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## Effect of Combined Treatment with Alpha Lipoic Acid and Acetyl-L-Carnitine on Vascular Function and Blood Pressure in Coronary Artery Disease Patients

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### Abstract

Mitochondria produce reactive oxygen species that may contribute to vascular dysfunction. Alpha-lipoic acid and acetyl-L-carnitine reduce oxidative stress and improve mitochondrial function. In a double blind, crossover study, we examined the effects of combined alpha-lipoic acid /acetyl-L-carnitine treatment and placebo (eight weeks per treatment) on vasodilator function and blood pressure in 36 subjects with coronary artery disease. Active treatment increased brachial artery diameter by 2.3% (P=0.008), consistent with reduced arterial tone. Active treatment tended to decrease systolic blood pressure for the whole group (P=0.07) and had a significantly effect in the subgroup with blood pressure above the median (151±20 to 142±18 mmHg, P=0.03) and in the subgroup with the metabolic syndrome (139±21 to 130±18 mmHg, P=0.03). Thus, mitochondrial dysfunction may contribute to the regulation of blood pressure and vascular tone. Further studies are needed to confirm these findings and determine the clinical utility of alpha-lipoic acid/acetyl-L-carnitine as antihypertensive therapy.

### Keywords

mitochondria; endothelium; blood pressure; anti-oxidants; and oxidative stress

### Hypothesis

In addition to serving as the site of oxidative phosphorylation, it is now clear that mitochondria regulate many cellular functions, in part, by producing reactive oxygen species that signal the adaptive response to environmental stress and injury.<sup>1</sup> Excess production of mitochondria-derived oxidants, however, may have maladaptive effects.<sup>2,3</sup> There is growing evidence that disturbances of mitochondrial function, including increased oxidant production and altered mitochondria-dependent signaling contribute to the pathogenesis of vascular disease in atherosclerosis and cardiovascular risk factors.<sup>1,4,5</sup>

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On the basis of these observations, we hypothesized that an intervention designed to improve mitochondrial function would have beneficial vascular effects in patients with cardiovascular disease. Recent experimental studies have shown that administration of alpha-lipoic acid and/or acetyl-L-carnitine can reduce oxidant production and improve mitochondrial function in models of aging<sup>6,7</sup> Furthermore, these compounds reduce blood pressure and improve endothelial function in animal models of hypertension<sup>8-12</sup> and diabetes<sup>13-16</sup> The present study was designed to examine the effects of combined alpha-lipoic acid/acetyl-L-carnitine treatment on vascular function and blood pressure in patients with coronary artery disease.

## Methods

### Study subjects

We enrolled consecutive patients receiving care at Boston Medical Center for stable coronary artery disease who were age 55 years or older. The presence of coronary disease was confirmed by coronary angiography, history of myocardial infarction,<sup>17</sup> or an imaging stress test demonstrating myocardial ischemia. Exclusion criteria included supplementation with alpha lipoic acid, acetyl-L-carnitine, vitamin E, or vitamin C. Since alpha-lipoic acid has the potential to increase insulin sensitivity,<sup>18</sup> we excluded patients with a history of symptomatic hypoglycemia. Finally, we excluded patients if their physicians made a change in their anti-hypertensive regimen during the month prior to the study or during the study. All subjects provided informed consent and the Boston Medical Center Institutional Review Board approved the protocol.

### Study Protocol

Eligible patients were enrolled into a double blind, placebo-controlled crossover study that evaluated vascular function and blood pressure before and at the end of two eight-week treatment periods. There was a four-week “washout” period between treatments and the order of treatments was determined by a computer-generated randomization scheme. Active treatment consisted of tablets containing 200 mg of alpha-lipoic acid and 500 mg of acetyl-L-carnitine (Juvenon Cellular Health Supplement™, Juvenon, Inc.) and placebo consisted of a similar appearing tablet containing vehicle alone. Subjects were instructed to take one tablet twice daily. Study medications were packaged and dispensed in a blinded manner by the Research Drug Service of Boston Medical Center. We contacted subjects by telephone one and four weeks after initiation of treatment to monitor any unanticipated effects and we confirmed compliance by pill count (no more than 5% of pills were returned).

### Assessment of Vascular Function and Blood Pressure

Prior to each of the four visits, subjects were asked to withhold vasoactive medications (nitrates, calcium channel blockers, angiotensin converting enzyme inhibitors, other vasodilators, and beta-adrenergic blockers) for 24 hours and to fast and refrain from smoking (if applicable) overnight. A blood sample was collected by venipuncture. Patients lay supine in bed in a darkened room for 10 minutes. We then used an automatic physiological monitor (Dynamap) to measure pulse and blood pressure in the left arm and recorded the average of three measurements made two minutes apart.

We then used vascular ultrasound to assess endothelium-dependent flow-mediated dilation and reactive hyperemia of the brachial artery in the right arm using established methodology.<sup>20-22</sup> Briefly, two-dimensional images and Doppler flow velocity signals were recorded from the brachial artery at baseline using a Toshiba Powervision 6000 ultrasound system (Toshiba Medical, Inc.). Reactive hyperemia was induced by five-minute occlusion of arterial flow with a narrow gauge blood pressure cuff positioned on the upper arm. Doppler signals were recorded immediately after cuff release and two-dimensional images were recorded from 55 to 65

seconds following cuff release. After a ten-minute rest period, we recorded two-dimensional images of the brachial artery before and three minutes after administering sublingual nitroglycerin (0.4 mg). Five minutes after nitroglycerin administration, we repeated the blood pressure measurement before allowing subjects to get out of bed. We did not administer nitroglycerin to subjects with a history of migraine headaches or with adverse effects to nitroglycerin in the past.

We measured brachial artery diameter using commercially available software (Brachial Analyzer, Medical Imaging Applications, Inc.) and measured the flow velocity integral with public domain image analysis software (Image J). Flow-mediated dilation was expressed as percentage change from baseline and as actual change in millimeters.

## Blood Markers

Serum lipids and glucose levels were measured in the Boston Medical Center Clinical laboratory and low-density lipoprotein cholesterol levels were calculated using the Friedewald formula.<sup>23</sup> Serum total carnitine levels were measured in a blinded manner using an established fluoroscopic method that has a published coefficient of variation less than 4.3%.<sup>24</sup>

## Statistical Analysis

We compared the clinical characteristics of the subjects randomized to placebo first and active treatment first using the unpaired t-test and the chi square test for continuous and categorical variables, respectively. We used repeated measures analysis of variance (ANOVA) to examine the effect of treatment on brachial artery diameter, brachial artery flow-mediated dilation, nitroglycerin-mediated dilation, extent of reactive hyperemia, systolic and diastolic blood pressure, lipoprotein levels, glucose levels, and total serum carnitine levels. This analysis considered the effects of visit (baseline vs. after treatment) and treatment (placebo vs. active) with treatment order (active first or placebo first) included as a between-subjects covariate. When the overall ANOVA was significant, we performed post hoc pair-wise comparisons to compare mean values at baseline and during treatment. The study was powered to detect a difference in flow-mediated dilation of 1.8 percentage points (e.g. 6.0 vs. 7.8%) with 90% power (alpha 0.05) with a sample size of 36 subjects.<sup>22</sup>

Since lipoic acid and acetyl-L-carnitine have been shown to have favorable effects on mitochondrial decay in the setting of aging,<sup>6,7,25</sup> diabetes mellitus/metabolic syndrome,<sup>26,27</sup> and hypertension<sup>8,9,13,14</sup> we completed secondary analyses in the subgroups of subjects above the median for age or systolic blood pressure and in subjects with the metabolic syndrome as defined by the National Cholesterol Education Panel or Type 2 diabetes mellitus.<sup>28</sup> We examined the relation between baseline carnitine level and clinical characteristics, and the relation between change in carnitine level and blood pressure response by calculating the Pearson correlation coefficients. All analyses were completed using SPSS 12.0. Data are expressed as mean  $\pm$  standard deviation, unless otherwise indicated. The criterion for statistical significance was  $P < 0.05$ .

## Results

### Study Subjects

At total of 41 eligible subjects were entered into the study. Two subjects withdrew because of adverse reactions (one with a pruritic rash and one with nausea). Both were taking active alpha-lipoic acid/acetyl-L-carnitine at the time of these reactions, which resolved after discontinuation of study medication. Three subjects were withdrawn because they had significant changes in medical status while taking placebo (one developed coronary restenosis, one developed unstable angina, and one suffered gastro-intestinal bleeding). Thus, 36 subjects

were included in the study; their clinical characteristics according to treatment order are presented in Table 1. As shown, the majority of subjects were men with a high prevalence of risk factors for coronary artery disease. Subjects in the placebo-first and active treatment-first groups had similar clinical characteristics.

### Effect of Treatment on Blood Markers

Table 2 displays the effects of placebo and lipoic acid/acetyl-L-carnitine treatment on total carnitine levels, lipid profiles, fasting glucose, serum insulin, C-reactive protein, and urinary F<sub>2</sub> isoprostanes. As shown, there was a strong trend for an effect of treatment on total carnitine levels, but no other significant effects on these blood markers.

### Effect of Treatment on Vasodilator Function

For analysis of vascular function, we excluded one additional subject because of technically inadequate ultrasound images. As shown in Table 3, lipoic acid/acetyl-L-carnitine treatment was associated with a significant 2% increase in baseline brachial artery diameter. There were no effects of treatment on baseline flow or vasodilator function. There also was no effect of lipoic acid/acetyl-L-carnitine on flow-mediated dilation or hyperemic flow in the pre-specified subgroups of older subjects (age >62 years), subjects with higher blood pressure (systolic blood pressure  $\geq$ 135 mmHg), or among the 24 subjects with the metabolic syndrome (data not shown).

### Effect of Treatment on Blood Pressure

As shown in Table 4, there was no statistically significant effect on systolic blood pressure on active treatment. Sublingual nitroglycerin produced a greater reduction in diastolic blood pressure during treatment with active alpha-lipoic acid/acetyl-L-carnitine compared to placebo, with a trend for a similar effect on systolic blood pressure after nitroglycerin.

As shown in Table 4, the subgroups of subjects with systolic blood pressure above the median and subjects with the metabolic syndrome had significant decreases in systolic blood pressure after active treatment. There was no effect in the subgroup of older subjects (data not shown).

### Correlates of Carnitine Levels

Serum total carnitine levels correlated inversely with age ( $r = -0.42$ ,  $P = 0.006$ ), but did not correlate with other risk factors, serum lipids, glucose, blood pressure, or the metabolic syndrome (data not shown). There was no relation between change in carnitine level and change in blood pressure in the group as a whole or in the subgroups with higher blood pressure or the metabolic syndrome (data not shown).

## Discussion

This randomized, placebo-controlled, double blind crossover study demonstrated that combined alpha-lipoic acid/acetyl-L-carnitine treatment was associated with an increase in baseline brachial artery diameter. Furthermore, we observed a non significant trend for a blood pressure lowering effect of alpha lipoic acid/acetyl-L-carnitine in all subjects and a significant reduction in systolic blood pressure in subjects with systolic blood pressures above the median and in subjects with the metabolic syndrome. These findings suggest the possibility that these mitochondria-directed antioxidants reduce basal arterial tone, particularly in two clinically relevant subgroups. In contrast, we observed no effect of treatment on the dilator responses to increased flow, nitroglycerin, or ischemia (reactive hyperemia).

A prior study demonstrated a decrease in systolic blood pressure and a direct vasodilator effect in nailfold capillaries after treatment with oral L-carnitine (3g/d for 20days) in patients with digital vasospastic disease.<sup>29</sup> An open-label study of patients with diabetic nephropathy,

reported that long-term alpha lipoic acid treatment (600 mg/d for 18 months) prevented the increases in blood pressure and urine albumin concentration observed in control patients.<sup>30</sup> Experimental studies have consistently demonstrated an anti-hypertensive effect of alpha-lipoic acid or L-carnitine in various rat models of hypertension, including spontaneously hypertensive rats,<sup>8,9</sup> uninephrectomized deoxycorticosterone acetate-salt (DOCA-salt) hypertensive rats<sup>10</sup> and salt-loaded Dahl and Wistar-Kyoto rats.<sup>11,12</sup>

Our study differs from several previous human studies that examined the effects of lipoic acid or carnitine on endothelial function. For example, Heitzer and colleagues observed an acute improvement in endothelium-dependent dilation of forearm microvessels following an intra-arterial infusion of lipoic acid (final concentration 0.2 mmoles/L) in patients with diabetes mellitus.<sup>26</sup> Sola and colleagues recently reported improved brachial artery flow-mediated dilation following treatment with lipoic acid 300 mg/d for four weeks in young patients with the metabolic syndrome (mean age 46 years).<sup>27</sup> Intravenous administration of L-carnitine (3 gram bolus) enhanced reactive hyperemia in patients with peripheral arterial disease.<sup>31</sup> The apparent discrepancies between the results of those prior studies and the present study likely relate to the marked differences in dose, route of administration, vascular bed studied and/or patient population.

The mechanisms accounting for the increased brachial artery diameter and suggestive anti-hypertensive effects of alpha-lipoic acid and acetyl-L-carnitine in our study remain undefined. We observed no effect of treatment on serum lipids, glucose, and insulin, which might have influenced endothelial function or arterial diameter. Experimental studies indicate that alpha-lipoic acid and acetyl-L-carnitine play important and potentially synergistic roles in normal mitochondrial function, and that reduced levels of these compounds are associated with increased mitochondrial oxidant production.<sup>6,25,32</sup> In addition, lipoic acid supplementation has favorable effects on cellular redox state and has been shown to decrease lipid peroxidation and cellular production of reactive oxygen species.<sup>6,7,32,33</sup> The effects of alpha-lipoic acid and acetyl-L-carnitine on oxidative stress which contributes to the pathogenesis and cardiovascular complications of hypertension suggests that these compounds may be useful adjuncts in treatment.<sup>34</sup> In the present study, we investigated the possibility that these compounds reduced oxidative stress and inflammation, but observed no effect of treatment on urinary F<sub>2</sub> isoprostanes or serum C-reactive protein. It is important to point out, however, that these systemic markers may not accurately reflect events in the vascular wall.

Despite the effects on blood pressure and basal diameter, it is notable that we only observed a trend for increased total serum carnitine following treatment. It is known that acetyl-L-carnitine and alpha-lipoic acid are rapidly metabolized in human subjects with plasma half lives of 4.2 hours<sup>35</sup> and 30 minutes,<sup>36</sup> respectively. Thus, it is likely that acetyl-L-carnitine and lipoic acid metabolites and/or tissue levels may be more relevant for the observed effects. Similarly, the lack of effect of treatment on urine F<sub>2</sub> isoprostanes does not rule out an effect of active treatment on oxidative stress at the tissue level.

We observed a particular benefit of alpha-lipoic acid/acetyl-L-carnitine in patients with the metabolic syndrome. This syndrome of insulin resistance is associated with hypertension; improvement of insulin sensitivity could have an anti-hypertensive effect. Consistent with our findings, several experimental studies suggest a blood pressure-lowering effect in models of diabetes mellitus or insulin resistance.<sup>13-16</sup> Those results and our findings are consistent with the growing evidence linking insulin resistance to mitochondrial dysfunction.<sup>37,38</sup>

Our study has a number of limitations. First, we observed a significant effect on baseline arterial diameter in all subjects, but the observed effects on blood pressure were significant only in subgroup analyses. These findings are difficult to reconcile, but could reflect a preferential

effect on basal conduit artery tone. Further studies will be required to confirm these findings and elucidate the responsible mechanisms. Secondly, arterial tissue was not available for mechanistic analysis in this human study, so it remains speculative whether our findings actually reflect improved mitochondrial function and reduced oxidative stress. Third, we studied the combination of alpha-lipoic acid because these compounds may act synergistically,<sup>32</sup> but it remains unknown whether either compound given alone would have had a similar effect. Finally, our observations about blood pressure were based on subgroup analyses, and as such, could reflect chance findings. Balancing these limitations is the double blind, prospective, crossover design of our study. Our results are consistent with prior experimental work, and the reduction in initial blood pressure, blood pressure after nitroglycerin, and the observed increase in brachial artery diameter all support an effect of active treatment on arterial tone and blood pressure.

The findings of the present study could have clinical implications. Hypertension remains the most prevalent form of cardiovascular disease, and there is a growing need for new and well-tolerated therapeutic approaches.<sup>39</sup> The observed reduction in systolic blood pressure during alpha-lipoic acid/acetyl-L-carnitine treatment (9 mmHg in subjects with higher blood pressure) could potentially have a major effect on cardiovascular risk.<sup>39</sup> Clearly, additional prospective studies are needed to confirm these findings and define the mechanism of benefit. However, our results appear to be consistent with the possibility that mitochondrial dysfunction contributes to the pathogenesis of hypertension, particularly in the setting of insulin resistance, and that therapy designed to restore mitochondrial function might prove useful for patient management.

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**Table 1**  
Baseline Clinical Characteristics by Treatment Order

Characteristic	Placebo first (n=21)	Active first (n=15)	P value
Age (years)	64 ± 7	62 ± 5	0.32
Male	16 (76%)	11 (73%)	0.85
African American	1 (5%)	5 (33%)	0.06
History of Type 2 diabetes mellitus	3 (14%)	2 (13%)	0.84
Metabolic syndrome	12 (57%)	12 (80%)	0.15
History of hypertension	16 (76%)	13 (87%)	0.67
History of hypercholesterolemia	17 (81%)	15 (100%)	0.13
Family history of premature coronary disease	12 (57%)	4 (27%)	0.08
History of cigarette smoking	15 (71%)	10 (67%)	0.99
Aspirin treatment	21 (100%)	15 (100%)	0.99
ACEI/ARB treatment	11 (52%)	8 (53%)	0.96
Lipid lowering therapy	19 (91%)	15 (100%)	0.50
Beta blocker therapy	16 (76%)	11 (73%)	0.85
Diuretic therapy	2 (10%)	2 (13%)	0.72
Systolic blood pressure, mmHg	137 ± 15	131 ± 22	0.39
Diastolic blood pressure, mmHg	76 ± 7	71 ± 9	0.11
Total cholesterol, mg/dl	172 ± 34	174 ± 29	0.89
HDL cholesterol, mg/dl	50 ± 19	42 ± 5	0.07
Triglycerides, mg/dl	156 ± 95	197 ± 144	0.31
LDL cholesterol, mg/dl	90 ± 21	92 ± 30	0.87
Glucose, mg/dl	103 ± 14	118 ± 33	0.11
Body mass index, kg/m <sup>2</sup>	30.0 ± 5.3	30.1 ± 5.5	0.93

Mean ± SD or number (%). ACEI/ARB = angiotensin converting enzyme inhibitor or angiotensin receptor blocker. HDL = high-density lipoprotein. LDL = low-density lipoprotein.

Effect of Treatment on Blood Markers

Table 2

	n	Before placebo	After placebo	Before active	After active	P*
Total carnitine, $\mu$ moles/L	32	101 $\pm$ 23	99 $\pm$ 20	104 $\pm$ 24	112 $\pm$ 23	0.06
Total cholesterol, mg/dL	34	171 $\pm$ 33	171 $\pm$ 36	178 $\pm$ 40	177 $\pm$ 38	0.94
LDL cholesterol, mg/dL	34	89 $\pm$ 24	93 $\pm$ 24	95 $\pm$ 32	97 $\pm$ 34	0.60
HDL cholesterol, mg/dL	34	49 $\pm$ 16	47 $\pm$ 15	48 $\pm$ 15	46 $\pm$ 13	0.78
Triglycerides, mg/dL	34	169 $\pm$ 120	151 $\pm$ 81	179 $\pm$ 114	169 $\pm$ 120	0.50
Fasting glucose, mg/dL	34	104 $\pm$ 14	105 $\pm$ 24	106 $\pm$ 25	104 $\pm$ 20	0.41
Insulin, IU/ml	32	9.6 $\pm$ 7.6	9.1 $\pm$ 6.2	12.0 $\pm$ 7.9	13.4 $\pm$ 11.4	0.40
C-reactive protein, mg/L	27	3.2 $\pm$ 3.4	3.3 $\pm$ 4.8	2.1 $\pm$ 2.6	2.8 $\pm$ 3.3	0.23
Urine F2 isoprostanes, ng/mg creatinine	16	1.2 $\pm$ 0.8	1.1 $\pm$ 0.5	1.0 $\pm$ 0.4	1.1 $\pm$ 0.6	0.96

\* Overall P for repeated measures ANOVA.

Table 3

## Effect of Treatment on Vascular Function

	n	Before placebo	After placebo	Before active	After active	P*
Baseline diameter, mm	35	4.82 ± 0.64	4.79 ± 0.68	4.69 ± 0.66	4.77 ± 0.65 <sup>†</sup>	0.008
FMD, mm	35	0.29 ± 0.16	0.34 ± 0.17	0.31 ± 0.14	0.33 ± 0.16	0.19
FMD, %	35	6.1 ± 4.4	7.5 ± 3.9	7.0 ± 3.5	7.1 ± 3.7	0.11
NMD, %	20	10.0 ± 4.1	9.6 ± 3.6	11.0 ± 4.2	10.0 ± 4.1	0.78
Baseline flow ml/min	33	230 ± 110	250 ± 140	230 ± 100	230 ± 100	0.20
Hyperemic flow ml/min	31	1240 ± 590	1330 ± 700	1240 ± 440	1240 ± 470	0.36

FMD = flow-mediated dilation expressed as % increase over baseline (%) or actual change (mm). NTG = nitroglycerin. NMD = nitroglycerin-mediated dilation. RH = reactive hyperemia.

\* Overall P for repeated measures ANOVA.

<sup>†</sup> P=0.01 compared to “Before active” by post hoc analysis. There was no difference between “Before placebo” and “Before active”, P=0.10 by post hoc analysis.

Effect of Treatment on Blood Pressure

Table 4

	n	Before placebo	After placebo	Before active	After active	P*
<i>All subjects</i>						
SBP, mmHg	36	133 ± 16	137 ± 22	135 ± 23	132 ± 18	0.07
DBP, mmHg	36	72 ± 8	73 ± 8	73 ± 10	72 ± 8	0.21
SBP after NTG, mmHg	24	117 ± 13	118 ± 15	120 ± 14	113 ± 13	0.09
DBP after NTG, mmHg	24	65 ± 7	67 ± 8	68 ± 7	64 ± 8 <sup>†</sup>	0.04
<i>SBP ≥ 135 mmHg</i>						
SBP, mmHg	18	145 ± 14	150 ± 23	151 ± 20	142 ± 18 <sup>‡</sup>	0.03
DBP, mmHg	18	76 ± 7	75 ± 9	78 ± 8	74 ± 9	0.12
<i>Metabolic Syndrome</i>						
SBP, mmHg	24	132 ± 15	137 ± 21	139 ± 21	132 ± 15 <sup>†</sup>	0.03
DBP, mmHg	24	72 ± 7	73 ± 8	76 ± 8	73 ± 8	0.06

SBP = systolic blood pressure, DBP = diastolic blood pressure, NTG = sublingual nitroglycerin.

\* Overall P for repeated measures ANOVA.

<sup>†</sup> P=0.01

<sup>‡</sup> P=0.04 compared to before active treatment by *post hoc* analysis.