Original Article

Modifiable Factors During Cardiopulmonary Bypass in Children and Neonates: What Predicts Early-Onset Neurocomplications After Cardiac Surgery?

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ABSTRACT

Background: Despite the great progress in the surgery of complex congenital heart diseases, there is still concern regarding adverse neurological events. We aimed to determine the pre- and on-pump modifiable factors that could predict the neurocomplications after pediatric cardiac surgery.

Methods: In a prospective study, modifiable factors such as arterial blood gas, serum lactate, serum glucose, mean arterial pressure, and nasopharyngeal temperature were measured before and during cardiopulmonary bypass (CPB). Moreover, the CPB time, the aortic cross-clamp time, and the deep hypothermic circulatory arrest time were recorded. If there were adverse neurological complications, brain computed tomography scan was done.

Results: From 435 patients with congenital heart diseases that underwent cardiac surgery, 364 patients at a mean age of 22 months were enrolled in the study. Thirty-three (9%) patients had adverse early-onset neurological events. Seizure and hemorrhage were the most common clinical and neuroimaging findings, respectively. Although the pre-pump oxygen saturation (P = 0.03), the blood CO_2 level (P = 0.04), and the serum glucose level (P = 0.03) showed statistical significance in the univariate analysis, the only predictive variables of neurocomplications in the multivariate analysis of logistic regression were the on-pump serum glucose level (P = 0.001) and the nasopharyngeal temperature (P = 0.004).

Conclusions: Among several modifiable factors exerting an influence on the neurological outcome of children undergoing cardiac surgery, special attention should be paid to the control of the intraoperative serum glucose level and the provision of the optimal cooling temperature. ***(Iranian Heart Journal 2020; 21(2): 48-56)***

KEYWORDS: Neurocomplications, Cardiac surgery, Cardiopulmonary bypass, Deep hypothermic circulatory arrest

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Received: April 28, 2019 **Accepted:** August 11, 2019

Since the introduction of cardiac surgery, surgical techniques and instruments have improved dramatically. [1,5] Nowadays, children of different ages including neonates undergo complex cardiac surgery and survive without any life-threatening heart condition. [6] Consequently, the recent decades have witnessed a great deal of attention paid to post-cardiopulmonary bypass (CPB) complications such as adverse neurological impairment, which continues to occur despite successful complex cardiac surgery. [7, 9] Neurological complications are associated with increased intensive care unit and hospital lengths of stay, higher mortality, and increased medical charges.

It is claimed that neuronal and axonal immaturity in early life is more susceptible to ischemic reperfusion insult. According to previous research, neurological impairment is a devastating complication that results in various forms of motor and sensory deficits such as altered levels of consciousness, choreoathetosis, seizure, visual impairment, stroke, and coma. [7,10-15] Currently, the prevention of subtle neurocognitive defects such as behavioral disorders, speech difficulties, and intellectual and cognitive deficits is the focus of attention. Factors affecting these defects can be divided into 2 groups of fixed and modifiable factors. [9, 16-18] Structural central nervous system malformations and known genetic syndromes are examples of fixed factors. Serum glucose levels, blood pressure, and oxygen saturation are examples of the modifiable factors, the correlation of which with the early onset of neurological complications after pediatric and neonatal cardiac surgery was the aim of our study.

METHODS

The current prospective study enrolled 435 patients who underwent cardiac surgery in our center between June 2015 and July 2017. The patients were divided into groups of the transposition of the great arteries, arch anomalies (coarctation of the aorta), right ventricular outflow tract obstruction (tetralogy of Fallot and pulmonary atresia), left ventricular outflow tract obstruction (aortic stenosis), left-to-right shunting (ventricular septal defects and atrial septal defects), and complex malformations (atrioventricular septal defects, total anomalous pulmonary venous connections, aortopulmonary windows, and tricuspid atresia). An early-onset neurological complication was defined as an event happened within 30 days after heart surgery. The patients' demographic characteristics including age, gender, and weight were recorded. Arterial blood gas, hemoglobin, hematocrit, serum sodium, potassium, glucose, and lactate were measured before and during CPB. Moreover, the mean values of the on-pump arterial pressure and the nasopharyngeal temperature were recorded, in addition to the mean values of the aortic cross-clamp time, the CPB time, and the deep hypothermic circulatory arrest (DHCA) time. If there were early postoperative neurological complications, brain computed tomography scan was performed. All patients with known structural central nervous system malformations and genetic syndromes were excluded.

The data were analyzed using SPSS software, version 21 (SPSS Inc, Chicago, IL). The association between the categorical variables was evaluated using the χ^2 test and the Fischer exact test. Variables with a *P* value of less than 0.05 were considered statistically significant. Thereafter, the prognostic value of the variables was assessed using multiple logistic regression models; and finally, the predictive ability of the fitted logistic model was assessed using a receiver operating characteristic (ROC) curve. This study was approved by the Ethics Committee of Tehran University of Medical Sciences. Informed

consent was obtained from all the patients' parents/custodians for data extraction from the patients' medical files.

RESULTS

From a total of 435 patients who underwent cardiac surgery, 364 patients were enrolled in the present study. Excluded cases were 28 patients undergoing off-pump cardiothoracic surgeries, 32 patients who died during the admission without evidence of neurological complications, and 11 patients with incomplete data. Thirty-three (9%) patients had neurological signs during the immediate postoperative period. The characteristics of the patients in the neurologically complicated group are depicted in Table 1. The male-to-female ratio in the entire study population was 33:16, and the mean of age at the time of surgery was 22 months with 17% of the patients less than 2 months old, 36% between 2 and 12 months old, and 47% more than 1 year old. Boys were more susceptible to neurological complications than girls (P = 0.02). Moreover, neurological complications were more common in younger infants (P = 0.04) with lower weight (P =0.04). However, the male gender, younger age, and lower weight were not predictive variables in the multivariate logistic regression analysis. The patients in the group of the transposition of the great arteries had the highest rate of neurological insult; nonetheless, statistically no difference was found between the diagnostic groups (the Fisher exact test, P = 0.074) (Table 2).

Table 1: Demographic characteristics of the study population

Variable	Patients With Neurological Complications	Patients Without Neurological Complications
Sex male	23 (69.7%)	168 (50.8%)
female	10 (30.3%)	163 (49.2%)
Age (mon) ± SD	13.43 ± 5.8	22.68 ± 1.37
Weight (kg) ± SD	6.54 ± 0.95	9.34 ± 0.43

Table 2: Incidence of neurological events after open-heart surgery in the diagnostic groups

Diagnostic Group	Patients that Underwent Surgery with CPB (n=364)	Frequency of Adverse Neurological Events (n=33)
Transposition of great arteries	41	8
Arch anomalies	45	5
Right ventricular outflow tract obstruction	94	8
Left ventricular outflow tract obstruction	11	0
Left-to-right shunting	146	8
Complex malformation	27	4

CPB, Cardiopulmonary bypass

Table 3: Incidence of early-onset postoperative neurological complications after pediatric cardiac surgery

Diagnostic Subgroup	Diagnosis	No.	Age (mon)	Weight (kg)	Operation	CT Scan Finding	Complication
TGA	TGA	3	<1	3.6	ASO	SAH	Seizure
	TGA	2	<1	3.7	ASO	SAH	Movement disorder
	TGA	2	2	3.6	ASO	Normal	DLOC
	TGA/VSD	1	<1	2.9	ASO/VSD closure	Hydrocephaly	Seizure
Arch anomalies	COA	3	4	5	TC	Normal	Seizure
RVOT	TOF	2	2	7.5	TAP	Ischemia	Seizure
	TOF	1	60	18	TAP	Normal	Headache
	TOF	2	24	11	TAP	SAH	Movement disorder
	PA	2	1.5	4.4	Homograft	SAH	Seizure
	PA	1	<1	3.5	Contegra	SAH	DLOC
Left-to-right shunting	VSD	1	3.5	4.9	Patch repair	SDH	Seizure
	VSD	2	180	30	Patch repair	Normal	DLOC
	VSD	2	6.5	5.2	Patch repair	Normal	Visional impairment
Complex malformation	APW	2	17	5	TC	ICH	Seizure
	TAPVC	2	5	6	TC	Ischemia	Seizure
	AVSD	2	7	5.2	TC	SAH	Movement disorder
	AVSD	2	3.5	5.9	TC	SAH	DLOC
	AVSD	1	3	6.5	TC	SDH	Seizure

APW, Aortopulmonary window; ASO, Arterial switch operation; AVSD, Atrioventricular septal defect; COA, Coarctation of aorta; DLOC, Decreased level of consciousness; ICH, Intracerebral hemorrhage; PA, Pulmonary atresia; RVOTO, Right ventricular outflow tract obstruction; SAH, Subarachnoid hemorrhage; SDH, Subdural hemorrhage; TAP, Transannular patch; TAPVC, Total anomalous pulmonary venous connection; T/C, Total correction; TGA, Transposition of the great arteries; TOF, Tetralogy of Fallot; VSD, Ventricular septal defect

The cardiac diagnosis, surgical operations, clinical signs and symptoms, and brain CT scan findings in the patients with neurological complications are illustrated in Table 3. Seizure was the most common complication in that it occurred in 17 (51%) cases. Decreased levels of consciousness in 7 (21%) patients, movement disorders in 6 (18%), visual disturbances in 2 (6%), and headache in 1 (3%) were the other neurological findings. Brain CT scans showed that hemorrhage was responsible for about one-third of the neurological complications. Ischemic stroke and hydrocephaly were the other CT findings in 6% and 3% of the complicated patients, respectively, while the remaining patients (61%) had normal imaging. The modifiable factors are shown in Table 4. Although in the univariate analysis, oxygen saturation (P = 0.03), blood CO_2 levels (P = 0.04), and serum glucose levels (P = 0.03) before CPB were statistically significant in predicting neurocomplications after surgery, the only predictive variables in the multivariate analysis of logistic regression were the serum glucose level during CPB (P = 0.001) (Fig. 1) and the nasopharyngeal temperature (P = 0.004) (Fig. 2). A 1-mg/dL increase in the level of blood glucose during CPB and 1 °C decrease in the nasopharyngeal temperature increased the risk of neurological complications by 1.6% and 15.6%, respectively. The cutoff points for the blood glucose level and the nasopharyngeal temperature were 173 mg/dL and 27.5 °C, respectively. The serum level of potassium during CPB was elevated in the neurologically complicated group, which might have been a sign of reperfusion syndrome (P = 0.016). However, its significance in predicting neurocomplications was not confirmed in the multivariate analysis. Moreover, the neurologically complicated patients had longer CPB and aortic cross-clamp times (univariate analysis, P = 0.009 and P = 0.037, respectively), but without any predictive significance in the multivariate analysis. Interestingly, the mean duration of DHCA was lower in the group of complicated patients; the

difference, however, failed to constitute statistical significance (P = 0.34) (Table 5).

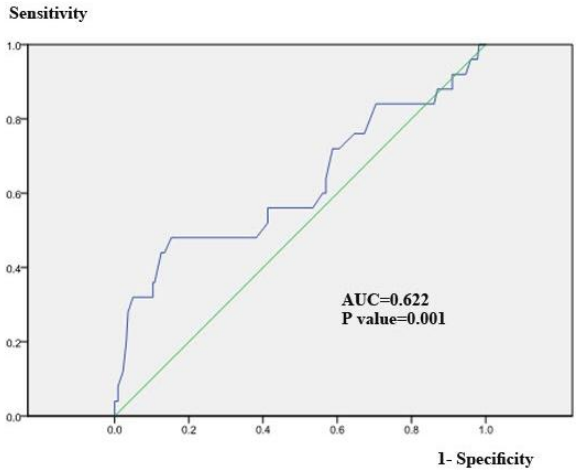

Figure 1: Receiver operating characteristic (ROC) curve of the predictive mathematical model (logistic regression) for predicting neurological complications based on hyperglycemia. The area under the curve (AUC) = 0.622.

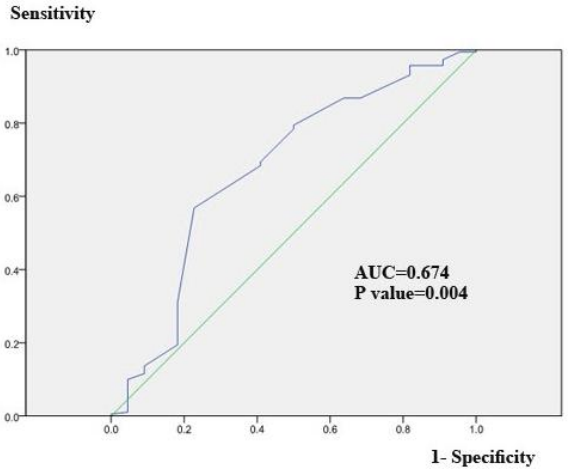

Figure 2: Receiver operating characteristic (ROC) curve of the predictive mathematical model (logistic regression) for predicting neurological complications based on the nasopharyngeal temperature. The area under the curve (AUC) = 0.674.

Table 4: Univariate analysis of the effective variables in neurological complications

Variable	Patients With Neurological Complications	Patients Without Neurological Complications	*P* value
ABG Parameters Before CPB			
Arterial PH	7.35±0.02	7.38±0.07	0.18
SO_2 (%)	77.23±5.38	79.16±1.93	0.72
PO_2 (mm Hg)	118.69±23.88	181.24±9.6	0.03
PCO_2 (mm Hg)	43.37±2.66	38.85±0.7	0.04
HCO_3 (meq/l)	23.47±0.81	23.06±0.29	0.64
BE (meq/l)	-1.8±0.9	-1.95±0.36	0.9
Hb (g/dl)	11.72±0.62	13.9±1.03	0.46
Hct (%)	35.52±1.89	36.35±0.74	0.71
Na (meq/l)	137.2±0.62	137.78±0.25	0.45
K (meq/l)	3.4±0.11	3.4±0.06	0.88
Glucose (mg/dl)	149.52±15.4	114.57±4.19	0.03
Lactate(mg/dl)	12.70±1.62	10.27±0.63	0.26
Mean arterial pressure (mm Hg)	43±7.5	48±15.3	0.065
ABG Parameters During CPB			
Arterial PH	7.4±0.05	7.4±0.01	0.76
SO_2 (%)	95±4	94±3	0.6
PO_2 (mm Hg)	286±17	280±5	0.77
PCO_2 (mm Hg)	50±16	34.3±1	0.36
HCO_3 (meq/l)	22±0.4	23.4±0.1	0.11
BE (meq/l)	-1.2±0.6	-4.9±0.1	0.23
Hb (g/dl)	9.7±0.2	9.3±0.1	0.38
Hct (%)	28.8±0.7	28.1±0.2	0.37
Na (meq/l)	137±1	140±1	0.09
K (meq/l)	4.1±0.2	3.7±0.5	0.016
Glucose (mg/dl)	204±17	167±3	0.04
Lactate (mg/dl)	32.43±3.6	27.9±5.4	0.7
Mean arterial pressure (mm Hg)	38±6.1	42±12.2	0.064
Nasopharyngeal temperature (°C)	25.3±0.9	27.4±0.2	0.02

BE, Base excess; Hb, Hemoglobin; HCO_3, Bicarbonate; Hct, Hematocrit; K, Potassium; Na, Sodium; PCO_2, Partial pressure of carbon dioxide; PH, Acidity of the blood; PO_2, Partial pressure of oxygen; SO_2, Oxygen saturation

Table 5: Comparisons of the CPB, ACC, and DHCA times between the patients with and without neurological complications

Variable	Patients With Neurological Complications	Patients Without Neurological Complications	*P* value
CPB time (min)	155±15	118±4.5	0.009
ACC time (min)	101±11.2	78±3.4	0.037
DHCA time (min)	22±5	26±1.9	0.34

ACC, Aortic cross-clamp; CPB, Cardiopulmonary bypass; DHCA, Deep hypothermic circulatory arrest

DISCUSSION

Cerebral damage and neurological outcomes after open-heart surgery have been well defined. These complications can range from subtle to profound, and their incidence has been declined from 25% to as low as 2% in some centers. [6, 9-15] It is due to the advances and innovations in the CPB technique and monitoring systems in addition to the control of modifiable factors. [1-5, 9, 16-18] The prevention of the gas and particulate emboli, ultrafiltration modification, the management of inflammatory responses to the CPB circuit, the avoidance of hemodilution and the steal phenomenon, and PH-stat blood gas management all have improved the neurological outcome after complex congenital heart surgery. [16-18]

Unfortunately, the incidence of neurological complications in our cohort was disappointingly high (0.9%) including a 20% incidence among patients undergoing the arterial switch procedure. Although the deleterious effects of postoperative hyperglycemia have been shown in patients with diabetes mellitus, [19] the perioperative adverse effects of hyperglycemia on the morbidity and mortality after cardiac surgery are still unclear in nondiabetic pediatric patients undergoing cardiac surgery. [20] Our results showed higher levels of glucose during the CPB time in the group with postoperative neurological complications. We found that for each 1 mg/dL increase above 173 mg/dL in the level of blood glucose during the CPB time, the risk of adverse neurological complications was increased by 1.6%. Moreover, the type of congenital heart defect or surgical procedure in our study did not have any significant association with the level of glucose during CPB. Hence, insulin resistance might have a certain relationship with the adverse postoperative neurological outcome. [20-23] We also found that the pre-pump glucose level did not have any influence on the postoperative neurological outcome. It has been suggested that a state of insulin resistance occurs during CPB. Still, the effect of confounding factors such as the administration of glucogenic drugs (catecholamine) on the neurological outcome should be kept in mind. [21] The endogenous release of cortisone and catecholamines as a response to stress, [21] the increase in circulating fatty acid after heparinization, [22, 23] and the release of inflammatory cytokines due to CPB all can impair the insulin-signaling network in cardiac surgery. [24] It has been postulated that hyperglycemia can exacerbate the ischemic neuronal injury through several mechanisms that finally compromise microvascular endothelial cell function and smooth muscle relaxation. [25] Intracellular acidosis, [26] advanced glycosylation end-products, and impaired glutamine transport are the proposed mechanisms. [27] Hyperglycemia increases cerebral lactate and tissue acidosis, worsening the mitochondrial function and culminating in infarct size enhancement. [28, 29] It can also cause cerebral edema by disrupting the blood-brain barrier and exacerbate the neurological outcome by converting ischemic stroke into symptomatic hemorrhagic insult. [28, 30] Accordingly, it has been hypothesized that elevated glucose levels aggravate the cell edema and lead to cell death surrounding the hemorrhagic tissue. [30] The safe level of serum glucose in critically ill patients has been reported to range from 80 mg/dL to 110

mg/dL in different studies. [31, 32] More investigations are required to determine the causes of hyperglycemia during CPB and then to treat the impairment to the insulin-signaling network and to improve the neurological outcome.

In our patients, the CPB and aortic cross-clamp times and, hence, the complexity of cardiac defects or surgical interventions did not show any relationship with the postoperative neurocomplications in the multivariate analysis. The multivariate analysis also identified the nasopharyngeal temperature as an independent predictor of postoperative neurological complications. Hypothermia inhibits hypoxic neuronal cell damage and necrosis by lowering the cellular anaerobic metabolism [33, 34] (less lactate accumulation) and less release of excitatory neurotransmitters such as glutamate. [35] The cell metabolism slows down by 5% to 7% if the body temperature drops by 1 °C. [36, 37] A reduction in inflammatory cytokines and free radicals and the inhibition of pro-apoptotic activity are the other mechanisms of protection in hypothermia. [38, 39] In traumatic brain injuries with elevated intracranial pressures, targeted temperature management (therapeutic hypothermia) has shown beneficial neuroprotective effects. [40] It has been shown that a target temperature of 33 °C can be safely used in patients with acute ischemic stroke following intra-arterial reperfusion therapy. [41] Nevertheless, therapeutic hypothermia may lower the seizure threshold in asphyxiated infants. [42] In a complex inter-related process, hypothermia will attenuate brain cell edema, neuronal apoptosis, and death. [43] Surprisingly, our patients with postoperative neurocomplications had a lower nasopharyngeal temperature and shorter duration of DHCA. We describe this finding with the recent theory proposed by Seltzer et al, [44] who concluded that the duration of isoelectric state—defined as the absence of brain activity—had a greater relationship with the neurodevelopmental outcome. They also found that cooling below the point of isoelectricity might have no benefit. This point was approximately 25 °C for most of their patients. Hence, more comprehensive investigations are necessary to address the optimal cooling temperature and the theory that minimizing hypothermia might result in fewer neurological complications.

Lack of adequate hospital facilities precluded us from utilizing the MRI modality for early postoperative neuroimaging. Its higher resolution and greater sensitivity for small ischemic lesions post cardiac surgery have been shown in different studies. [15] Hence, the absence of MR neuroimaging in our study was a major limitation to understanding the exact pathology to devise preventive strategies. Another limitation and of particular concern was the overall high incidence of intracranial hemorrhage, most of which occurred in the group of the transposition of the great arteries as subarachnoid hemorrhage. The obstruction in venous drainage, for example due to a poorly placed venous cannula, could not be ruled out.

CONCLUSIONS

In light of the findings of the present study, we recommend that in addition to the monitoring of several controllable factors that influence the neurological outcome of children undergoing cardiac surgery, special attention be paid to the control of intraoperative serum glucose levels and provide the optimal cooling temperature during CPB.

REFERENCES

1. Aberg T, Kihlgren M. Cerebral protection during open-heart surgery. Thorax. 1977; 32(5): 525-33.

2. Laussen PC. Neonates with congenital heart disease. Curr Opin Pediatr. 2001; 13(3): 220-6.

3. Cooley DA. Early development of congenital heart surgery: open heart procedures. Ann Thorac Surg. 1997; 64(5): 1544-8.

4. Branthwaite MA. Prevention of neurological damage during open-heart surgery. Thorax. 1975; 30(3): 258-61.

5. Russell RW, Bharucha N. The recognition and prevention of border zone cerebral ischaemia during cardiac surgery. Q J Med. 1978; 47(3): 303-23.

6. Arrowsmith JE, Grocott HP, Reves JG, Newman MF. Central nervous system complications of cardiac surgery. Br J Anaesth. 2000; 84(3): 378-93.

7. Menache CC, du Plessis AJ, Wessel DL, Jonas RA, Newburger JW. Current incidence of acute neurologic complications after open-heart operations in children. Ann Thorac Surg. 2002; 73(6): 1752-8.

8. Sotaniemi KA. Brain damage and neurological outcome after open-heart surgery. J Neurol Neurosurg Psychiatry. 1980; 43(2): 127-35.

9. Hsia TY, Gruber PJ. Factors influencing neurologic outcome after neonatalcardiopulmonary bypass: what we can and cannot control. Ann Thorac Surg. 2006; 81(6):S2381-8.

10. Ehyai A, Fenichel GM, Bender HW Jr. Incidence and prognosis of seizures in infants after cardiac surgery with profound hypothermia and circulatory arrest. JAMA. 1984; 252: 3165-7.

11. Ferry PC. Neurologic sequelae of open-heart surgery in children. An 'irritating question'. Am J Dis Child. 1990;144(3): 369-73.

12. Miller G, Eggli KD, Contant C, Baylen BG, Myers JL. Postoperative neurologic complications after open heart surgery on young infants. Arch Pediatr Adolesc Med. 1995; 149(7): 764-8.

13. Fallon P, Aparício JM, Elliott MJ, Kirkham FJ. Incidence of neurological complications of surgery for congenital heart disease. Arch Dis Child. 1995; 72(5): 418-22.

14. Bellinger DC, Wypij D, Kuban KC, et al. Developmental and neurological status of children at 4 years of age after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. Circulation. 1999; 100(5): 526-32.

15. Pérez-Vela JL, Ramos-González A, López-Almodóvar LF, et al. Neurologic complications in the immediate postoperative period after cardiac surgery. Role of brain magnetic resonance imaging. Rev Esp Cardiol. 2005; 58(9): 1014-21.

16. Wong PC, Barlow CF, Hickey PR, et al. Factors associated with choreoathetosis after cardiopulmonary bypass in children with congenital heart disease Circulation. 1992; 86(5 Suppl): 18-26.

17. Trittenwein G, Nardi A, Pansi H, et al. Early postoperative prediction of cerebral damage after pediatric cardiac surgery. Ann Thorac Surg. 2003; 76(2): 576-80.

18. Dominguez TE, Wernovsky G, Gaynor JW. Cause and prevention of central nervous system injury in neonates undergoing cardiac surgery. Semin Thorac Cardiovasc Surg. 2007;19:269-77.

19. Doenst T, Wijeysundera D, Karkouti K, et al. Hyperglycemia during cardiopulmonary bypass is an independent risk factor for mortality in patients undergoing cardiac surgery. J Thorac Cardiovasc Surg. 2005; 130(4):1144.

20. Duncan AE . Hyperglycemia and perioperative glucose management. Curr Pharm Des. 2012; 18(38):6195-203.

21. Huang MT, Lee CF, Dobson GP. Epinephrine enhances glycogen turnover and depresses glucose uptake in vivo in rat heart. FASEBJ. 1997; 11(12):973–80.

22. Lee KU, Lee HK, Koh CS, Min HK. Artificial induction of intravascular lipolysis by lipid-heparin infusion leads to insulin resistance in man. Diabetologia. 1988; 31(5): 285–90.

23. Wittnich C, Dewar ML, Chiu RC. Myocardial protection: heparin induced free fatty acid elevation during cardiopulmonary bypass andits prevention. J Surg Res. 1984; 36(6): 527–31.

24. Hotamisligil GS, Shargill N, Spiegelman BM. Adipose Expression of tumor necrosis factor alpha: direct role in obesity-linked insulin resistance. Science.1993; 259(5091): 87-91.

25. Davies MG, Hagen PO. Alterations in venous endothelial cell and smooth muscle cell relaxation induced by high glucose concentrations can be prevented by aminoguanidine. J Surg Res. 1996 1; 63(2): 474-9.

26. Li PA, Siesjö BK. Role of hyperglycaemia-related acidosis in ischaemic brain damage. Acta Physiol Scand. 1997; 161(4): 567-80.

27. Kawai N, Stummer W, Ennis SR, Betz AL, Keep RF. Blood-brain barrier glutamine transport during normoglycemic and hyperglycemic focal cerebral ischemia. J Cereb Blood Flow Metab. 1999; 19(1): 79-86.

28. Alvarez-Sabín, J., Molina, C. A., Montaner, J., Arenillas, J. F., Huertas, R., Ribo, M., et al. (2003). Effects of admission hyperglycemia on stroke outcome in reperfused tissue plasminogen activator-treated patients. Stroke, 34, 1235–1241.

29. Parsons, M. W., Barber, P. A., Desmond, P. M., Baird, T. A., Darby, D.G., Byrnes, G., et al. (2002). Acute hyperglycemia adversely affects stroke outcome: A magnetic resonance imaging and spectroscopy study. Annals of Neurology, 52, 20–28.

30. Song, E., Chu, K., Jeong, S., Jung, K., Kim, S., Kim, M., et al. (2003). Hyperglycemia exacerbates brain edema and perihematomal cell death after intracerebral hemorrhage. Stroke, 34, 215–2220.

31. Capes, S., Hunt, D., Malmberg, K., Pathak, P., & Gerstein, H. (2001). Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: A systemic overview. Stroke, 32, 2426–2432.

32. Krinsley, J. (2003). Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clinic Proceedings, 78(, 1471–1478.

33. Mora CT, Henson MB, Weintraub WS, et al. The effect of temperature management during cardiopulmonary bypass on neurologic and neuropsychologic outcomes in patients undergoing coronary revascularization. J Thorac Cardiovasc Surg. 1996; 112(2): 514-22.

34. Michenfelder JD. The hypothermic brain in Anesthesia and the brain. New York, Churchill Livingstone; 1988: 23-34.

35. Choi DW, Maulucci-Gedde M, Kriegstein AR. Glutamate neurotoxicity in cortical cell culture. J Neurosci. 1987; 7(2): 357-68.

36. Small DL, Morley P, Buchan AM. Biology o f ischemic cerebral cell death.Prog Cardiova sc Dis. 1999; 42(3): 185-207 9.

37. Schaller B, Graf R.Hypothermia and stroke: the pathophysiological background. Pathoph ysiology. 2003; 10(1): 7-35.

38. Ma H, Sinha B, Pandya RS, et al. Therapeutic hypothermia as a neuroprotective strategy in neonatal hypoxic-ischemic brain injury and traumatic brain injury. Curr Mol Med. 2012; 12(10): 1282-96.

39. Perlman JM. Intervention strategies for neonatal hypoxic-ischemic cerebral injury. Clin Ther. 2006; 28(9): 1353-65.

40. Jiang JY, Xu W, Li WP, et al. Effect of long-term mild hypothermia or short-term mild hypothermia on outcome of patients with severe traumatic brain injury. J Cereb Blood Flow Metab. 2006 Jun. 26 (6):771-6.

41. Horn CM, Sun CH, Nogueira RG, et al. Endovascular reperfusion and cooling in cerebral acute ischemia (ReCCLAIM I). J Neurointerv Surg. 2014 Mar. 6 (2):91-5.

42. Battin MR, Penrice J, Gunn TR, Gunn AJ. Treatment of term infants with head cooling and mild systemic hypothermia (35.0 degrees C and 34.5 degrees C) after perinatal asphyxia. Pediatrics. 2003 Feb. 111 (2):244-51.

43. Negovsky VA. Postresuscitation disease. Crit Care Med. 1988 Oct. 16 (10):942-6.

44. Seltzer L, Swartz MF, Kwon J, et al. Neurodevelopmental outcomes after neonatal cardiac surgery: Role of cortical isoelectric activity. J Thorac Cardiovasc Surg. 2016; 151(4): 1137-42.