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Acute myocardial ischaemia induces cardiac carnitine release in man

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In animal studies, prolonged periods of ischaemia decrease the cardiac carnitine content. However, whether in humans the heart loses carnitine during short-term ischaemia, and whether this is related to ischaemia-induced cardiac dysfunction, is as yet unknown. Carnitine kinetics were investigated in 28 normotensive patients with significant left coronary artery disease, during and after incremental atrial pacing. To evaluate carnitine kinetics from the ischaemic area, patients were grouped as those with (n=22) or without (n=6) myocardial lactate production. Atrial pacing resulted in a comparable maximal heart rate and ST depression in both groups. Carnitine kinetics did not change in those without lactate production. In contrast, coronary venous free carnitine levels increased significantly by 9% during pacing in those with lactate production. Cardiac free carnitine balance changed from uptake (255 ± 107 pmol . min^{-1}, mean ± SEM) to release (-150 ± 66 pmol . min^{-1}) at 30 min after pacing in the group with lactate production. Arterial and coronary venous differences in free carnitine were significantly correlated with myocardial lactate extraction immediately after pacing. The change in coronary venous free carnitine was significantly correlated with the change in left ventricular ejection fraction at 10 min after pacing. Thus, in patients with coronary artery disease, short-term mild myocardial ischaemia results in significant cardiac free carnitine loss. **(Eur Heart J 1997; 18: 84–90)**

Key Words: L-carnitine, myocardial ischaemia, humans.

Introduction

L-Carnitine plays a pivotal role in fatty acid metabolism, the major source of myocardial energy production[1]. L-Carnitine not only mediates the transport of long-chain fatty acid from the cytosol to the mitochondrial matrix, but, in addition, regulates mitochondrial ATP/ADP exchange, and the flux of pyruvate into the citric acid cycle[2,3]. As L-carnitine is synthesized by liver, kidney and brain, but not by the heart, the latter relies on an external supply of L-carnitine. Cellular membrane transport of carnitine is a slow process, probably mediated by a carnitine/deoxycarnitine exchange mechanism[4].

During brief periods of mild myocardial ischaemia in animals, cardiac tissue levels of free carnitine decline, whereas the acetylcarnitine content of the heart increases, the total amount of carnitine remaining unaltered[5]. However, prolonged periods of myocardial ischaemia decrease cardiac carnitine content.

L-Carnitine deficiency aggravates the detrimental metabolic changes induced by ischaemia as a result of increased accumulation of intermediates of fatty acid metabolism. Increasing evidence suggests that administration of L-carnitine may reverse some of the metabolic changes following myocardial ischaemia, probably through its buffering capacity for acyl-CoA esters[6–8].

In humans, a 70% reduction in cardiac carnitine content following myocardial infarction has been reported[9]. However, whether in humans the heart already loses carnitine during mild or short-term periods of ischaemia, is as yet unknown. In the present study, we investigated myocardial carnitine kinetics during pacing-induced myocardial ischaemia in man. Secondly, we studied the temporal relationship between changes in carnitine and cardiac function during ischaemia.

Methods

Patients

In this study, 28 normotensive patients (27 men and one woman), aged 46 to 73 years (mean 59 years) with exercise-induced ischaemia were included. All patients gave informed consent according to the rules of the local Ethical Review Board. Patients with unstable angina, arterial hypertension (systolic pressure >200 mmHg, diastolic pressure >100 mmHg), symptoms or signs of congestive heart failure, atrioventricular conduction disturbances, valvular heart disease, diabetes mellitus, and

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renal or hepatic dysfunction, were excluded. Previous myocardial infarctions had to be at least 1 month old. All cardiac medication was withheld 24 to 72 h before the investigations. Only short-lasting nitroglycerin was allowed until 6 h pre-study. To participate, patients had to have at least one diameter stenosis of >70% in either the left anterior descending artery, a diagonal branch, the proximal part of the left circumflex artery or a proximal marginal branch. In addition, patients had to have objective signs of myocardial ischaemia, i.e. ST-segment depression and/or myocardial lactate production during subsequent incremental atrial pacing.

Instrumentation

Studies were conducted in the morning, after an overnight fast, without premedication. First, left and right coronary angiography was performed, using the Seldinger technique. If the patients then met the inclusion criteria, instrumentation for the study was carried out. A no. 7 Fr thermodilution pacing catheter (Wilton Webster Laboratories, Baldwinpark, CA, U.S.A.) was positioned in the mid portion of the coronary sinus via a brachial vein, such that its position was stable, blood could be drawn easily, and the proximal thermistor was at least 3 cm beyond the orifice of the coronary sinus. The absence of atrial reflux was confirmed by a bolus injection of saline at room temperature in the right atrium. Next, a no. 7 Fr balloon-tipped triple-lumen thermodilution catheter was advanced into a pulmonary artery through a Desilet introducer system in the right femoral vein. Care was taken that the catheter tip was stable without baseline drift on the thermodilution signal. Finally, a no. 8 Fr Sentron pigtail microtip manometer catheter was positioned in the left ventricle through a no. 9 Fr Desilet introducer in the right femoral artery. The side arm of this system was used to monitor arterial pressures. The position of the catheters was recorded on video tape and regularly checked throughout the study.

Haemodynamic and electrocardiographic measurements

All fluid-filled catheters were calibrated using a zero reference level set at mid chest. Pressures in the right atrium, and the femoral and pulmonary arteries were measured using Bentley transducers (Baxter–Bentley, Uden, The Netherlands). The microtip manometer pressure curve was superimposed on the conventional pressure tracing. All pressures and the first derivative of left ventricular pressure were recorded on paper at different paper speeds, i.e. at 10, 25 and 100 mm . s^{-1}, using a CGR 1000 cath lab system. Throughout the study, pressure-derived contractility (V_{max}) was determined on-line by a Mennen Cath lab computer system. In a beat-to-beat analysis this system averages 15 to 20 consecutive beats to level out respiratory variations. Coronary sinus blood flow was determined during a continuous 30–45 s infusion of 50 ml of glucose 5% at room temperature[10]. Electrocardiographic leads I, II and V_5 were continuously monitored for heart rate, and to determine the ST-segment level. The latter was measured by using a calibrated magnifying lens, in five consecutive beats, 0·08 s after the J-point, at paper speed of 100 mm . s^{-1}.

Scintigraphic measurements

During the study, nuclear angiography was performed using an in vivo labelling technique of erythrocytes with 1000 MBq pertechnetate. Imaging was carried out with a mobile LEM gamma camera (Siemens), equipped with a low-energy, all purpose collimator, and connected on-line with a mobile MCS/560 nuclear computer system (General Electric). A 35 to 40° left anterior oblique projection with a 10° cranial tilt was used to achieve an optimal separation of the left and right ventricle. The calculation of the left ventricular ejection was carried out with a Sophy P computer (Sopha Medical, Brussels, Belgium), using methods described by Magorien *et al.*[11].

Metabolic measurements

Blood sampling for metabolite determination was carried out simultaneously from the left ventricle and the coronary sinus. Oxygen saturation was measured using an OSM-80 oximeter (Waters Associates, Portanje, Utrecht, The Netherlands). For the analysis of lactate, exactly 1 ml of blood was sampled in 2 ml of ice-cold 0·6 M perchloric acid, and analysed as reported previously[12]. For the analysis of free and total L-carnitine, 2 ml of blood was collected in pre-cooled tubes containing 500 IU heparin. Free L-carnitine was determined by radio-enzymatic assay (SD=0·8 μmol . l^{-1}). and total L-carnitine, after hydrolysis by 0·1 M potassium hydroxide and neutralization with 0·5 M HEPES (N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]), was determined by a similar radio-enzymatic assay (SD=1·0 μmol . l^{-1})[13].

Study protocol

After positioning of the catheters, a stabilization period of at least 20 min was allowed to achieve a minimal interval of 45 min between coronary angiography and the study. Subsequently, multiple control determinations of all haemodynamic variables were carried out to ensure stable baseline values, and simultaneous arterial and coronary venous blood was sampled for metabolic measurements. Next, atrial pacing stress test was carried out with increments in heart rate of 10 beats per 2 min, until angina or atrioventricular block occurred, or a maximal heart rate of 170 beats . min^{-1} was reached. Repeat determinations of all haemodynamic parameters were carried out at maximal pacing and at 15 s, 1, 10 and

Table 1 Patients' characteristics

	LP	NLP
Number	22	6
Sex	22 male	5 male, 1 female
Age (years)	59 ± 2	57 ± 1
Previous myocardial infarction	17*	2
Anterior	7	0
Inferior	9	0
Non-Q	3	2
Number of vessels diseased		
One vessel	7	2
Two vessels	6	2
Three vessels	9	2
LVEF (%)	43 ± 3	55 ± 4
LVEDV (ml . m^{-2})	71 ± 5	61 ± 5

LP=patients with lactate production; LVEDV=left ventricular end-diastolic volume; LVEF=left ventricular ejection fraction; NLP=patients without lactate production: *P<0·05 LP vs NLP. Values are mean ± SEM.

30 min post-pacing. Nuclear angiography and simultaneous arterial and coronary venous blood sampling for metabolic measurements was performed at control, at maximal pacing heart rate, and at 1, 10 and 30 min after pacing.

Data analysis

The statistical analysis consisted of a t-test for paired observations and an analysis of variance (ANOVA) to differentiate between-group differences at the respective time points. The patients' baseline characteristics were analysed by using a Fisher's exact test. The correlation of the arterial and coronary venous differences in free carnitine with metabolic and haemodynamic parameters was examined using linear regression analysis. The statistical analysis was performed using SAS statistical software, and a two-tailed P-value <0·05 was indicative of a significant difference. The data are expressed as mean ± SEM.

Results

All patients had objective signs of myocardial ischaemia during atrial pacing. To differentiate between cardiac carnitine changes in ischaemic vs non-ischaemic myocardium, the patients were subdivided in two groups, one with (LP, n=22) and one without (NLP, n=6) myocardial lactate production. The clinical and angiographic characteristics of both groups are presented in Table 1. Groups were comparable except for the number of previous myocardial infarctions, which was higher in patients with lactate production than in those without lactate production.

At baseline, myocardial lactate extraction was similar in all groups (Table 2). By design, in the NLP group, myocardial lactate extraction remained unchanged throughout the study. In contrast, myocardial lactate extraction changed to release in the LP group at maximal pacing and during the first minute after pacing. However, during atrial pacing, ST-segment depression

Table 2 Haemodynamic and electrocardiographic variables

		Control	Maximal	15 s p-p	1 min p-p	10 min p-p	30 min p-p
HR (min^{-1})	LP	73 ± 2	143 ± 4*	75 ± 3	75 ± 3	75 ± 2	73 ± 2
	NLP	69 ± 5	150 ± 8*	78 ± 7	80 ± 6	75 ± 6	73 ± 6
RPP (10^3 mmHg . min^{-1})	LP	10 ± 0·4	21 ± 0·8*	11 ± 0·7	11 ± 0·6*	11 ± 0·5	11 ± 0·4
	NLP	11 ± 1·1	22 ± 1·5*	13 ± 1·9	13 ± 1·1*†	12 ± 1·2*†	12 ± 1·3*
V_{max} (s^{-1})	LP	47 ± 2	57 ± 3*		48 ± 3	45 ± 2*	45 ± 2*
	NLP	44 ± 2	62 ± 4*†		46 ± 3	45 ± 2	44 ± 3
MAP (mmHg)	LP	99 ± 3	113 ± 4*	103 ± 4	104 ± 3*	102 ± 3	104 ± 3
	NLP	110 ± 8	124 ± 5*	113 ± 8	115 ± 9	113 ± 9	112 ± 9
MVO_2 (ml . min^{-1})	LP	18 ± 2	27 ± 3*			16 ± 2	16 ± 2
	NLP	19 ± 6	25 ± 5*			16 ± 3	15 ± 2
CSBF (ml . min^{-1})	LP	125 ± 11	191 ± 16*			122 ± 11	113 ± 10*
	NLP	143 ± 36	198 ± 33*			125 ± 19	113 ± 18
ST (mV)	LP	0·03 ± 0·01	0·21 ± 0·05*		0·12 ± 0·02*	0·04 ± 0·01	0·03 ± 0·01
	NLP	0·06 ± 0·02	0·25 ± 0·07*		0·13 ± 0·03*	0·07 ± 0·04	0·07 ± 0·04
LVEDP (mmHg)	LP	14 ± 1	12 ± 2	25 ± 2*	18 ± 2*	14 ± 1	13 ± 1*
	NLP	11 ± 2	6 ± 2	16 ± 2*	12 ± 3	11 ± 2	11 ± 3
LVEF (%)	LP	43 ± 3	38 ± 3		44 ± 3	40 ± 3	42 ± 3
	NLP	55 ± 4	62 ± 6*†		56 ± 4	54 ± 3	51 ± 3
L ext (%)	LP	22 ± 3	− 3 ± 6*†	− 51 ± 13*†	− 22 ± 9*†	21 ± 3	17 ± 3
	NLP	21 ± 6	18 ± 5	22 ± 6	28 ± 6	21 ± 11	23 ± 8

CSBF=coronary sinus blood flow; HR=heart rate; L ext=myocardial lactate extraction; LP=patients with lactate production; LVEDP=left ventricular end-diastolic pressure; LVEF=left ventricular ejection fraction; MAP=mean arterial pressure; MVO_2=myocardial oxygen consumption; NLP=patients without lactate production; p-p=post-pacing; RPP=rate-pressure product; ST=ST-segment depression; V_{max}=contractility variable; *P<0·05 vs control; †P<0·05 pacing-induced change vs pacing-induced change in group LP; Values are mean ± SEM.

was similar in LP (0·21 ± 0·05 mV) and NLP (0·25 ± 0·07 mV).

Haemodynamic parameters

Atrial pacing resulted in a significant 95% and 96% increase in heart rate and rate-pressure product, a measure for myocardial oxygen demand, respectively, in the LP group (Table 2). During pacing, contractility increased significantly, as indicated by a 21% increase in Vmax. These changes in myocardial oxygen demand resulted in a 50% and a 56% increase in myocardial oxygen consumption and coronary blood flow, respectively, in the LP group. In this group, mean arterial pressure increased by 14% during pacing. Moreover, immediately after pacing, left ventricular end-diastolic pressure increased by 78% as a result of the pacing-induced myocardial ischaemia. In the NLP group similar changes occurred during and after pacing, except for Vmax and left ventricular ejection fraction, which increased significantly more during pacing in the NLP group than in the LP group.

Myocardial carnitine kinase

The arterial and coronary venous levels of total carnitine [48 ± 1 and 47 ± 1 μM (LP), 47 ± 2 and 47 ± 2 μM (NLP), respectively], observed at baseline, remained unchanged throughout the study. As a consequence, cardiac total carnitine uptake did not change in either group. Moreover, arterial free carnitine levels did not change during pacing in either group or after pacing in the NLP group. However, a small 5% and 4% decrease occurred at 10 and 30 min after pacing, respectively, in the LP group (Fig. 1). Coronary venous free carnitine levels increased from 34·4 ± 1·3 μmol . l^{-1} at control to 36·9 ± 1·5 μmol . l^{-1} at maximal pacing in the LP group ($P<0·05$). This increase was maintained after pacing and lasted until the end of the study at 30 min after pacing. As a result, myocardial free carnitine uptake (255 ± 107 pmol . min^{-1}) at control changed towards a sustained release pattern, with a peak value of free carnitine loss of − 150 ± 66 pmol . min^{-1} at 30 min after pacing in the LP group (Fig. 2). The difference in arterial and coronary venous free carnitine levels at 1 and 10 min after pacing were significantly correlated with myocardial lactate production at 15 s after pacing (r=0·49 and r=0·45 respectively) (Fig. 3). Moreover, the change from baseline of the difference in arterial and coronary venous free carnitine levels at 1 min after pacing was also significantly correlated with myocardial lactate production 15 s after pacing (r=0·42). No significant correlations were present between arterial and coronary venous levels of free carnitine and change in haemodynamic parameters during pacing or early after pacing. In contrast, the changes from baseline of coronary venous free carnitine 10 min after pacing were significantly correlated with the change from baseline of left ventricular ejection fraction 10 min after pacing (r= − 0·62) (Fig. 4).

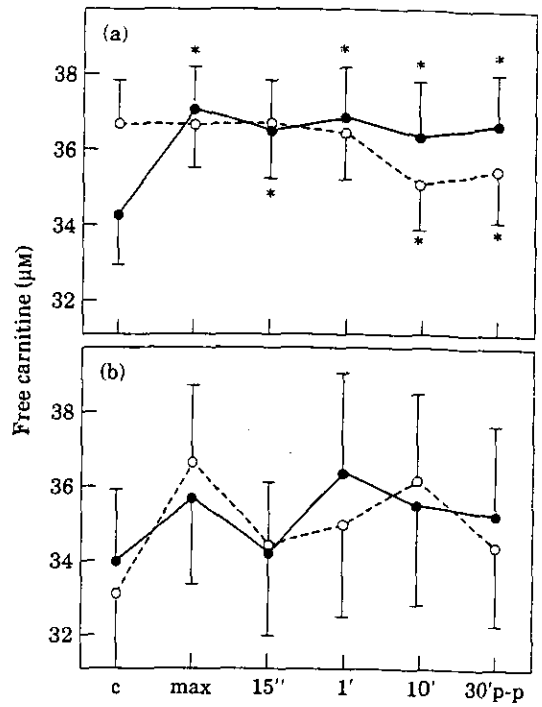

Figure 1 **Arterial (○) and coronary venous (●) free carnitine levels at control (c), maximal pacing (max), 15 s after pacing (15") and 1, 10 and 30 min after pacing (1', 10' and 30' p-p). (a) Patients with myocardial lactate production. Arterial free carnitine decreased at 10 and 30 min after pacing, and coronary venous free carnitine increased by 8% during pacing and remained at this level thereafter. (b) Patients without myocardial lactate production. Plasma levels of free carnitine remained unchanged throughout the study. Data are presented as mean ± SEM. *$P<0·05$ vs control.**

Discussion

The mild and short-term myocardial ischaemia induced by atrial pacing in this study resulted in a significant and sustained release of cardiac free L-carnitine. The most likely origin of the L-carnitine release is the ischaemic myocardium, because in the non-lactate producers, under identical ischaemic conditions but with blood most likely sampled from the non-ischaemic myocardium, no changes in L-carnitine levels were detected. Similarly, these changes in cardiac free L-carnitine uptake were not related to the level of atrial pacing or to changes in coronary sinus blood flow. The presence of myocardial lactate production was used as a marker of ischaemia in this study for several reasons. First, in the case of pacing-induced ischaemia, it is more sensitive than the three-lead ECG recordings used in this study[14]. Secondly, by selecting only patients with lactate production it was ensured that (part of) the coronary venous effluent, collected during the study, represented an ischaemic area and might allow identification of changes in carnitine kinetics from that area. Sampling from the coronary sinus has the disadvantage that admixture with venous blood from non-ischaemic areas cannot be

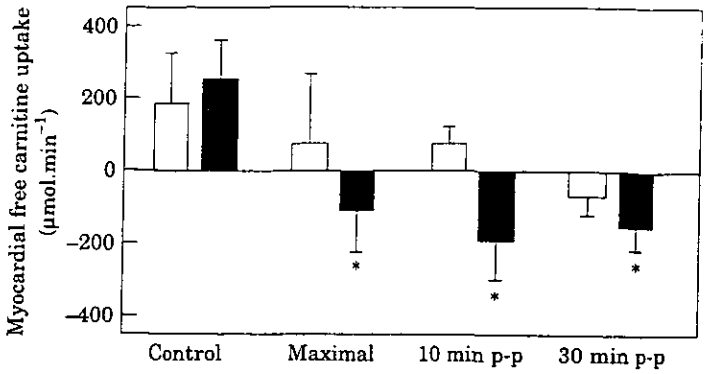

Figure 2 **Myocardial free carnitine uptake at control, at maximal pacing rates and 10 and 30 min after pacing (10 min p-p and 30 min p-p) in patients with myocardial lactate production (■), and in patients without myocardial lactate production (□). Myocardial free carnitine uptake at control changed to release during pacing and thereafter until 30 min after pacing in the group with lactate production. No such changes occurred in those without lactate production. Data are presented as mean ± SEM. *$P<0.05$ vs control.**

prevented. The latter and the variability in size of the ischaemic area in the different patients decrease the sensitivity of the study and consequently may lead to underestimation of the myocardial carnitine release. The most striking finding in this study was that cardiac free carnitine release, although moderate, already occurred following mild myocardial ischaemia, in contrast to the findings following severe ischaemia in animals[5].

Carnitine kinetics in animal studies of myocardial ischaemia

Coronary artery occlusion in dogs resulted in a 70% reduction in myocardial tissue levels of L-carnitine, one week after the event[15], but this had already begun to recover one week later. The changes in L-carnitine concentration were paralleled by an early decrease in carnitine palmityltranferase activity followed by subsequent normalization. Besides these marked changes after severe myocardial ischaemia, moderate ischaemia may induce changes in carnitine kinetics. In the open chest dog model, 10 min of myocardial ischaemia induced by a 30% reduction in coronary flow resulted in a 24% decrease in free carnitine and a 32% increase in long-chain acylcarnitine, whereas total carnitine levels remained unchanged[5]. Following more severe ischaemia, i.e. 30 min of coronary occlusion, tissue levels of free carnitine decreased by 44%, long-chain acylcarnitine increased by 38%, and total carnitine levels decreased by 7%.

In the intact, working heart in the open-chest swine model, 30 min of global ischaemia (35·7% of control flow) lead to a two-fold increase in long-chain

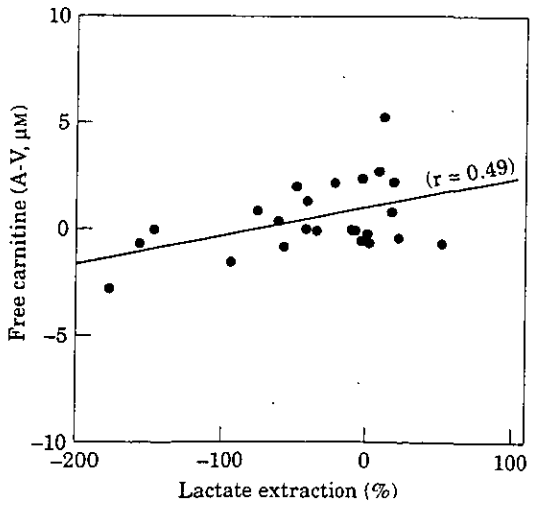

Figure 3 **Scatter plot: Correlation between myocardial lactate extraction at 15 s after pacing and the difference in arterial and coronary venous (A-V) free carnitine at 1 min after pacing.**

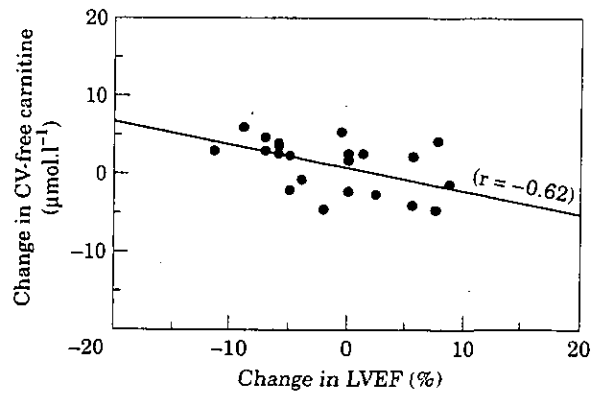

Figure 4 **Scatter plot: Correlation between the change from baseline in coronary venous (CV) free carnitine and the change from baseline in left ventricular ejection fraction (LVEF) at 10 min after pacing.**

acyl-CoA and an 18-fold increase in long-chain acylcarnitine, whereas free and acetylcarnitine decreased by 20%[16]. The addition of excess free fatty acid aggravated the observed changes.

The rapid exchange between the plasma and cardiac mitochondrial and cytosolic carnitine pools is only feasible with a quick carnitine transport mechanism. However, cell barriers are not readily permeable to carnitine. Hülsmann *et al.*[17] therefore suggested that the (acyl)carnitine pool in the interstitial spaces plays an important role during ischaemia. As soluble interstitial components, e.g. L-carnitine, may be lost during ischaemia-induced oedema, other, more lipophilic components, e.g. acylcarnitine, may adhere to cell membranes. The interstitial long-chain acylcarnitine, a cationic membranophilic molecule, may have anti-ischaemic properties, because it reduces cellular Ca^{2+} overload. The early, but sustained release of free carnitine suggests a combination of early extra-cellular and late cellular carnitine release.

Correlations between L-carnitine loss and metabolic and haemodynamic variables

The time points during which significant correlations were observed between cardiac carnitine and lactate release are of importance. At 15 s after pacing, the myocardial effluent of lactate is at its optimum and decreases rapidly thereafter[12]. The weak correlation between cardiac carnitine and lactate effluent may indicate a different release kinetics or a different origin of both metabolites.

The late correlation between the change in coronary venous free carnitine and the change in left ventricular ejection fraction may indicate that the sustained increase in coronary venous free carnitine is related to left ventricular dysfunction following myocardial ischaemia and may indicate late cellular carnitine release. However, the size of the study population in the present study may be too small to obtain clear correlations, because of the wide scatter of the carnitine measurements. As a result it is uncertain, whether there is a causal relationship between cardiac carnitine loss and post-ischaemic left ventricular dysfunction.

Effect of carnitine administration

Suppletion of carnitine can reverse the inhibition of adenine nucleotide translocase by acyl-CoA[3,5]. Moreover, administration of L-carnitine increases mitochondrial oxygen uptake after inhibition by acyl-CoA[8]. Several animal studies have reported anti-ischaemic effects of L-carnitine[7,18], and there is clinical evidence of the beneficial effects of L-carnitine administration in patients with ischaemic heart disease. Intravenous administration of 40 mg . kg^{-1} L-carnitine reduces pacing-induced myocardial ischaemia in patients with coronary artery disease[19]. The naturally occurring derivative of L-carnitine, L-propionylcarnitine also reduces myocardial ischaemia and improves the recovery of cardiac function following ischaemia in animals[20–22]. Moreover, intravenous administration of 15 mg . kg^{-1} L-propionylcarnitine prevented ischaemia-induced left ventricular dysfunction, in a pacing model similar to that used in the present study, in patients with coronary artery disease[23]. L-Propionylcarnitine may be more effective because it is more rapidly accessible to the cardiocyte and may increase the citric acid flux through newly formed propionyl-CoA[24–26].

Clinical implications

The moderate changes in carnitine metabolism during short periods of moderate myocardial ischaemia observed in this study may indicate that cardiac carnitine loss occur in situations with acute ischaemic, metabolic stress and that these changes are rapid but sustained. Moreover, during severe ischaemia or following myocardial infarction, cardiac carnitine content is markedly reduced[5,9]. Several studies reported that suppletion with L-carnitine or its derivative L-propionylcarnitine increases cardiac carnitine content, reduces myocardial ischaemia and improves cardiac function[6–8,18,26].

The present study illustrates that changes in carnitine metabolism already take place during short-lasting periods of mild myocardial ischaemia. This may indicate that carnitine supplementation may not only be useful in severe, advanced ischaemic conditions, such as mimicked experimental ischaemia–reperfusion models or myocardial infarction in man, but also be useful in patients with transient mild myocardial ischaemia.

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