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Nutrition and the heart

K. N. JEEJEEBHOY, M. J. SOLE

Department of Medicine, St. Michael's Hospital, Toronto, Ontario, Canada (Correspondence to: Dr KNJ, 3-035 Queen Wing, St. Michael's Hospital, Toronto, ON Canada, M5B 1W8)

Abstract—Protein-energy malnutrition is associated with cardiac atrophy and adaptive reduction in cardiac output. Refeeding increases cardiac output and oxygen consumption. Rapid refeeding of severely malnourished patients can precipitate heart failure. Micronutrient deficiencies also contribute to cardiac dysfunction. Cardiac failure can cause weight loss and malnutrition. The most extreme degrees of cardiac malnutrition occur in patients with right heart failure and tricuspid incompetence. These patients have increased mortality but feeding protein and energy does not improve cardiac function. The hearts in patients with cardiac failure have mitochondrial dysfunction and these mitochondria are depleted of carnitine, coenzyme Q10 and taurine. The severity of depletion is related to the severity of heart failure. In controlled trials, repletion of carnitine and coenzyme Q10 improves outcome. Furthermore, in heart failure oxidative stress is increased and there may be thiamin deficiency. It is proposed that the nutritional therapy of heart failure should be directed to the replacement of carnitine, coenzyme Q10 and taurine as well as antioxidants and thiamin rather than protein-energy. © 2001 Harcourt Publishers Ltd.

Key words: heart failure; nutritional support; mitochondrial function; micronutrients; antioxidants

Introduction

Severe malnutrition is known to be associated with atrophy of the heart. Prior to the advent of antibiotic therapy, a condition of 'Brown Atrophy' of the heart was recognized by pathologists in autopsy material from patients with advanced tuberculosis and malnutrition (1). More recently cardiac wasting has been noted in patients with anorexia nervosa (2). On the other hand, heart failure is also associated with malnutrition. It has been claimed that malnutrition is a widespread problem in patients with heart failure (3) and that patients with heart failure and weight loss have increased mortality (4). The question therefore arises as to whether improvement of nutrition in patients with heart failure would improve outcome.

Effect of protein-energy nutrition on cardiac function

A well-functioning heart, among other characteristics, beats slowly and ejects a large volume with each stroke. In addition, as the ventricle stretches the wall thickness is reduced. Hence, the stroke volume and muscle wall thickness in relation to ventricular diameter has been used to determine the effect of protein-energy nutrition on cardiac function. Studies have been done in individuals with weight loss (5), and normal and obese subjects (6). When these data are compiled it is clear that with weight loss the stroke volume falls and the ventricular wall becomes thinner and vice versa. In addition, malnutrition is associated with reduced oxygen consumption and a corresponding fall in cardiac output.

Effect of refeeding the malnourished patient on cardiac function

On refeeding, oxygen consumption increases and cardiac output rises. In general, if the intake of calories is increased gradually then the heart responds with an increase in contractility and later the wall thickness increases. However, if a seriously malnourished patient is fed rapidly then the malnourished heart fails to respond and the patient goes into cardiac failure with the development of tachycardia, oedema, pulmonary congestion and breathlessness (7). In a mild form this is called refeeding oedema but the condition may become life-threatening if the increase in energy intake is excessive. In very malnourished patients it is very easy to feed excessively. For example, a 2100 kcal intake, which is not excessive for a normal weight person, amounts to 70 kcal/kg/day in an anorexic woman weighing only 30 kg!

Micronutrient deficiency and the heart

There are a number of micronutrient deficiencies that have an adverse effect on the heart. Thiamin deficiency

can cause cardiac failure because thiamin is an integral part of pyruvate dehydrogenase which is responsible for converting pyruvate to acetyl CoA which is then oxidized in the tricarboxylic acid (TCA) cycle. Therefore in thiamin deficiency glucose oxidation is inhibited. Magnesium and potassium deficiency cause arrhythmia. Selenium and phosphorus deficiency cause cardiomyopathy and heart failure. Poor cardiac status of taurine, carnitine and coenzyme Q10 has also been associated with impaired cardiac function (discussed later).

Heart failure and nutrition

Weight loss in heart failure: an adaptive response

Normally, as the blood flow to the heart increases, for example with exercise, the ventricle is stretched at the end of diastole. Increased ventricular stretch increases contractility and the process continues until outflow rises to equal inflow. This relationship between ventricular stretch and contractility is called the Frank-Starling law. However, if the heart is stretched excessively, it fails to respond to increased stretch and the output falls. In heart failure, the relationship between stretch and contractile activity is altered so that the heart is dilated and the contractile response to stretch is reduced. In short, the heart cannot respond to increased inflow of blood. The patient initially responds to this limitation by reducing activity. With increasing heart failure the heart is unable to respond to the resting venous inflow. Since cardiac output increases with the metabolic rate, a fall in metabolic rate would reduce cardiac output and thus reduce the work of a failing heart. Since the lean body mass is the major determinant of the resting metabolic rate, a fall in lean body mass will reduce metabolic rate and cardiac output, thus protecting the failing heart. These theoretical considerations are supported by observations on patients with heart failure. Toth et al. (8) noted that activity associated energy expenditure, but not resting energy expenditure was reduced in patients with heart failure without weight loss. In those with weight loss, both activity and resting energy expenditure were reduced. In addition, the most significant determinant of wasting in heart failure was severe bi-ventricular failure with increased right atrial pressure and tricuspid incompetence (9). These patients have a very low and fixed cardiac output so that they can only increase oxygen consumption to a very limited extent. Wasting in these patients is adaptive.

Effect of energy and protein intake in patients with heart failure

Increased energy intake either as carbohydrate or fat increases oxygen consumption (10). Therefore it is not surprising that high amounts of energy given as total parenteral nutrition (TPN) is associated with a marked increase in cardiac output and oxygen consumption (11). On the other hand, protein intake did not increase cardiac output (10). Therefore, energy intake should be increased cautiously in patients with marked malnutrition and severe heart failure. However, it may be possible to increase protein intake without adding stress to the failing heart.

Does nutritional support improve cardiac and muscle function in patients with heart failure?

Heymsfield et al. (11) undertook tube feeding that provided 35 kcal/kg/day in cachectic patients with heart failure. These patients initially lost weight due to diuresis and then started to gain weight. They were in positive nitrogen and elemental balances and as expected oxygen consumption increased. Despite nutritional support and positive balances, cardiac wall thickness and cardiac function did not improve over a period of 3 weeks. Borqvist et al. (12) in a randomized controlled trial lasting 8 weeks with a protein supplement of 30 g and energy supplement of 750 kcal/day did not show any benefit in markers of heart failure or skeletal muscle energetics despite a marked positive energy balance. It is of interest that these patients did not gain the weight expected based on the positive energy balance.

Do growth factors benefit heart failure?

In heart failure the thickness of the ventricle is reduced. Growth hormone was given to patients with heart failure, in the belief that this hormone would increase the muscle mass of the heart and thus improve the pumping efficiency of the failing heart. This possibility was tested in two randomized controlled trials (13, 14) which showed that while growth hormone increased the muscle mass of the ventricle, it did not improve cardiac failure. Therefore, factors that promote muscle growth of the ventricle do not seem to have a positive effect on heart failure.

Role of protein-energy supplements in the treatment of heart failure

Anker et al. (4) showed that patients with heart failure and a low ejection fraction had markedly shortened survival. Unfortunately, from the above considerations, it is obvious that simply feeding protein and energy or promoting the growth of the thickness of the ventricle by giving growth hormone cannot improve heart failure. While refeeding the malnourished patient with cardiac failure may increase body weight, this therapy will not alter cardiac function. The above mentioned

information indicates that protein-energy supplementation is unlikely to improve the reduced survival noted by Anker et al. (4). Furthermore, if wasting is adaptive, increasing body mass may even be harmful. Therefore, measures are required to improve the muscle function of the failing heart. The obvious connection between function and nutrition is the energetics of cardiac muscle.

Energetics of cardiac muscle

Creatine kinase reaction and heart failure

The ATP content of cardiac muscle is no different between the normal and failing heart. ATP levels are buffered by the creatine kinase reaction:

$$PCr + ADP + H^+ \rightarrow ATP + Cr \quad \text{(i)}$$

This buffering is very important when there is marked demand on cardiac function such as during a race. However, on a long-term basis, ATP is synthesized by aerobic oxidative phosphorylation:

$$ADP + Pi \rightarrow ATP \quad \text{(ii)}$$

The equilibrium of (i) is set far to the right so that ATP is maintained at the expense of PCr and a higher creatine (Cr). Therefore if there is an abnormality of energetics then the PCr/Total Cr (TCr) will be reduced as PCr will fall and creatine will rise. In the failing heart, PCr is reduced but the ratio PCr/TCr is not changed (15, 16) indicating a loss of creatine. In the normal heart the higher level of creatine results in the absolute rate of (i) being 11 times faster than (ii) so that there is a lot of reserve when energy demands increase. However, even with the lower creatine levels in the failing heart the rate of (i) is still 5 times greater than (ii). Therefore, there is still a lot of reserve that can only become limiting at extremes of exercise. Furthermore, creatine supplementation of rats subjected to myocardial infarction with reduced cardiac creatine did not improve function (17). In humans with heart failure, creatine supplements did not improve cardiac function but had some effect on skeletal muscle function (18). Hence, creatine is not limiting in cardiac failure as far as the heart is concerned.

Mitochondrial function and heart failure

NADH and succinate derived from the TCA cycle enter the mitochondrial electron transport chain at Complex I (NADH : ubiquinone oxidoreductase) and Complex II (succinate ubiquinone oxidoreductase) respectively where the electrons of the hydrogen atom from these TCA cycle substrates reduce ubiquinone to ubiquinol (Figure 1). The hydrogen ion so formed is extruded through the inner mitochondrial membrane to form an energy gradient. The ubiquinol is reoxidised to ubiquinone by Complex III (ubiquinol cytochrome c oxidase) and transfers its electrons to oxidised cytochrome c that is reduced. The reduced cytochrome c is oxidixed by Complex IV (cytochrome oxidase) using oxygen. Complex V (ATP synthase) uses the proton gradient as a source of energy to synthesise ATP from ADP.

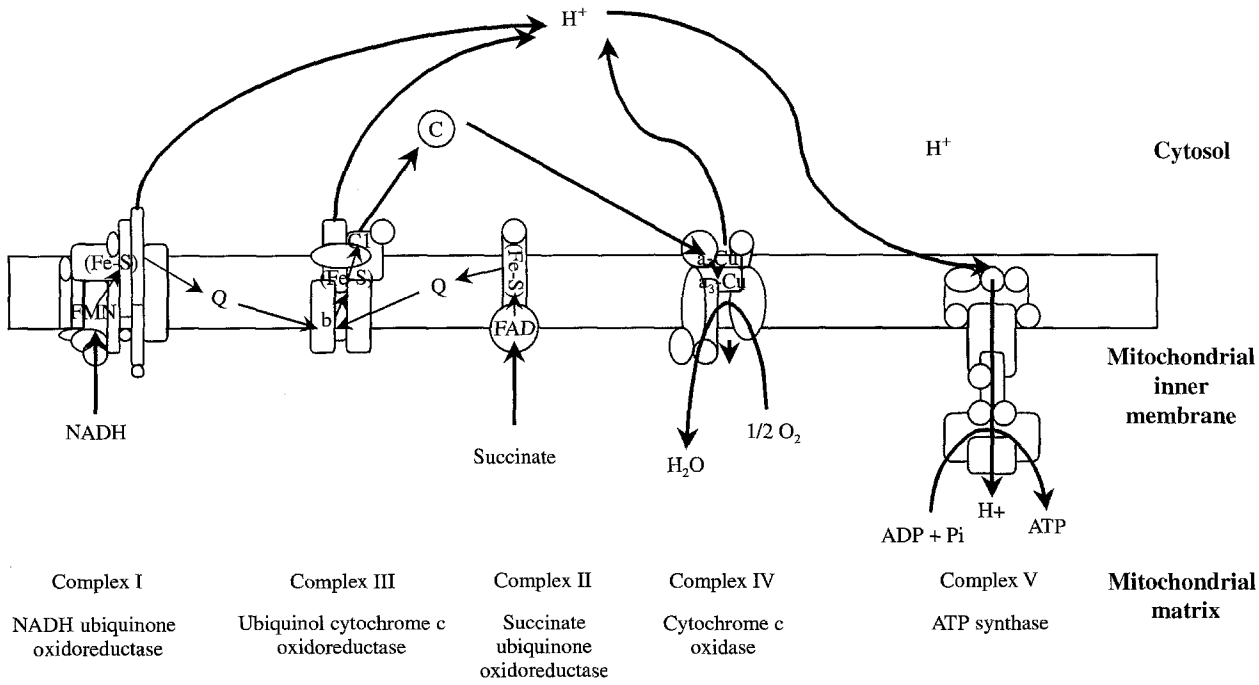

Fig. 1 The mitochondrial electron transport chain (OXPHOS system) and the role of coenzyme Q10. FMN: flavine mononucleotide; Fe-S: iron sulphur complex; Q: coenzyme Q_{10}; b, a, a_3: Heme b, a, a_3; C: Cytochrome C; FAD: flavine adenine dinucleotide.

In heart failure the cardiac muscle is deficient in Complex IV (19). In addition, skeletal muscle energetics are also abnormal and contribute to disability such as fatigue. It has been shown that during exercise PCr is reduced because excessive demand causes the creatine kinase reaction to use PCr to maintain ATP levels. After exercise the rate at which PCr is restored is an index of mitochondrial oxidative function. In patients with heart failure the restoration of skeletal muscle PCr is much slower than in controls (20), demonstrating abnormal mitochondrial function.

Calcium accumulation in the myocardium in heart failure

Extracellular calcium is extremely high compared with intracellular calcium and this calcium gradient is partly maintained by active energy requiring processes which maintain very low levels of intracellular calcium. In heart failure associated with abnormal energetics, myocyte calcium increases and contributes to cellular and mitochondrial injury (21).

Nutritional strategies to improve cardiac function in patients with heart failure

On the basis of the above considerations nutrition has to be used to promote mitochondrial function. In order to do so it is necessary to:

1. Promote optimal substrate oxidation;
2. Ensure that electron flow is facilitated;
3. Prevent mitochondrial injury.

Optimal substrate oxidation

The heart functions best when glucose oxidation is facilitated. It is now recognized that carnitine, by removing long chain fatty acids from acryl CoA, makes free CoA available in the cell which in turn promotes the oxidation of pyruvate derived from glycolysis (Figure 2).

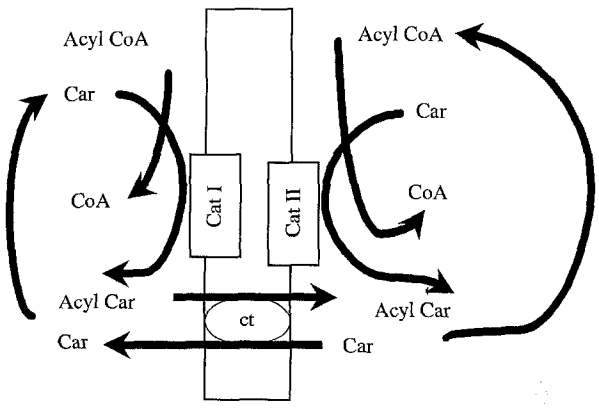

Fig. 2 The role of carnitine on cellular substrate flow. The role of carnitine in increasing free CoA is shown on the right side of the figure. Car = carnitine. Cat I and II: Carnitine acyl transferase I and II.

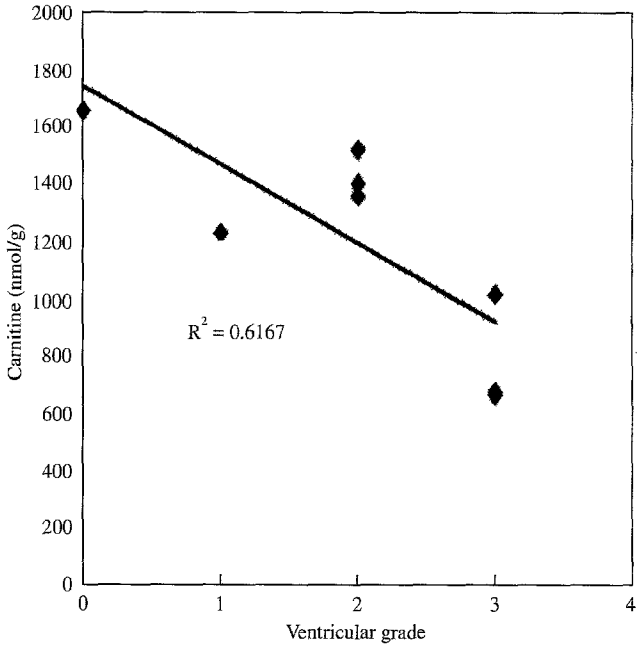

Fig. 3 The relationship between ventricular status and cardiac L-carnitine. Ventricular dysfunction is graded from 0 to 4.

The net result is that glucose oxidation is facilitated. In heart failure from a variety of causes it has been shown that cardiac muscle free carnitine is reduced, and furthermore, the level of carnitine correlates with ejection fraction (22). Our own preliminary data (Figure 3) confirm the observation by Regitz et al. (22). In heart failure, cardiac carnitine is mainly bound to fatty acid and there is little free carnitine available to remove fatty acid from fatty acid-CoA complex (23). Therefore, it is likely that feeding L-carnitine should improve outcome in patients with cardiac failure. In a controlled trial, 80 patients with New York Heart Association (NYHA) class III or IV were randomized to receive oral L-carnitine (2 g/day) or placebo. Over a mean of 34 months the carnitine supplemented group exhibited significantly better survival ($P<0.04$) on log-rank test (24).

Facilitation of electron flow

Coenzyme Q10 (CoQ10) or ubiquinone has been described by Mitchell, who formulated the theoretical basis of mitochondrial function (25), as the river through which electrons flow. In patients with heart failure, Folkers et al. (26) showed that cardiac muscle was deficient in CoQ10 and feeding CoQ10 restored cardiac levels. We have shown that cardiac CoQ10 correlates negatively with the ventricular grade (Figure 4). The question is whether feeding CoQ10 benefits outcome. Six hundred and forty-one patients, NYHA class III to IV, were randomized to receive oral CoQ10 (2 mg/kg/day) or placebo for 52 weeks. The

supplemented group had shorter hospital stay and fewer episodes of pulmonary oedema (27).

Prevention of mitochondrial and myocyte injury

A major cause of cell injury is calcium accumulation (28) and it has been shown that taurine modulates voltage dependent Ca2+channels and regulates Na-Ca exchange and Na-taurine co-transport (29). The net effect is to protect cardiomyocytes from calcium overload on the one hand and low calcium states on the other. We have found a negative correlation between cardiac taurine and ventricular grade (Figure 5). In

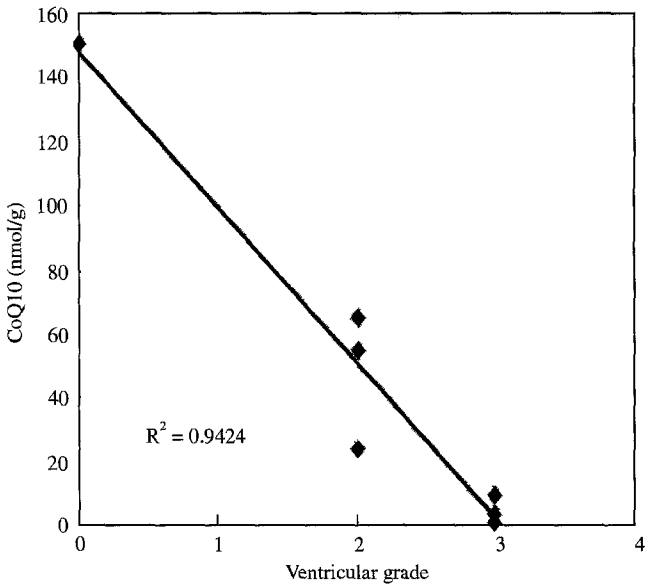

Fig. 4 The relationship between ventricular status and cardiac coenzyme Q10.

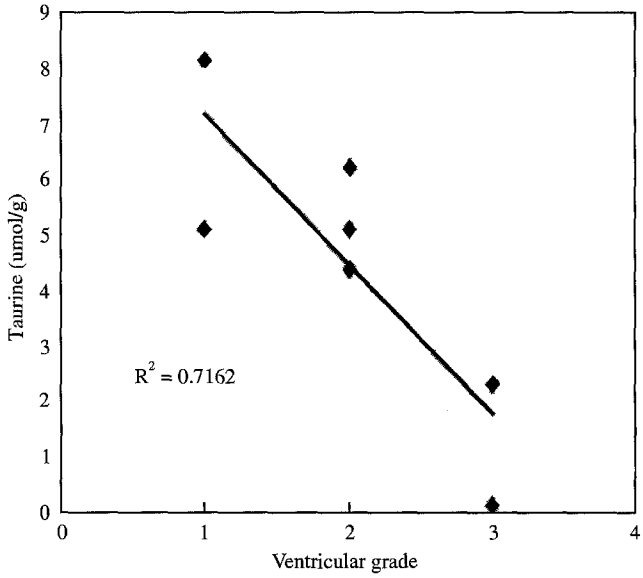

Fig. 5 The relationship between ventricular status and cardiac taurine.

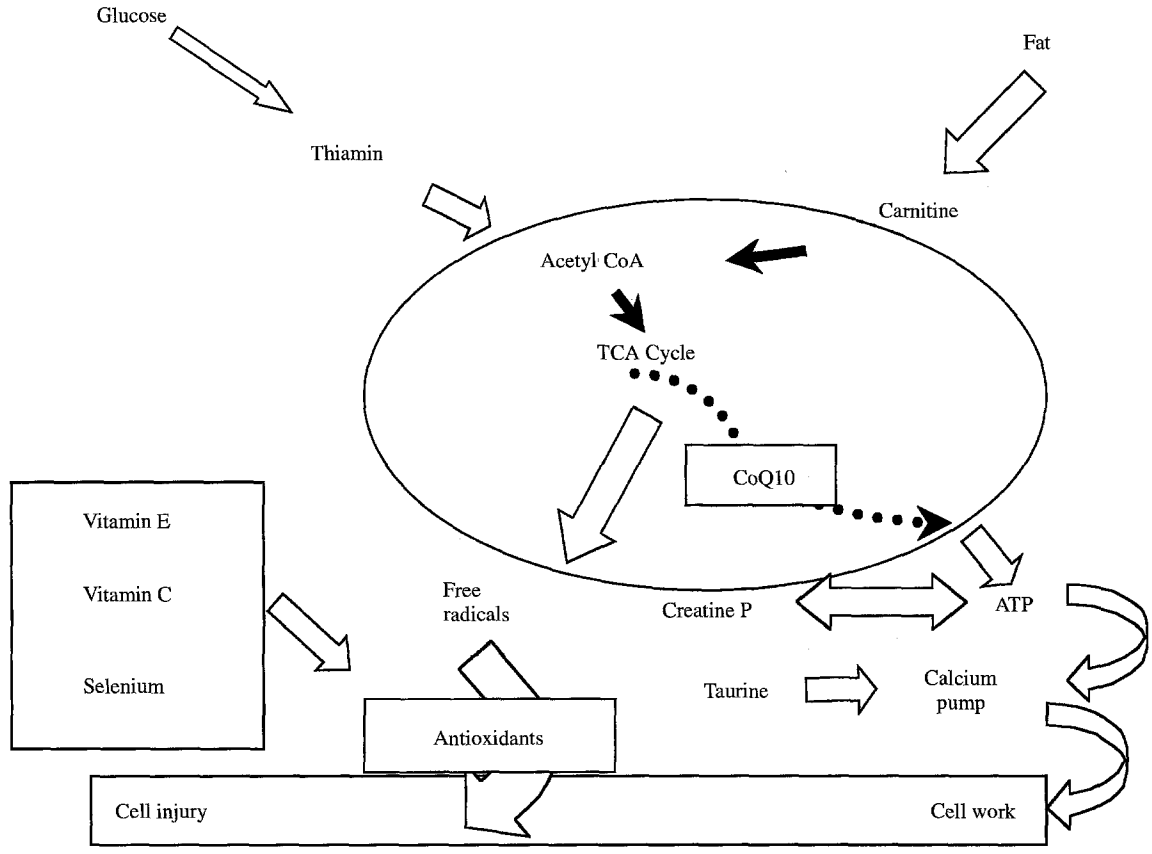

Fig. 6 A scheme showing the role of nutrients in the promotion of myocyte energetics. The interacting effects of carnitine, coenzyme Q10 (C_0Q_{10}) and taurine are shown with the supportive roles of antioxidants and thiamin.

cardiomyopathic hamsters, taurine supplementation reduced muscle calcium and cardiac damage (30). Another cause of cardiac injury is oxidative stress and Keith et al. (31) have previously shown that oxidative stress increases with the degree of heart failure.

Combination therapy

While there is clear evidence that individual supplements aid cardiac function, is there evidence that combinations are better? In rat hearts subjected to ischaemia, individual supplements of carnitine or CoQ10 did not restore cardiac work to that seen in the non-ischaemic heart but a combination did restore cardiac work to control levels (32).

Conclusion

In order to optimize cardiac function in patients with heart failure it is necessary to attack the problem at multiple points. These are summarized in Figure 6. Thiamin is supplemented because patients on diuretics may become thiamin deficient. Thiamin deficiency results in reduced glucose oxidation. Carnitine also aids glucose oxidation. CoQ10 promotes electron flow and taurine together with antioxidants protect mitochondria and myocytes from injury.

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