

L-CARNITINE IN CARADIOGENIC SHOCK THERAPY: PHARMACODYNAMIC ASPECTS AND CLINICAL DATA

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Summary: *Following our previous work on biochemical and clinical aspects of cardiogenic shock, we carried out an open study on 27 patients hospitalized in shock condition and investigated for the entire period of permanence in intensive care units (ICU). The subjects were treated with high doses of L-carnitine following previous results on the use of this molecule in conditions of oxidative damage due to acute cellular hypoxia. When compared with the data reported in the literature, the results obtained in this study show a surprisingly positive trend for the carnitine-treated patients in terms of survival rate to the cardiogenic shock. This finding and statistical analysis of the clinical parameters confirm the suggestion that L-carnitine could be credited with a new and interesting role in the therapy of cardiogenic shock.*

Introduction

Cardiogenic shock is clinically defined as a state of severe tissue hypoperfusion resulting from underlying pump dysfunction; autopsy generally evidences necrosis of more than 40% of the left ventricular mass. Common patterns are those of either a small myocardial infarction superimposed on extensive previous damage, or a large anterior myocardial infarction with ongoing extension (1).

The shock evolves in two phases, of which the first is extracellular (circulatory alterations), and this is followed by the intracellular stage (metabolic alterations), which includes all of the modifications of the intracellular regulation of the enzymatic reactions. All of these alterations, along with the

metabolic derangements (end-organ hypoperfusion, acidosis, hypoxaemia etc.) further impair heart function, triggering a vicious circle.

Carnitine plays a crucial role in energy production and utilization at the cellular level, and it is heavily involved in myocardial ischaemia as well as in shock. In both pathological conditions it has been shown that a deficiency of free carnitine occurs (2, 3); furthermore, its administration improves the survival rate of animals with experimental shock, as well as restoring energetic metabolism and improving haemodynamic performance in experimental ischaemia.

Preliminary data exist on the use of L-carnitine in the treatment of patients in shock. Some workers had shown how 4 g of L-carnitine i.v. administered as a single bolus to patients in circulatory shock exerted a significant protective action on the cytochrome oxidase during the initial phases of shock (4). Other authors reported a significant decrease in

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lactacidaemia already evident only an hour after administration of 2 g of L-carnitine i.v. to patients with serious metabolic acidosis hospitalized in an intensive care unit (ICU) in a state of hypovolaemic shock (5). Lastly, an unexpected and statistically significant reduction was observed in the mortality rate for patients treated with L-carnitine in a recent multicentre trial carried out on 136 patients admitted to ICU with initial cardiogenic shock often due to AMI (6), the aim being to compare the effects on acidosis of L-carnitine and of bicarbonate and consequently the treatment and blood gas determinations were limited to the first 24 hours. This suggested that such a result could be attributed to the ability of L-carnitine to reduce the metabolic damage induced by ischaemia and reperfusion on the myocardial cells, through reactivation of a mitochondrial enzymatic mechanism devoted to energy production and utilization.

On this basis, we decided to carry out a pilot open study administering high dose of L-carnitine for the entire duration of the state of cardiogenic shock in patients with acute myocardial infarction, evaluating the effects of the drug from the results of the metabolic haemodynamic and blood gas parameters, even if the statistical analysis of the survival rate to cardiogenic shock represented the point of major interest of the study.

Materials and methods

27 patients, hospitalized in the Cagliari Intensive Care Unit for acute myocardial infarction (AMI), were admitted to the trial according to precise inclusion criteria (ascertained AMI, systolic arterial pressure <80 mm Hg, urine output <60 ml/h, progressive severe acidosis, altered mental status, signs of low peripheral perfusion). In association of the standard treatment, the patients received an i.v. bolus of 4 g of L-carnitine (Sigma-Tau, Pomezia, Italy) followed by a continuous infusion of 6 g/day of the drug for the entire duration of the

shock condition. Over this period, the patient condition was carefully evaluated by determination of haemodynamic (by means of Swan-Ganz catheter), blood gas analytical and biochemical parameters.

Results

The data obtained in this trial, summarized in Table I and Figs. 1 and 2, confirm the results of previous studies, by showing that L-carnitine administration was able to improve the patients' condition. This is evident from the statistical analysis of the results obtained in patients treated with L-carnitine, whose survival rate from cardiogenic shock, assessed over a period of 10 days in the ICU, is equal to 77.8%, whilst data reported in the literature regarding patients who were not treated with the molecule generally show a survival rate of 25–30% (6–16). Analysis of the trend of the evaluated parameters shows that the modifications of haemodynamic and of biochemical/gas-analytical measurements are parallel, highlighting that the therapeutic effect of L-carnitine is in direct relationship to the metabolic properties of the drug, i.e. to its ability to counteract the life-threatening con-

Table I Absolute and percent cumulative frequencies of survivor patients ($n = 21$) among the L-carnitine-treated patients ($n = 27$)

Times of evaluations	Survivor patients	
	Abs. freq	% Cum. freq
Baseline	–	
24 hours	0	0.0%
2 days	2	7.4%
3 days	2	7.4%
4 days	10	37.0%
5 days	11	40.7%
6 days	14	51.8%
7 days	14	51.8%
8 days	17	63.0%
9 days	17	63.0%
10 days	21	77.8%

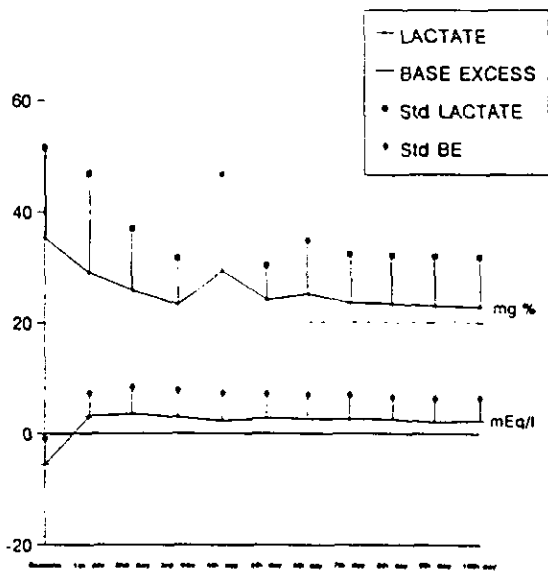


Fig. 1 Metabolic parameters evaluated in cardiogenic shock. Abbreviations: standard lactate, standard base excess

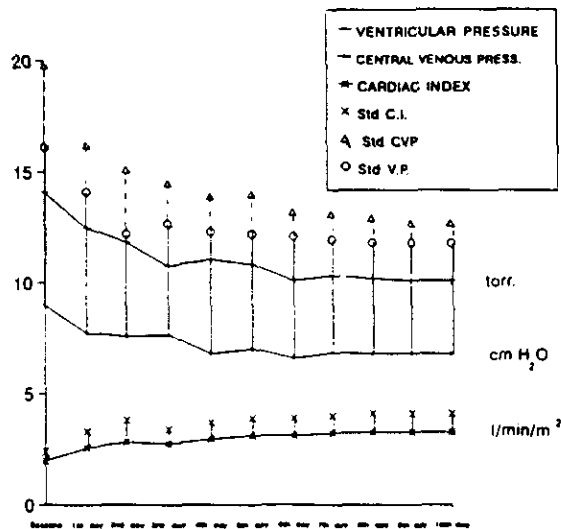


Fig. 2 Clinical aspects evaluated in cardiogenic shock. Abbreviations: standard cardiac index, standard venous pressure, standard ventricular pressure

sequences of acute ischaemia, maintaining energy levels compatible with the survival of myocardial cells.

Discussion

Some authors have reported that in the initial phase of experimental shock the most evident metabolic alteration is represented by the inhibition of transport mechanisms across the inner mitochondrial membrane, as demonstrated by the increase in the lactate/pyruvate ratio which reflects that of the NADH/NAD⁺ ratio (2-7). The initial metabolic responses to shock-induced stimuli (gluconeogenesis in particular) are quickly followed by exhaustion and biochemical cellular disorganization which subsequently turn into functional and organic insufficiency.

A progressive reduction in free carnitine content was found (while the acetyl-CoA and acetyl-carnitine both increase) along with inhibition of the passage of the acylCoAs inside the mitochondria and their subsequent oxidation, an increase of them in the cytoplasmic space, and diminished ATP production. The accumulated acyl-CoAs antagonize the adenine-nucleotide-translocase of the mitochondrial membrane and the Na-K-ATPase of the cytoplasmic membrane. The inhibition of the ATP/ADP exchange provokes a deterioration in cellular function associated with lower availability of ATP, the blockage of the ionic pump can give rise to facilitated transmembranal exchange with release of potassium from the cell and an intracellular accumulation of sodium.

The accumulation of acetyl-CoA still has a consequent depression of pyruvic dehydrogenase activity, with a resulting shift of the lactate/pyruvate balance towards the former; it therefore accumulates intra- and extra-cellularly, leading to an acidotic state which causes the inhibition of the gluconeogenesis, and has further negative effects including negative inotropic action, peripheral venous con-

striction with diversion of blood volume towards the central compartment, pulmonary vascular alterations (shock lung), and inhibition of the liver utilization of lactate (8).

The effects of ischaemia at the cellular level are very similar: the ischaemic event causes an increase in blood free fatty acids (FFAs), leading to an increase in the oxygen requirement for their metabolism, and at the same time an increase in their esters in the myocardium (both as acyl-CoA and acyl-carnitine). An increase in the acyl-CoA/CoA ratio, a reduction in ATP synthesis and ADP/ATP exchange (due to inhibition of the mitochondrial adenine-nucleotide-translocase), and myocardial damage aggravated by an increased need for oxygen (9), rapidly follow. At the same time a deficiency of free carnitine develops, due both to its loss by the cells and to its esterification (3). On autopsy of patients whose death was attributable to AMI, some authors found a significant carnitine deficiency in the necrotic area of the heart and a reduction in the peri-infarctual area (10). Administration of L-carnitine in experimental ischaemia is able to increase myocardial levels of free carnitine and to decrease those of long-chain acyl-CoA esters, to restore adenine nucleotide translocase activity, significantly increasing the reduced high-energy phosphate levels; the metabolic modifications are accompanied by the reduction of ischaemic ECG changes and the improvement of haemodynamic performance (11–14).

The utilization of L-carnitine in the treatment of AMI patients evidenced its ability to decrease the extension of the infarctual area, as shown by the reduction in the time and entity of MB-CK release (15) and by the reduction of the drop in the ECG voltage especially in patients with anterior infarction (16), and to reduce the incidence of arrhythmias (17, 18) with increased urinary excretion of fatty acids in the form of carnitine esters.

Thus, it could be hypothesized that the administration of L-carnitine for the entire period of shock

state, and above all in the initial reversible stage of the syndrome, by counteracting the metabolic derangements induced by acute ischaemia, prevents the occurrence of the vicious circle which through further impairment of heart function leads to the irreversible phase of cardiogenic shock.

Further studies, to be carried out according to a randomized controlled design, must be planned to confirm the encouraging results of the present trial.

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