Evaluation of Neurocognitive Dysfunction after Coronary Artery Bypass Surgery

Tawfiq Ahmed[1], Md. Rezaul Karim[2], Jahangir Haider Khan[2], Shahriar Moinuddin[2]

[1]Department of Cardiac Surgery, Sir Salimullah Medical College, Dhaka, [2]Department of Cardiac Surgery, NICVD, Dhaka

Keywords: *Neurocognitive dysfunction, Ischaemic heart disease, Coronary artery bypass surgery.*

Abstract:

Objective: *The Neurological injury is an important complication after coronary artery bypass surgery (CABG). The incidence of neurocognitive impairment after cardiac surgery varies from 20% to 80%. In this study we tried to analyze this difference of neurologic dysfunction between On-pump CABG and Off-pump CABG (OPCAB).*

Methods: *This is a case control study done in National Institute of Cardiovascular Disease (NICVD), Dhaka during the period of July 2012 to June 2014. Sixty Patients with Ischemic heart disease were the study population. Group- A includes 30 patients underwent on pump CABG, Group-B 30 patients underwent OPCAB. All the patients of both the groups were followed up to 2 month's postoperatively to find out any neurological and neurocognitive dysfunctionby observing motor function, sensory function,Mini Mantel state (MMS) Examination, orientation, memory, attention and calculation, recall and language test.*

Results: *Neurocognitive dysfunction in the early postoperative period is significantly different among the groups.Neurocognitive dysfunction was more in Group A in comparison to Group B, On 3rd and 8th POD the MINI Mental Scores were found to be significantly lower in On-pump group than those in Off-pump group (22.0 ± 5.28 vs. 25.67 ± 3.34, $p = 0.002$ and 25.93 ± 3.11 vs. 26.63 ± 2.50, $p = 0.023$ respectively).This neurocognitive dysfunction gradually improved by the end of two month postoperative period. Only 6.66% patient in Group-A was found neurocognitically dysfunctional and was referred to neurophysician for further treatment. In case of OPCAB Group, no patient suffered fromneuorocognitive dysfunction.*

Conclusion: *This study has convincingly shown cardio-pulmonary bypass (CPB) has had detrimental effect on neurocognitive function in patients who underwent CABG.*

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Introduction:

The Neurological injury is an important complication after CABG. There is considerable evidence that early postoperative cognitive dysfunction is related to a combination of three factors often associated with CPB: (micro) embolism, hypoperfusion, and the systemic inflammatory response. Intraoperative formation of gaseous emboli and aggregated platelets, atherosclerotic debris, hypoperfusion, hypotension, hyperthermia, hyperglycaemia, surgical trauma, blood loss, Anaesthetic agents, arrhythmia and transfusion all enhance the risk of cognitive dysfunction.

There are two types of Neurological injury, Type-I includes stroke, transient ischemic attack and coma and the incidence is approximately 3 to 6 percent. Type-II injury is more subtle and includes impairment of cognitive functions. These defects associated with attention, concentration, short term memory, fine motor function and speed of the mental response. The incidence of neurocognitive impairment after cardiac surgery varies from 20% to 80%.[1] Based on prospective studies, however it is apparent that the incidence of subtle postoperative neurologic and neuropsychological abnormalities is much higher, closer to 50 percent in the first week after cardiac surgery.[2] These apparent high rate of subtle neurologic impairment detected prospectively are in sharp contrast to the considerably lower incidence of stroke after cardiac surgery, reported as 1-5 percent, in several large retrospective series from different centers.[3] There are several reasons for these apparent differences in the reported incidences the timing, thoroughness and the reproducibility of the neurologic examinations, as well as the incorporation of the preoperative assessment for comparison, all determine the sensitivity and

Address of Correspondence: Dr. Tawfiq Ahmed, Department of Cardiac Surgery, Sir Salimullah Medical College, Dhaka, Bangladesh. Email: tawfiq.ahmed@yahoo.com

accuracy with which postoperative neurologic dysfunction can be detected. Most importantly, many of the earlier studies were based on a retrospective chart review, which only detected the most clinically obvious neurologic dysfunction syndromes as was elegantly demonstrated by Sotaniemi and his colleagues.[4] In a study of 100 patients in whom a 37 percent incidence of neurologic dysfunction had been diagnosed by careful neurologic examination, the prevalence of cerebral abnormalities detected by retrospective analysis of the same patient pool was only 4 percent.[5] The incompleteness of the records, a reluctance to document apparently minor complication and most importantly insensitivity to subtle neurologic dysfunction are being the main reason for there apparent disparities. Many of the type of impairment now being investigated are sub-clinical and are not readily detectable by a standard "foot of the bed" assessment. The fact that many of these abnormalities are apparently transient also contributes to the tendencies to minimize their clinical relevance. It is now established that such reproducible and quantifiable dysfunction is an objective outcome measure and can at least act as a benchmark.

Vast literature on the risk factors of neurobehavioral disorders after cardiac surgery indicates that postoperative decreased of neurological function seems to be associated with advanced age lower preoperative cognitive performance, higher degree of proximal atherosclerosis and length of clump or perfusion time.[6, 7, 8]

Methods:

This cross-sectional study was performed in the Department of Cardiovascular Surgery, National Institute of Cardiovascular Disease (NICVD), Sher-E-Bangla Nagar, Dhaka, Bangladesh from July 2012 to June 2014. The study was carried out on patients with ischemic heart disease who underwent CABG. Total number of Patient was sixty, thirty in each group. Data were analyzed by statistical program for Social Science (SPSS). All patients with Ischemic heart disease underwent Coronary artery bypass graft surgery with or without cardiopulmonary bypass were included. Exclusion criteriawere Patient associated with cerebro-vascular disease, neurological and psychological abnormality, hepatic and renal insufficiency, patient who underwent any emergency cardiac surgery, redo cardiac surgery, valve surgery and congenital surgery.

Each group included thirty patients. Group - A: On pump CABG, Group-B OPCAB.In both the groups the risk factors, such as diabetes mellitus, hypertension, smoking and hyperlipidemia were recorded and compared. A standard 12 lead ECG were taken in all cases pre-operatively and post-operatively and was examined for rate, rhythm, axis deviation, chamber enlargement and evidence of ischemia. Pre-operative Q-wave were recorded in all the patients of both the groupsand compared. Echocardiography was performed pre-operatively in both the groups to assess the functional status of the myocardium. Ejection fraction were recorded and competed among the groups. Coronary angiogram (CAG) was evaluated in all patients in both groups to find out the site to lesion percentage of luminal stenosis, distal flow of dye and assessment of graftable site and the number of diseased vessels. Only double and triple vessel diseases were included in the study. Neurological examination was done in both the groups pre-operatively and post-operatively for assessment. Muscle power, Muscle tone and reflexes were recorded for motor function and pain and touch sensation was recorded for sensory function. Mini Mantel state (MMS) Examination was done in both the groups pre-operatively and post-operatively and at the time of discharge and follow up. The Mini–Mental State Examination (MMSE) or Folstein test is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment. Any score greater than or equal to 24 points (out of 30) indicates a normal cognition. Below this, scores can indicate severe (d"9 points), moderate (10–18 points) or mild (19–23 points) cognitive impairment. [9, 10]

Orientation, antegrade memory, attention and calculation, recall and language test were done. And the score were compared in both the groups. ACCT (Aortic crossclamp time), ECCT (Extracorporeal circulatory time) and total operation time were recorded in on-pump group

per-operatively to see the distributionin the group. All the patients of both the groups were followed up to 2 month's postoperatively to find out any neurological and neurocognitive dysfunction and were consulted with neurophysician for further management, if needed.

Results:

This study was carried out in the Department of Cardiovascular Surgery, NICVD. The results and observations of the study are being presented as follows: There were 60 patients. The Sixty (60) percent of the patients in On-pump group and 53.3% in Off-pump group were between 50 – 60 years of age. Nearly one-quarter (23.3%) of the patients in each group were between 40 – 50 years of age. Very few patients in each group were below 40 years of age or of 60 years and above. No significant variation was observed between groups in terms of age (50.17 ± 8.31 vs. 49.23 ± 7.99 years, p = .659). It was found that there is also no significant difference between two groups. The groups were almost homogeneous in terms of sex as well (p = 0.306). Risk factors considering in both groups A and Group-B patients are hypertension, diabetes, smoking, hyperlipidemia and old MI, more than 50% of the patients in both groups were diabetic, hypertensive and hyperlipidemic and more the 60% patients of both groups had old MI. Less than 40% of both groups were smoker. So there was no significant difference in the presence of risk factor among the groups.

In pre-operative echocardiographic study left ventricular ejection fraction were studied in all patients. LVEF was divided into two groups. One was more than 50% and other was less than 50%. In group A more than 18 (60%) of the patient had LVEF<50% and 12 (40%) had LVEF<50. In Group-B 14 (46.6%) patient had LVEF>50% of 16 (54.4%) patient had LVEF > 50. But there was no significant difference in LVEF among the groups(Table-I).

Coronary angiogram of all the 60 patients in both group revealed significant stenosis of double vessel in 4 (13.3%) patients, triple vessel stenosis in 26 and left main in 7 patients in group A and double vessel disease in 10 (33.3%) patients triple vessels disease in 20 patients and left main disease in 3 in group B(Table-II).

In On-pump group nearly half 46.6% of the patients needed 3 grafts followed by 26.7% patients 2 grafts and the rest 26.7% cases 4 grafts, where as in Off-pump group 56.6% of the cases required 3 grafts, 30% cases 2 grafts and 13.3% cases 4 grafts. The groups were found to be homogenous with respect to number of grafts needed (p = 0.055)(Table-III).

In group A, Two-third (60%) of the cases had their aorta cross-clamped for 60 minutes or more, while the rest one-third (40%) for less than

Table-I

Echo cardiographic findings of the study population.

Findings	Group-A		Group-B		p-value
	No	%	No	%	
LVEF > 50%	18	60%	14	46.6%	0.46
LVEF < 50%	12	40%	16	54.4%	0.52

Table-II

Coronary artery lesions of the study population.

Vessel Involved>75%	Group-A		Group-B	
stenosis	No	%	No	%
2 vessel	4	13.3%	10	33.3%
3 vessel	26	86.6	20	66.6%
Left main	7	23.1%	3	10%

Table-III

Comparison of number of grafts in the study population.

No. of graftsGiven	Group-A		Group-B		p-value
	No	%	No	%	0.055
2	8	26.6%	9	30%	
3	14	46.6%	17	56.6%	
4	8	26.6%	4	13.3%	

60 minutes during operation. The mean ACCT was 67.54 minutes and the lowest and highest ACCT were observed to be 51 and 107 minutes respectively. 66.7% of the cases had ECCT less than 100 minutes and the rest 33.3% 100 minutes or more. The mean ECCT was 95.6 minutes and the minimum and maximum ECCT were 84 and 202 minutes respectively.

Total operation time-Comparison of the outcome shows total operation time was 352.67 ± 50.61 minutes in group A and 311.47 ± 44.86 minutes in group B. There is significant difference between two groups (Table-IV).

The ventilation time, postoperative ICU stay and hospital stay was significantly higher in the Group A than those in Group B (19.4 3.12 vs. 8.23 ± 2.92 hours, $p < 0.001$; 4.93 ± 1.01 vs. 4.03 ± 0.62 days, $p < 0.001$ and 11.27 ± 1.55 vs. 9.73 ± 1.89 days, $p = 0.001$ respectively) (Table-V).

The Group-B demonstrated a significantly better outcome in muscle tone and strength (13.3%) compared to Group-A counterpart (40%) ($p< 0.05$).Reflexes were sluggish in 33.3% in group A and 16.7% in group B and difference was insignificant (Table-VI).

The early sensory function test demonstrated 100% normal outcome in Group A, while Group B had somewhat less normal outcome (93.3%). The groups were not found to be significantly different in terms of early sensory functions ($p > 0.05$) (Table-VII).

Table VIII compares the late neurological assessment between groups. All the neurological functions like motor, sensory and reflexes were found 100% intact in both the groups.

Table IX demonstrates the comparison of postoperative neurocognitive function using MINI Mental Score. On 3rd and 8th POD the MINI Mental Scores were found to be significantly lower in On-pump group than those in Off-pump group (22.0 ± 5.28 vs. 25.67 ± 3.34, $p = 0.002$ and 25.93 ± 3.11 vs. 26.63 ± 2.50, $p = 0.023$ respectively) suggesting that return of cognitive function following CABG in the OPCAB group is achieved much earlier than On pump group.By the end of the study period after (2 month) most of the patients had normal recovery. Only 2 patients in Group A had dysfunctional cognitive scores.

Table-IV

Comparison of total operation time in both groups.

Group-A	Group-B	p-value
352.67 ± 50.61	311.47 ± 44.86	0.0015

Data were analyzed using Student's t- Test and the difference was significant.

Table-V

Comparison of outcome between groups.

Outcome	Group		p-value
	On-pump	Off-pump	
Post Operative Ventilation time (hours)	19.40 ± 3.12	8.23 ± 2.92	< 0.001
Post Operative ICU stay (days)	4.93 ± 1.01	4.03 ± 0.62	< 0.001
Post Operative Hospital stay (days)	11.27 ± 1.55	9.73 ± 1.89	0.001

Data were analysed using Student's t-Test and presented as mean ± SD; level of significance was 0.05.

Table-VI

Comparison of motor function impairment between the groups.

Motor functionimpairment	Group-A (n=30)		Group-B (n=30)		p-value
	No	%	No	%	
Tone and strength	12	40%	4	13.3%	0.02
Reflexes	10	33.3%	5	16.7%	0.136

Data were analyzed by Chi-Square test with Yates correction.

Table-VII

Comparison of early sensory function impairment between the groups.

Sensory functionimpairment	Group-A (n=30)		Group-B (n=30)		p-value
	No	%	No	%	
Pain and touch	2	6.7%	0	0%	0.246

Data were analyzed by Chi-Square test with Yates correction.

Table-VIII

Neurocognitive function between the groups on 3rd post operative day, 8th post operative day and 2 months after operation.

NeurocognitiveImpairment	Group-A (n=30)		Group-B (n=30)		p-value
	No	%	No	%	
3rd post operative day					
Orientation	8	26.6%	4	13.3 %	0.55
Antegrade memory	4	13.3%	2	6.6 %	0.60
Attention	24	72%	12	40 %	0.05
Recall	16	53.3%	10	33.3 %	0.05
Language	11	36.6%	5	16.6 %	0.045
8th post operative day					
Orientiation	5	16.6%	4	13.3 %	0.689
Antegrade memory	2	6.6%	0	0 %	0.5
Attention	18	60%	10	33.3 %	0.0549
Recall	13	43.3%	8	26.6 %	0.47
Language	7	23.3%	2	6.6 %	0.49
2 months after operation					
Orientiation	0	0%	0	0 %	
Antegrade memory	0	0%	0	0 %	
Attention	6	20%	0	0 %	0.4
Recall	4	13.3 %	0	0 %	
Language	0	0%	0	0 %	

Data were analyzed by Chi-Square test with Yates correction.

Table-IX

Comparison of neurocognitive function between the groups

Time of evaluation	Mini mental score (Mean +_ SD)		p-value
	On-pump (n=30)	Off-pump (n=30)	
3rd POD	22.00+_5.28	25.67+_3.34	0.002
8th POD	25.93+_3.11	27.63+_2.50	0.023
2nd month POP	28.63+_1.94	29.30+_0.99	0.101

Data were analyzed with help of Student's t-Test.

Discussion:

This study was performed in NICVD, Dhaka. Included 60 patients of them 56 were male and only (four) were female. Total male female ratio being 93.3% male and only 6.7% female. The patients were divided into two groups. Group A includes CABG (on pump) and Group B includes OPCAB. There was slightly higher percentage of female in Group A (10%) than in Group B (3.3%).

In Group-A the age ranged from 32 to 70 years with a mean ± SD of 50.166 ± 8.31 years. The majority of the patients are in the age group of 50-60 years. In Group-B the age ranged from 32 to 67 years with a mean ± SD of 49.23 ± 7.99 years, majority of the patients are in the age range of 50 to 60 years. So there is no significant difference in age among the groups. But there is a definite male predominance in both the groups as the incidence of coronary artery disease is higher in male.Risk factors considering in both groups A and Group-B patients are hypertension, diabetes, smoking, hyperlipidemia and old MI, more than 50% of the patients in both groups were diabetic, hypertensive and hyperlipidemia and more the 60% patients of both groups had old MI. Less than 40% of both groups were smoker. So there was no significant difference in the presence of risk factor among the groups. These findings were similar with the study done by Slogoff and his colleagues.[16]

In pre-operative echo cardiographic study left ventricular ejection fraction were studied in all patients. LVEF was divided into two groups. One was more than 50% and other was less than 50%. In group A more than 18 (60%) of the patient had LVEF<50% and 12 (40%) had LVEF<50. In Group-B 14 (46.6%) patient had LVEF>50% of 16 (54.4%) patient had LVEF > 50. But there was no significant difference in LVEF among the groups.This findings were similar with the study done by Gorlitzer and his colleagues.[16]

The development of coronary angiography by Manson Sones and Shirey was the Landmark achievement that permitted precise definition of the anatomic obstruction and laid the foundation for coronary artery by pass surgery.[13] Coronary angiogram of all the 60 patients revealed significant stenosis of double vessel-4 (13.3%) patents, triple vessel in 26 (86.6%) patents and left main in 7 (23.1%) patients in Group-A and in Group-B, double vessel 10 (33.3%) patents, Triple vessel 20 (66.6%) patients and left main 3 (10%) were present. All the stenosis vessels were graft table.

The number of grafts need in both the groups were for on pump group nearly half 14 (46.6%) of patients required 3 grafts, 8 (26.6%) patients required 4 grafts and 8 (26.6%) patients required 2 grafts, where as in off pump group-17 (56.7%) patients needed 3 grafts, 9 (30%) patients needed 2 grafts and 4 (13.3%) patient needed 4 grafts. So the groups were found to be homogenous with respect to the number of graft required. So there is no significant difference among the groups.The Aortic Cross clump time (ACCT) and extra corporeal Circulation time (ECCT) was recorded only for on pump group. So only the distribution of patients were studied in the group. With respect to ACCT patient were divided in two groups. Patient ACCT required more than 60 minutes and less than 60 minutes. 18 (60%) patients required 60 minutes or more while 12 (40%) patient needed less than 60 minutes. The range was 51 minutes to 107 minutes mean was 67.54 minutes with respect of ECCT 20 (66.7%) patient need less than 100 minutes and rest 10 (33.3%) required more than 100 minutes range was 84 to 202 minutes with mean of 95.6 minutes. These findings were similar with the study done by Kalterand his colleagues.[5]

Total operation time in Group A and Group B was studied and compared among the groups and there was difference in the total operation time. 352.67 ± 60.61 minutes in Group A and 311.47 ± 44.86 minutes in Group B were recorded, which was significant. The post operative ventilation time (hour) ICU stay (days) and total post operative hospital stay (days) were studied and compared among the groups. All of them shows significantly higher in the On pump group than those in off pump (19.4 ± 3.12 VS 8.23 ± 2.92 hours, 4.93 ± 1.01 VS 4.03 ± 0.62 days, 11.27 ± 1.55 VS 9.73 ± 1.89 days, respectively).This findings were similar with the study done by Gorlitzer and his colleagues.[16]

Neurophysiological and neuro cognitive function were assessed prior to intended operative

procedure. Neurophysiological and neuropsychometric tests were done and a base line was set. Patients with abnormal neurological or neuropsychometric function were excluded from the study.

The incidence of post operative cerebral complications following coronary artery bypass surgery widely depends on the study design, methods and criteria used to assess neurologic injury and timing of follow up examination, type of cardiac surgical procedure.[15]

The incidents of cerebral dysfunction after cardiac surgery with CPB varied over a wide range from 4 to 70%. These variability is due to several difference in CPB, surgical and anesthetic technique.[14]In a study of 100 patient in whom a 37% incidents of neurologic dysfunction had been diagnosed by a careful neurological examination by Kalterand his colleagues.[5] In a study done by Diedderik and his colleagues, there was some substantial neurocognitive dysfunction after cardio pulmonary bypass surgery in the early post-operative period which was less marked in off-pump procedure.[11]Study done by Gorlitzer and his colleagues found that cognitive brain dysfunction is an significant adverse event related to on-pump coronary artery bypass surgery (20% to 80%) which may affect length of hospital stay, quality of life, the rehabilitation process and work performance.[12]

Post operative neurophysiological functions are divided into motor and sensory function. Motor function is assessed by muscle tone, strength and reflexes. Sensory function is tested by pain and touch sensation. They were grouped in early includes 3rd and 8thpost operative and late that is after 2 month.

In the early motor function test the off pump group demonstrated a significantly better outcome in muscle tone and strength (13.3%) compared to on pump (40%). Reflexes were sluggish in (33.3%) in Group A and (16.3%) in Group B and difference was non-significant.

In early sensory function test demonstrated 100% normal outcome in off pump group, while the on pump group had somewhat less normal outcome (93.3%). The groups were not found to be significantly different in terms of early sensory function.

The neurologic dysfunction after CPB range from 1% to 9% of stroke, 3% to 4% alter mental status and 24% to 40% of neuropshycometric deficits.[17]

In late neurophysiological assessment between the groups all the functions like motor, sensory and reflexes were found 100% intact. Neurocognitive function between the groups demonstrates the comparison of postoperative neurocognitive function using Mini Mental Score Examination on 3rd, 8thpost operative day and after 2 months post operatively. On 3rd and 8thpost operative days Mini Mental Score were found to be significantly lower in on pump groups than those in off pump group (22.0 ± 5.28 vs 25.67 ± 3.34 and 25.93 ± 3.11 vs 26.63 ± 2.50 respectively). After 2nd month post operative period Mini Mental Score Examination shows much improved in cognitive function in both groups. 28.63 ± 1.94 in on pump groups and 29.30 ± 0.99 (almost nil) in off pump group.

From the study we found that on the 3rd and 8thpost operative days the neurocognitive dysfunction occurred in both the groups but significantly higher in on pump then OPCAB group. After 2 month only 6.6% patients were found dysfunctional in on pump group where as none was found dysfunctional in OPCAB group.

In a study done by Dijk and his colleagues there was some early neuropsychometric dysfunction found in both on pump and off pump groups which was significant. But in the late cognitive function there was no impairment in both the groups which is more or less similar to my study results.[11]

By the end of the study period after (2 month) most of the patients had normal recovery. Only 2 patients in Group A had dysfunctional cognitive scores. This (6.6%) dysfunction result is similar to that of Slogoffand his colleagues.[16] There is considerable evidence that early postoperative cognitive dysfunction is related to a combination of three factors often associated with CPB: (micro)embolism, hypoperfusion, and the systemic inflammatory response. Intraoperative formation of gaseous emboli and aggregated platelets, atherosclerotic debris, hypoperfusion, hypotension, hyperthermia, hyperglycaemia, surgical trauma, blood loss, and transfusion all enhance the risk of cognitive

dysfunction. The majority of these causative factors, however, may occur independently of CPB for different reasons.

A much larger study focusing on these will help to determine the statistical significance of these observations.

Conclusion:

This study has convincingly shown cardio-pulmonary bypass had detrimental effect on neurological function. There is a higher incidence of neurocognitive dysfunction in on pump CABG than OPCAB. Neuropsychometric abnormalities often remain unrecognized. This study helped in establishing the extent of the problem which can be minimized.

Conflict of Interest - None.

References:

1. Zamvar V, Khan NU, Madhavan A, Kulatilake N, Butchart EG. Clinical outcomes in coronary artery bypass graft surgery: comparison of off-pump and on-pump techniques. *Heart Surgery Forum* 2000; 5(2): 109-113.
2. Heyer EJ, Adams DC. Neurological assessment and cardiac surgery. *J Cardiothorac Vasc Anesth* 1996; 10: 99-104.
3. Murkin JM, Jeffery S. Central nervous system dysfunction after Cardiopulmonary bypass. In: Joel A Kaplan. Ed. Cardiac anesthesia. 3rd edition, Philadelphia: WB Saunders 1993: 1225-1238.
4. Sotaniemi KA. Mononen H, Hokkannen TE. Long term cerebral outcome after open-heart surgery. *Stroke* 1986; 17: 410-416.
5. Kalter RD, Saum CM, Westein L. Cardiopulmonary bypass-associated hemostatic abnormalities. *J Thorac Cardiovasc Surg* 1979; 77: 427.
6. HofsteA WJ, Linssen CAM, Boezeman EHJF, Hengeveld JS, Leusink JA et al. Delirium and cognitive disorders after cardiac operations: relationship to pre and intraoperative quantitative electroencephalogram. *Int J Clin Monit Comput* 1997; 14: 6-29.
7. Westaby S, Saatvedt S, White S, Katsumata T, van Oevern W et al. Is there a relationship between s-100 protein and neuropsychologic dysfunction after cardiopulmonary bypass? *J Thorac Cardiovasc Surg* 2000; 119: 132-137.
8. Roach G, Kanchuger M, Mangano C. Adverse cerebral outcome after coronary artery bypass surgery. Multicenter study of Perioperative Ischemia Research Group and the Ischemia Reaserch and Education Foundation Investigators. *N Engl J Med* 1996; 335: 1857-1863.
9. Pangman VC, Sloan J,Guse L. An Examination of Psychometric Properties of the Mini-Mental Status Examination and the Standardized Mini-Mental Status Examination: Implications for Clinical Practice. *Applied Nursing Research* 2000; 13 (4): 209–213.
10. Mungas D. In-office mental status testing: a practical guide. *Geriatrics* 1991; 46 (7): 54–58.
11. Dijk DV, Keizer AMA, Diephais JC, Durand C. Neurocognitive dysfunction after coronary artery bypass surgery. *J Thorac Cordiovasc Surgery* 2000; 120: 629-632.
12. Gorlitzer M, Kilo J, Czerny M, Zimpfer D, Baumer H, et al. Cardiopulmonary bypass affects cognitive brain function after coronary artery bypass graft. *Ann Thorac Surg* 2001; 72: 1926-1932.
13. Sones FM, Shirey EK. Cine Coronary arteriography. *Mod Concepts Cardiovascular Disease* 1962; 31: 735.
14. Padaychee TS, Parsons S, Theobold R. The effect of arterial filtration on reduction of gaseous microemboli in the middle cerebral artery during cardiopulmonary bypass. *Ann Thorac Surg* 1988; 45: 647-649.
15. Schell RM, Kem FH, Greely W. Cerebral Blood flow and metabolism during cardiopulmonary bypass. *Anesth Analg* 1993; 76: 849-865.
16. Slogoff S, Girgis KZ, Keats AZ. Etiologic factors in neuropsychiatric complication associated with cardiopulmonary bypass. *Anesth Analg* 1982; 61: 903-911.
17. Dijk D, Moons KGM, Keizer AMA, Janson EWL, Hijman R, et al. Association between early and three month cognitive outcome after off-pump and on-pump coronary bypass surgery. *Heart* 2004; 90: 131-134.