Myocardial Carnitine in End-Stage Congestive Heart Failure

Mary Ella M. Pierpont, MD, PhD, Dianne Judd, BS, Irvin F. Goldenberg, MD, W. Steves Ring, MD, Maria Teresa Olivari, MD, and Gordon L. Pierpont, MD, PhD

To test the hypothesis that carnitine is decreased in the myocardial tissue of patients with end-stage congestive heart failure (CHF), left ventricular myocardial carnitine was measured in 51 patients undergoing orthotopic cardiac transplantation. The study group included patients with idiopathic dilated cardiomyopathy, coronary artery disease, myocarditis and rheumatic heart disease. Myocardial carnitine varied in different cardiac chambers. In normal control hearts, the left and right ventricular total carnitine was similar, but the ventricles had higher levels than the atria ($p < 0.005$); in 30 hearts in CHF, the left ventricular total carnitine was higher than in the right ventricle ($p < 0.001$) and both ventricles had higher total carnitine than the atria ($p < 0.005$). Only 7 of 51 patients with CHF had low myocardial carnitine, whereas plasma carnitine was elevated in all diagnostic groups of end-stage CHF studied.

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The heart derives its predominant energy production from mitochondrial oxidation of long chain fatty acids. Carnitine, a quaternary ammonium compound, is essential for transport of long chain fatty acids across the inner mitochondrial membrane to the site of beta-oxidation. Myocardial carnitine deficiency has been documented in several animal models of cardiac failure, including cardiomyopathic Syrian hamsters,[1] guinea pigs with diphtheria,[2] rats with pressure-overload myocardial hypertrophy[3] and dogs with regional myocardial ischemia caused by surgical ligations.[4] Markedly reduced levels of myocardial carnitine have also been reported in children with cardiomyopathy and systemic carnitine deficiency.[5,6] To test the hypothesis that carnitine is depleted from the myocardium in end-stage human congestive heart failure (CHF), we measured carnitine from the hearts of 51 patients who underwent orthotopic cardiac transplantation.

METHODS

In 51 patients undergoing orthotopic cardiac transplantation because of severe CHF, a transmural section of the left ventricular free wall was obtained immediately after surgical removal of the recipient heart. The section (50 to 100 mg) was frozen immediately on dry ice and stored at −80°C. These samples and all other samples, including blood, were obtained under a protocol approved by the Committee on the Use of Human Subjects in Research of the University of Minnesota. In the first 21 of the 51 subjects, only a transmural section removed from the left ventricular anterolateral free wall along the circumflex marginal coronary artery (3.0 cm from origin) was obtained. In the second group of 30 subjects, myocardial sections were obtained from the right ventricle (anterior free wall, 2.0 cm below the infundibulum), right atrium (appendage) and left atrium (appendage) in addition to the left ventricular sample. Similar sections of each chamber were also obtained at autopsy of 5 control subjects with normal hearts (no malformations or evidence of coronary artery disease) who died of noncardiac causes. Blood plasma samples were obtained from 23 of the 51 subjects within 24 hours before cardiac transplantation. Plasma and myocardial carnitine were measured by a radioisotopic method as previously described.[7,8] All data are presented as mean ± standard deviation.

RESULTS

Subject population: The 51 patients in this study ranged in age from 6 months to 64 years (mean 39 ±

From the Ray and Hattie Anderson Center for the Study of Hereditary Cardiac Disease, the Departments of Pediatrics, Medicine and Surgery, University of Minnesota, Veterans Administration Medical Center, and Minneapolis Heart Institute Foundation, Minneapolis, Minnesota. This study was supported in part by the American Heart Association, Minnesota Affiliate, the Vikings Children's Fund, the Minnesota Medical Foundation and the Variety Club Association, Minneapolis, Minnesota. Manuscript received January 23, 1989; revised manuscript received and accepted April 3, 1989.

Address for reprints: Mary Ella M. Pierpont, MD, PhD, University of Minnesota, Box 94, 420 Delaware Street SE, Minneapolis, Minnesota 55455.

TABLE I Clinical Characteristics of End-Stage Congestive Heart Failure

	All Pts (n = 51)	Dilated Cardiomyopathy (n = 31)	Coronary Artery Disease (n = 13)	Myocarditis (n = 5)	Rheumatic Heart Disease (n = 2)
Age (yrs)	39 ± 17	36 ± 17	50 ± 8*	25 ± 19	47 ± 13
Dur Sx (yrs)	2.8 ± 2.9	3.0 ± 1.5	2.6 ± 4.0	1.3 ± 2.1	4.0 ± 4.2
EF (%)	18 ± 9	19 ± 10	16 ± 6	20 ± 6	15 ± 6
PAW (mm Hg)	28 ± 7	28 ± 7	27 ± 8	31 ± 10	25 ± 4
CO (liters/min)	3.6 ± 1.0	3.7 ± 1.0	3.5 ± 0.8	3.3 ± 1.2	3.3 ± 1.3
CI (liters/min/m^2)	2.0 ± 0.5	2.0 ± 0.5	1.9 ± 0.4	2.1 ± 1.0	1.7 ± 0.7
RAP (mm Hg)	14 ± 7	15 ± 7	8 ± 5*	18 ± 2	9 ± 5
PAR (dynes s cm^{-5})	234 ± 126	225 ± 120	270 ± 140	186 ± 141	261 ± 111

All values are mean ± standard deviation.
* $p < 0.01$.
CI = cardiac index; CO = cardiac output; Dur Sx = duration of symptoms; EF = ejection fraction; PAR = pulmonary arteriolar resistance; PAW = pulmonary artery wedge pressure; RAP = right atrial pressure.

17 years) at the time of cardiac transplantation. There were 41 males and 10 females. The etiology of severe CHF determined by pathologic and microscopic examination of the explanted heart was idiopathic dilated cardiomyopathy in 31, severe coronary artery disease in 13, acute or chronic myocarditis in 5 and rheumatic heart disease in 2. Virtually every patient was receiving digoxin, diuretics, vasodilator preparations and anticoagulant drugs. The severity of left ventricular dysfunction of all 51 patients was documented by hemodynamic measurements at cardiac catheterization, and by determination of left ventricular ejection fraction using gated radionuclide left ventriculography (45 patients), quantitative left ventricular angiography (1 patient) or 2-dimensional echocardiography (5 patients).

Clinical and hemodynamic data: The mean left ventricular ejection fraction of the study group (18 ± 9%) was low, and the mean pulmonary arterial wedge pressure high (28 ± 7 mm Hg) compared to normal values for both adults and children. When the study group was divided according to etiology of CHF (Table I), duration of symptoms, ejection fraction, pulmonary arterial wedge pressure, cardiac output, cardiac index and pulmonary arteriolar resistance were similar in all groups. Patients with coronary artery disease were significantly older than those with idiopathic dilated cardiomyopathy ($p < 0.01$) or myocarditis ($p < 0.001$). The right atrial pressure was significantly lower in the group with coronary artery disease compared to those with dilated cardiomyopathy ($p < 0.01$) or myocarditis ($p < 0.001$).

Intracardiac carnitine variability: Table II presents a comparison of myocardial carnitine levels in different cardiac chambers for the 5 normal hearts obtained at autopsy and 30 hearts of CHF patients. Analysis of variance for repeated measures on the same elements revealed that in normal hearts, the left ventricular and right ventricular myocardial total carnitine levels were similar, but both ventricular levels were significantly higher than either the left atrium or right atrium ($p < 0.005$). Similarly, in the 30 patients with CHF, the right ventricular and left ventricular myocardial total carnitine levels were both significantly higher than either the left atrium or right atrium. In addition, left ventricular total carnitine was significantly higher than in the right ventricle ($p < 0.001$). In both normal hearts and CHF hearts, the right and left atria had similar values.

TABLE II Intracardiac Variability of Carnitine Levels

Chamber Location	Normal Hearts Total Carnitine (n = 5)	CHF Hearts Total Carnitine (n = 30)	CHF Hearts Free Carnitine (n = 30)
Left ventricle	5.7 ± 1.0	6.2 ± 1.7	3.4 ± 1.4
Right ventricle	6.2 ± 1.8	5.2 ± 1.6	2.8 ± 1.2
Left atrium	4.1 ± 0.5	4.1 ± 1.3	2.2 ± 1.0
Right atrium	3.7 ± 0.1	4.2 ± 1.1	2.1 ± 0.8

All values are mean ± standard deviation, nmol/mg noncollagenous protein.
CHF = congestive heart failure.

Free carnitine was not measured in the 5 normal hearts because postmortem alterations in the levels of unesterified (free) carnitine during the interval from death to autopsy would probably invalidate the results. Total carnitine, however, is stable during the interval from death to autopsy.[9,10] Free carnitine in the CHF hearts (Table II) showed a distribution similar to that for total carnitine—namely, left ventricle higher than right ventricle ($p < 0.01$) and both ventricles greater than either atria ($p < 0.001$).

Variation in left ventricular carnitine: The mean value of left ventricular total carnitine for the 51 patients with severe CHF was not significantly different from control values: 6.0 ± 2.0 vs 5.7 ± 1.0 nmol/mg noncollagenous protein. The mean values of total carnitine for patients with dilated cardiomyopathy (5.7 ± 2.0, n = 31), coronary artery disease (6.7 ± 1.6, n = 13) and myocarditis (5.9 ± 2.0, n = 5) were also not significantly different from control. However, Figure 1 shows the striking finding of marked variation in left ventricular total carnitine among the 51 patients undergoing cardiac transplantation according to the overall group and within each subgroup as well. Seven of the 51 hearts (13.7%) had left ventricular total carnitine levels that were more than 2 standard deviations below the mean of the 5 normal hearts. Of the 7 with very low myocardial carnitine, 5 individuals had idiopathic dilated cardiomyopathy, 1 had acute myocarditis and 1 had rheumatic heart disease. No patient with coronary artery disease had low myocardial total carnitine. The extent of variation of left ventricular total carnitine in individuals with severe CHF is further evident by noting that

relatively high values for myocardial carnitine (>2 standard deviations) are present in 8 (15.7%) of the patients in Figure 1 (4 with idiopathic dilated cardiomyopathy, 3 with coronary artery disease and 1 with myocarditis).

Quantitative correlations: As seen in Table III, total myocardial carnitine did not correlate significantly with any of the hemodynamic variables, age or duration of symptoms for either the CHF group as a whole (n = 51), or the subgroup with dilated cardiomyopathy (n = 31). In the 13 patients with coronary artery disease, myocardial total carnitine correlated with cardiac output ($r = 0.62$, $p < 0.05$) and cardiac index ($r = 0.70$, $p < 0.01$), while there was a negative correlation with right atrial pressure ($r = -0.67$, $p < 0.05$). In the 5 patients with severe myocarditis, only the pulmonary arterial wedge pressure correlated with myocardial total carnitine ($r = 0.99$, $p < 0.01$).

Plasma carnitine: None of the 23 patients in whom blood samples were obtained before surgery had deficiency of plasma carnitine (total carnitine <20 nmol/ml). Moreover the mean value of total plasma carnitine (Figure 2) for all of the 23 patients was significantly higher than 36 normal healthy control subjects ($p < 0.001$). Each subgroup sorted by etiology of CHF also had a mean plasma carnitine value significantly higher than control. The highest plasma carnitine values were measured in those patients with severe myocarditis.

Relation of plasma total carnitine and creatinine clearance: Of the 23 patients who had plasma total carnitine measurements, all had concomitant measurements of serum creatinine and 20 had measurement of creatinine clearance. Using linear regression analysis, serum creatinine correlated poorly with both plasma total carnitine ($r = 0.54$, $p < 0.01$) and free carnitine ($r = 0.50$ $p < 0.05$). Creatinine clearance did not correlate significantly with either total or free plasma carnitine. Similarly, the natural logarithm of creatinine clearance did not correlate with the natural logarithm of either total or free plasma carnitine.

DISCUSSION

Plasma or myocardial carnitine deficiency has been reported in patients with endocardial fibroelastosis, idiopathic dilated cardiomyopathy or hypertrophic cardiomyopathy.[5,6,11-17] In addition, alterations in carnitine levels have been described in patients with cardiac dysrhythmias and CHF.[8,18] Little baseline data are available on normal values for myocardial total carnitine Values ranging from 4.5 to 12.5 nmol/mg noncollagenous protein have been reported, with the majority in the

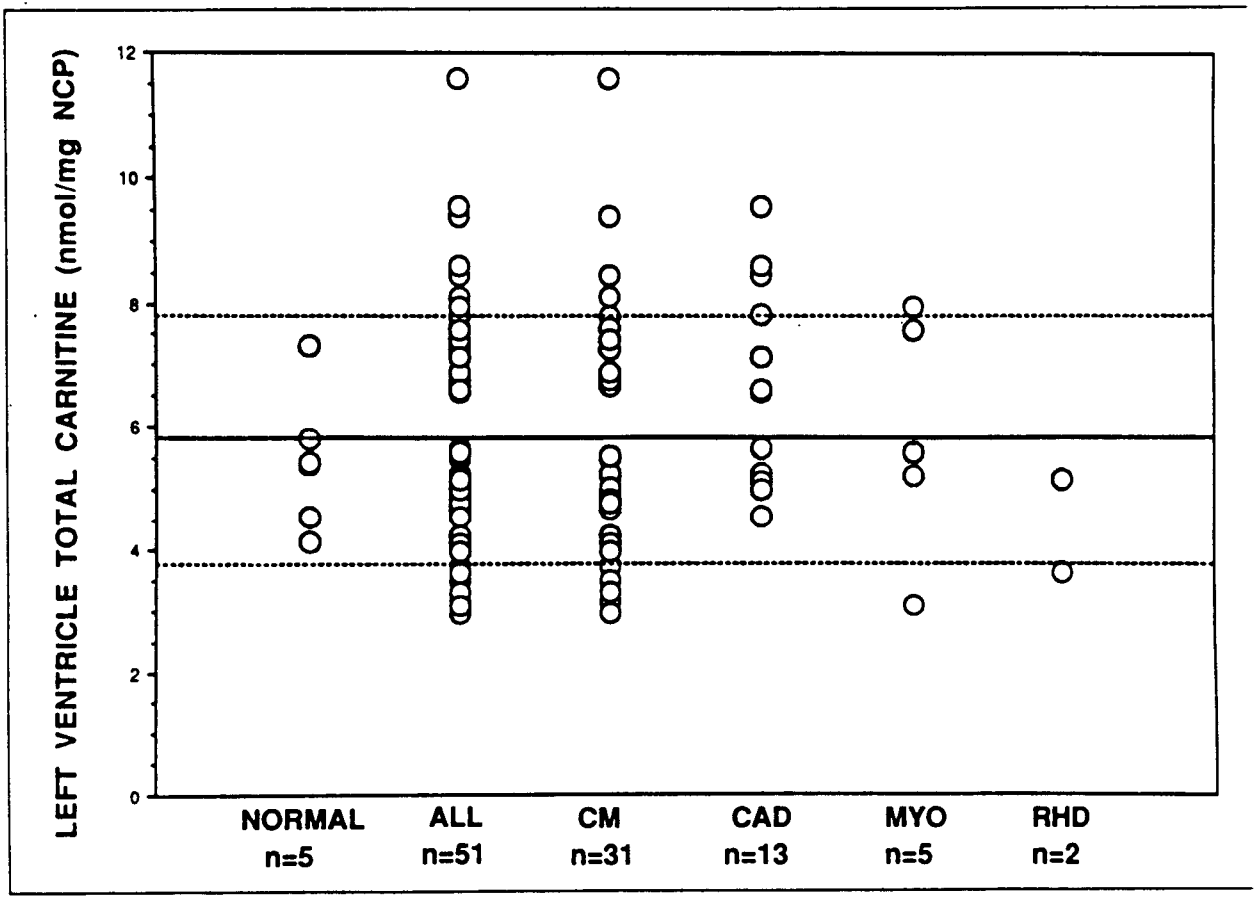

FIGURE 1. Left ventricular total carnitine from the hearts of 51 patients undergoing cardiac transplantation and from 5 normal autopsy hearts. ALL = all patients; CAD = patients with coronary artery disease; CM = patients with idiopathic dilated cardiomyopathy; MYO = patients with myocarditis; RHD = patients with rheumatic heart disease.

TABLE III Correlation Coefficients for Myocardial Total Carnitine with Hemodynamics and Other Variables

Variable	Correlation Coefficients			
	All Pts (n = 51)	Dilated Cardiomyopathy (n = 31)	Coronary Artery Disease (n = 13)	Myocarditis (n = 5)
Age	0.14	0.10	−0.21	0.21
Dur Sx (yrs)	0.25	0.18	0.62*	0.47
EF (%)	−0.04	−0.08	0.20	0.27
PAW (mm Hg)	0.17	0.17	−0.17	0.99†
CO (liters/min)	0.26	0.18	0.62*	0.61
CI (liters/min/m^2)	0.19	0.11	0.70†	0.35
RAP (mm Hg)	−0.29	−0.25	−0.67*	0.65
PAR (dynes s cm^{-5})	0.12	0.08	0.14	−0.03

* $p < 0.05$; † $p < 0.01$.
Abbreviations as in Table I.

6 to 7 range.[10,16,19-21] Our values for normal left ventricular total carnitine (5.7 ± 1.0 nmol/mg noncollagenous protein) compare favorably with these values. Moreover, our findings that both total and free carnitine vary depending on the cardiac chamber sampled could explain some of the differences among previous reports, and suggest that measurement of right ventricular carnitine from endomyocardial biopsies may not accurately reflect left ventricular carnitine concentration.

There was remarkable variability in the myocardial carnitine in our CHF patients, with 7 of the 51 (13.7%) having left ventricular total carnitine >2 standard deviations below normal and 8 (15.7%) being >2 standard deviations above normal. In the group of 51 patients with CHF, these myocardial carnitine levels did not correlate with any hemodynamic variable. Myocardial free carnitine has previously been shown to be depleted in areas of acute myocardial infarction,[10] but none of our

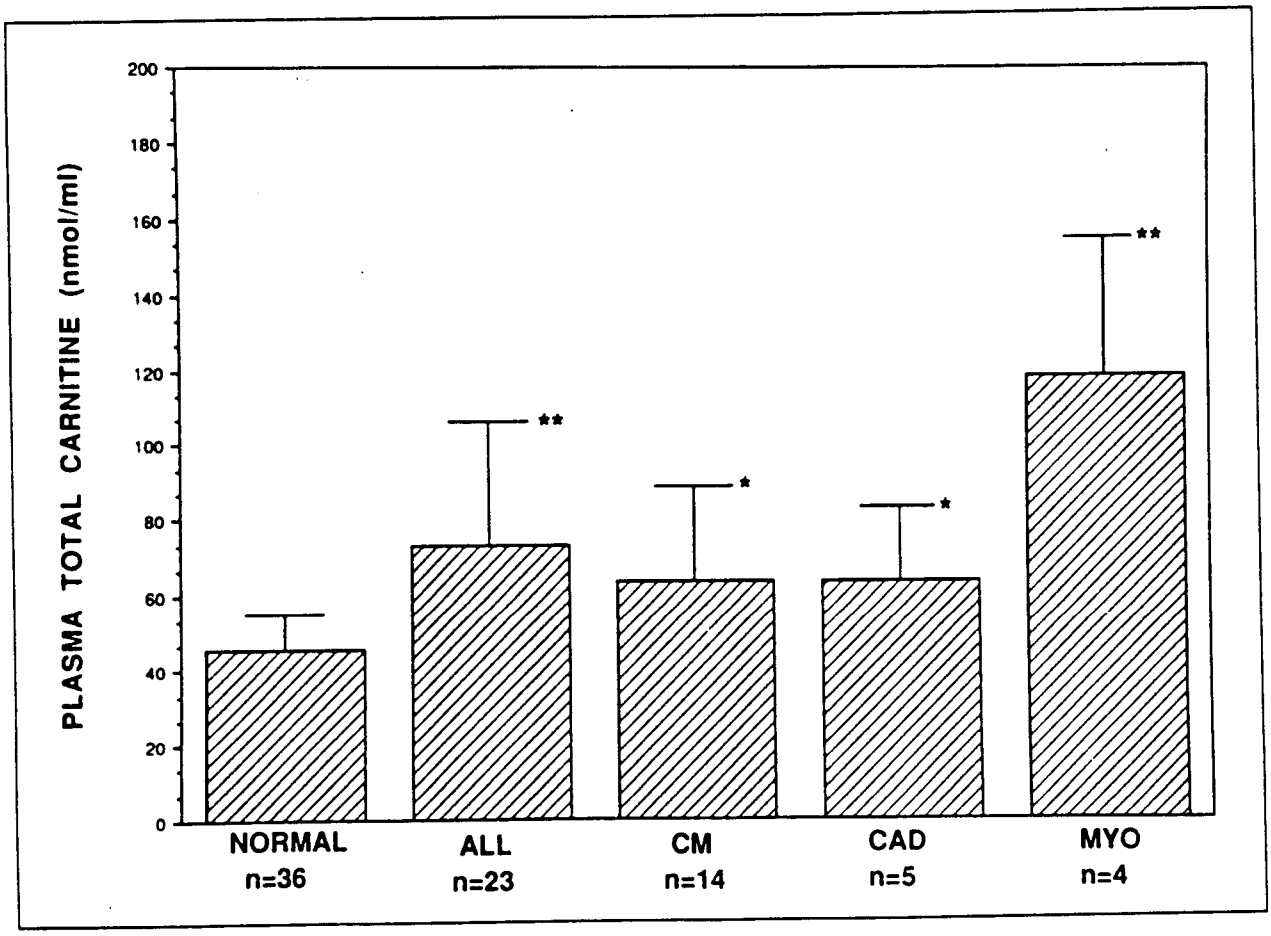

FIGURE 2. Plasma total carnitine measurements in 36 healthy adult volunteers (NORMAL) and 23 patients with severe heart failure before cardiac transplantation. *p <0.01; **p <0.001. Abbreviations as in Figure 1.

13 patients with coronary artery disease had severely depleted myocardial carnitine. Decreased myocardial carnitine has also been reported in papillary muscle biopsies[9] and endomyocardial biopsies[16] from patients with chronic CHF. In the latter study by Regitz et al,[16] the decreased myocardial carnitine was relatively consistent, including both patients with idiopathic dilated cardiomyopathy and coronary insufficiency. Another study by Regitz et al[17] found myocardial carnitine levels in explanted human hearts similar to ours, but concluded they were low based on comparison to relatively high normal values obtained from 3 donor hearts. It is tempting to speculate that the severe carnitine deficiency in some patients may be clinically relevant, since Ghidini et al[22] reported that L-carnitine supplementation in elderly patients with heart failure reduced heart rate, improved diuresis, reduced edema, alleviated dyspnea and decreased digitalis requirements. Our study did not examine the efficacy of dietary carnitine supplementation, but our results suggest that relatively few CHF patients would benefit based on their myocardial levels.

We did not find plasma carnitine deficiency in any of the 23 patients in whom it was measured. This is in contrast to 6 of 27 adults with dilated cardiomyopathy studied by Feldman et al[12] and 2 of 25 patients (both young children) reported by Tripp et al.[11] However, plasma total carnitine levels can be normal even in patients with systemic carnitine deficiency[23] who can have marked variation in plasma carnitine from day to day. Thus, a single normal plasma carnitine measurement may not reflect deficiency of carnitine in tissues. The poor correlation between plasma carnitine and myocardial carnitine in our study and that of Regitz et al[16] further supports this statement.

The mean plasma carnitine in our patients was higher than normal, and 12 of our patients had plasma total carnitine >60 nmol/ml. This finding is consistent with those of Tripp,[11] Feldman[12] and co-workers in cardiomyopathy patients, and Conte et al[24] in patients with dilated, hypertrophic and alcoholic cardiomyopathy and CHF from other causes.

The cause of elevated plasma carnitine in severe CHF is not clear. Because carnitine is excreted by the kidney and can be removed by hemodialysis,[25] Feldman et al[12] suggested that decreased excretion of carnitine is a likely cause. They found a good correlation between the natural logarithms of plasma carnitine and creatinine clearance in 15 patients they studied, but we were unable to confirm this finding. A correlation between total plasma carnitine and serum creatinine was also reported by Bartel et al[25] in a group of patients with severe renal failure undergoing hemodialysis. Due to the selection process for cardiac transplantation, renal dysfunction in our patients was minimal and thus the 2 study groups are not directly comparable. We found a weak correlation between plasma total carnitine and serum carnitine, whereas Regitz et al[17] and Conte et al[24] found no such correlation. It would appear that decreased renal function alone cannot account for the elevated plasma carnitine, and some alterations in carnitine metabolism in CHF still remain unknown.

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