European Journal of Anaesthesiology 2004; **21:** 85–88

ISSN 0265-0215

Editorial

Postoperative cognitive deficits: more questions than answers

Advancements in surgical and anaesthetic techniques have improved overall morbidity and mortality in patients undergoing major general and cardiac surgery. However postoperative cognitive deficits remain as significant complications, particularly in elderly patients [1,2]. Postoperative cognitive deficits result in prolonged hospitalization, increased morbidity and mortality, increased costs and have an adverse impact on quality of life [3]. Postoperative cognitive deficits are generally characterized as limitations of attention, cognition, recognition, orientation, memory and learning. While numerous synonyms such as acute brain syndrome, mental dysfunction and acute confusional state exist, it is important to discriminate between an early and mostly short-term postoperative delirium and the longer lasting postoperative cognitive dysfunction (POCD).

Delirium, defined in the International Statistical Classification of Diseases and Related Health Problems (ICD-10, World Health Organization), describes a nonspecific organic brain syndrome that is characterized as simultaneously occurring disturbances of consciousness, cognition, memory, emotion and psychomotor function as well as the sleep-wake cycle [4]. Postoperative delirium usually develops acutely with a peak onset on the second postoperative day and has a fluctuating clinical course [5]. The incidence of postoperative delirium varies with patient age, type of surgery, preoperative patient cognitive performance and level of education, coexisting disease as well as the method of diagnosis [6]. In a large review of 80 primary data-collection studies on postoperative delirium, the authors reported an average incidence of 36.8% while a range anywhere from 10 to 70% can be found in the literature [6,7]. Potential but unproven aetiologies of postoperative delirium include disturbances of central cholinergic and glutaminergic neurotransmission, electrolyte or fluid deficits and withdrawal symptoms [8]. As postoperative delirium often has one or more causes that can be identified and treated, good assessment and documentation leading to an immediate and correct diagnosis are essential [9]. It appears that a multifactorial and interdisciplinary approach, including assessment and treatment of underlying causes backed by excellent nursing care are key elements for successful prevention and treatment of postoperative delirium [10,11]. This is important as untreated postoperative delirium is a risk factor for POCD [12].

Postoperative cognitive dysfunction is more subtle and therefore neuropsychometric tests are needed to detect and quantify it. Similar to postoperative delirium, the incidence depends on the type of surgery, patient age, method of detection, preoperative level of education, coexisting disease and preoperative patient cognitive performance. Following cardiac surgery employing cardiopulmonary bypass, POCD can be detected in hospital in up to 80% of patients and is still present in as many as 42% 3–5 yr later [2,13,14]. The aetiology of such POCD is most likely multifactorial, including the effects of emboli and generalized cerebral hypoperfusion during cardiopulmonary bypass. In addition, other potential contributors to POCD include systemic inflammation [15–17], genetic predisposition [18] and rapid cerebral rewarming or hyperthermia after cardiopulmonary bypass [19,20].

The incidence of POCD after non cardiac surgery appears to be much lower. Following a large international multicentre trial investigating long-term POCD after general surgery in the elderly, the short-term incidence (1 week) was reported to be 25.8% while the longer-term incidence was 9.9% at 3 months and 1% at 2 yr [1,21]. Possible but unproven aetiologies following non-cardiac surgery include hypotension, cerebral hypoxaemia, the effects of long-acting sedatives or anaesthetics and metabolic disturbances as well as cerebral embolization, e.g. during hip replacement surgery or carotid artery surgery [1,22,23]. The hypothesis that regional anaesthesia might reduce the long-term incidence of POCD following major non-cardiac surgery has not been substantiated by large randomized studies of elderly patients [24–26].

As the incidence of POCD is very much higher in the cardiac surgery population compared to patients undergoing major non-cardiac surgery, it is tempting

Correspondence to: G. Burkhard Mackensen, Klinik für Anaesthesiologie, Technische Universität München, Klinikum rechts der Isar, Ismaninger Strasse 22, 81765 Munich, Germany. E-mail: b.mackensen@lrz.tum.de; Tel: +49 (0)89 4140 6274; Fax: +49 (0)89 4140 4985

Accepted for publication November 2003 EJA 1687

to extrapolate hypotheses and study results from the 'cardiac surgery model of cerebral injury' especially as smaller numbers of patients are needed to conduct these clinical studies. For example, it has recently been demonstrated that hyperthermia commonly occurs during the first 24 h after coronary artery bypass grafting and that there is a direct relationship between postoperative hyperthermia and adverse cognitive outcome [27,28]. Whether the hyperthermia caused the worsened outcome or whether processes that resulted in the worsened outcome also produced hyperthermia remains to be investigated. However, the potential importance of this study is twofold: first, it points to the postoperative period as an important and thus far understudied phase to investigate in non-cardiac surgery as well. Further, a simple but yet unproven intervention such as the prevention of postoperative fever could alter cognitive outcome. As a second example, it has recently been demonstrated that atrial fibrillation is associated with poorer cognitive function 6 weeks after coronary artery bypass surgery [29]. Although the mechanism of this association has yet to be determined, the prevention or treatment of perioperative atrial fibrillation may result in improved neurocognitive function especially as 30% of perioperative strokes in non-cardiac surgery patients are associated with atrial fibrillation. Further evidence for an association between atrial fibrillation and poor cognitive function independent of stroke, high blood pressure and diabetes was also documented in a non-surgical population of elderly men [30].

It is likely that certain genotypes are more vulnerable to perioperative cognitive dysfunction. Again, there is evidence from the cardiac literature that certain genotypes might function as indicators of increased susceptibility to POCD. In a small clinical study by Tardiff and colleagues the presence of the apolipoprotein E ε-4 allele was shown to alter neurocognitive function following coronary artery bypass graft surgery [31]. Interestingly, this preliminary study has not been followed by a larger trial which might be due to the fact that numerous genetic covariates such as single nucleotide polymorphisms may have an effect on neurocognitive outcome. The latter emphasizes why large patient populations need to be enrolled when an association between a genetic marker or polymorphism and clinical outcomes is to be tested [32].

Despite the above examples, extreme caution is advised with any extrapolation from the cardiac scenario as the role of cardiac surgery-related idiosyncrasies such as the cardiopulmonary bypass circuit and surgical techniques (e.g. aortic cross-clamping, cardiac manipulation) as contributors to POCD remain under active investigation. The 'cardiac model' may be a quicker way to test hypotheses about POCD but ultimately both positive and negative results have to be tested in more general populations before applying the results to non cardiac patients.

What are some of the characteristics of 'ideal' studies and what topics are most promising for future investigation? First, it is important to prospectively study large multicentre patient populations with randomized, placebo-controlled, double-blind methods and having control groups that are both hospitalized and not. This is essential to monitor for a practice effect, variability related to specific neuropsychological tests, and other unknown effects of hospitalization [33]. Second, clinical endpoints and outcomes need to be internationally accepted and reproducible. Computer-based systems will facilitate the application of neuropsychological test batteries and questionnaires but these require appropriate validation for multicultural and multi-linguistic use [34]. A (simple) bedside test for early detection would obviously be invaluable. Third, although difficult to quantitate, the impact of POCD on quality of life needs to be further evaluated [3]. Fourth, genetic markers or polymorphism, or both, should be studied as they may also help to identify the underlying pathophysiology and potential new targets for prophylaxis and treatment [35,36]. Fifth, biochemical markers such as the inflammatory serum markers haptoglobin and C-reactive protein that have lately been shown to be indicators for impaired cognitive performance in a 6 yr follow-up study in a healthy aging population appear as potentially important components of future studies [37]. Other factors that have not been sufficiently investigated include the effects of the primary disease, e.g. cancer and chronic diseases, and hospitalization on POCD and postoperative delirium.

In conclusion, continuous investigation of postoperative delirium and POCD is warranted. This is important as the aged population presenting for major non-cardiac and cardiac surgery steadily grows and the social and economic impact of these complications increases. The need for simple, reproducible, standardized and quantifiable tests, both for research as well as for day to day clinical use is evident. The utilization of cardiac surgery as a disease model of POCD for major non-cardiac surgery should be employed with great caution and, at best, for hypothesis generation only.

G. Burkhard Mackensen
Klinik für Anaesthesiologie
Technische Universität München
Munich, Germany

Adrian W. Gelb
Department of Anesthesia and
Perioperative Medicine
University of Western Ontario
London, Canada

References

1. Moller JT, Cluitmans P, Rasmussen LS, *et al.* Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. *Lancet* 1998; **351**: 857–861.
2. Newman MF, Kirchner JL, Phillips-Bute B, *et al.* Longitudinal assessment of neurocognitive function after coronary artery bypass surgery. *N Engl J Med* 2001; **344**: 395–402.
3. Newman MF, Grocott HP, Mathew JP, *et al.* Report of the substudy assessing the impact of neurocognitive function on quality of life 5 years after cardiac surgery. *Stroke* 2001; **32**: 2874–2881.
4. O'Keeffe ST, Ni Chonchubhair A. Postoperative delirium in the elderly. *Br J Anaesth* 1994; **73**: 673–687.
5. Marcantonio ER, Juarez G, Goldman L, *et al.* The relationship of postoperative delirium with psychoactive medications. *JAMA* 1994; **272**: 1518–1522.
6. Dyer CB, Ashton CM, Teasdale TA. Postoperative delirium. A review of 80 primary data-collection studies. *Arch Intern Med* 1995; **155**: 461–465.
7. Gustafson Y, Brannstrom B, Norberg A, Bucht G, Winblad B. Underdiagnosis and poor documentation of acute confusional states in elderly hip fracture patients. *J Am Geriatr Soc* 1991; **39**: 760–765.
8. Parikh SS, Chung F. Postoperative delirium in the elderly. *Anesth Analg* 1995; **80**: 1223–1232.
9. Aldemir M, Ozen S, Kara IH, Sir A, Bac B. Predisposing factors for delirium in the surgical intensive care unit. *Crit Care* 2001; **5**: 265–270.
10. Milisen K, Foreman MD, Abraham IL, *et al.* A nurse-led interdisciplinary intervention program for delirium in elderly hip-fracture patients. *J Am Geriatr Soc* 2001; **49**: 523–532.
11. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. *J Am Geriatr Soc* 2001; **49**: 516–522.
12. Rogers MP, Liang MH, Daltroy LH, *et al*. Delirium after elective orthopedic surgery: risk factors and natural history. *Int J Psychiatry Med* 1989; **19**: 109–121.
13. Blumenthal JA, Mahanna EP, Madden DJ, White WD, Croughwell ND, Newman MF. Methodological issues in the assessment of neuropsychologic function after cardiac surgery. *Ann Thorac Surg* 1995; **59**: 1345–1350.
14. Selnes OA, Goldsborough MA, Borowicz LM, McKhann GM. Neurobehavioural sequelae of cardiopulmonary bypass. *Lancet* 1999; **353**: 1601–1606.
15. Murkin J. Cardiopulmonary bypass and the inflammatory reponse: a role for serine protease inhibitors? *J Cardiothorac Vasc Anesth* 1997; **11**: 19–23.
16. Hall R, Stafford Smith M, Rocker G. The systemic inflammatory response to cardiopulmonary bypass: pathophysiological, therapeutic, and pharmacological conderations. *Anesth Analg* 1997; **85**: 766–782.
17. Hindman BJ. Emboli, inflammation, and CNS impairment: an overview. *Heart Surg Forum* 2002; **5**: 249–253.
18. Newman MF, Laskowitz DT, Saunders AF, Grigore AM, Grocott HP. Genetic predictors of perioperative neurologic and neuropsychological injury and recovery. *Sem Cardiothorac Vasc Anesth* 1999; **3**: 34–46.
19. Cook DJ, Orszulak TA, Daly RC, Buda DA. Cerebral hyperthermia during cardiopulmonary bypass in adults. *J Thorac Cardiovasc Surg* 1996; **111**: 268–269.
20. Grigore AM, Grocott HP, Mathew JP, *et al.* The rewarming rate and increased peak temperature alter neurocognitive outcome after cardiac surgery. *Anesth Analg* 2002; **94**: 4–10.
21. Abildstrom H, Rasmussen LS, Rentowl P, *et al.* Cognitive dysfunction 1–2 years after non-cardiac surgery in the elderly. ISPOCD group. International Study of Post-Operative Cognitive Dysfunction. *Acta Anaesthesiol Scand* 2000; **44**: 1246–1251.
22. Gaunt ME, Martin PJ, Smith JL, *et al.* Clinical relevance of intraoperative embolization detected by transcranial Doppler ultrasonography during carotid endarterectomy: a prospective study of 100 patients. *Br J Surg* 1994; **81**: 1435–1439.
23. Rasmussen LS, Steentoft A, Rasmussen H, Kristensen PA, Moller JT. Benzodiazepines and postoperative cognitive dysfunction in the elderly. ISPOCD group. International Study of Post-Operative Cognitive Dysfunction. *Br J Anaesth* 1999; **83**: 585–589.
24. Nielson WR, Gelb AW, Casey JE, Penny FJ, Merchant RN, Manninen PH. Long-term cognitive and social sequelae of general versus regional anesthesia during arthroplasty in the elderly. *Anesthesiology* 1990; **73**: 1103–1109.
25. Williams-Russo P, Sharrock NE, Mattis S, Szatrowski TP, Charlson ME. Cognitive effects after epidural vs general anesthesia in older adults. A randomized trial. *JAMA* 1995; **274**: 44–50.
26. Rasmussen LS, Johnson T, Kuipers HM, *et al.* Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. *Acta Anaesthesiol Scand* 2003; **47**: 260–266.
27. Mackensen G, Grocott H, Cohen W, Phillips-Bute B, Newman M. Post-operative temperature following cardiac surgery: the influence of warm versus cold bypass. *Anesthesiology* 2000; **93**: A-166.
28. Grocott HP, Mackensen GB, Grigore AM, *et al.* Postoperative hyperthermia is associated with cognitive dysfunction after coronary artery bypass graft surgery. *Stroke* 2002; **33**: 537–541.
29. Stanley TO, Mackensen GB, Grocott HP, *et al.* The impact of postoperative atrial fibrillation on neurocognitive outcome after coronary artery bypass graft surgery. *Anesth Analg* 2002; **94**: 290–295.
30. Kilander L, Andren B, Nyman H, Lind L, Boberg M, Lithell H. Atrial fibrillation is an independent determinant of low cognitive function: a cross-sectional study in elderly men. *Stroke* 1998; **29**: 1816–1820.
31. 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**: 715–720.
32. Long AD, Langley CH. The power of association studies to detect the contribution of candidate genetic loci to variation in complex traits. *Genome Res* 1999; **9**: 720–731.
33. Rasmussen LS, Larsen K, Houx P, Skovgaard LT, Hanning CD, Moller JT. The assessment of postoperative cognitive function. *Acta Anaesthesiol Scand* 2001; **45**: 275–289.

34. Schatz P, Browndyke J. Applications of computer-based neuropsychological assessment. *J Head Trauma Rehabil* 2002; **17**: 395–410.
35. Schwinn DA, Booth JV. Genetics infuses new life into human physiology: implications of the human genome project for anesthesiology and perioperative medicine. *Anesthesiology* 2002; **96**: 261–263.
36. Ziegeler S, Tsusaki BE, Collard CD. Influence of genotype on perioperative risk and outcome. *Anesthesiology* 2003; **99**: 212–219.
37. Teunissen CE, van Boxtel MP, Bosma H, *et al.* Inflammation markers in relation to cognition in a healthy aging population. *J Neuroimmunol* 2003; **134**: 142–150.