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Level of Cardiac Biomarkers in Immediate Post-Operative Period after Off-Pump CABG and Its Comparison with On-Pump CABG: A Prospective Analytical Study

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Abstract

Background: Coronary artery bypass grafting (CABG) is an important modality of treatment for ischemic heart disease. Both off-pump and on-pump CABG have direct effect on the level cardiac biomarkers in the perioperative period. The use of cardiopulmonary bypass (CPB) and aortic cross-clamping may cause additive myocardial damage leading to further elevation of blood markers. The present study is aimed at measuring and comparing the cardiac biomarker levels in immediate post-operative period after on-pump CABG (ONCAB) and off-pump CABG (OPCAB). **Methods:** All the patients who underwent CABG from January 2015 to June 2016 on elective or emergency basis at Nilratan Sircar Medical College & Hospital have been included in the study. Total 106 patients were operated for CABG of which 75 patients were operated for OPCAB and 31 patients were operated for ONCAB. For the comparison of data the blood markers Troponin-T (Trop-T) and Creatine Kinase-MB (CK-MB) are measured during anesthesia before surgery, post-operatively after 1 hour, post-operatively after 4 hours and post-operatively after 20 hours. All recorded data are analyzed using standard statistical methods. **Results:** We found the markers are elevated immediately after surgery and gradually come down within 24 hours after surgery in both OPCAB and ONCAB groups. The elevation is more after ONCAB than OPCAB group in immediate post-operative period but the difference is not significant after 20 hours of surgery. **Conclusion:** Elevated levels of cardiac biomarkers in the immediate post-operative period indicate myocardial damage during surgery, especially after ONCAB in comparison to OPCAB. This may attribute to the better hemodynamic stability in the immediate post-operative period after

OPCAB than ONCAB assuming comparable and adequate revascularization in patients of both groups. The avoidance of CPB and cross-clamp may explain better myocardial functioning immediately after OPCAB. But after 20 hours, the level of cardiac markers is comparable in both groups indicating little difference in post-operative recovery and long-term prognosis.

Keywords

Coronary Artery Bypass Grafting (CABG), Perioperative Period, Myocardial Damage, Cardiopulmonary Bypass, Cardiac Biomarkers

1. Introduction

Ischemic Heart Disease (IHD) is the world's leading cause of mortality [1]. Premature deaths caused by the heart and blood vessel disease even among the productive age group (35 - 64 years) are expected to rise by 41% by 2030 [2]. Coronary artery disease syndrome includes chronic stable angina, unstable angina, myocardial infarction, cardiogenic shock and ischemic cardiomyopathy. Coronary artery disease (CAD) can be managed by medical therapy or myocardial revascularization, Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Grafting. Several studies have shown a better 5 years survival for CABG over medical therapy [3]. The use of CPB during surgery is associated with many systemic insults (systemic inflammatory response) and deleterious effects including complement activation, multiple organ dysfunction, neurocognitive dysfunction and coagulation abnormalities [4]. The use of the cardioplegic arrest of the heart to perform CABG also has negative effects on myocardial contractility despite the major advances in cardioplegic solutions and myocardial protection. To avoid the deleterious effects of CPB [5] a resurgence of CABG on a beating heart, also known as off-pump CABG or OPCAB took place in the middle of 1990s though it was first introduced in 1967 by Kolesov. Initially, off-pump surgery was restricted to patients with isolated single vessel or double vessel CAD and to patients with significant co-morbidities, such as renal failure, calcified aortas or significant peripheral and cerebrovascular disease; patients who could derive maximum benefit from avoiding CPB [4] [5]. Initially, the practice of OPCAB was also bedeviled by crude instrumentation and limited exposure of the lateral, posterior and inferior target coronary vessels. With the improvement of anesthetic and surgical techniques along with newer equipment for retraction and exposure, the proportion of CABG done by OPCAB has increased with figures of between 20% - 30% being quoted [5] [6] [7] [8] and has expanded to include more complex coronary anatomy than single or double vessel disease. Off-pump coronary artery bypass grafting (OPCAB) avoids the deleterious effects of CPB and is increasingly reported to have better outcomes than ONCAB [9] [10] [11]. Troponin-T (Trop-T) is a major protein in Tropomyosin which is present in contractile apparatus of cardiac muscle. Although

typically present in low levels, it rises after myocardial infarction and is considered as a marker of myocardial damage. After cardiac surgery, its level rises before coming to baseline level and the level correlates with duration of cardioplegia. Creatine kinase-myocardial band (CK-MB), an isoenzyme of Creatine kinase, is specific to heart and is involved in cardiac inflammation. Both of these enzymes are released to interstitial space from damage myocardial cells resulting rise of their concentration in serum. The serum level of these biomarkers may correlate with the extent of myocardial damage after surgery and hence can affect the cardiovascular functioning accordingly [12]. The present study aims to compare the myocardial damage in terms of blood level of these biomarkers after surgery among the both groups of OPCAB and ONCAB.

2. Materials & Methods

This is prospective type of observational analytical study where all the patients who underwent CABG from January 2015 to June 2016 on elective or emergency basis at Nilratan Sircar Medical College & Hospital have been included in the study. Total 106 patients were operated for CABG which includes both OPCAB and ONCAB. Exclusion criteria includes patients with age <40 years or >80 years, with left ventricular Ejection fraction <30%, with Serum creatinine >2 mg/dl and patients with Redo operation. The patients were operated through a median sternotomy. All proximal anastomoses were performed by the use of a side-biting clamp. Protamine was administered at the end of the operation to fully reverse the heparin effect. For OPCAB Heparin 150 IU/kg was given and ACT was kept above 300 s. Positioning of the heart was achieved by a deep pericardial stay suture or a suction device. Octopus stabilizers were used for distal anastomoses. An intracoronary shunt was used during distal anastomoses whenever possible. For ONCAB Heparin 300 IU/kg was administered to obtain activated clotting time (ACT) over 480 s before start of CPB. Standard cannulation of the ascending aorta and the right atrium were employed. CPB was conducted with a flow rate of 2.4 l/m^2/min, alpha-stat acid-base management and a nasopharyngeal temperature of 34 - 35 degree C. If required after aortic cross clamping 700 - 1000 ml of antegrade cold blood cardioplegia were infused. During cross clamping cardioplegia was given antegradely every 15 min. Rewarming was initiated when the last distal anastomosis was started. The patients were weaned from CPB when the nasopharyngeal temperature was above 36 degree C. For the comparison of data the blood markers Troponin-T (Trop-T) and Creatine Kinase-MB (CK-MB) are measured during anesthesia before surgery, post-operatively after 1 hour, post-operatively after 4 hours and post-operatively after 20 hours (Next day). All recorded data are analyzed with suitable diagrams, figures, tables and findings are discussed in details to draw appropriate conclusions using standard statistical analysis. Troponin T (Trop-T measured in ng/L) and creatine kinase-MB (CK-MB measured in mcg/L) were analyzed with electrochemiluminescence immunoassay technique (Elecsys 1010/2010 Systems,

Roche, Basel, Switzerland). Perioperative myocardial infarction was defined as CK-MB 50 mcg/L and a new q-wave on the ECG. Statistical analysis has been done using Microsoft Excel and GraphPad Prism (GraphPad Software Inc., USA) software. For comparison among the parameters at different time-points in the off-pump group, repeated measures analysis of variance (ANOVA) has been done, followed by *post hoc* comparison using Holm-Sidak test when *p*-value is significant. For comparison between the on- and off-pump groups at different time-points, a two-way ANOVA has been used followed by *post hoc* comparison using Holm-Sidak test when *p*-value is significant. A one-way ANOVA has been done to compare the time-dependent effects of off-pump surgery on cardiac biomarkers, followed by *post hoc* comparison using Holm-Sidak test when *p*-value is significant. Comparisons between two groups have been made using unpaired Student's *t*-test. A $p < 0.05$ has been considered statistically significant. All data have been presented as mean ± standard error of mean (SEM).

3. Results & Analysis

Total 106 patients were operated for CABG during the study period. 75 patients were operated for off-pump CABG and 31 patients were operated for on-pump CABG. The preoperative characteristics of both the groups have been depicted in Table 1. All of the patients in on-pump (ONCAB) group have multivessel disease with majority of the patients (74%) having borderline or low LVEF (<50%). In off-pump (OPCAB) group a small number of patients have single vessel disease (7%) and majority of the patients have multivessel disease (93%). LVEF is >50% in 37% patients and less <50% in rest 63%. 58% patients in the ONCAB group and 27% patients in the OPCAB group had previous history of myocardial infarction. The comorbid conditions were equally prevalent in both the groups. In both the groups around 29% patients had diabetes mellitus and around 9% patients had chronic obstructive pulmonary disease. 52% patients of OPCAB group and 58% patients of ONCAB group had treated systemic hypertension. 59% patients of OPCAB group and 55% patients of ONCAB group had treated hypercholesterolemia. 60% patients of OPCAB group and 42% patients of ONCAB group had recent or past history of smoking. Average body surface area is 1.8 m^2 and average serum creatinine level is 0.9 mg/dl in both the groups.

As evident from Figure 1, there is significant time-dependent increase in the CK-MB levels after OPCAB [$F(3, 296) = 181.6$, $p < 0.0001$ (BS [before surgery] <<<< 1 h AS [after surgery] <<<< 4 h AS <<<< 20 h AS)]. The Trop-T also significantly increases from 1 h to 4 h AS and then significantly decreases at 20 h AS. [$F(2, 213) = 34.11$, $p < 0.0001$ (1 h AS <<<< 4 h AS >>>> 20 h AS << 1 h AS)]. The unit of CK-MB is mcg/L while that of Trop-T is ng/L.While comparing OPCAB with ONCAB, we found (Figure 2), there is a significant interaction between the types of CABG (on-pump vs. off-pump) and time-points [$F(3, 416)$

= 49.62, $p < 0.0001$]. The effects of the type of CABG (on-pump vs. off-pump) [$F(1, 416) = 18.30$, $p < 0.0001$] and that among the time-points [$F(3, 416) = 226.7$, $p < 0.0001$] were both significant. CK-MB in on-pump group BS <<<< 1 h AS = 4 h AS >>>> 20 h AS; CK-MB BS: On-pump = Off-pump; CK-MB 1 h AS: On-pump >>>> Off-pump; CK-MB 4 h AS: On-pump >>>> Off-pump; CK-MB 20 h AS: On-pump <<<< Off-pump. For Trop-T also there is asignificant interaction between the types of CABG (on-pump vs. off-pump) and time-points [$F(2, 303) = 151.7$, $p < 0.0001$]. The effects of the type of CABG (on-pump vs. off-pump) [$F(1, 303) = 614.2$, $p < 0.0001$] and that among the time-points [$F(2, 303) = 356.7$, $p < 0.0001$] were both significant. Trop-T in on-pump group: 1 h AS <<<< 4 h AS >>>> 20 h AS; Trop-T 1 h AS: On-pump >>>> Off-pump; Trop-T 4 h AS: On-pump >>>> Off-pump; Trop-T 20 h AS: On-pump = Off-pump. (</> indicates $p < 0.05$, <</>> indicates $p < 0.01$, <<</>>> indicates $p < 0.001$, <<<</>>>> indicates $p < 0.0001$ between the groups).

Table 1. Preoperative baseline characteristics of off-pump and on-pump CABG patients.

Patient Characteristics	Off-Pump CABG (n = 75)	On-Pump CABG (n = 31)
Mean Age (years)	58.87	57.19
Number of male patients (percentage of total)	61 (81.33%)	23 (74.19%)
Number of female patients (percentage of total)	14 (18.67%)	8 (25.81%)
Single vessel disease	5 (6.67%)	0 (0%)
Multiple vessel disease	70 (93.33%)	31 (100%)
Ejection fraction > 50%	28 (37.33%)	8 (25.81%)
Ejection fraction < 50%	47 (62.67%)	23 (74.19%)
Diabetes mellitus	22 (29.33%)	9 (29.03%)
Previous history of myocardial infarction	20 (26.67%)	18 (58.06%)
Peripheral vascular disease	3 (4%)	2 (6.45%)
Chronic obstructive pulmonary disease (COPD)	7 (9.33%)	3 (9.68%)
Treated hypertension	39 (52%)	18 (58.06%)
Treated hypercholesterolemia	44 (58.67%)	17 (54.84%)
Smoking (current or former)	45 (60%)	13 (41.93%)
Average body surface area (m^2)	1.8	1.8
Average serum creatinine level (mg/dl)	0.9	0.86

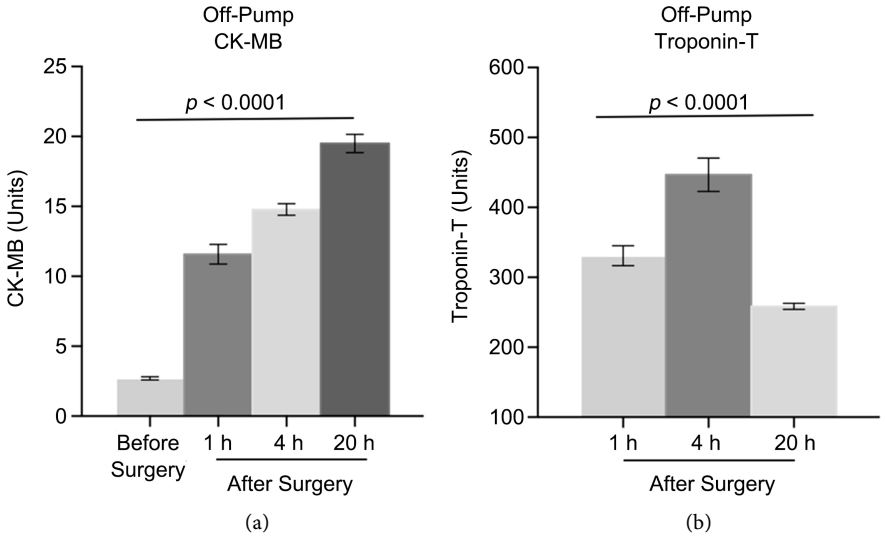

Figure 1. Effects of Off-Pump CABG on cardiac biomarkers: (a) CK-MB (b) Trop-T (The unit of CK-MB is IU/L while that of Trop-T is ng/mL).

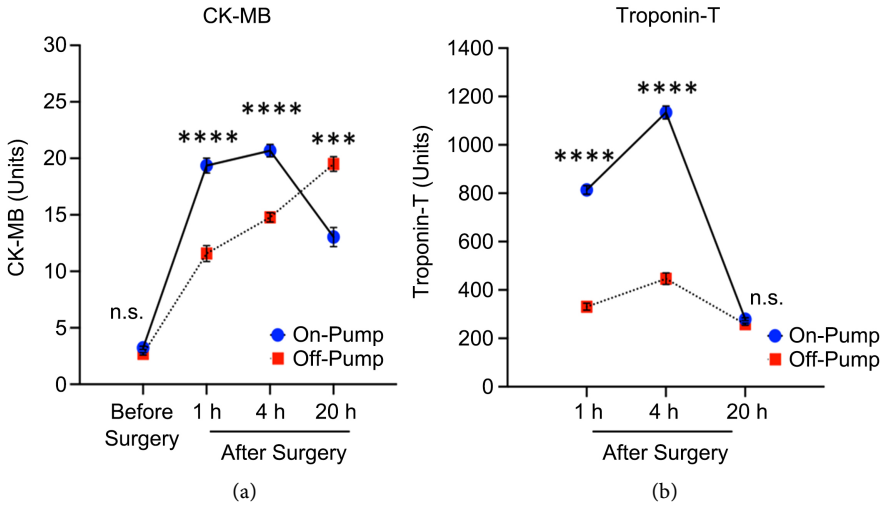

Figure 2. Comparison of the effects of Off-Pump CABG and On-Pump CABG on the cardiac biomarkers: (a) CK-MB (b) Trop-T (*indicates $p < 0.05$, **indicates $p < 0.01$, ***indicates $p < 0.001$, ****indicates $p < 0.0001$. "n.s." indicates non-significant difference between the two groups at that particular time-point. The unit of CK-MB is IU/L while that of Trop-T is ng/mL).

Trop-T and CK-MB were measured as markers of cardiac damage. In off-pump group Trop-T rises significantly at 1 h and 4 h after surgery from its baseline value (<100 units) and then decreases significantly at 20 h. While comparing with on-pump CABG patients the level of Trop-T is significantly higher at 1 and 4 h post-operatively in on-pump group than off-pump group but the level is same at 20 h post-operatively in both groups. This indicates more intense cardiac damage in the immediate post-operative period in on-pump group because of the effect of CPB. The level of CK-MB also rises significantly in off-pump group in a time dependent manner up to 20 h. The level of the marker

is significantly higher at 1 and 4 h post-operatively in the on-pump group than off-pump group although it reverses at 20 hours post-operatively. Both the results suggest that release of CK-MB and Troponin-T was less after 1 h and 4 h in off-pump group.

4. Discussion

Coronary artery bypass grafting with cardiopulmonary bypass (ONCAB) is a routine operation with well documented long-term results. However, cardiopulmonary bypass (CPB) per se leads to a systemic inflammatory reaction which may cause postoperative dysfunction of the heart, lungs, kidney, and brain [13]. Furthermore, aortic cross clamping and cardioplegic arrest induces an ischemic insult to the heart and is a risk factor for neurologic injury [14] [15]. During the last 10 years off pump coronary artery bypass grafting (OPCAB) has become an established and safe alternative to ONCAB. OPCAB can be performed in a large percentage of the patients on all coronary artery systems with good graft patency [9] and good early [10] and midterm [11] results.

Previous studies show less release of cardiac enzymes [10] [16] [17], fewer myocardial infarctions [18], reduced incidence of arrhythmias [16] and reduced frequency of low cardiac output [19] following OPCAB. However, others fail to show such differences [20] [21]. Studies also show shorter stay in the intensive care unit (ICU) and overall shorter length of stay in hospital [14]. The prospective, randomized trial carried upon by Vedin J. *et al.* [22] showed that patients undergoing OPCAB had improved cardiovascular performance immediately after surgery as compared to ONCAB patients. This may be important during very early critical period because hemodynamic stability during the first few hours after cardiac surgery is important for the further post-operative course. The improved cardiovascular performance may be due to better cardiac function, less myocardial damage and better peripheral vasodilation in the OPCAB patients.

The rise of biomarkers after CABG is multifactorial. Myocardial injury may be due to direct cardiac manipulation during positioning or suturing, reperfusion injury of myocardium, myocardial injury mediated by free oxygen radicals, failure to re-perfuse areas of myocardium not supplied by graft vessels, inadequate myocardial protection including effects of CPB and cardioplegia in case of ONCAB. The elevation of biomarkers may be due to other underlying pathologies or other peri-operative complications which may not be related to vascular event. Da costa *et al.* concluded from their study that in contrast with CK-MB considerable cardiac troponin release occurs after an elective OPCAB procedure, even in absence of evidence of a new myocardial infarction (MI) detected by late gadolinium enhancement on cardiac magnetic resonance imaging [23].

However, the release of myocardial damage markers is less in the immediate post-operative periods of OPCAB patients compared to ONCAB patients as revealed in various studies. Vedin J. *et al.* found release of CK-MB and Troponin-T was less after 1 and 6 hours in the OPCAB patients [22]. This is similar to

the findings of other studies as well. Ascione *et al.* [16] found lower Troponin-I release at 1, 4, 12 and 24 hours postoperatively. Kilger *et al.* [17] found lower CK-MB and Troponin-I up to 24 (CK-MB) and 36 (Troponin-I) hours after OPCAB surgery and Van Dijk *et al.* [10] found lower CK-MB levels up to 20hours after OPCAB. The well-documented low incidence of mortality and morbidity in the majority of both off-pump and on-pump CABG patients increases the difficulty in comparing these procedures.

Although prospective, randomized trials comparing elevations of Cardiac biomarkers after OPCAB and ONCAB have been performed, a trial of sufficient size showing significant statistical difference specially in immediate post-operative period is not available in literature. Several large, retrospective, nonrandomized multicenter series have reported lower incidence of death, stroke, intra-aortic balloon pump requirement, postoperative transfusion, time on ventilator, and length of stay for OPCAB compared to contemporaneous ONCAB procedures at the same institution and national database statistics. This may be explained by less myocardial damage in OPCAB patients indicated by less release of myocardial damage markers in immediate post-operative period as revealed from many studies [10] [16] [17] [22]. However the impact of selection bias in determining operative technique for any given patient in these series may be a confound variable. Similar results suggesting superiority of the OPCAB procedure have been reported when propensity scores were used in an attempt to decrease the impact of selection bias in an unselected group of patients and in high-risk subgroups. Propensity scoring decreases dissimilarity between the two groups being compared with respect to major cardiac and non-cardiac morbidities. The results, however, do not consider intraoperative findings which themselves are significant factors for increasing the level of cardiac enzymes after CABG independent of use of CPB. Small, calcified, diffusely atherosclerotic coronary arteries, intra-myocardial or intra-adipose coronary arteries, or other conditions that make revascularization technically more demanding may increase the level of biomarkers due to manipulation of heart, inadequate revascularization or inappropriate grafting [23]. These factors also increase the likelihood of the procedure being performed with CPB. As such, technically difficult revascularizations are more prevalent in the ONCAB group. Conversion from OPCAB to CABG-CPB intra-operatively occurs occasionally for several reasons including anatomical factors like inadequate exposure of target vessel, deep intra-myocardial course of target vessel, small vessels, adhesions or an enlarged heart, hemodynamic instability due to manipulation or repositioning of the heart, mitral and/or aortic regurgitation, bleeding, acute ischemia as detected by ST segment or wall motion changes, left ventricular dysfunction and electrical disturbances during the procedure like ventricular fibrillation, ventricular tachycardia, heart block or severe bradycardia [22]. A large number of patients are converted during grafting of the obtuse marginal vessels or the ramus intermedius due to difficult positioning particularly in large hearts [24]. The consequence of intra-operative conversion

is increased peri-operative mortality which may be up to 6 - 12 fold more than in the unconverted group [22] [25]. The conversion rate quoted in literature ranges between 0% - 8.8% [26]-[31]. This has a direct impact on elevation of cardiac enzymes immediately after surgery.

5. Conclusion

The present study shows that the cardiac biomarkers are significantly elevated in the immediate postoperative period after on-pump CABG patients. In off-pump group, the markers are much less in comparison to on-pump group in immediate post-operative period indicating less myocardial damage after off-pump surgery. This may be the cause of hemodynamic instability and low cardiac output being more prevalent in the immediate post-operative period after on-pump CABG. However after 20 hours of surgery, the levels of both the markers are comparable indicating a little effect of CPB or clamp related myocardial injury in long-term recovery.

Limitation of the Study

Although this is a prospective observational study but the patients were not randomly allocated in both the groups and the study was not completely free from selection bias because of ethical issues. Single vessel disease was exclusively operated by OPCAB and all ONCAB patients have multi-vessel involvement. Also the ONCAB group had a relatively higher number of patients with poor LV function. The number of patients is relatively small and different in both the groups. Some of the confounding factors like history of previous myocardial infarction and history of smoking were unevenly distributed among both the groups. These factors may have direct or indirect effect on the outcome of the study.

Ethics Declarations

The present prospective study has been approved by Institutional Ethical committee of NRS Medical College No/NMC/127. The need to obtain informed consent was waived by the local ethical committee.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Murray, C.J. and Lopez, A.D. (1997) Mortality by Cause for Eight Regions of the World: Global Burden of Disease Study. *The Lancet*, **349**, 1269-1276. https://doi.org/10.1016/S0140-6736(96)07493-4

[2] Leeder, S., Raymond, S. and Greenberg, H. (2004) Race against Time: The Challenge of Cardiovascular Disease in Developing Economies. Columbia University,

New York.

[3] Yusuf, S., Zucker, D. and Peduzzi, P. (1994) Effect of Coronary Artery Bypass Graft Surgery on Survival: Overview of 10 Year Results from Randomized Trials by the Coronary Artery Bypass Surgery Trialists Collaboration. *The Lancet*, **344**, 563-570. https://doi.org/10.1016/S0140-6736(94)91963-1

[4] Lee, J.H., Capdeville, M., Marsh, D., Abdelhady, K., Poostizadeh, A. and Murrell, H. (2002) Earlier Recovery with Beating-Heart Surgery: A Comparison of 300 Patients Undergoing Conventional versus Off-Pump Coronary Artery Bypass Graft Surgery. *Journal of Cardiothoracic and Vascular Anesthesia*, **16**, 139-143. https://doi.org/10.1053/jcan.2002.31053

[5] Magee, M.J., Jablonski, K.A., Stamou, S.C., Pfister, A.J., Dewey, T.M., Dullum, M.K.C., Edgerton, J.R., Prince, S.L., Acuff, T.E., Corso, P.J. and Mack, M.J. (2002) Elimination of Cardiopulmonary Bypass Improves Early Survival for Multivessel Coronary Artery Bypass Patients. *The Annals of Thoracic Surgery*, **73**, 1196-1203. https://doi.org/10.1016/S0003-4975(01)03587-1

[6] Niranjan, G., Asimakopoulos, G., Karagounis, A., Cockerill, G., Thompson, M. and Chandrasekaran, V. (2006) Effects of Cell Saver Autologous Blood Transfusion on Blood Loss and Homologous Blood Transfusion Requirements in Patients Undergoing Cardiac Surgery On- and Off-Cardiopulmonary Bypass: A Randomised Trial. *European Journal of Cardio-Thoracic Surgery*, **30**, 271-277. https://doi.org/10.1016/j.ejcts.2006.04.042

[7] Varghese, D., Yacoub, M.H., Trimlett, R. and Amrani, M. (2001) Outcome of Non-Elective Coronary Artery Bypass Grafting without Cardio-Pulmonary Bypass. *European Journal of Cardio-Thoracic Surgery*, **19**, 245-248. https://doi.org/10.1016/S1010-7940(01)00583-8

[8] Kerendi, F., Puskas, J.D., Craver, J.M., Cooper, W.A., Jones, E.L., Lattouf, O.M., Vega, J.D. and Guyton, R.A. (2005) Emergency Coronary Artery Bypass Grafting Can Be Performed Safely without Cardiopulmonary Bypass in Selected Patients. *The Annals of Thoracic Surgery*, **79**, 801-806. https://doi.org/10.1016/j.athoracsur.2004.08.010

[9] Puskas, J.D., Wright, C.E., Ronson, R.S., Brown, W.M., Parker Gott, J. and Guyton, R.A. (1999) Clinical Outcomes and Angiographic Patency in 125 Consecutive Off-Pump Coronary Bypass Patients. *The Heart Surgery Forum*, **2**, 216-221.

[10] Van Dijk, D., Nierich, A.P., Jansen, E.W.L., Nathoe, H.M., Suyker, W.J.L., Diephuis, J.C., Van Boven, W.-J., Borst, C., Buskens, E., Grobbee, D.E., Robles De Medina, E.O. and De Jaegere, P.P.T. (2001) Early Outcome after Off-Pump versus On-Pump Coronary Bypass Surgery: Results from a Randomized Study. *Circulation*, **104**, 1761-1766. https://doi.org/10.1161/hc4001.097036

[11] Angelini, G.D., Taylor, F.C., Reeves, B.C. and Ascione, R. (2002) Early and Midterm Outcome after Off-Pump and On-Pump Surgery in Beating Heart against Cardioplegic Arrest Studies (BHACAS 1 and 2): A Pooled Analysis of Two Randomised Controlled Trials. *The Lancet*, **359**, 1194-1199. https://doi.org/10.1016/S0140-6736(02)08216-8

[12] Preeshagul, I., Gharbaran, R., Jeong, K.H., *et al.* (2013) Potential Biomarkers for Predicting Outcomes in CABG Cardiothoracic Surgeries. *European Journal of Cardio-Thoracic Surgery*, **8**, Article No. 176. https://doi.org/10.1186/1749-8090-8-176

[13] Edmunds Jr., L.H. (1998) Inflammatory Response to Cardiopulmonary Bypass. *The Annals of Thoracic Surgery*, **66**, S12-S16.

https://doi.org/10.1016/S0003-4975(98)00967-9

[14] Vinten-Johansen, J. and Nakanishi, K. (1993) Postcardioplegia Acute Cardiac Dysfunction and Reperfusion Injury. *Journal of Cardiothoracic and Vascular Anesthesia*, **7**, 6-18. https://doi.org/10.1016/1053-0770(93)90092-Y

[15] Vaage, J., Jensen, U. and Ericsson, A. (2000) Neurologic Injury in Cardiac Surgery: Aortic Atherosclerosis Emerges as the Single Most Important Risk Factor. *Scandinavian Cardiovascular Journal*, **34**, 550-557. https://doi.org/10.1080/140174300750064468

[16] Ascione, R., Lloyd, C.T., Gomes, W.J., Caputo, M., Bryan, A.J. and Angelini, G.D. (1999) Beating versus Arrested Heart Revascularization: Evaluation of Myocardial Function in a Prospective Randomized Study. *European Journal of Cardio-Thoracic Surgery*, **15**, 685-690. https://doi.org/10.1016/S1010-7940(99)00072-X

[17] Kilger, E., Pichler, B., Weis, F., Goetz, A., Lamm, P., Schütz, A., Muehlbayer, D. and Frey, L. (2000) Markers of Myocardial Ischemia after Minimally Invasive and Conventional Coronary Operation. *The Annals of Thoracic Surgery*, **70**, 2023-2028. https://doi.org/10.1016/S0003-4975(00)01848-8

[18] Arom, K.V., Flavin, T.F., Emery, R.W., Kshettry, V.R., Janey, P.A. and Petersen, R.J. (2000) Safety and Efficacy of Off-Pump Coronary Artery Bypass Grafting. *The Annals of Thoracic Surgery*, **69**, 704-710. https://doi.org/10.1016/S0003-4975(99)01510-6

[19] Boyd, W.D., Desai, N.D., Del Rizzo, D.F., Novick, R.J., Mckenzie, F.N. and Menkis, A.H. (1999) Off-Pump Surgery Decreases Postoperative Complications and Resource Utilization in the Elderly. *The Annals of Thoracic Surgery*, **68**, 1490-1493. https://doi.org/10.1016/S0003-4975(99)00951-0

[20] Kshettry, V.R., Flavin, T.F., Emery, R.W., Nicoloff, D.M., Arom, K.V. and Petersen, R.J. (2000) Does Multivessel, Off-Pump Coronary Artery Bypass Reduce Postoperative Morbidity? *The Annals of Thoracic Surgery*, **69**, 1725-1730. https://doi.org/10.1016/S0003-4975(00)01419-3

[21] Lund, O., Chistensen, J., Holme, S., Fruergaard, K., Olesen, A., Kassis, E. and Abildgaard, U. (2001) On-Pump versus Off-Pump Coronary Artery Bypass: Independent Risk Factors and Off-Pump Graft Patency. *European Journal of Cardio-Thoracic Surgery*, **20**, 901-907. https://doi.org/10.1016/S1010-7940(01)00972-1

[22] Vedin, J., Jensen, U., Erricson, A., Bitkover, C., Samuelsson, S., Bredin, F. and Vaage, J. (2003) Cardiovascular Function during the First 24 Hours after Off Pump Coronary Artery Bypass Grafting—A Prospective, Randomized Study. *Interactive Cardiovascular and Thoracic Surgery*, **2**, 489-494. https://doi.org/10.1016/S1569-9293(03)00119-1

[23] Da Costa, L.M., Hueb, W., Nomura, C.H., *et al.* (2017) Significant Elevation of Biomarkers of Myocardial Necrosis after Coronary Artery Bypass Grafting without Myocardial Infarction Established Assessed by Cardiac Magnetic Resonance. *Medicine*, **96**, e6053. https://doi.org/10.1097/MD.0000000000006053

[24] Meharwal, Z.S. and Trehan, N. (2002) Off-Pump Coronary Artery Bypass Grafting in Patients with Left Ventricular Dysfunction. *The Heart Surgery Forum*, **5**, 41-45.

[25] Edgerton, J.R., Dewey, T.M., Magee, M.J., Herbert, M.A., Prince, S.L., Jones, K.K. and Mack, M.J. (2003) Conversion in Off-Pump Coronary Artery Bypass Grafting: An Analysis of Predictors and Outcomes. *The Annals of Thoracic Surgery*, **76**, 1138-1143. https://doi.org/10.1016/S0003-4975(03)00747-1

[26] Kapetanakis, E.I., Stamou, S.C., Dullum, M.K.C., Hill, P.C., Haile, E., Boyce, S.W., Bafi, A.S., Petro, K.R. and Corso, P.J. (2004) The Impact of Aortic Manipulation on

Neurologic Outcomes after Coronary Artery Bypass Surgery: A Risk-Adjusted Study. *The Annals of Thoracic Surgery*, **78**, 1564-1571. https://doi.org/10.1016/j.athoracsur.2004.05.019

[27] Sergeant, P., Worm, E., Meyns, B. and Wouters, P. (2001) The Challenge of Departmental Quality Control in the Re-Engineering towards Off-Pump Coronary Artery Bypass Grafting. *European Journal of Cardio-Thoracic Surgery*, **20**, 558-543. https://doi.org/10.1016/S1010-7940(01)00852-1

[28] Vassiliades, T.A., Nielsen, J.L. and Lonquist, J.L. (2017) Hemodynamic Collapse during Off-Pump Coronary Artery Bypass Grafting. *The Annals of Thoracic Surgery*, **73**, 1874-1879.

[29] Ascione, R., Narayan, P., Rogers, C.A., Lim, K.H.H., Capoun, R. and Angelini, G.D. (2003) Early and Midterm Clinical Outcome in Patients with Severe Left Ventricular Dysfunction Undergoing Coronary Artery Surgery. *The Annals of Thoracic Surgery*, **76**, 793-800. https://doi.org/10.1016/S0003-4975(03)00664-7

[30] Hernanadez, F., Cohn, W.E., Baribou, Y.R., Tryzelaar, J.F., Charlesworth, D.C. Clough R.A., Klemperer, J.D., Morton, J.R., Westbrook, B.M., Olmstead, E.M. and O'Connor, G.T. (2001) In-Hospital Outcomes of Off-Pump versus On-Pump Coronary Artery Bypass Procedures: A Multicentre Experience. *The Annals of Thoracic Surgery*, **72**, 1528-1534. https://doi.org/10.1016/S0003-4975(01)03202-7

[31] Jones, R.H. (2005) Intraoperative Crossover: The Well-Kept Surgical Secret to Apparent Surgical Success. *Journal of the American College of Cardiology*, **45**, 1529-1531.