Carnitine And The Heart: General

• Carnitine is not produced by the heart but …

• The heart is dependent on Carnitine as FFA are the major sources of myocardial energy (80% of oxygen consumption is used to oxide FFA).

• Carnitine from diet or from liver and kidney is actively transported to the heart across the sarcolemma.
Carnitine Deficiency

• 1973 Firstly described as cause of human myopathy.

• There are several forms:
  ▪ Primary muscular deficiencies.
  ▪ Primary systemic deficiencies.
  ▪ Secondary deficiencies.
PHENOTYPE:
Progressive muscular myopathy with lipid accumulation.

CARNITINE LEVEL:
Low muscular Carnitine content.

TREATMENT:
Oral L-Carnitine improves muscle bulk, strength and performance.

Rarely unsuccessful → likely to be a "Riboflavin-responsive multiple ACYL-COA dehydrogenoases deficiency".
PRIMARY SYSTEMIC DEFICIENCY

• PHENOTYPE:
  Recurrent episodes of hepatic encephalopathy, hypotonia, progressive myopathy and/or cardiomyopathy (leading to death) with multi-organ lipid accumulation.

• CARNITINE ASSAY:
  Low levels in plasma, liver, muscle and heart.

• TREATMENT:
  Oral L-Carnitine always successful.
SECONDARY DEFICIENCIES

• Genetic organic aciduria.

• Genetic defects of beta oxidation.

• Prolonged haemodialysis.

• Ischaemic heart and peripheral disease.
Secondary Carnitine deficiency causes:

• Cytosolic accumulation of ACIL COA.

• Excess ACIL COA further impairs metabolism and function of the ischaemic heart by causing:
  - Membrane damage $\rightarrow$ arrhythmias.
  - Inhibition adenin nucleotide translocase $\rightarrow$ Compartimentalization of ATP in the mitochondria.
  - Alteration of calcium homeostasis $\rightarrow$ Deterioration of mechanical function.
  - Depauperation of glutathione $\rightarrow$ Oxidative stress $\rightarrow$ Apoptosis.
EFFECTS OF L-CARNITINE ON POSTISCHEMIC NECROTIC AND APOPTOTIC CARDIOMYOCYTE DEATH IN ISOLATED RAT HEARTS.

(Cui J et al. In press)

**INFARCT SIZE (%)**

<table>
<thead>
<tr>
<th></th>
<th>CONTROL</th>
<th>L-CARNITINE</th>
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</thead>
<tbody>
<tr>
<td>50</td>
<td>24%</td>
<td>17%</td>
</tr>
<tr>
<td>40</td>
<td>20%</td>
<td>15%</td>
</tr>
<tr>
<td>30</td>
<td>25%</td>
<td>20%</td>
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<tr>
<td>20</td>
<td>30%</td>
<td>30%</td>
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</table>

**APOPTOSIS (%)**

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<thead>
<tr>
<th></th>
<th>CONTROL</th>
<th>L-CARNITINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>44%</td>
<td>30%</td>
</tr>
<tr>
<td>20</td>
<td>40%</td>
<td>35%</td>
</tr>
<tr>
<td>15</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>10</td>
<td>25%</td>
<td>20%</td>
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</tbody>
</table>

*(Cui J et al. In press)*
Ischaemia Induced Deficiencies In Man

• During attack of angina (A-Cs)
• In CAD patients subjected to heart surgery.
• After myocardial infarction.
• In CAD patients subjected to trombolysis (A-Cs).
• In patients heart failure (myocardial biopsy).
• In cardiogenic shock.

Data is scarce. High individual variations. Important area to invest.
Effects of L-Carnitine in CAD patients

• Haemodynamic and metabolic action at rest and during exercise and/or pacing induced ischaemia.

• Large clinical trials in angina and acute myocardial infarction.
**EFFECT OF L-CARNITINE (40 mg / Kg) ON HAEMODYNAMIC PARAMETERS AT REST**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>After L-Carnitine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate (beats / min)</td>
<td>79 ± 4</td>
<td>76 ± 3</td>
</tr>
<tr>
<td>Mean Aortic Systolic Pressure (mmHg)</td>
<td>146 ± 4</td>
<td>144 ± 6</td>
</tr>
<tr>
<td>Mean Aortic Diastolic Pressure (mmHg)</td>
<td>76 ± 6</td>
<td>73 ± 2</td>
</tr>
<tr>
<td>Pulmonary Artery Pressure (mmHg)</td>
<td>18 ± 1</td>
<td>18.2 ± 3</td>
</tr>
<tr>
<td>Cardiac Output (l / min)</td>
<td>5.9 ± 0.7</td>
<td>5.9 ± 0.6</td>
</tr>
<tr>
<td>Coronary Sinus Blood Flow (ml / min)</td>
<td>127 ± 14</td>
<td>129 ± 12</td>
</tr>
<tr>
<td>Heart Rate x Systolic Blood Pressure</td>
<td>11.53 ± 0.12</td>
<td>11.38 ± 0.14</td>
</tr>
</tbody>
</table>

Study on 18 patients  
EFFECT OF L-CARNITINE (40 mg/Kg) ON MYOCARDIAL METABOLISM AT REST

STUDY ON 18 CAD PATIENT
R. FERRARI et al. - International Journal of Cardiology - 1984
EFFECT OF L-CARNITINE ON MYOCARDIAL OER %

THE OER FOR EACH SUBSTRATE BEING CALCULATED FROM THE A-CS DIFFERENCE

BEFORE

OER %

100

70

50

25

0

LACTATE 8%

GLUCOSE 18%

FFA 47%

AFTER OXFENICINE

100

70

50

25

0

LACTATE 6%

GLUCOSE 6%

FFA 75%
CORONARY SINUS ATRIAL PACING

- 140 b/m
- For 10 minutes or until the onset of chest pain
Phase IV open label study in 3500 CAD patients treated for 1 year with oral L-Carnitine (2gr daily):

- No side effects.
- Reduction of concomitant anti-anginal treatment ($\beta$ blockers, nitrates, CA$^{2+}$ antagonists).

Fernandez et al JAMA 210, 1985
HIGH DOSES OF L-CARNITINE IN ACUTE MYOCARDIAL INFARCTION: METABOLIC AND ANTIARRHYTHMIC EFFECTS
P. Rizzon et al...... European Heart Journal, 1988

i.v. ADMINISTRATION OF HIGH DOSES OF L-CARNITINE (100 mg/kg) IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION INCREASES URINARY EXCRETION OF ACYLCARNITINE AND REDUCES EARLY VENTRICULAR ARRHYTHMIAS
Effects of L-Carnitine on LV remodelling after acute anterior myocardial infarction  CEDIM I (JACC; 26, 1995)

• Objectives:
  Effects of L-Carnitine (9g / day iv for 5 days followed by oral dose for 12 months) on long term ventricular dilation in 472 patients with AMI

• Methods:
  High quality two dimensional echo cardiograms with 24 hour of onset of chest pain and at pre-discharge and 3,6,12 months later.
CEDIM 1
(JACC 1995)
Furthermore:

• No significant differences in left ventricular ejection fraction

• A trend towards a reduction of the combined incidence of death and CHF after discharge:
  14 (6%) in L-Carnitine group
  23 (9.6%) in placebo group
CEDIM-2

• **Population:**
  2047 patients with acute anterior infarct.

• **Randomization:**
  Within 12 hours from symptom.

• **Primary end point:**
  CV mortality and HF at six months.

• **Secondary end point:**
  Early mortality (7 and 30 days).

• **Treatment:**
  as in CEDIM-1.
PRIMARY END-POINT
(mortality and HF)

2% 4% 6% 8% 10%
1 2 3 4 5 6 months

PLACEBO
L-CARNITINA

p = NS
Cumulative Number of deaths

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Carnitine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>23</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>44</td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>46</td>
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<tr>
<td>10</td>
<td>37</td>
<td>47</td>
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<tr>
<td>15</td>
<td>42</td>
<td>50</td>
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<tr>
<td>30</td>
<td>46</td>
<td>60</td>
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<tr>
<td>60</td>
<td>54</td>
<td>67</td>
</tr>
<tr>
<td>90</td>
<td>58</td>
<td>69</td>
</tr>
<tr>
<td>180</td>
<td>66</td>
<td>77</td>
</tr>
<tr>
<td>365</td>
<td>69</td>
<td>78</td>
</tr>
</tbody>
</table>
**Relative Risk (of death)**

P = 0.04

<table>
<thead>
<tr>
<th></th>
<th>3</th>
<th>5</th>
<th>7</th>
<th>10</th>
<th>15</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>180</th>
<th>365</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>1.1</td>
<td>0.98</td>
<td>1.05</td>
<td>1.19</td>
<td>1.25</td>
<td>1.11</td>
<td>1.14</td>
<td>1.17</td>
<td>1.17</td>
<td>1.21</td>
</tr>
<tr>
<td>Low</td>
<td>0.38</td>
<td>0.37</td>
<td>0.42</td>
<td>0.5</td>
<td>0.55</td>
<td>0.51</td>
<td>0.55</td>
<td>0.58</td>
<td>0.61</td>
<td>0.63</td>
</tr>
<tr>
<td>Close</td>
<td>0.65</td>
<td>0.61</td>
<td>0.66</td>
<td>0.78</td>
<td>0.83</td>
<td>0.75</td>
<td>0.79</td>
<td>0.83</td>
<td>0.84</td>
<td>0.87</td>
</tr>
</tbody>
</table>
**CONCLUSION:**

- L-Carnitine treatment is useful in all primary deficiencies.

- In secondary deficiencies and particularly in ischaemic heart disease it improves cardiac metabolism.

- This results in an improvement of angina symptoms, reduced early mortality after MI and improvement of left ventricular remodelling.
**PROPIONYL – L - CARNITINE**

Propionyl-L-Carnitine is a carnitine derivative able to improve muscle metabolism:

- it is highly specific for muscle carnitine transferase
- it increases cellular carnitine content, allowing FFA transport across the mitochondria
- it carries propionate, an anaplerotic substrate for Kreb’s cycle

Propionyl-L-Carnitine has been shown to:

- improve cardiac muscle function in several experimental models of heart failure
- improve maximal walking distance in patients with peripheral arterial disease (9 parallel, randomized, double-blind studies; 1406 patients totally, in pubbl.)
- improve exercise capacity of CAD patients (double-blind study, in 32 patients, Am J Cardiol, 1994)
Propionyl-L-Carnitine in Chronic Heart Failure

1. type of study: phase-III, double-blind, randomized, parallel, multicentre, comparing Propionyl-L-Carnitine and placebo

2. primary end-point: maximum exercise duration at day 180

3. study design:
   - 14 days run-in with placebo
   - 6 months randomized double-blind treatment period
   - evaluation at 2 and 6 months

4. study population:
   - NYHA class II or III; EF <40%
   - under stable mandatory therapy with ACE-inhibitors and diuretics, with or without digitalis

5. centres involved: 49 centres in 8 European countries

6. study duration: 29 months
Primary Endpoint - Maximal Exercise Duration

**Intention To Treat Analysis**

(n = 537)

**Efficacy Analysis**

(n = 353)

**Mean Changes from Baseline**

(mean of percent changes)

- **Placebo** = 1.0 sec (0.6 %); N = 266
- **PLC** = 4.0 sec (1.9 %); N = 271

- **Placebo** = 12.8 sec (4.0 %); N = 165
- **PLC** = 22.0 sec (6.7 %); N = 188
Primary Endpoint stratified by baseline ejection fraction

INTENTION TO TREAT ANALYSIS (n = 537)
Interaction Test: p<0.05
EF ↑ 30%  p<0.05
EF ↓ 30%  NS

EFFICACY ANALYSIS (n = 353)
Interaction Test: p<0.05
EF ↑ 30%  p<0.05
EF ↓ 30%  NS

EXERCISE DURATION (seconds)

PLACEBO  DAY 60  DAY 180

MEAN CHANGES FROM BASELINE (mean of percent changes)

- □ - PLACEBO (EF ↑ 30%) = -6.7 sec (-2.4 %); N = 99
- ■ PLC (EF ↑ 30%) = 33.2 sec (9.4 %); N = 112
- ○ - PLACEBO (EF ↓ 30%) = 5.6 sec (2.4 %); N = 167
- ● PLC (EF ↓ 30%) = -16.6 sec (-3.4 %); N = 159

PLACEBO  DAY 60  DAY 180

MEAN CHANGES FROM BASELINE (mean of percent changes)

- □ - PLACEBO (EF ↑ 30%) = 8.3 sec (1.9 %); N = 57
- ■ PLC (EF ↑ 30%) = 39.8 sec (11.4 %); N = 84
- ○ - PLACEBO (EF ↓ 30%) = 15.1 sec (5.1 %); N = 108
- ● PLC (EF ↓ 30%) = 7.7 sec (2.9 %); N = 104
Primary Endpoint stratified by baseline exercise duration and EF
(Exploratory Analysis, not described in the statistical plan)

INTENTION TO TREAT ANALYSIS \((n = 537)\)
Descriptive Analysis

**Mean Changes from Baseline**
(mean of percent changes)

- **PLACEBO** (↑ 419 sec; EF ↑ 30%) = 3.4 sec (0.1%); \(N = 51\)
- **PLC** (↑ 419 sec; EF ↑ 30%) = 26.0 sec (5.6%); \(N = 64\)
- **PLACEBO** (↑ 419 sec; EF ↓ 30%) = -5.7 sec (-0.9%); \(N = 80\)
- **PLC** (↑ 419 sec; EF ↓ 30%) = -30.4 sec (-6.1%); \(N = 71\)

**Mean Changes from Baseline**
(mean of percent changes)

- **PLACEBO** (↓ 419 sec; EF ↑ 30%) = -17.6 sec (-5.0%); \(N = 48\)
- **PLC** (↓ 419 sec; EF ↑ 30%) = 42.9 sec (14.5%); \(N = 48\)
- **PLACEBO** (↓ 419 sec; EF ↓ 30%) = 16.1 sec (5.4%); \(N = 87\)
- **PLC** (↓ 419 sec; EF ↓ 30%) = -5.4 sec (-1.3%); \(N = 88\)

**Median: 419 Seconds**
Primary Endpoint stratified by baseline exercise duration and EF
(Exploratory Analysis, not described in the statistical plan)

Efficacy Analysis \( (n = 353) \)
Descriptive Analysis

Mean Changes from Baseline
(mean of percent changes)

- PLACEBO (↑419 sec; EF↑30%) = 16.4 sec (2.9%); \( N = 30 \)
- PLC (↑419 sec; EF↑30%) = 31.1 sec (6.3%); \( N = 46 \)
- PLACEBO (↑419 sec; EF↓30%) = 6.5 sec (1.3%); \( N = 57 \)
- PLC (↑419 sec; EF↓30%) = -6.9 sec (-1.5%); \( N = 52 \)

Median: 419 seconds

Mean Changes from Baseline
(mean of percent changes)

- PLACEBO (↑419 sec; EF↑30%) = -0.8 sec (0.8%); \( N = 27 \)
- PLC (↑419 sec; EF↑30%) = 50.3 sec (17.7%); \( N = 38 \)
- PLACEBO (↑419 sec; EF↓30%) = 24.7 sec (9.4%); \( N = 51 \)
- PLC (↑419 sec; EF↓30%) = 22.3 sec (7.3%); \( N = 52 \)