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Evaluation of Factors Affecting Liver Function Test in Patients Underwent Coronary Artery Bypass Graft Surgery

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ABSTRACT:- Objectives: Coronary artery bypass graft (CABG) along with cardiopulmonary bypass (CPB) is a frequently used cardio-vascular revascularization method to treat coronary artery disease. The liver is one of the most vital organs and is highly prone to damage during CABG. This study was designed to identify the factors associated with the change in liver function test indices after isolated CABG.

Methods:- A retrospective study was carried out at King Khalid University Hospital (KKUH) in Riyadh, Saudi Arabia. All patients who underwent isolated CABG were identified during the period from July 1st 2013 to June 30, 2015 covering a 24 month period. Medical records of 286 patients who met the inclusion criteria were enrolled in this study. Some pre-operative and intra-operative variables were identified and then compared to the change in pre-operative liver function test indices to the post-operative ones.
Results:- The comparison of liver function test indices before and after surgery were all statistically significant at the alpha level of 0.05. The comparison of liver function test indices pre- and post-operative between men and women demonstrated significant changes in the levels of GGT and ALP, no significant difference in the level of AST and ALT. Likewise, there was no significant difference of liver function test indices before and after surgery in patients with and without history of diabetes mellites, previous stroke, COPD, and smoking. Moreover, the cross-clamp duration and cardiopulmonary bypass time had a direct significant correlation with ALT and AST ($P<0.05$), no significant correlation with GGT and ALP.
Conclusion:-The alteration of hepatic enzymes after coronary artery bypass graft surgery presumably attributed to prolonged cross-clamp duration and cardiopulmonary bypass time.

Keywords:- coronary artery bypass grafting, liver function test, diabetes mellites, stroke, Chronic obstructive pulmonary disease, cross-clamp duration, cardiopulmonary bypass time

Abbreviations:
CABG: Coronary artery bypass graft
CPB: cardiopulmonary bypass
KKUH: King Khalid University Hospital
GGT: Gamma-glutamyl transferase
ALP: Alkaline phosphatase
AST: Aspartate aminotransferase
ALT: alanine aminotransferase
BMI: Body mass index
COPD: Chronic obstructive pulmonary disease
DM: Diabetes mellitus
MI: Myocardial infarction
LV: Left ventricle
ICU: Intensive care unit

I. INTRODUCTION

Coronary artery bypass graft (CABG) is a surgical procedure performed to relieve anginal symptoms and reduce the death risk from coronary artery disease. CABG along with cardiopulmonary bypass (CPB) is a frequently used cardio-vascular revascularization method to treat coronary artery disease [(1)]. Open cardiac surgery requires using CPB which takes over the function of the heart, lung, and circulatory system. The pump or extracorporeal circulation has important effects on body organs, including liver [(2)]. The liver is one of the most vital organs and is highly prone to damage during CABG. During CPB, the possibility of liver damage increases owing to the non-pulsatile perfusion, low-flow state, free radicals formation, and increased levels of catecholamines [(3)]. Some trials have shown that the consumption of coagulation factors during CPB leads to reduced coagulation factors and compromised liver function by micro thrombi formation in centrilobular hepatic sinusoids [(4)]. On the other hand, in some controversial studies, short CPB time less than two hours were not associated with compromised hepatic function test [(5)]. Furthermore, an elevation of serum liver enzymes after uncomplicated CPB has been reported in some studies. These changes could be transient but not permanent alterations of hepatic enzymes after coronary artery bypass grafting presumably attributed to the decreased hepatic flow, hypoxia, or pump-induced inflammation [(6)].

Given the importance of liver function for health, an increase in liver enzymes levels introduces the damage to hepatocytes which leads to longer hospital stay of patients and more costs. This study was designed to identify the factors associated with the change in liver function test indices after isolated CABG.

II. PATIENTS AND METHODS

i. Study design and participants

This retrospective study was carried out at King Khalid University Hospital (KKUH) in Riyadh, Saudi Arabia. Ethical approval was obtained from the ethics committee [(reference number 15/0526/IRB on December 27; 2015)]. All patients who underwent isolated Coronary Artery Bypass Graft (CABG) were identified during the period from July 1st 2013 to June 30, 2015 covering a 24 month period. Medical records of 286 patients who met the inclusion criteria were enrolled in this study. The exclusion criteria were set up in order to eliminate any other known cause of possible liver function disturbances that includes having simultaneous cardiac valvular surgery, right-sided heart failure, viral/non-viral hepatitis, chronic liver disease, hematological disorders and patients with incomplete data. Data collection sheet was designed by the principal investigator, all data was entered in an Excel Microsoft spread sheet. Variables were identified and recorded as follows: Descriptive data: Age, Gender, calculated Body mass index (BMI), and Smoking status. Medical history: Chronic obstructive pulmonary disease (COPD), Diabetes mellitus (DM), History of Myocardial infarction (MI), and History of stroke. Also, the data about patients' serum creatinine and LV ejection fraction were collected. The outcome variables: Liver enzymes (GGT, AST, ALT, ALP) were measured preoperatively and at 24, 48, 72, and 96 hours following surgery. The total of five measurements were obtained.

ii. Operative procedure

The operative procedure was almost similar in all patients. General anesthesia was induced and maintained with total intravenous anesthesia, consisting of propofol (100 mcg/kg/min) and fentanyl (1 mcg/kg/hour). And atracurium (5 mcg/kg/min) was infused intravenously. After that, a median sternotomy was performed, followed by aortic and atrial cannulation. The aortic cannula is secured to a rubber tourniquet with a heavy silk tie. Once in place, the cannula is de-aired and connected to the arterial pump tubing. The venous cannula is inserted into the right atrial appendage in a similar fashion, with the end of the cannula positioned in the inferior vena cava. Adequate anticoagulation is confirmed by assessing the activated clotting time; once this is done, cardiopulmonary bypass can be commenced. Cardio-pulmonary bypass was established using membrane oxygenation, non-pulsatile perfusion, and moderate systemic hypothermia. Myocardial protection was achieved by cold hyperkalemic crystalloid cardioplegia and topical cooling with iced slush and cold saline solution. Coronary artery bypass graft was performed using the left internal mammary artery and reversed saphenous vein in most instances.

iii. Statistical Analysis

The data was analyzed using IBM SPSS software [(version 22)]. Continuous variables such as liver enzymes were expressed as mean with standard deviation (mean±Standard Deviation) and compared using the student's t test. A value of $P<0.05$ was considered statistically significant. One-way analysis of variance (ANOVA) test was used to compare liver enzymes in regard with multiple factors such as gender, COPD, past MI history. The association between each liver enzyme and risk factors such as Cross-clamp duration, age and body mass index (BMI) was represented by Pearson Correlation (R). Liver enzymes levels pre-operative and four days post-operatively were compared using repeated measures test. Difference between pre-operative and post-operative

liver enzymes was calculated. Paired t-test was used to compare pre-operative enzymes and fourth day post-operative. Change in liver enzymes was expressed in percent.

III. RESULTS

Totally, two hundred eighty-six patients who fulfilled criteria were included in this study. There were 246 men (86.05%) and 40 women (13.95%). Out of 286 patients, 32 (11.2%) are smokers, 16 (5.6%) had history of COPD, 224 (78.4%) had history of diabetes mellitus [46 (16.1%) are type I DM and 178 (62.3%) are type II DM], 193 (67.5%) had history of myocardial infarction, and 18 (6.3%) had history of previous stroke. (Table 1.) shows the mean±SD of some of the patients' quantitative variables.

Table 1. Patients' quantitative variables (mean±SD)

Variable	mean±SD
Age (years)	57.5±10.1
BMI $(kg/m)^2$	28.2±5.1
Ejection Fraction (%)	44.3±13.6
Creatinine (mg/dl)	1.09±0.76
Cardiopulmonary Bypass Time (minutes)	98.8±41.8
Cross-Clamp Duration (minutes)	78.0±39.0

BMI: body mass index

At the alpha level of 0.05, The preoperative GGT, AST, ALT, and ALP (50±27.6; 31.5±18.5; 45.5±21.8; and 93.4±27.8) were significantly increased by 52.8%, 34.9%, 22.6%, and 5.2%, respectively in fourth post-operative day (76.4±55; 42.5±40.0; 55.8±43.4; and 98.3±38.4). (Table 2.)

Table 2. Comparison of Pre- and Post-operative liver function tests by ANOVA repeated measures

Indices	Pre-operative	Day 1	Day 2	Day 3	Day 4
GGT	50±27.6	44±23.8	50.1±29.3	61.9±44.1	76.4±55
AST	31.5±18.5	60.6±41.7	63.3±47.9	53.4±47.3	42.5±40.0
ALT	45.5±21.8	46.04±23.7	49.1±29.5	54.9±50.07	55.8±43.4
ALP	93.4±27.8	71.4±20.5	77.2±27.4	89.5±32.7	98.3±38.4

Table 3. Comparison of liver function test indices before and after surgery (mean±SD)

Indices	Pre-operative	Post-operative	P-value
GGT	50±27.6	57.3±26.8	<0.05*
AST	31.5±18.5	55±32.7	<0.05*
ALT	45.5±21.8	50.4±24.5	<0.05*
ALP	93.4±27.8	83.2±23.2	<0.05*

*Significant

The comparison of liver function test indices pre- and post-operative between men and women demonstrated significant changes in the levels of GGT and ALP, no significant difference in the level of AST and ALT. Likewise, there was no significant difference of liver function test indices before and after surgery in patients with and without history of diabetes mellites, previous stroke, COPD, and smoking. (Table 4.)

There was no significant correlation between post-operative liver function test indices and age, creatinine, and ejection fraction. On the other hand, the body mass index had a reverse significant correlation with ALT ($P<0.05$), no significant correlation with other liver function test indices. Moreover, the Cross-clamp duration and cardiopulmonary bypass time had a direct significant correlation with ALT and AST ($P<0.05$), no significant correlation with GGT and ALP. (Table 5.)

Table 4. Comparison between the change in the liver function test indices in regard with gender and diabetes mellitus

	Gender			History of Myocardial Infarction			
	Males (n=247)	Females (n=40)	P-value	No (n=93)	NSTEMI (n=130)	STEMI (n=63)	P-value
GGT	-2.8±38.6	-15.4±31.8	0.05*	58.1±28.9	58.9±35.6	60.4±29.8	0.9
AST	-19.8±48.2	020.7±44.8	0.9	-22.1±30.8	-18.4±41.6	-19.8±73.7	0.8
ALT	-3.8±33.1	-14.1±33.2	0.07	-2.2±33.8	-5.5±301	-9.1±38.5	0.4
ALP	11.8±24.3	-7.2±35.4	0.00*	8.02±23.2	9.8±26	9±33.5	0.8

	History of Diabetes Mellitus			
	No	Type I	Type II	p-value
GGT	-7.2±43.5	-5.5±30.6	3.1±49.3	0.3
AST	-20.7±67.9	-18.1±36.8	-24.8±39.9	0.7
ALT	-3.3±41.3	-4±27.1	-12±37.5	0.2
ALP	10.5±26.4	9.5±26.9	5.3±27.9	0.5

	History of Previous Stroke			Smoking Status			History of COPD*		
	No (n=268)	Yes (n=18)	P-value	No (n=254)	Yes (n=32)	P-value	No (n=270)	Yes (n=16)	P-value
GGT	-4.9±38.4	0.95±30.2	0.5	-3.2±38	14.4±35.7	0.1	-4.5±38.9	-5.1±11.4	0.9
AST	-19.7±48.8	-23.5±24.2	0.7	-20.2±48.6	-17.4±40.2	0.7	-19.6±46	-26.1±71.6	0.5
ALT	-5.3±34.2	-3.5±13.2	0.8	-4.7±31.3	-8.5±46.8	0.5	-5±34.1	-7.7±15	0.7
ALP	8.7±27.2	15.9±21	0.2	8.9±25.4	11.4±37.4	0.6	9.2±27.3	9.7±18.7	0.9

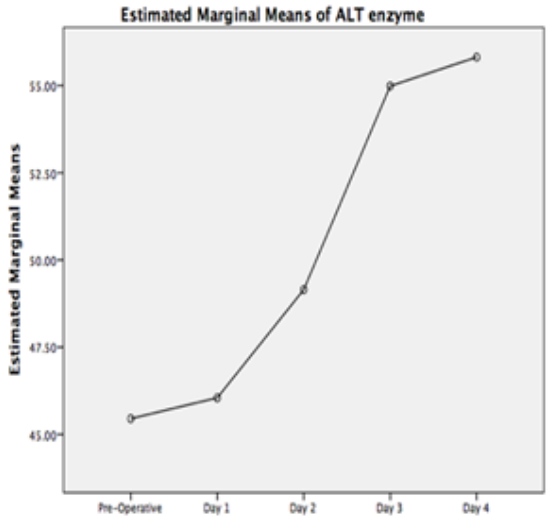
*COPD: chronic obstructive pulmonary disease

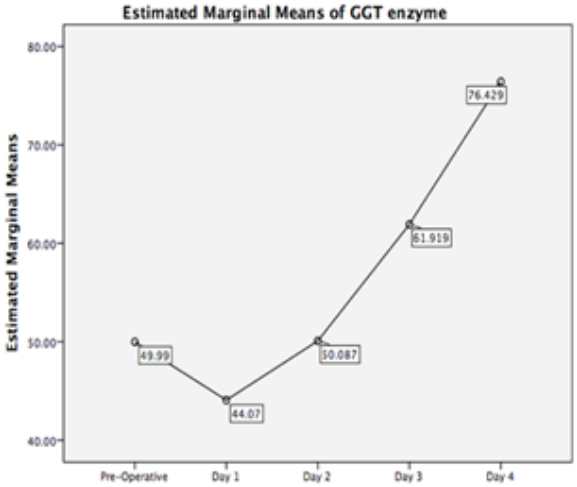
Table 5. Correlation between post-operative liver function test indices and the studied quantitative variables

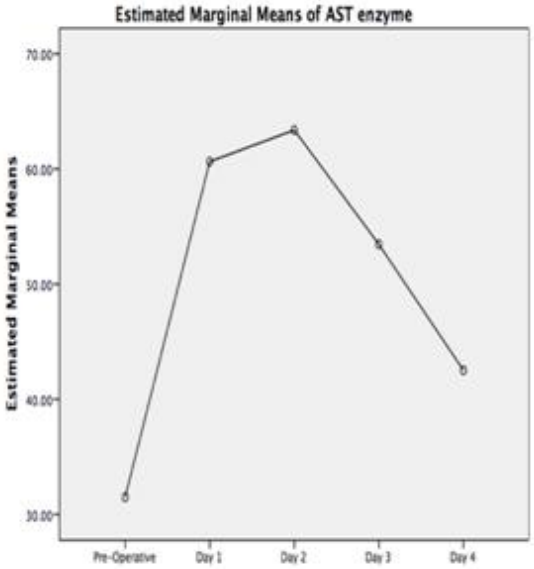
	GGT		AST		ALT		ALP	
	R	P-value	R	P-value	R	P-value	R	P-value
Age (years)	-0.03	0.6	0.04	0.5	-0.04	0.4	0.02	0.7
BMI $(kg/m)^2$	-0.03	0.6	-0.07	0.2	-0.16	0.008*	-0.026	0.6
Ejection Fraction (%)	0.05	0.4	0.07	0.2	0.04	0.5	-0.04	0.9
Creatinine (mg/dl)	0.06	0.3	0.08	0.2	-0.01	0.8	0.02	0.7
Cross-Clamp duration	-0.003	0.9	0.21	0.001*	0.17	0.008*	0.05	0.4
CPB time (min)	0.09	0.14	0.26	0.00*	0.18	0.003*	0.014	0.8

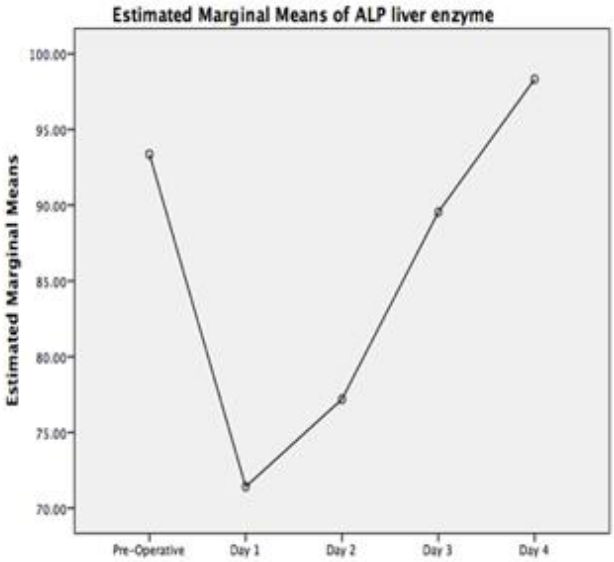
*Significant

One-way repeated measured analysis of variance (ANOVA) was conducted to evaluate the null hypothesis that there is no significant change in patients' liver enzyme levels when measured before and four days after isolated CABG (N=286). The results of ANOVA indicate a significant increase in GGT enzyme levels. (chart 1). Wilks Lambda = 0.69, F (4,31.5)= , P<0.05. n^2 =0.309. Thus, there is enough evidence that GGT enzyme increased significantly after the isolated CABG. Follow up comparison indicated that each pairwise difference was significant P<0.05. There was significant increase in GGT enzyme over the four days after the isolated CABG. Similarly, the results of ANOVA for AST were similar to GGT, there was significant difference between pre and post operative AST levels. Wilks lambda=0.59, F (2,48.1) =, P<0.05, n^2 =0.4. AST enzyme plot showed a significant increase in day 1 followed by gradual decrease. The change in AST levels was significant. However, the one-way ANOVA test showed that there was a gradual increase in ALP and ALT levels after the isolated CABG. Wilks lambda=0.38, 0.93, F (2) =118 ,48.1 respectively, P<0.05, n^2 =0.92, 0.06. The levels of ALP and ALT varied in significance difference. Post hoc results showed that the main difference was between pre-operative ALP /ALT levels and day four post-operative (P-value=0.001).









IV. DISCUSSION

Eipel et al. [7] emphasize the well-known physiological concept that among parenchymal organs, blood flow to the liver is unique due to the dual supply from the portal vein and the hepatic artery. Knowledge of the mutual communication of both the hepatic artery and the portal vein is essential to understand hepatic physiology and pathophysiology. The liver receives about 25% of the cardiac output as the largest visceral organ. The hepatic artery supplies 20% to 25% and the portal system supplies 75% to 80% of the blood flow to the liver. This dual blood supply and the liver's ability to extract as much as 95% of oxygen from the blood make the liver relatively resistant to necrosis from hypoperfusion. However, a critical reduction in perfusion or significant hypoxemia may overwhelm the protective mechanisms and cause hypoxic liver damage [8]. There are several theories to explain the mechanism for postoperative liver dysfunction at the cellular level. The systemic inflammatory response syndrome and oxidative stress from CPB can contribute to postoperative hepatic injury [9]. Konstantina et al. [10] proposed that Aortic cross-clamping results in an immediate decrease in blood flow to the distal tissues. One of the most significant manifestations of clamping is the release of catecholamines, which increases systemic vasospasm and results in venoconstriction and decrease in venous capacity [11]. In our study, the cardiopulmonary bypass time and aortic-cross clamp duration had a direct significant relationship with AST and ALT levels.

Some researchers have reported that the underlying cause of liver injury is a multi-factorial. Mc Sweeny et al. [12] stated that a history of myocardial infarction, revascularization, and ejection fraction below 40% were the independent factors affecting postoperative gastrointestinal complications. Moreover, the authors found that a history of renal failure was effective in the occurrence of gastrointestinal complications. Also,

Raman et al. [13] reported that a history of diabetes mellitus and heart failure could cause severe liver ischemia after cardiac surgeries. In our study, the history of diabetes mellites, history of myocardial infarction, history of stroke, history of COPD, and smoking status had no significant relationships with liver function tests. In this study, any COPD patient with degree of right ventricular failure has been excluded, in order to avoid any known liver function abnormality, which it could affect liver enzymes post-operatively? Also, pre-operative creatinine levels and ejection fraction did not have a significant relationship with liver function tests. However, the body mass index had a reverse significant relationship with ALT levels.

Holmes proposed that using inotrope and vasopressors could increase visceral vascular resistance and cause ischemia by vascular contracture. The epinephrine adversely affected organ function, systemic perfusion, and survival compared with norepinephrine and vasopressin [14]. This is one of the limitations in our study, the data regarding inotropes and vasopressors were incomplete for some of the patients. Therefore, we were unable to assess their effect on the liver function tests.

The severity of liver dysfunction varies widely after cardiac surgery. The presentation of liver dysfunction ranges from transient to frank liver failure [15, 16]. It is associated with increased morbidity and mortality. The presence of hypoxic hepatitis is a strong risk factor for mortality in the ICU in patients requiring vasopressor therapy [17].

V. CONCLUSION

It appears that the best way theoretically to decrease the incidence of post-operative hepatic injury is by reduce cardiopulmonary bypass and aortic cross-clamp durations. We recommend including the different types of cardiopulmonary bypass pumps and compared their effects on liver function tests in future studies, and to be conducted on a large population with a single surgeon to improve the accuracy of results.

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Ethical Issues
The study was approved by the Local Ethics Committee.

Conflict of Interests
Authors declare no conflict of interest in this study.

REFERENCES

[1]. IQBAL U.J., HANIF M.I. AND IQBAL N. EFFECT OF CARDIOPULMONARY BYPASS ON LIVER FUNCTION IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFTING, D:\Biomedica Vol. 31, Issue 1, Jan. – Mar., 2015\Bio-1.Doc P. 27 – 29 (KC)

[2]. Mohamad Golitaleb1, Mehrdad Haghazali2, Farzaneh Golaghaie[1], Behshid Ghadrdoost2, Ali Sahebi4 and Faranak Kargar2*, Changes in Liver Enzymes in the Patients Undergoing Open Cardiac Surgery and Related Factors, International Journal of Advanced Biotechnology and Research (IJBR) ISSN 0976-2612, Online ISSN 2278–599X, Vol-8, Issue-3, 2017, pp2086-2091

[3]. Shahbazi Sh, Panah A, Sahmeddini MA. Evaluation of Factors Influencing Liver Function Test in On-Pump Coronary Artery Bypass Graft Surgery. Iran J Med Sci. 2013;38(4):308-313.

[4]. Varghese D, Varghese B, Kelley K, et al. Prospective randomized study to evaluate changes in alpha-GST as a novel marker of hepatocellular necrosis in patients at high-risk of hepatic injury undergoing coronary revascularization with and without cardiopulmonary bypass. Ind J Thorac Cardiovasc Surg 2007; 23: 63.

[5]. Braun JP, Schroeder T, Buehner S, et al. Splanchnic oxygen transport, hepatic function and gastrointestinal barrier after normothermic cardiopulmonary bypass. Acta Anaesthesiol Scan 2004; 48: 697-703. doi: 10.1111/j.1399-6576.2004.00392.x

[6]. Feridoun Sabzi1, Reza Faraji2*,Liver Function Tests Following Open Cardiac Surgery, Cardiovasc Thorac Res, 2015, 7(2), 49-54 doi: 10.15171/jcvtr.2015.11

[7]. Eipel C, Abshagen K, Vollmar B. Regulation of hepatic blood flow the hepatic arterial buffer response revisited. World J Gastroenterol. 2010;16(48):6046–6057.

[8]. Poelzl G, Auer J. Cardiohepatic syndrome. Curr Heart Fail Rep 2015;12: 68–78.

[9]. Wark HJ. Hepatic failure after cardiopulmonary bypass is unlikely to be isoflurane hepatitis. Anesthesiology 2002;97:1323.

[10]. Konstantina Katseni, Athanasios Chalkias, Thomas Kotsis, Nikolaos Dafnios, Vassilis Arapoglou, Georgios Kaparos, Emmanuel Logothetis, Nicoletta Iacovidou, Eleni Karvouni, and Konstantinos

Katsenis. The Effect of Perioperative Ischemia and Reperfusion on Multiorgan Dysfunction following Abdominal Aortic Aneurysm Repair. Volume 2015, Article ID 598980.

[11]. L. M. Cuzick, A. R. Lopez, and J. R. Cooper Jr., "Pathophysiology of aortic cross-clamping," in Thoraco-Abdominal Aorta: Surgical and Anesthetic Management. Eds., pp. 65–72, Springer, Milan, Italy, 2011.

[12]. McSweeney ME, Garwood S, Levin J, Marino MR, Wang SX, Kardatzke D, et al. Adverse gastrointestinal complications after cardiopulmonary bypass: can outcome be predicted from preoperative risk factors? Anesth Analg. 2004;98:1610-7. doi: 10.1213/01. ANE.0000113556.40345.2E.

[13]. Raman JS, Kochi K, Morimatsu H, Buxton B, Bellomo R. Severe ischemic early liver injury after cardiac surgery. Ann Thorac Surg. 2002;74:1601-6. doi: 10.1016/S0003- 4975(02)03877-8.

[14]. Holmes CL. Vasoactive drugs in the intensive care unit. Curr Opin Crit Care. 2005;11:413-7. doi: 10.1097/01.ccx.0000176696.70013.da.

[15]. M. Megan Chacon, MD, Thomas E. Schulte, MD. Liver Dysfunction in Cardiac Surgery – What Causes It and Is There Anything We Can Do? Editorial / Journal of Cardiothoracic and Vascular Anesthesia 32 (2018) 1719–1721.

[16]. Yamada T, Ochiai R, Takeda J, Kikuchi H, Ishibashi M, Watanabe K. Off-pump coronary artery bypass attenuates transient hepatocellular damage after myocardial revascularization. J Cardiothorac Vasc Anesth. 2005 Oct;19(5):603-7.

[17]. Valentin Fuhrmann, Nikolaus Kneidinger, Harald Herkner, Gottfried Heinz, Mariam Nikfardjam, Anja Bojic, Peter Schellongowski, Bernhard Angermayr, Maximilian Schöniger-Hekele, Christian Madl, Peter Schenk. Impact of hypoxic hepatitis on mortality in the intensive care unit. August 2011, Volume 37, Issue 8, pp 1302–1310.