Metabolic Aspects of Myocardial Disease and a Role for L-Carnitine in the Treatment of Childhood Cardiomyopathy

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ABSTRACT. *Objectives.* **A multicenter retrospective study was conducted to investigate the possible metabolic causes of pediatric cardiomyopathy and evaluate the outcome of patients treated with L-carnitine.**

Methods. **Seventy-six patients diagnosed with cardiomyopathy were treated with L-carnitine in addition to conventional cardiac treatment, and 145 patients were treated with conventional treatment only. There were 101 males and 120 females between 1 day and 18 years old. Cardiomyopathy diagnoses included dilated (148 patients), hypertrophic (42 patients), restrictive (16 patients), mixed diagnosis (11 patients), and 4 with an unknown type. Of 76 L-carnitine-treated patients, 29 (38%) had evidence to suggest a disorder of metabolism, and of 145 control patients, 15 (10%) were suspected to have a disorder of metabolism. These metabolic disorders were thought to be the cause for the cardiomyopathy of the patients. The duration of L-carnitine treatment ranged from 2 weeks to >1 year. Information was collected on length of survival (time-to-event), clinical outcome, echocardiogram parameters, and clinical assessments. Data were collected at intervals from baseline to study endpoint, death, transplant, or last known follow-up visit.**

Results. **L-Carnitine-treated patients were younger than control patients and had poorer clinical functioning at baseline, yet they demonstrated lower mortality and a level of clinical functioning and clinical severity comparable to control patients on conventional therapy by the end of the study. An analysis of the interaction between clinical outcome and concomitant medications unexpectedly revealed that the population of patients treated with angiotensin-converting enzyme (ACE) inhibitors (40% of patients) had significantly poorer survival (although their greater likelihood for poor survival may possibly have made them more likely to receive ACE inhibitors).**

Conclusion. **Results suggest that L-carnitine provides clinical benefit in treating pediatric cardiomyopathy. There is a need for further exploration of potential explanatory factors for the higher mortality observed in the population of patients treated with ACE inhibitors.** *Pediatrics* **2000;105:1260–1270;** ***pediatric, cardiology, cardiomyopathy, L-carnitine, metabolism, genetics.***

ABBREVIATIONS. ATP, adenosine 5′-triphosphate; LCAD, long-chain acyl-CoA dehydrogenase; LCHAD, long-chain L-3-hydroxyacyl-CoA dehydrogenase; ACE, angiotensin-converting enzyme; ANOVA, analysis of variance.

Cardiomyopathy is a serious disease with a poor prognosis and high mortality. Estimates of incidence vary widely but range between 2 to 8 cases per 100 000[1] to 17.2 per 100 000[2] among all age groups. In the first year of life, the incidence has been estimated at 1 in 10 000 live births[3] and ~5000 cases are reported annually for the pediatric population. Survival rates in children remain dismal; despite treatment, a review of reports in the literature[4–13] finds a median mortality of ~37% with even poorer survival noted for older children.

Conventional approaches to treatment, especially in older children and for the more intractable forms of cardiomyopathy, are often only palliative. The development of effective treatments has been hampered by a poor understanding of the underlying cellular and molecular biology of the disease. Recent advances, however, have begun to yield some important clues into the nature of myocardial disease, including contributions from genetic and metabolic studies. With these insights have come implications for treatment based on a better understanding of the pathogenesis of heart failure.

The objective of this study was to investigate the treatment of certain cardiomyopathy-associated metabolic disorders using levocarnitine (L-carnitine), the fatty acid shuttle of the cell. An evolving literature describes the integral role that L-carnitine plays in myocardial metabolism. Cardiomyopathy is an associated symptom in metabolic disorders, where the intramitochondrial accumulation of toxic organic acid intermediates leads to the depletion of L-carnitine stores, such as in fatty acid oxidation defects and mitochondrial disorders. L-Carnitine conjugates with organic acid intermediates and serves to remove them from the mitochondria with excretion in the urine. Therefore, cardiomyopathy-associated metabolic disorders have seemed to be reasonable candidates for treatment with L-carnitine.

Therefore, we have had great interest in evaluating

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clinical data from patients treated for pediatric cardiomyopathy, who have received conventional therapy in comparison to patients who were treated for a possible underlying metabolic cause. A group of pediatric cardiologists and metabolic specialists were identified who had used L-carnitine over a 10-year period to treat several forms of cardiomyopathy. The present study is a retrospective evaluation of that collective experience.

A brief review of the cause and pathogenesis of cardiomyopathies and a survey of recent advances in the molecular biology and genetics of these disorders are instructive. Here, we review the highlights of these developments as a basis for discussing the role that L-carnitine plays in myocardial energy metabolism and its therapeutic potential.

OVERVIEW OF THE CARDIOMYOPATHIES

Classification

The definition of cardiomyopathy has undergone many changes.[14] In the strictest sense, cardiomyopathy refers to primary myocardial disease of unknown origin, so called idiopathic cardiomyopathy. In the broader sense, the term includes specific heart muscle diseases resulting from known disorders or causes (eg, hypertensive and metabolic). An expanding classification scheme continues to organize by cause and morphology. The classification system originally proposed by Goodwin et al[15] and subsequently adopted and modified by the World Health Organization/International Society and Federation of Cardiologists[16] reflects a distinctly empirical approach; the division between primary and secondary cardiomyopathies[a] was created by recognizing cause as essentially morphologic (ie, unknown cause; I–III) or physiologic (ie, known cause; IV–XI) in nature (Table 1). Dilated, hypertrophic, and restrictive cardiomyopathies (the 3 primary cardiomyopathies) have been classified morphologically. The remaining cardiomyopathies are divided according to putative cause.

TABLE 1. Current Classification of Cardiomyopathies

I.	Dilated
II.	Hypertrophic
III.	Restrictive
IV.	Arrhythmogenic right ventricular dysplasia
V.	Unclassified
VI.	Specific heart muscle diseases
VII.	Infectious
IX.	General system disease
X.	Heredofamilial
XI.	Sensitivity and toxic reaction

General Pathophysiologic and Morphologic Features of Myocardial Disease

In general, myocardial disease is characterized by at least some histomorphologic derangement and diminished compliance of the ventricular myocardium, usually the left ventricle, although diffuse, multichamber involvement is not infrequent. Histopathologic studies often find some form of fibrosis, diffuse loss of myocytes, or myocyte and myofibrillar disarray. Nonspecific findings often complicate diagnosis. The 3 forms of primary disease differ mostly in terms of type and location of morphologic remodeling and resulting hemodynamic dysfunction.

The distinguishing feature of dilated cardiomyopathy, accounting for >90% of all cases, is a notably enlarged ventricle (left ventricle) or ventricles, disproportionately thinner septal and free wall thickness, and diminished myocardial contractility. In the diffuse form, all chambers are involved, whereas in the nondiffuse form, 1 or more chambers remain uninvolved.

Hypertrophic cardiomyopathy is characterized by a notably exaggerated ventricular mass (ie, often 3 times greater than normal for body size) with a typically disproportionate interventricular septum. The ventricular chamber is stiff and noncompliant, and the volume of the ventricular cavities (characteristically the left ventricle) is grossly diminished. Atria, however, may be dilated.

Restrictive cardiomyopathy, the least prevalent form, is characterized by diffuse fibrosis and rigidity of the endocardium and subendocardium resulting in severely decreased atrial and ventricular compliance. The ventricular chamber may be reduced in volume and compensatory hypertrophy may be present.

Multidetermined Nature of Myocardial Disease

Currently, the diagnosis of cardiomyopathy as idiopathic or as a specific heart muscle disease depends almost entirely on whether an explicit cause is found. If the cause remains indeterminate after clinical evaluation and testing, a diagnosis of primary myocardial disease is made. Such empirical diagnoses have primarily been responsible for the current dual classification system. It is evident from the literature, however, that an evolution in understanding of myocardial disease is emerging.

Confounds to Diagnosis

In the past, a diagnosis of specific heart muscle disease implied a single cause. This idea has generally been discounted.[14,17] A clinical finding that leads to a diagnosis of specific heart muscle disease will frequently stop the search for additional contributory factors.[17] A diagnosis of toxic cardiomyopathy, for example, will stop the investigation from finding a gene defect, viral cause, or underlying congenital abnormality. Diagnosis is made even more difficult because there is often no direct relationship between pathogenesis and myocardial condition.[18] There are >100 specific disease conditions identified[17] producing cardiomyopathy, each sharing clinical and morphologic features, often indistinguishable.

Mechanisms of Myocardial Dysfunction

With idiopathic disease, it is important to consider the complex interrelationships among acquired, her-

[a] The term secondary cardiomyopathy, in fact, has been deemed inappropriate and has been supplanted by specific heart muscle disease (of known cause).

itable, and environmental factors. Lethality and symptom severity vary according to the impact of a gene defect, intensity of an environmental stress, and severity of an acquired disease. A variety of disorders are known to manifest only when several factors interact in concert. Organic acidemias, fatty acid oxidation defects, and urea cycle defects are examples of heritable, occasionally benign disease states in which symptoms may manifest only during catabolic crisis, as during acute infection. Diet can play a role, where the quantity or mix of amino acids, carbohydrate, or lipid consumption can overload a partially defective metabolic pathway.

The myocardium is similarly susceptible to a spectrum of inherited, acquired, and environmental factors. Mutations in the genes coding for β-myosin heavy chain,[19] troponin T, and α-tropomysin are associated with familial hypertrophic cardiomyopathy.[20] Familial restrictive cardiomyopathy have been identified.[21,22] Such instances of heritable forms of cardiomyopathy likely effect the contractile apparatus directly; in β-myosin heavy chain mutation, a myosin head malfunction is thought to underlie myocardial dysfunction.

Heritable disorders of metabolism with myocardial involvement include glycogen storage disease type 2 (Pompe's disease), glutaric aciduria type II, the fatty acyl-CoA dehydrogenase deficiencies, carnitine membrane transport defects, and carnitine acyl translocase and transferase defects. Mitochondrial DNA mutations have been identified in some patients with idiopathic dilated cardiomyopathy.[18] These disorders result in impaired myocardial energy metabolism. Many nonmetabolic genetic disorders also have associated cardiomyopathy, including Noonan's syndrome, muscular dystrophies, and some chromosomal anomalies.[23]

Viral myocarditis is believed to precede some cases of dilated cardiomyopathy.[24,25] Although controversial, there is some evidence that enteroviruses causing myocarditis may eventually lead to dilated cardiomyopathy.[26] Much of the evidence is indirect and suggests that dilated cardiomyopathy develops secondary to the acute enteroviral syndrome, the enterovirus, therefore, having an indirect role. Recent advances in molecular biology, however, have uncovered the presence of enteroviral genomes in the myocardium of patients with idiopathic dilated cardiomyopathy.[27,28] Other studies, however, have found enteroviral DNA in comparable proportions of control subjects[29] or have not found enteroviral DNA in dilated cardiomyopathy patients at all.[30] Although there is no clinical or prognostic importance in these findings, it would seem unlikely if enteroviral presence in the myocardium proved benign.

There is considerable interest in the idea that autoimmune disorders may play a significant role in dilated cardiomyopathy, particularly in idiopathic disease. There is suggestion that a chronic autoimmune response may develop in the wake of infectious myocarditis and that dilated cardiomyopathy results from the long-term autoimmune state.[24] There is also evidence that acute myocarditis may be an autoimmune disease[31] because cytolytic cardiac autoantibodies have been detected[32] in inflammatory disease. These autoantibodies act specifically on sarcolemma and myolemma.

Between 30% and 40% of patients with dilated cardiomyopathy have cardiac autoantibodies, and for the remainder of patients, it is believed that autoimmunity does not play a role. Although putative causes are often ascribed to cardiomyopathy, it is unlikely that any single pathogenic culprit is singly responsible.

Energy Production in the Heart

Myocardial contractility depends primarily on lipid metabolism—the oxidation of fatty acids—in the mitochondria to provide energy (adenosine 5′-triphosphate [ATP]); less important sources of fuel include glucose and lactate. Fatty acid oxidation is a complex process involving ~20 steps and 18 enzymes. The major steps of mitochondrial energy production include uptake of fatty acids, the carnitine cycle, β-oxidation, Krebs cycle, and oxidative phosphorylation to ATP.[34] Impairments to the carnitine cycle and β-oxidation will be considered here, with an emphasis on defects that lead to L-carnitine deficiency.

Other defects in mitochondrial functioning, ie, in the Krebs cycle, oxidation/phosphorylation coupling, and electron transport chain, although essential to energy production, are beyond the scope of this review and excellent reviews are available elsewhere.[35] Also, because the myocardium depends only marginally on glycogenolysis and glycolysis, disorders of these pathways will not be considered, nor will overall diagnostic considerations or supportive measures because these are likewise presented elsewhere in definitive texts.[35]

Significance of L-Carnitine Deficiency

The significance of L-carnitine lies in its primary role of shuttling fatty acids across the mitochondrial membrane delivering them for β-oxidation and the production of energy (ATP). Clinical manifestations secondary to carnitine deficiency syndromes have been well-described[36–38] and almost always impact muscle tissue. Deficiency of L-carnitine, depending on severity, results in accumulation of lipid in muscle, muscle myopathy, and weakness and can involve the myocardium.

L-Carnitine is a natural substance obtained from diet and endogenous synthesis from muscle protein degradation with the final step of synthesis being hepatic. Muscle carnitine exists in a free form and an esterified form (bound to organic acids removed from mitochondria). Carnitine deficiency can be primary attributable to a recessively inherited defect in muscle transport of carnitine or secondary attributable to decreased availability of free carnitine with many causes. These secondary deficiencies can be attributable to decreased dietary intake (as with TPN), decreased absorption (as with cystic fibrosis), increased loss (as with dialysis or renal Fanconi's

syndrome, and increased use), and excretion of esterified (acyl) carnitine (as with organic acidurias).

Plasma carnitine concentrations may be observed in a range from profoundly low levels to normal levels depending on the severity of the primary disorder and dietary intake. In general, clinical manifestations related strictly to the deficiency state are significantly correlated with plasma and/or tissue L-carnitine levels. Although a primary or secondary carnitine deficiency syndrome may be the only concomitant entity accompanying cardiomyopathy, it may also be counted among the many factors that are potentially contributory.

The Carnitine Cycle

In order for ATP to be ultimately produced from free fatty acids, they must be transported from the cytosol across the mitochondrial membranes and into the mitochondrial matrix, where they are metabolized. To accomplish this, they are first activated to form fatty acyl CoA in the cytosol by the enzyme acyl CoA synthetase. Since the resulting fatty acyl CoA cannot traverse mitochondrial membranes alone, the enzyme carnitine acyl transferase I, located on the outer surface of the inner mitochondrial membrane, must conjugate fatty acyl CoA and L-carnitine to form a new complex, fatty acyl carnitine. This compound may then be transported across the inner mitochondrial membrane by the integral enzyme, carnitine acyl translocase. On arrival into the mitochondrial matrix, acyl carnitine transferase II transfers the fatty acyl carnitine to CoA. This fatty acyl CoA complex subsequently undergoes β-oxidation to produce acetyl CoA.

Acetyl CoA is metabolized by Krebs cycle to provide H^+ for the electron transport chain which, in turn, produces ATP. In the process, free carnitine is recycled into the mitochondrial matrix and is transported to the cytosol by carnitine acyl translocase. Alternatively, carnitine may conjugate with acyl CoA (by acyl carnitine transferase II) and may also be transported out by translocase. The significance of this latter mechanism is that it allows for the removal of acyl carnitine derivatives (eg, toxic organic acids that accumulate during pathologic catabolism) from the cell for excretion.

The carnitine shuttle, therefore, is integral to normal intramitochondrial events, ATP production, and regulation of the acyl CoA:free CoA ratio; availability of free CoA is crucial for the production of ATP and an imbalance in the acyl CoA:free CoA ratio signals metabolic disturbance. An increased acyl CoA:CoA ratio inhibits pyruvate dehydrogenase activity, an enzyme normally allowing pyruvate to enter Krebs cycle. Administration of L-carnitine can correct this imbalance and restore normal functioning of the dehydrogenase enzyme. L-Carnitine also reduces long-chain acyl CoA in heart tissue. This lowers the inhibition of adenine–nucleotide translocase and facilitates the formation and transportation of ATP from long-chain acyl CoA to the cytosol.[39]

Defects of the Carnitine Cycle[b]

Four defects of the carnitine cycle, not all of which create a carnitine deficiency, are known.[34] These include: 1) carnitine transport defect, 2) carnitine palymitoyltransferase I deficiency, 3) carnitine/acylcarnitine translocase deficiency, and 4) carnitine palymitoyltransferase II deficiency. Carnitine transport defect creates a primary systemic carnitine deficiency, resulting in markedly low plasma and tissue carnitine levels, and often presents with cardiomyopathy and skeletal muscle weakness among other symptoms. In documented cases, treatment with L-carnitine supplementation has led to improvement in skeletal muscle and ventricular function.

In carnitine palmitoyltransferase II deficiency, normal to elevated carnitine levels are typical, accompanied by normal muscle and cardiac function.

In contrast, carnitine/acylcarnitine translocase deficiency can present with severe muscle weakness, mild hypertrophic cardiomyopathy, and low total and free carnitine levels. Of the 2 forms of carnitine palmitoyltransferase II deficiency, the less common but more severe form presents with low plasma and tissue carnitine levels, cardiomegaly, and cardiomyopathy. Because of the rarity of the disorder, there are no data on effects of treatment with L-carnitine.

Defects of the β-Oxidation Cycle

The fatty acid oxidation cycle occurs in 4 steps and involves 13 enzymes. The fatty acyl-CoA ester provided at the end of the carnitine cycle is metabolized and shortened by 2 carbons per cycle during β-oxidation, releasing an acetyl-CoA moiety to the Krebs cycle with each iteration. Of the potential number of enzyme deficiencies or impairments, there are 5 identified enzyme deficiency states and there is evidence that 4 can create a secondary L-carnitine deficiency; of these, 3 have been associated with cardiomyopathy. Long-chain acyl-CoA dehydrogenase (LCAD)[c] deficiency, long-chain L-3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, and medium-chain acyl-CoA dehydrogenase deficiency create low to low-normal plasma and tissue carnitine levels and often an associated cardiomyopathy.

The logic underlying treatment with L-carnitine in this group of disorders lies in the fact that enzyme deficiencies create an accumulation of the normally metabolized corresponding substrate; L-carnitine provides a route of removal of these often toxic organic intermediates and this accounts for the low tissue and plasma-free L-carnitine levels observed. Supplementation restores these levels, at least in plasma, and can allow normalization of mitochondrial energy production and improvement in myocardial functioning.[40] Restoration of normal tissue levels is often difficult attributable either to transport

[b]Although diagnosed rarely in the general population, heritable defects creating primary carnitine deficiency states are briefly reviewed to make inclusive factors that may be unrecognized in contributing to idiopathic disease.

[c]Many of the previously diagnosed cases of LCAD have now been reclassified as LCHAD.

defects or continuous urinary loss. Fortunately, even partial restoration of tissue losses can have significant clinical benefit.

Clinical Basis for L-Carnitine Supplementation

There is considerable precedent in the literature for using L-carnitine to treat various forms of cardiomyopathy. Virtually all reports to date involve small groups of patients (<20) with diverse causes and varying methods of assessing outcome. Not all reports demonstrate an improved outcome; this is primarily dependent on the pathogenic mechanism responsible for L-carnitine deficiency, progression of the disease at treatment initiation, and nature of any accompanying disorders. For example, treatment of disorders of L-carnitine transport (ie, L-carnitine transport defects), which typically result in low plasma levels and deficient tissue levels, rarely restore tissue levels to normal. Nonetheless, there are numerous reports of amelioration or dramatic resolution of cardiomyopathy and associated signs and symptoms in L-carnitine transport defect patients.[42–44] Although the normal route of L-carnitine transport is impaired, passive diffusion is thought to allow sufficient quantities of L-carnitine to reach tissue.[45]

L-Carnitine supplementation has been recommended in secondary deficiency syndromes resulting from the fatty acid oxidation disorders medium-chain acyl-CoA dehydrogenase,[45] LCAD[3],[46,47] and LCHAD.[46] It has also been shown to be effective in hypertrophic cardiomyopathy associated with mitochondrial myopathy, demonstrating clinical and echocardiographic improvement.[48]

There are a host of other disorders that lead to secondary carnitine deficiency and occasionally patients develop a cardiomyopathy. These include organic acidurias, such as methylmalonic aciduria and propionic aciduria. Certainly, any organic aciduria leading to carnitine deficiency could increase the risk for cardiomyopathy.

Conventional Treatment

Despite advances in understanding myocardial disease, treatment has remained relatively unchanged in the past decade in terms of novel therapies. Besides efforts directed to treat primary causal factors (eg, toxic and infectious), conventional therapy consists primarily of pre- and afterload reducing agents, inotropic agents, and β-blockers and Ca-blockers. Treatment is primarily directed at functional improvement, and there is little evidence that long-term outcome is changed. Here, we present an analysis of our collective clinical experience in treating these disorders with both conventional therapy and L-carnitine therapy.

METHODS

Study Design and Objectives

This investigation had a retrospective, multicenter protocol for cardiomyopathy in pediatric-aged patients and included 232 cases. The objective of this investigation was to compare the outcome of cardiomyopathy patients treated with L-carnitine plus conventional therapies with control patients treated with only conventional therapies. Outcome was assessed primarily in terms of overall outcome for mortality or transplantation, time to outcome, and changes in the patient's clinical severity, clinical functioning, and echocardiographic parameters obtained at time of diagnosis (baseline) and at end of study.

Investigators and Patients

Eight investigators at 7 centers reviewed all cases within their service for patients who had been diagnosed with cardiomyopathy and who met inclusion and exclusion criteria (Table 2). A total of 87 L-carnitine-supplemented patients and 145 control patients were identified who met inclusion and exclusion criteria; however, a minimum of 2 weeks of treatment with L-carnitine was required for treated cases to be included for analysis. Of the 232 total patients identified, 11 cases (5%) did not meet this requirement. Four patients died from cardiomyopathy and/or other cause before the end of 2 weeks of treatment; in 3 patients, it is unknown why treatment was stopped at <2 weeks (2 of these 3 patients were alive by end of study and 1 eventually went to transplant); 1 patient went to transplant before the end of 2 weeks of treatment; 1 patient received <2 weeks of treatment and went to transplant just after 2 weeks of starting treatment; 1 patient received <2 weeks of treatment and died from an unknown cause the month after starting treatment. All summaries and statistical analyses were performed on the 221 remaining patients.

The distribution of patients by center and treatment group is presented in Table 3. There was an approximately equal proportion of males and females in the study (Table 4), with slightly more females enrolled in both treatment groups. Patients in the control group were significantly older than were patients in the L-carnitine-treated group (6.5 years vs 2.1 years old, respectively; $P < .001$). The majority of patients were diagnosed with dilated cardiomyopathy, followed by the hypertrophic form. The remainder of patients had restrictive or mixed forms (Table 5).

The distribution of patients with a suspected metabolic cause for their cardiomyopathy diagnoses are shown in Tables 6 and 7; the most frequent metabolic abnormalities identified were glutaric acidemia type II, dicarboxylic aciduria, and long chain acyl CoA dehydrogenase deficiency. Certainly, these categories are not always diagnostic of a metabolic disorder, such as dicarboxylic aciduria. We placed any patient into this category who had an abnormality of organic acids, carnitine level, tissue biopsy, enzyme study, or family history suggestive of a metabolic disorder.

L-Carnitine Treatment

Patients were treated with intravenous L-carnitine and/or oral L-carnitine. Intravenous L-carnitine was generally given to inpatients (eg, for treatment of acute catabolic episodes at the time of hospitalization) and oral L-carnitine was provided to outpatients.

The mean dose of carnitine administered was 96 mg/kg and ranged from 14 mg/kg/day to 455 mg/kg/day. Table 8 summarizes the distribution of patients by dose duration.

Data Collection

Hospital and clinic charts were reviewed and data were collected on patient outcome, clinical severity, clinical functioning, echocardiographic parameters, concomitant medications, concomitant illnesses, L-carnitine treatment dose and duration, and patient demographics.

Data were captured by clinical visit using a sampling schedule,

TABLE 2. Inclusion/Exclusion Criteria

Inclusion criteria
Diagnosis of cardiomyopathy
Males and females up to 18 y of age, living or expired
Availability of at least 1 clinical visit with history and physical examination, tests supportive of diagnosis, and outcome
For treated patients, at least 2 wk of treatment with L-carnitine
Exclusion criteria
Conditions that preclude or confound evaluation
History of use of an investigational drug other than L-carnitine
Autosomal dominant β-myosin defect

TABLE 3. Distribution of Patients by Center and Treatment Group

Site	Treated $n = 76$ (100%)	Control $n = 145$ (100%)	Total $n = 221$ (100%)
Fresno, CA	34 (44.7%)	1 (.7%)	35 (15.8%)
Pittsburgh, PA	7 (9.2%)	13 (9.0%)	20 (9.0%)
Rochester, MN	1 (1.3%)	39 (26.9%)	40 (18.1%)
Indianapolis, IN	14 (18.4%)	27 (18.6%)	41 (18.6%)
Durham, NC	4 (5.3%)	13 (9.0%)	17 (7.7%)
Danville, PA	6 (7.9%)	16 (11.0%)	22 (10.0%)
Minneapolis, MN	10 (13.2%)	36 (24.8%)	46 (20.8%)

TABLE 4. Sex and Age of Patients

	Treated $n = 76$ (100%)	Control $n = 145$ (100%)	Total $n = 221$ (100%)
Male	37 (48.7%)	64 (44.1%)	101 (45.7%)
Female	39 (51.3%)	81 (55.9%)	120 (54.3%)
Mean age (y)*	2.1	6.5	
Standard deviation	3.2	6.4	
Minimum	1 d	1 d	
Maximum	15.7 y	18 y	

* $P < .001$.

TABLE 5. Classification of Cardiomyopathy by Treatment Group

Diagnosis	Treated $n = 76$ (100%)	Control $n = 145$ (100%)	Total $n = 221$ (100%)
Dilated	62 (81.6%)	86 (59.3%)	148 (67.0%)
Hypertrophic	8 (10.5%)	34 (23.5%)	42 (19.0%)
Restrictive	1 (1.3%)	15 (10.3%)	16 (7.2%)
Restrictive and hypertrophic	0 (0%)	3 (2.1%)	3 (1.4%)
Hypertrophic and dilated	4 (5.3%)	3 (2.1%)	7 (3.2%)
Dilated and restrictive	1 (1.3%)	0 (0%)	1 (.4%)
Unknown	0 (0%)	4 (2.7%)	4 (1.8%)

TABLE 6. Inferred Metabolic Disorder Diagnoses Among L-Carnitine-Treated Patients*

Inferred Diagnosis	Total $n = 29$ (100%)
Glutaric acidemia, type II	7 (24.2%)
Dicarboxylic acidemia	3 (10.4%)
LCAD deficiency	3 (10.4%)
Carnitine transport defect	2 (7.0%)
3-OH-acyl CoA dehydrogenase deficiency	1 (3.4%)
Fatty acid oxidation defect	1 (3.4%)
Glutaconic acidemia	1 (3.4%)
Glycogen storage disease	1 (3.4%)
Lipid storage myopathy	1 (3.4%)
Mitochondrial defect	1 (3.4%)
Primary carnitine deficiency	1 (3.4%)
Unspecified metabolic disorder	7 (24.2%)

* Based on organic acid testing ± L-carnitine levels, ± biopsy studies, ± enzyme studies, and ± family history suggestive of a metabolic cause.

recording at or as close to the following intervals as possible: baseline (day of diagnosis of cardiomyopathy), 7 days, 3 months, 6 months, 9 months, 1 year, every 6 months thereafter up to 3 years, and yearly thereafter.

Data were collected on all patients until the study endpoint of July 31, 1994. At that point, patient outcome was coded as alive, died, transplanted, or lost to follow-up. For patients who underwent transplantation, data were not collected after the date of transplantation. Patients who died were further categorized as having died from cardiomyopathy, other disorder (unspecified), cardiomyopathy and a comorbid disorder (unspecified), or an unknown cause.

TABLE 7. Inferred Metabolic Disorder Diagnoses Among Control Patients*

Inferred Diagnosis	Total $n = 15$ (100%)
LCAD deficiency	3 (20.0%)
Abnormal carnitine levels	3 (20.0%)
Skeletal muscle abnormalities	2 (13.3%)
Pyruvate metabolism defect	1 (6.7%)
Glycogen storage disease	1 (6.7%)
Fatty acid oxidation defect	1 (6.7%)
Unspecified	4 (26.6%)

* Based on organic acid testing ± L-carnitine levels, ± biopsy studies, ± enzyme studies, and ± family history suggestive of a metabolic cause.

TABLE 8. Duration of L-Carnitine Treatment

Dose Duration	$n = 76$ (100%)
2 wk to 1 mo	4 (5.3%)
1–3 mo	11 (14.5%)
3–6 mo	14 (18.4%)
6 mo to 1 y	12 (15.8%)
>1 y	35 (46.0%)

Clinical Severity and Clinical Functioning Scales

Three scales were developed before the investigation to assess clinical severity and clinical functioning. A set of signs and symptoms, considered by investigators to reflect key indicators of the patient's clinical status and acuity resulting from their cardiomyopathy, was developed by investigators. A total of 37 signs and symptoms were categorized into respiratory, cardiovascular, and systemic groups. The occurrence of each sign or symptom was recorded as documented in the record.

Each sign or symptom was weighted according to it's relative clinical severity. Cough, for example, was weighted as a 1, whereas pulmonary edema was weighted as a 3. The composite (summed score) of recorded signs and symptoms was deemed a proxy of clinical severity. Possible scores ranged between 0 and 71 points inclusive.

Two similar scales were developed to measure functional level, depending on patient age. The first was developed for school-aged children and the second for nonschool-aged children. The latter, however, was to be scored for all patients. The scales consisted of 5 points: 1 = normal activity (for age); 2 = mildly decreased activity; 3 = moderately decreased activity; 4 = no unnecessary activity allowed; and 5 = patient hospitalized. Scores were assigned based on the patient chart.

Statistical Methods

All statistical analyses were performed with BMDP statistical analysis software (SPSS, Chicago, IL). Distributions of demographic and baseline variables were summarized with descriptive statistics for each treatment group. The mean ages of patients in the 2 treatment groups were compared with Student's t test. Comparisons between the distributions of clinical outcomes for the treatment groups at study termination were made with χ^2 statistics.

Proportional hazards regression models were applied to assess times to clinical outcomes for the treatment groups and subgroups of clinical interest. For these analyses, both orthotopic transplantations and deaths were included as treatment failure outcomes. Patients who had died from an unknown cause (an exact cause was unavailable from the chart of 9 patients) or died from a known cause that was unrelated to cardiomyopathy (1 patient) were managed as censored in all time-to-event analyses and were excluded from clinical outcome summary tables. These patients were included in all other summary tables, however. Patients whose last follow-up visit occurred before end of study (July 31, 1994) were managed as censored in time-to-event analyses and were included in all summaries.

The proportional hazards model additionally enabled assessments of covariates, particularly those such as clinical severity with noteworthy imbalance for the treatment groups at baseline. The Wald statistic was used to make comparisons for parameters in the model for the treatment groups and for subgroups according to the covariates.

Incidence Density

For each treatment group and for subgroups within them according to whether the patient was treated with angiotensin-converting enzyme (ACE) inhibitors, time-to-clinical-outcome was further described with means and standard deviations for the duration of follow-up for the patients with and without treatment failure as well as the corresponding numbers of such patients. These quantities were then transformed to incidence densities by dividing the proportion of patients with treatment failure in a group by the mean duration of follow-up for all patients in that group. The incidence density is interpretable as the number of treatment failures per person-day of follow-up. The ratio of the incidence density for the control group to that for the L-carnitine-treated group represents the extent to which treatment failures occur sooner over time for the control group. Such incidence density ratios were determined for all patients and for the subgroups according to whether patients were treated with ACE inhibitors.

Analysis of Variance (ANOVA)

Repeated-measures ANOVAs were used to compare treatment groups at baseline and at end of study (posttreatment) for echocardiographic, clinical severity, and clinical functioning variables. Only patients with both baseline and end-of-study scores available were included for analysis of each variable.

RESULTS

Clinical Outcome

The distributions of clinical outcome are summarized by treatment group in Table 9. These distributions were significantly different ($P = .010$) in an overall sense. The pattern for such differences corresponded to tendencies for L-carnitine-treated patients to have lower mortality from cardiomyopathy as the primary diagnosis than do control patients (6.8% vs 17.9%), and less transplantation among L-carnitine-treated patients than control patients (9.6% vs 15.0%). L-Carnitine patients had higher mortality from cardiomyopathy with a comorbid diagnosis (9.6% vs 2.1%).

An analysis of the association between clinical outcome and concomitant medications unexpectedly revealed that the population of patients who received ACE inhibitors had significantly poorer survival. Although data were captured on whether ACE inhibitors were used, complete and reliable information was not available for dose and duration and dose relationship analyses were not possible.

Overall, 85 of the 213 total patients (40%) in Table 9 were treated with ACE inhibitors. Among the 85 ACE inhibitor-treated patients, 42 (49%) died from cardiomyopathy or underwent transplantation, and among 128 patients not treated with an ACE inhibitor, only 26 (20%) died from cardiomyopathy or underwent transplantation ($P < .001$; Table 10). The difference in clinical outcome between these 2 groups is mostly accounted for by more patients undergoing transplantation in the ACE inhibitor-treated group (25.9%) in comparison to the untreated group (4.7%), so ACE inhibitor treatment might possibly have been a consequence of their deterioration before transplantation rather than a possible cause of such deterioration.

Within the L-carnitine-treated group, 36 of the 73 patients (49%) received ACE inhibitors, and within the control group, 49 of the 140 patients (35%) received ACE inhibitors (Table 11). When distributions of clinical outcomes for L-carnitine treatment was examined in combination with and without ACE inhibitor treatment, overall differences were significant under both conditions ($P = .047$). Table 11 shows the comparison between treatment groups for each ACE inhibitor subgroup separately. The comparisons produced similar results to the overall outcome analysis in Table 9, although the bigger differences for mortality and transplantation were found in the ACE inhibitor-treated group, whereas the lowest proportions for mortality from cardiomyopathy and transplantation were found in the L-carnitine-treated, ACE inhibitor-untreated group.

Survival (Time-to-Event)

The comparison of time to death or transplantation between groups had exploratory modification to account for use of ACE inhibitor treatment. Better survival for ACE inhibitor-untreated versus ACE inhibitor-treated patients was clearly significant among all patients ($P < .001$; Fig 1).

Two further analyses were performed: 1) patients who were treated with L-carnitine and no ACE inhibitors versus all control patients, and 2) control patients who received ACE inhibitors versus control patients who did not receive ACE inhibitors. Significant improvement in survival was observed for L-

TABLE 9. Distribution of Outcome by Treatment Group

Outcome	Treatment Group		Total 213 (100%)
	L-Carnitine 73 (100%)	Control 140 (100%)	
Died from CMY	5 (6.8%)	25 (17.9%)	30 (14.0%)
Died from CMY and other	7 (9.6%)	3 (2.1%)	10 (4.7%)
Alive	54 (74.0%)	91 (65.0%)	145 (68.1%)
Transplant	7 (9.6%)	21 (15.0%)	28 (13.2%)
	$\chi^2 = 11.4$, $df = 3$; $P = .0096$		

CMY indicates cardiomyopathy.
Not included: 7 died of unknown cause (2 L-carnitine treated [1 on ACE inhibitors and 1 not on ACE inhibitors], 5 controls [3 on ACE inhibitors and 2 not on ACE inhibitors]); 1 died of other illness (L-carnitine treated [not on ACE inhibitors]).

TABLE 10. Distribution of Outcome by Use of ACE Inhibitors

	ACE Inhibitor 85 (100%)	No ACE Inhibitor 128 (100%)	Total 213 (100%)
Died from CMY	16 (18.8%)	14 (10.9%)	30 (14.0%)
Died from CMY and other	4 (4.7%)	6 (4.7%)	10 (4.7%)
Alive	43 (50.6%)	102 (79.7%)	145 (68.1%)
Transplant	22 (25.9%)	6 (4.7%)	28 (13.2%)
	$\chi^2 = 26.1$; $df = 3$; $P < .001$		

CMY indicates cardiomyopathy.
Not included: 7 died of unknown cause (2 L-carnitine treated [1 on ACE inhibitors and 1 not on ACE inhibitors], 5 controls [3 on ACE inhibitors and 2 not on ACE inhibitors]); 1 died of other illness (L-carnitine treated [not on ACE inhibitors]).

TABLE 11. Distribution of Outcome by Treatment Group and Use of ACE Inhibitor

Outcome	ACE Inhibitor		No ACE Inhibitor		Total 213 (100%)
	L-Carnitine 36 (100%)	Control 49 (100%)	L-Carnitine 37 (100%)	Control 91 (100%)	
Died from CMY	4 (11%)	12 (24%)	1 (2.5%)	13 (14%)	30 (14%)
Died from CMY and other	3 (8%)	1 (2%)	4 (11%)	2 (2%)	10 (5%)
Alive	23 (64%)	20 (41%)	31 (84%)	71 (78%)	145 (68%)
Transplant	6 (17%)	16 (33%)	1 (2.5%)	5 (6%)	28 (13%)
	$\chi^2 = 7.95$; $df = 3$; $P = .047$		$\chi^2 = 7.93$; $df = 3$; $P = .047$		

CMY indicates cardiomyopathy.
Not included: 7 died of unknown cause (2 L-carnitine-treated [1 on ACE inhibitors and 1 not on ACE inhibitors], 5 controls [3 on ACE inhibitors and 2 not on ACE Inhibitors]); 1 died of other illness (L-carnitine-treated [not on ACE inhibitors]).

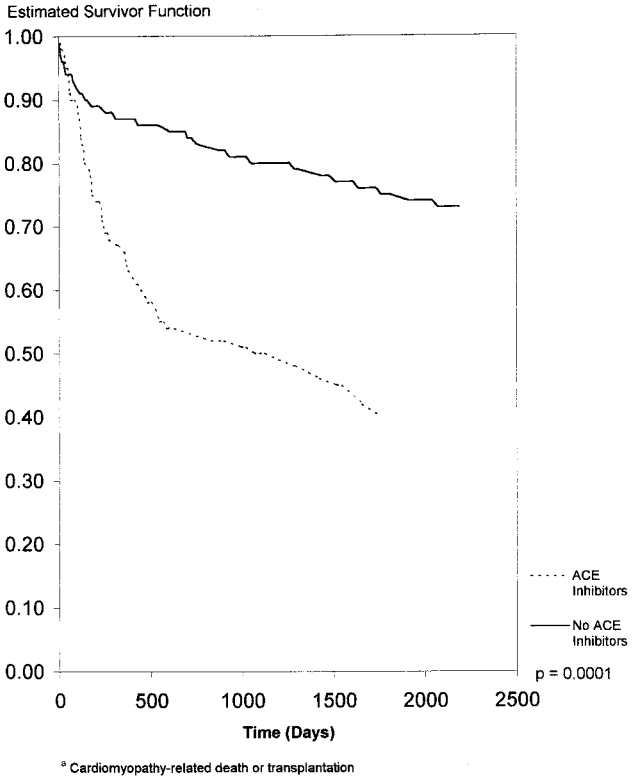

Fig 1. Time-to-outcome[a]: patients on ACE inhibitors versus patients not on ACE inhibitors (all patients).

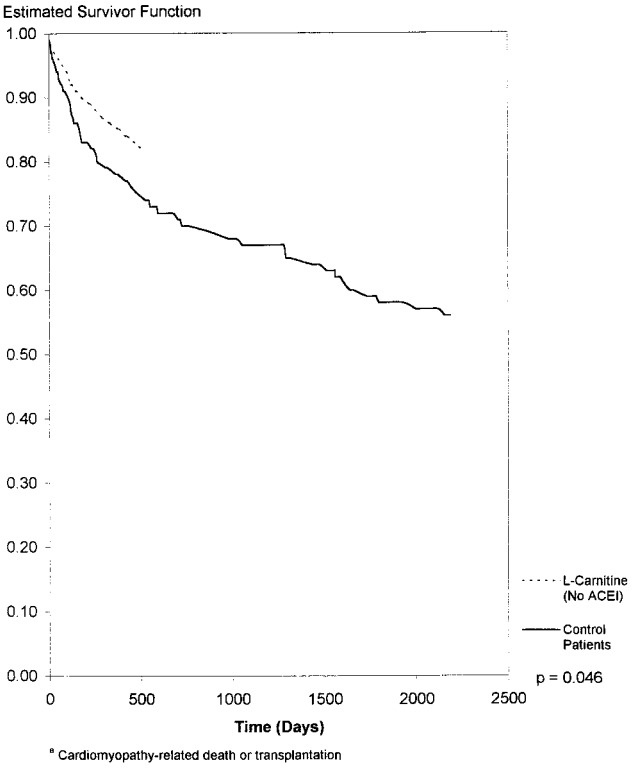

Fig 2. Time-to-outcome[a]: L-carnitine-treated patients (no ACE inhibitors) versus all control patients.

carnitine-treated patients who did not receive ACE inhibitors versus control patients (Fig 2; $P = .046$), and improved survival was noted for control patients who did not receive ACE inhibitors compared with those who did (Fig 3; $P = .0001$).

An exploratory proportional hazards regression model was fit to compare survival for patients who were younger than and older than 1 year, 9 months of age; this was the age at which the maximum separation in survival time (regardless of treatment) was suggested. Patients younger than 1 year, 9 months of age at the time of diagnosis demonstrated better survival with descriptive $P = .065$, than those older than 1 year, 9 months of age (Fig 4).

Incidence Density

The incidence density (ie, the number of deaths or transplantations per person-day of follow-up) was used for further description of times to clinical outcome for the treatment groups in relation to ACE inhibitor use (Table 12). The incidence density was 1.35 times greater in the control group than in the L-carnitine-treated group for both ACE inhibitor-treated and -untreated patients. This ratio thereby describes the greater extent of deaths or transplantations per person-day of follow-up time for the control group. Also, the incidence density in the ACE inhibitor-treated group was ~4.4 times higher than the non-ACE inhibitor-treated group in both the L-carnitine-treated and control groups, indicating a substantially greater extent of events per person-day of follow-up among ACE inhibitor-treated patients.

Echocardiographic Data

Mean ejection fraction values are shown by treatment group at baseline and at end of study in Fig 5. Repeated-measures ANOVA of the ejection fraction values did not indicate any noteworthy differences between the treatment groups with respect to ejection fraction, but there was a significant time effect

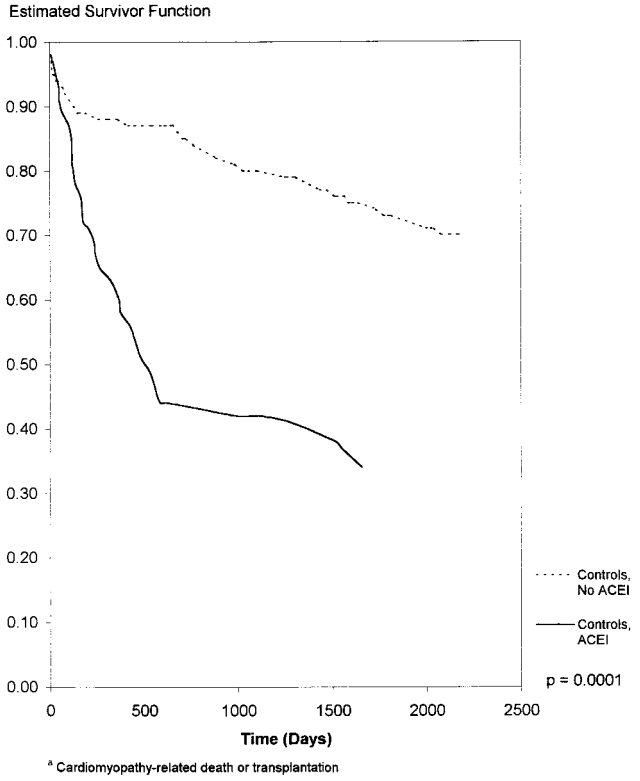

Fig 3. Time-to-outcome[a]: patients on ACE inhibitors versus patients not on ACE inhibitors (all control patients).

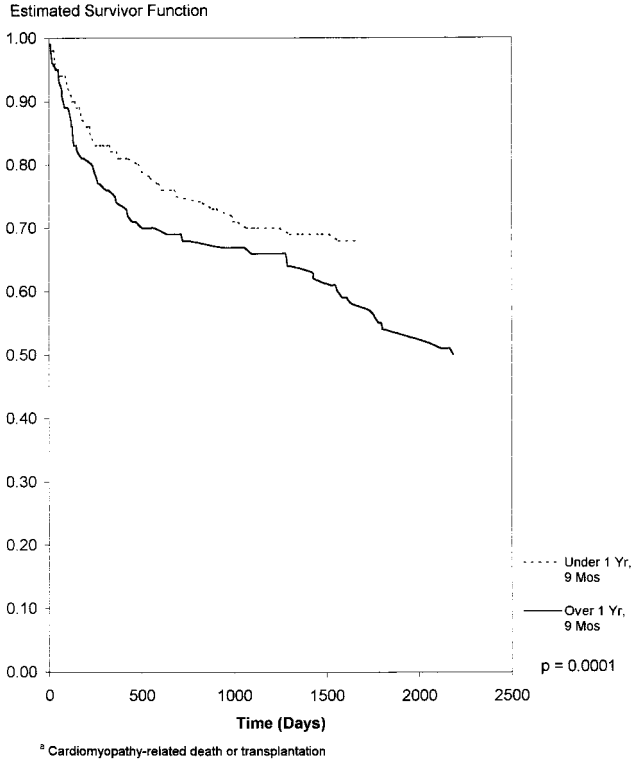

Fig 4. Time-to-outcome[a]: patients younger than 1 year 9 months of age versus patients older than 1 year 9 months of age (all patients).

($P = .001$); the ejection fraction values were similarly higher at the end of study than baseline for both groups.

Clinical Severity, Clinical Functioning, and Patient Status at Baseline

Mean clinical functioning scores and clinical severity scores by treatment group and time are shown in Figs 6 and 7, respectively (higher severity and functioning scores indicate a clinically worse condition). The repeated-measures ANOVA models indicated significant treatment and time effects for both clinical functioning and clinical severity ($P < .001$ for both effects). The model for clinical functioning also produced a highly significant interaction between treatment and time, indicating that the change between baseline and end of study differed for the treatment groups. This interaction comes from the L-carnitine patients improving to have nearly the same clinical functioning and severity as control patients at the end of the study, although they were substantially worse at baseline. In this regard, the percent hospitalized at baseline was twice as large for the L-carnitine group as the control group (Table 13).

DISCUSSION

Although a better prognosis might be attributed to patients 3 times younger at onset than their control counterparts, L-carnitine-treated patients were also manifestly clinically worse as demonstrated by significantly poorer clinical severity scores, clinical functioning scores, and ejection fraction values. Moreover, 2.5 times as many patients were hospitalized at baseline in the L-carnitine-treated group compared with the control group (Table 13).

Level of clinical functioning, age of patient at time of treatment, and use of ACE inhibitors become important covariates in determining efficacy. L-Carnitine-treated subjects, compared with control subjects, likely represent patients suffering from sufficient morbidity, progression of disease, and advanced risk of death to prompt clinicians to seek this alternative treatment. In contrast, patients treated conventionally may have been more clinically stable and thought to have a better prognosis to forestall consideration of alternative intervention, although a higher proportion of these patients eventually died or received transplant.

The unfavorable experience of patients receiving ACE inhibitor treatment was unexpected and required subgroup analysis of the data. The implications of this observation, in view of the efficacy reports in the literature and the observational nature of this investigation, are unclear and must be approached tentatively. Nonetheless, the unfavorable survival of patients on ACE inhibitors (Fig 1) deserves further attention. The follow-up period in this investigation is longer than that of many reports and may suggest uncertainty for improvement in long-term mortality from ACE inhibitor use, although there might possibly be short- to intermediate-term improvements in myocardial function. It is difficult to precisely quantify the relationship between ACE inhibitors, survival, and other parameters recorded in this investigation because the dose, frequency, and precise duration of concomitant medications were often not available from clinical charts.

TABLE 12. Incidence Density* Summary With Incidence Density Ratio for L-Carnitine-Treated Versus Control Patients, Subgrouped by ACE Inhibitor Use

	L-Carnitine Treated			Control			Incidence Density Ratio: Control/L-Carnitine
	Censored (*n*)	Outcome (*n*)	Incidence Density	Censored (*n*)	Outcome (*n*)	Incidence Density	
ACE Inhibitor (Mean, SD, *n*)	945 830 (23)	401 520 (13)	.176	1622 1144 (20)	424 483 (29)	.237	1.35
No ACE Inhibitor (Mean, SD, *n*)	1745 1197 (31)	216 1767 (6)	.040	1719 1157 (71)	657 697 (20)	.054	1.35
Total (Mean, SD, *n*)	1409 1122 (54)	342 444 (19)	.084	1697 1149 (91)	519 584 (49)	.10	1.19

SD indicates standard deviation.
* Mean time-to-event in days, per person-year of follow-up.
Censored: alive at end of study, lost-to-follow-up before end of study, or died from unknown cause or cause unrelated to cardiomyopathy.
Outcome: died from cardiomyopathy or cardiomyopathy plus other disorder or went to transplant.

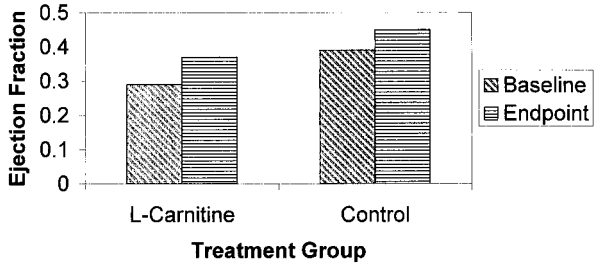

Fig 5. Mean ejection fraction baseline versus endpoint in L-carnitine-treated patients versus control subjects.

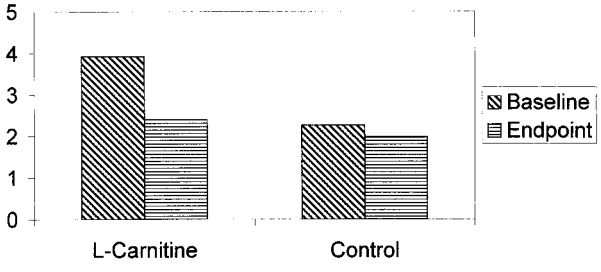

Fig 6. Mean clinical functioning at baseline versus endpoint in treated subjects versus control subjects.

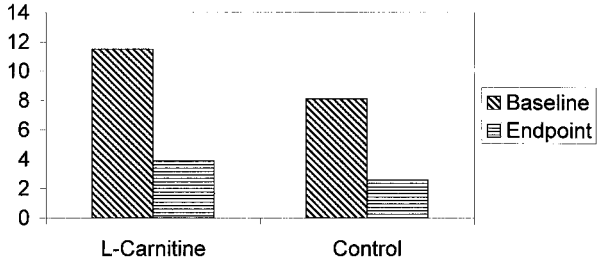

Fig 7. Mean clinical severity at baseline versus endpoint in treated subjects versus control subjects.

In the L-carnitine-treated group, the poorer survival of ACE inhibitor-treated patients was a suggestive trend. This finding is perhaps analogous to the protective effect against hepatotoxicity suggested for L-carnitine in patients treated with valproic acid. In this series of patients, this exploratory finding may be the most supportive to the benefits from L-carnitine treatment. Evaluating the benefit from L-carnitine for patients not treated with ACE inhibitors was more challenging because of reduced sample size, effects of other possible concomitant medications, and significant imbalances of baseline clinical severity and age relative to the corresponding control patients.

TABLE 13. Clinical Functioning at Baseline

Functioning Level	Treated 76 (100%)	Control 136 (100%)	Total 212
Hospitalized for chronic illness	48 (63.2%)	35 (25.7%)	83
Chronically ill, not eating orally, no extra activity	0 (0%)	1 (.7%)	1
Chronic poor eater with decreased activity	6 (7.9%)	2 (1.5%)	8
Intermittently eats poorly with decreased activity for age	10 (13.1%)	36 (26.5%)	46
Eats normally with normal activity for age	12 (15.8%)	62 (45.6%)	74

Note: 9 cases had clinical functioning scores unavailable at baseline (6 patients not on ACE inhibitors, 3 patients on ACE inhibitors).

Among the clinical parameters, each showed improvement by the end of study; ejection fraction values improved for both treated and control groups, slightly more for treated patients. Likewise for clinical severity and clinical functioning, treated and control patients ended the study within ~1 scale point of each other. This is a clinically significant difference in improvement for L-carnitine-treated patients because they started with substantially poorer measures at baseline.

CONCLUSION

In summary, our study showed a significant improvement in clinical severity and functioning of L-carnitine-treated patients versus control patients. Attributable to the retrospective nature of this study, several demographic and clinical parameters between treatment groups were imbalanced, making further conclusions difficult. ACE inhibitors were associated with unfavorable long-term outcome, but these exploratory results need further investigation because the study did not originally intend to eval-

uate the outcome of the pediatric use of ACE inhibitors. Metabolic causes of cardiomyopathy were, in general, not identified or considered, and appropriate testing was not ordered. Only 34 of 221 patients had any evidence to suggest a metabolic cause. We suspect the observed frequency to be low attributable to the lack of consideration or investigation for these disorders. Further prospective studies to investigate metabolic causes and L-carnitine therapy of pediatric cardiomyopathy would be helpful.

REFERENCES

1. Manolio TA, Baughman KL, Rodeheffer R, et al. Prevalence and etiology of idiopathic dilated cardiomyopathy: summary of a National Heart, Lung, and Blood Institute workshop. *Am J Cardiol*. 1992;69: 1458–1466
2. National Center for Health Statistics. Washington, DC: National Center for Health Statistics; 1990
3. Ferencz R, Neill CA. Cardiomyopathy in infancy: observations in an epidemiologic study. *Pediatr Cardiol*. 1992;13:65–71
4. Kelly DP, Strauss AW. Inherited cardiomyopathies. *N Engl J Med*. 1994;330:913–919
5. Keogh AM, Freund J, Baron DW, Hickie JB. Timing of cardiac transplantation in idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1988;61: 418–422
6. Stevenson LW, Fowler MB, Schroeder JS, et al. Poor survival of patients with idiopathic cardiomyopathy considered too well for transplantation. *Am J Med*. 1987;83:871
7. Akagi T, Benson LN, Lightfoot NE, Chin K, Wilson G, Freedom RM. Natural history of dilated cardiomyopathy in children. *Am Heart J*. 1991;121:1502–1506
8. Friedman RA, Moak J, Garson A. Clinical course of idiopathic dilated cardiomyopathy in children. *J Am Coll Cardiol*. 1991;18:152–156
9. Wiles HB, McArthur PD, Taylor AB, et al. Prognostic features of children with idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1991;68: 1372–1376
10. Lewis AB, Chabot M. Outcome of infants and children with dilated cardiomyopathy. *Am J Cardiol*. 1991;68:365–369
11. Chen C, Nouri SA, Balfour IB, Jureidini S, Appleton RS. Clinical profile of congestive cardiomyopathy in children. *J Am Coll Cardiol*. 1990;15: 189–193
12. Ino T, Benson LN, Freedom RM, Rowe RD. Natural history and prognostic risk factors in endocardial fibroelastosis. *Am J Cardiol*. 1988;62: 431–434
13. Greenwood RD, Nadas AS, Fyler DC. The clinical course of primary myocardial disease in infants and children. *Am Heart J*. 1976;92:549–560
14. Benson LN, Freedom RM. Classification of cardiomyopathies of childhood. *Prog Pediatr Cardiol*. 1992;1:4–7
15. Goodwin JF, Gordon H, Hollman A, Bishop MB. Clinical aspects of cardiomyopathy. *Br Med J*. 1961;1:69–79
16. World Health Organization/ISFC Task Force. Report of the WHO/International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathy. *Br Heart J*. 1980;44: 672–673
17. Abelmann WH. Classification and natural history of primary myocardial disease. *Prog Cardiovasc Dis*. 1984;27:73–94
18. Davies MJ, McKenna WJ. Dilated cardiomyopathy: an introduction to pathology and pathogenesis. *Br Heart J*. 1994;72(suppl):S24
19. Carter LF, Rubin SA. The molecular and cellular biology of heart failure. *Curr Sci*. 1994;9:264–271
20. Watkins H. Multiple disease genes cause hypertrophic cardiomyopathy. *Br Heart J*. 1994;72(suppl):S4–S9
21. Aroney C, Bett N, Radford D. Familial restrictive cardiomyopathy. *Aust N Z J Med*. 1989;18:877–887
22. Fitzpatrick AP, Shapiro LM, Rickards AF, Poole-Wilson PA. Familial restrictive cardiomyopathy with atrioventricular block and skeletal myopathy. *Br Heart J*. 1990;63:114–118
23. Schwartz ML, Cox GF, Lin AE, et al. Clinical approach to genetic cardiomyopathy in children. *Circulation*. 1996;94:2021–2038
24. Caforio ALP. Role of autoimmunity in dilated cardiomyopathy. *Br Heart J*. 1994;72(suppl):S30–S34
25. Burch GE, De Pasquale NP. Viral myocarditis. In: *Cardiomyopathies*. London, UK: JA Churchill; 1964:99–115
26. Keeling PJ, Tracy F. Link between enteroviruses and dilated cardiomyopathy: serologic and molecular data. *Br Heart J*. 1994; 72(suppl):S25–S29
27. Schwaiger A, Umlauft F, Weyrer K, et al. Detection of enterovirus ribonucleic acid in myocardial biopsies from patients with idiopathic dilated cardiomyopathy by polymerase chain reaction. *Am Heart J*. 1993;126:406–410
28. Weiss LM, Liu XF, Chang KL, Billingham ME. Detection of enteroviral RNA in idiopathic dilated cardiomyopathy and other human cardiac tissues. *J Clin Invest*. 1992;90:156–159
29. Keeling PJ, Jeffery S, Caforio AL, et al. Similar prevalence of enteroviral genome within the myocardium from patients with idiopathic dilated cardimyopathy and controls by the polymerase chain reaction. *Br Heart J*. 1992;68:554–559
30. Liljeqvist JA, Bergstrom T, Holmstrom S, et al. Failure to demonstrate enterovirus aetiology in Swedish patients with dilated cardiomyopathy. *J Med Virol*. 1993;39:6–10
31. Richardson PJ, Why HJF, Archard LC. Virus infection and dilated cardiomyopathy. *Postgrad Med J*. 1992;68(suppl 1):S17–S20
32. Maisch B, Drude L, Hengstenberg C, Hufnagel G, Schonian U, Schwab D. Cytolytic anticardiac membrane antibodies in the pathogenesis of myopericarditis. *Postgrad Med J*. 1992;68(suppl 1):S11–S16
33. Beaudet AL, Scriver CR, Sly WS, Valle D. Genetics, biochemistry, and molecular basis of variant human phenotypes. In: Scriver CR, Beaudet AL, Sly WS, Balle D, eds. *The Metabolic and Molecular Bases of Inherited Disease, I*. New York, NY: McGraw Hill; 1995:53–118
34. Bremer J, Osmundsen H. Fatty acid oxidation and its regulation. In: Numa S, ed. *Fatty Acid Metabolism and Its Regulation*. Amsterdam, The Netherlands: Elsevier; 1984:113
35. Scriver CR, Beaudet AL, Sly WS, Valle D. *The Metabolic and Molecular Bases of Inherited Disease*. New York, NY: McGraw Hill; 1995
36. Karpati G, Carpenter S, Engel AG, et al. The syndrome of systemic carnitine deficiency: clinical, morphologic, biochemical, and pathophysiologic features. *Neurology*. 1975;25:16–24
37. Rebouche CJ, Engel AG. Carnitine metabolism and deficiency syndromes. *Mayo Clin Proc*. 1983;58:533–540
38. Chalmers RA, Roe CR, Stacey TE, Hoppel CL. Urinary excretion of L-carnitine and acylcarnitines by patients with disorders of organic acid metabolism: evidence for secondary insufficiency of L-carnitine. *Pediatr Res*. 1984;18:1325
39. Visioli O, Pasini E, de Giuli F, Ferrari R. Molecular mechanism of action of L-carnitine in treatment of myocardial disorders at the experimental level. In: Ferrari R, Dimauro S, Sherwood G, eds. *L- Carnitine and Its Role in Medicine: From Function to Therapy*. San Francisco, CA: Academic Press; 1992:243
40. Servidei S, Bertini E, DiMauro S. Hereditary metabolic cardiomyopathies. *Adv Pediatr*. 1994;41:1–32
41. Rebouche CJ, Engel AG. Carnitine metabolism and deficiency syndromes. *Mayo Clin Proc*. 1983;58:533–540
42. Pierpont ME. Carnitine membrane transport defect: resolution of cardiac failure and preservation of cardiac function by L-carnitine. Presented at: Role of L-Carnitine in Cardiomyopathies of Infancy Symposium; June 21, 1993; Paris, France
43. Waber LJ, Valle D, Neill CA, DeMauro S, Shug AL. Carnitine deficiency presenting as familial cardiomyopathy: a treatable defect in carnitine transport. *J Pediatr*. 1982;101:700
44. Tein I, De Vivo DC, Bierman F, et al. Impaired skin fibroblast carnitine uptake in primary systemic carnitine deficiency manifested by childhood carnitine-responsive cardiomyopathy. *Pediatr Res*. 1990;28:247–255
45. Roe CR, Coates PM. Mitochondrial fatty acid oxidation disorders. In: Scriver CR, Beaudet AL, Sly WS, Balle D, eds. *The Metabolic and Molecular Bases of Inherited Disease, I*. New York, NY: McGraw Hill; 1995: 1501–1533
46. Tripp ME. Metabolic cardiomyopathies. *Prog Pediatr Cardiol*. 1992;1:1–12
47. Hale DE, Batshaw ML, Coates PM, et al. Long-chain acyl coenzyme A dehydrogenase deficiency: an inherited cause of nonketotic hypoglycemia. *Pediatr Res*. 1985;19:666–671
48. Campos Y, Huertas R, Lorenzo G, et al. Plasma carnitine insufficiency and effectiveness of L-carnitine therapy in patients with mitochondrial myopathy. *Muscle Nerve*. 1993;16:150–153

in the United States."[2] Thus, we feel our data provide a far better estimate of the age distribution of the onset of puberty in US girls than the Marshall and Tanner study of 192 institutionalized white British girls published in 1969 upon which the 8-year cutoff has been based. We also pointed out that the girls could have been brought in selectively because of a problem with puberty, one of the mechanisms for selection bias discussed by Drs Rosenfield et al. We further stated that if such a bias had occurred we should have expected to see the same bias operating among parents of the older girls with no development, leading to a decrease in the prevalence of secondary sexual characteristics in that age group, a finding which did not occur.[2] For such a "hidden agenda" to affect the findings, the majority of parents would have had to be reluctant to bring up a concern about puberty even though that was the reason for the visit. It seems unlikely that so many would be reticent to discuss their reason for bringing a child to their pediatrician.

We noted that the age of menses had not dropped for white girls over the past 45 years and had dropped by several months for African-American girls since MacMahon's analysis of HANES data from the 1960s.[3] Our colleagues correctly noted that the implications of our study are that the tempo of puberty is slower. The purpose of our study was not to offer explanations for any of the findings, but simply to note the proportions at a given age with secondary sexual characteristics and menses from a large population of girls. Earlier puberty has been noted to be associated with a longer duration until menses.[4] It is interesting to note that the lengthening tempo has also been noted among Hong Kong girls. With 10% of their study population now with stage 2 breast development *before* the age of 8, the mean duration from breast budding to menses for Hong Kong girls is 6 months longer than it was in the early 1960s.[5]

We agree that puberty at an early age may not be "normal" even though a large proportion of girls are experiencing it because factors that may be contributing are not yet understood. We do not dispute that some girls with early signs of puberty may be at risk for subsequent reproductive dysfunction. However, we question the recommendation that all girls with the sole factor of breast development or pubic hair growth before 8 and 9 years of age, respectively, have a diagnostic evaluation. If this recommendation (which reflects standard practice before the recent revised guidelines) was followed, about 8% of all white girls in this country and 34% of all African-American girls would need such an evaluation. We believe the new recommendations for the evaluation of early puberty[1] are sound. They were approved by the leadership of the Lawson Wilkins Pediatric Endocrine Society in large part because 7- to 8-year-old white and 6- to 8-year-old African-American girls are commonly referred to endocrinologists for pubertal changes and are rarely found to have a pathologic cause.

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REFERENCES

1. Kaplowitz PB, Oberfield SE, and the Drug and Therapeutics and Executive Committees of the Lawson Wilkins Pediatric Endocrine Society. Reexamination of the age limit for defining when puberty is precocious in girls in the United States: implications for evaluation and treatment. *Pediatrics.* 1999;104:936–941
2. Herman-Giddens ME, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research and Office Settings network. *Pediatrics.* 1997;99:505–512
3. MacMahon B. *Age of the menarche: United States, 1973.* Rockville, MD: National Center for Health Statistics; 1974. DHEW publication (HRA) 74-1615
4. Marti-Heeneberg C, Vizmanos B. The duration of puberty in girls is related to the timing of its onset. *J Pediatr.* 1997;131:618–621
5. Huen KF, Leung SSF, Lau JTF, et al. Secular trend in the sexual maturation of Southern Chinese girls. *Acta Pediatr.* 1997;86:1121–1124

ERRATUM

Due to an oversight, a source of funding was inadvertently omitted from a recent article (Helton E, et al. Metabolic aspects of myocardial disease and a role for L-carnitine in the treatment of childhood cardiomyopathy. *Pediatrics*. 2000;105: 1260–1270). The Acknowledgments section for this article should have read as follows:

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We apologize for any confusion this omission might have caused.

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Metabolic Aspects of Myocardial Disease and a Role forl-Carnitine in the Treatment of Childhood Cardiomyopathy

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