

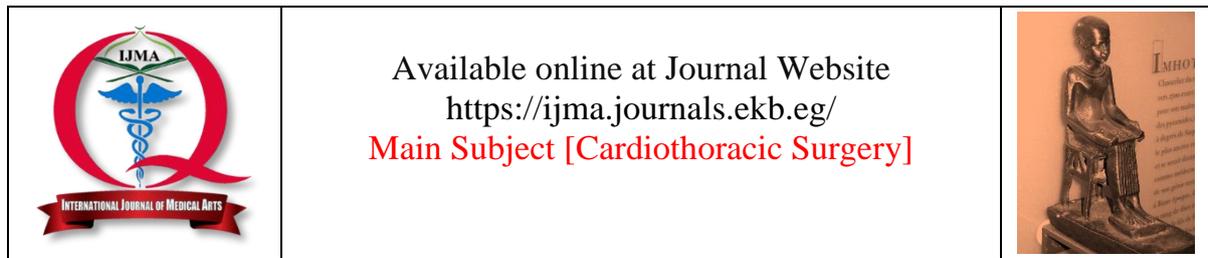
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Original Article

Correlation between The Duration of Cardiopulmonary Bypass Time and The Occurrence of Morbidity and Mortality in Conventional Adult Cardiac Surgery

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ABSTRACT

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Background: In the current era of surgical practice, conventional cardiac surgery still occupies the main bulk of operations, but its postoperative complications are numerous and can lead to morbidity and mortality. Cardiopulmonary bypass time is a major risk factor in cardiac surgery. Several surgeons underestimate the importance of reducing bypass time and its effect on patient outcomes, and there is no known cutoff time for bypass that is associated with higher complications.

Aim of the work: To assess the correlation between bypass time and patient outcomes and clarify the relevant period or a cutoff time for safe cardiopulmonary bypass.

Patients and Methods: A retrospective single-center comparative study of 450 cases of conventional cardiac surgery, 300 valve surgeries and 150 coronary bypass surgeries in the Cardiothoracic Surgery Department, Tanta University between January 2018 and January 2023, categorized into 3 groups: Group A: bypass time less than 60 minutes, Group B: bypass time from 60 to 120 minutes, Group C: bypass time more than 120 minutes.

Results: There was a significant difference between the 3 groups in favor of Group A with the least bypass time regarding post-operative renal complications [p-value = 0.002], respiratory complications [p-value = 0.013], neurologic complications [p-value = 0.001], multiple blood transfusions [p-value = 0.04], infections [p-value = 0.04] and mortality [p-value = 0-001]. However, no significant difference regarding demographic data, comorbidities, creatinine level and ejection fraction.

Conclusion: Bypass time is a major predictor and is proportionally related to morbidity and mortality in cardiac surgery; a bypass time up to 60 minutes is the safest with the least morbidity and mortality.

Keywords: Cardiopulmonary bypass time; Morbidity; Mortality.



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INTRODUCTION

Cardiopulmonary bypass [CPB] technology is widely used in almost all the conventional cardiovascular surgical operations, including cardiac valve surgery operations and coronary artery bypass surgery [CABG] surgery and several other open-heart surgeries ^[1].

Detrimental effects of CPB on the patients' outcome are attributed to complex-associated systemic inflammatory response syndrome, and also attributed to the re-infusion of the cardiotomy suction blood that is exposed to the pericardial and the mediastinal surfaces, in addition to the hyperthermia that is induced during CPB and the fast rewarming throughout the late phases of weaning from CPB, the occurrence of micro-emboli [gaseous emboli or particulate emboli] and the presence of foreign material in the CPB circuit ^[1].

The peri-operative care of these cardiac surgical studied patients has been related to the substantial utilization of many healthcare resources due to the prolongation of the stay of these patients in the intensive care units [ICU] and the total length of patients' stays in the hospitals [LOS] ^[2].

The CPB is still necessary and mandatory for most conventional open-heart surgeries, despite the fact that multiple studies have shown that off-pump coronary artery bypass graft surgery considerably lowers the systemic inflammatory response and lessens the patient's post-operative morbidity ^[3].

In spite of the continuous improvement and the development of several new methods, several strategies that aim at reduction of the [post-CPB] complications ^[4], post-pump systemic inflammatory response is mainly caused by the patients blood's exposure to the abnormal shear forces from the heart lung machine roller pumps, the air-blood interface and its contact with the artificial surface of the bypass circuit, as confirmed by numerous previous reports claiming the beneficial impacts of reduction of the CPB circuit surface area ^[5].

The CPB initiates the release of cytotoxic enzymes and several inflammatory mediators, including tumor necrosis factor alpha [α] [TNF- α], interleukin-1 [IL-1], interleukin-6 [IL-6], and interleukin-8 [IL-8], in addition to the fibrinolytic system, the complement system, activated leukocytes with subsequent degranulation and the coagulation system cascade, including the activation of the platelets and the endothelial cells ^[6].

Thus, the negative impacts of the CPB will worsen the longer its duration during cardiac surgery operations and the longer the patient's blood is exposed to its artificial surfaces. However, despite numerous previous studies investigating the impact of CPB on patient morbidity and mortality following cardiac surgery, very few have specifically examined the impact of CPB duration, rather than the use of CPB itself, on the post-operative results and outcomes of cardiac surgery patients studied ^[7].

This study aimed to assess the correlation between the duration of the cardiopulmonary bypass time and the occurrence of post-operative morbidity and mortality in adult patients undergoing conventional cardiac surgery and to clarify the relevant period or a cut off time for cardiopulmonary bypass beyond it there would be the occurrence of higher complications.

PATIENTS AND METHODS

This study is a retrospective single-center comparative and observational study that included 450 studied patients who had been scheduled for conventional elective adult cardiac surgery operations in the Cardiothoracic Surgery Department, Tanta University throughout the period between January 2018 and January 2023.

These 450 patients were classified as being [300 valve surgery patients and 150 coronary artery bypass surgery patients] studied cases. They were categorized according to the cardiopulmonary bypass time duration into 3 equal groups each group included 150 patients: group A: CPB time [less than 60 minutes], Group B: CPB time from [60 to 120 minutes] and Group C: CPB time [more than 120 minutes].

Inclusion criteria: Adult [≥ 18 -year-old] studied cases scheduled for elective conventional cardiac surgery operations either valve surgery or coronary artery bypass surgery or combined valve and CABG surgery.

Exclusion criteria: Studied cases undergoing off-pump coronary bypass surgery, cases of emergency cardiac surgery and patients with missing data on their post-operative co-morbidities or patients with missed cardiopulmonary bypass data registration.

Methods of the study

All the studied patients were subjected to the basic demographic data registration such as sex, age, number of diseased coronary vessels, weight and body mass index, operation type [isolated

valve surgery operation, CABG + valvular surgery, cardiac surgery + vascular intervention or isolated CABG surgery, considered as reference intervention], diabetes mellitus, hypertension, previous myocardial infarction, stroke, dialysis & operative priority.

Pre-operative data: New York Heart Association class [NYHA], echocardiographic left ventricular ejection fraction class [$> 50\%$ = good; 40% to 50% = fair; $< 40\%$ = poor] and pre-operative creatinine level and pre-operative medications.

Coronary artery disease [CAD] severity scoring: In the 150 patients undergoing CABG surgery, the pre-operative scoring of CAD severity was based on the findings obtained from the interpretation of their coronary angiography [CAG] and their percutaneous coronary intervention [PCI] performed up to [7 days and 365 days] after hospital discharge for the index myocardial infarction [MI] and stable post-MI patients, respectively. CAD severity was defined according to the collective number of the obstructed coronary arteries corresponding to about [50% or more than 50%] coronary artery luminal narrowing and were classified into [7 groups]: no significant coronary artery stenosis, [1-vessel CAD], [2-vessel CAD], [3-vessel CAD], left main coronary artery stenosis [LMS], missing angiographic data or if no CAG was performed. LMS with or without additional other diseased coronary vessels were categorized as LMS only. For the CAD patients with >1 angiography record, the CAG record with the most severe CAD disease was retained for the analysis. Multi-vessel CAD [MVD] was defined as [2-vessel CAD] or [3-vessel CAD] or LMS.

Operative technique

The standard conventional cardiac surgery techniques were employed for the studied patients as standardized for isolated cardiac valve surgery, isolated [CABG] surgery or combined surgery [valve + CABG] with all operations using the standard institution conventional CPB technique.

The standard [Tanta Institution] CPB Technique

Standard general cardiac surgical anesthesia induction using the continuous intravenous infusion of propofol [3-5 mg/kg/h IV] or inhaled anesthetics [sevoflurane or isoflurane], as well as divided doses of intravenous fentanyl [25 - 50 mg] IV, were used to maintain general anesthesia after it is initiated with sodium thiopental [3.5–5 mg/kg IV] and fentanyl [100–250 mg IV]. After tracheal intubation, all the studied cases had been ventilated using

intermittent positive-pressure breathing with minute volume of 0.1 L/kg and fraction of inspired oxygen [FIO₂] of 0.5 to 1 depending on the stage of cardiac surgery. Muscle relaxation had been achieved using intravenous pancuronium [0.1 mg/kg IV]. Nitroglycerin was administered intravenously as a vasodilator when indicated, IV dopamine and IV dobutamine as inotropes, and IV norepinephrine and IV ephedrine as vasopressors, when necessary according to the attending anesthesiologist to keep stable patients' hemodynamics, with intermittent IV insulin boluses or infusions, blood glucose level had been maintained controlled in the diabetic cases [> 140 mg/dL]. No studied case received corticosteroids.

All the included conventional cardiac surgeries had been performed using the standard full median sternotomy incision. The whole blood activated coagulation time [ACT] had been maintained [> 400 seconds] for the whole length of the CPB with intermittent IV heparin administration after the administration of the initial pre-bypass bolus heparin dose of unfractionated heparin [300 IU/kg IV]. A roller pump [Stockert heart lung machine; Sarns terumo system-1 heart lung machine] were used for the CPB. With these roller pumps, either the extracorporeal circuit with synthetic phosphorylcholine-coated oxygenator [Sarns-Terumo Group] or the extracorporeal circuit with microporous polypropylene membrane oxygenator with integrated venous cardiotomy reservoir had been employed. Only oxygenator membrane had been handled with biocompatible coating. Non-heparin-bonded arterial and venous polyvinyl chloride cannulae were used. [1500 mL] of Ringers solution, [60 mL] of sodium bicarbonate 7.5 %, and 2500 Units of unfractionated heparin were used as the prime oxygenator. All the studied cases had CPB while using mild hypothermic temperature control approach [$32 - 34$ °C] and alpha-stat [α -stat] blood gas management.

Throughout the CPB, the pump blood flow had been kept at average of [2.4 L/min] and the mean arterial pressure had been kept among 60 to 90 mmHg. The blood potassium level had been managed between [4.0 - 5.5 mEq/L], the hematocrit level had been maintained at average of 24 to 28%, and the urine output with or without induced diuresis had been kept between 100 and 150 mL/h, with the administration of mannitol and furosemide as needed. Depending on each surgeon's preference, myocardial protection had been performed using intermittent antegrade and retrograde cold blood or cold crystalloid cardioplegic solution [standard Custodiol crystalloid cardioplegic solution] [4 °C]. Throughout the cross-clamping period, the cardioplegia

had been repeated every [30 to 40 minutes] or whenever electrical activity had been restored.

All the studied cases had been transferred to the intensive care unit [ICU] before recovering from general anesthesia and received mechanical ventilation while receiving continuous IV infusion of propofol [1–3 mg/kg/h]. Remaining heparin had been neutralized by protamine sulphate in ratio of [1:1] at the end of the CPB, with additional protamine given as required to return the ACT to the baseline pre-operative ACT values. The propofol infusion had been discontinued gradually, and the studied cases had been weaned from the ICU ventilator and were extubated in the ICU after confirming that there was no significant post-operative bleeding from the drainage chest tubes [< 50 mL/h], the core body temperature had been maintained higher than [36 °C], the circulatory hemodynamic status had been maintained stable, and the arterial blood gas [ABG] data had been adequately corrected as needed to maintain their normal range values and the studied cases had been discharged from the ICU when they matched the ICU discharge criteria [alert, cooperative, extubated, stable hemodynamics, adequate urine output, normal hematologic values, chest X-rays, ECG without any significant cardiac arrhythmia. As general rule, the studied cases received blood transfusion when their hemoglobin level reduced under [8 gm/dL].

Outcomes

The patient results that had been analyzed include mortality [throughout the same hospitalization], morbidity items such as renal function impairment, respiratory system complications, neurologic insults, abdominal complications, and post-operative infection. Other factors analyzed were post-operative blood losses, re-operation for post-operative bleeding, length of stay in the ICU, total hospital length of stay. Renal complications were defined as oliguria [> 1 mL/kg/h], anuria, or a serum creatinine increase exceeding 2 mg/dL. Respiratory complications were defined as mechanical ventilation lasting longer than twenty-four hours without an apparent cardiac reason or Acute Respiratory Distress Syndrome [ARDS]. Neurologic complications were defined as coma or a new permanent focal neurologic deficit. Abdominal upper or lower gastrointestinal complications were identified as gastrointestinal bleeding, perforation, or intestinal ischemia. Multiple blood transfusions were defined as the transfusion of 3 or more units of red blood cells, including

intraoperative transfusions. Infections were defined as fever with an increased white blood cell count and positive culture specimens.

Ethics of study: An ethical approval for research had been obtained from the ethical committee of Faculty of medicine, Tanta University number [36264 PR 44/1/23] and there was adequate provision to maintain the privacy of the participants and confidentiality of the data through putting a code number for each participant from the beginning to end of research and outcomes of this research were used only for scientific purposes.

Statistical analysis: Using SPSS 26.0 for Windows [SPSS Inc., Chicago, IL, USA], all study data had been gathered, tabulated, and statistically analyzed. Number and percentage had been used for defining qualitative data. range [minimum and maximum], mean, standard deviation, median had been used to characterize quantitative data. Every statistical comparison used 2-tailed significance test. P-value levels ≤ 0.05 denote substantial differences, while P-value of 0.05 denotes nonsignificant differences. The used tests had been Chi-square [X^2] test of significance had been used to compare proportions among qualitative parameters and independent t-test: had been used to compare between 2 independent groups with parametric quantitative data.

RESULTS

There was no significant statistical difference among the 3 groups as regard to the age, sex, diseased coronary vessels, body weight or body mass index [Table 1].

There was no significant statistical difference among the 3 groups as the pre-operative comorbidities [Table 2].

There was no significant statistical difference among the 3 groups as regard to the pre-operative serum creatinine level and the pre-operative LVEF % [Table 3].

There had been a significant statistical difference among the 3 groups of the studied patients as regard to the post-operative renal complications, the respiratory complications, the neurologic complications, the need for repeated or multiple blood transfusion and the incidence of the post-operative infection and the occurrence of post-operative patients' mortality [Table 4].

Table [1]: Comparison between the 3 groups as regard the patients' demographic data

		Group A [CPB up to 60 minutes]	Group B [CPB from 60 to 120 minutes]	Group C [CPB more than 120 minutes]	P-value
Age [years]	Mean \pm SD	55.4 \pm 3.71	55.30 \pm 3.65	55.39 \pm 3.70	0.97
	Median [Min. – Max.]	55 [49-63]	56 [49-63]	55 [49-63]	
Sex, n [%]	Male	91	89	89	
	Female	59	61	61	
Weight [Kg]	Mean \pm SD	72.2 \pm 5.88	72.60 \pm 5.2	72.62 \pm 5.15	0.18
	Median [Min. – Max.]	71.5 [63-84]	72 [63-84]	72 [63-84]	
BMI [kg/m²]	Mean \pm SD	25.2 \pm 1.42	25.25 \pm 1.55	25.19 \pm 1.55	0.47
	Median [Min. – Max.]	25.1 [22.4-28.1]	25.2 [22.4-28.3]	25.2 [22.4-28.3]	
Diseased coronary vessels [CAD]					
	One vessel CAD	31	29	30	
	Two vessel CAD	52	54	53	
	Multi-vessel CAD	67	67	67	

Chi Square, ANOVA, p value >0.05: nonsignificant, p value

Table [2]: Comparing the 3 groups as regards the patients' co-morbidities

	Group A	Group B	Group C	P-value
Diabetes Mellitus [DM]	110	106	110	0.69
Hypertension [HTN]	122	119	122	0.37
Chronic obstructive pulmonary disease [COPD]	121	117	121	0.65
Previous myocardial infarction [MI]	45	42	45	0.8
Stroke	1	0	1	0.31
Dialysis	0	0	0	-
Smoking	80	79	80	0.64
New York Heart Association Class [NYHA class]				
	[NYHA class] I	13	12	10
	[NYHA class] II	99	96	93
	[NYHA class] III	25	29	32
	[NYHA class] IV	13	13	15

Chi Square, p value >0.05: nonsignificant, p value

Table [3]: Comparing among the 3 groups as regard the pre-operative level of serum creatinine and the pre-operative LVEF %

	Group A	Group B	Group C	P-value	
Pre-operative creatinine level					
	Mean \pm SD	1.14 \pm 0.25	1.13 \pm 0.26	1.09 \pm 0.26	0.859
	Median [Minimum - Maximum]	1.15 [0.65-1.64]	1.12 [0.65-1.68]	1.06 [0.65-1.62]	
Pre-operative left ventricular ejection fraction [LVEF %]					
	Mean \pm SD	57.83 \pm 7.21	58.25 \pm 8.02	58.07 \pm 7.67	0.430
	Median [Minimum - Maximum]	58 [44-73]	58 [44-73]	58 [44-73]	

ANOVA Test, p value >0.05: nonsignificant, p value

Table [4]: Comparing among the 3 groups as regard the pre-operative level of serum creatinine and the pre-operative LVEF %

	Group A [CPB up to 60 minutes]	Group B [CPB 60 to 120 minutes]	Group C [CPB more than 120]	P-value
Renal complications	2	5	14	0.002
Respiratory complications	1	6	11	0.013
Neurologic complications	0	3	10	0.001
Abdominal gastrointestinal complications	0	2	4	0.13
Multiple blood transfusion	0	3	6	0.04
Post-operative infection	0	3	6	0.04
Mortality	0	3	10	0.001

Chi Square, p value >0.05: nonsignificant, p value

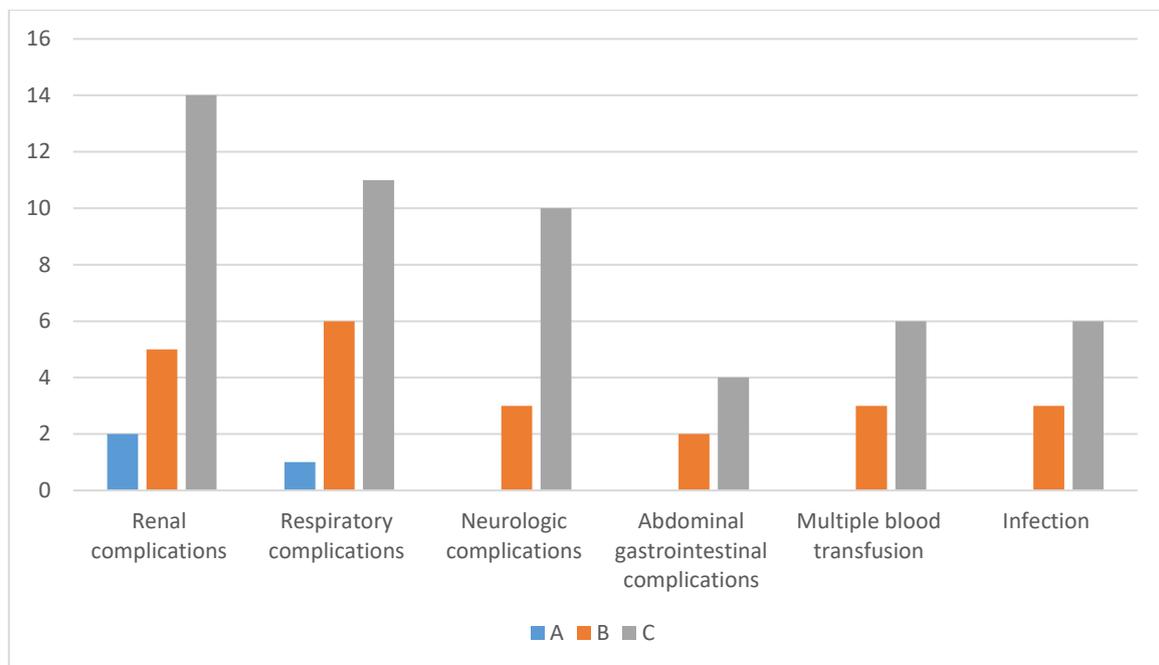


Figure [1]: Comparison between the 3 groups as regard the occurrence of post-operative complications

DISCUSSION

The cardiopulmonary bypass [CPB] is the extracorporeal circulation via the heart lung machine and its tubing systems used during open heart surgery and is one of the greatest developments that allowed for the growth and the advancements of the field of cardiac surgery [8].

In 1980, **Kirklin** [9] indicated that the CPB causes “whole-body systemic inflammatory response.” This “post-perfusion syndrome,” is similar to the pathophysiologic entity referred to as “SIRS” [systemic inflammatory response syndrome], which is manifested by hyperdynamic circulatory state, with reduction of the systemic vascular resistance and increase of the cardiac work, in addition to increase of capillary permeability, increase of 3rd space body fluid retention, leukocytosis, and parenchymatous multi-organ dysfunction. Such risks and complications are worsened by the increasing or the prolongation of the duration of CPB time. Several investigators attempted to reveal link between duration of CPB time and the duration of the aortic cross-clamp time and the severity of the resulting systemic inflammatory response.

Over the past decades, several technologies have been conducted and improved with the goal of reducing the CPB related complications. These technologies included the heart lung machine sensors as the level detector, the bubble detector,

the arterial blood gases [ABG] analyzer, the pressure sensor, the centrifugal pumps, the improved membrane oxygenators, the activated clotting time [ACT] system and the heparin-bound circuit tubing systems. These advancements aimed to reduce air emboli and reduce thrombus formation within the CPB circuit, and thus decrease and minimize the possible thrombo-embolic complications. Despite such advancements, Magnetic resonance imaging [MRI]-using studies have revealed significant high rates of new, but clinically insignificant, brain lesions detected after on-pump cardiac surgery [10].

Additionally, the duration of CPB runs are also related to elevation of the pro-inflammatory cascades, which can result in systemic vasoplegia and multiple end-organ mal-perfusion and multi-organ dysfunction. As the heart lung machines are essential and even mandatory for the field of cardiac surgery, the CPB technology remains an area for improvement. Because of the known and evident complications and increased morbidity and mortality risks with prolonged CPB usage, it is universally accepted that pump runs or cardiopulmonary bypass time should be kept to the minimum adequate time or inevitable duration needed for conduction and completion of the open heart surgery operations, and that cardiac procedures can be planned to be conducted in such a smart way to eliminate the unnecessary CPB time and to decrease the aortic cross-clamp time as much as possible [11].

Our study is a retrospective observational and comparative single-center study that assessed effect of the CPB time duration on the post-operative patients' outcome and on the occurrence of post-operative patients' morbidity and mortality such as the impact of CPB on the renal function and on the development of acute kidney injury [AKI]. The study results revealed that length of the CPB time duration had been proportionally related to the increase incidence of the occurrence of post-operative renal dysfunction, post-bypass systemic vasoplegia, postoperative pulmonary complications, post-bypass hemolysis and post-operative anemia, post-operative hemodynamic instability and post-operative disseminated intravascular coagulation [DIC].

The results of our study revealed no statistically significant difference among the 3 studied groups regarding the demographic data as the patients age, sex, diseased coronary vessels, body weight or body mass index and that there had been no statistically significant difference among the 3 groups as regard to the pre-operative serum creatinine levels and the pre-operative left ventricular ejection fraction percent and also revealed that there is a statistically significant difference among the 3 groups regarding the post-CPB complications like renal complications, respiratory complications, neurologic complications, the need for repeated or massive blood transfusions and the rate of occurrence of post-operative infection.

Results of our study agreed with the results of the study done by **Mangano et al.** [12] who found that the postoperative renal impairment had been related to the prolonged CPB time lasting for 3 or more hours. The systemic inflammatory response following contact exposure to CPB circuit plays significant role in pathophysiologic mechanisms hypothesized for post-CPB renal failure, which have been like mechanisms for post-pump adult respiratory distress syndrome [ARDS].

Results of our study also agreed with the results of the study done by **Bucerius et al.** [13] who detected that the CPB time longer than 2 hours was independent predictor of stroke. The length of CPB time had been found to be a reliable predictor of post-operative stroke.

Results of our study also agreed with the results of the study done by **Parr et al.** [14] who concluded that the higher chance of receiving 2

or more units of blood products transfusion including packed red blood cells, platelets, fresh frozen plasma, or cryoprecipitate, as well as the surgical re-exploration for post-operative bleeding, were found to be related to length of CPB time duration and there was very correlation between the CPB time and the occurrence of post-operative bleeding [chest drain outputs], the need for multiple or repeated blood transfusions [3 or more units of red blood cells], and the frequency of surgical re-exploration for bleeding.

Results of our study also agreed with the results of the study done by **Naughton et al.** [15] who found that the longer the duration of extracorporeal circulation predicts significantly prolonged intubation time and mechanical ventilation time, and that CPB time [in 30-minute increments] has been the only intra-operative variable that increased the risk of postoperative respiratory failure. Prolonged CPB time is implicated as a reason for "post-pump" ARDS, triggered by the systemic inflammatory response that leads to increased pulmonary endothelial permeability. This response together with the sequestration of neutrophils in the pulmonary capillaries with elevation in interleukins and enzymes activity, are correlated with the post-operative pulmonary complications.

Results of our study also agreed with the results of the study done by **Boldt et al.** [16] who found that although the CPB times in their study had been 58 ± 12 minutes and 116 ± 18 minutes, respectively, the baseline creatinine before CPB had been without variations among groups.

Results of our study also agreed with the results of the study done by **Taniguchi et al.** [17] who compared the postoperative hospital result of on-pump coronary artery bypass grafting surgery in studied cases with shorter CPB time duration versus the outcome of patients with longer CPB time duration. They reported similar findings regarding body mass index [BMI] and other anthropometric measures. They also found a statistically significant difference regarding the incidence of acute kidney injury as it was 1.3% in the shorter CPB group and 12.5 % in the longer CPB group with significant [p-value = 0.01].

Results of our study also agreed with the results of the study done by **Salis et al.** [7] who found that multi-variate statistical analysis revealed a significant [p-value < 0.001] relationship among

the prolonged CPB and the occurrence of post-operative neurologic complications.

Results of our study also agreed with the results of the study done by **Nissinen *et al.*** ^[4] who suggested that the optimal CPB time should be kept under [180-240 minutes] to minimize the risk of severe complications and/or mortality. They also found that, the prolonged CPB time was associated with increased rates of [30-day] mortality.

Results of our study also agreed with the results of the study done by **Madhavan *et al.*** ^[18] who found that the prolonged cumulative CPB time [> 180 minutes] had been significant in determining post-operative problems, extended stay in intensive care unit, and extended use of mechanical ventilation.

Results of our study also agreed with the results of the study done by **Axtell *et al.*** ^[2] who found that the prolonged CPB time was associated with the occurrence of statistically significant postoperative renal dysfunction [P-value = 0.001] had been significantly variation in the studied groups.

Results of our study also agreed with the results of the study done by **Arif *et al.*** ^[19] who found that the difference between baseline serum creatinine levels among the short CPB time group and the prolonged CPB time group had not been statistically significant [p-value 0.093]. They also found a significant relationship between existence of acute renal Injury and the CPB duration.

Limitations of the study: Main limitation of our research has been its nature being a retrospective research, it has many confounding variables. Another limitation, being a single-center study so the cohort of studied patients was limited to the study center location.

Conclusion: The conclusion of this study is that the prolongation of [CPB] duration has been major predictor of increase of the post-operative patients' morbidity and mortality after conventional cardiac surgery operations. The length of [CPB] duration is proportionally related to the increase of the incidence of patients' overall morbidity and mortality post-cardiac surgery with the cardiopulmonary bypass time that is up to [60 minutes] being the safest time with the least post-operative complications and the least mortality.

Financial and conflict of interest: None

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