Neth Heart J (2013) 21:70–73
DOI 10.1007/s12471-012-0347-x

SPECIAL ARTICLE

Cognitive dysfunction after cardiac surgery: Pathophysiological mechanisms and preventive strategies

E. F. Bruggemans

Published online: 27 November 2012

Abstract Despite improvements in surgical techniques and the implementation of effective brain protection strategies, the incidence of brain injury after cardiac surgery has remained relatively constant over the years as patients have become older and sicker. Cognitive dysfunction is the most common clinical manifestation of brain injury after cardiac surgery. Its occurrence is related to a combination of three factors that are often associated with cardiopulmonary bypass (CPB): embolism, hypoperfusion, and the inflammatory response. However, such factors and their potential cerebral consequences are not exclusive to CPB. Postoperative cognitive dysfunction also afflicts patients who undergo cardiac surgery without CPB as well as nonsurgery patients who undergo transcatheter interventions. There is growing evidence that patient-related factors such as the presence of (cerebro)vascular risk factors play an important role in both early and late postoperative cognitive dysfunction.

Keywords Cardiac surgery · Cardiopulmonary bypass · Brain injury · Cognitive dysfunction

Brain injury after cardiac surgery still occurs despite improvements in surgical techniques over the years and the implementation of effective neuroprotective strategies. Yet, today's patients undergoing cardiac surgery have become older and present with more comorbidity. Current stroke and encephalopathy rates are approximately 2 % to 5 % and 10 % to 30 %, respectively [1]. A far more common form of brain injury is cognitive dysfunction, with clinical manifestations such as deterioration in memory, attention, (psycho)motor speed, and visuospatial ability. The incidence of cognitive dysfunction varies considerably but may be as high as 50 % to 70 % at 1 week after surgery, declining to 30 % to 50 % after 2 months [2]. Many of the cognitive changes appear to be transient. Nevertheless, cognitive dysfunction at 5 years after surgery has been noted in 40 % of the patients [3].

E. F. Bruggemans (✉)
Department of Cardiothoracic Surgery, Leiden University Medical Center, Albinusdreef 2, P.O. Box 9600, 2300 RC Leiden, the Netherlands
e-mail: e.f.bruggemans@lumc.nl

Assessment of cognitive dysfunction

Cognitive dysfunction can be detected by neuropsychological testing. Important heterogeneity in the assessment, however, may exist due to differences in the selection of neuropsychological tests, the timing of postoperative measurements, and the definition of cognitive dysfunction. Several attempts to standardise the assessment, starting with the Statement of Consensus in 1995 [4], have only provided a platform from which a comprehensive assessment can be developed. In general, the use of a battery of approximately 10 standardised neuropsychological tests selected to measure varying domains of cognitive functioning, including verbal and non-verbal memory, attention, higher-order executive ability, and visuospatial ability, is recommended. The tests should be selected on the basis of their psychometric properties (i.e., reliability and validity) and should be sensitive to small changes in cognitive functioning. Typically, patients perform the tests before surgery to obtain a baseline measure, and one or more times after surgery.

It has long been the gold standard to define postoperative cognitive dysfunction in an individual by a worsening in cognitive performance on at least two neuropsychological tests in the battery, with test performance being defined as significantly deteriorated if a patient's pre-to post-operative test score decrement is at least one standard deviation (SD), the SD being determined on the distribution of the preoperative scores in the patient sample. Another commonly used definition is

a 20 % decrement in test score from baseline on at least 20 % of the tests. However, such definitions of cognitive dysfunction can be criticised for three reasons: (1) they do not deal with chance fluctuations in test scores due to measurement error (i.e., imperfect reliability of test scores), (2) they do not address practice effects that often arise from repeated neuropsychological testing, and (3) they do not take into account the multifocal nature of the dysfunction and the varying extent to which specific cognitive domains may be affected. More recently, alternative statistical indices of cognitive deterioration have been put forward to overcome these problems [5, 6].

Pathophysiology

Neuroimaging and electrophysiological studies in the first week after cardiac surgery have demonstrated global brain swelling, global or regional decrease of brain metabolism, cerebral blood flow changes, increased fast (beta) activity in the electroencephalogram, and slowing and weakening of brain-evoked potentials [7]. New brain lesions at diffusion-weighted magnetic resonance imaging were detected in 25 % to 50 % of cardiac surgery patients [8]. These brain alterations are thought to be primarily caused by global or focal ischaemia induced by transient restriction of cerebral blood flow. Especially vulnerable to ischaemia are the areas

Table 1 Pathophysiological mechanisms of cognitive dysfunction in cardiac surgery and neuroprotective strategies

Mechanism	Source	Risk factor	Neuroprotective intervention
Embolism	CPB equipment	Oxygenator	Use of membrane oxygenator
		Filter	Use of arterial line filter/dynamic bubble trap
		Venous reservoir	Avoidance of venous air entrainment
		Cardiotomy suction	Avoidance/reduction of cardiotomy suction
	Iatrogenic factors	Cannulation	Careful (de)cannulation of the aorta
		Clamping of the aorta	Careful/minimal aortic and cardiac manipulation
		Cardiac manipulation	Insufflation with carbon dioxide
		Drug administration	Use of continuous infusions
		Blood sampling	Minimal blood sampling
	Patient-related factors	Aortic atherosclerosis	Use of epiaortic ultrasound imaging
		Atrial fibrillation Recent myocardial infarction	Use of transoesophageal echocardiography
Hypoperfusion	CPB equipment	Prime volume (haemodilution)	Use of mini CPB circuit
		Pump and pulsatility	Pulsatile perfusion[1]
	Iatrogenic factors	Temperature	Moderate hypothermia (32–34 °C)
		Pump flow rate	Avoidance of rapid/excessive rewarming
		Mean blood pressure	Avoidance of systemic hypoperfusion
		Acid–base management	Avoidance of prolonged arterial hypotension
		Oxygen management	Use of alpha-stat regimen
		Glycaemic control	Avoidance of hypercapnia and hypocapnia
		Anaesthetic agents	Avoidance/treatment of hyperglycaemia
	Patient-related factors	Carotid artery stenosis Hypertension	Use of carotid Duplex scanning
		Diabetes mellitus	
Inflammation	CPB equipment	Tubes and coating	Use of heparin-bonded circuit
		Prime volume	Use of mini CPB circuit/avoidance of CPB
		Oxygenator	Use of membrane oxygenator
		Pump	Use of centrifugal pump[1]
	Iatrogenic factors	Temperature	Moderate hypothermia (32–34 °C)
		Surgical trauma	Use of corticosteroids[1]
			Use of modified ultrafiltration
	Patient-related factors	Blood loss and transfusion need	Use of leukocyte depletion

[1] controversial

CPB Cardiopulmonary bypass

between the great vascular territories in both the cerebrum and cerebellum, the so-called watershed areas. For instance, pyramidal cells within area CA1 of the hippocampus are injured very rapidly and belong to the earliest sites of neuronal injury during global ischaemia [9]. Given the role of the hippocampus in memory, this might explain why of all cognitive problems, anterograde memory deficits are most frequently reported after cardiac surgery.

From the beginning, studies examining the pathophysiological mechanisms of cerebral ischaemia in cardiac surgery have focused on the cardiopulmonary bypass (CPB) procedure. 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 (Table 1). 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. This has been highlighted by recent randomised studies which found no significant difference in postoperative cognitive dysfunction in patients undergoing conventional coronary artery bypass grafting (CABG) with CPB and those undergoing CABG without CPB [10].

Patient-related factors

Factors negatively related to the condition of blood vessels, including those of the brain, such as advanced age, preexisting (cerebro)vascular disease, and the presence of (cerebro) vascular risk factors, play an important role in the pathogenesis of cognitive dysfunction after cardiac surgery. In fact, preoperative small ischaemic lesions and cognitive impairment have been reported in a considerable proportion of candidates for cardiac surgery and have been shown to be predictors of both early and late postoperative cognitive dysfunction [11, 12]. It has been suggested that the apolipoprotein E (APOE) ε4 allele, a genetic risk factor for both atherosclerosis and Alzheimer's disease, plays an explanatory role. A positive association between the presence of this APOE allele and cognitive dysfunction after CABG found by Tardiff and colleagues [13], however, could not be confirmed by others [14, 15].

Valve surgery has been associated with higher rates of cognitive decline when compared with CABG [16, 17], presumably due to the increased number of microemboli that occur during an open chamber procedure [18]. However, valve surgery patients also show a slower and less complete cognitive recovery after the operation. This might be related to the fact that cerebral microembolism remains present in patients with mechanical valve prostheses, even years after the implantation. In vitro studies on mechanical heart valves have demonstrated that high-pressure gradients may cause cavitation, in particular at valve closure, leading to the formation of gas bubbles and eventually stable bubbles [19]. It is tempting to speculate that chronic cerebral microembolism could be at least partly responsible for the late cognitive dysfunction in mechanical valve recipients. At Leiden University Medical Center, we are now examining patients at 8 years after their valve replacement to study this phenomenon.

Prevention

Consequent to the understanding of the mechanisms of postoperative cognitive dysfunction, several preventive strategies have been established (Table 1). Marked improvement has been achieved by the universal application of membrane oxygenators, arterial line filters, alpha-stat acid–base management, new warming techniques, and cell salvage. There is currently insufficient evidence from clinical trials that pharmacological neuroprotection is effective [20].

Conclusion

With candidates for cardiac surgery becoming older and less healthy, individualisation of the surgical approach might be the only option to reduce the risk of postoperative cognitive dysfunction in these high-risk patients. In patients with severe atherosclerosis, for instance, preoperative carotid artery screening and/or intraoperative epiaortic scanning should be considered. To achieve reduction in late cognitive decline, control of modifiable patient-related risk factors, such as hypertension and diabetes, will become more important.

References

1. McKhann GM, Grega MA, Borowicz Jr LM, et al. Stroke and encephalopathy after cardiac surgery: An update. Stroke. 2006;37:562–71.
2. Newman MF, Mathew JP, Grocott HP, et al. Central nervous system injury associated with cardiac surgery. Lancet. 2006;368:694–703.
3. Newman MF, Kirchner JL, Phillips-Bute B, et al. Neurological Outcome Research Group and the Cardiothoracic Anesthesiology Research Endeavors Investigators. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med. 2001;344:395–402. Erratum in: N Engl J Med. 2001;344:1876.
4. Murkin JM, Newman SP, Stump DA, et al. Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery. Ann Thorac Surg. 1995;59:1289–95.

5. Bruggemans EF, Van de Vijver FJ, Huysmans HA. Assessment of cognitive deterioration in individual patients following cardiac surgery: Correcting for measurement error and practice effects. J Clin Exp Neuropsychol. 1997;19:543–59.
6. Collie A, Darby DG, Falleti MG, et al. Determining the extent of cognitive change after coronary surgery: A review of statistical procedures. Ann Thorac Surg. 2002;73:2005–11.
7. Bokeriia LA, Golukhova EZ, Polunina AG, et al. Neural correlates of cognitive dysfunction after cardiac surgery. Brain Res Brain Res Rev. 2005;50:266–74.
8. Sun X, Lindsay J, Monsein LH, et al. Silent brain injury after cardiac surgery: A review: Cognitive dysfunction and magnetic resonance imaging diffusion-weighted imaging findings. J Am Coll Cardiol. 2012;60:791–7.
9. Nunn J, Hodges H. Cognitive deficits induced by global cerebral ischaemia: Relationship to brain damage and reversal by transplants. Behav Brain Res. 1994;65:1–31.
10. Marasco SF, Sharwood LN, Abramson MJ. No improvement in neurocognitive outcomes after off-pump versus on-pump coronary revascularisation: A meta-analysis. Eur J Cardiothorac Surg. 2008;33:961–70.
11. Maekawa K, Goto T, Baba T, et al. Impaired cognition preceding cardiac surgery is related to cerebral ischemic lesions. J Anesth. 2011;25:330–6.
12. Selnes OA, Royall RM, Grega MA, et al. Cognitive changes 5 years after coronary artery bypass grafting: Is there evidence of late decline? Arch Neurol. 2001;58:598–604.
13. Tardiff BE, Newman MF, Saunders AM, et al. Preliminary report of a genetic basis for cognitive decline after cardiac operations. The Neurologic Outcome Research Group of the Duke Heart Center. Ann Thorac Surg. 1997;64:715–20.
14. Steed L, Kong R, Stygall J, et al. The role of apolipoprotein E in cognitive decline after cardiac operation. Ann Thorac Surg. 2001;71:823–6.
15. Silbert BS, Evered LA, Scott DA, et al. The apolipoprotein E epsilon4 allele is not associated with cognitive dysfunction in cardiac surgery. Ann Thorac Surg. 2008;86:841–7.
16. Herrmann M, Ebert AD, Tober D, et al. A contrastive analysis of release patterns of biochemical markers of brain damage after coronary artery bypass grafting and valve replacement and their association with the neurobehavioral outcome after cardiac surgery. Eur J Cardiothorac Surg. 1999;16:513–8.
17. Ebert AD, Walzer TA, Huth C, et al. Early neurobehavioral disorders after cardiac surgery: A comparative analysis of coronary artery bypass graft surgery and valve replacement. J Cardiothorac Vasc Anesth. 2001;15:15–9.
18. Braekken SK, Russell D, Brucher R, et al. Cerebral microembolic signals during cardiopulmonary bypass surgery. Frequency, time of occurrence, and association with patient and surgical characteristics. Stroke. 1997;28:1988–92.
19. Johansen P. Mechanical heart valve cavitation. Expert Rev Med Devices. 2004;1:95–104.
20. Klein KU, Engelhard K. Perioperative neuroprotection. Best Pract Res Clin Anaesthesiol. 2010;24:535–49.