Nutritional supplementation with MyoVive repletes essential cardiac myocyte nutrients and reduces left ventricular size in patients with left ventricular dysfunction

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Background Congestive heart failure depletes the myocardium of carnitine, coenzyme Q10 (CoQ10), and taurine—substances known to influence mitochondrial function and cell calcium. We hypothesized that feeding patients a nutritional supplement that contained carnitine, CoQ10, and taurine would result in higher myocardial levels of these nutrients and improve left ventricular function.

Methods Forty-one patients who underwent aortocoronary artery bypass with an ejection fraction ≤40% at referral were randomly assigned to a double-blind trial of supplement or placebo. Radionuclide ventriculography was performed at randomization and before surgery. Surgical myocardial biopsies, adjusted for protein content, were analyzed for carnitine, CoQ10, and taurine levels.

Results The groups were well matched. Minor exceptions were supplement group versus placebo group for digoxin use (7 vs 0, respectively; $P = .009$) and age (62 ± 11 years vs 69 ± 5 years, respectively; $P = .04$). There were significantly higher levels in the treated group compared with the placebo group for myocardial levels of CoQ10 (138.17 ± 39.87 nmol/g wet weight and 56.67 ± 23.08 nmol/g wet weight; $P = .0006$), taurine (13.12 ± 4.00 μmol/g wet weight and 7.91 ± 2.81 μmol/g wet weight; $P = .003$), and carnitine (1735.4 ± 798.5 nmol/g wet weight and 1237.6 ± 343.1 nmol/g wet weight; $P = .06$). The left ventricular end-diastolic volume fell by −7.5 ± 21.7 mL in the supplement group and increased by 10.0 ± 19.8 mL in the placebo group ($P = .037$).

Conclusions Supplementation results in higher myocardial CoQ10, taurine, and carnitine levels and is associated with a reduction in left ventricular end-diastolic volume in patients with left ventricular dysfunction before revascularization. Because the risk of death for surgical revascularization is related to preoperative left ventricular end-diastolic volume, supplementation could improve outcomes. (Am Heart J 2002;143:1092-100.)

Left ventricular dysfunction leading to congestive heart failure (CHF) affects approximately 1.5% of the population and is most frequently caused by ischemic heart disease. Currently, with best medical practice, the death rate ranges from 50% in 5 years to as high as 40% to 50% in 2 years, depending on the severity of the heart failure and the underlying cause. There is an urgent need for therapies that improve left ventricular function and outcomes in patients with CHF.

It is known that CHF leads to malnutrition in 50% to 68% of patients with CHF.[1] Severe malnutrition in patients with CHF is termed cardiac cachexia,[2] which is an independent risk factor for mortality.[2] Traditionally, it is believed that a deficit of protein and energy intake is the most important cause of malnutrition in patients with CHF. However, supplementation of protein-calories in patients with CHF does not improve cardiac function, despite a gain in lean body mass.[4] Conversely, patients with severe CHF have lower levels of adenosine triphosphate in skeletal muscle, which also does not improve with protein-calorie supplementation,[5] suggesting an abnormality of muscle energetics rather than macronutrient deficiency in CHF. To support this concept, studies have shown that patients with ventricular dysfunction have an abnormality of

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the mitochondrial respiratory chain[6] and that their myocytes are depleted of carnitine,[7,8] coenzyme Q10,[9,10] and taurine.[11] In a small series, the severity of depletion has been shown to be related to the severity of the heart failure.[12] In patients with CHF in some controlled trials, repletion of L-carnitine[13] and coenzyme Q10[14] improves survival and reduces episodes of pulmonary edema, respectively.

In addition, there is some evidence that L-carnitine supplementation will reduce the amount of left ventricular dilatation after myocardial infarction.[15] A randomized, double-blind, placebo-controlled, multicenter trial was conducted to address this question and found that supplementation with L-carnitine resulted in attenuation in the left ventricular dilation during the first year after an acute myocardial infarction.[15]

Supplementation with coenzyme Q10 in patients with CHF may have a slight effect on maximal exercise capacity and quality of life[16]; however, the data are conflicting, with another randomized trial showing no effect on ejection fraction (EF), peak oxygen consumption, or exercise duration in patients receiving standard medical therapy.[17]

Myocardial calcium accumulation occurs in the failing heart and in hamster cardiomyopathy; taurine supplementation reduces calcium accumulation and myocardial injury.[18] Thus, there is potential for taurine, carnitine, and coenzyme Q10 to improve ventricular function in patients with heart failure. A recent review article emphasized the potential relation between micronutrient deficiency and CHF and stressed the need for a large-scale trial of dietary micronutrient supplementation in patients with CHF.[19]

We hypothesize that feeding a mixture of carnitine, coenzyme Q10, and taurine to patients with ventricular dysfunction who undergo elective coronary artery bypass surgery will increase myocardial levels of these nutrients and also improve left ventricular function as assessed by radionuclide ventriculography.

Methods

Study design

This was a single-center, randomized, double-blind, placebo-controlled study. Informed consent was obtained. The research protocol was approved by the institutional review board.

Patient selection

Stable patients taking medical therapy who were scheduled for elective aortocoronary bypass surgery were approached for consent if referral EF was ≤40% on the basis of contrast ventriculography or 2-dimensional echocardiography, and if ischemic heart disease only was present; the presence of symptomatic CHF was not required for enrollment in the study.

Table I. Composition of MyoVive

Component	Amount per 250 mL
Energy (kcal)	200
Protein (g)	15
Carbohydrates (g)	17.7
Fat (g)	7.8
Carnitine (g)	3.0
Coenzyme Q10 (mg)	150
Taurine (g)	3.0
Creatine (g)	2.25
Sodium (mg)	108
Potassium (mg)	750
Chloride (mg)	203
Calcium (mg)	315
Phosphorus (mg)	183
Magnesium (mg)	20
Iron (mg)	1.0
Zinc (mg)	15
Copper (mg)	1.5
Manganese (mg)	3.0
Fluoride (mg)	1.0
Molybdenum (μg)	50
Selenium (μg)	50
Chromium (μg)	33
Iodine (μg)	100
Retinol ester (μg)	688
Cholecalciferol (μg)	5
α-Tocopherol acetate (mg)	538
Thiamin (mg)	25
Riboflavin (mg)	3.0
Niacin (mg)	20
Pantothenate (mg)	4.0
Pyridoxine (mg)	6.0
Folate (μg)	600
Cynocobalamin (μg)	3.0
Biotin (μg)	100
Ascorbate (mg)	250

Patients with significant valve disease and/or planned valve surgery, unstable blood pressure and/or heart rhythm, major comorbid disease, and patients taking supplements containing carnitine, taurine, and coenzyme Q10 were excluded from the study.

Consecutive outpatients fulfilling the criteria were enrolled from the St Michael's Hospital population of candidates for cardiovascular surgery from September 1999 to August 2000.

Supplement

A palatable drink, MyoVive (Numico Research, Zoetermeer, The Netherlands), which contains a mixture of carnitine, coenzyme Q10, and taurine, was given to patients receiving the supplement. The composition of the supplement is given in Table I. Although the supplement contains other components, these components did not influence the primary aim of the study, which was to determine if supplementation increased myocardial concentrations of taurine, carnitine, and coenzyme Q10. A placebo drink, containing carbohydrate, coloring, and flavoring in identical cartons, was provided for this trial, and an independent pharmacist dispensed the cartons through the hospital investigational drug service.

Protocol

At the time of enrollment, the patients had a baseline assessment of Canadian Cardiovascular Society (CCS) class angina, New York Heart Association (NYHA) class CHF, complete blood count, liver and renal function biochemistry, and radionuclide ventriculography. Patients were then randomly assigned to receive supplement or placebo in a 1:1 ratio at a dose of 250 mL per day for the duration of the study (until their 30- to 45-day visit after the procedure). Investigators and patients were unaware of the treatment. At the patients' routine preoperative visit, the assessment was repeated. During the operation, a single left ventricular cardiac muscle biopsy was taken and snap-frozen in liquid nitrogen. The biopsies were stored in liquid nitrogen until they were analyzed. The tolerability of the liquid supplement (supplement or placebo) was monitored throughout the study with biweekly telephone calls conducted by the study coordinator.

The primary end point was a comparison of the myocardial levels of taurine, carnitine, and coenzyme Q10 between placebo- and MyoVive-fed patients. The secondary end points were (1) the safety and tolerability of supplementation (assessed by biochemical measurements and symptomatic questionnaire) and (2) left ventricular end-diastolic (LVEDV) and end-systolic volume (LVESV) and EF as assessed by radionuclide ventriculography.

Method of radionuclide ventriculography

Left ventricular (LV) function was assessed with radionuclide ventriculography. Studies were acquired in the anterior, 45-degree left anterior oblique and 70-degree left anterior oblique with multigated acquisition of 32 frames per cardiac cycle after in vitro labeling of red blood cells with 30 mCi of technetium-99m. The technologist was unaware of treatment assignment. Global LVEF was calculated with the use of a semiautomated method for definition of end-diastolic and end-systolic regions, with calculation of background from the left paraventricular region of interest. LV activities were calculated from a region of interest manually drawn around the LV perimeter at end diastole. LV time-activity curves were generated from counts within the region of interest from the 32 frames of the summed cardiac cycle corrected for decay and attenuation. A 2-mL blood sample was withdrawn during the gated left anterior oblique image and counted on the camera for volume calculation. LV volumes were attenuation-corrected by taking a geometric measurement of the LV depth with a point source marker and the camera and applying an attenuation coefficient of 0.15/cm. Decay correction of the radioisotope was made on the basis of the law of radioactive decay. LV curve plotted from the LV region of interest of the gated left anterior oblique images yielded cardiac parameters, such as EDV and ESV.

Myocardial analysis for coenzyme Q10, taurine, and carnitine

These analyses have all been standardized before measurement, and their precision and accuracy were checked by performing repeated measurements and comparing the measurements with published data. The reproducibility of our biochemical analysis was found to be 8.3% for coenzyme Q10, 3% for taurine, and 7% for carnitine. In instances in which hamster data are not available, human data obtained in our laboratory are almost identical to published values.

Coenzyme Q10 levels

Myocardial biopsies were prepared for the determination of coenzyme Q10 concentration by use of high-performance liquid chromatography.[20]

Taurine

Taurine was analyzed by high-performance liquid chromatography with the pico-tag method.[21] Briefly, weighed tissue was homogenized in cold 0.1 N HCl. After a short centrifugation, the supernatant went through an ultrafiltration process. The filtrate was diluted 1:1 with methionine sulfone (internal standard). Twenty-five microliters of the resulting sample and known concentrations of taurine standard were dried in separate tubes. The samples were redried with a solution containing methanol, sodium acetate, and triethylamine. The dried material was derivatized with phenylisothiocyanate to produce phenylthiocarbamyl amino acids. These amino acid derivatives were analyzed by high-performance liquid chromatography with a specific Pico-Tag Column (Waters Co, Mississauga, Ontario, Canada) and a gradient system. The concentration of taurine was calculated from the peak area ratios of the sample and the taurine standard.

Carnitine

Carnitine was measured by spectrophotometric enzymatic assay, which measures the formation of 5-thio-2-nitrobenzoate from CoAsh and 5,5-dithiobis-2-nitrobenzoate in the presence of carnitine acetyl transferase.[22] The formed 5-thio-2-nitrobenzoate is proportional to the amount of carnitine present in the sample. Briefly, tissues were homogenized in cold high-performance liquid chromatography–grade water with a ground glass homogenizer. Free carnitine was determined by mixing fixed volumes of 1 M potassium hydroxide (KOH) in methanol, 10% phosphoric acid, and saturated potassium phosphate monobasic with a sample of the tissue homogenate. The mixture was spun down, and the supernatant was assayed for free carnitine.

Total carnitine was determined by mixing a sample of the tissue homogenate with alcoholic KOH. The mixture was heated for 1 hour at 65°C to hydrolyze the acylcarnitines. After cooling the sample to room temperature, 10% phosphoric acid and saturated potassium phosphate were added to the sample. The sample was spun down, and the supernatant was analyzed for total carnitine.

To analyze the samples for carnitine, the spectrophotometer was heated electronically to 37°C, and a cuvette was placed in the sample compartment to equilibrate to 37°C. A fixed volume of sample and reaction mixture was pipetted into the cuvette and incubated for 1 minute followed by the addition of carnitine acetyl transferase solution. The absorbance readings were taken at 412 nm and at fixed time intervals. A standard curve was prepared with different concentrations of L-carnitine, the same way as described above.

Statistical analysis

Continuous variable data are presented as means and the corresponding standard deviation, and the categoric data are

Table II. Baseline characteristics of patients

Variable	MyoVive (n = 20)	Placebo (n = 18)	P
Age (y)	62 ± 11	69 ± 5	.03
Male (%)	19 (90.5)	18 (100)	.99
Weight (kg)	87.4 ± 17.2	94.9 ± 36.4	.62
Height (cm)	171.2 ± 7.7	172.5 ± 5.9	.6
Cardiac history (%)			
Previous MI	15 (75)	16 (88.9)	.41
Previous thrombolysis	7 (38.9)	3 (17.7)	.26
Previous PTCA	3 (15)	3 (16.7)	.99
Previous CABG	0	1 (5.6)	.47
Valve disease	3 (15)	2 (11.1)	.99
Clinical history (%)			
Hypertension	15 (75)	10 (55.6)	.3
Diabetes	9 (45)	6 (33.3)	.52
Family history	15 (75)	8 (44.4)	.05
Current smoker	7 (35)	8 (47.1)	.44
Peripheral vascular disease	3 (16.7)	5 (29.4)	.44
Hyperlipidemia	14 (73.7)	11 (64.7)	.72
CCS class (%)			.38
I	2 (10)	4 (22.2)	
II	12 (60)	6 (33.3)	
III	5 (25)	7 (38.9)	
IV	1 (5)	1 (5.6)	
NYHA class (%)			.22
II	5 (25)	10 (50)	
III	12 (60)	7 (38.9)	
IV	3 (15.0)	1 (5.6)	
Radionuclide ventriculography	n = 19	n = 18	
Ejection fraction (%)	42.8 ± 12.2	44.6 ± 3.6	.69
End-diastolic volume (mL)	170.5 ± 50.0	178.9 ± 61.8	.78
End-systolic volume (mL)	99.8 ± 42.5	105 ± 55.9	.84
Medications (%)			
Angiotensin-converting enzyme inhibitor	15 (75)	10 (55.6)	.3
Aspirin	18 (90)	15 (83.3)	.65
β-Blocker	17 (85)	17 (94.4)	.6
Calcium-channel blocker	6 (30)	11 (61.1)	.1
Digoxin	7 (35)	0	.008
Diuretics	6 (30)	6 (33.3)	.99
Nitroglycerin	8 (40)	12 (66.7)	.11
Vitamin supplements	8 (40)	6 (33.3)	.74

presented as frequencies and percentages. Comparison between the 2 groups for continuous variables was performed with the nonparametric Wilcoxon rank sum test. Comparison between the 2 treatment groups for categoric variables was performed with the Pearson χ^2 test or the Fisher exact test.

Results

Fifty-three patients were approached for the study. Twelve refused to participate—4 because it was too difficult to travel to the hospital and 8 because they did not want to be randomly assigned to receive the placebo. Forty-one patients were recruited from St Michael's Hospital. At baseline, the patients were well matched. Minor exceptions included greater digoxin use in the MyoVive group and younger age (Table II). The compliance was 93% and 99% ($P = .0104$) for the MyoVive and placebo groups, respectively. The number of days patients took the supplement at the preoperative visit was 29.7 ± 10.2 days and 30.2 ± 9.6 days (P = not significant [NS]) for the MyoVive and placebo groups, respectively. The biopsies were conducted after 34.1 ± 12.7 days and 34.9 ± 8.4 days (P = NS) of supplementation in the MyoVive and placebo groups, respectively.

After supplementation, the MyoVive group had a significantly higher myocardial content of coenzyme Q10, taurine, and total carnitine, by 144%, 66%, and 40%, respectively, compared with the placebo group (Table III). The mean LVEDV in the MyoVive group fell by a significant amount from the baseline to the preoperative assessment (170.5 ± 50 mL vs 158.9 ± 51 mL; $P < .05$) (Table IV), and the paired data also showed a significant reduction in the preoperative LVEDV compared with placebo (−7.5 ± 22 mL vs

Table III. Heart muscle biopsy results

Variable	MyoVive	Placebo	*P*
Total carnitine (nmol/g wet weight)	1735.4 ± 798.5	1237.6 ± 343.1	.0569
Coenzyme Q10 (nmol/g wet weight)	138.17 ± 39.87	56.67 ± 23.08	.0006
Taurine (μmol/g wet weight)	13.12 ± 4.00	7.91 ± 2.81	.0016

Table IV. Radionuclide ventriculography results

	MyoVive			Placebo		
Variable	Baseline (n = 19)	Preoperative (n = 19)	Change prebaseline (paired data)	Baseline (n = 18)	Preoperative (n = 17)	Change prebaseline (paired data)
EF (%)						
Mean ± SD	42.8 ± 12.2	43.7 ± 12.5	0.9 ± 4.7	44.6 ± 13.6	46.7 ± 13.4	1.6 ± 4.0
Median (Q1, Q3)	43 (31, 53)	46 (33, 56)	0.0 (−3, 5)	44.5 (36, 56)	47 (42, 57)	2 (−1, 4)
Min to max	26-59	22-60	–7-7	19-70	23-70	–5-8
EDV (mL)						
Mean ± SD	170.5 ± 50	158.9 ± 51*	−7.5 ± 22†	178.9 ± 61.8	179.9 ± 52.8	10 ± 19.8
Median (Q1, Q3)	161 (140, 206)	158.5 (126, 171)	–7.5 (–18, 5)	172 (117, 224)	168 (145, 220.5)	8.5 (–8.5, 28)
Min to max	98-306	79-295	–48, 43	88-306	101-293	–17-40
ESV (mL)						
Mean ± SD	99.8 ± 42.5	94.2 ± 46.4	–4.7 ± 18.1	105 ± 55.9	101 ± 52.7	1.4 ± 17.2
Median (Q1, Q3)	91.2 (61.7, 124)	78.1 (64.7, 132)	–5.4 (–14, 4)	105 (64, 138)	88.3 (63, 121.4)	–0.5 (–14, 4)
Min to max	48-211	43.6-203.6	–39.3-40.8	26.4-247.9	33.9-225.6	–22.3-29.4

*$P < .05$ vs baseline.
†$P < .05$ vs placebo.

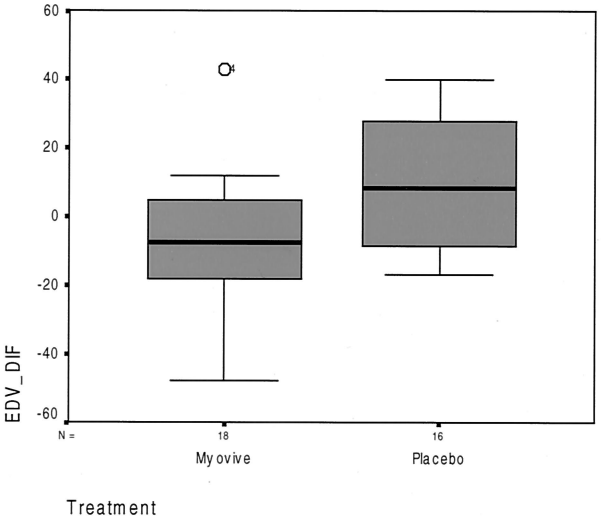
10 ± 19.8 mL; $P < .05$) (Figure 1). The difference between the baseline and preoperative LVEDV in the MyoVive group was still significant ($P = .0311$) when adjusted for calcium-channel blockers and angiotensin-converting enzyme inhibitors. In the placebo group, there was no significant change in the mean LVEDV from baseline to the preoperative assessment (178.9 ± 61.8 mL vs 179.9 ± 52.8 mL) (Table IV). There was a trend toward a reduction in the mean LVESV in the MyoVive-fed patients from baseline to the preoperative assessment (99.8 ± 42.5 mL vs 94.2 ± 46.4 mL) (Table IV), and the paired data also showed a trend toward a reduction compared with placebo (−4.7 ± 18.1 mL vs 1.4 ± 17.2 mL) (Figure 2). In the placebo group, there was no significant difference in the mean data from baseline LVESV to the preoperative assessment (105 ± 55.9 mL vs 101 ± 52.7 mL) (Table IV). There was no significant change in the EF in MyoVive and placebo groups, and the paired measurements between the MyoVive and placebo groups were not different (Figure 3 and Table IV).

One patient in the MyoVive group had nausea and 1 had a single episode of vomiting. Two patients developed diarrhea and 1 of them dropped out of the study as a result. None of the other patients dropped out because of these symptoms. None of the patients in the placebo group had any adverse symptoms (Table V). The difference between groups was not significant.

The administration of supplement compared with placebo did not influence blood biochemistry, with the exception of significantly higher creatinine levels at the preoperative assessment. However, the blood urea nitrogen was not increased (Table VI).

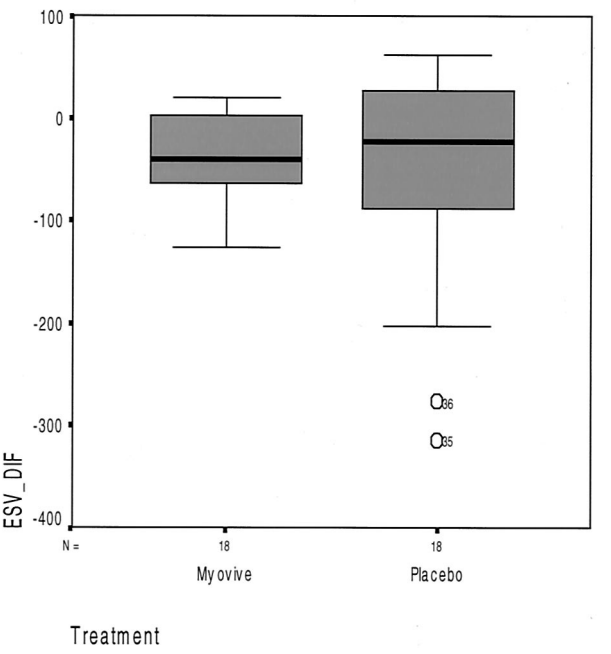
Clinically significant adverse events were few. One patient from each group had a preoperative myocardial infarction; both of these patients went on to surgery successfully. One patient who had a body mass index of 42 in the placebo group developed sepsis after the operation and spent 3 weeks in the intensive care unit before being transferred to the floor. One patient in the MyoVive group developed pneumonia and had a 6-day stay in the intensive care unit. Clinically significant renal failure developed after surgery in 2 of the patients in the placebo group, both secondary to retention caused by prostate obstruction. In the MyoVive group, 3 patients developed clinically significant renal failure, 1 patient had renal artery stenosis, 1 patient had renal failure related to diabetes, and the final patient had multiple medical problems after the

Figure 1



Box-whisker plot of the paired difference between baseline and preoperative left ventricular end-diastolic volume (*EDV DIF*) for the MyoVive group (−7.5 ± 22 mL) and the placebo group (10 ± 19.8 mL; $P < .05$).

Figure 2



Box-whisker plot of the paired difference between baseline and preoperative left ventricular end-systolic volume (*ESV DIF*) for the MyoVive group (−4.7 ± 18.1 mL) and the placebo group (1.4 ± 17.2 mL; P = NS).

operation with a wound infection, urinary tract infection, and atrial fibrillation.

Only 1 patient was lost to observation (MyoVive group). Two patients died during the study, 1 from each group: the patient in the MyoVive group developed coagulopathy after the operation, and the patient in the placebo group developed severe mitral regurgitation, which was complicated by cardiogenic shock and CHF, after the operation and died during a second operation. Four patients dropped out of the study, 2 from each group. Of the 2 patients in the MyoVive group, 1 dropped out after developing diarrhea and the other patient dropped out after developing renal failure caused by renal artery stenosis. Of the patients who dropped out of the placebo group, 1 dropped out after family members had concerns about the patient being enrolled in the study and the other patient dropped out after developing atrial fibrillation after the operation.

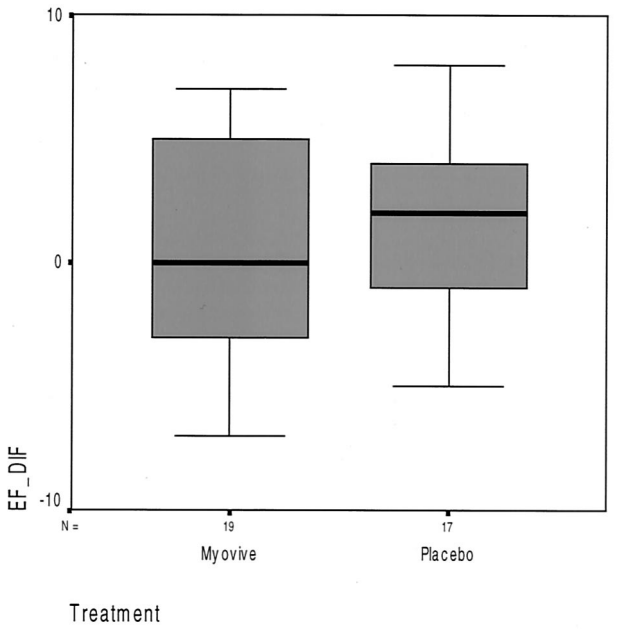
Discussion

The patients were selected on the basis of the LV function assessed by either cardiac catheterization with LV angiogram or echocardiography conducted by the referring institution. Our baseline radionuclide angiography results indicated that the average EF was 42.8% ± 12.2% and 44.6% ± 13.6% (P = NS) for the MyoVive and placebo groups, respectively. It is accepted that radionuclide ventriculography results often show a higher EF than echocardiography and LV angiogram. In any case, the groups were well matched for baseline EF.

Overall, the patients tolerated MyoVive well and compliance was better than in most studies. There was a significant increase in creatinine in the MyoVive group from the baseline assessment to the preoperative assessment. However, there was no rise in blood urea nitrogen. In our study, there was no clinical significance to this rise in creatinine, and the rise in creatinine did not affect the outcome in the patients who were given MyoVive. In MyoVive, 50% of the creatine is in the form of creatinine, which can raise blood creatinine levels without a change in creatinine clearance. However, measuring the creatinine clearance in future studies with MyoVive will be important to confirm this hypothesis.

The physiologic functions of coenzyme Q10, carnitine, and taurine have been well described. Ubiquinone or coenzyme Q10 plays a pivotal role as a rate-limiting carrier for the flow of electrons through the first stages of the mitochondrial respiratory chain and is an important endogenous antioxidant.[23] Taurine is a unique amino acid that has no role as a component of

Figure 3



Box-whisker plot of the paired difference between baseline and preoperative ejection fraction (*EF DIF*) for the MyoVive group (0.9 ± 4.7 mL) and the placebo group (1.6 ± 4.0 mL; *P* = NS).

Table V. Tolerability data

	Preoperative		
Variable	**MyoVive**	**Placebo**	***P***
Adverse symptoms (%)			
Cramps	0	0	–
Diarrhea	2 (9.5)	0	.4899
Fullness	0	0	–
Nausea	1 (4.8)	0	.5385
Reflux	0	0	–
Vomiting	1 (4.8)	0	.5385
Total	4	0	.0519

protein synthesis or as a substrate for metabolism; it is, however, the most plentiful amino acid in the myocyte, and it plays a critical role in intracellular calcium homeostasis.[24] Carnitine is essential for long-chain fatty acid transport from the cytoplasm to the mitochondrial matrix; it also plays an important role in the balance between glycolysis and glucose oxidation.[25] Therefore, these nutrients are essential for normal cell and mitochondrial function and calcium homeostasis. This study has shown that feeding patients a mixture of carnitine, coenzyme Q10, and taurine resulted in higher myocardial levels of these components. To date, the only available data on supplementation and the subsequent increase in myocardial levels are with coenzyme Q10.[9] A study of endomyocardial biopsies taken from patients with predominantly dilated cardiomyopathy measured coenzyme Q10 levels.[9] Five of the 43 patients in this study subsequently received supplementation with coenzyme Q10 and underwent biopsy again.[9] The results showed a 20% to 85% increase of myocardial coenzyme Q10.[9] Our study is the only randomized, double-blinded, placebo-controlled trial that has been conducted specifically to demonstrate that supplemen-tation with carnitine, coenzyme Q10, and taurine results in higher myocardial levels of these components. The finding that feeding these components, which have a potential to improve myocardial function, results in higher myocardial levels is important. If myocardial levels were not higher with oral supplements, then the validity of such supplements could be questioned.

In addition to the increases in myocardial levels of carnitine, coenzyme Q10, and taurine, an improvement in LV dimensions in the form of a significantly reduced LVEDV and a trend toward a smaller LVESV was noted. These changes are important because LVEDV has been shown to be an independent prognostic factor in patients with advanced heart failure.[26] In addition, the risk of death in patients undergoing surgical revascularization[27] is related to the preoperative LVEDV. Therefore, a preoperative reduction of the LVEDV could potentially reduce the risk of surgical revascularization. Furthermore, a reduction in LV volume has resulted in improved prognosis in several drug trials in patients with heart failure.[28-31] The mechanistic question is whether one or more of carnitine, coenzyme Q10, or taurine improve function, or the action of other constituents in MyoVive improves function. As previously mentioned, on the basis of previous observations, protein-calories and the standard vitamin-micronutrients in this formulation should not influence cardiac function. MyoVive also contains creatine, but this constituent, although improving skeletal muscle function, does not improve cardiac function in patients with CHF[32] or in animals.[33] However, larger studies are required to determine whether creatine supplementation does not have an effect on cardiac function. Finally, MyoVive contains a high dose of vitamin E. However, a recent controlled clinical trial of vitamin E supplementation found no reduction in oxidative stress in patients with heart failure.[34] Therefore, it is likely that improvement in function can be ascribed to the independent or synergistic action of 1 or more of carnitine, coenzyme Q10, or taurine, and not to the other constituents of MyoVive. A possible physiologic basis for these data is the recent observation (unpublished data) that the action of a combination of

Table VI. Safety data

	Baseline			Preoperative		
Variable	**MyoVive**	**Placebo**	***P***	**MyoVive**	**Placebo**	***P***
ALP (μ/L)	77.2 ± 17.2	81.3 ± 25.8	.9883	78.5 ± 20.4	78.9 ± 22.5	.8367
ALT (μ/L)	33.1 ± 15.5	27.1 ± 9.8	.3036	29 ± 9.3	26.6 ± 10	.3485
AST (μ/L)	26.0 ± 11.0	25.4 ± 6.6	.7261	26.8 ± 15.4	25.3 ± 8.7	.8306
BUN (mmol/L)	7.2 ± 3.3	7.1 ± 2.0	.7065	7.2 ± 2.9	7.3 ± 2.7	.6189
Creatinine (mmol/L)	108.1 ± 37.6	101.4 ± 22	.9442	153.3 ± 60.1	108.2 ± 28.7	.0196

taurine, carnitine, and coenzyme Q10 in vitro on isolated mitochondria from cardiomyopic hamsters is similar to that seen with β-blockers.[35] Perhaps it is the reduction in the rate of oxygen consumption, which results from this combination of nutrients, that subsequently causes a match between limited oxygen delivery caused by ischemia and the consumption rate. This so-called flow match created by MyoVive supplementation would benefit the ischemic patient and result in improved cardiac function.

The potential limitations of our study are the small sample size and short duration of observation. Our hypothesis would need to be confirmed in larger studies with a longer follow-up period.

In summary, oral supplementation of carnitine, taurine, and coenzyme Q10 results in higher myocardial levels of these constituents, which are known to influence myocardial function. In addition, there is a reduction of LVEDV, which is an important marker of prognosis in a variety of cardiac conditions. The findings of this study support the potential role of these components in the management of patients with ventricular dysfunction. Larger clinical trials of these supplements need to be performed to evaluate their effect in improving cardiac function and outcome.

References

1. Freeman L, Roubenoff R. The nutrition implications of cardiac cachexia. Nutr Rev 1994;52:340-7.
2. Pittman JG, Cohen P. The pathogenesis of cardiac cachexia. N Engl J Med 1964;271:403-9.
3. Anker SD, Ponikowski P, Varney S, et al. Wasting as independent risk factor for mortality in chronic heart failure. Lancet 1997;349: 1050-3.
4. Heymsfield SB, Casper K. Congestive heart failure: clinical management by use of continuous nasogastric feeding. Am J Clin Nutr 1989;50:539-44.
5. Broqvist M, Arnqvist H, Dahlstrom U, et al. Nutritional assessment and muscle energy metabolism in severe chronic congestive heart failure: effects of long-term dietary supplementation. Eur Heart J 1994;15:1641-50.
6. Quigley AF, Kapsa RMI, Esmore D, et al. Mitochondrial respiratory chain activity in idiopathic dilated cardiomyopathy. J Card Fail 2000;6:47-55.
7. Regitz V, Shug AL, Fleck E. Defective myocardial carnitine metabolism in congestive heart failure secondary to dilated cardiomyopathy and coronary, hypertensive and valvular heart diseases. Am J Cardiol 1990;65:755-60.
8. Masumura Y, Kobayashi A, Yamazaki N. Myocardial free carnitine and fatty acylcarnitine levels in patients with chronic heart failure. Jpn Circ J 1990;54:1471-6.
9. Folkers K, Vadhanavikit S, Mortensen SA. Biochemical rationale and myocardial tissue data on the effective therapy of cardiomyopathy with coenzyme Q10. Proc Natl Acad Sci USA 1985;82: 901-4.
10. Folkers K. Heart failure is a dominant deficiency of coenzyme Q10 and challenges for future clinical research on CoQ10. Clin Invest Med 1993;71:S51-4.
11. Suleiman MS, Fenando HC, Dihmis WC. A loss of taurine and other amino acids from ventricles of patients undergoing bypass surgery. Br Heart J 1993;69:241-5.
12. Jeejeebhoy KN, Sole MJ. Nutrition and the heart. Clin Nutr. 2001; 20(1 Suppl):181-6.
13. Rizos I. Three-year survival of patients with heart failure caused by dilated cardiomyopathy and L-carnitine administration. Am Heart J 2000;139:S130-3.
14. Morisco C, Trimarco B, Condorelli M. Effect of coenzyme Q10 therapy in patients with congestive heart failure: a long-term multicenter randomized study. Clin Invest Med 1993;71:S134-6.
15. Iliceto S, Scrutinio D, Bruzzi P, et al. Effects of L-carnitine administration on left ventricular remodeling after acute anterior myocardial infarction: the L-carnitine Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM) Trial. J Am Coll Cardiol 1995;26:380-7.
16. Hofman-Bang C, Rehnqvist N, Swedberg K, et al. Coenzyme Q10 as an adjunctive in the treatment of chronic congestive heart failure. The Q10 Study Group. J Card Fail 1995;1:101-7.
17. Khatta M, Alexander BS, Krichten CM, et al. The effect of coenzyme Q10 in patients with congestive heart failure. Ann Intern Med 2000;132:636-40.
18. Azari J, Brumbaugh P, Barbeau A, et al. Taurine decreases lesion severity in the hearts of cardiomyopathic hamsters. Can J Neurol Sci 1980;7:435-40.
19. Witte KK, Clark AL, Cleland JG. Chronic heart failure and micronutrients. J Am Coll Cardiol 2001;37:1765-74.
20. Okamoto T, Fukui K, Nakamoto M, et al. High performance liquid chromatography of coenzyme Q-related compounds and its application to biological materials. J Chromatogr 1985;342:35-46.
21. Cohen SA, Strydom DJ. Amino acid analysis utilizing phenylisothiocyanate derivatives. Anal Biochem 1988;174:1-16.
22. Maeda J, Dudrick SJ. Rapid spectrophotometric determination of

plasma carnitine concentrations. J Parenter Enteral Nutr 1990;14: 527-32.
23. Littaru GP. Energy and defense. In: Facts and perspectives on coenzyme Q10 in biology and medicine. Rome: Casa Editrice Scientifica Internazionale; 1995. p. 1-91.
24. Azuma J, Swanamura A, Awata N. Usefulness of taurine in chronic congestive heart failure and its prospective application. Jpn Circ J 1992;56:95-9.
25. Lopaschuk GD, Belke DD, Gamble J, et al. Regulation of fatty acid oxidation in the mammalian heart in health and disease. Biochim Biophys Acta 1994;1213:263-76.
26. Koelling TM, Semigran MJ, Mijller-Ehmsen J, et al. Left ventricular end-diastolic volume index, age, and maximum heart rate at peak exercise predict survival in patients referred for heart transplantation. J Heart Lung Transplant 1998;17:278-87.
27. De Carlo M, Milano A, Borzoni G, et al. Predicting outcome after myocardial revascularization in patients with left ventricular dysfunction. Cardiovasc Surg 1998;6:58-66.
28. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling-concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. J Am Coll Cardiol 2000;35:569-82.
29. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303-10.
30. Cohn JN, Johnson G, Zshabetai R, et al. Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias and plasma norepinephrine as determinants of prognosis in heart failure. Circulation 1993;87(6 Suppl):5-16.
31. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. N Engl J Med 1992;327:669-77.
32. Gordon A, Hultman E, Kaijser L, et al. Creatine supplementation in chronic heart failure increases skeletal muscle creatine phosphate and muscle performance. Cardiovasc Res 1995;30:413-8.
33. Horn M, Remkes H, Dienesch C, et al. Chronic high-dose creatine does not attenuate left ventricular remodeling in rat hearts post-myocardial infarction. Cardiovasc Res 1999;43:117-24.
34. Keith M, Jeejeebhoy KN, Langer A, et al. A controlled clinical trial of vitamin E supplementation in patients with congestive cardiac failure. Am J Clin Nutr 2001;73:219-24.
35. Katyare SS, Rajan RR. Altered energy coupling in rat heart mitochondria following in vivo treatment with propanolol. Biochem Pharmacol 1991;42:617-23.

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No variants in the cardiac actin gene in Finnish patients with dilated or hypertrophic cardiomyopathy

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Background Dilated and hypertrophic cardiomyopathies are primary myocardial diseases that cause considerable morbidity and mortality. Although these cardiomyopathies are clinically heterogeneous, genetic factors play an important role in their etiology and pathogenesis. The defects in the cardiac actin (ACTC) gene can cause both cardiomyopathies. The aim of our study was to screen for variants in the ACTC gene in patients with dilated or hypertrophic cardiomyopathy from Eastern Finland.

Materials and Methods Altogether, 32 patients with dilated and 40 patients with hypertrophic cardiomyopathy were included in the study. Commonly approved diagnostic criteria were applied, and secondary cardiomyopathies were carefully excluded. All 6 exons of the ACTC gene were amplified with polymerase chain reaction and screened for variants with single-strand conformation polymorphism analysis.

Results and Conclusion We did not find any new or previously reported variants. Our results indicate that defects in the ACTC gene do not explain dilated cardiomyopathy or hypertrophic cardiomyopathy in subjects from Eastern Finland and confirm earlier results that the ACTC gene does not play an important role in the genetics of dilated or hypertrophic cardiomyopathies. (Am Heart J 2002;143:e6.)

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