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RESEARCH ARTICLE

ROLE OF PYRUVATE, LACTATE AND L-CARNITINE SERUM LEVEL ASSAYS IN EVALUATION AND REDUCING THE GLOBAL INTRAOPERATIVE CARDIAC ISCHEMIA AMONG PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFTING

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ABSTRACT

Background: Myocardial ischemia is a metabolic phenomenon that occurs in patients undergoing open heart surgery like coronary artery bypass grafting (CABG)**.** In myocardial ischemia, secondary myocardial carnitine deficiency has been observed.
Objectives: Recording the perioperative hemodynamic changes among patients undergoing coronary artery bypass. Evaluation of the intraoperative cardiac ischemia via biochemical assessment of serum levels of Pyruvate, Lactate, L-carnitine and calculation of lactate/pyruvate ratio preoperative, intraoperative and postoperative.
Methods: A prospective case control and clinical observational study was carried out on 17 ischemic heart disease male patients undergoing elective coronary artery bypass grafting who admitted at cardiothoracic surgery department-Faculty of Medicine- Assiut University. This was in addition to 25 apparently healthy age matched males as control group. Serum levels of pyruvate and lactate were estimated using spectrophotometric methods, while serum levels of L-carnitine were estimated using ELISA assay kit.
Results: There were significant hemodynamic changes regarding the heart rate, arterial blood pressure and central venous pressure, preoperative versus one hour postoperative ($p< 0.001$). Also, there were significant lower serum pyruvate levels and higher serum lactate levels and lactate /pyruvate ratio intraoperatively when compared with the control group ($p < 0.01$) .A significant lower serum L-carnitine levels intraoperatively when compared with the control group ($p < 0.01$) and when compared with the preoperative assay levels ($p < 0.05$).There was a negative correlation between intraoperative seum L-carnitine levels versus the clamping time ($r= -0.607$, $p=0.01$).
Conclusions: The myocardial ischemia in various degrees that developed during the intraoperative phase of coronary bypass operations causes significant changes in the serum levels of pyruvate, lactate, lactate/pyruvate ratio and L-carnitine, which should be non-elevating and decreasing towards the control levels post-operatively to indicate good myocardial function with its return to aerobic metabolism with lower morbidity and mortality. Preoperative administration of L-carnitine in such group of patients is recommended as a protector against the intraopeartive cardiac ischemia.

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INTRODUCTION

Myocardial ischemia is a metabolic phenomenon that occurs in patients undergoing open heart surgery like coronary artery bypass grafting (CAPB), valvular heart surgery, vascular surgeries etc. due to stress imposed during cardiopulmonary bypass (CPB), obligatory interruption of coronary blood flow during aortic cross clamp and reperfusion after aortic cross clamp release. These effects manifest as hemodynamic instability, arrhythmias, greater use of inotropes, difficulty in weaning from CPB, use of intra-aortic balloon pump

(IABP)/ventricular assist devices (VADs). The oxygen debt imposed during CPB heralds the onset of postoperative complications in the form of increased need of inotropes, prolonged mechanical ventilation, renal/hepatic dysfunction, prolonged intensive care unit (ICU) stay and adds to the morbidity and mortality of patients (Kapoor *et al*., 2011). It is a well-known fact that tissue hypoperfusion is associated with lactic acidosis owing to anaerobic metabolism. Measurement of blood lactate levels can hence be used as a marker to assess the adequacy of tissue perfusion (Shinde *et al*., 2006). Perioperative myocardial injuries are one of the most frequent causes of morbidity and mortality after cardiac surgery, the most common etiology being the poor myocardial protection during aortic cross clamp. During aortic cross clamp progressive accumulation of lactate and intracellular acidosis are well-known phenomena, and are associated with alteration of myocardial contractile function (Raicea *et al*., 2015). Lactate is produced from pyruvate as a by-product of glucose metabolism. During typical glucose metabolism, the supply of oxygen is adequate (aerobic conditions), and plenty of NAD^+ is generated. This condition favors conversion of pyruvate to acetyl CoA in the mitochondria. Subsequent oxidation of acetyl CoA in the Krebs cycle and by electron transport in the mitochondria produces a large amount of ATP (Toffaletti, 1991). However, if oxygen is in short supply, a decrease in NAD^+ favors the conversion of pyruvate to lactate. While this process generates some NAD^+, it is far less than by aerobic metabolism (Krebs cycle and electron transport), and only a small amount of ATP is generated. Ultimately, a high ratio of NAD^+ to NADH leads to production of large amounts of ATP (Toffaletti, 1991). Once anaerobic conditions prevail, pyruvate a substrate for oxidative phosphorylation cannot be utilized, its level increases and it is diverted to the formation of lactate (Kapoor *et al*., 2011). Lactate is a crucial metabolite in the two main energy (ATP)-producing processes that power life: glycolysis and oxidative phosphorylation (OxPhos). Glycolysis, a process that occurred very early in evolution (approximately 3 billion years ago), converts glucose into two molecules of pyruvate with the concomitant generation of 2ATP. When atmospheric oxygen levels rose (1billion years ago), mitochondria developed to generate far more energy from glucose (36ATP molecules for 1 glucose molecule), although following a much more complicated process (Krebs cycle and OxPhos) (Bakker *et al*., 2013). Glycolysis and OxPhos steadily metabolize glucose when conditions are stable. Pyruvate is the molecule that links these two reactions. Because the rate of glycolysis can increase two to three orders of a magnitude faster than OxPhos, glycolysis can briefly provide far more ATP. Excess pyruvate will rapidly accumulate and is diverted to lactate in order for glycolysis to proceed. During recovery lactate is converted into pyruvate. In both directions this is catalyzed by the ubiquitous enzyme lactate dehydrogenase (LDH). Thus, when rapidly large amounts of energy are required, such as under circumstances of cellular stress, lactate serves as a critical buffer that allows glycolysis to accelerate. Cori cycle involves energy-consuming hepatic or renal gluconeogenesis to convert lactate into glucose (Bakker *et al*., 2013).

Increases in LP ratio occur in conditions of tissue hypoxia. Few studies have found out that serum LP ratio is an excellent indicator of adequacy of cellular oxygenation, has shown good correlation with postoperative outcome (Kapoor *et al*., 2011). L-Carnitine (β-hydroxy-ɤ-trimethyl-amino-butyric acid) is a crucial component of activated fatty acids transport mechanism across the mitochondrial membrane (Lango *et al*., 2001). Carnitine is the requisite carrier for transport of activated FA across the mitochondrial membrane for β-oxidation. In the absence of carnitine, β-oxidation ceases, lipid accumulates, and organ dysfunction results. In some specific conditions, such as myocardial ischemia, cardiac hypertrophy, and hemodialysis, secondary myocardial carnitine deficiency has been observed. Carnitine is an essential cofactor for fatty acid (FA) metabolism, the predominant source of ATP in the normal aerobic heart. During myocardial ischemia, FA metabolism is impaired and tissue carnitine levels are depleted. Since the heart cannot synthesize carnitine, plasma carnitine could play an important role in maintaining myocardial carnitine levels during reperfusion. It is reported that FA metabolism was significantly depressed after cardioplegic arrest in coronary bypass surgery. Al-though the precise mechanisms of the impaired FA metabolism are unclear, the carnitine deficiency also might have an important role in this abnormal metabolism after open heart surgery (Nemoto *et al*., 2004).

MATERIALS AND METHODS

Study population and matched controls

This study is a prospective case control and clinical observational study and it was carried out on 17 ischemic heart disease male patients with multiple partial or complete vessel occlusions with failure of medical therapy and failure of cardiac catheterization and stent selected as candidate for elective coronary artery bypass grafting who admitted at the department of Cardiothoracic surgery-Faculty of Medicine-Assiut University, after obtaining approval of university hospital ethics committee and informed consent from the included patients. Patients with previous cardiac surgery, ejection fraction less than 40%, requirement for inotropic drugs, L-Carnitine administration, chronic renal insufficiency (serum creatinine >1.7 mg/dl) or renal failure on dialysis or use of steroids are excluded from the study. This is in addition to 25 apparently healthy age matched males selected as control group. The study was carried out during the period from Jan. 2012 to Dec. 2012. No deaths in the studied patients and all the patients involved completed the study.

Data collection

Routine blood analysis had been done preoperative for every included patient in the form of complete blood count, liver and kidney function tests, serum sodium and potassium. Three mls venous blood was drawn from all patients (preoperative, intraoperative and 15 days postoperative) and control group which is divided into: 1 ml on plain tube for assay of L-carnitine, 2 ml on fluorinated tube for lactate and pyruvate assays, they were then centrifuged at 3500 rpm for 15 min at 4 °C and the plasma were transferred into 1 ml cryotubes, and stored at -80 °C for later analyses. Because erythrocytes have no mitochondria, lactate is the normal product of glucose

metabolism in red cells, and lactate increases rapidly in whole blood after collection. With no glycolytic inhibitors present in whole blood at room temperature, lactate increases by 0.3-0.5 mmol/L (a 30-50% increase) in only 30 min. Ice storage slows this increase to about 0.05 mmol/L in 30 min, while fluoride/oxalate slows the increase to about 0.1 mmol/L in 30 min at room temperature (Astles *et al*., 1994).

A.Using commercially available assay kit according to manufacturer protocol for measurements of:

1. L-Carnitine (Catalog No.: WH-1775 WEKA MED supplies corp. 206 building 6 Chenguang Gardon, Qianjen street Changchun 130012, China) (using enzyme-linked immune-sorbent assay (ELISA) multiskan EX microplate photomter, thermo scientific, STAT FAX-2100, USA).
2. Lactate (Spectrum Diagnostics liquizyme Lactate reagent CATALOG #: 274001, Germany) using T60 UV visible spectrophotometer. PG INSTRUMENTS LIMITED, alma park wibtoft, Leicester shreshire, England. LE17SBE. Serial No. 20-1650-01-0010.

B.Spectrophotometric assay of pyruvate by enzymatic method according to Marbach and Weil (1967) using a single enzyme (lactic dehydrogenase) and a single protein-free filtrate (in 5% metaphosphoric acid)

To measure pyruvate, an excess of NADH was used in a Tris buffer at pH 7.5. Absorbance at 340 nm, using spectrophotometer, allows the calculation of the original amount of pyruvate present due to oxidation of NADH to NAD.

Anesthesia Technique

Anesthetic management was uniform in all patients. All patients were premedicated with intravenous midazolam (0.03 mg/kg) 30 minutes before the operation. Anesthesia was induced with fentanyl (3µg/kg) with propofol (1-2 mg/kg). Mechanical ventilation was used to maintain normocapnia. Anesthesia was maintained by using continuous infusion of fentanyl (1 µg/kg) and isoflourane 2%. During CPB, isoflourane was discontinued and anesthesia maintained by propofol infusion. Fentanyl infusion of 1 µg/kg/hour was continued postoperative in the I.C.U.

Operative procedure

All patients were approached via a median sternotomy approach. Standard aortic and biacaval cannulation was done. An initial dose of 400 µg/kg heparin was used to obtain an activated clotting time. Range blood pressure of 50-70 mmHg and blood flow 2-2.4 L/min. Priming solution contains mannitol and heparin. Hypothermia for 25-30 minutes. Cold (4^0C) crystalloid cardioplegic arrest was used after aortic cross clamping. Coronary bypass grafting was done using venous and arterial conduits. Flow up in the I.C.U for the hemodynamic changes in the heart rate, arterial blood pressure and central venous pressure. Antipyretics and potent antibiotic therapy were given. Before discharge the patient must meet the followings: aware, impulsive breathing, detached endotracheal tube.

Statistical methods

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS-version 17) software. The results were expressed as mean ± standard deviation. One way ANOVA (analysis of variance) test was used to compare more than two groups as regard quantitative variable (LSD =least significant difference).Pearson correlation analysis was used to evaluate the correlations between different parameters. P values of less than 0.05 were considered significant.

RESULTS

Patient Demographics

The demographic data of patients and duration of stay at ICU and ward are found in Table 1. All included patients were males with their mean age were 60.8 ±9 years and their mean body mass index "BMI" was 25.9±2.6. The mean bypass, clamping and whole surgery times were 150.5±8.5, 118±5.6, 353.8±9.2 minutes respectively, whereas the mean intensive care unit "I.C.U" stay and ward stay were 2.5±0.6 and 13.2±1.3 days respectively.

Perioperative hemodynamic changes

Preoperative, one hour and six hours postoperative recording of hemodynamic changes are presented in Table 2, which reveal significant hemodynamic changes regarding the heart rate, arterial blood pressure and central venous pressure, preoperative versus one hour postoperative.

Perioperative serum pyruvate, lactate, lactate/pyruvate ratio and L-carnitine levels

Comparative analysis of the mean±SD of the serum levels of some biochemical parameters (pyruvate, lactate, lactate/pyruvate ratio and L-carnitine) preoperative, intraoperative and postoperative versus the control group reveal significant lower intraoperative serum pyruvate levels when compared with the control group, with significant higher serum lactate levels and lactate /pyruvate ratio intraoperatively when compared with the control group. See Table 3 and Figure 2. A significant lower intraoperative serum L-carnitine levels when compared with the control group. Comparison of the mean±SD of the serum levels of some biochemical parameters (pyruvate, lactate, lactate/pyruvate ratio and L-carnitine) preoperative, intraoperative and postoperative reveal significant higher intraoperative serum lactate levels and lactate /pyruvate ratio when compared with the preoperative assay levels.

Also, a significant lower intraoperative serum L-carnitine levels when compared with the preoperative assay levels. See Table 4. The correlation of intraoperative serum levels of pyruvate, lactate, lactate/pyruvate ratio and L-carnitine versus

Table 1. Demographic data of patients and duration of stay at ICU and ward expressed as mean±SD

Variables	Minimum	Maximum	Mean±SD
Age (years)	43	75	60.8±9
BMI	22	30	25.9±2.6
Time of bypass (Min.)	135	163	150.5±8.5
Clamping time (Min.)	110	130	118±5.6
Time of surgery (Min.)	330	370	353.8±9.2
ICU stay (days)	2	3.5	2.5±0.6
Ward stay (days)	11	15	13.2±1.3

Table 2. Mean±SD of some hemodynamic parameters of the patients preoperative, one hour and six hours postoperative, using one way analysis of variance "ANOVA" followed by LSD multiple comparisons

Hemodynamic parameters	Preoperative	One hour postoperative	Six hours postoperative	P1	P2	P3
Heart rate "Beat/min."	91.8±3.7	100.9±1.2	80±4.4	***	***	***
Arterial blood pressure "mmHg"	89.7±2.5	77.4±1.8	83.2±3.9	***	***	***
Central venous pressure "mmHg"	9.1±0.2	8.1±0.2	8.3±1.9	***	0.097^{NS}	0.702^{NS}

P1= preoperative versus one hour postoperative.
P2= preoperative versus six hours postoperative
P3= one hour postoperative versus six hours postoperative.
* indicate significant change at P < 0.05; ** indicate significant change at p < 0.01; *** indicate significant change at p < 0.001. NS means non significant ((p>0.05).

Table 3. Comparison of the mean±SD of the serum levels of some biochemical parameters (pyruvate, lactate, lactate/pyruvate ratio and L-carnitine) preoperative, intraoperative and postoperative versus the control group, using one way analysis of variance "ANOVA" followed by LSD multiple comparisons

Biochemical parameters	Control group (n=25)	Patients (n=17)			P1	P2	P3
		Preoperative	Intraoperative	Postoperative			
Pyruvate "mmol/l"	0.049±0.014	0.041±0.013	0.035±0.012	0.043±0.003	*	**	0.141^{NS}
Lactate "mmol/l"	1.16±0.56	2.06±0.3	2.69±0.56	1.87±0.27	**	**	**
Lactate/ pyruvate ratio "L/P"	24.8±12	56.3±20.07	82.96±27.59	47.65±15.82	**	**	**
L-carnitine "ng/ml"	4.42±1.31	2.96±0.96	2.25±0.88	1.89±0.64	**	**	**

P1= Control versus Preoperative.
P2= Control versus Intraoperative.
P3= Control versus Postoperative.
* indicate significant change at P < 0.05; ** indicate significant change at p < 0.01; *** indicate significant change at p < 0.001. NS means non significant ((p>0.05).

Table 4. Comparison of the mean±SD of the serum levels of some biochemical parameters (pyruvate, lactate, lactate/pyruvate ratio and L-carnitine) preoperative, intraoperative and postoperative, using one way analysis of variance "ANOVA" followed by LSD multiple comparisons

Biochemical parameters	Patients (n=17)			P1	P2	P3
	Preoperative	Intra-operative	Post-operative			
Pyruvate "mmol/l"	0.041±0.013	0.035±0.012	0.043±0.003	0.240^{ns}	0.599^{ns}	0.092^{ns}
Lactate "mmol/l"	2.06±0.3	2.69±0.56	1.87±0.27	**	0.163^{ns}	**
Lactate/ pyruvate ratio "L/P"	56.3±20.07	82.96±27.59	47.65±15.82	**	0.251^{ns}	**
L-carnitine "ng/ml"	2.96±0.96	2.25±0.88	1.89±0.64	*	**	0.211^{ns}

P1=Preoperative versus intraoperative.
P2= Preoperativeversus postoperative.
P3= Intraoperative versus Postoperative.
* indicate significant change at P < 0.05; ** indicate significant change at p < 0.01; *** indicate significant change at p < 0.001. NS means non significant ((p>0.05).

Table 5. Correlation of intraoperative serum levels of pyruvate, lactate, lactate/pyruvate ratio and L-carnitine versus both time of bypass and clamping time among the studied patients, using person correlation coefficient

Biochemical parameters	Time of bypass		Clamping time	
	r	p	r	p
Pyruvate	0.350	0.169	0.317	0.216
Lactate	-0.076	0.771	-0.146	0.577
Lactate/ pyruvate ratio "L/P"	-0.405	0.107	-0.461	0.063
L-carnitine	0.007	0.978	-0.607	0.010**

**Statistically significant correlation (p level <0.01)

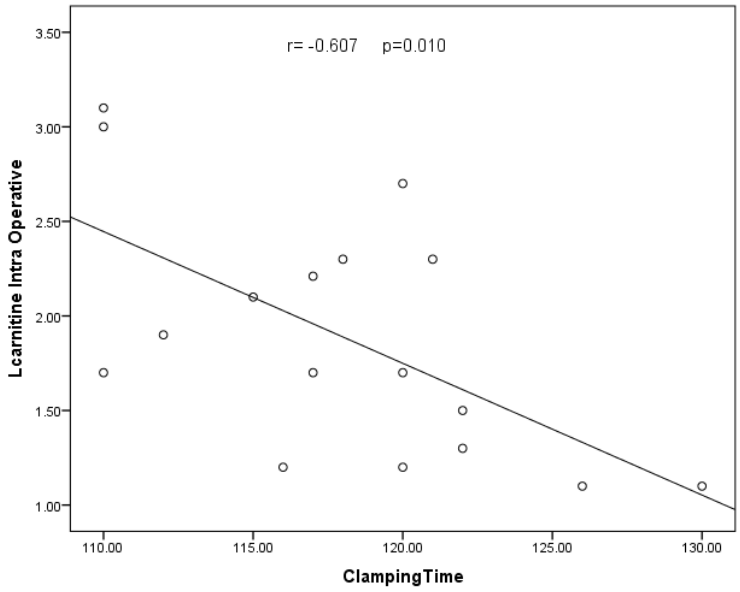

Fig.1. Negative correlation between the clamping time and intraoperative L-carnitine levels

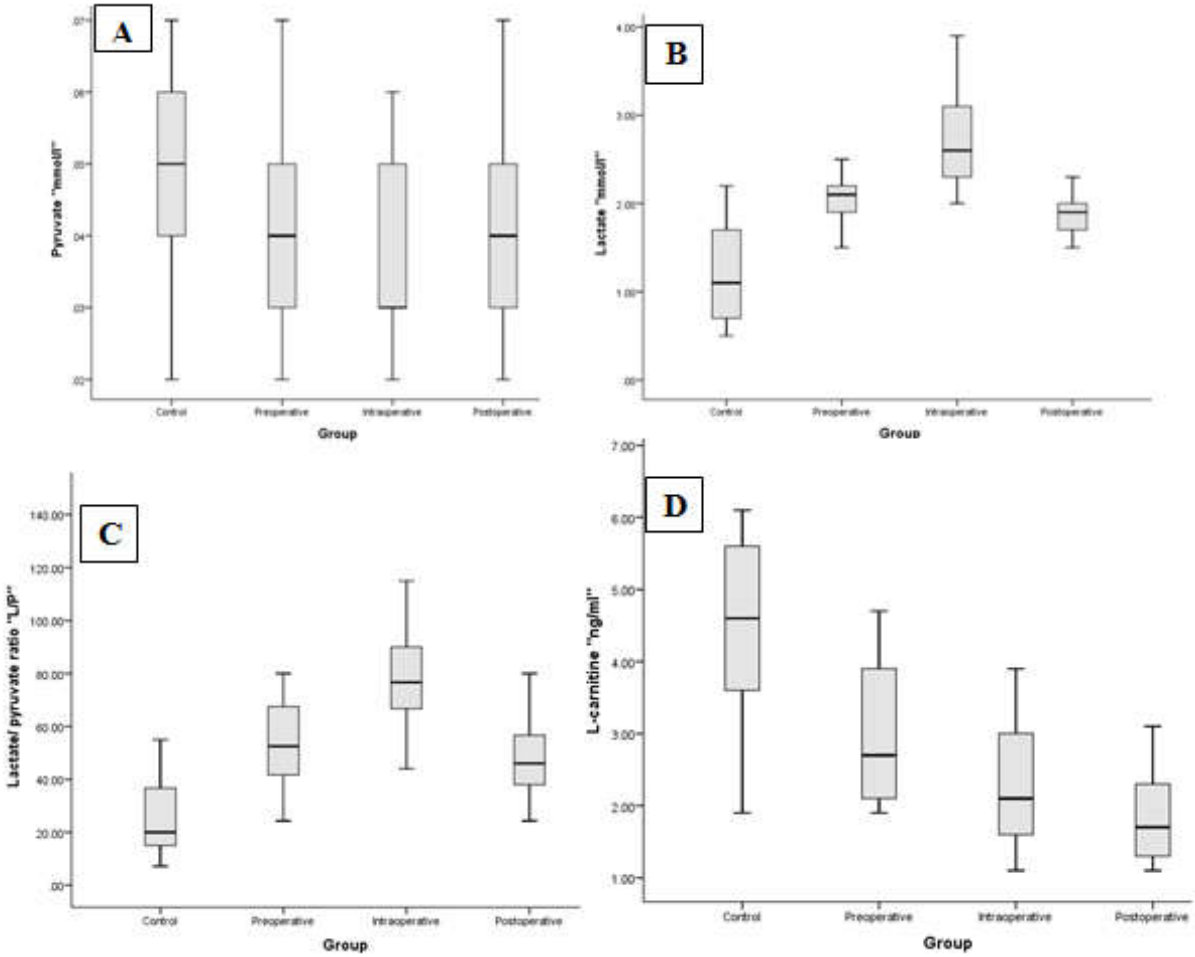

Fig.2. Comparison of the mean serum levels of pyruvate (A), lactate (B), lactate/pyruvate ratio (C) and L-carnitine (D) among the control group and patients group (preoperative, intraoperative and postoperative)

both time of bypass and clamping time among the studied patients reveal a negative correlation between intraoperative seum L-carnitine levels versus the clamping time. See Table 5 and Figure 1.

DISCUSSION

During cardiac surgery two consecutive sequences may damage the myocardium. Ischemia during cross- clamping of the aorta and reperfusion after aortic unclamping (Ezzeldin and Mostafa, 2006). Myocardial ischemia in various degrees may develop during the intraoperative phase of coronary bypass operations due to such reasons as manipulation of the heart, inadequate myocardial protection, and incomplete revascularization (Kanko *et al*., 2012). As regards the hemodynamic parameters of the studied patients including mean heart rate, mean arterial blood pressure and mean central venous pressure, they were recorded preoperative, one hour and six hours postoperative, see table.2, which show significant differences. The mean heart rate was significantly higher one hour postoperative when compared with the heart rate preoperative and six hours postoperative ($p < 0.001$), while the mean heart rate six hours postoperative was significantly lower when compared with the mean heart rate preoperative and one hour postoperative ($p < 0.001$). The mean arterial blood pressure was significantly lower one hour postoperative when compared with the preoperative and six hours postoperative mean value ($p < 0.001$), while the mean arterial blood pressure six hours postoperative was significantly higher when compared with the mean arterial blood pressure one hour postoperative ($p < 0.001$) but significantly lower when compared with the preoperative mean value ($p < 0.001$). The mean central venous pressure was significantly lower one hour postoperative versus the preoperative mean value ($p < 0.001$) with no significant difference between the mean central venous pressure six hours postoperative mean value when compared with either one hour postoperative or preoperative mean values. These findings were in agreement with Kapoor *et al*. (2011).

As a routine part of cardiopulmonary bypass (CPB) surgery, cardiac arrest is induced, which normally results in increased production of lactate (Demers *et al*., 2000). Following surgery, the heart is reperfused with blood and lactate normally declines. If lactate continues to be produced following reperfusion, as indicated by an elevated or non-decreasing blood lactate concentration, there may be a delayed return to normal oxygen utilization (aerobic metabolism) in the heart. This correlates with depressed myocardial function which may require additional support with cardiac stimulants or intraaortic balloon pumping (Rao *et al*., 2001). Hyperlactataemia may also occur and may be related to regional hypoperfusion associated with non-pulsatile flow during and after cardio-pulmonary bypass, altered metabolism with temperature changes, exogenous catecholamines and altered lactate clearance (Baker and Cadogan, 2005). The findings of our study reveal statistically significant lower serum pyruvate levels intraoperatively when compared with the control group ($p < 0.01$)-Table.3 and Fig.2, with statistically significant higher serum lactate levels and lactate /pyruvate ratio intraoperatively when compared with the control group and the preoperative assay levels ($p < 0.01$)- Table.3,4 and Fig.2. In addition, there was significant lower serum lactate levels and lactate /pyruvate ratio postoperatively when compared with the control group and preoperative levels ($p < 0.01$) - Table.3, 4 and Fig.2. These findings were in agreement with Raicea *et al*. (2015), Kapoor *et al*. (2011) and Shinde *et al*. (2006). As it is known that carnitine is necessary for the transport of activated long-chain fatty acid esters cross the mitochondrial membrane and stored to be used in Krebs cycle and oxidative phosphorylation. Restoration of normal cardiac metabolism is predicated on maintenance of adequate cellular levels of this substance (Eren, 2002). Conversion from anaerobic glycolysis to aerobic is one of the earliest reactions after reperfusion. The available plasma carnitine during ischemia supports substrates to the aerobic glycolysis, which is the main mechanism for ATP production for the cell. Of course increased amount of ATP production will fasten recovery of metabolic functions of the myocyte, which will cause less reperfusion injury (Eren, 2002). The present study showed, statistically significant lower serum L-carnitine levels intraoperatively when compared with the control group ($p < 0.01$) – Table 3 and Fig.2 and when compared with the preoperative assay levels ($p < 0.05$) - Table. 4 and Fig.2. There was a negative correlation between intraoperative seum L-carnitine levels versus the clamping time ($r = -0.607$, $p=0.01$)-Table 5, Fig.1. These findings were in agreement with Nemoto *et al*. (Toffaletti, 1991) and Guimara˜es *et al*. (2013).

Conclusion

The findings of this study prove that myocardial ischemia developed during the intraoperative phase of coronary bypass operations and causes significant decrease in the serum levels of pyruvate and L-carnitine and significant elevation of serum level of lactate and lactate/pyruvate ratio, so these biochemical parameters can be used to monitor the degree of intraopeartive cardiac ischemia and hence predict the patients morbidity and mortality. Preoperative administration of L-carnitine in such group of patients is recommended as a protector against the intraopeartive cardiac ischemia.

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Ethical approval: The Research Committee at Faculty of Medicine, Assiut University approved this study (R. Nr. 17/02/016).

Authors' contributions

AFAH, AMFG, KAA were responsible for study concept and design; the cardiac and anesthesia database and contributed to data interpretation and manuscript review. MHH, THS carried

out biochemical assays, data acquisition/ analysis; data interpretation wrote the first draft of manuscript and shared in statistical analysis and interpretation of results. All authors revised and approved the manuscript.

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