

Early Neurological Complications after Cardiac/Aortic Surgery with Cardiopulmonary Bypass: Incidence and Risk Factors

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Objective: To examine the incidence and risk factors of early neurological complications after cardiac or aortic surgery using cardiopulmonary bypass technique in King Chulalongkorn Memorial Hospital, Thailand.

Materials and Methods: The present study was a retrospective cohort study. Clinical data of adult patients that underwent cardiac or aortic surgery using cardiopulmonary bypass technique in 2018 were reviewed from the electronic medical record in the authors' center.

Results: Early postoperative neurological complications occurred in 33 (8.3%) of the 400 patients. Twenty of them (60.6%) had non-specific encephalopathy, three (9.1%) had hypoxic-ischemic encephalopathy, five (15.2%) had provoked seizure, four (12.1%) had cerebral infarction, and one (3.0%) had intracranial hemorrhage. Associated clinical factors included history of essential hypertension [adjusted odds ratio 3.448 (95% CI 1.266 to 9.391)], combined coronary artery bypass grafting and valve surgery [adjusted odds ratio 4.759 (95% CI 1.182 to 19.170)], multi-valve surgery [adjusted odds ratio 5.201 (95% CI 1.227 to 22.049)], aortic surgery [adjusted odds ratio 17.260 (95% CI 4.168 to 71.468)], higher midazolam dosage [adjusted odds ratio 1.009 (95% CI 1.002 to 1.015)], higher serum lactate prior to discontinuing cardiopulmonary bypass [adjusted odds ratio 1.263 (95% CI 1.093 to 1.460)], and presence of intraoperative intra-aortic balloon pump use [adjusted odds ratio 6.160 (95% CI 1.883 to 20.150)].

Conclusion: Early postoperative neurological complications rate of cardiac or aortic surgery using cardiopulmonary bypass technique in the present study settings was 8.3%. Preoperative and intraoperative clinical factors associated with such complications were the history of essential hypertension, the type of surgery such as combined coronary artery bypass grafting and valve surgery, multi-valve surgery, and aortic surgery, the higher midazolam dosage, the higher serum lactate prior to discontinuing cardiopulmonary bypass, and the presence of intraoperative intra-aortic balloon pump use.

Keywords: Cardiac surgery; Aortic surgery; Cardiopulmonary bypass; Postoperative neurological complications; Encephalopathy

Received 19 May 2020 | Revised 19 May 2021 | Accepted 26 May 2021

J Med Assoc Thai 2021;104(7):1060-6

Website: <http://www.jmatonline.com>

Neurological complications after cardiac surgery are the important problems as they commonly lead to morbidity, prolonged length of hospital stay, and even mortality^(1,2). The incidence rate of neurological complications after cardiac and

aortic surgery were 0.9% to 24.7% and depended on multiple factors such as age group and type of surgery⁽³⁻¹⁰⁾. Early neurological complications were defined as neurological abnormalities detected within 24 hours after surgery⁽¹¹⁾ and suspected to occur intraoperatively⁽¹²⁾. In one study, they were classified into reversible and irreversible complications, based on a presence of neurological sequelae⁽¹³⁾. In other studies, the classification was based on clinical presentation, which were stroke, seizure, and encephalopathy^(1,11).

Risk factors of neurological complications after cardiac surgery were varied across studies^(8,10-14). These included previous ischemic stroke, preoperative bilateral carotid stenosis, hypertension, previous cardiac surgery, infection including endocarditis, emergency surgery, prolonged use of cardiopulmonary bypass (CPB) machine more than two hours, and

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How to cite this article:

Thanprasertsuk R, Thanprasertsuk S, Sirinawin C, Indrambarya T. Early Neurological Complications after Cardiac/Aortic Surgery with Cardiopulmonary Bypass: Incidence and Risk Factors. J Med Assoc Thai 2021;104:1060-6.

doi.org/10.35755/jmedassocthai.2021.07.11427

blood component transfusion. Clinical surveillance for early diagnosis and management of postoperative neurological complications can be promptly initiated based on this information.

However, study regarding incidence rate and risk factors of early neurological complications after cardiac or aortic surgery in Thailand, even in tertiary care center, is still lacking. To explore these points, the authors retrospectively reviewed the incidence rate and risk factors of the early neurological complications after cardiac and aortic surgery in King Chulalongkorn Memorial Hospital (KCMH), Thailand.

Materials and Methods

Study population

All patients older than 18-year-old that underwent cardiac or aortic surgery with the use of CPB in KCMH in 2018 were included in the present study. The authors excluded the patients if their neurological status before surgery had not been recorded or if the patient died during the operation. The present study was approved by the Institutional Review Board Committee (IRB No. 225/62) and the informed consent was waived due to the retrospective study design.

Data collection

The authors retrospectively reviewed and collected patients' baseline characteristics and perioperative data from their medical records and databases of the operative room and intensive care unit (ICU). Results of brain computed tomography (CT) were also noted in cases with early postoperative neurological complications.

Definitions of neurological complications

Early postoperative neurological complications were defined as neurological dysfunction detected within 24 hours following surgery that did not occur prior to the surgery. The authors classified early postoperative neurological complications into ischemic stroke, intracranial hemorrhage, provoked seizure, hypoxic ischemic encephalopathy, and non-specific encephalopathy. The authors diagnosed ischemic stroke when the patient rapidly developed clinical signs of focal neurological deficit without evidence of intracranial hemorrhage in the brain CT image. Intracranial hemorrhage was diagnosed when the patient developed neurological symptoms or signs with demonstrable evidence of any acute intracranial hemorrhage in the brain CT image relevant to the

neurological deficits. Provoked seizure was diagnosed in the patient who developed transient abnormal motor activity (seconds to minutes) consistent with seizure activity at least one time with 1) a previous history of seizure, or 2) demonstrable old focal lesion(s) in the brain CT image. The authors defined hypoxic-ischemic encephalopathy as a comatose or near-comatose status with 1) an obvious intraoperative record of prolonged shock such as a mean arterial pressure (MAP) of less than 50 mmHg for more than five minutes, or 2) a record of prolonged intraoperative cardiac arrest, or 3) a demonstrable evidence of global cerebral ischemia in the brain CT image. Lastly, non-specific encephalopathy included patients who had altered level of consciousness, delirium or confusion and were not compatible with other diagnoses. Anesthesiologist and neurologist in the study team (Thanprasertsuk R and Thanprasertsuk S, respectively) were responsible for diagnosing and categorizing the early neurological complications. At the time of assessment, these two members were not aware of patients' risk factors and intraoperative data, except for the data on prolonged intraoperative shock or cardiac arrest.

Statistical analysis

Descriptive statistics for continuous and categorical variables were reported as mean \pm standard deviation (SD) and absolute number (percentage), respectively. Comparisons of the variables between patients with and without postoperative neurological complications were made. Student's t-test was performed for continuous variables and Pearson's chi-squared or Fisher's exact tests were performed for categorical variables. Clinically relevant factors from the univariate analyses were then applied in the multivariate logistic regression model to identify independent risk factor(s). A p-value of less than 0.05 indicated a statistical significance. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA).

Results

In 2018, 406 patients had undergone cardiac or aortic surgery with CPB in KCMH. Two patients were excluded due to lack of information regarding preoperative neurological condition and four patients were excluded due to intraoperative death, leaving 400 patients for analyses. Based on the American Society of Anesthesiologists physical status (ASA-PS) classification system, all included patients were

Table 1. Demographic data and perioperative variables in patients with and without early neurological complications

	Patients with neurological complications (n=33); mean±SD	Patients without neurological complications (n=367); mean±SD	p-value
Demographic data and preoperative variables			
Age (years)	63.9±15.2	60.3±15.6	0.208
Female; n (%)	14 (42.4)	144 (39.2)	0.720
BMI (kg/m ²)	23.1±5.4	24.1±4.3	0.231
Serum creatinine (mg/dL)	1.5±1.3	1.2±0.9	0.060
LVEF (%)	57.0±13.3	55.9±21.4	0.770
Hypertension; n (%)	24 (72.7)	209 (56.9)	0.078
Diabetes mellitus type II; n (%)	11 (33.3)	108 (29.4)	0.638
Previous stroke; n (%)	4 (12.1)	28 (7.6)	0.321
Previous heart surgery; n (%)	4 (12.1)	27 (7.4)	0.308
Active endocarditis; n (%)	1 (3.0)	5 (1.4)	0.405
Recent myocardial infarction ^a ; n (%)	0 (0.0)	3 (0.8)	1.000
Pulmonary hypertension ^a ; n (%)	12 (36.4)	123 (33.5)	0.740
Presence of preoperative IABP use ^a ; n (%)	4 (12.1)	16 (4.4)	0.072
Intraoperative variables			
Emergency surgery; n (%)	11 (33.3)	32 (8.7)	<0.001*
Type of surgery; n (%)			<0.001*
• CABG	5 (15.2)	134 (36.5)	
• Single valve surgery	4 (12.1)	79 (21.5)	
• Combined surgery (CABG + valve)	6 (18.2)	28 (7.6)	
• Multi-valve surgery (more than 1 valve)	5 (15.2)	48 (13.1)	
• Aortic surgery	11 (33.3)	27 (7.4)	
• Adult congenital heart surgery	1 (3.0)	25 (6.8)	
• Heart transplantation	0 (0.0)	14 (3.8)	
• Others	1 (3.0)	12 (3.3)	
Operative time (minutes)	398.0±153.3	303.9±106.2	0.001*
CPB time (minutes)	214.2±101.6	136.5±58.3	<0.001*
Aortic cross clamping time (minutes)	111.2±61.9	99.8±53.4	0.247
Use of circulatory arrest technique; n (%)	8 (24.2)	13 (3.5)	<0.001*
• Circulatory arrest time ^b (minutes)	43.8±32.0	45.2±19.0	0.900
• Use of cerebral perfusion technique ^b	7 (87.5)	10 (76.9)	1.000
• Cerebral perfusion duration ^c (minutes)	44.9±27.5	36.2±26.1	0.479
Hypotension during CPB ^a ; n (%)	22 (66.7)	130 (35.4)	0.001*
Serum lactate prior to discontinuing CPB (mmol/L)	4.2±3.8	1.9±1.6	0.002*
Blood transfusion; n (%)	32 (97.0)	347 (94.6)	1.000
• Packed red cells (units)	4.9±4.4	2.4±2.4	0.002*
• Fresh frozen plasma (units)	5.0±4.4	2.9±2.9	0.011
• Leukocyte-poor platelet concentrate (units)	1.4±0.8	0.9±0.6	0.002*
• Cryoprecipitate (units)	9.3±10.8	2.6±6.2	0.001*
Midazolam dosage (mcg/kg)	133.0±68.3	106.9±65.8	0.041*
Fentanyl dosage (mcg/kg)	9.5±4.3	9.2±3.0	0.730
Dexmedetomidine use; n (%)	1 (3.0)	36 (9.8)	0.343
Tranexamic acid use; n (%)	27 (81.8)	265 (72.2)	0.234
Tranexamic acid dosage (mg/kg)	15.8±10.6	12.5±9.4	0.060
Presence of mechanical circulatory support; n (%)	9 (27.3)	23 (6.3)	0.002*
• IABP ^{a,d}	8 (24.2)	21 (5.7)	0.001*
• LVAD ^d	0 (0.0)	1 (0.3)	1.000
• ECMO ^d	1 (3.0)	1 (0.3)	0.158
Postoperative variables			
Vasoactive inotropic score ^a upon arrival at ICU	33.0±61.8	10.8±22.2	0.048*
Arterial blood gas upon arrival at ICU			
• pH	7.37±0.08	7.420±0.06	0.002*
• Lactate level (mmol/L)	6.5±5.1	3.6±2.9	0.003*
• PaO ₂ (mmHg)	184.9±104.1	184.7±87.1	0.990
P/F ratio upon arrival at ICU	249.8±141.4	264.7±30.6	0.541
Body temperature upon arrival at ICU (°C)	36.3±0.8	36.8±0.7	0.001*
Postoperative fever ^a in first 24 hours; n (%)	15 (45.5)	220 (59.9)	0.105

BMI=body mass index; CABG=coronary artery bypass grafting; CPB=cardiopulmonary bypass; ECMO=extracorporeal membrane oxygenation; IABP=intra-aortic balloon pump; ICU=intensive care unit; LVAD=left ventricular assist device; LVEF=left ventricular ejection fraction; SD=standard deviation

* Comparisons showing significant difference between the groups

^a Recent myocardial infarction: history acute coronary syndrome within 24 hours prior to surgery; Pulmonary hypertension: mean pulmonary arterial pressure of equal to or more than 25 mmHg at rest, measured by right heart catheterization or echocardiography; Presence of preoperative IABP use: patient with the use of IABP, which has been initiated prior to the operation; Presence of intraoperative IABP use: patient with the use of IABP, which is initiated prior to or during the operation; Hypotension during CPB: mean arterial pressure of less than or equal to 50 mmHg for more than 5 consecutive minutes during CPB; Vasoactive inotropic score: summation of dobutamine dose, dopamine dose, 10 times of milrinone dose, 100 times of epinephrine dose, and 100 times of norepinephrine dose (mcg/kg/min); Fever: rectal temperature of equal to or more than 37.8°C; ^b Applicable only in the patients underwent circulatory arrest technique; ^c Applicable only in the patients with the use of cerebral perfusion technique; ^d Percentage within the patients who had mechanical circulatory support

Table 2. Univariate analysis of risk factors for neurological complications

	Crude odds ratio (95% CI)	p-value
Hypertension	2.016 (0.912 to 4.457)	0.083
Presence of preoperative IABP use	3.026 (0.949 to 9.645)	0.061
Emergency surgery	5.234 (2.330 to 11.761)	<0.001*
Type of surgery		
CABG	1	
Single valve surgery	1.357 (0.354 to 5.202)	0.656
Combined surgery (CABG + valve)	5.743 (1.638 to 20.140)	0.006*
Multi-valve surgery	2.792 (0.774 to 10.068)	0.117
Aortic surgery	10.919 (3.509 to 33.973)	<0.001*
Adult congenital heart surgery	1.072 (0.120 to 9.570)	0.950
Heart transplantation	0.000	0.999
Others	2.233 (0.241 to 20.703)	0.479
Operative time (minutes)	1.006 (1.003 to 1.008)	<0.001*
CPB time (minutes)	1.013 (1.008 to 1.018)	<0.001*
CPB time >2 hours	4.676 (1.766 to 12.378)	0.002*
Circulatory arrest technique	8.714 (3.304 to 22.978)	<0.001*
Hypotension during CPB	3.646 (1.714 to 7.755)	0.001*
Serum lactate prior to discontinuing CPB (mmol/L)	1.372 (1.209 to 1.558)	<0.001*
Blood transfusion (unit)		
Packed red cells	1.297 (1.154 to 1.459)	<0.001*
Fresh frozen plasma	1.139 (1.048 to 1.239)	0.002*
Leukocyte-poor platelet concentrate	2.320 (1.497 to 3.596)	<0.001*
Cryoprecipitate	1.094 (1.053 to 1.137)	<0.001*
Midazolam dosage (mcg/kg)	1.006 (1.001 to 1.012)	0.032*
Intraoperative mechanical circulatory support	4.786 (1.944 to 11.785)	0.001*
Presence of intraoperative IABP use	5.272 (2.123 to 13.097)	<0.001*
Vasoactive inotropic score upon arrival at ICU	1.014 (1.006 to 1.022)	0.001*
Arterial blood gas upon arrival at ICU		
Lactate level (mmol/L)	1.199 (1.105 to 1.300)	<0.001*

CABG=coronary artery bypass grafting; CI=confidence interval; CPB=cardiopulmonary bypass; IABP=intra-aortic balloon pump; ICU=intensive care unit

* Statistically significant

in the definition of ASA III or IV. Early postoperative neurological complications occurred in 33 patients (8.3%). Four of them (12.1%) had ischemic stroke, one (3.0%) had intracerebral hemorrhage, five (15.2%) had provoked seizure, three (9.1%) had hypoxic-ischemic encephalopathy, and 20 (60.6%) had non-specific encephalopathy. Table 1 shows the demographic data and perioperative variables in the patients with and without early neurological complications.

According to the univariate analyses, potential

Table 3. Multivariate analysis of risk factors for neurological complications

	Adjusted odds ratio (95% CI)	p-value
Hypertension	3.448 (1.266 to 9.391)	0.015*
Type of surgery		
CABG	1	
Single valve surgery	2.244 (0.506 to 9.954)	0.287
Combined surgery (CABG+valve)	4.759 (1.182 to 19.170)	0.028*
Multi-valve surgery	5.201 (1.227 to 22.049)	0.025*
Aortic surgery	17.260 (4.168 to 71.468)	<0.001*
Adult congenital heart surgery	4.748 (0.418 to 53.892)	0.209
Heart transplantation	0.000	0.999
Others	4.189 (0.332 to 52.901)	0.268
Serum lactate prior to discontinuing CPB (mmol/L)	1.263 (1.093 to 1.460)	0.002*
Midazolam dosage (mcg/kg)	1.009 (1.002 to 1.015)	0.010*
Presence of intraoperative IABP use	6.160 (1.883 to 20.150)	0.003*

CABG=coronary artery bypass grafting; CI=confidence interval; CPB=cardiopulmonary bypass; IABP=intra-aortic balloon pump

* Statistically significant

risk factors of early postoperative neurological complications in the present setting included emergency surgery, combined surgery, aortic surgery, longer operative time, longer CPB time, use of circulatory arrest technique, presence of hypotension during CPB, higher serum lactate prior to discontinuing CPB, presence of blood component transfusion, higher dose of midazolam, presence of intraoperative intra-aortic balloon pump (IABP) use, higher vasoactive inotropic score, and higher lactate level upon arrival at ICU (Table 2). History of essential hypertension, combined surgery, multi-valve surgery, aortic surgery, higher midazolam dosage, higher last serum lactate during CPB, and presence of intraoperative IABP use were found to be independently associated with and might predict early neurological complications (Table 3).

Discussion

The present study revealed that the incidence of early neurological complications after cardiac or aortic surgery in a Thai university hospital was 8.3%. This incidence rate is comparable to many previous reports^(11,12,15-17). Some other studies, however, reported a very much lower or higher incidence rate^(3-5,9). Dissimilarity of study population may account for this difference. For example, two studies in patients that underwent aortic and aortic valve surgery reported higher incidence of early neurological complications at 24.7% and 19.0%,

respectively^(5,9). While another two studies in patients underwent coronary artery bypass grafting (CABG) and surgery for adult congenital heart disease reported lower incidence at 2.0% and 0.9%, respectively^(3,4).

There are several causes of cerebral injury after cardiac surgery. These include micro- and macroembolization, cerebral hypoperfusion, arrhythmias, systemic inflammatory response, genetic factors, anesthetic agents, and pre-existing cerebrovascular disease^(1,18). During cardiac or aortic surgery, there are many sources of embolism, including atherosclerotic debris, surgical debris, lipid, and air⁽¹⁹⁾. Brain magnetic resonance images (MRI) in patients with stroke after cardiac surgery demonstrated areas of acute or subacute infarction in different locations, mainly distributed in the watershed areas^(17,19). In cases with severe encephalopathy, brain MRI showed diffuse cortical necrosis⁽¹⁷⁾. In the present study, history of essential hypertension, combined surgery, multi-valve surgery, aortic surgery, higher midazolam dosage, higher serum lactate prior to discontinuing CPB, and presence of intraoperative IABP use were identified as independent risk factors of early neurological complications by multivariate analysis. There were several mechanisms that may explain how these risk factors are associated with cerebral injury.

Chronic hypertension was found to be an independent risk factor of neurological complications as in several previous studies^(8,11,16). The association between history of chronic hypertension and risk of early postoperative neurological complications is possibly due to the changes in cerebral perfusion autoregulatory curve. Generally, low blood pressure during surgery can increase postoperative neurological complications because of cerebral hypoperfusion. The brain, however, has autoregulation mechanism to maintain the cerebral perfusion during low blood pressure state. Nevertheless, the cerebral perfusion autoregulatory curve in patients with chronic hypertension may shift to the right, leading to a more ischemic vulnerability of brain tissue comparing to normal population⁽¹⁾.

Combined surgery and multi-valve surgery may associate with the higher risk of neurological complications by many ways. Firstly, these operations have higher chance of cerebral embolism from both tissue debris and air. Secondly, these operations generally require longer operative time and longer CPB time. Thirdly, clinical baseline of the patients underwent these operations is usually worse because of diseases with multiple pathologic sites. One

previous work also rated postoperative stroke to be higher in multi-valve surgery or combined surgery, comparing to other types of cardiac surgery⁽⁸⁾. While in the aortic surgery, inadequate cerebral perfusion during the process of hypothermic circulatory arrest technique should be responsible for the higher rate of neurological complications⁽⁹⁾. Additionally, most of this operation is likely performed in an emergency, which the patient's condition may not have been prepared adequately.

There has been no study regarding the association between early neurological complications after cardiac surgery and intraoperative use of benzodiazepine. In the present study, midazolam use was found to be significantly higher in patients with neurological complications and was identified as a risk factor by univariate and multivariate analyses. However, the clinical relevance may not be outstanding since the adjusted odd ratio was only 1.008 (1.001 to 1.014).

Another interesting risk factor from the present study analysis is the higher level of serum lactate prior to discontinuing CPB, which is under the definition of early onset hyperlactatemia⁽²⁰⁾. Hyperlactatemia can be the result from both hypoxic, either regional or generalized hypoxia, and non-hypoxic mechanisms. Stress-induced accelerated aerobic metabolism has major contribution to non-hypoxic mechanism. Early onset hyperlactatemia is strongly associated with adverse surgical outcomes⁽²⁰⁻²²⁾. It was hypothesized to be associated with microcirculatory dysfunction due to the pro-inflammatory effects of CPB⁽²⁰⁾. In any case, the cause of hyperlactatemia should be instantly explored, and the management should be promptly initiated to prevent further organ damage. The authors normally apply this practice in the real-world clinical situation. Unfortunately, the authors have had no data for a comparison of postoperative neurological outcome between patients with reversible and persistent hyperlactatemia yet.

IABP is the most commonly used mechanical circulatory support in post-cardiotomy low cardiac output syndrome. Prophylactic and postoperative use of IABP has been commonly used in high-risk patients undergoing CABG or percutaneous coronary intervention (PCI)⁽²³⁾. Meta-analysis of IABP insertion in patients with acute myocardial infarction showed benefits with respect to long-term survival rates compare to non-IABP group, but significant higher incidence of severe bleeding and stroke⁽²⁴⁾. There was a case report of patient who developed embolic stroke after CABG associated with IABP inflation fragmented the aortic plaque of thoracic aorta⁽²⁵⁾.

There are some potential limitations in the present study including the single-centered and the retrospective study design. In addition, the authors collected only routine clinical and laboratory data. The authors also have no clinical and radiological information regarding preoperative carotid stenosis and aortic plaque. Future larger prospective study is needed to address the present study limitations.

Conclusion

Early neurological complications rate of cardiac or aortic surgery in the present study settings was 8.3%. History of essential hypertension, combined CABG and valve surgery, multi-valve surgery, aortic surgery, higher midazolam dosage, higher serum lactate prior to discontinuing CPB, and presence of intraoperative IABP use were identified as the independent factors associated with such complications. In the presence of these clinical and perioperative factors, awareness of postoperative neurological complication should be considered.

What is already known on this topic?

Several studies have demonstrated the incidence of immediate neurological complications after cardiac or aortic surgery and its predictive factors.

What this study adds?

This study emphasizes the association among several factors and early neurological complications after cardiac or aortic surgery. These include the history of essential hypertension, the type of surgery, the higher serum lactate prior to discontinuing CPB, and the presence of intraoperative IABP use. The higher serum lactate is a condition that the cause should be instantly investigated, and the treatment should be promptly applied. The authors also distinctively found that the higher midazolam dosage was independently associated with unfavorable neurological outcome after cardiac or aortic surgery. The clinical significance of this issue, however, is still questionable. In any case, when there are in presence of these clinical and perioperative factors, awareness of postoperative neurological complication should be considered.

Conflicts of interest

The authors declare no conflict of interest.

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