Review Article

Cerebral complications in conventional coronary bypass graft surgery

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Four decades ago, after on-pump coronary artery bypass graft surgery (CABG) was introduced for treating symptomatic coronary artery disease (CAD), operative mortality had continuously declined to below 5%.[1-3] While the mortality had fallen, the operative morbidity had been rising as CABG gradually enrolled more complicated elderly cases with advanced CAD and co-morbidities.[1-4] Among surgical morbidity, cerebral complications were the most devastating events, since they increased the length of stay, medical expense as well as hospital mortality.[5-19] Although the available data showed the declining incidence of peri-operative CNS injury, the incidence of overt cases still varied from 2-7%.[20, 21]

Post-operative cerebral events were formally categorized in three groups: ***1. stroke*** (focal motor, sensory or visual deficit), ***2. diffuse encephalopathy syndrome or DES,*** (obtunded, stupor and coma) and ***3. neuropsychological impairment or cognitive dysfunction*** (changes in behavior, intellectual or thinking process).[8] In Thailand, on-pump conventional CABG remains the standard operation in most cardiac centers but its cerebral complications are less known. Therefore, it was our purpose to address the causes and consequences of these serious complications and to review the alternative options for reducing cerebral complication.

Prevalence, etiologies and outcomes of post-CABG cerebral complications:

1. Strokes

Prevalence: The prevalence of post-CABG stroke varied from 0.6-5%, depending on timing and method of evaluation.[7, 9-11] In a retrospective analysis of a total of 3,279 post-CABG patients, Gardner et al., reported the increasing stroke rate from 0.6 % in 1979, to 2.4% in 1983.[9] Shaw and colleagues prospectively performed neurological evaluation in 312 post-CABG cases and found a much higher post-CABG stroke rate, up to 5%.[12] They further detected other neurological complications such as prolonged encephalopathy (3%), ophthalmic abnormalities (25%), peripheral nerve damage (12%) and primitive reflexes (39%). The post-CABG stroke rate also increased with age and its prevalence rose from 1% in patients aged between 51-60 years to ≥ 9% in patients aged over 80 years.[9]

Etiology: Intra-operative embolization remained a major cause of post-CABG stroke.[23-35] Two-third of strokes resulted from numerous small atheroemboli that predominantly affected the occipital lobe and the area lying between the supply of middle cerebral and posterior cerebral arteries.[8] In one-third of cases, infarct lesion was single and involved the area supplied by the middle cerebral, vertebral and basilar arteries.[8]

Prognosis: Post-CABG stroke increased mortality, the length of stay and cost of treatment.[5-7] In a multicenter prospective study from 24 US institutions involving 2,108 patients, Roach and coworkers categorized adverse, cerebral outcomes into two subsets, **type I** (death due to stroke or hypoxic encephalopathy, nonfatal stroke, transient ischemic attack or stupor, coma at the time of discharge) and **type II** cerebral complications (a new deterioration in intellectual function, confusion, agitation, disorientation, memory deficit or seizure without focal injury). Although both groups were equally detected in about 3%, patients with type I complication had a significant higher hospital mortality (21 % vs. 10% vs. 2%, $p < 0.001$) and had a longer hospital stay (25 days vs. 21 days vs. 10 days, $p < 0.001$) when compared with those of type II and the uncomplicated group respectively.[7]

2. Diffuse encephalopathy syndrome (DES)

Prevalence and prognosis: The manifestation of DES widely ranged from post-operative somnolence, decreased alertness and activity, confusion, agitation and disorientation, to irreversible coma. Among those symptoms, decreased alertness and changes in mental function were quite common and the prognosis was fairly favorable. In the Newcastle study, Shaw and coworkers found that only 3% of post-CABG patients did not regain consciousness to the normal level within 24 hours, although most of them recovered within 12 days.[12] Since most of DES was transient and reversible, it was rather difficult to detect the true prevalence.

Etiology: In contrast to stroke, no definite cerebral CT finding was found in DES and multi-factorial causes had been proposed. Typical DES patients were elderly, having a history of alcoholic consumption and/or renal disease. It was believed that several medications used during or after surgery such as sedatives, narcotics (especially morphine) and psychotropic drugs became the key contributing factors of DES.[8]

3. Neuro-psychological deficits or cognitive dysfunction

Prevalence and prognosis: Cognitive dysfunction generally manifested as inappropriate perception, new memory deficits, deterioration in concentration or attention and delay in response. It was more common than stroke or DES with the prevalence varying from 2.6% - 43% in some prospective reports.[7, 13-17, 22, 35] For example, Roach, et al., found only 55 cases (2.6%) that had deterioration of intellectual function and 8 cases of seizure with no focal injury.[7] This wide range of prevalence suggested the variation in time and methods of neuropsychological assessment. Unlike the DES, cognitive dysfunction lasted longer, from several months to years or even persisted. Venn and colleagues reported persisting cognitive abnormalities in 35% of cases at 12 months after CABG surgery.[17] At three years, Martzke, et al., reported 20% of post CABG cases still had cognitive dysfunction.[18] McKhann, et al., studied 60 post-CABG cases and found rapid decline in memory, psychomotor speed and constructional abilities within 5 years.[19]

Etiology: Microembolization was the major cause of cognitive dysfunction.[8, 32, 33] Multiple small infarctions were usually found in cortical area of frontal, parietal and temporal regions.[8] The prevalence of cognitive dysfunction increased with age and the amount of embolism.[32, 33] By using a transcranial doppler ultrasound, Clark and colleagues found that the neuropsychological complications increased from 2.4% in patients who had less than 30 emboli to 35% in those who had more than 60 emboli.[32] Pugsley, et al., noted that the rate of cognitive dysfunction (at 8 weeks after surgery) rose from 8.6% in patients who had less than 200 emboli to 43% of cases with > 1,000 microembolization.[33] Other contributing factors of impaired cognitive function included pre-existing diseases such as Alzheimer's, diabetes mellitus and the effects of psychotropic drugs used during and after surgery.[8, 22] Kadoi, et al., reported a significant higher incidence of peri-CABG cognitive impairment in patients with type 2 diabetes mellitus at 7 days and the difference still persisted at 6-months.[22]

Clinical risk factors to predict post-CABG cerebral outcomes:

Roach identified 8 clinical risk factors for developing stroke (type I neurologic adverse outcome) and 6 other factors for impaired intellectual function (type II neurologic adverse outcome) (Table 1).[7] The presence of ascending aortic atheroma, prior neurological disease, the use of intraaortic balloon pump (IABP) and diabetes mellitus were strong predictors of developing stroke with the odd ratio (OR) of 4.52, 3.19, 2.60 and 2.59 respectively. For intellectual dysfunction, advancing age, hypertension and history of alcoholic intake were significant predictors (Table 1).

A large observational study by Khan, et al., involving 1,000 patients who underwent isolated CABG, demonstrated the presence of increased age, diabetes mellitus, aortic disease and intramural thrombi were in favor of adverse cerebral outcomes.[6] The influence of diabetes mellitus for developing cognitive disorders was further studied by Kadoi and colleagues in 180 post-CABG type 2 diabetic patients by matching age, sex and educational level.[22]

Table 1: Factors predicted the CABG related cerebral complications.[7]

Risk factors	Odd Ratio (95% CI)
A. Risk factors for stroke	
a. Proximal aortic atherosclerosis	4.52 (2.50-8.09)
b. History of neurological disease	3.19 (1.65-6.15)
c. Use of intra-aortic balloon pump	2.60 (1.21-5.58)
d. Diabetes mellitus	2.59 (1.46-4.60)
e. History of hypertension	2.31 (1.20-4.47)
f. History of pulmonary disease	2.09 (1.14-3.85)
g. History of unstable angina	1.83 (1.03-3.27)
h. Age	1.75 (1.27-2.43)
B. Risk factors for decreased intellectual capacity	
a. Age	2.20 (1.60-3.02)
b. Admission systolic BP > 180 mmHg	3.47 (1.41-8.55)
c. History of excess alcohol consumption	2.64 (1.27-5.47)
d. History of prior CABG	2.18 (1.14-4.17)
e. Dysrhythmias on day of surgery	1.97 (1.12-3.46)
f. Antihypertensive therapy	1.78 (1.02-3.10)

Six risk factors were significantly associated with cognitive dysfunction at 7 post-operative days including advanced age (OR 1.5, CI 1.3-1.8), hypertension (OR 1.8, CI 1.3-2.0), jugular venous oxygen saturation < 50% (OR 1.5, CI 1.1-2.6), ascending atherosclerosis (OR 1.5, CI 1.1-2.6), diabetic retinopathy (OR 2.0, CI 1.3-3.0) and insulin use (OR 2.0, CI 1.3-3.0). At 6 months, only insulin treatment (OR 2.0, CI 1.3-3.8), diabetic retinopathy (OR 1.3, CI 1.2-2.9) and high HbA1C (OR 1.9, CI 1.3-3.1) were the predictors of persisting cognitive disorders.[22]

To minimize the peri-operative cerebral complications, the associated risk factors mentioned above and high risk candidates should be identified before surgery. The details of pathophysiologic mechanisms and how to reduce complications are discussed below.

Pathophysiologic mechanisms of post-CABG cerebral complications:

1. Embolization from proximal aortic atherosclerosis and aortic clamping:

The most common cause of post-CABG stroke was embolization of atherothrombotic plaque from aortic arch.[23, 25-30] McKhann, et al., found that the prevalence of atheroembolism increased from 2% (in patients with no significant aortic disease) to 37% in those who had severe atheromatous disease.[19] Clamping, releasing and canulating the diseased aorta potentially dislodged atheromatous plaque and caused ischemic stroke.[23-26, 35] (Figure 1a-b)

2. Embolization due to pre-existing mural thrombi from cardiac chamber and intra-cardiac operation:

Most single cerebral infarction occurring after CABG were usually caused by emboli originating from intra-cardiac chambers.[8] Mural thrombi from prior myocardial infarctions (Figure 1d), cardiomyopathies, valvular calcification, vegetation and atrial fibrillation were all possible sources of embolization.[8] In a multi-center study involving 2,264 post-CABG patients, Wolman, et al., found that neurological complications increased by almost twice in patients who underwent CABG combined with other intracardiac surgery.[34]

3. Embolization from pre-existing thrombus in the left atrium in patients with atrial fibrillation:

Atrial fibrillation (AF) was the most common complication after cardiac operation and its prevalence ranged from 25-50%.[36-38] AF was associated with an increase in mortality, morbidity, cost of care and doubled the incidence of post operative stroke.[38] The preexisting atrial fibrillation (AF) in CABG patients was independently associated with increased late mortality, morbidity and poor long-term outcome.[39, 40] Most embolic stroke in AF solely originated from thrombus in left atrial appendage.[41]

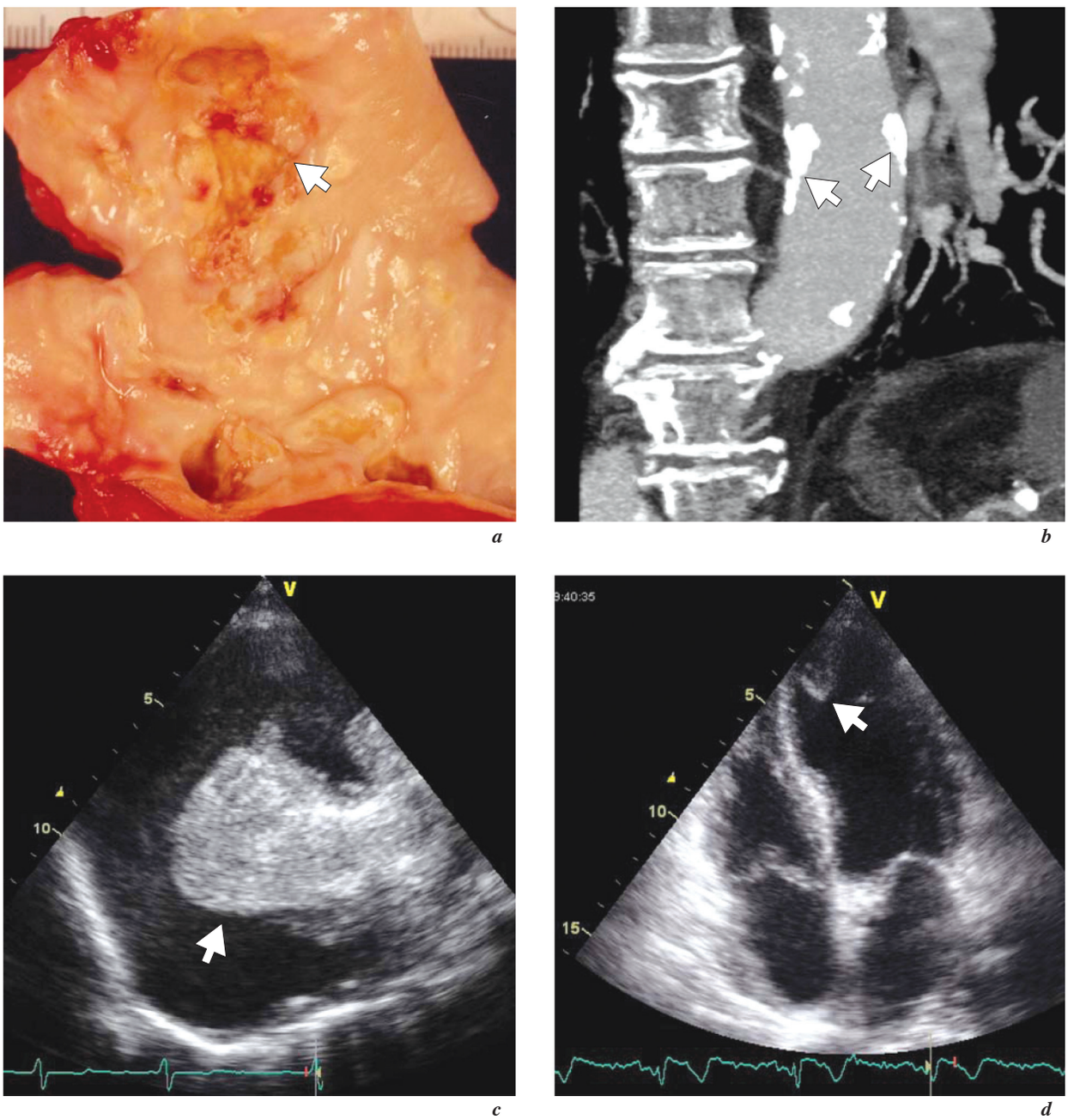

Figure 1: *Arrow head above elucidated the potential sources of coronary artery bypass graft surgery (CABG) related cerebral embolism and stroke.*
a. *Complicated atheromatous plaque in aortic arch.*
b. *Calcified aortic atheroma detected by multi-slice CT scan.*
c. *Large left atrial thrombus.*
d. *Apical thrombus in left ventricle.*

Figures courtesy of Forensic department of Denver General hospital (a), Cardiac imaging unit, Bangkok Heart hospital (b) and Cardiovascular Research and Prevention Center, Bhumibol Adulyadej hospital (c, d)

Risk factors of developing AF included advanced age, chronic obstructive pulmonary disease, preoperative arrhythmia, use of digoxin within two weeks before surgery, low resting pulse rate, high resting systolic blood pressure and intra-operative procedures i.e., cardiac venting via right superior pulmonary vein, mitral valve repair or replacement, the use of inotropic agents for greater than 30 minutes, prolonged ventilation > 24 hours, and CPB.[38, 41]

4. Hemodynamically significant carotid stenosis:

Carotid bifurcation disease is a marker of global atherosclerotic burden and is associated with aortic atheroma and CAD.[41] Significant carotid stenosis reduced cerebral blood flow and increased risk of stroke during cardiopulmonary bypass operation.[31] The risk of peri-operative stroke rose along with the degree of carotid luminal narrowing i.e., from 2% in patients with no significant carotid stenosis (< 50% luminal narrowing) to 10% and up to 18.8% in those patients who had 50-80% and > 80% carotid stenosis respectively.[42]

5. Air embolization during open heart operation:

A significant amount of air could be introduced to the cardiac chambers during open heart operation through CPB machine and might be difficult to remove.[8] The gaseous micro-emboli that potentially cause neurological damage could be visualized by transesophageal echocardiogram.[43, 44]

6. Combined effects of transient cerebral hypoperfusion, increased coagulation in the presence of prior cerbrovascular disease:

Prior history of cerebrovascular diseases i.e., stroke or TIA indicated an impaired cerebral auto-regulation, inadequate cerebral blood flow and underlying atherosclerosis.[7] Transient hypotension during bypass operations further decreased brain perfusion and increased neurological deficits.[8, 45, 46] Tufo and colleagues studied the mean arterial pressure (MAP) during CPB and found that neurological deficits rose from 27% in patients whom MAP was maintained above 60 mmHg to 78% in patients with MAP below 40 mmHg.[45] In a prospective randomized controlled study of 248 cases, Gold and colleagues found that the stroke rate was low, only 2.4%, in the group that had MAP ranging from 80 to100 mmHg, but it increased to 7.2% in patients who had lower MAP, in the range of 50-60 mmHg.[46] In addition, the intraaortic balloon counter pulsation (IABP) that is commonly used in hemodynamically unstable cases was also associated with dislodgement of pre-existing aortic atheroma.[7]

Procedures which potentially reduce adverse cerebral outcomes:

1. Pre-detection of atheroma in ascending aorta by ultrasound sonography, magnetic resonance imaging and CT scan.

Identification of aortic atheroma and thus minimizing the risk of embolization remained in class 1C recommendation by AHA/ACC.[55] Detection included manual palpation by surgeons or ultrasound sonogram.[27, 30] Using an 8 MHz epi-aortic transducer enhanced detection of non-palpable atheroma in 17% of cases and it changed the plan of surgery.[27] Transesophageal echocardiogram has been used to locate aortic calcification and monitor emboli during bypass operation.[29, 30] Currently magnetic resonance imaging (MRI) technique and multi-slice CT scan have been applied to delineate amount and severity of aortic atheroma (Figure 1b). The result of in vivo MRI study of human aorta is closely related with the findings from transesophageal echocardiogram.[28]

2. Avoid aortic clamping and cardio-pulmonary bypass, by MIDCAB and off-pump CABG.

In 70% of operation centers worldwide, CABG are still performed with extracorporeal circulation system (CPB) and partial or total aortic clamping was required to allow proximal anatomosis.[41] Manipulation of atheromatous ascending aorta by clamping, releasing and cannulation potentially dislodged atheromatous plaque and caused embolic stroke.[23-26] Current guidelines recommend minimizing aortic manipulation or avoiding touching atheromatous aorta whenever possible.[41] In addition, the CPB machine used in conventional CABG only provided a non-pulsatile blood flow that further compromised vital organ perfusion and enhanced cerebral ischemia. To avoid aortic clamping and CPB, surgery on beating heart (Off-pump CABG, OPCAB) and a minimally invasive direct coronary artery bypass (MIDCAB) surgery had been successfully performed in 1990's.[47-50]

By avoiding CPB machine, OPCAB potentially offered further advantages such as reduced inflammatory response created by contact of blood and artificial surface of CPB, decreased myocardial injuries, less inotropic drugs used and less blood transfusion. The benefit of an OPCAB in lowering mortality, renal, respiratory, neurological and bleeding complications, had been demonstrated in many studies.[48-50] The large observational study in 2001 to 2004, involving 13,889 OPCAB and 35,941 on-pump CABG patients, the matched analysis showed the benefit of OPCAB by decreasing in-hospital mortality (OR 0.81) and reducing neurological and respiratory complications (OR 0.7 and 0.8 respectively).[51] However, the long term result of OPCAB was of concern. At 3 years, although there was no mortality difference between the two groups, the OPCAB patients had higher revascularization rate (Hazard Ratio (HR) 1.55).[51]

The randomized trials between off-pump CABG vs. conventional procedures showed no clear benefit of OPCAB in terms of operative mortality and neurologic complications.[52-54] In a recent large randomized trial enrolling 1,104 OPCAB patients and 1,099 on-pump CABG cases, there was no statistical difference of the 30 day composite outcome (death or complication, coma, stroke, renal failure, cardiac arrest, reoperation and new mechanical support) between two groups.[54] At one-year, OPCAB patients had higher composite outcome (9.9% vs. 7.4%, $p = 0.04$) and had lower graft patency (82.6% vs. 87.8%, $p < 0.01$) on follow-up angiogram.[54] These conflicting data also suggested that the surgical skill was of great importance: performing OPCAB requires a longer learning curve than the on-pump CABG.

Despite the existing controversies, the current AHA/ACC 2009 and ESC guideline 2010 still recommend off-pump surgery and/or hybrid percutaneous coronary intervention (PCI) as an alternative option for patients with severe atheromatous disease of ascending aorta and aortic arch.[41, 55]

3. Percutaneous transluminal coronary intervention (PCI) alone or combining with OPCAB as hybrid operation.

Unlike the conventional CABG, there was no aortic manipulation involved in PCI therefore, cerebrovascular complications were relatively low, in the range of 0.07-0.23%.[53, 54] Long-term data over 16 years, from one PCI center showed a steady incidence of PCI related cerebrovascular events (CVE) with the total CVE rate of 0.37%.[55] In multi-vessel CAD, meta-analysis of ten randomized controlled clinical trials which compared PCI and CABG favored surgery in terms of 5-fold reduction in revascularization rate.[59]

Although CABG offered either no or only a modest survival benefit overall, surgery was still better than PCI in selected cases i.e., in elderly at age > 65 years old (HR 0.82) and in diabetic patients (HR 0.7).[59] It should be noted that most of the randomized patients had normal LV function with single or double vessel but had no proximal left anterior descending (LAD) disease.[41]

In isolated proximal LAD disease, two meta-analysis studies enrolling over 1,000 patients showed no significant differences in mortality, myocardial infarction or cerebrovascular accidents between PCI and CABG but PCI group carried a three-fold higher incidence of recurrent angina and a five-fold increase in repeat target vessel revascularization at 5 years follow-up.[60, 61]

In patients who had extensive aortic sclerosis, alternative options including OPCAB and hybrid procedures were recommended by current guidelines from ESC and AHA/ACC.[41, 55] The hybrid revascularization referred to a planned combination of minimally invasive surgery (MIDCAB) by grafting the internal mammary artery to the left anterior descending artery with PCI of other vessels during the same hospital stay.[62] Both procedures could be performed consecutively in a hybrid operating room or sequentially on separate occasions.[63]

4. Carotid artery stenosis detection and revascularization before CABG.

The risk of stroke after CABG was quite high in patients with carotid stenosis (50-99%), so it is recommended by current European guidelines to perform duplex ultrasound scanning of carotid artery in patients with a prior history of TIA/nondisabling stroke or carotid bruit on auscultation (class I, C).[41] This suggestion was extended to patients with left main disease, severe peripheral arterial disease or age ≥ 75 years as class IIa, C. In patients with significant carotid stenosis (≥ 70%) by ultrasound, further evaluation with MRA, CT or digital angiography is also recommended (class IIb, C). It remains unclear whether the timing of carotid and coronary revascularization should be synchronous or staged.[41] The choice of carotid revascularization should be individualized after discussion by a multidisciplinary team including a neurologist (class I, C). The most recent data indicates that carotid endarterectomy (CEA) remains the procedure of choice but selection of CEA versus carotid stenting (CAS) depended on multidisciplinary assessment (class I, B).[63, 65] In a meta-analysis study comparing CEA versus CAS, stented group had a significant higher chance of 30 day mortality or stroke (OR 1.6, CI 1.26-2.01) than those of surgical cases.[66]

In the International Carotid Stent study involving over 1,600 cases randomized to CAS and CEA, CAS group was associated with a higher rate of death, stroke, myocardial infarction, HR 1.69, $p = 0.006$.[64] In the substudy analysis, CAS had more new postprocedural brain lesions detected by MRI when compared with those of CEA patients (OR 5.2, $p < 0.0001$).[67]

5. Reduction of atrial fibrillation and its complication.

Post-operative atrial fibrillation (AF) could be reduced by administration of beta-blockers, sotalol and amiodarone.[68-71] The efficacy and safety of beta-blockers in reducing post-operative AF had been documented in the meta-analytic studies with the odd ratio of 0.36 (CI 0.28-0.47).[69] Amiodarone was also effective in AF prevention as shown in several randomized controlled trials and meta-analytic studies.[69-71] In one large randomized placebo controlled trial, amiodarone significantly reduced atrial arrhythmia by 13.4% with hazard ratio of 0.52 (CI 0.34-0.69).[71]

Among the multiple risk factors of developing AF, systemic inflammatory response created by CPB machine remained of interest. Administration of systemic steroids to prevent AF had been shown in two randomized trials. By giving methylprednisolone 1 gm before operation and dexamethasone 4 mg every 6 hours for 24 hours, AF was significantly reduced but higher post-operative complications were also noted in steroid treated group.[72, 73] Pre-treatment with statin drugs effectively prevented AF, as shown in the two randomized trials with the OR of 0.57 (CI 0.42-0.77).[74, 75]

Conclusion

CABG related cerebral complications are devastating events and increase in elderly patients who have advanced atherosclerosis and co-morbid diseases. The degree of cerebral adverse outcomes widely ranges from vivid irreversible coma, peri-operative stroke to transient disorientation and long-term memory deficit which might not be detected. Routine neurological examination, before and after surgery, therefore has been recommended to identify these events early. Prevention of cerebral disorders may be achieved by identifying high-risk cases (i.e., elderly who had preexisting neurological disease, carotid stenosis etc.) and their associated risk factors such as aortic atheroma, use of IABP, diabetes mellitus and atrial fibrillation etc. Several preventive procedures are recommended by current revascularization guidelines, such as hybrid operation with MIDCAB and PCI in patients with advanced aortic atheroma, revascularization of significant carotid stenosis and prevention of AF with beta-blockers, amiodarone and statin.

Finally, we hope that this review will ensure Thai physicians increase attention to identifying post-CABG cerebral complications, since conventional, on-pump CABG remains as yet the standard of care in Thailand.

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