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ORIGINAL ARTICLE

Carnitine supplementation improves cardiac strain rate in children on chronic hemodialysis

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Abstract
Background Carnitine plays a key role in energy production in the myocardium. Carnitine deficiency commonly occurs in patients on chronic hemodialysis (HD) and may contribute to cardiomyopathy.
Methods Carnitine levels and cardiac function of nine children on HD were assessed before and after 6 months of intravenous levocarnitine supplementation. Standard echocardiographic (ECHO) measures of left ventricular (LV) function as well as strain and strain rate analysis using novel speckle-tracking echocardiography were performed and the results compared to those of a control group of children on chronic HD.
Results Following carnitine supplementation, total (49.0±1.67 vs. 298.0±31.8 μmol/L) and free carnitine (29.0±1.20 vs. 180.4±19.2 μmol/L) increased ($p<0.0001$), and the acyl:free (A:F) carnitine ratio improved (0.73±0.04 vs. 0.65±0.05; $p=0.02$). There were no changes in standard ECHO measures of LV function, including end diastolic dimension, mass index, ejection fraction, and fractional shortening. There was significant ($p=0.017$) improvement in the longitudinal strain rate (−1.48±0.11 vs −1.91±0.12) after carnitine supplementation in the study group. No improvements in LV function, strain, or strain rate occurred in controls.
Conclusions Levocarnitine supplementation improved carnitine levels, the A:F ratio, and longitudinal strain rate in children on HD.

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Introduction

Cardiovascular disease is a leading cause of death among both children and adults with kidney disease, accounting for 40 % of deaths among pediatric patients with end-stage renal disease [1]. Cardiac abnormalities described in patients undergoing chronic hemodialysis (HD) include left ventricular (LV) hypertrophy, vascular calcifications, and atherosclerosis. It has recently been shown that children receiving chronic HD also experience myocardial stunning, characterized by regional LV dysfunction which may be due to ischemia from fluid shifts during the HD session [2]. Over time, repeated HD-induced myocardial injury contributes to a reduction in LV function [3].

Carnitine is essential for the transport of fatty acids into mitochondria and energy production in the myocardium. It is also needed to protect myocyte cell membranes from oxidative damage by removing excess acyl carnitine groups [4]. Chronic HD patients are at increased risk for carnitine deficiency as a result of losses incurred during dialysis, lack of endogenous carnitine synthesis by the kidney, and inadequate dietary intake [5]. Chronic HD sessions result in a progressive decline in plasma and muscle carnitine levels with concurrent accumulation of medium and long chain acylcarnitine ("non-acetyl" acyl carnitine) over time [6, 7]. Dialysis-related plasma and muscle carnitine deficiency have been well documented in the pediatric population [8–13]. A number of studies in adult chronic HD patients have demonstrated a beneficial effect of carnitine supplementation on LV function, as indicated by improved ejection fraction (EF) [14–17]. However, other studies have failed to

demonstrate any improvement in fractional shortening (FS) or EF; however, it should be noted that carnitine supplementation was of short duration (≤2 months) in these studies [18, 19]. In contrast, one uncontrolled study did show an improvement in FS and EF in 6 children after 18 months of oral carnitine supplementation [11]. Little is known about the effect of intravenous (IV) carnitine supplementation on cardiac function in hemodialyzed children. Only one such controlled pediatric study has been published which reported no improvement in cardiac function assessed by standard echocardiography (ECHO) [20]. ECHO measures of strain (percentage deformation of the myocardium) and strain rate may be more sensitive indicators of function than the traditional measures of EF and FS and may provide a means for early detection of cardiac dysfunction [21]. Assessment of strain utilizes new technology that analyzes myocardial motion by tracking natural acoustic markers (or speckles) within the myocardium [22]. Strain rate measures the speed at which deformation occurs and may a superior marker to strain in the dialysis population, as it is preload- and afterload-independent. The aim of our study was to assess cardiac response to IV levocarnitine supplementation in children on chronic HD using standard ECHO methods, as well as the more sensitive speckle-tracking echocardiography.

Subjects and methods

This was a prospective, longitudinal, open-labeled, controlled study designed to assess carnitine levels and cardiac function after levocarnitine supplementation, with each participant serving as their own control. In addition, a retrospective control group of children on chronic HD who did not receive levocarnitine was added for comparison of cardiac function. All patients (study and controls) had predialysis blood pressure (BP) and percent interdialytic weight gain (%IDWG) measured at each dialysis session for the duration of the study. All participants received supplementation with IV iron sucrose and erythropoietin according to standardized dialysis center protocols to maintain iron repletion (transferrin saturation >20%, ferritin >100 μmol/L) and hemoglobin levels (10–12 g/dl; measured weekly). The study was approved by the Institutional Review Board at Children's National Medical Center in Washington, D.C. and informed consent was obtained.

Study group

Children (2–21 years) receiving chronic HD for ≥3 months were eligible to participate if they were iron replete and on erythropoietin therapy for >8 weeks. Patients with iron deficiency, severe hyperparathyroidism, hemoglobin >13 g/dL, history of recent gastrointestinal bleed, severe infection, inborn error of metabolism, or underlying congenital heart lesions or on myelosuppression were excluded.

Carnitine levels and supplementation

Prior to the initiation of carnitine therapy, five baseline measures (two drawn predialysis at consecutive dialysis sessions and three drawn at 1-month intervals thereafter) of plasma total carnitine and free carnitine were obtained. Acylcarnitine was calculated from the measured plasma carnitine levels as [total carnitine − free carnitine], and the acyl:free (A:F) ratio was calculated as [acylcarnitine/free carnitine]. Following the collection of baseline data, all participants were supplemented with IV levocarnitine at dose of 20 mg/kg dry body weight as a 2- to 3-min bolus injection into the venous return line after each dialysis session for 6 months. During the treatment period, total and free carnitine levels were measured monthly.

Cardiac function assessment by ECHO

Study patients had an ECHO performed at baseline and after 6 months of carnitine supplementation. Children on HD not receiving levocarnitine with two ECHO studies performed at least 6 months apart were included as controls. All participants had ECHOs performed at least 1 but <3 h after completing the HD session in order to avoid dialysis-induced stunning effect while ensuring that measurements were done at dry weight. Traditional measures of LV systolic function, including EF and FS, and indicators of diastolic function (mitral inflow E/A ratio and tissue Doppler derived E/E′ ratio) were evaluated. LV mass indexed to body surface area and tricuspid regurgitation velocity as an indicator of pulmonary artery pressure were obtained. All measurements were performed by a pediatric cardiologist according to American Society of Echocardiography standards [23].

Strain analysis was performed using Syngo Velocity Vector Imaging software (Siemens, Germany) on DICOM standard digital echocardiograms and analyzed by a physician blinded to patient diagnosis. Endocardial tracings were performed on the parasternal short axis, and apical four chamber images were obtained twice during end systole for each patient; the average was then recorded. A single observer was used, as multiple studies have shown minimal intra- and inter-operator variability [24, 25]. Short axis measurements, including circumferential and longitudinal strain (%) and circumferential and longitudinal strain rate (1/s) were recorded. Strain was calculated by measuring the end systolic distance between two speckles of tracked endocardium minus the original distance divided by the original distance. Because the myocardium contracts in the longitudinal and circumferential directions during systole, these values are negative percentages.

Control group

In order to differentiate cardiac changes due to levocarnitine supplementation from cardiac changes that may naturally occur with HD over time, we selected a retrospective control group. Children (2–21 years) on chronic HD for≥3 months who did not receive levocarnitine and had at least two ECHOs, performed at least 6 months apart, were included. Standard measures of LV size and function as well as circumferential and longitudinal strain and strain rate using speckle-tracking echocardiography were performed on the initial and follow-up ECHOs of each control patient. Hemoglobin, BP, and %IDWG over the time period between initial and follow-up ECHOs were obtained from medical records. The BP *Z* scores for age and sex were calculated.

Statistical analysis

Comparison of baseline carnitine (5 values per patient) versus post-treatment carnitine level (measured upon completion of 6 months of carnitine supplementation) were assessed using Student's paired *t* test with STATA 11.0 (StataCorp LP, College Station, TX). Pre- and post-treatment ECHO, mean BP *Z* scores, % IDWG, and hemoglobin levels of the study patients were compared by Student's paired *t* test. The baseline and final ECHO of the controls were also compared by Student's paired *t* test. Demographics and clinical parameters of the study patients were compared to those of the controls using Student's unpaired *t* test. The results are given, where appropriate, as the mean ± standard error of the mean (SEM) and the 95% confidence interval.

Results

Demographics and clinical characteristics

The demographics and clinical characteristics of the study and control groups are given in Table 1. Nine children on chronic HD (mean age 12.7±1.9 years) completed the prospective study. Eight children (mean age 14.9±1.3 years) were included as controls. The age and dialysis vintage of the study and control groups did not differ.

Carnitine levels

Pre- and post-therapy carnitine levels are shown in Table 2. Total (49.0±1.67 vs. 298.0±31.8 μmol/L), free (29.0±1.20 vs. 180.4±19.2 μmol/L), and acyl (20.0±0.84 vs. 118.2±14.1 μmol/L) carnitine increased ($p<0.0002$), whereas the A:F ratio decreased (0.73±0.04 vs. 0.65±0.05) after 6 months of levo carnitine supplementation ($p=0.02$).

Table 1 Demographics and clinical characteristics of study and control groups

Demographics/clinical characteristics	Study group (*n*=9)	Control group (*n*=8)	*p*
Age (years)±SEM	12.7±0.6	14.9±1.3	0.14
Range	9–16	9–19	
Ethnicity			
African American	4	5	
Hispanic	3	3	
Caucasian	2	0	
Sex			
Male	6	4	
Female	3	4	
Duration on dialysis, months (mean ± SEM)	9.3±2.2	11.2±3.8	0.67
Cause of ESRD (*n*)			
Hypoplastic/dysplastic	4	2	
Nephrotic syndrome	1	1	
Neurogenic bladder	1	0	
Chronic GN	2	4	
Other	1	1	
%IDWG ± SEM (95% CI)	4.46±0.53 (3.7–5.2)	3.9±1.3 (2.6–5.3)	0.43
SBP *Z* ± SEM (95% CI)	1.2±0.13 (0.93–1.5)	1.5±0.39 (0.64–2.5)	0.29
DBP *Z* ± SEM (95% CI)	0.04±0.11 (−0.19–0.29)	0.50±0.33 (−0.28–1.28)	0.23
Hb ± SEM (95% CI)	11.6±0.06 (11.5–11.7)	11.9±1.1 (11.5–12.2)	0.43

SEM, Standard error of the mean; ESRD, end stage renal disease; GN, glomerulonephritis; % IDWG, percent interdialytic weight gain; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; CI, confidence interval

Table 2 Pre- and post-treatment plasma carnitine measurements (study group)

Carnitine measurements	Pre-treatment plasma carnitine level	Post-treatment plasma carnitine level	*p* value
Total carnitine (μmol/L)	49.0±1.67 (45.6–52.4)	298.0±31.8 (222.8–373.3)	<0.0001
Free carnitine (μmol/L)	29.0±1.20 (26.6–31.4)	180.4±19.2 (135.1–225.8)	<0.0001
Acyl carnitine (μmol/L)	20.0±0.84 (18.3–21.7)	118.2±14.1 (84.9–151.6)	<0.0002
Acyl:free carnitine ratio	0.73±0.04 (0.65–0.80)	0.65±0.05 (0.53–0.77)	0.02

Data are presented as the mean ± standard error of the mean (SEM), with the 95% confidence interval (CI) given in parenthesis

Assessment of cardiac function

Study group There were no significant changes in the standard measures of LV function after carnitine supplementation; however, there was a dramatically significant improvement in longitudinal strain rate (−1.48±0.11 vs. −1.91±0.12; *p* value 0.017 by both paired Student's *t* test and non-parametric Wilcoxon signed-rank test) (Table 3). The change reflected an average of 33 % improvement compared with pretreatment longitudinal strain rate (Table 4). There were no significant changes in longitudinal or circumferential strain or in circumferential strain rate.

Control group There were no significant changes in standard ECHO measures of LV function in the controls over time. Baseline and follow-up strain parameters, including longitudinal strain rate (−1.35±0.13 vs. −1.29±0.09; $p=0.38$) did not improve in controls.

Comparison of blood pressure, interdialytic weight gain, and anemia

To ensure that cardiac changes were not affected by anemia, BP, and fluid overload, we compared these parameters between the study and control groups (Table 1) and also within the study group (pre- versus post-treatment with levocarnitine; data not shown).

Study versus control group Mean %IDWG, BP *Z* scores, and hemoglobin over the entire period between the baseline and follow-up ECHOs for the study and control groups are shown in Table 1. Neither %IDWG nor hemoglobin differed significantly between the study and control groups ($p=0.43$ each). Mean systolic and diastolic BP *Z* scores of the study group were not significantly different from those of the controls (systolic BP: 1.2±0.13 vs. 1.5±0.39, respectively, $p=0.29$; diastolic BP: 0.04±0.11 vs. 0.50±0.33, respectively, $p=0.23$).

Pre- versus post-treatment parameters within the study group The mean BP *Z* score of study patients did not change significantly between pre- and post-treatment with levocarnitine (systolic BP: 1.23±0.20 vs. 1.19±0.19, respectively, $p=0.83$; diastolic BP: 0.0±0.19 vs. 0.09±0.14, $p=0.57$). Mean %IDWG of the study patients was also similar during the pre- versus post-treatment (4.45±1.7 vs. 4.48±1.4%, respectively, $p=0.86$). The mean hemoglobin level of the study group remained within normal limits and did not differ pre- versus post-treatment (11.7±0.9 vs. 11.5±1.1, respectively, $p=0.27$) (data not shown in tables).

Discussion

Plasma and muscle carnitine deficiency are well-known consequences of chronic HD, although there are as yet no

Table 3 Echocardiographic measures of pre- and post-treatment left ventricular function (study group)

ECHO parameter	Pre-treatment ± SEM	Post-treatment ± SEM	*p* value
LV end diastolic dimension *Z* score	−0.65+0.29	−1.03+ 0.32	0.46
LV Mass/Ht $^{2.7}$	35.6±4.5	33.3±4.2	0.59
Ejection fraction (%)	65.6±2.7	65.6±1.6	0.99
Shortening fraction (%)	39.1±1.8	37.9±1.8	0.64
E/A	1.59±0.13	1.45±0.15	0.40
E/E′	8.03±0.65	7.79±0.81	0.79
Longitudinal strain	−17.8±1.2	−19.7±1.6	0.24
Circumferential strain	−26.5±1.6	−25.4±1.7	0.48
Longitudinal strain rate	−1.48±0.11	−1.91±0.12	0.017
Circumferential strain rate	−2.50±0.21	−2.46±0.13	0.88

ECHO, Echocardiogram; LV, left ventricular; Ht, height; SEM, Standard error of the mean

Table 4 Pre and post-carnitine treatment longitudinal strain rate in each patient (study group)

Patient	Pre-carnitine treatment	Post-carnitine treatment	Percentage change
1	−1.49	−1.84	24
2	−1.38	−1.52	10
3	−1.21	−2.03	68
4	−1.69	−2.43	44
5	−1.07	−1.34	25
6	−1.71	−1.89	11
7	−2.04	−1.86	−9
8	−1.13	−2.35	109
9	−1.63	−1.90	17
Mean	−1.48	−1.91	33

established guidelines to assess and treat carnitine deficiency in children on chronic HD. A number of previous studies have assessed carnitine status according to the plasma free carnitine level; compared with previously published free carnitine levels of healthy children, all of the children in our study group suffered from a carnitine deficiency [9, 20]. Other studies have suggested that a plasma A:F carnitine ratio of >0.4 is indicative of carnitine deficiency, and all of the patients in the our study group were carnitine deficient at baseline according to this definition as well. Plasma free carnitine has a low molecular weight and is non-protein bound, so its level decreases by approximately 70 % with each HD treatment [5]. The body then draws carnitine from the liver and muscle stores in an attempt to re-equilibrate with the plasma carnitine, resulting in a progressive depletion of muscle stores and eventually to a depletion of plasma carnitine over time [7]. Compared with published free carnitine levels of healthy children, free carnitine deficiency was present in all of the children in our study group. Muscle carnitine stores are difficult to measure directly due to the invasive nature of muscle biopsy, and there are no sensitive non-invasive methods for evaluating muscle carnitine deficiency. In this study, total and free carnitine levels significantly increased and the A:F ratio significantly decreased after 6 months of IV levocarnitine. Although improved, the post-treatment A:F ratio remained above the proposed cut-off ratio of 0.4. The change in carnitine levels and A:F ratio observed in our study are in agreement with those of a previous multicenter double-blind placebo controlled study of adult HD patients given the same dose and duration of IV levocarnitine therapy [26]. One possible explanation is that carnitine therapy initially distributed into depleted muscles, increasing cardiac muscle carnitine stores, resulting in improvement in the longitudinal strain rate. A higher dose or longer duration of carnitine supplementation may be required to optimally reduce the plasma A:F carnitine ratio to <0.4. Additionally, newer evidence suggests that the proportion of harmful non-acetyl acylcarnitines within the total carnitine pool is a more important indicator of response to carnitine supplementation than total acylcarnitine, which includes both acetyl and non-acetyl fractions [27]. Chronic HD results in a decrease in acetyl acylcarnitine and a concurrent increase in non-acetyl aclycarnitine over time, and supplementation with carnitine reverses this by increasing plasma and muscle acetyl acylcarnitine while decreasing the harmful non-acetyl groups [7]. Non-acetyl acylcarnitines impair energy production in the myocardial mitochondria that can be restored by carnitine supplementation [28, 29]. The harmful non-acetyl acylcarnitines may have improved in response to carnitine supplementation in our study to a greater degree than what may be reflected in the total A:F ratio because the expected increase in acetyl acylcarnitine would partially mask a decrease in non-acetyl aclycarnitine.

Chronic HD patients are at high risk for cardiovascular-related morbidity and mortality, with an increased risk of more than 700-fold seen in pediatric patients with end stage renal disease [1]. Because carnitine plays a key role in supplying energy to the myocardium, repletion of muscle carnitine stores is critical in these children who are high risk for both carnitine deficiency and cardiac complications. Impairment of energy production due to carnitine deficiency further increases the risk of cardiac morbidity in this high-risk group [14]. Carnitine therapy has been shown to prevent cardiomyocyte apoptosis [30] and increase adenosine triphosphate (ATP) production in ischemic dog hearts [31]. Numerous studies have documented improved LV function in adults on chronic HD after carnitine supplementation [5]. Only two previous controlled studies have investigated the effects of carnitine on cardiac function in children on HD, one using oral and the other using IV levocarnitine. Our study is the first to assess the cardiac effects of IV levocarnitine supplementation using speckle-tracking ECHO in this population.

Topaloglu et al. investigated the effects of 3 months of IV levocarnitine supplementation on cardiac function in 13 carnitine-deficient children on HD compared with healthy controls using standard ECHO. Their results showed that some measures of cardiac function, including FS, in the carnitine-deficient children on HD were significantly worse at baseline compared to controls, and they did not improve after 3 months of IV levocarnitine supplementation [20]. These authors speculated that the duration of treatment may not have been sufficient to replete cardiac muscle carnitine stores. El-Metwally et al. studied the effect of 2 months of oral levocarnitine supplementation on cardiac dysfunction in 24 children on HD compared to healthy controls. They found that children on chronic HD had increased cardiac diameters and thickness as well as decreased systolic and diastolic function (SF, EF, and E/A ratio) compared with the controls at baseline. Two months

of oral levocarnitine supplementation reduced the cardiac diameters and increased diastolic function in these children, but did not improve LV systolic function, mass, and volume indices, or reduce cardiac wall thickness [32]. The authors similarly concluded that a longer duration of carnitine supplementation may be needed to replete carnitine muscle tissue stores, reduce the accumulation of acyl groups, and increase the activity of carnitine palmitoyltransferase in order to achieve improvement in cardiac function.

Strain and strain rate are relatively new measures of cardiac function, and the clinical implications of a decreased strain and strain rate are emerging in different patient populations. Previous studies have demonstrated that, in certain patient populations, impaired strain and strain rate carry a higher rate of mortality [33, 34]. Impaired strain and strain rate have been shown to be indicative of early myocardial dysfunction in septic shock in children [35] and of prognostic value for myocardial recovery after an episode of myocardial infarction [36]. Of all the cardiac strain parameters (longitudinal and circumferential strain and strain rate), longitudinal strain and strain rate may be most affected in early myocardial disease, whereas circumferential strain may remain normal or show exaggerated compensation for preserving LV systolic performance [22]. Longitudinal strain rate may be more useful than strain in chronic HD patients since it is not affected by volume and blood pressure changes in the interdialytic period. These factors could explain the improvement only in longitudinal strain rate in response to carnitine therapy in this study.

We were not able to detect LV abnormalities at either baseline nor changes in the LV function of children on HD after 6 months of IV levocarnitine supplementation using standard ECHO techniques. The mean dialysis vintage of the children in our study was shorter (9.3±2.2 months) than that of the children studied by El-Metwally [32] (19.1± 2.5 months) and Topaloglu et al. [20] (all patients on HD for at least 1 year), all of whom had evidence of cardiac abnormalities by standard ECHO. However, usage of more sensitive speckle-tracking ECHO in our study population revealed a significant improvement in the longitudinal strain rate in response to levocarnitine supplementation, which was not observed in our control group or in children on chronic HD who did not receive levocarnitine supplementation. The findings suggest that the early effects of carnitine deficiency on cardiac function in children on chronic HD may be subtle and therefore not evident on the standard ECHO images and that these changes can be ameliorated by supplementation with IV levocarnitine.

Limitations

This was a single-center study with a small sample size and a retrospective control group. Although the control group was not prospective, demographics and clinical characteristics of the study and control groups were similar. Another limitation was that assessment of acylcarnitine included both acetyl and non-acetyl carnitine fractions together, which prevented us from assessing the degree to which the non-acetyl acylcarnitine component improved with supplementation.

Conclusions

In this study, we detected improvements in LV function by longitudinal strain rate analysis in children on chronic HD receiving levocarnitine which were not detected by standard ECHO. Speckle-tracking ECHO analysis was able to detect early signs of LV dysfunction, and supplementation with IV levocarnitine improved the longitudinal strain rate in this population, which may confer a reduction in cardiovascular risk. Six months of IV levocarnitine also improved carnitine levels and decreased the A:F carnitine ratio significantly. A longer duration of therapy may be needed to optimally reduce acylcarnitine accumulation. The findings of this pilot study suggest that larger prospective randomized studies are needed to further investigate the role of speckle-tracking to identify early signs of myocardial dysfunction and assess the response to treatment with levocarnitine in children on chronic HD.

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