Comparison of neurological outcomes in patients undergoing conventional coronary artery bypass grafting, on-pump beating heart coronary bypass, and off-pump coronary bypass

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ABSTRACT

Objective: To study the differences in the prevalence of neurological complications following coronary artery bypass (CAB) carried out by conventional, on-pump beating and off-pump techniques.

Methods: A retrospective analysis of all isolated coronary bypass operations (n=127) performed in King Fahad Cardiac Center, Riyadh over a period of one year starting from January 2005. Out of 127 patients, 73 underwent conventional CAB graft (CABG), 33 patents on-pump beating heart coronary bypass, and 21 had off pump coronary bypass grafting (OPCAB). All patients had preoperative carotid scans and those who developed neurological complications underwent CT-brain and expert neuro-psychiatric assessment.

Results: Preoperative characteristics of patients in all 3 groups were similar. The bypass times in the conventional CABG group were significantly longer than the on-pump beating group. The maximum number of grafts was in the on-pump beating group, followed by the conventional CABG, and the least in the OPCAB group. Seven out of 73 cases in the conventional bypass group developed neurological events of various severities. Only one out of 33 patients developed acute confusional state in the on-pump beating group and no neurological events were noticed in 21 patients operated by the OPCAB technique. Low ejection fraction, preoperative congestive cardiac failure, non-elective surgery and preoperative catastrophic state were found to be significant risk factors independent of the bypass technique.

Conclusion: This study shows no significant difference in the prevalence of neurological complications among different types of bypass surgery in our institution. There was a trend towards less neurological outcomes in the OPCAB and on-pump beating groups.

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Despite all the developments in cardiac surgery, prevention of neurological complications following open-heart surgery remains a challenge of major priority.[1] Brain injury following open-heart surgery has multi-factorial etiology. Well-documented risk factors include older age, atherosclerotic aorta, and effects of cardiopulmonary bypass.[2] In order to avoid deleterious effects of cardiopulmonary bypass, off-pump coronary artery bypass (OPCAB) surgery has gained popularity worldwide. It has been claimed that complete shift from routine use of cardiopulmonary bypass to non-selective off-pump coronary bypass operation is possible with a low rate of conversion to the conventional technique, and without an apparent increase in morbidity.[3] More recently, on-pump beating heart coronary bypass surgery has emerged as another method of coronary artery bypass graft (CABG) in high risk patients. There is a growing need to study the impact of these techniques on brain injury. The main objective of this study was to evaluate the role of these techniques in causing neurological complications.

Methods. A retrospective study of all patients who underwent isolated coronary bypass grafting in the King Fahad Cardiac Center, Riyadh, Saudi Arabia for one year starting January 2005. These operations were performed by 4 experienced consultant cardiac surgeons. The total number of patients was 127. Out of these, 73 patients had conventional CABG, 33 underwent on-pump beating coronary artery bypass, and 21 had OPCAB. The choice between these 3 techniques depended on the surgeon's assessment. All patients had preoperative echocardiography and carotid duplex scanning as routine. History of cerebro-vascular accident (CVA) was defined as

'neurological dysfunction affecting ambulation or day to day function'. Transient ischemic attack (TIA) was defined as any neurological deficit that disappeared completely within 24 hours. Acute confusional state was defined as state of agitation, inappropriate behavior or loss of orientation in time and space developing within the first week following the operation. Preoperative catastrophic state was defined as any of the following events necessitating emergency surgery: aborted sudden death, ventricular tachycardia, ventricular fibrillations, patient requiring cardiac massage for severe hemodynamic compromise, dependence on mechanical ventilation or inotropic support before arriving at the operating room. Recent myocardial infarction (MI) was defined as one occurring within 8 weeks of operation. Preoperative renal dysfunction was defined as a serum creatinine >200 micro mol/l. Operative mortality was defined as death occurring within 30 days of operation. Any patient who developed neurological events after surgery was subjected to CT-brain immediately, and detailed neurological assessment by a consultant neurologist. The CT-brain was repeated after 48 hours. Expert psychiatric evaluation was offered to patients who developed neuro-psychiatric disturbance. The anesthetic technique was standardized in the 3 groups; patients were premedicated with lorazepam 2 mg orally the night before surgery and morphine 0.1 mg/kg intramuscular one hour before operation. Anesthesia was induced with sufentanil 1-1.5 µg/kg, midazolam 0.05-0.1 mg/kg and rocuronium 0.9 mg/kg, and was maintained with infusion of sufentanil 0.2 µg/kg/hr, midazolam 1.5 ug/kg/hr, and rocuronium 0.5 mg/kg/hr. It was further supplemented with sevoflurane as required. Supplementation of further induction as well as anesthetic maintenance doses was guided by signs of lack of analgesia correlated with hemodynamic changes. All patients in the conventional CABG groups underwent cardiopulmonary bypass (CPB) with a single venous and ascending aortic cannula using a membrane oxygenator equipped with an arterial filter and under hypothermia (28-30^{0}C). The CPB circuit was primed with a crystalloid solution with or without colloid solution (albumin). Myocardial protection was achieved with ante-grade sanguineous cardioplegic solution and local hypothermia. The heparin dose was 300 U/Kg in the CPB groups and 100 U/Kg in the OPCAB group. In the on-pump beating heart group, the cardiopulmonary bypass was established similar to the conventional group, however, the patients were kept normo-thermic and the aorta was not clamped. The coronary artery immobilization was achieved with mechanical stabilizers, namely, Octopus and Urchin devices. Vessel occlusion was achieved by external encircling with silicone rubber bands. Intra-coronary shunts were used in all vessels where stenoses were non-critical. For the OPCAB group, the technique of stabilization was the same as the on-pump beating group. However, the CPB was not used.

The patients data was acquired from electronic database (Cascade Cardiac Surgery 2005, Cascade Databases, Lahore) and exported to Excel spread sheet. The analysis was carried out using SPSS 10 for Windows (SPSS Inc, Chicago, IL) and StatsDirect (StatsDirect Statistical Software v2.4.5 Cheshire, UK). The comparison among results of the 3 groups was carried out using ANOVA for continuous variables and chi-square test for categoric variables. The *p*-values were used to evaluate the significance of differences: *p*-value <0.05 was considered significant. Univariate analysis of the risk factors was also performed, and odds ratios with 95% confidence intervals were calculated wherever possible. Those risk factors that showed *p*-value 0.1 or below were entered into multivariate logistic regression analysis.

Results. The preoperative characteristics of the 3 groups are presented in **Tables 1 & 2**. These tables indicate that the risk profiles of all 3 groups were very similar. The univariate analysis also confirms this. Height and ejection fraction were the only 2 variables that had a statistical significant difference. A close review of actual figures clearly shows that even these differences have little clinical relevance since the mean ejection fraction in all groups is above 30% and less than 50%, namely, moderate left ventricular dysfunction. With regard to operative characteristics, the patients in the conventional CABG group had a significantly longer duration of CPB than the on-pump beating group, namely, 105 ± 38.37 minutes versus 78.83 ± 31.25 minutes (p<0.001). This difference is because in the conventional CABG group,

Table 1 - Preoperative patient characteristics: continuous variables.

Characteristics	Conventional CABG n=73	On-pump beating n=33	OPCAB n=21	*P*-value
Age (year)	59.1±10.47	63.8±10.3	55.9±12.7	0.26
Height (cm)	159.0±14.36	165.6±7.7	164.8±7.1	0.01
Weight (kg)	73±17.0	74.3±17.2	80.4±16.9	0.22
BMI	30.9±2.4	29.9±4.9	29.5±6.9	0.23
EF (%)	46.6±9.6	40.1±11.2	45.8±10.9	0.01
Hb (gm%)	12.7±1.95	12.4±1.77	13.4±2.34	0.17
Creatinine (umol/L)	86.1±38.3	70±30.76	86.8±27.1	0.09

OPCAB - Off-pump coronary bypass graft, BMI - Body Mass Index, EF - Ejection Fraction, Hb - Hemoglobin

Table 2 - Preoperative patient characteristics: categoric variables.

Characteristic		Conventional CABG n=73	On-pump beating n=33	OPCAB n=21	*P*-value
CCS Class	I	11	3	2	0.35
	II	29	9	2	
	III	23	6	7	
	IV	10	15	10	
ASA Class	I	20	15	2	0.13
	II	9	3	4	
	III	30	10	10	
	IV	13	3	5	
	V	1	2	0	
NYHA Class	I	7	8	5	0.31
	II	29	9	5	
	III	28	14	8	
	IV	9	2	3	
CCF	Not present	70	28	20	0.11
	Present	3	5	1	
Previous CVA	Not present	72	33	21	0.69
	Present	1	0	0	
Hypertension	Nil	28	9	12	0.11
	Controlled	41	24	8	
	Uncontrolled	4	0	1	
Diabetes	Nil	26	8	10	0.81
	Diet controlled	1	1	2	
	Oral therapy	37	15	8	
	Insulin	9	9	1	
Atrial fibrillation	Not present	70	33	21	0.74
	Present	3	0	0	
Smoking	Non smoker	53	23	14	0.62
	Ex-smoker	14	5	3	
	Smoker	6	5	4	
Hypothyroidism	Not present	72	33	21	0.69
	Present	1	0	0	
Hypercholesterolemia (cholesterol >5.2 mmol /l)	Not present	68	31	17	0.18
	Present	5	2	4	
History of respiratory disease	Not present	69	33	20	0.98
	Present	4	2	1	
Peripheral vascular disease	Not present	73	32	20	0.22
	Present	0	1	1	
Pre-op catastrophic state	Not present	68	31	21	0.47
	Present	5	2	0	
Priority	Elective	59	26	13	0.13
	Urgent	12	3	6	
	Emergency	1	2	2	
	Salvage	1	2	0	
Nationality	Arabs	61	25	16	0.14
	South Asian	10	3	4	
	South East Asians	1	1	1	
	Africans	1	4	0	

CCS - Canadian Cardiac Society, ASA - American Society of Anesthetists, NYHA -New York Heart Association, CCF - Congestive cardiac failure, CVA - Cerebro-vascular accident, Pre-Op - pre-operative, CABG - coronary artery bypass graft, OPCAB - off-pump coronary artery bypass

Table 3 - Postoperative characteristics.

Characteristics	Conventional CABG n=73	On-pump beating n=33	OPCAB n=21	*P* (ANOVA)
Time to extubation (hours)	17.8±22.1	33.3±100	9.1±3.9	0.27
Inotropic support (hours)	20.3±23.9	36.5±40.8	8.8±15.8	0.02
Max CK MB	11.9±19.4	12.1±13.6	5.8±6.4	0.29
ICU stay (hours)	67.2±81.2	82.6±140.2	40.8±21.91	0.29
Hospital stay (days)	13.5±43.02	10.1±15.32	7.3±5.1	0.73
Chest drains (ml)	1586±1956	1453±1175	1143±646	0.55
Death (n)	3	2	0	0.53

CABG - coronary artery bypass graft, OPCAB - off-pump coronary artery bypass,
Max CK MB - maximum creatinine kinase myocardial band, ICU - intensive care unit

Table 4 - Analysis of risk factors: univariate analysis of continuous variables.

Variable	Neurological deficit	Mean±SD	*P*-value
Age (years)	No deficit Deficit	59.79±10.95 60.25±12.16	0.91
Cholesterol Level (mmol/lit)	No deficit Deficit	2.01±2.26 3.12±2.06	0.18
Ejection fraction (%)	No deficit Deficit	45.29±10.12 37±13.75	0.03
LVIDS (mm)	No deficit Deficit	31.96±8.98 36.87±11.31	0.14
LVIDD (mm)	No deficit Deficit	49.36±10.87 54.75±8.36	0.17
Pre-op Hb (gm/dl)	No deficit Deficit	12.82±1.94 11.25±2.11	0.03
Pre-op creatinine (mmol/lit)	No deficit Deficit	82.02±31.38 94.12±47.07	0.31
BMI (kg/m)	No deficit Deficit	29.6±19.29 29.96±2.82	0.96

LVIDD -Left ventricular internal dimension in diastole,
LVIDS - Left ventricular internal dimension in systole,
Pre-OP - pre-operative, Hb - Hemoglobin, BMI - Body mass index

the operations were carried out on moderate hypothermia requiring longer duration on pump for rewarming. On the contrary, patients in the on-pump beating group were kept normo-thermic during surgery. The mean number of distal anastomoses was maximum in the on-pump beating group (3.66 ± 1.22), followed by the conventional CABG group (2.87 ± 0.97), and the least in the OPCAB group (2 ± 0.77). This difference was statistically significant (p<0.001). The mean aortic clamp time in the conventional CABG group was 57 ± 16.77. The postoperative data is shown in **Table 3**. Patients in the on-pump beating group received inotropic support for significantly longer duration compared to the conventional CABG group and the OPCAB group. No deaths were observed among the OPCAB group. Three patients expired in the conventional CABG group, and 2 in the on-pump beating group (p=0.53). Two out of 3 deaths in the conventional CABG group were directly related to neurological complications. The deaths in the on-pump beating group were not related to neurological events. The total chest tube drainage, postoperative peak creatinine kinase myocardial band (CK MB) level within the first 24 hours, and the overall hospital stay did not show a statistically significant difference (p>0.05). There were no neurological complications among the OPCAB group. In the on-pump beating group, one patient developed acute confusional state. In the conventional CABG group, 3 patients developed acute confusional state, 2 patients developed localized stroke, and 2 patients died due to brain damage. The analysis of risk factors (**Tables 4 & 5**) showed that irrespective of the method of operation, the patients who had neurological deficit had significantly lower ejection fractions and preoperative hemoglobin levels. Other

Table 5 - Analysis of risk factors: univariate analysis of categoric variables.

Variable		Neurological deficit		*P*-value	Odds Ratio	95% CI
		Present	Not present			
Age > 70 years	Not present	6	99	0.55	1.6	0.35-7.8
	Present	2	20			
CCF	Not present	4	5	<0.001	22.8	4.3-118.7
	Present	4	114			
Hypertension	Not present	5	73	0.9	1.05	0.23-4.6
	Present	3	46			
Diabetes	Not present	6	77	0.55	1.63	0.35-7.37
	Present	2	42			
Atrial fibrillation	Not present	7	117	0.19	NA	NA
	Present	1	2			
Smoking	Non smoker	6	85	0.48	NA	NA
	Ex-smoker	0	21			
	Current smoker	1	14			
Respiratory Illness	Not present	7	113	0.37	NA	NA
	Present	1	6			
Previous CVA	Not present	0	1	0.79	NA	NA
	Present	8	118			
Hypothyroidism	Not present	0	1	0.79	NA	NA
	Present	8	118			
Peripheral vascular disease	Not present	0	2	0.71	NA	NA
	Present	8	117			
Pre-op catastrophic state	Not present	3	4	<0.001	17.25	3.4-91.5
	Present	5	115			
Non-elective surgery	No	5	24	0.005	6.59	1.61-268
	Yes	3	95			
Nationality	Arab	7	95	0.99	NA	NA
	South Asians	1	16			
	South East Asians	0	3			
	African	0	5			

CCF – congestive cardiac failure, CVA – cerebrovascular accident, Pre-Op – pre-operative, CI - confidence interval

Table 6 - Impact of neurological complications.

Variable	Neurological deficit	Mean±SD	*P*-value
ICU stay (hours)	Not present	58.43±67.26	<0.0001
	Present	192.5±258.8	
Ventilation time (hours)	Not present	13±14.26	<0.0001
	Present	130.87±183.67	
Duration of inotropes (hours)	Not present	19.02±26.1	<0.0001
	Present	83.86±16.79	
Hospital stay (days)	Not present	10.88±33.73	<0.0001
	Present	22.25±31.22	

ICU – intensive care unit

factors that significantly increased the risk of neurological complications included history of congestive cardiac failure, pre-operative catastrophic state, and non-elective surgery. However, multivariate logistic regression analysis excluded catastrophic state from significant risk factors and showed that congestive cardiac failure (odds ratio 19.67 CI 3.37-114.63, p=0.001) and urgent surgery (odds ratio 5.59 CI 1.06-29.49, p=0.043) are the only significant risk factors. **Table 6** shows that patients who developed neurological events had significantly longer duration of mechanical ventilation, ICU stay, and dependence on inotropic agents. These patients also had relatively longer overall hospital stay, but this difference was not statistically significant.

Discussion. Major neurological complications after cardiac surgery constitute a growing percentage of serious postoperative morbidity. In a landmark prospective study, Roach et al[4] evaluated 2108 patients from 24 US institutions. Adverse cerebral outcomes occurred in 129 (6.1%) patients. Type I and II neurological complications had equal incidence. Type I complications include embolic stroke, intracerebral bleed, stupor or coma, whereas the Type II complications included decreased intellectual function or seizures. These complications resulted in higher in-hospital mortality, longer hospitalization and a higher rate of dependence on facilities for intermediate- or long-term care after discharge from hospital. Predictors of type I outcomes were proximal aortic atherosclerosis, a history of neurological disease, and older age; predictors of type II outcomes were older age, systolic hypertension on admission, pulmonary disease, and excessive alcohol consumption. Changes in cognitive function with CPB are generally subtle and may persist for very long times. Newman et al[5] reported an incidence of cognitive decline up to 53% at discharge, 36% at 6 weeks, 24% at 6 months, and 42% at 5 years.

Many of the neurological complications during cardiac surgery are attributed to hypo-perfusion during CPB,[6] micro emboli of gaseous or particulate nature,[7,8] and the result of inflammatory changes that affect an increase in permeability across the blood-brain barrier with resultant cerebral edema.[9] It was therefore, natural that surgeons showed great enthusiasm in adopting the off-pump technique to avoid the deleterious effects of extracorporeal circulation. Unfortunately, this has not resulted in a uniform decrease in adverse neurological events. In fact, results of various studies are contradictory and have so far failed to provide definitive evidence in favor of OPCAB. The randomized controlled trials by Lloyd et al,[10] van Dijk et al,[11] Keizer et al,[12] and Muneretto et al,[13] could not prove any benefit of OPCAB over conventional CABG in reducing neurocognitive dysfunction. A few retrospective,[14] as well as non-randomized prospective studies[15,16] have shown less incidence of stroke in the off-pump group as compared to conventional CABG. Nevertheless, these differences could not reach a statistically significant level. However, one large retrospective, propensity score-matched analysis of over 10,000 patients has shown a significantly lower incidence of stroke in minimally invasive coronary bypass surgery.[17] Despite the fact that there are very important differences in the way different surgeons treat the ascending aorta during OPCAB, all of the above-mentioned studies have treated OPCAB as one group. Many surgeons believe that real benefits of OPCAB surgery can only be achieved by following a no-touch policy for the ascending aorta and therefore use frequent sequential arterial grafts or anastomose the proximal ends of arterial grafts to the pedicled internal mammary arteries, completely avoiding manipulation of the aorta. A large retrospective study by Patel et al,[18] has looked into this matter. In their retrospective study of 2,327 cases of coronary revascularization, they reported the prevalence of focal neurological deficit to be 1.6% in the on-pump group, 0.4% in the off-pump with aortic manipulation group, and 0.5% in the off-pump without aortic manipulation group (p=0.027).

The development of drug eluting stents has made a strong impact on the practice of coronary artery bypass surgery. Many surgeons have noticed an up to 20% decrease in the referral of cases for CABG.[19] Moreover, especially in the Asian region, coronary bypass surgery has become much more challenging as the cases referred for surgery are generally elderly with diffuse coronary disease and many co-morbid conditions.[20] These challenges have pushed us to modify our methodology of CABG surgery. On-pump beating heart surgery is one of the examples of these modifications, which we found very useful in sick hearts. Theoretically, the risk of neurological complications in this technique should be the same as conventional CABG. However, we have persistently witnessed a much better neurological outcome than the conventional group. In our practice, we routinely use a partial occluding clamp for proximal anastomosis. Our results, however, indicate that the partial occluding clamp is perhaps not as deleterious as the cross clamp. In fact, the study by Pugsley[7] also observed that the embolic load is much higher at the time of application and removal of cross clamp than any other manipulation, including the use of the partial occluding clamp.[7] Moreover, we believe that ischemic reperfusion injury caused by aortic cross clamp might have a major role in initiating systemic inflammatory response,[21] which can result in brain injury. The on-pump beating heart surgery therefore has a theoretical advantage as

there is no global ischemia and a much lower degree of ischemic-reperfusion insult.

Our study has 3 limitations: first, this is a retrospective analysis and therefore all the limitations of a retrospective analysis apply (for example, no randomization), second, there was the inherent selection bias among surgeons and the third, is the small total number of patients, which is probably the reason why the traditionally known risk factors like older age and hypertension failed to appear significant in this analysis. The study is however, unique because it has also included the method of on-pump beating coronary bypass, which is a relatively new technique and many surgeons are not convinced of its role.

In conclusion of this study, although adverse neurological events occurred less frequently in the on-pump beating and OPCAB group compared to the conventional CABG group, the difference did not have statistical significance. Preoperative congestive cardiac failure and non-elective surgery were found to be significant risk factors, irrelevant of the method used for CABG.

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