine. The concentration of total creatine in normal adult human myocardium or skeletal muscle is

140 μmol/g protein [49]. There is evidence that increased adrenergic drive, a prominent feature of heart failure, can decrease myocardial creatine and creatine kinase [50].

Creatine depletion in animals results in structural, metabolic and functional abnormalities in muscle [49]. In the failing heart, myocardial creatine content is reduced, with the expected concomitant reduction in creatine phosphate, by up to 50% [50,51]. It has been reported that myocardial creatine phosphate:adenosine triphosphate ratio may be a better predictor of patient mortality than ejection fraction or functional class in patients with dilated cardiomyopathy [51].

Creatine supplementation has been shown to improve short term intense exercise by mediating a reduction in lactate production in skeletal muscle [52]. There are very few studies examining the role of creatine phosphate in heart failure. 20 g of creatine given to 9 heart failure patients for 10 days was found to increase skeletal muscle creatine phosphate and improve skeletal strength and endurance [53]. In this study there was no change in ejection fraction following treatment with creatine phosphate.

3. Taurine and the regulation of intracellular calcium

The failing myocardium exhibits increased intracellular and mitochondrial calcium, which results in a decrease in myocardial energy production and an increase in oxidative stress. Taurine is an amino acid that is both a critical regulator of intracellular calcium and an antioxidant. Through interaction with calcium channels and ion exchangers in the sarcoplasmic reticulum and sarcolemma, it exhibits a biphasic action to both increase and decrease calcium levels and maintains calcium homeostasis [54].

Taurine is unique in that it is a sulfonated amino acid that does not enter into protein synthesis. It is present in high concentrations in mammalian plasma and cells and it is the most abundant free amino acid in cardiac muscle [27]. It is not an essential amino acid in healthy humans, as it can be synthesized from methionine and cysteine within the liver and spleen. However, the activity of cysteine sufinic acid decarboxylase, which is the enzyme required for the biosynthesis of taurine, is very low in humans, and the majority of body stores appear to be dependent on dietary intake from seafood and meat [55]. Experimental studies in animals have shown that TNF-α infusions inhibit taurine biosynthesis and decrease tissue taurine levels. These studies suggest that the increased TNF-αactivity seen in heart failure may increase the need for exogenous taurine [56]

In studies of cats and dogs, taurine deficiency has been linked to the development of a cardiomyopathy that resolves with taurine administration [57, 58]. In humans, depletion of this amino acid has been found to render the heart more susceptible to doxorubicin toxicity or ischemic damage [59]. Taurine levels are known to be altered in patients with heart disease. A reduction of taurine concentration is seen in the ischemic myocardium [60]. Normal levels are found in non-ischemic cardiomyopathy [55], but these levels may be inadequate relative to the intracellular calcium burden.

Studies of animal models have found that orally administered taurine significantly reduces myocardial damage induced by the calcium paradox, doxorubicin, isoproterenol, or in hamster cardiomyopathy [61, 62]. It has also been found to increase survival in rabbits with aortic insufficiency [63] and to have a protective effect in the murine model of iron overload cardiomyopathy [64]. There is a paucity of studies examining taurine administration to patients with CHF. There was one study published that found that taurine taken at a dose of 1 g three times a day to be well tolerated and improve both the hemodynamic state and functional capacity in patients with heart failure [55]. More studies are required to better examine the role of taurine in this patient population.

4. Reducing oxidative stress in heart failure

There is evidence that oxidative stress mediated by reactive oxygen species plays a role in the pathogenesis of heart failure [65]. Nutrients such taurine and coenzyme Q10, along with vitamins E and C, function as non-enzymatic antioxidants within the cell, modulating the effect of free radicals produced in the mitochondria.

Increased oxidative stress has been demonstrated in many different animal models of heart failure [65, 66]. Decreases in alpha-tocopherol and antioxidant enzymes such as glutathione peroxidase with a concomitant increase in protein oxidation has been demonstrated in Syrian hamsters with end stage cardiomyopathy [67]. The administration of vitamin E in these animals appeared to normalize these findings.

Despite experimental data in animal studies, trials of antioxidant therapy in heart failure have been disappointing and somewhat conflicting. Significant increases in plasma lipid peroxide and malonyldialdehyde levels, markers of oxidative stress, have been found to be significantly elevated in patients with heart failure [68]. Oxidative stress was observed to be highest in patients with worsening functional class of heart failure. One small study of 12 patients did find that supplementation with vitamin E normalized markers of oxidative stress, but this did not translate to have any observed clinical effect on functional status or quality of life [69]. A larger randomized study of 50 patients with class II–IV heart failure did find high serum markers of oxidative stress, but treatment with 1000 IU of vitamin E daily failed to reduce these

markers [70]. These negative findings are similar to the negative findings in other studies of vitamin E in the treatment of patients with cardiovascular disease [71, 72].

These data suggest that while oxidative stress plays an important role in the pathogenesis of heart failure, to date there is little evidence that antioxidant supplements are of benefit in heart failure patients. Living cells have both enzymatic and nonenzymatic defense mechanisms to balance the multitude of oxidative challenges presented to them. The nonenzymatic group includes a wide variety of biological molecules that are both endogenous synthesized and/or exogenously supplied. The latter may be simple molecules such as vitamins A, C and E or a wide variety of complex compounds such as those in colored fruits and vegetables, teas, cocoa and other foods. Addressing these nutritional requirements in heart failure has failed because contemporary strategies remain based on rudimentary knowledge.

5. Combined nutritional supplementation

The failing myocardium has a cascade of interconnected metabolic abnormalities that may not be corrected by supplementation with a single nutrient.

We randomized a placebo diet against one supplemented with taurine, carnitine, creatine, CoQ10, thiamine, vitamins E,C and selenium to cardiomyopathic hamsters during the late stages of their dilated cardiomyopathy [73]. We observed a depletion of myocardial creatine, carnitine, taurine, CoQ10 and vitamin E in the hearts of diseased animals; supplementation for 3 months markedly improved both myocyte function and structure.

There have been two studies that have looked at multinutrient supplementation in human patients. The first was a double-blinded, randomized study in 41 patients awaiting coronary artery bypass surgery [74]. The supplement was given for 30 days, until surgery, and contained taurine, coenzyme Q10, carnitine, thiamine, creatine, vitamin E, vitamin C and selenium. A significant decrease in left ventricular end diastolic volume was seen in patients receiving the nutrient cocktail compared to controls. At the time of surgery, cardiac biopsy in the patients revealed significant reductions in carnitine, coenzyme Q10 and taurine in the placebo group, confirming their deficiency in heart failure; biopsy in supplemented patients showed significantly restored myocardial levels, confirming the nutritional benefit of the supplement.

In a second study, 30 patients with CHF were randomized to receive placebo or a supplement containing calcium, magnesium, zinc, copper, selenium, vitamin A, thiamine, riboflavin vitamin B_6, folate, vitamin B_{12}, vitamin C, vitamin E, vitamin D and coenzyme Q10 [75]. After 9 months of treatment, a significant reduction in left ventricular volume and a 5% improvement in ejection fraction were seen in those receiving micronutrient supplementation. Small improvements in quality of life scores were also seen in patients, but treatment did not have any impact on 6 min walk time.

6. Nutritional supplementation in clinical practice

Federal authorities in most developed nations rely on healthcare professionals to define nutritional guidelines for patients. It is important to remember that these recommendations are often derived from nutritional data from healthy patients, and they do not take into consideration the needs of specific disease states. Based on the data presented in this discussion, we believe that patients with cardiac and other disease states have specific conditioned nutritional deficiencies that should be addressed by supplements–at this point a B vitamin supplement at the minimum.

Restoring myocardial nutrition in conjunction with traditional therapeutic modalities would appear to be a strategy that could benefit patient with heart failure. Well-designed and adequately powered clinical trials with nutritionals are needed. However nutritional companies face the constraints of reduced profit margins and more precarious patent protection than that potentially enjoyed by traditional pharmaceutical companies following the development of a new molecular entity. Thus such trials need to be encouraged by government scientific and financial support; if the trial is successful health claims should be restricted to the sponsoring company for an appropriate period.

7. Conclusions

There is considerable evidence that patients with congestive failure, even with normal dietary intake, exhibit conditioned nutritional requirements that are unique to this patient population. These nutrients play important roles in controlling energy metabolism, calcium balance and oxidative stress within the failing myocardium. If uncorrected, these deficiencies may contribute to progressive myocyte dysfunction, the hallmark of congestive heart failure, and ultimately death. For example primary deficiencies in carnitine, taurine or thiamine alone, have been shown to be a cause of heart failure in humans, correctable by supplementation. There is also evidence that tissue levels of the nutrients respond to the specific intake of these dietary substances. Therefore repletion of these important nutrients should be considered as part of the therapeutic management of heart failure. From this review, although it is obvious that much more basic and clinical research is needed in this field, the cavalier dismissal of nutritional therapy in the current

American [76] and Canadian [77] guidelines for heart failure is not warranted.

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