Postoperative cognitive deficit in the elderly surgical patient

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Postoperative confusion is frequent in elderly patients, particularly after major emergency surgery. Berggren and colleagues described confusion in 44% of elderly patients after surgical fixation of a fractured neck of femur. Changes in anxiety levels, personality and memory impairment may also occur and contribute to morbidity. Longer-term effects may be possible, such as changes in personality, social integration and cognitive powers and skills, which can be described collectively as postoperative cognitive dysfunction (POCD). Over the past 40 yr many studies have been performed to assess the relationship of these features to anaesthesia and surgery. The incidence reported has varied. Despite radical changes in anaesthetic practice with the development of new drugs and monitoring techniques which should have improved safety, the proportion of patients affected remains similar to earliest reports. Although the incidence appears unchanged, the number of elderly patients has been increasing, and changing expectations, in addition to advanced and more available surgical techniques means that a larger number of elderly patients undergo surgery. Survival of elderly patients after surgery has been documented in a study of the 5-yr survival of 900 postoperative patients. After an initial high mortality, related to the surgical diagnosis and the urgency of surgery, mortality later approached that of an age-matched population, suggesting that age alone should not be a reason not to operate. If long-term survival is not related to surgery, proportionately more procedures will be performed in older subjects, and increasing expectations of the elderly could extend the “demand” into higher age groups. This possible growth in surgical demand makes it important to establish the features, incidence and causes of POCD.

History

In 1955, Bedford reported dementia in old people after operations under general anaesthesia. He concluded that minor degrees of dementia were common and described 18 extreme examples. No controls were available and the anaesthetic records were incomplete. From the notes that were available, several of the patients experienced severe and pro-longed hypotension and the outcome was perhaps not surprising. However, the effects were attributed to the anaesthetic drugs with the recommendation that “operations on elderly patients should be confined to unequivocally necessary cases”.

This prompted Simpson and colleagues to prospectively survey physical and mental changes occurring after anaesthesia and elective surgery in an unselected group of elderly patients. A total of 741 patients were investigated; 472 had general anaesthesia, 206 had local anaesthesia and 63 were discharged without an anaesthetic or operation. Patients were asked standardized questions on physical activity, mental ability, personality and general social integration, and scored according to a five-point scale. In addition, patients thought to be at highest risk of deterioration were tested by a psychologist. No patient showed gross dementia. Lesser degrees of deterioration occurred in some patients, as measured by a decrease in grades on the scoring system. Patients who were subjected to formal mental testing showed no change in basic mental ability and nearly all survivors showed good reasons for deterioration unrelated to organic cerebral damage or anaesthesia. They concluded that anaesthesia had no effect on physical activity, mental ability or personality and recorded the clinical impression of an overall benefit of elective surgery in old people. Unfortunately, there were flaws in the testing of these patients and at least one of the patients described has clear postoperative cognitive deficit.

Blundell measured psychological changes with daily ratings before and after operation in 86 elderly patients undergoing elective surgery. Fifty-one healthy patients were also given formal mental tests, which were focused on memory and intellectual functioning. These included Raven’s progressive matrices, sub-tests from the Wechsler adult intelligence scale, memory tests for current events and past personal events, the peg board test, star test, pathways tests and delayed recognition tests. They were compared with two control groups. The surgical group showed marked deterioration after operation in the arithmetic and memory tests, both immediately and in the long term. These differences were greatest on the tests requiring organization of thought and continued for several weeks. In addition, five patients were confused for more than 1 week, and a few were noted to have an acute abreaction experience although no permanent effects were
found. This deterioration was believed to be a result of the effects of the anaesthetic drugs on the cerebral cortex which was aggravated in some cases by additional complications, such as fever, or the drugs given to combat it. However, there is no information on the nature of the surgery or anaesthesia, and the second control group were not matched to the surgical patients.

In a Finnish study of morbidity and mortality,13 174 patients, aged 70–92 yr, were followed for 4 weeks after surgery. Mortality rate was 11% overall; 6% in elective cases and 33% in emergency surgery. Patients were asked to report on their own mental and physical activity 4 weeks after operation using a postal questionnaire. Twenty-five patients did not return the questionnaire. Dementia occurred in five patients (2%) but in four it was caused by severe primary disease. However, another 8% of patients reported deterioration of physical or mental activity that was not explained by pre-existing disease or surgical complications.

After these early studies and the persisting controversy, interest was renewed with speculation on possible causative mechanisms. The emphasis moved from pure “incidence” reporting to the search for causes and incidence.

### Why does POCD occur?

Bedford1 believed that anaesthetic drugs were the causative agents, and this was obviously supported by Blundell.2 In the 1960s, the role of anaesthetic drugs in POCD was investigated. These observational studies continued into the 1980s when many studies were performed comparing the difference in POCD in patients having general anaesthesia with those having regional anaesthesia.

Others, from the 1970s onwards, studied the hypothesis that postoperative mental changes were caused by the physiological effects of the anaesthetic, such as hyperventilation, hypotension or hypoxia, alone or in combination. Other hypotheses speculated on the role of catecholamines or cholinergic transmission in the central nervous system. More recently, genetic markers from dementia studies have been investigated for their predictive value as either indicators or causative elements in POCD.

### Is POCD caused by general or regional anaesthesia?

A variety of studies (table 1) have examined changes in mental function in patients having either general or regional anaesthesia, and the differences between the techniques. The surgical procedures have varied from minor (cataract surgery)17 18, to intermediate procedures (transurethral resection of the prostate) and major surgery (total hip replacement and total knee replacement). Other investigators followed more than one type of operation, for example total hip replacement and total knee replacement, hysterectomy, prostatectomy or joint replacement, transurethral resection of the prostate or hysterectionomy. The variety in both type and severity of operation may have distorted the results when small numbers of patients were studied. The studies also differed in whether or not they excluded patients with a wide range of medical and surgical conditions that may have influenced outcome, in particular, emergency or urgent patients.

Some workers identified no long-term difference in postoperative mental function between patients receiving general or regional anaesthesia.2 9 17 45 62 70 87 Others noted a transient decline in both groups, which was measured at either 4 h,17 4 days,27 0 1 week or 1–7 days.36 These reflect merely the time chosen by the investigators for the first set of follow-up tests.

Many studies have focused on the differences in outcome in groups of patients receiving either general or regional anaesthesia. Studies comparing elective patients include those of Jones and colleagues,45 Riis and colleagues70 and Campbell and colleagues.17 In a study of functional and cognitive competence after anaesthesia for total hip replacement or total knee replacement,45 tests of cognitive function showed no change in either the general anaesthetic or regional group. The general anaesthetic group showed a decrease in choice reaction time compared with the regional group (i.e. psychomotor speed had improved), but there was no explanation for this. Subjective complaints of dysfunction of attention, memory, psychomotor coordination and orientation were assessed with a cognitive difficulties scale. Twelve patients in the general anaesthetic group and 11 in the regional group thought that their memory had deteriorated over the 3-month period, but this was not supported by formal psychometric testing.

Riis and colleagues89 included a combined general and regional anaesthetic group in addition to the two other groups, to test the hypothesis that mental changes may be caused by increased metabolic demands induced by the endocrine–metabolic response to surgery. Patients having regional anaesthesia only, avoid this response and general anaesthesia (the two postulated causative factors in this study) and discrimination of a possible causative factor is not possible. Increases in plasma cortisol and glucose concentrations were inhibited in the two groups receiving extradural anaesthesia. The group receiving extradural anaesthesia alone showed a similar decline on testing as the other groups, and the cause of the decline was thought to be a factor other than the general anaesthetic or stress response. However, other differences were present in this study. Arterial pressure was lower during operation than before induction of anaesthesia in all groups and the decrease differed significantly between groups, being least in the general anaesthetic group. This raised the possibility that hypotension may be involved, and this was also raised in the study by Campbell and colleagues.17

Campbell and colleagues17 showed a decrease in performance in tests of verbal recall, verbal learning, psychomotor speed and tactile naming at 24 h. Although the decrease in the general anaesthetic group was greater, this was not statistically significant. Recovery was apparent 2 weeks after operation, with possible further improvement at 3 months. The Felix Post Unit questionnaire, a test of orientation and memory used to detect postoperative confusional states, showed no significant changes between groups at any time. Nineteen percent of patients in the general anaesthetic group experienced at least one episode of desaturation (less than 91%) in the peroperative period compared with no patients in the local anae-
Postoperative cognitive deficit in the elderly

... than 30% of pre-induction values in 61% of patients. Patients who experienced hypoxia or hypotension showed no gross changes in psychometric performance, and there was no evidence of long-term POCD in either group. Similar studies by Nielson and colleagues62 and Bigler and colleagues9 did not identify differences caused by the anaesthetic technique.

A study by Williams-Russo and colleagues87 of 262 patients undergoing total knee replacement differed from the other studies in that a minimum clinically important difference (CID) in score for each test was defined, using a Delphi panel to reach consensus before the start of the study. A comprehensive battery of 10 neuropsychological tests was devised to test linguistic, psychomotor/attention and memory domains. CID scores at 6 months were compared with baseline and a score of −1, 0 or +1 given depending on whether the observed change was worse, the same or improved. An overall score was then calculated by combining CID scores and a patient was defined as having long-term cognitive deficit if the total score was −3 or less. Unlike many of the earlier studies,17 42 70 patients with co-morbidity, such as diabetes or previous myocardial infarction, were not excluded from this study nor were patients with psychiatric illness (excluded in17 36 49 62 70). When cognitive outcome was analysed as a within-patient change, there was no significant difference between the two anaesthetic groups from before operation to 1 week or before operation to 6 months after operation. Similarly, there was no significant difference between the two groups in the percentage of patients with a decline in score on any of the 10 neuropsychological tests at either 1 week or 6 months. The generalized pattern was a decline at 1 week followed by an improvement or return to baseline at 6 months on most tests. The memory tests were found to be the most sensitive to early and late dysfunction. The incidence of delirium was 11% and not significantly different between groups. Long-term cognitive deterioration occurred in three of the 24 delirious patients (12.5%) compared with nine (4.5%) of 198 non-delirious patients, a finding that was not significant. Six percent of patients taking the anticholinergic drug scopolamine and 4% in the general anaesthetic group experienced overall long-term cognitive deficit (P = 0.50). Increasing age was a predictor of poorer outcome on the digit span and digit symbol test but did not predict overall long-term deficit. There was no interaction between increasing age and type of anaesthesia. Preoperative depression or IQ scores were not found to be predictors of long-term outcome. It was not known if the 5% of patients showing deterioration over the 6 months of the study was in excess of what would be expected in a population not undergoing anaesthesia or surgery. However, epidemiological data from a French study22 described an incidence of 3% for newly diagnosed dementia in a population of 2726 non-demented elderly over a 3-yr period. Hence the changes after surgery are far more frequent than one would expect naturally.

Two-thirds of the 12 patients who experienced long-term deficits showed signs of deterioration at 1 week, suggesting that long-term effects may be related to perioperative factors. Alternatively, these patients were perhaps at an advanced stage of their natural ageing process which was decompensated and revealed by anaesthesia and surgery. After recovery from the operative insult they continued to age normally and then revealed signs of deterioration at 6 months. In other words, anaesthesia may reveal and hence predict deterioration rather than cause it.

Hole, Terjesen and Breivik62 were the only group to show a marked decline in the mental function of patients having general anaesthesia compared with those having spinal anaesthesia. Mental function in 60 patients having total knee replacement was assessed before and after operation by an interview with an unblinded investigator. Only major and obvious changes were recorded, such as amnesia for personal details or lack of orientation. In most cases this was confirmed by relatives. Between 4 and 10 months after operation, patients were sent a written questionnaire asking about mental changes noted by the patient or relatives. Daily activity samples revealed significant postoperative hypoxaemia on days 1 and 3 in the general anaesthetic group compared with the regional group. Mental changes were found in eight of the 31 patients after general anaesthetic and in one of the 29 patients after regional anaesthesia. In one patient in each group this was attributed to the central anticholinergic syndrome and resolved after physostigmine. Of the seven remaining patients with mental changes in the general anaesthetic group, three had persistent mental deterioration. One of these died on day 9 and the others were discharged after 14 days. In the follow-up questionnaire of the six remaining patients, who were initially judged to have had mental changes, only two thought their mental function had returned to normal. One patient had complete dementia. The reasons for these mental changes were unclear but it was noted that the seven patients developing mental changes immediately after operation had a greater decrease in \( P_{O_2} \) compared with the rest of the group (11.6 to 9.2 kPa). Although arterial pressure during surgery was significantly lower in the regional group compared with the general anaesthetic group, it was concluded that regional anaesthesia was preferable and should be offered whenever possible. Equal numbers of patients in each group (eight) who did not demonstrate mental changes immediately after operation subsequently complained of them on the follow-up questionnaire. These were judged to be slight and not seriously affecting their quality of life.

With the possible exception of this article, no other studies support an adverse effect related to anaesthetic technique or provide evidence against general anaesthesia. However, these articles suggest that other factors may be responsible, such as drug effects, hypoxia or hypotension.

**Does anaesthesia per se cause POCD?**

Subtle changes in mental function after operation occur in patients of all ages.70 76 78 Smith and colleagues78 demonstrated postoperative memory deficit...
### Table 1  Studies of general anaesthesia compared with regional anaesthesia

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Hoke</td>
<td>60</td>
<td>THR</td>
<td>56–84 (71)</td>
<td>Mo + H</td>
<td>D</td>
<td>Interview</td>
<td>P,1,3,7,12 d</td>
<td>↓ Mental function 7/31 GA grp</td>
<td>Yes</td>
<td>Yes</td>
<td>Slight both grps</td>
</tr>
<tr>
<td>1980</td>
<td></td>
<td></td>
<td></td>
<td>or A</td>
<td></td>
<td></td>
<td>4–10 m</td>
<td>No change epi grp</td>
<td>Equal nos C/O long-term change both grps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaarhune</td>
<td>60F</td>
<td>CAT</td>
<td>&gt; 65</td>
<td>A + P</td>
<td>F and D</td>
<td>6 Subtests WMS</td>
<td>P,1 wk</td>
<td>↓</td>
<td>in WMS + Luria tests at 1 week only stat. Significant between grps on Luna tests</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>1982</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Finger tapping</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riis</td>
<td>30</td>
<td>THR</td>
<td>&gt; 60</td>
<td>P + Pr</td>
<td></td>
<td>Interview</td>
<td>P,3 m</td>
<td>↓</td>
<td>Learning retention scores day 2, normal day 7</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>1983</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Battery 1–12 Tests 1−5, 19</td>
<td>P,2,4,7 d</td>
<td>↓</td>
<td>tests 1–5 day 2, normal day 4</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Bigler</td>
<td>40</td>
<td>Acute Hip</td>
<td>&gt; 60 (78.9)</td>
<td>P</td>
<td>D</td>
<td>3</td>
<td>P,1 wk, 3 m</td>
<td>↑</td>
<td>AMT both at 1 wk</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

#### Key to tables

**Tests used in cognitive battery**

1. Trail making A  
2. Trail making B  
3. Symbol digit modalty  
4. Digit span forwards  
5. Digit span backwards  
6. Selective reminding  
7. Visual gestalts learning  
8. Visual gestalts recall  
9. Picture recognition learning  
10. WAIS block design  
11. Sorting test (willanger)  
12. Reaction time  
13. Tapping  
14. Card sorting  
15. Immediate free recall  
16. Delayed free recall  
17. Delayed recognition  
18. Paired associate learning  
19. Addition  
20. Stroop colour word interference  
21. Story recall  
22. Visual memory tests  
23. Object learning test  
24. Digit copying test (DCT)  
25. Controlled oral word association test  
26. Two point discrimination test  
27. Hand preference  
28. Verbal recall—Rivermead behavioural memory test (PRM)  
29. Visual learning—Pud object memory test (POMTN)  
30. Tactile naming  
31. Symbol cancellation  
32. Boston naming test  
33. Digit symbol from WAIS  
34. Benton visual recognition  
35. Mattis Kovner verbal recall  
36. Mattis Kovner verbal recognition  

**Drugs used for premedication, sedation or reversal**

- Mo = morphine
- D = diazepam
- P = pethidine
- Dr = droperidol
- O = omnopon
- F = fentanyl
- A = atropine
- DHI = dihydrobenzperidol
- H = hyoscine
- N = neostigmine
- Pr = promethazine
- G = glycopyrrolate
- L = lorazepam
- M = midazolam

**Abbreviations for test**

- AMT = Abbreviated mental test
- WMS = Wechsler memory scale
- WMS-R = Wechsler memory scale—revised
- MMS = Mini-mental state
- GEMS = Genetric mental status examination
- VAS = Anxiety visual analogue scale
- WAIS = Wechsler adult intelligence scale
- WAIS-R = Wechsler adult intelligence scale—revised
- SCL-90 = Assessment of psychological symptoms
- CAPE = Clifton assessment procedure for the elderly

**Other abbreviations**

- P = preoperative
- d = day
- wk = week
- m = month
- Sed = sedation
- f = female
- Arrows:
  - ↓ = Decrease
  - ↑ = Increase
  - → = No change
<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>Gender</th>
<th>Procedure</th>
<th>Duration</th>
<th>Measures</th>
<th>Follow-up</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chung 1987</td>
<td>60–93</td>
<td>None</td>
<td>TURP</td>
<td>6h</td>
<td>MMS in GA grp at 6 h on tests of recall, attention + calculation</td>
<td>Yes</td>
<td>Notification of recall + attention at 6 h, no change in score</td>
</tr>
<tr>
<td>Hughes 1988</td>
<td>50–80</td>
<td>T</td>
<td>THR</td>
<td>5h–6h</td>
<td>No change in post-op recall &amp; recognition</td>
<td>Yes</td>
<td>No difference in recall &amp; recognition at 5h</td>
</tr>
<tr>
<td>Chung 1987</td>
<td>60–93</td>
<td>None</td>
<td>TURP</td>
<td>6h</td>
<td>MMS in GA grp at 6 h on tests of recall, attention + calculation</td>
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<td>Hughes 1988</td>
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<td>T</td>
<td>THR</td>
<td>5h–6h</td>
<td>No change in post-op recall &amp; recognition</td>
<td>Yes</td>
<td>No difference in recall &amp; recognition at 5h</td>
</tr>
<tr>
<td>Asbjørn 1989</td>
<td>60–80</td>
<td>D</td>
<td>TURP</td>
<td>&gt;60</td>
<td>Paired associate learning and general slight decline postop.</td>
<td>No</td>
<td>No difference in paired associate learning and general slight decline postop.</td>
</tr>
<tr>
<td>Jones 1990</td>
<td>&gt;80</td>
<td>M</td>
<td>THR</td>
<td>3m</td>
<td>Paired associate learning and general slight decline postop.</td>
<td>No</td>
<td>No difference in paired associate learning and general slight decline postop.</td>
</tr>
<tr>
<td>Nielsen 1990</td>
<td>60–86</td>
<td>D</td>
<td>TKR</td>
<td>24h</td>
<td>↑ in full IQ scale and SIP score in verbal/visual memory, delayed recall and attention/concentration both grps, no difference between groups</td>
<td>No</td>
<td>No difference in paired associate learning and general slight decline postop.</td>
</tr>
<tr>
<td>Campbell 1993</td>
<td>65–98</td>
<td>O + H</td>
<td>CAT</td>
<td>6m</td>
<td>↑ in full IQ scale and SIP score in verbal/visual memory, delayed recall and attention/concentration both grps, no difference between groups</td>
<td>No</td>
<td>No difference in paired associate learning and general slight decline postop.</td>
</tr>
<tr>
<td>Williams-Russo 1996</td>
<td>65–98</td>
<td>M</td>
<td>TKR</td>
<td>6m</td>
<td>↑ in full IQ scale and SIP score in verbal/visual memory, delayed recall and attention/concentration both grps, no difference between groups</td>
<td>No</td>
<td>No difference in paired associate learning and general slight decline postop.</td>
</tr>
</tbody>
</table>

**Notes:**
- MMS: Mental Status Examination
- GEMS: Global Evaluation of Mental Status
- VAS: Visual Analog Scale
- P,1,3,5d: Postoperatively, 1,3,5 days
- P,1,3,5m: Postoperatively, 1,3,5 months
- TURP: Transurethral Resection of the Prostate
-THR: Total Hip Replacement
- TKR: Total Knee Replacement
- CAT: Cataract Surgery

**Abbreviations:**
- GA: General Anesthesia
- H: Hospital
- M: Medical
- GA grp: General Anesthesia group
- Regional grp: Regional Anesthesia group
- MMS: Medical Status Examination
- GEMS: Global Evaluation of Mental Status
- VAS: Visual Analog Scale
- P,1,3,5d: Postoperatively, 1,3,5 days
- P,1,3,5m: Postoperatively, 1,3,5 months
- TURP: Transurethral Resection of the Prostate
- THR: Total Hip Replacement
- TKR: Total Knee Replacement
- CAT: Cataract Surgery

**Findings:**
- ↑: Improvement
- ↓: Decrease
- ns: No significant difference
- Not tested
regardless of age when patients were tested on the second day after surgery, and elderly patients also had problems with orientation and concentration (table 2). A positive correlation was found between postoperative deficit and poor preoperative cognitive function. The relationship between duration of anaesthesia and postoperative deficit was unexpected in that larger deficits were associated with surgery of shorter duration.

Smith and colleagues studied choice reaction times in 112 patients after transurethral procedures at 1, 2 and 3 days after operation; 26 orthopaedic patients, studied at least 12 days after operation were used as controls. An increase in variability in reaction time at 24 h was shown in the study patients but not in controls. Risk factors were a reduced CAPE score before operation, extent of surgery, postoperative pain and postoperative sedative drugs, but age, duration of anaesthesia, minimum arterial pressure, minimum and maximum perioperative $P_CO_2$ values, postoperative pyrexia and poor sleep were not contributing factors. Chung and colleagues who studied only 40 patients undergoing cholecystectomy, found no age-related difference apart from performance on the trail making test, which was noted only on the first day after operation.

Tzabar, Asbury and Millar studied 54 patients undergoing day-case anaesthesia for a variety of surgical procedures. Patients were asked to complete the cognitive failures questionnaire (CFQ) for the 3 days before and after operation to provide a subjective assessment of cognitive function. The CFQ consists of 25 questions relating to lapses or mistakes that commonly occur in everyday life. They were compared with 30 patients having local anaesthesia. They reported significantly more cognitive failures in the general anaesthetic group after compared with before operation, and also in the general anaesthetic group compared with the local anaesthetic group. Unfortunately, this study has serious flaws; patients could not be randomized between local and general anaesthesia because of the different surgical procedures. The general anaesthetic group were significantly younger, included more females and had a higher drop out rate, with only 68% returning the second questionnaires. This highly selected group formed the 54 general anaesthetic patients.

### Specific anaesthetic-operative techniques causing POCD

#### POCD in Cardiac Surgery

Cognitive decline is well documented after cardiac surgery (table 3). The extent depends on the time of measurement and the cognitive functions studied. These complications are usually attributed to the adverse effects of cardiopulmonary bypass on the brain. The proposed causes are legion, and include preoperative cerebral dysfunction, limited autoregulatory capacity, hypothermia, intraoperative hypotension, loss of pulsatile flow, macro- or micro-embolization of air, or particulate matter or cellular aggregates which may compromise cerebral perfusion. Combinations of these causes may also be harmful; Newman and colleagues reported that the combination of hypotension (mean arterial pressure...
Table 3  Studies of POCD and cardiac anaesthesia

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Surgery</th>
<th>Age (yr) mean</th>
<th>Tests</th>
<th>Time</th>
<th>Follow-up rate</th>
<th>Results</th>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>short-term</td>
</tr>
<tr>
<td>Savageau</td>
<td>245</td>
<td>Cardiac-CABG</td>
<td>25–69 (54.7)</td>
<td>Visual reproduction (WMS) Tests 1 + 2</td>
<td>P,9d,6m</td>
<td>83%</td>
<td>28% decrease on at least 1 test day 9</td>
</tr>
<tr>
<td>Valve</td>
<td></td>
<td></td>
<td></td>
<td>Logical memory (WMS)</td>
<td>P,6m</td>
<td></td>
<td>By 6 m more than 80% of these pts normal range</td>
</tr>
<tr>
<td>Combination</td>
<td>11%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>% pts showing decrease on tests = 17% on 1 test, 6% on 2 tests and 1% on 3 tests</td>
</tr>
<tr>
<td>Shaw</td>
<td>312</td>
<td>Cardiac-CABG</td>
<td>33–70 (53.4)</td>
<td>Tests 2,11</td>
<td>P,7d</td>
<td>96%</td>
<td>▲ Neuro and neuropsychological complications cardiac grp compred with surg. grp but complications exist both grps</td>
</tr>
<tr>
<td>1987</td>
<td></td>
<td></td>
<td></td>
<td>7 subtests WMS</td>
<td>/discharge</td>
<td></td>
<td>Not tested</td>
</tr>
<tr>
<td>Control surg.</td>
<td>50</td>
<td></td>
<td>41–68 (57.4)</td>
<td>WAIS vocab sub test</td>
<td></td>
<td></td>
<td>↓ On all tests surg.grp compared to controls day 8</td>
</tr>
<tr>
<td>Control non-surg.</td>
<td>20</td>
<td></td>
<td>31–61 (46)</td>
<td></td>
<td></td>
<td></td>
<td>↑ Levels of anxiety and depression surg. grp day 8</td>
</tr>
<tr>
<td>Townes</td>
<td>90</td>
<td>Cardiac-CABG</td>
<td>(7–7) (59)</td>
<td>Shipley Institute of living scale</td>
<td>P,8d,7m</td>
<td>87%</td>
<td>General improvement in surg. grp on higher functions</td>
</tr>
<tr>
<td>1989</td>
<td>47</td>
<td>intracardiac</td>
<td></td>
<td>WAIS digit symbol from the Halstead-Reitan neuropsychological battery: Trail making Finger oscillation Sensory perceptual examination Aphasia screening test from the repeatable cognitive-perceptual-motor battery: Peg board Visual search Digit vigilance tasks Selective reminding test WMS—Logical passages and visual designs Hamilton depression scale ratings the subjects subjective anxiety rating</td>
<td></td>
<td></td>
<td>31% showed a decline at 7 m and included a group who were impaired preop. and remained so 11% showed a decline on at least half of the tests</td>
</tr>
<tr>
<td>Control non-surg.</td>
<td></td>
<td></td>
<td>(7–7) (59)</td>
<td></td>
<td></td>
<td></td>
<td>At 1 month</td>
</tr>
<tr>
<td>McKhann</td>
<td>172</td>
<td>Cardiac-CABG</td>
<td>41–86 (63)</td>
<td>CES-D depression score Written alphabet test Rey auditory verbal learning tests 1–8 Rey complex figure copy and immediate and delayed recall Grooved pegboard and tests 3–5, 21,34</td>
<td>P,1m,1yr</td>
<td>73%</td>
<td>At 1 yr Improved most pts</td>
</tr>
<tr>
<td>1997</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Small no. remain impaired</td>
</tr>
</tbody>
</table>

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results were attributed to cardiopulmonary bypass.

Savageau and colleagues assessed neuropsychological dysfunction at 9 days and 6 months after elective cardiac surgery, and 83% of patients completed both tests. They were classified as having significant deterioration if their score on a test was more than 1 SD below their preoperative score. Twenty-eight percent of patients showed deterioration in one or more tests on day 9. At 6 months, 76% of patients showed no significant deterioration on any of the five tests, 17% showed deterioration on one test and 6% on two tests. The greatest deterioration showed, poor performance on three tests, affected only 1% of patients. Of great interest was the finding that only 5% of patients had deficits at both times. Most deficits identified at 6 months had occurred subsequent to the test on day 9. Factors associated with decreased function at 6 months were total estimated blood loss greater than 3000 ml and the use of propranolol during operation. Greater fatigue and depression after operation were also associated with poorer performance.

In 1987, Shaw and colleagues examined the effects of cardiopulmonary bypass by comparing neurological and neuropsychological complications in 312 patients undergoing coronary artery bypass graft with 50 patients undergoing major surgery for peripheral vascular disease. A battery of 10 tests was used, consisting of eight subtests from the Wechsler memory scale (WMS) and two from the Wechsler adult intelligence scale (WAIS). A second control group of 20 non-surgical patients was included to demonstrate the effects of repeating the tests after an interval of 7 days. Reproducibility of results was confirmed by a high Spearman re-test reliability coefficient. Intellectual deterioration was defined as mild (deterioration on 1–2 tests), moderate (3–4 tests) or severe (5 or more tests). In the cardiac group, 61% developed early neurological abnormalities and 79% developed early neuropsychological abnormalities compared with 18% and 31% in the control group. By the time of discharge, 17% of the cardiac group had neurological disability and 38% had neuropsychological symptoms. Of the patients with neurological complications in the CABG group, 48 had minor disability and four major functional disability compared with none in the surgical control group. Twenty-four percent of patients in the cardiac group showed moderate or severe intellectual deterioration compared with none in the control group. Potential risk factors for cerebrovascular disease were more common in the control group and the different results were attributed to cardiopulmonary bypass.

Townes and colleagues also used a non-surgical control group in a study to elucidate the severity and duration of new organic brain dysfunction after cardiac surgery. A group of 65 patients CABG were compared with 25 patients for intra-cardiac surgery to see if there was a difference in incidence caused by the bypass itself. The community volunteers used for the control group had a higher level of education but otherwise there were no differences. A comprehensive battery of psychometric tests were studied. No significant differences were found between the groups undergoing CABG or intra-cardiac surgery at any time, although there was a discernible difference in 31% of patients in either clinical or test performance. At the 7-month follow-up, there was no significant difference between the surgical and control groups for any test except that the surgical group were still rated as more depressed. Patients who started with a poor performance on clinical rating remained so, and eight other patients showed a decline on clinical rating. Increased age was the only significant difference in the impaired group.

Although the level of depression before operation had an impact on tasks such as problem solving and the overall degree of impairment, it did not account for it fully. Depression alone accounted for differences in aphasia and overall impairment at the 7-month follow-up. Membrane oxygenators, arterial filters or pulsatile flow which can improve cognitive outcome were not used. The decrease in cognitive function before discharge may also be attributed to the large doses of long-acting drugs used for anaesthesia and analgesia.

McKann and colleagues studied the frequency of depression in patients after CABG and its link with cognitive deficit; 176 patients were assessed using the Center for Epidemiological Study of Depression (CES-D) scale and a series of cognitive tests. The CES-D score ranges from 0 to 60 with a score greater than 16 indicating depressed mood. Depression was found to be present in 27% of patients before surgery. In patients depressed before operation, 53% were still depressed at 1 month, and 47% at 1 yr after operation. In the non-depressed group before operation, 13% were depressed at 1 month and 9% at 1 yr. Preoperative depression is thus a good predictor of depression after operation but when cognitive function was compared before operation between the depressed and non-depressed groups, there was a difference in only one area of cognitive function, visuoconstruction. Aspects of cognitive function, such as attention where impairment might be expected in depression, were not affected. This study concluded that postoperative depression (a total incidence of 32% in this study) is linked closely to preoperative depression and is not responsible for the decline in cognitive function demonstrated at 1 month and 1 yr. Patients with prolonged decline and delayed decline had little sign of cognitive impairment at 1 month, suggesting that perioperative hypoxia is an unlikely cause of this decline.

**Drug effects**

**GENERAL ANAESTHETIC DRUGS**

Anaesthetic drugs may continue to exert effects on cognitive function at trace concentrations, and this has been investigated over several years. Bruce, Bach and Arbit showed that students exposed to 4 h inhalation of nitrous oxide 500 ppm and halothane 15 ppm in air showed significant decrement in performance on tasks involving auditory and visual signals, memory tests involving digit span, and recall of word pairs. Subjects exposed to nitrous oxide in air showed only a change in the digit span test. Bruce and Bach showed that students exposed to 4 h inhalation of halothane showed significant decrements in performance on tasks involving auditory and visual signals, memory tests involving digit span, and recall of word pairs.
later reported that inhalation of trace amounts of halothane (1 ppm) and nitrous oxide (50 ppm) produced decrements on tasks of visual perception, immediate memory and a combination of perception, cognition and motor skills. Nitrous oxide alone also produced this effect. Other workers found similar effects related to small (20–30%) amounts of nitrous oxide while still others found no effect with either 10% nitrous oxide or halothane 100–150 ppm in air on anaesthetists or students.

PREMEDICATION AND/OR GENERAL ANAESTHESA

Initial reports of drowsiness and amnesia after general anaesthesia and the possible influence of premedication have led to many studies comparing different drug combinations, and the evaluation of new drugs as they emerge to reduce such side effects. The cognitive impact of premedicant and sedative drugs was investigated by several groups. Feldman compared the effects of four different combinations of premedicant drugs. Patients were assessed using a questionnaire. Amnesia for the preoperative period was only significant for the Luria tests. Patients undergoing cataract surgery under either general or regional anaesthesia showed a significantly greater degree of postoperative amnesia than patients receiving spinal anaesthesia. Kalman and colleagues compared the effects of propofol and isoflurane anaesthesia (with and without nitrous oxide) on early and late recovery after major abdominal surgery. During the first 2 h, the Steward recovery scale was used, and orientation, comprehension and sedation were assessed. Before and on days 1, 2, 3, 7 and 30 after operation, psychomotor function was tested using simple reaction time and finger tapping. Patients also answered a questionnaire to assess symptoms and mood. Psychomotor function after operation was similar in all three groups and there was significant prolongation of the reaction time and a reduction in finger tapping speed. Patients anaesthetized with isoflurane reported more vegetative symptoms than those anaesthetized with propofol. Patients receiving propofol also reported greater subjective control and were more socially orientated. Addition of nitrous oxide did not change the results.

One of the possible effects of general anaesthetic drugs on cognitive function is an alteration in memory processing. Nordstrom and Sandin demonstrated that patients who were temporarily capable of cognitive action during intermittent propofol anaesthesia had no subsequent explicit recall of intraoperative events. Implicit memory itself appears to be spared during propofol anaesthesia.

Effects of physiological changes during anaesthesia

HYPOVENTILATION

Hyperventilation leading to profound hypocapnia and cerebral vasoconstriction seems a logical cause for cognitive deficits, and this was confirmed by Wollman and Orkin who found that extremes of hypocapnia during anaesthesia were associated with a prolonged reaction time for at least 3–6 days after hyperventilation. This was particularly worrying because hyperventilation was for relatively short periods and in relatively young people. However, other groups could identify no significant effect of hyperventilation on cognitive performance.

HYPOTENSION

It was speculated many years ago that POCD may occur as a result of physiological changes during anaesthesia and surgery which adversely affect cerebral perfusion. Intuitively, hypotension may cause cognitive deficits, and such changes have been used by several groups to investigate the role of cerebral perfusion. Unfortunately, the results are less than robust. Gruvstad, Kebben and Lo found a slightly greater impairment in psychiatric and psychometric tests after hypotensive anaesthesia but considered these changes unimportant in daily living. Eckenhoff and colleagues tested perception and short-term memory, which were considered to be important to
Hypoxia is commonly implicated when changes in mental function occur. The pathophysiology is complex and the effects depend on the degree of hypoxia, the time course over which it develops, and whether ischemia is also present. In mild to moderate hypoxia, the supply of energy to the brain is normal and cerebral ATP concentrations are maintained. In contrast, central neurotransmitter turnover is very sensitive to mild hypoxia. Investigations in which chemical hypoxia and tissue hypoxia were induced in mice showed a decrease in cerebral acetylcholine synthesis. The importance of this in the neurological symptoms of hypoxia was tested by treating mice with an acetylcholinesterase inhibitor. This delayed the time to seizures or death, suggesting that Central neurotransmitters, including acetylcholine, may be the cause of impaired brain function in hypoxia. The direct role of hypoxia in POCD has been examined frequently. No difference in cognitive deficit was seen when either air or oxygen was used as the vaporizing gas in elderly patients undergoing prostatectomy. Similarly, when examining the role of pulse oximetry, the difference in the rates of postoperative cognitive deficit when pulse oximetry was used (7%) were not found to be significantly different compared with when it was not used (11%). An observer study of hypoxaemia in a PACU demonstrated a lower risk of hypoxaemia in patients who had undergone regional anaesthesia compared with general anaesthesia, but this could not be related to postoperative morbidity.

The pattern of memory deficit after hypoxic ischaemic injury secondary to cardiac arrest has been described and found to have some similarities to the amnesia associated with alcoholic Korsakoff’s syndrome, herpes encephalitis and temporal lobe resection. They have the following features in common: (1) intact short-term memory, (2) poor free recall, (3) less depressed recognition ability, (4) some responsiveness to retrieval cues and (5) increased susceptibility to interference. Unlike Korsakoff’s syndrome, these patients are orientated and do not confabulate. These clinical features are not commonly seen after operation where disorientation in time and poor short-term memory are the cardinal features.

Studies of patients with severe sleep apnoea syndrome provide further evidence that the role of hypoxia is unlikely to be a direct cause of cognitive impairment. Despite profound and very frequent episodes of arterial oxygen desaturation, occurring every night for years, there has been great difficulty in separating the effects of sleep deprivation from those related to hypoxia. Treating sleep apnoea with nasal CPAP improves the results of vigilance tests but has little effect on the mild cognitive deficits that have been found. Such studies support the hypothesis that secondary mechanisms, sensitive to hypoxia, are responsible rather than a simple direct action.

Neurotransmitter or neuro-modulation causes

CATECHOLAMINES

In 1975, Drummond reviewed the assessment of postoperative mental function and discussed the possible causes of a decrease in function and the possible role of catecholamines. Wyatt and colleagues studied the effects of altering brain catecholamine concentrations on human sleep. Potent, specific inhibitors of catecholamine synthesis increased total REM sleep with no change in non-REM sleep; serotonin was also found to augment REM sleep. Sung, Frederickson and Holtzman studied the effects of ketamine and thiopental on monoamine concentrations in rat brain. Ketamine caused a slight increase in serotonin and a decrease in norepinephrine concentration. It decreased the apparent synthesis rate of serotonin by 50% while the rate of dopamine synthesis doubled. Thiopental did not affect brain monoamine content but caused a slight decrease in the rate of synthesis of serotonin and a 30% decrease in the rate of synthesis of dopamine, Eger noted that drug induced changes in central catecholamine concentrations affected the potency of anaesthetic agents. It was speculated that the changes in catecholamine concentrations caused by anaesthetic drugs could be directly responsible for the changes in mental function, rather than being the residual effects of the drugs themselves.

The cognitive problems seen with the β-blocking...
drugs gave support for this hypothesis, but there is little recent information to confirm a close relationship with circulating or central catecholamines and POCD.

CHOLINERGIC SYSTEM

More recently, the central cholinergic system has been identified as a possible site of action and damage leading to POCD. Smith and colleagues\(^5\) speculated that the memory deficits seen after operation in patients of all ages could result from the anticholinergic effects of atropine used as premedication and also for reversal of residual block. This is supported by the fact that patients with pre-existing cognitive impairment and Parkinson’s disease are susceptible to deterioration when prescribed anticholinergic agents.

Delirium is another strong predictor of postoperative cognitive deficit, and could be related to disordered central cholinergic pathways. Knill, Novick and Skinner\(^5\) studied 61 elderly patients undergoing elective abdominal or orthopaedic surgery under general or local anaesthesia, and compared cognitive outcome in patients developing idiopathic postoperative delirium (IPD) with those who did not. IPD developed in 20% of patients, and three of the 12 patients with IPD had significant reductions in minimal state (MMS) scores at both times, reflecting performance deficits in two or more functions, compared with only one of the 49 patients without IPD (\(P=0.009\)). Knill, Novick and Skinner concluded that IPD was associated with persistent cognitive deficit in some elderly patients. It is not clear if persistent cognitive decline results from delirium itself, if they both result from a separate pathology or an intraoperative event, or if IPD indicates reduced cholinergic reserves.

There is further convincing evidence in geriatric research that confirms that dementia is caused by failure of cortical cholinergic arousal mechanisms.\(^5\)\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\) Markers for the genetic component of this process have been tentatively identified—the apolipoprotein-E\(^6\)\(^5\) gene system. The E4 gene appears to be a marker of poor outcome while the E2 gene appears to be protective. Unfortunately, this has not provided a robust marker in dementia research.\(^4\)\(^5\)\(^6\) The potential of this gene system to identify patients at risk during cardiac surgery\(^8\)\(^6\)\(^8\) has proved debatable. The use of cholinergic enhancing drugs has equally been unsuccessful in the long term.

CONFOUNDING PROBLEMS

One confounding element common to all of the above studies is the possibility that a learning effect on some cognitive tests has occurred, as has been suggested by some authors.\(^5\)\(^6\)\(^2\)\(^7\)\(^8\) However, this has not been confirmed in all studies, for instance a control group of 50 patients\(^5\) on the waiting list for elective joint replacement showed no change over time with the tests used, and no practice effects. Moller and colleagues\(^5\) used a matched control group to determine performance of their cognitive test battery on repeated tests, and this weighting was then applied to their patient data set. This successfully avoids the concerns of practice and learning of such cognitive tests.

Recent research data

THE ISPOCD 1 MULTICENTRE STUDY

The conflicting evidence presented from previous studies, and the possibility that combinations (such as hypoxia and hypotension) may be important, indicated that a definitive study designed specifically to avoid confounding variables was required. Earlier studies suffered from problems with methodology such as small numbers, lack of controls, insensitive psychometric testing, inclusion of patients with pre-existing disease, different medications and incomplete testing. Such problems cause significant bias. A multicentre study, ISPOCD,\(^5\) was performed in 13 centres in eight countries from November 1994 to May 1996, recruiting 1200 patients aged more than 60 yr, undergoing major abdominal, thoracic (non-cardiac) or orthopaedic surgery. Patients with an MMSE equal to or less than 23, CNS disease or receiving interactive drugs were excluded.

The study tested the hypothesis that prolonged cognitive dysfunction occurred after operation, that age was a risk factor and that the combination of hypoxaemia and hypotension were causative factors. A comprehensive battery of six psychometric tests were selected from 12 tests evaluated initially in 50 elderly patients. The battery takes approximately 45 min to complete. It was applied to 176 British volunteers as a normal control population, and a total of 145 national control subjects, aged more than 60 yr, using the same exclusion criteria and time intervals as in the patient study. The test battery was presented to patients before operation, and at 1 week and 3 months after surgery. Patients also performed an IQ test, the Zung mood test, a self-assessment of cognitive decline from the short cognitive failures questionnaire (CFQ) and an estimate of the activity of daily living (ADL) score before operation. The orientation section of the MMSE was administered daily after operation to screen for confusion and delirium. The test battery and Zung scale were repeated on discharge or day 7, and again at 3 months, in addition to the CFQ and ADL. The learning effect was countered by taking the scores of the control individuals and subtracting from the patient scores. The results confirmed that there was a 25.8% (95% CI 23.1–28.5%) incidence of postoperative cognitive deficit at 7 days, and that this still affected 9.9% (95% CI 8.1–12%) of patients at 3 months. Detailed analysis identified only age as a predictor of deficit, and surprisingly that hypoxia, hypotension, or both, were not. The cognitive changes related to decreases in ADL scores showed that these were clinically important changes and not just subtle psychological variations.

FUTURE RESEARCH

There are some firm indications for the directions further research should follow. It is clear that the most promising area where both causation and perhaps prevention may be possible is the central cholinergic system. While the present genetic markers are less than ideal, others may be found that are more specific. The development of drugs for the treatment of dementia will also offer hope that their prophylactic use during operation can reduce the onset of these cognitive deficits.
Equally, there may be subgroups of the population who have critical cognitive functioning, with little reserve, who are vulnerable to the effects of hypoxia and hypotension. Large studies may overwhelm the association of these features in small subgroups, and certainly at present there remains the need to maintain physiological stability during the operation.

Further work is necessary to identify how long the identified deficits last, whether or not they become modified over time, and the social and economic significance of these deficits. It would be valuable to ascertain if regional anaesthesia for major surgery causes similar problems, although current data would support this. Extension of the study groups to include younger patients and ambulatory elderly patients would inform the planning of surgery more precisely.

Conclusions

There is no debate as to whether or not postoperative cognitive deficit exists. It is common and persistent, and should attract the same interest in further research that a similar 25% incidence would obtain if it were found in a young adult or paediatric group. Collaboration with basic science research in progress in the fields of dementia, and in the neurochemistry of the central cholinergic system, may be fruitful in predicting those elderly patients who are most at risk from POCD, and providing effective therapeutic agents to either prevent or reduce the serious effects of POCD on patients and their families.

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References


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