L- Carnitine

Cardiovascular applications

• Heidi Fritz MA, ND

Introduction

L-carnitine is a trimethylated amino acid- derivative whose most well described biological function is as a cofactor of fatty acid metabolism (Alt Med Rev 2005). L-carnitine is a key component of the intracellular shuttle system that transports free fatty acids from the cytosol and across the mitochondrial membrane where they undergo beta oxidation and transformation to ATP (Karlic 2004). Long chain fatty acids represent up to 80% of the body's energy sources during most physiological states with the exception of high intensity exercise (Karlic 2004) and are the preferred substrate in cardiac muscle (Carvajal 2003). L-carnitine also impacts other cellular energy- producing pathways (Mate 2010). Optimization of mitochondrial metabolism through supplementation with L-carnitine, which is known to concentrate in cardiac and skeletal muscle (Flanagan 2010), could be an effective intervention for a variety of conditions characterized by fatigue, pain, and impaired muscle function. This paper focuses on the evidence base for L-carnitine in cardiovascular medicine.

Physiology

L-carnitine is considered to be conditionally essential, meaning that although there are rare genetic conditions causing primary deficiency, and secondary deficiency resulting commonly from hemodialysis in patients with kidney disease, most healthy individuals can synthesize L-carnitine from dietary lysine and methionine and cofactors vitamin C, iron, pyroxidine, and niacin (Flanagan 2010, Mate 2010). Despite this, alterations of L-carnitine metabolism are common in cardiovascular disease, most likely due to a combination of increased utilization and the inability of myocardiocytes to synthesize carnitine endogenously.

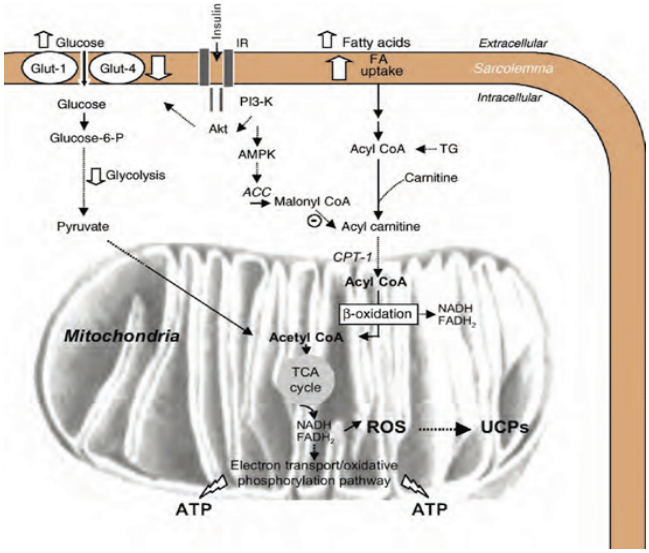
Cardiac ischemia is well recognized in the literature to be accompanied by a rapid depletion in myocardial carnitine content and a concurrent rise in intracellular long chain free fatty acids (Gurlek 2000, Regitz 1990A, Regitz 1990B, Tarantini 2006). In patients with heart failure, serum carnitine has been correlated with impaired left ventricular systolic function as measured by echocardiography (El-Aroussy 2000). During ischemia L-carnitine is thought to offset rising concentrations of free fatty acids by facilitating mitochondrial uptake and utilization, thereby preventing the damaging effects of elevated free fatty acids: membrane damage with consequent cell swelling and microvascular compression, arrhythmias, and metabolic inefficiency with consequent deterioration of myocardial function (Tarantini 2006).

Heidi Fritz MA, ND
Research Fellow
Canadian College of Naturopathic Medicine
Bronte Naturopathic Clinic

1255 Sheppard Avenue East
Toronto, Ontario, Canada M2K 1E2
905 876 3047 ext 204
hfritz@ccnm.edu

In addition to its facilitating fatty acid transport into the mitochondria, L-carnitine performs a second key metabolic function: the removal from the mitochondria of short and medium chain fatty acids (acetyl groups) formed as products of beta oxidation and bound to CoA as acetyl-CoA (Mate 2010). Mitochondrial accumulation of this byproduct is toxic, inhibiting pyruvate dehydrogenase activity and glucose oxidation. On the other hand, the removal of acetyl groups and consequent increase in free CoA stimulates energy production through the Kreb's cycle (Mate 2010). In this way, L-carnitine can regulate both fatty acid and glucose metabolism in ischemic cardiac tissue. See Figure 1. Importantly, since myocardium is unable to synthesize carnitine itself, exogenous administration may be necessary to restore optimal levels and metabolic function.

Figure 1. Overview of the role of carnitine in cellular respiration



Human Evidence

Oral and intravenous L-carnitine has been shown to be beneficial for a number of cardiovascular conditions including angina (Bartels 1996, Cacciatore 1991), acute myocardial infarction (Gurlek 2000), chronic heart failure (Rizos 2000), and peripheral vascular disease (Brevetti 1999); because it is more accessible, this summary focuses on oral L-carnitine in particular. The typical dosage is 2g per day in divided doses (Gurlek 2000, Singh 1996); some studies have used up to 6g per day (Iliceto 1995). No adverse events beyond mild gastrointestinal upset, which was rare, were reported (Kumar 2007). It should be noted that most of the studies cited here included patients also receiving standard medications for their conditions, and that L-carnitine was studied as an "add on" therapy; space constraints limit the detail in which this can be described for each study.

Angina

There are at least eight controlled human trials of oral L-carnitine for the treatment of angina. Of these, all found benefit (Bartels 1995, Bartels 1996, Cacciatore 1991, Cherchi 1985, Cherchi 1990, Iyer 2000, Kamikawa 1984, Lagioia 1992, McMackin 2007). L carnitine has been shown to:

- Improve cardiac function (eg. cardiac output, maximal heart rate) during exercise and improve overall exercise performance (eg. exercise time, exercise workload) despite having no effect on myocardial oxygen requirements (Bartels 1996, Bartels 1995, Cacciatore 1991, Cherchi 1985, Iyer 2000, Kamikawa 1984, Lagioia 1992);
- Reduce myocardial ischemia upon exercise testing, measured as the time to ST-segment depression or the degree of ST-depression on ECG (Bartels 1996, Bartels 1995, Cacciatore 1991, Cherchi 1985, Cherchi 1990, Kamikawa 1984, Lagioia 1992);
- Reverse angina, with a number of patients becoming angina- free during treatment (up to 22.7% of patients compared to 9.1% in the placebo group according to Cherchi 1985, 2 out of 12 patients according to Kamikawa 1984);
- Decrease frequency of angina attacks by up to 70% and nitroglycerin consumption by 57% according to Bartels 1996, comparable to treatment with diltiazem;
- One additional study in patients without angina but with established coronary artery disease showed L-carnitine to increase brachial artery diameter by 2.3%, consistent with reduced arterial tone (McMackin 2007).

L-carnitine exerts these effects without reducing myocardial oxygen demand, as do select cardiac medications such as beta blockers. Bartels showed that: "[proprionyl-L-carnitine] prevents ischemia-induced ventricular dysfunction, not by affecting the myocardial oxygen supply-demand ratio but as a result of its intrinsic metabolic actions, increasing pyruvate dehydrogenase activity and flux through the citric acid cycle" (1994).

Acute Myocardial Infarction

Eight controlled trials have examined the effect of L-carnitine in the treatment of acute myocardial infarction (AMI), often with intravenous administration for an initial period, followed by long term oral administration. These are summarized in Table 1. When added to standard therapies, L-carnitine has been found to:

- Improve myocardial pumping ability: increasing left ventricular ejection fraction (LVEF) (Gurlek 2000), and end- diastolic and end- systolic volumes (Iliceto 1995)
- Reduce myocardial damage: reduced infarct size when administered acutely (Singh 1996), and reduced deleterious left ventricular remodeling and dilation when administered acutely and long term (Iliceto 1995)

- Decrease angina following MI by up to half that experienced by patients receiving placebo (Davini 1992, Singh 1996)
- Decrease incidence of arrhythmias following MI (Mondillo 1995, Singh 1996)
- Reduce number of second cardiac events to 15.6%, compared to 26% in placebo (Singh 1996)
- Reduce overall mortality, with 1.2% rate reported in LC group compared to 12.5% in the placebo group according to Davini 1992. Reduced mortality also demonstrated by De Pasquale (1995).

Two large randomized controlled trials have been conducted by Italian researchers. The CEDIM1 (Carnitine Ecocardiografia Digitalizzata Infarto Miocardico) and CEDIM2 trials investigated the use of intravenous L-carnitine 9g/d for the first five days after AMI, followed by 4 to 6 g/d orally for 6 to 12 months in 472 and 2230 patients respectively (Iliceto 1995, Tarantini 2006). Although the studies differed in their long term (6-12 months) findings, both demonstrate that L-carnitine can reduce early mortality post AMI. CEDIM2 found significantly reduced early mortality, risk of death at 5 days HR 0.61 (95% CI 0.37-0.98), and upon reanalysis, it was found that much of the apparent benefit seen in CEDIM1 was also due to lower early mortality (Tarantini 2006).

Of the eight studies, seven found significant positive effects (Davini 1992, De Pasquale 1995, Gurlek 2000, Iliceto 1995, Mondillo 1995, Singh 1996, Tarantini 2006). Iyer found no effect on cardiac function in a smaller trial of 60 patients using L-carnitine 6g/d intravenously for the first 7 days, then 3g/d orally for 3 months, and it has been suggested that this may be due to the smaller trial size compared to CEDIM 1 and 2, or the lower dosage used (1999).

Heart Failure

Nine controlled trials have investigated L-carnitine for patients with chronic/ congestive heart failure (CHF) (Anand 1998, Caponetto 1994, Ghidini 1988, Kumar 2007, Loster 1999, Mancini 1992, No authors 1999, Pucciarelli 1992, Rizos 2000). L-carnitine has been shown to:

- Improve exercise performance (maximum exercise time) (Caponetto 1994, Kumar 2007, Loster 1999, Mancini 1992, No authors 1999, Pucciarelli 1992, Rizos 2000)
- Improve cardiac function during exercise (eg. peak exercise heart rate, ejection fraction) (Anand 1998, Mancini 1992, No authors 1999)
- Increase cardiac pumping ability (eg. cardiac output, stroke volume index, left ventricular ejection fraction, pulmonary blood pressure) (Caponetto 1994, Pucciarelli 1992, Rizos 2000)
- Decrease left ventricular size (Anand 1998)
- Decrease signs and symptoms associated with CHF, including dyspnea, palpitations, fatigue, edema, and improved diuresis (Ghidini 1988, Kumar 2007)
- Reduce long term mortality: in one study 3-year mortality was 3% for patients receiving L-carnitine, compared to 18% for those on placebo ($p<0.04$) (Rizos 2000).

Interestingly, Loster found that the beneficial effects of L-carnitine continued to persist for up to 60 days after cessation of treatment (1999).

Peripheral Vascular Disease

Nine controlled trials have investigated L-carnitine, mostly as proprionyl-L-carnitine (PLC), for the treatment of peripheral vascular diseases secondary to smoking or diabetes (Barker 2001, Brevetti 1999, Brevetti 1997, Brevetti 1995, Brevetti 1988, Dal Lago 1999, Greco 1992, Hiatt 2001, Santo 2006). PLC appears to benefit predominantly those patients with moderate to severe disease, with limited effect in mild disease (Brevetti 1999, 1997, Silvestro 2006). PLC has been shown to:

- Increase walking time and/ or distance, by up to 98% in those with moderate to severe disease (Brevetti 1999, Brevetti 1995, Brevetti 1988, Dal Lago 1999, Greco 1992, Hiatt 2001)
- Increase intermittent claudication distance (the distance walked until onset of claudication) (Brevetti 1999, Santo 2006)
- Improve ankle-brachial index (Greco 1992, Santo 2006)
- Improve quality of life (Brevetti 1997)

Intravenous PLC infused 3 times weekly has also been shown to augment the effects of a physical training program in patients with moderate to severe intermittent claudication (Andreozzi 2008). Biopsy of ischemic muscle has shown that supplementation with PLC increases muscle total carnitine content after 15 days (Brevetti 1988); and uncontrolled trials have shown an ability of PLC to attenuate cold induced decreases in blood flow in patients with vasospastic disease such as Raynaud's (Gasser 1997) and reduce exercise induced increases in serum adhesion molecules, suggesting vasoprotective effects (Signorelli 2001).

Conclusion

L-carnitine is a necessary cofactor for mitochondrial function, stimulating oxidative metabolism of glucose and fatty acids particularly under conditions of ischemia. L-carnitine protects against ischemia-induced myocardial dysfunction and has been demonstrated to improve cardiac function and exercise performance in patients with angina, myocardial infarction, and heart failure. L-carnitine can decrease frequency of angina attacks; reduce deleterious cardiac remodeling and arrhythmias, and improve survival after MI; and decrease symptoms of CHF while increasing long term survival. L-carnitine also benefits peripheral vascular disease. L-carnitine has been administered alongside standard cardioactive medications in many of the trials described above without report of any serious adverse events, and can be safely considered for comanagement of the cardiac patient. •

Table 1. Human Trials of L-Carnitine for the Treatment of Acute Myocardial Infarction

Design & Dose	Outcomes	Ref.
RCT of 51 patients with ischemic cardiomyopathy post MI on ACEI, digitalis and diuretics, + 20 healthy controls; LC 2g/d x 2mo	↑LVEF in both groups (37.8-42.3%, P<0.001 in group I; 41. 5-43.8%, P<0.001 in group II), but the improvement in LVEF was more significant in the L-carnitine group (4.5% vs. 2.3%, P<0.01).	Gurlek 2000
RCT of 160 patients with a recent MI; LC 4g/d x 1y	• improved heart rate ($p < 0.005$) and systolic BP ($p < 0.005$) c/t controls; • ↓anginal attacks ($p < 0.005$) c/t controls. • ↓mortality in the treated group (1.2%, $p < 0.005$) c/t 12.5% in the controls.	Davini 1992
Non randomized controlled trial of 146 patients hospitalized with AMI; LC or usual care alone	• Deaths within 28 days of admission were zero in the LC group c/t 18 (18.6 percent) in the controls. • Estimation of predicted deaths using a multivariate model suggested a "protective role of the drug against early fatalities."	De Pasquale 1995
CEDIM1 Trial: RDBPCT of 472 patients with AMI; LC 9 g/d IV x 5d, then 6 g/d orally x 12mo vs placebo	• Significant attenuation of left ventricular dilation in the first year following acute AMI in patients treated with LC c/t placebo. • ↓ increase in both end-diastolic and end-systolic volumes from AMI to 3-, 6- and 12-months in the L-carnitine group, signifying better heart pumping ability. • Non significantly lower incidence of death and congestive heart failure after discharge was in the LC group, 14 (6%) vs 23 (9.6%) in the placebo group.	Iliceto 1995
RCT of 50 patients with effort angina and ventricular ectopic beats (VEB); LC 6g/d x 2wk	There were five groups each receiving different combinations of carnitine and/ or cardiovascular medications. Study concluded that "L-carnitine exerts a significant reduction of the VEB and its administration potentiates the anti-arrythmic effect of propafenone and mexiletine."	Mondillo 1995
RDBPCT of 101 patients with suspected MI. LC 2g/d x 28d	• ↓mean infarct size assessed by cardiac enzymes and ECG in LC group c/t placebo • LD on day 6 or 7 day post-MI showed a smaller rise in the L-carnitine group. • Incidence of the following were significantly ↓in LC c/t placebo: o angina pectoris (17.6 vs 36.0%) o NYHA class III and IV heart failure, plus left ventricular enlargement (23.4 vs 36.0%) o total arrhythmias (13.7 vs 28.0%) • Total cardiac events including cardiac deaths and nonfatal infarction were 15.6% in the carnitine group vs 26.0% in the placebo group.	Singh 1996
CEDIM 2 Trial: RDBPCT of 2230 patients with AMI; LC 9g/d IV x5d, then 4g/d orally x 6mo	↓mortality was seen in the L-carnitine arm on day 5 from randomization (HR = 0.61, 95% CI 0.37-0.98, p = 0.041). Non significant 12% reduction in mortality at 6 months (p=0.48). Non significant effect on a composite of mortality plus heart failure at 6months (p=0.27).	Tarantini 2006
RDBPC trial of 60 patients with AMI LC 6g/d IV x7d, then 3g/d orally x 3mo	No effect on the EF, ESV and EDV at discharge and after three months (p>0.05).	Iyer 1999

Key: AMI acute myocardial infarction; CHF congestive heart failure; c/t compared to; EF ejection fraction; EDV end diastolic volume; ESV end systolic volume; LC L carnitine; LVEF left ventricular ejection fraction; MI myocardial infarction; NYHA New York Heart Association (staging system for heart failure); RDBPCT randomized double blind placebo controlled trial

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