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.

PRIMARY MUSCULAR 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 dehydrogenoses deficiency*".

PRIMARY SYSTEMIC DEFICIENCY

- **PHENOTYPE:**

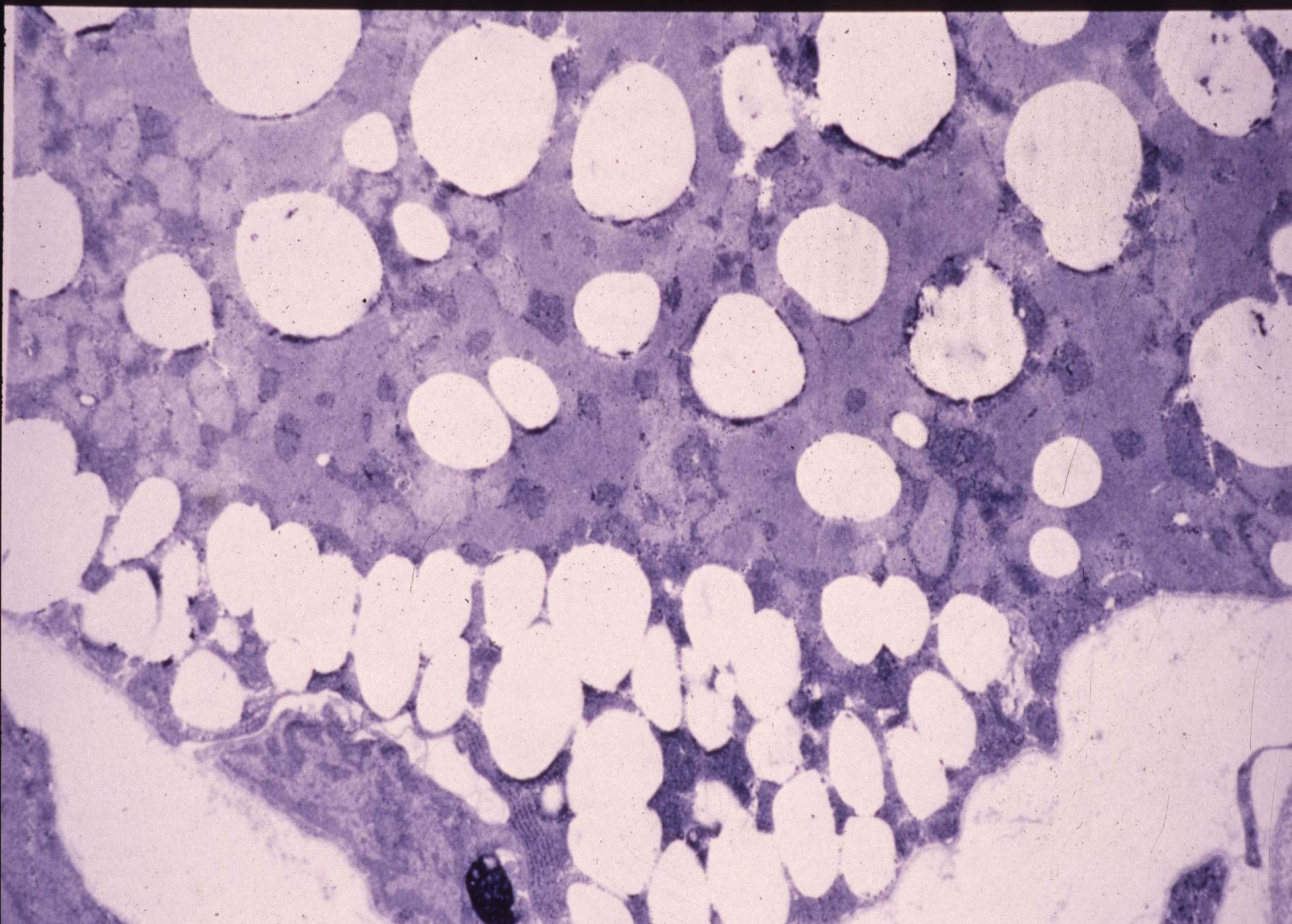
  Recurrent episodes of hepatic encephalopathy, hypotonia, progressive myopathy and / or cardiomyopathy (leading to death) with multi-organ lipid accumulation.

- **CARNITINE ASSAY:**

  Low levels in plasma, liver, muscle and heart.

- **TREATMENT:**

  Oral L-Carnitine always successful.

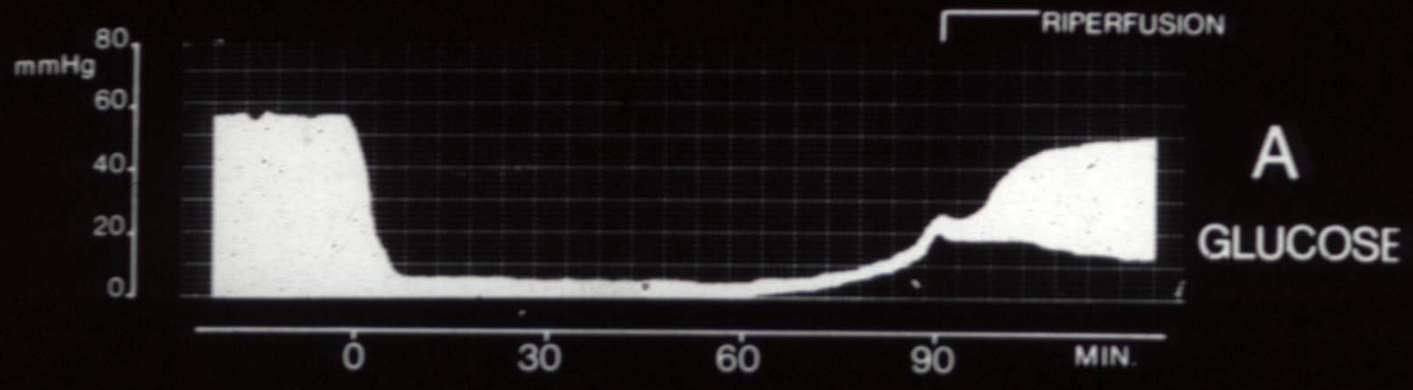


SECONDARY DEFICIENCIES

- Genetic organic aciduria.
- Genetic defects of beta oxidation.
- Prolonged haemodialysis.
- *Ischaemic heart* and peripheral disease.

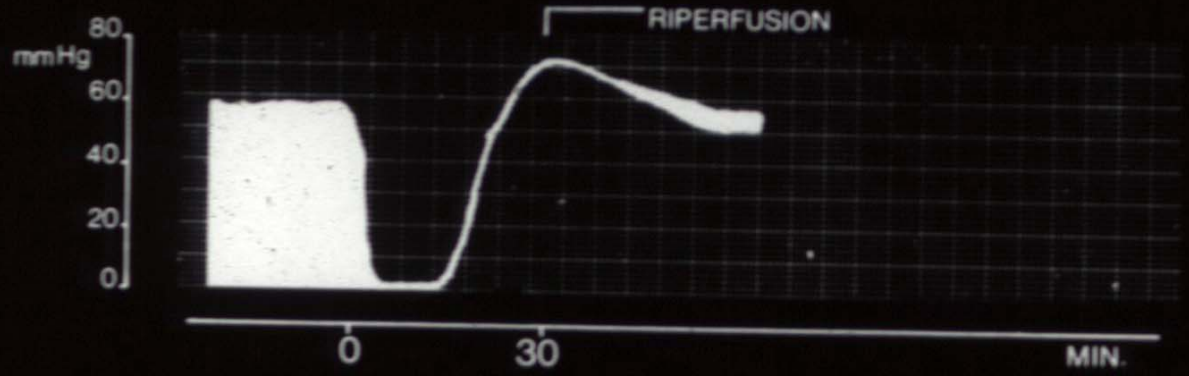
Secondary Carnitine deficiency causes:

- Cytosolic accumulation of ACIL COA.
- Excess ACIL COA further impairs metabolism and function of the ischaemic heart by causing:
  - Membrane damage → arrhythmias.
  - Inhibition adenin mucleotide translocase → Compartimentalization of ATP in the mitochondria.
  - Alteration of calcium homeostasis → Deterioration of mechanical function.
  - Depauperation of glutathione → Oxidative stress → Apoptosis.



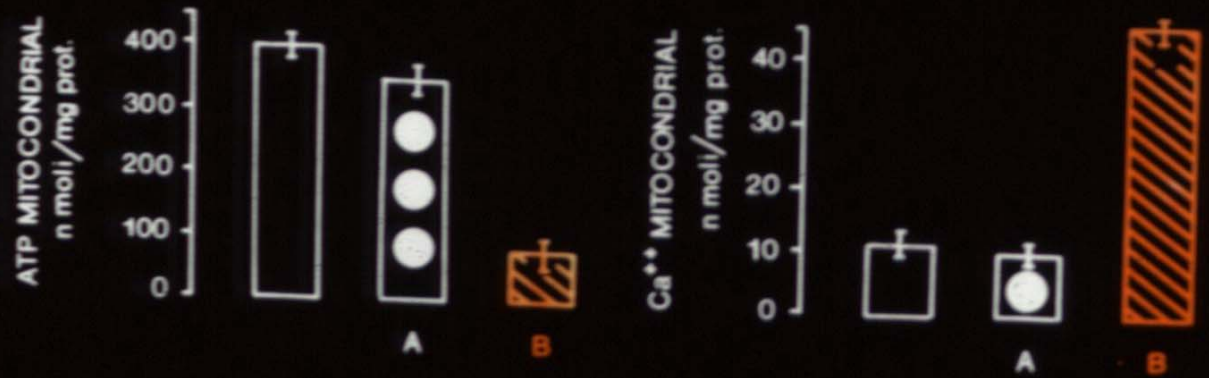
A

GLUCOSE

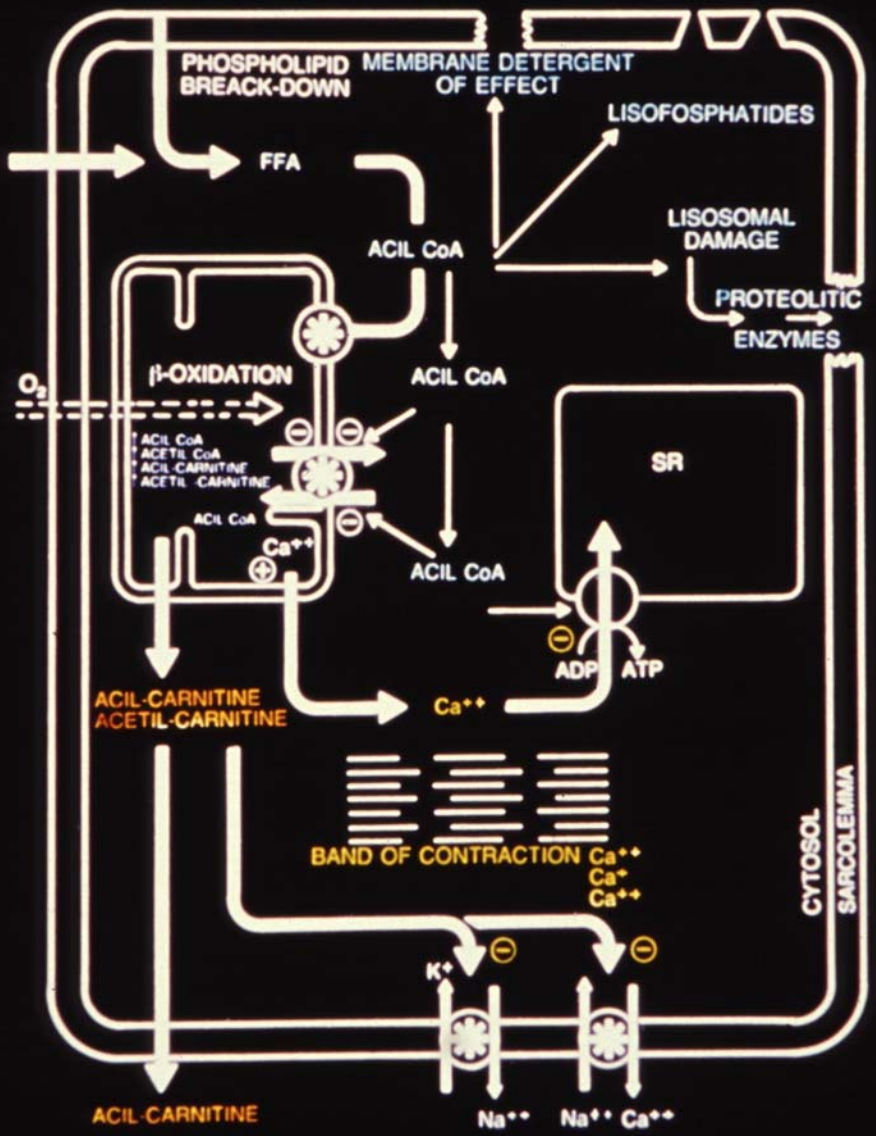


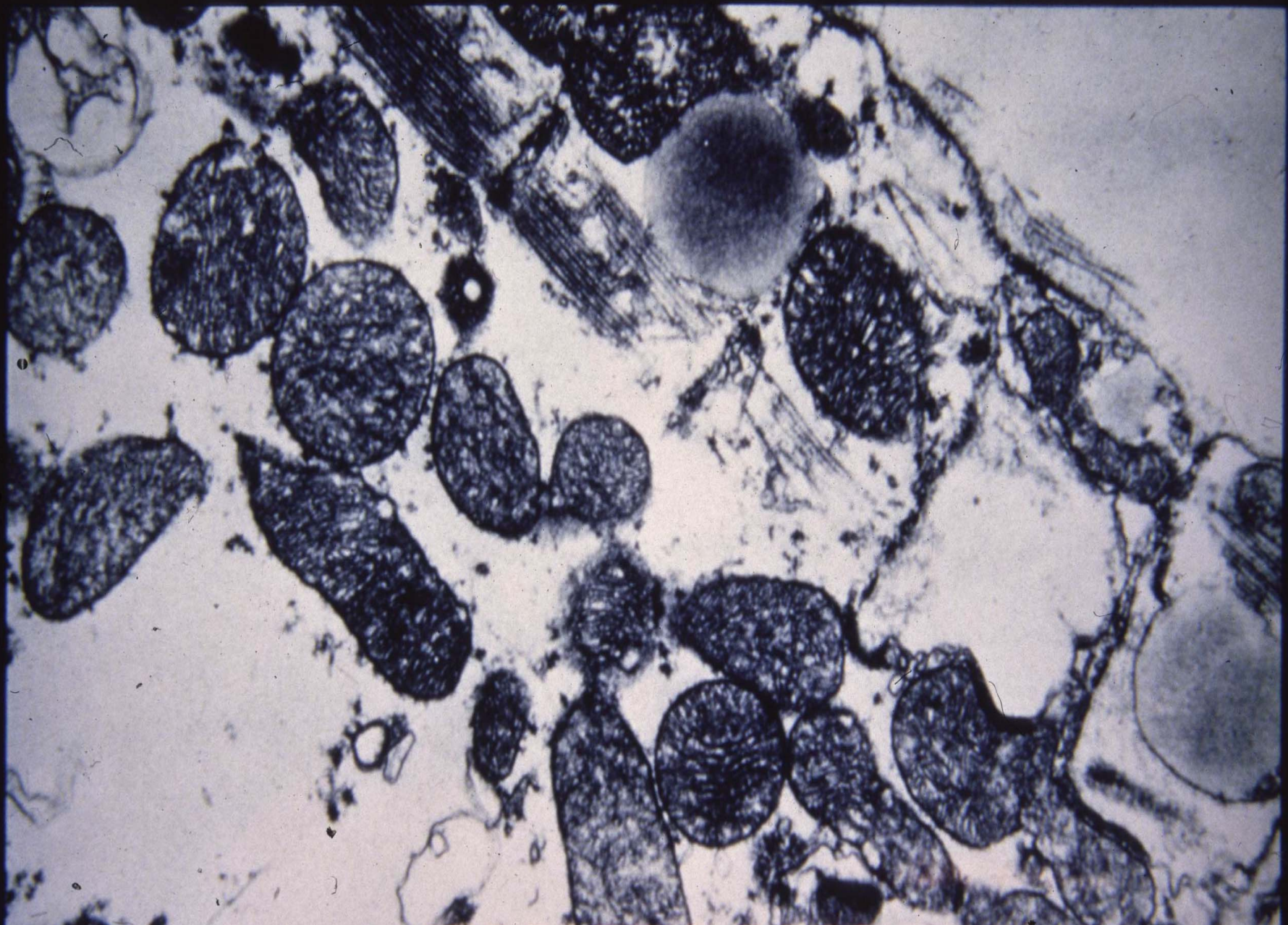
B

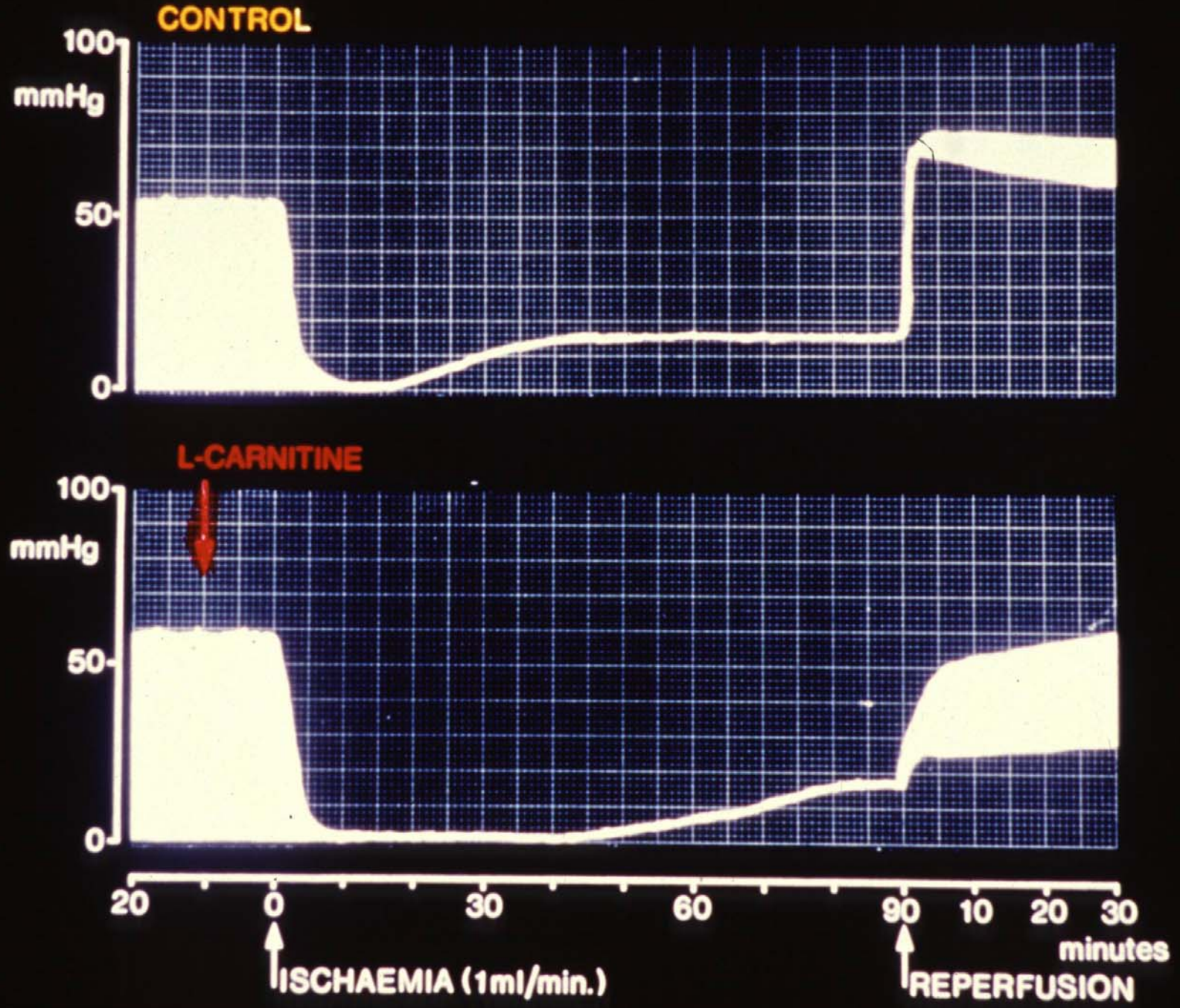
FFA



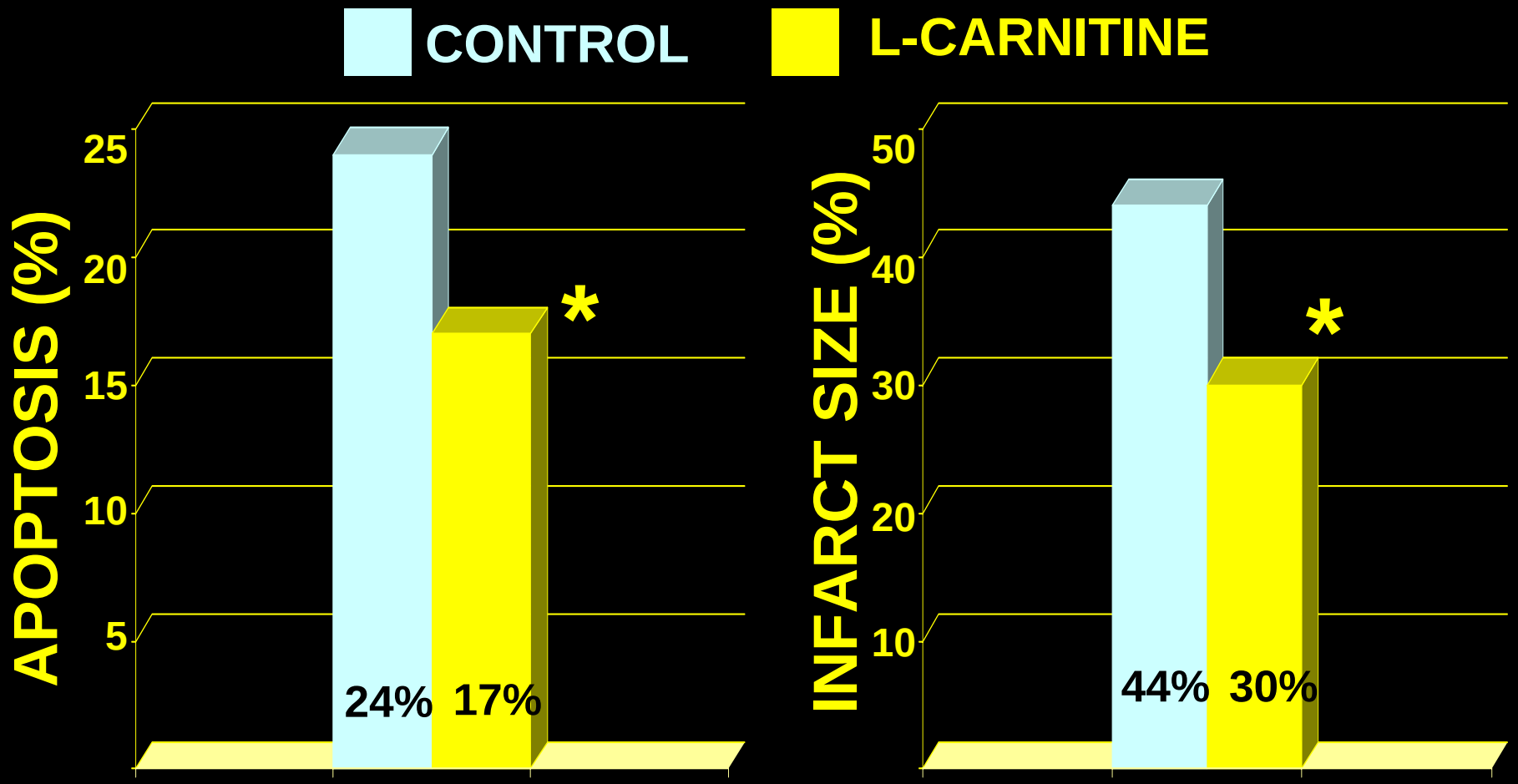
METABOLICAL TOXICITY OF FFA






CONTROL
100
mmHg
50
0
L-CARNITINE
100
mmHg
50
0
20
0
30
60
90
10
20
30
minutes
ISCHAEMIA (1ml/min.)
REPERFUSION

EFFECTS OF L-CARNITINE ON POSTISCHEMIC NECROTIC AND APOPTOTIC CARDIOMYOCYTE DEATH IN ISOLATED RAT HEARTS.



(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.

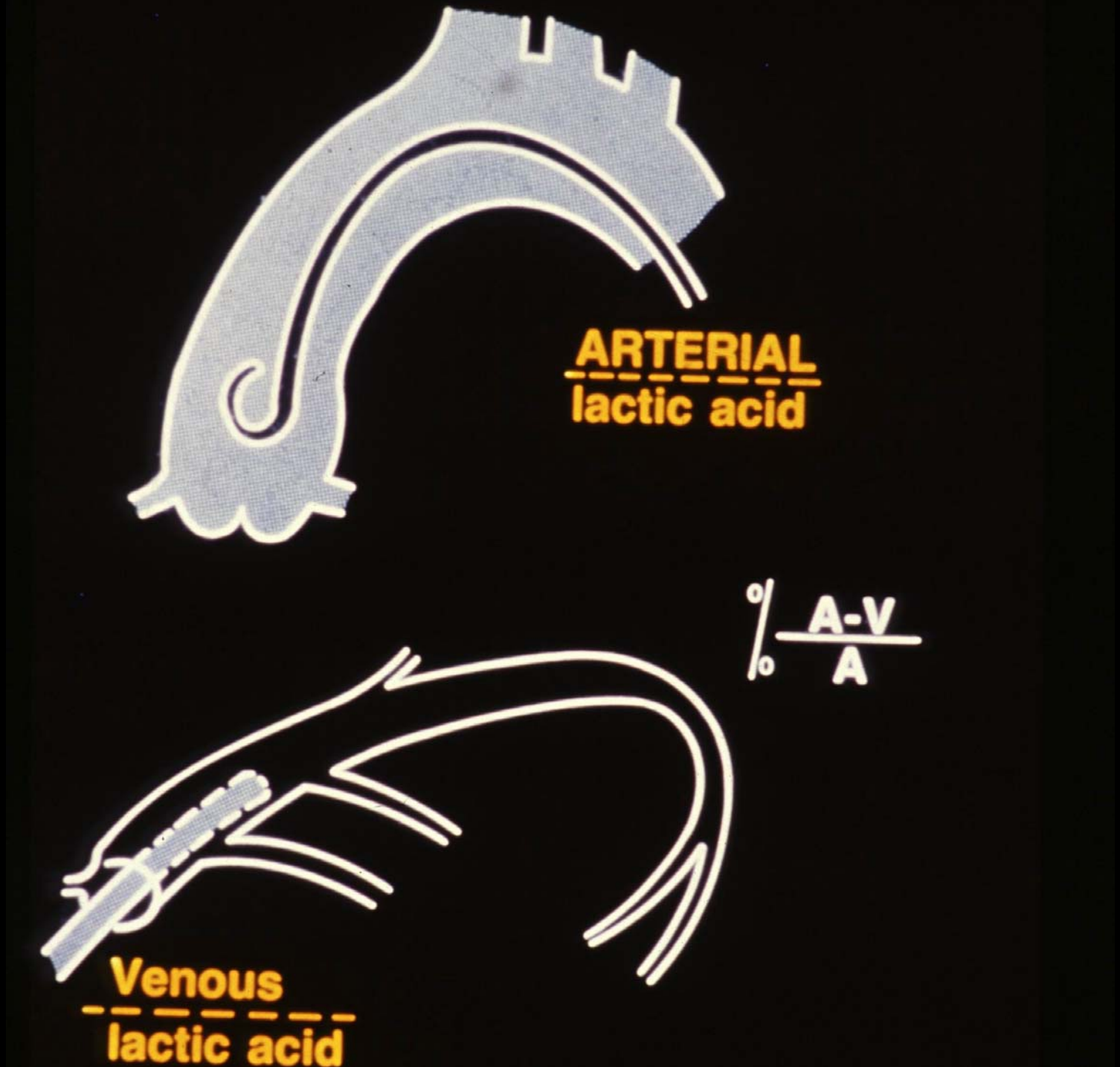
Effects of L-Carnitine in CAD patients

- Haemodynamic and metabolic action at rest and during exercise and / or pacing induced ischaemia.
- Large clinical trials in angina and acute myocardial infarction.

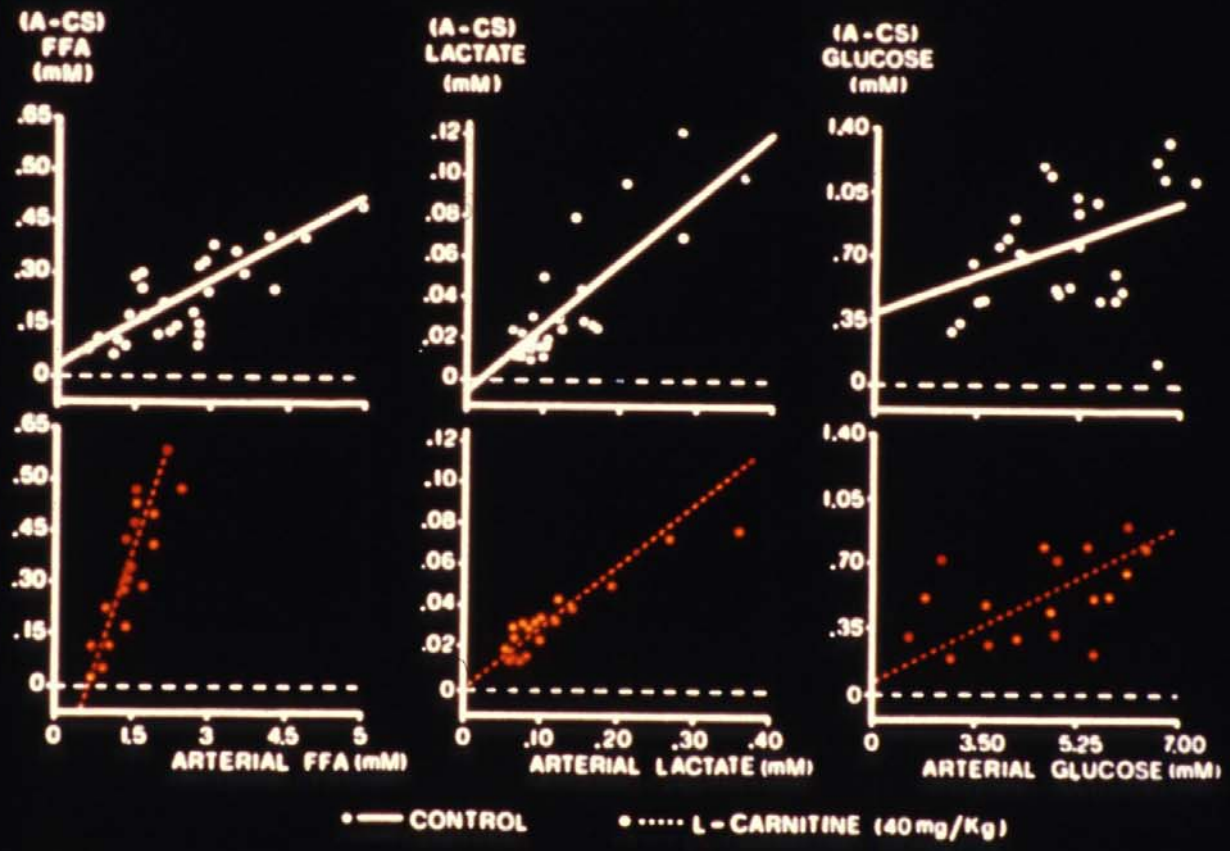
EFFECT OF L-CARNITINE (40 mg / Kg) ON HAEMODYNAMIC PARAMETERS AT REST

	BEFORE	AFTER L-CARNITINE	
HEART RATE (beats / min)	79 ± 4	76 ± 3	N.S.
MEAN AORTIC SYSTOLIC PRESSURE (mmHg)	146 ± 4	144 ± 6	N.S.
MEAN AORTIC DIASTOLIC PRESSURE (mmHg)	76 ± 6	73 ± 2	N.S.
PULMONARY ARTERY PRESSURE (mmHg)	18 ± 1	18.2 ± 3	N.S.
CARDIAC OUTPUT (l / min)	5.9 ± 0.7	5.9 ± 0.6	N.S.
CORONARY SINUS BLOOD FLOW (ml / min)	127 ± 14	129 ± 12	N.S.
HEART RATE x SYSTOLIC BLOOD PRESSURE	11.53 ± 0.12	11.38 ± 0.14	N.S.

Study on 18 patients
R. Ferrari - O. Visioli - Journal of Molecular and cellular cardiology 1983


ARTERIAL
lactic acid
% A-V / A
Venous
lactic acid

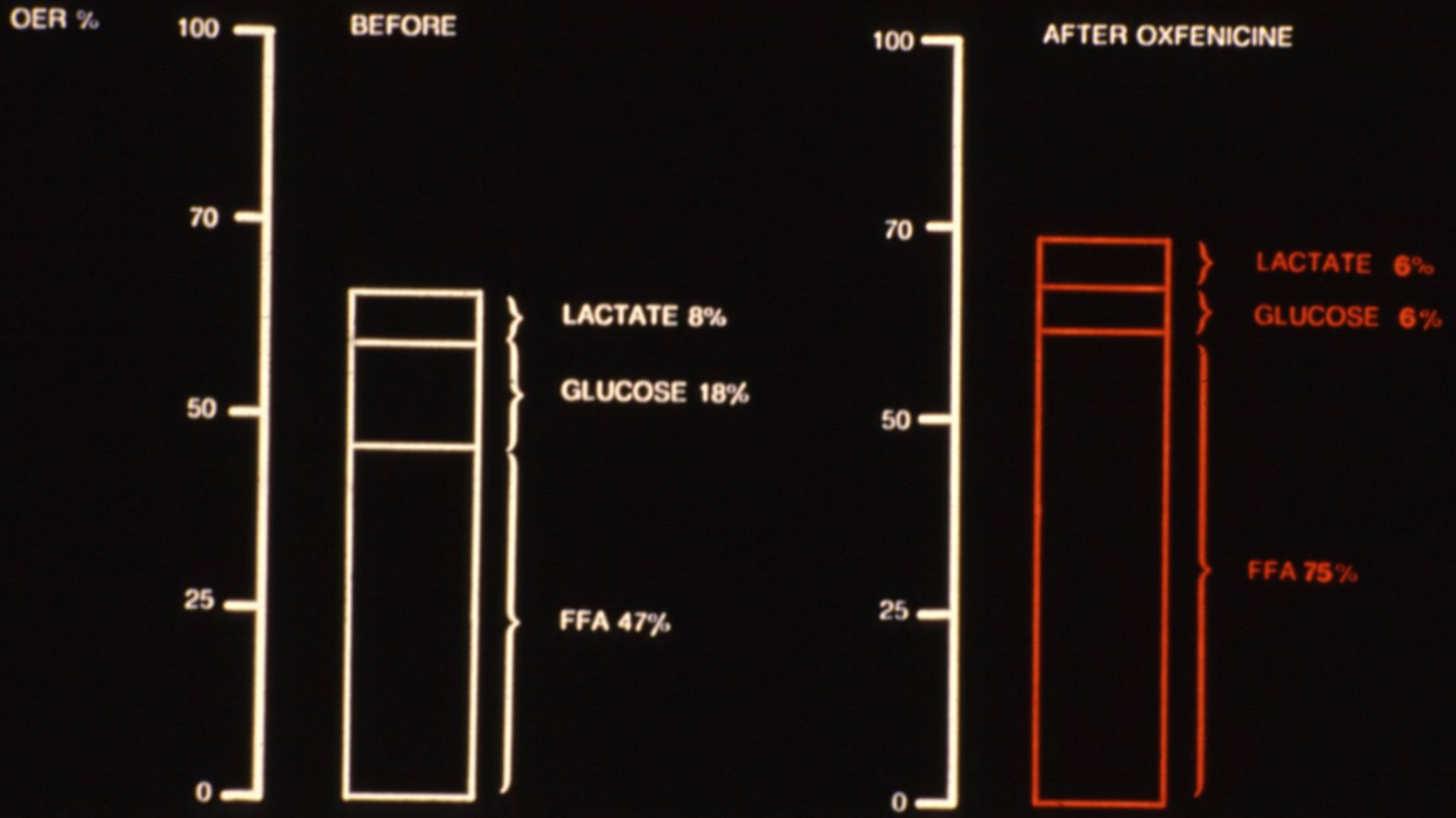
EFFECT OF L-CARNITINE (40 mg/Kg) ON MYOCARDIAL METABOLISM AT REST



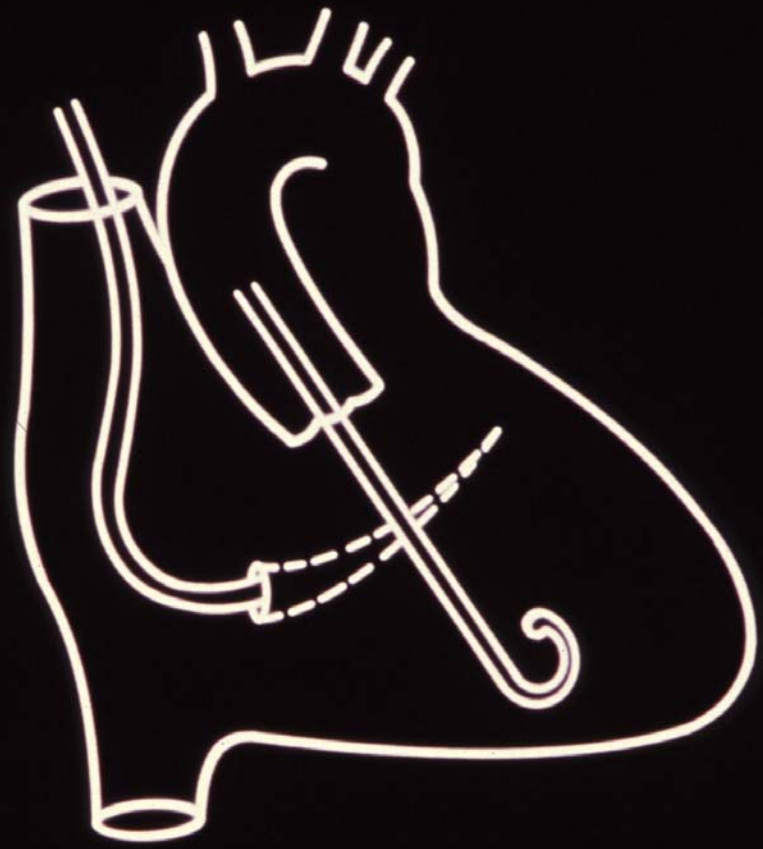
STUDY ON 18 CAD PATIENT

R. FERRARI et al. - International Journal of Cardiology - 1984

EFFECT OF L-CARNITINE ON MYOCARDIAL OER %

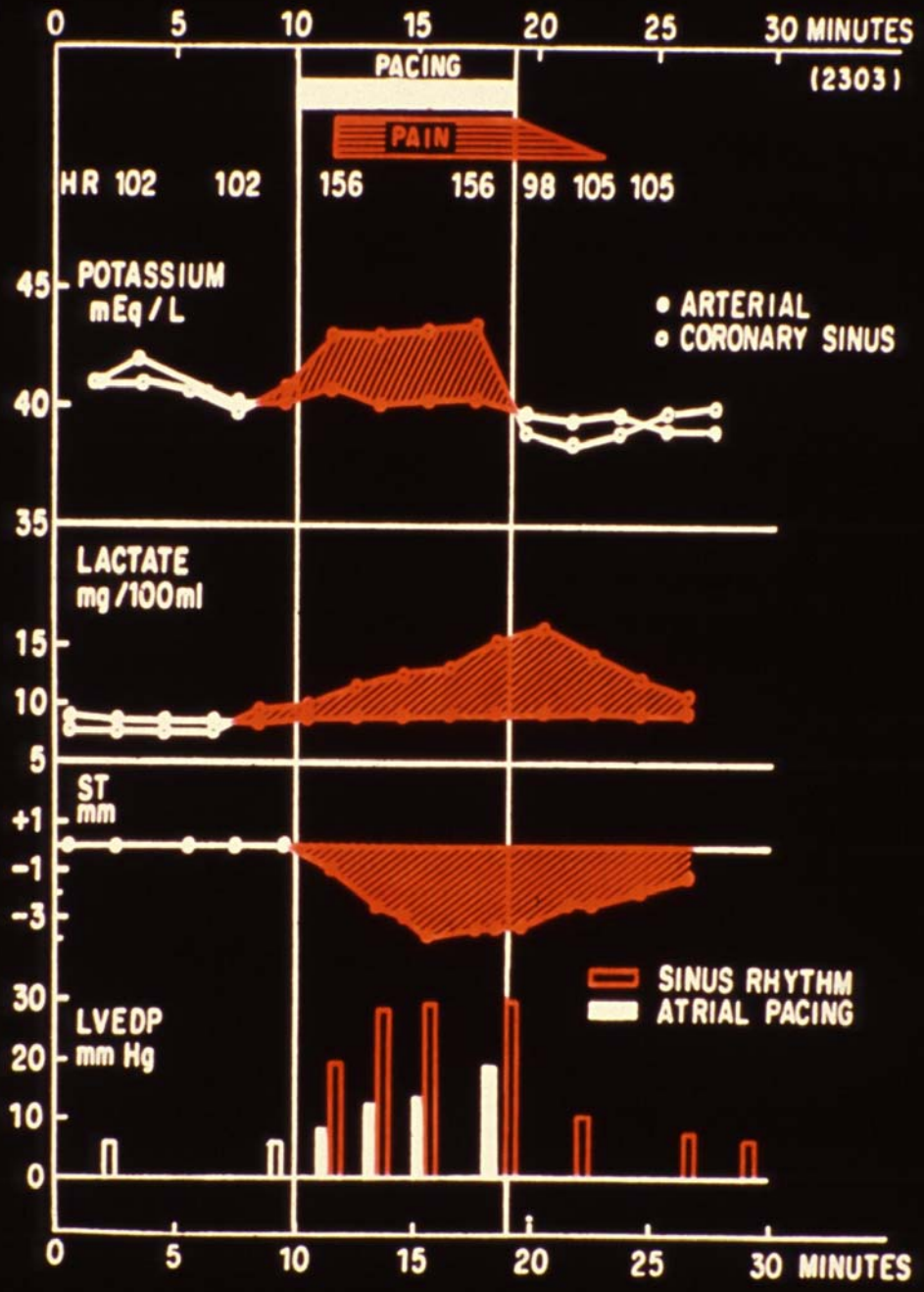


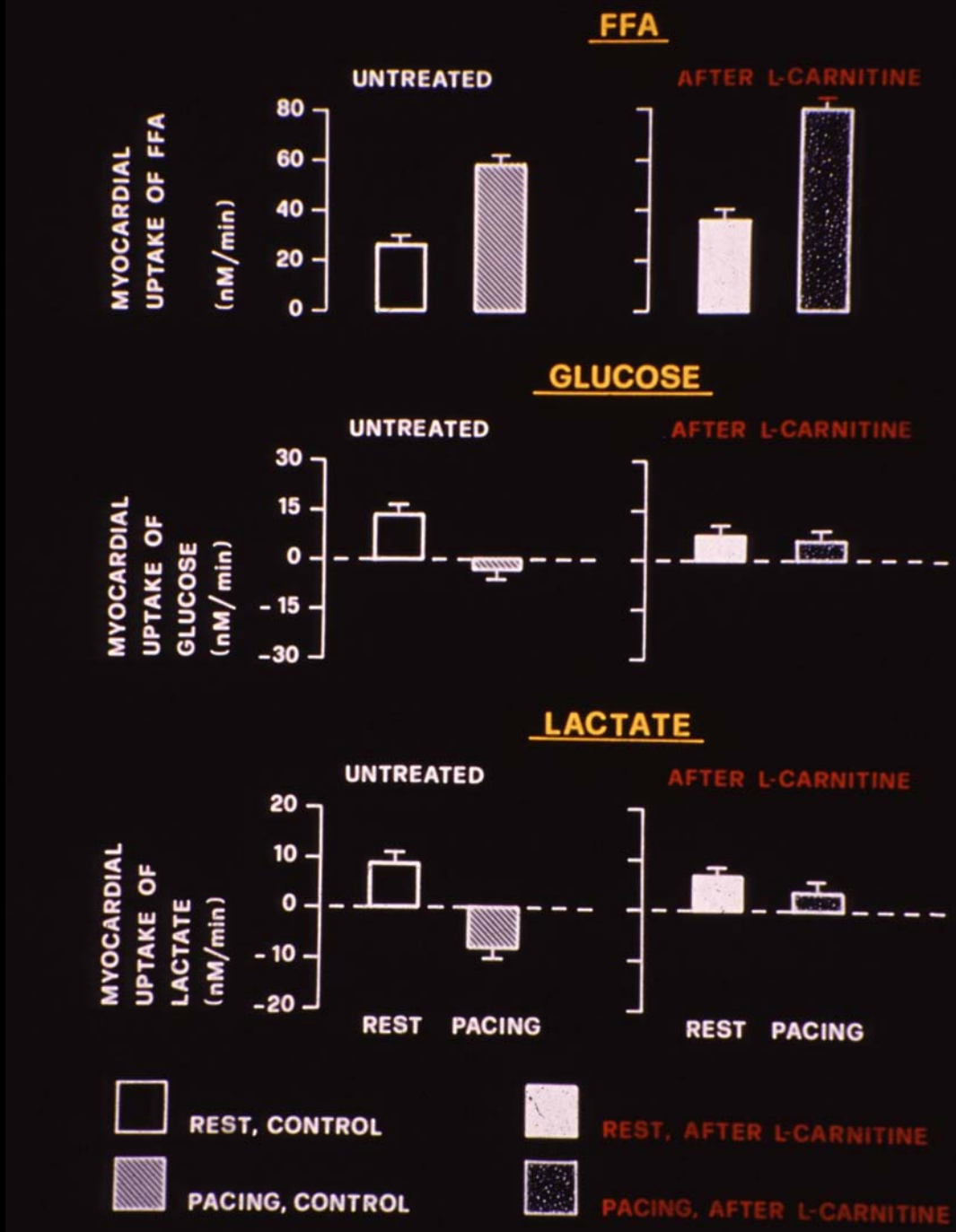
THE OER FOR EACH SUBSTRATE BEING CALCULATED FROM THE A-CS DIFFERENCE

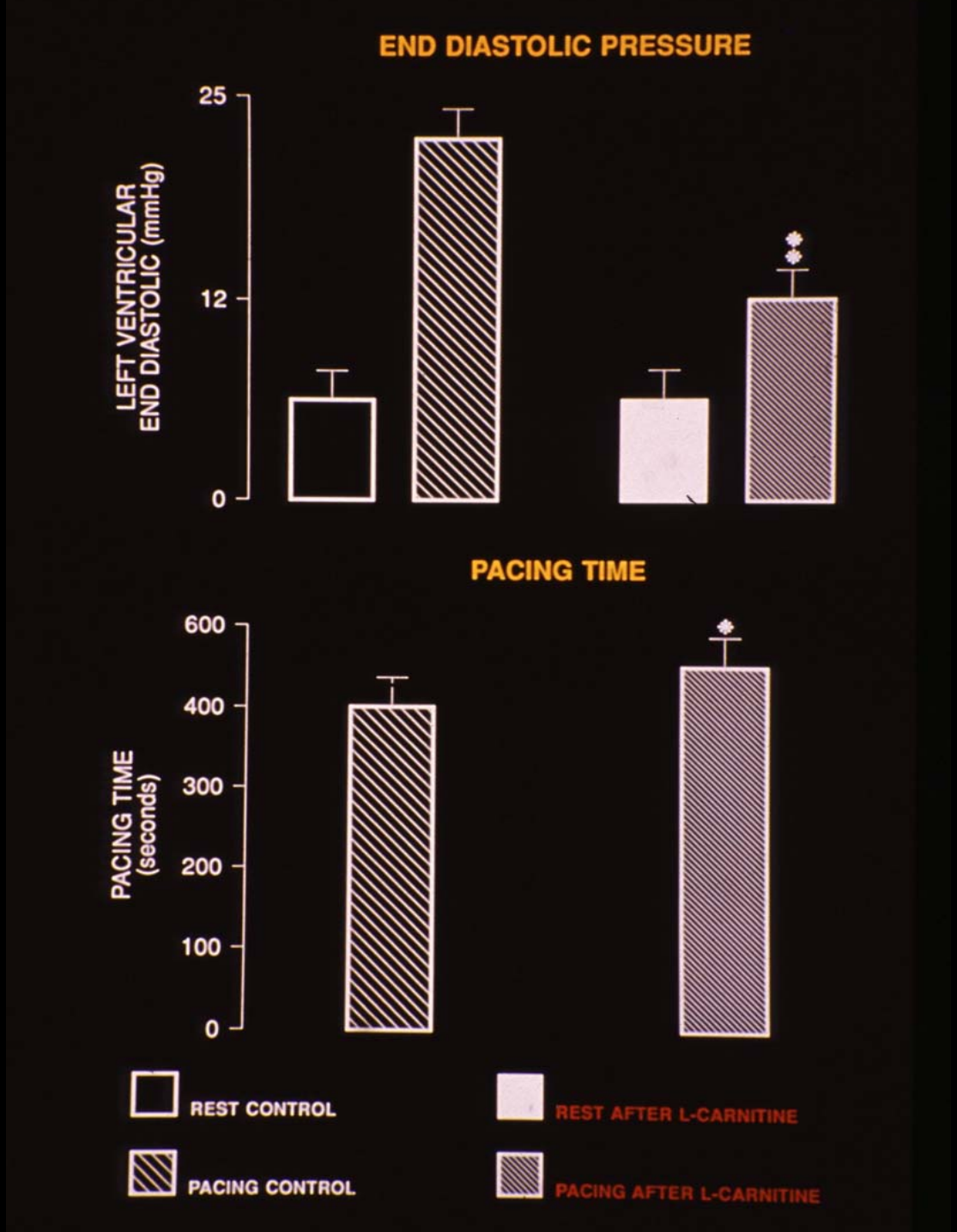


CORONARY SINUS ATRIAL PACING

- 140 b/m
- For 10 minutes or until the onset of chest pain


0 5 10 15 20 25 30 MINUTES
PACING
(2303)
PAIN
HR 102 102 156 156 98 105 105
POTASSIUM
mEq/L
45
40
35
ARTERIAL
CORONARY SINUS
LACTATE
mg/100ml
15
10
5
ST
mm
+1
-1
-3
SINUS RHYTHM
ATRIAL PACING
LVEDP
mm Hg
30
20
10
0
0 5 10 15 20 25 30 MINUTES


FFA
UNTREATED
AFTER L-CARNITINE
MYOCARDIAL UPTAKE OF FFA (nM/min)
80
60
40
20
0
GLUCOSE
UNTREATED
AFTER L-CARNITINE
MYOCARDIAL UPTAKE OF GLUCOSE (nM/min)
30
15
0
-15
-30
LACTATE
UNTREATED
AFTER L-CARNITINE
MYOCARDIAL UPTAKE OF LACTATE (nM/min)
20
10
0
-10
-20
REST
PACING
REST
PACING
REST, CONTROL
PACING, CONTROL
REST, AFTER L-CARNITINE
PACING, AFTER L-CARNITINE


END DIASTOLIC PRESSURE
LEFT VENTRICULAR END DIASTOLIC (mmHg)
25
12
0
*
PACING TIME
PACING TIME (seconds)
600
400
300
200
100
0
*
REST CONTROL
REST AFTER L-CARNITINE
PACING CONTROL
PACING AFTER L-CARNITINE

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 (β 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

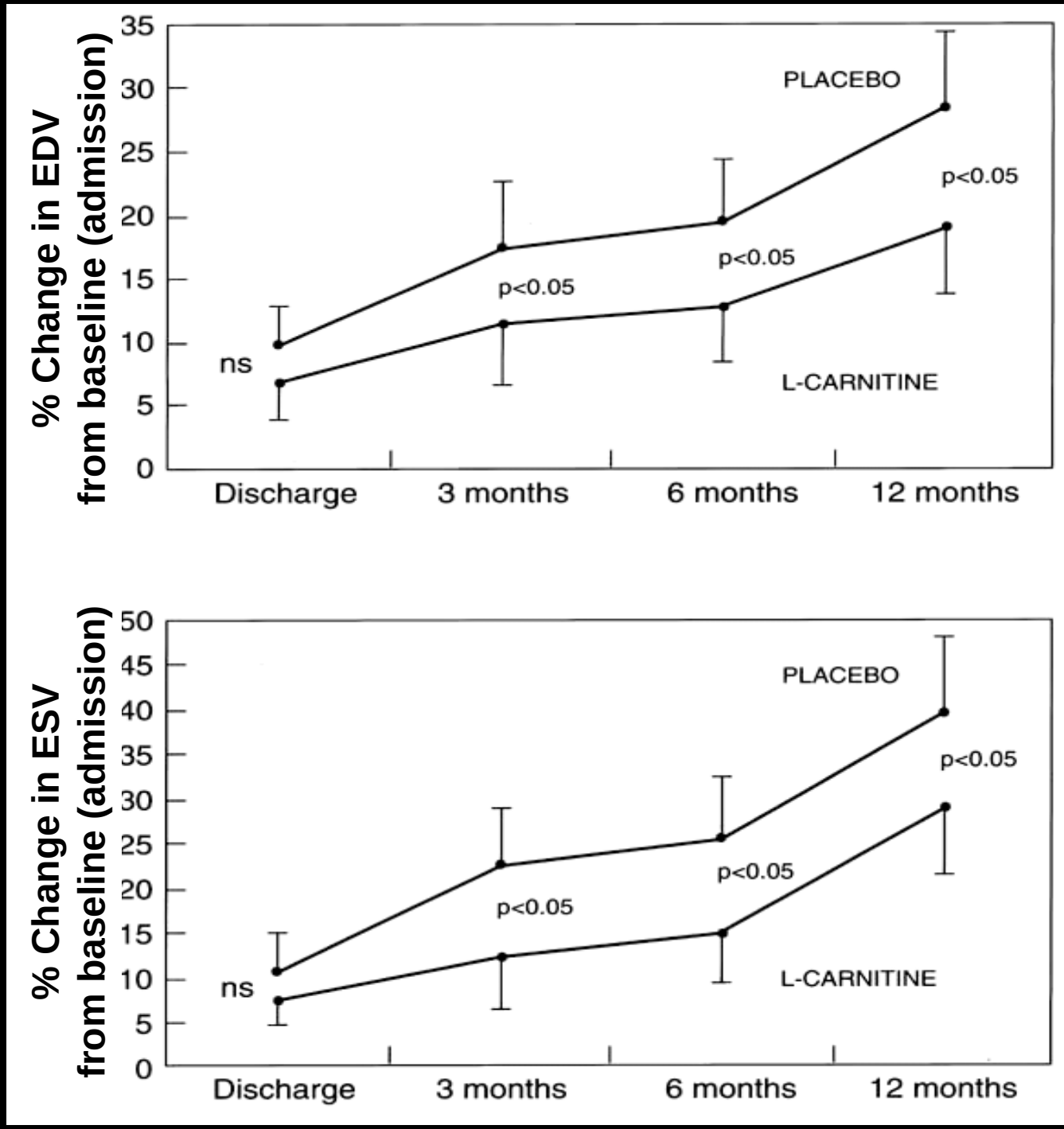
- i.v. ADMINISTRATION OF HIGH DOSES OF L-CARNITINE (100 mg/kg) IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION INCREASES URINARY EXCRETION OF ACYLCARNITINE AND REDUCES EARLY VENTRICULAR ARRHYTHMIAS

Effects of L-Carnitine on LV remodelling after acute arterior 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 .

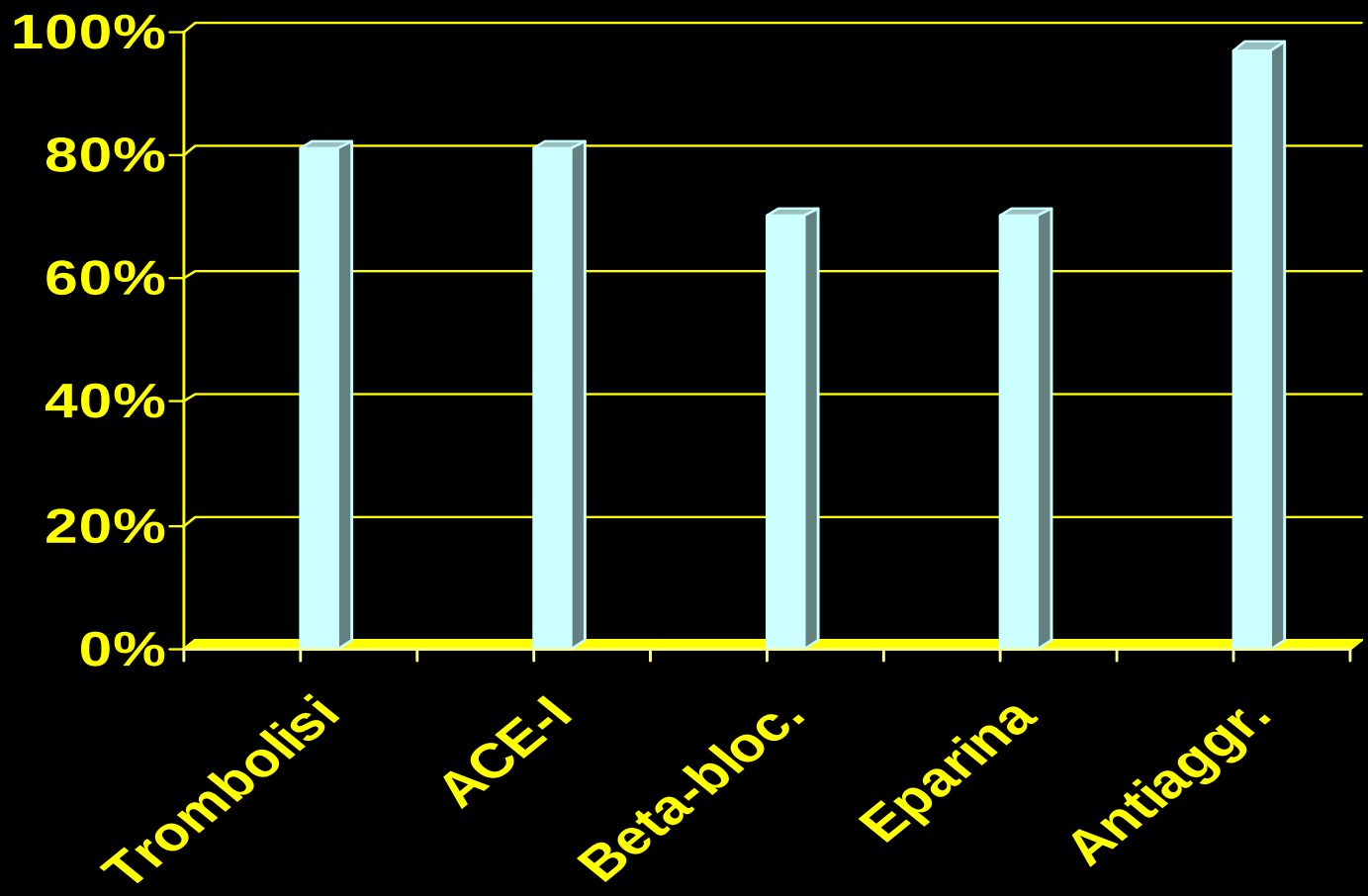
- **Randomization:**
  Within 12 hours from symptom.

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

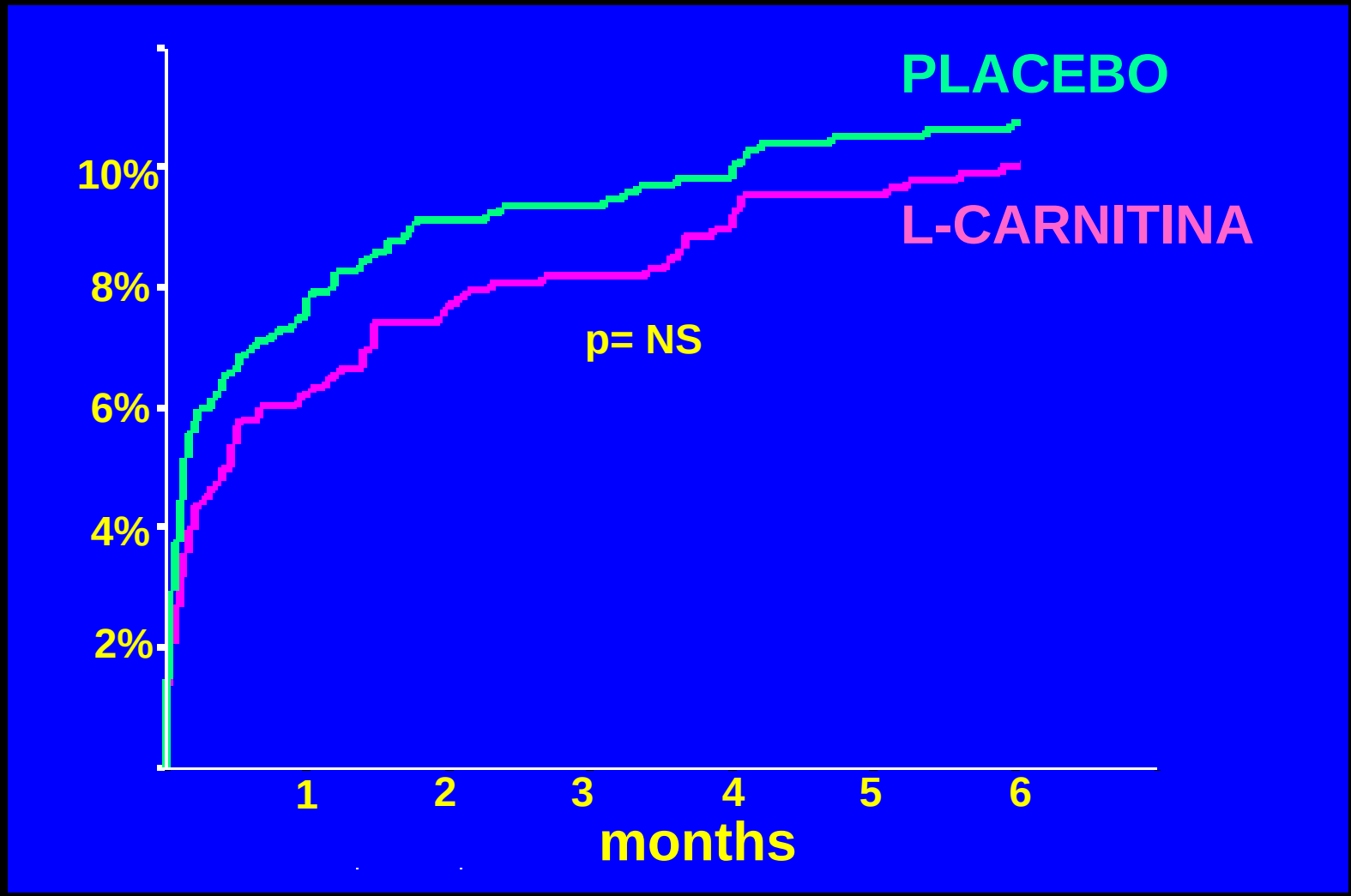
- **Secondary end point:**
  Early mortality (7 and 30 days).

- **Treatment:**
  as in CEDIM-1.

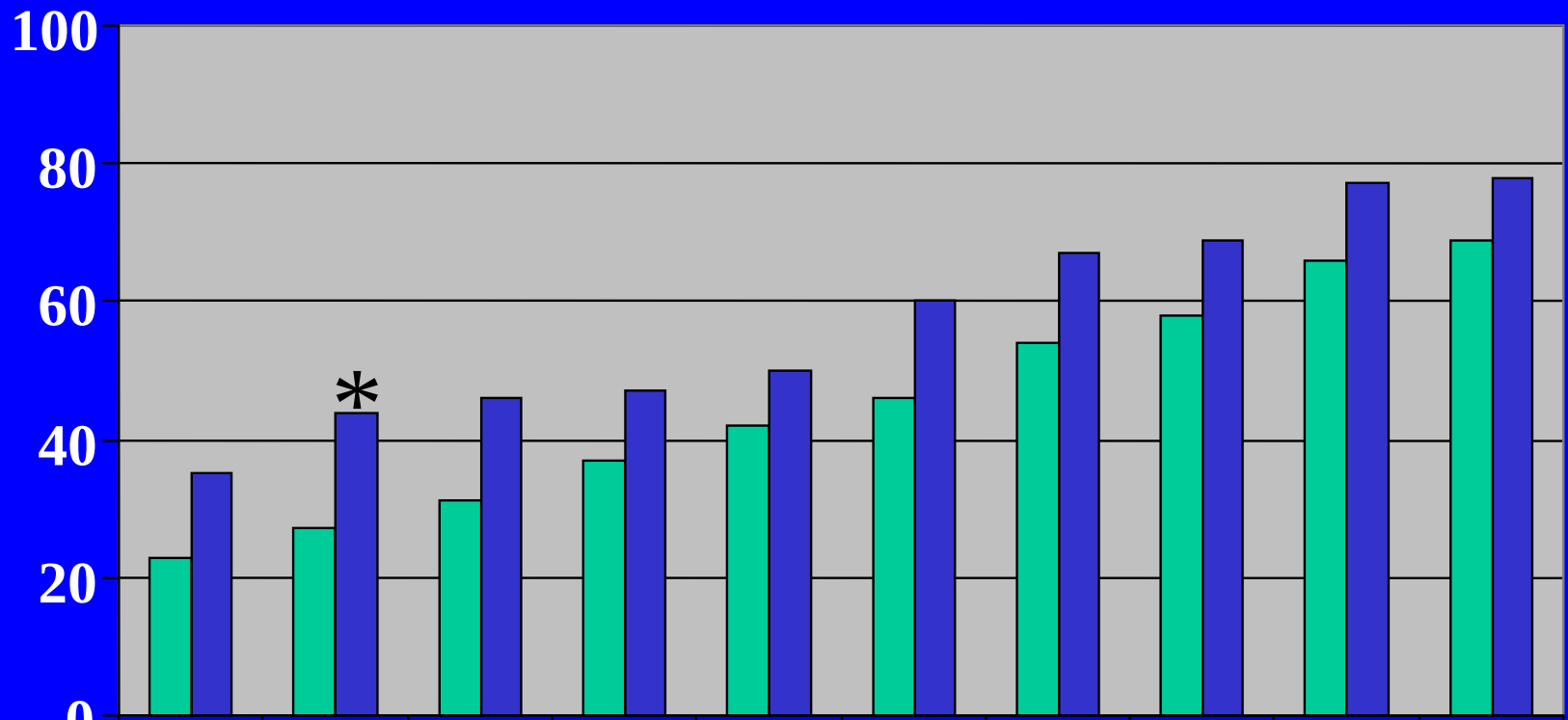
CEDIM-2
CONCOMITANT TREATMENT



PRIMARY END-POINT (mortality and HF)

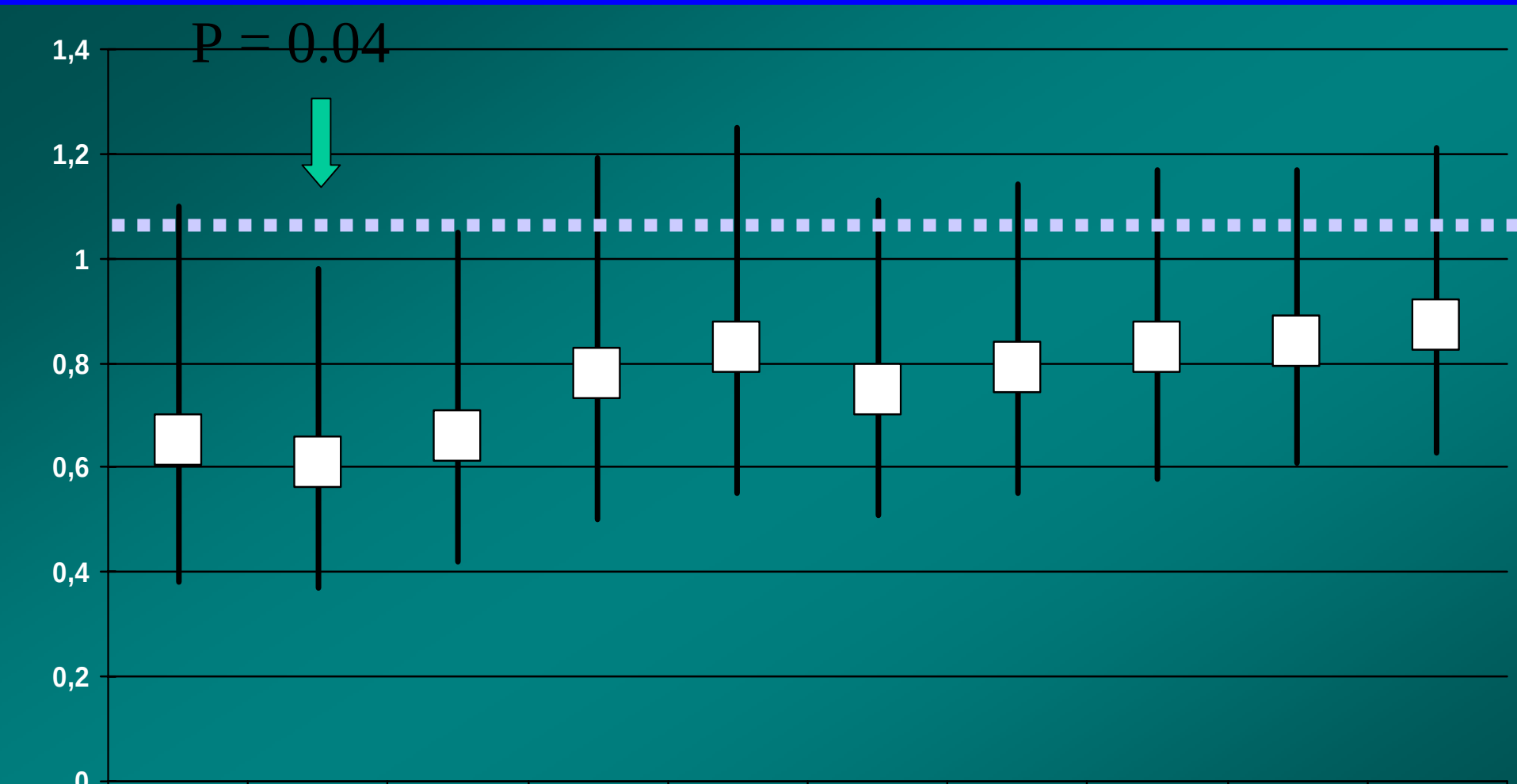


Cumulative Number of deaths

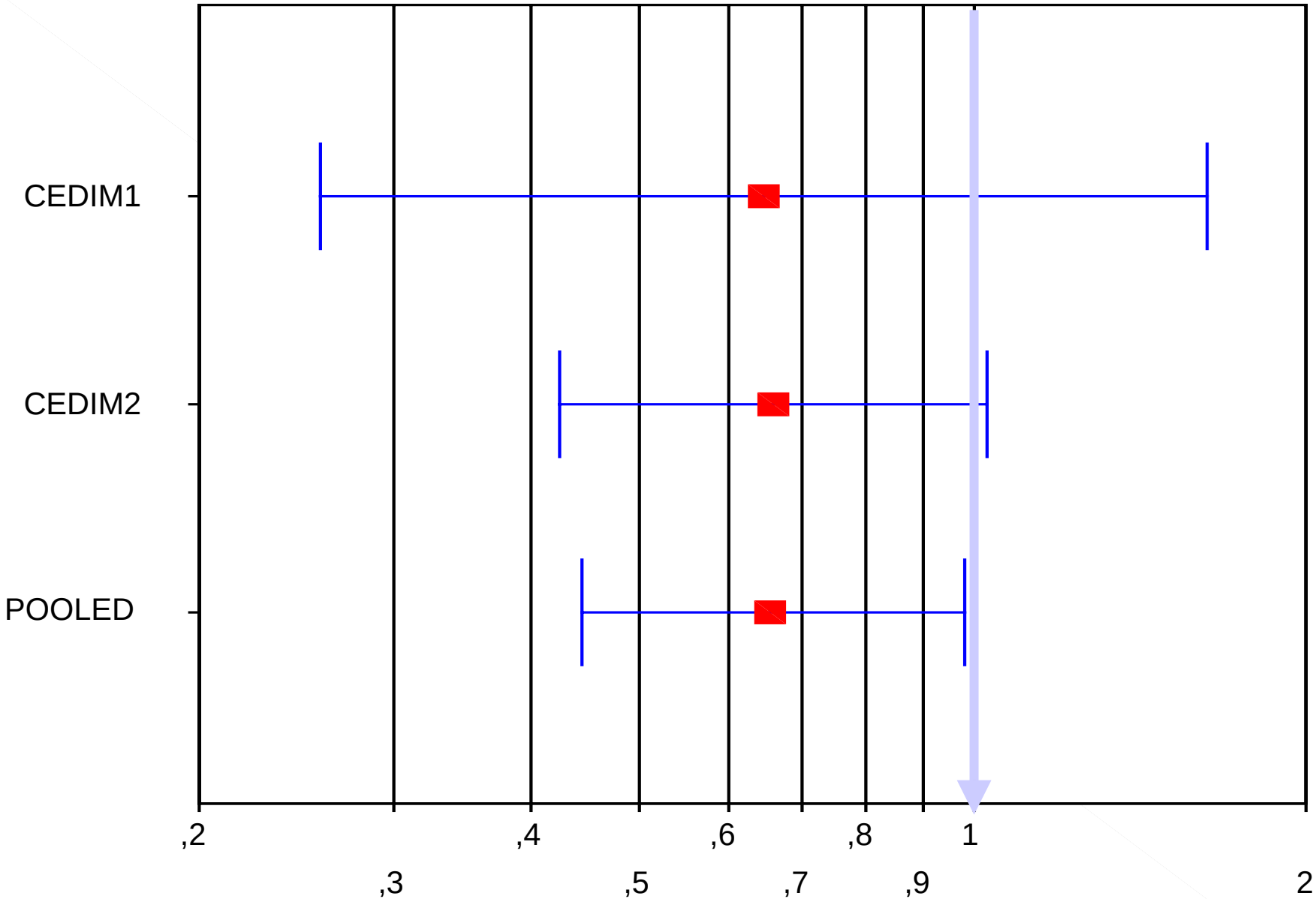


	3	5	7	10	15	30	60	90	180	365
Carnitine	23	27	31	37	42	46	54	58	66	69
Placebo	35	44	46	47	50	60	67	69	77	78

Relative Risk (of death)



	3	5	7	10	15	30	60	90	180	365
High	1,1	0,98	1,05	1,19	1,25	1,11	1,14	1,17	1,17	1,21
Low	0,38	0,37	0,42	0,5	0,55	0,51	0,55	0,58	0,61	0,63
Close	0,65	0,61	0,66	0,78	0,83	0,75	0,79	0,83	0,84	0,87



DAY 7

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*

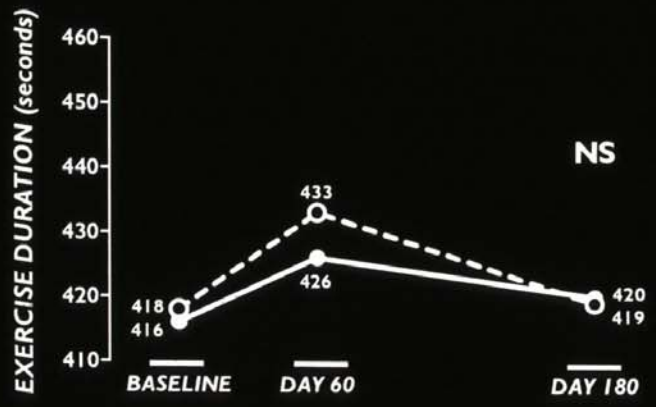
- **Propionyl-L-Carnitine has been shown to:**
  - ***improve cardiac muscle function in several experimental models of heart failure***
  - ***improve maximal walking distance in patients with peripheral arterial disease*** *(9 parallel, randomized, double-blind studies; 1406 patients totally, in pubbl.)*
  - ***improve exercise capacity and oxygen consumption in patients with heart failure*** *(double-blind, placebo controlled study in 80 pts, European Heart J, 1995 and parallel study in 20 pts, Cardiovasc. Drugs & Ther, 1996)*
  - ***improve exercise capacity of CAD patients*** *(double-blind study, in 32 patients, Am J Cardiol, 1994)*

Propionyl-L-Carnitine in Chronic Heart Failure

❶	type of study:	*phase-III, double-blind, randomized, parallel, multicentre, comparing Propionyl-L-Carnitine and placebo*
❷	primary end-point:	*maximum exercise duration at day 180*
❸	study design:	▪ *14 days run-in with placebo* ▪ *6 months randomized double-blind treatment period* ▪ *evaluation at 2 and 6 months*
❹	study population:	▪ *NYHA class II or III; EF <40%* ▪ *under stable mandatory therapy with ACE-inhibitors and diuretics, with or without digitalis*
❺	centres involved:	*49 centres in 8 European countries*
❻	study duration:	*29 months*

— Primary Endpoint - Maximal Exercise Duration —

INTENTION TO TREAT ANALYSIS
(n = 537)



MEAN CHANGES FROM BASELINE
(mean of percent changes)

--○-- PLACEBO = 1.0 sec (0.6 %); N = 266

—●— PLC = 4.0 sec (1.9 %); N = 271

EFFICACY ANALYSIS
(n = 353)

MEAN CHANGES FROM BASELINE
(mean of percent changes)

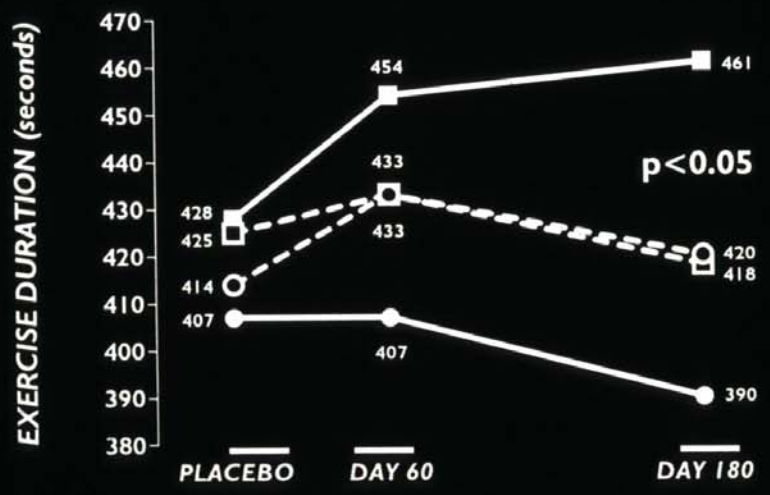
--○-- PLACEBO = 12.8 sec (4.0 %); N = 165

—●— 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

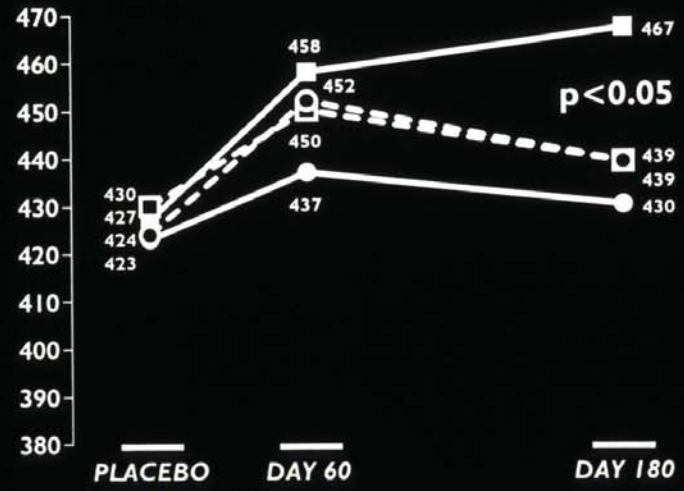


MEAN CHANGES FROM BASELINE
(mean of percent changes)

- 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

EFFICACY ANALYSIS (*n = 353*)

Interaction Test: p<0.05
EF ↑30% p<0.05
EF ↓ 30% NS

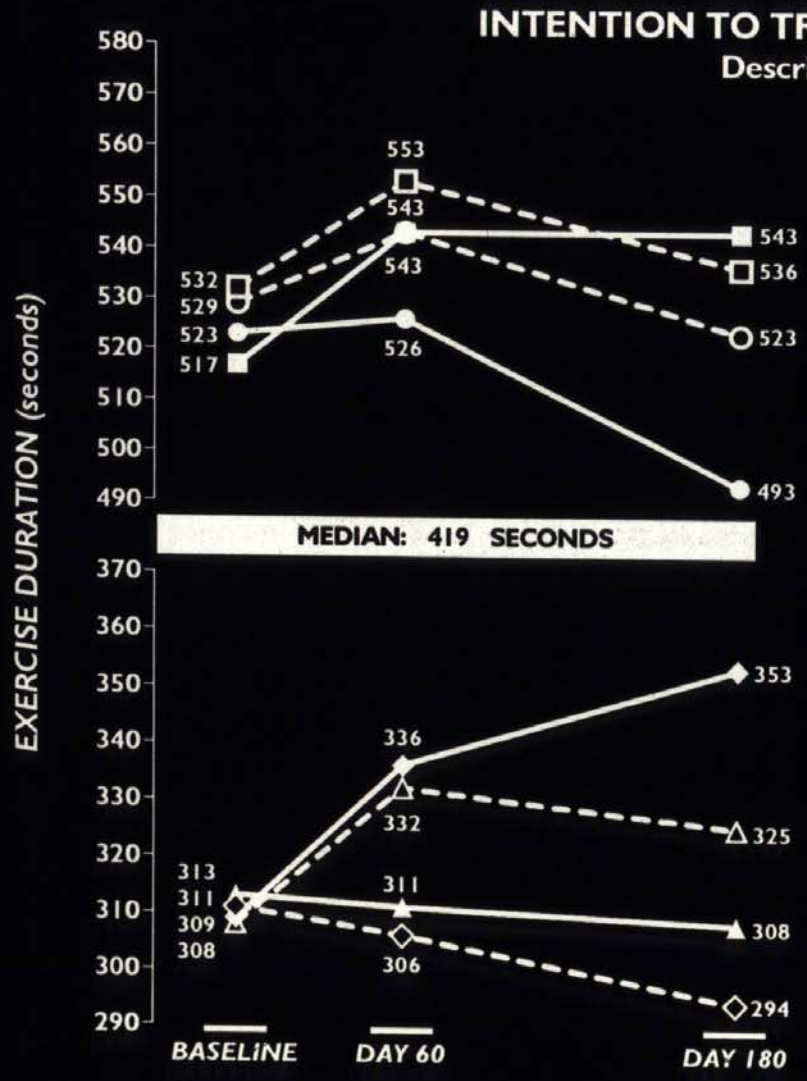


MEAN CHANGES FROM BASELINE
(mean of percent changes)

- 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)



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)

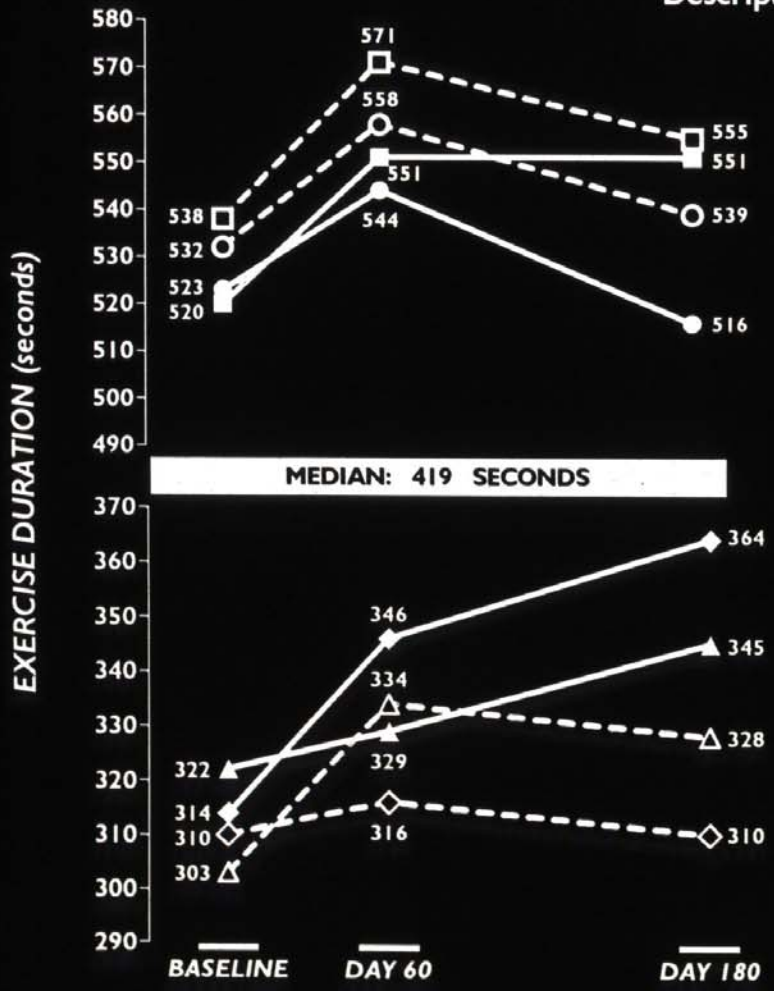
- PLACEBO (↓419 sec; EF↑ 30%) = -17.6 sec (-5.0 %); N = 48
- PLC (↓419 sec; EF↑ 30%) = 42.9 sec (14.5 %); N = 48
- PLACEBO (↓419 sec; EF↓ 30%) = 16.1 sec (5.4 %); N = 87
- PLC (↓419 sec; EF↓ 30%) = -5.4 sec (-1.3 %); N = 88

— 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

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