

## *Neuropsychiatric consequences of coronary artery bypass grafting and noncardiovascular surgery*

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*This paper reviews findings regarding short- and long-term neuropsychiatric consequences of coronary artery bypass grafting (CABG) and noncardiac surgery. Stroke is one of the potentially most serious complications of CABG; studies have identified some demographic and medical risk factors. Short-term neuropsychological deficits are common after CABG, but have been similarly documented in noncardiac surgery patients, and may therefore not be specific to this procedure. Neuropsychological deficits in some cognitive areas may persist over time. Patients with depression before surgery are likely to have persistent depression afterwards. Also, depression does not account for the cognitive decline after CABG. Conflicting findings, and the possible methodological limitations of current published studies, are presented and discussed.*

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**E**ach year, more than half a million people in the USA and almost one million worldwide undergo coronary artery bypass grafting (CABG).<sup>1</sup> Many more undergo noncardiac surgery. There is little question that surgery is very effective in reducing angina and in stabilizing ventricular function in most patients.

With advances in surgical techniques and anesthesia, CABG is now being carried out in people with other concomitant diseases, such as hypertension and diabetes; these patients may be at higher risk of complications, as are older patients. Although patients in their 70s and 80s generally tolerate the procedures and have an excellent outcome, the inclusion of patients at higher risk has led to the realization that serious and potentially fatal neurological difficulties are associated with CABG. Furthermore, adverse cerebral outcomes are associated with substantial increases in mortality, length of hospitalization, and use of intermediate- or long-term care facilities. The neurobehavioral outcomes range from the well-documented incidence of stroke to postoperative delirium, cognitive impairment, and depression. Neurological and psychological adverse outcomes have also been suggested in noncardiac patients following surgery, but this matter has received far less attention.

This article reviews and discusses recent findings regarding the possible neuropsychiatric consequences of CABG and noncardiac surgery. Findings regarding rates and predictors of stroke, delirium, and depression will be reviewed, and neurocognitive abnormalities following surgery will be discussed in detail.

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# Clinical research

## Coronary artery bypass surgery

The procedure of bypassing blocked coronary arteries involves placing a patient under general anesthesia. In order to perform the bypass operation, it has been traditional procedure to stop the heart. In order to maintain oxygen delivery and perfusion to the body while the heart is stopped, the patient is connected to a heart-lung machine or cardiopulmonary bypass pump. To keep the patient's blood from clotting in the pump circuit, major anticoagulant therapy is instituted. After the pump is removed, the anticoagulation is reversed to prevent bleeding, both from the heart and in the brain. Many of the neuropsychiatric complications associated with CABG surgery have been ascribed to the pathophysiological effects associated with the use of the bypass pump. In recent years, a technique for performing the surgery without using the bypass pump has been utilized; this is referred to as off-pump CABG, or OPCAB. Early studies are beginning to evaluate the neuropsychiatric impact of this technique.<sup>2</sup>

## Stroke

Stroke is a well-recognized complication of CABG, being reported in 1% to 5% of patients.<sup>1,3</sup> Roach et al,<sup>4</sup> in a prospective study, evaluated 2108 patients from 24 institutions in the United States for focal injury, or stupor/coma at discharge. A total of 3.1% of patients had such neurologic complications. Hypertension, diabetes, and age have been associated with increased risk for stroke following CABG.<sup>3</sup> As discussed in detail by Selnes and colleagues,<sup>1</sup> these risk factors can be assessed before surgery by general physicians, so that the information can assist informed decision-making by patients, their families, and their physicians, and necessary modifications in treatment or intervention can be set up. For example, some patients may be better candidates for continued medical management or percutaneous transluminal coronary angioplasty. For others, modification of the surgical procedure can be considered, such as changes in the placement of the aortic cannula from the cardiopulmonary pump.<sup>1</sup>

## Postoperative delirium

Delirium, also known as acute confusional state, is typically a transient syndrome characterized by altered consciousness with decreased attention span and changes in

cognition or perception not explained by dementia.<sup>5</sup> It evolves over hours to days, and waxes and wanes over the course of the day. Associated symptoms include sleep-wake and psychomotor and emotional disturbances. The onset of postoperative delirium is commonly between postoperative days 1 through 3. It may be sustained for more than a week, and is associated with other medical complications.<sup>5,6</sup>

The reported frequency of delirium after CABG has varied. In older studies, it was reported to occur in as many as 10% to 28% of patients, but more recent studies suggest that the incidence may be lower.<sup>1,4,7</sup> Postoperative delirium has also been extensively studied in medical patients undergoing noncardiac surgery. In one of the few prospective studies, Marcantonio and colleagues<sup>8</sup> found that postoperative delirium occurred in 117 (9%) of 1341 patients undergoing noncardiac surgery.

Most cases of postoperative delirium do not have an identifiable etiology, although a range of suspects has been investigated. Studies aimed at identifying the risk factors for postoperative delirium have found that increased age, type of surgery, alcohol abuse, certain medications, infection, and pain increase the likelihood of delirium. Preoperative hypotension and postoperative hypoxia and use of anticholinergic drugs have also been associated with increased risk of delirium.<sup>6</sup> Unfortunately, many of the risk factors associated with delirium are not easily modifiable.

## Neuropsychological functioning

Once an anecdotal phenomenon, postoperative cognitive dysfunction (POCD) is now the focus of sophisticated epidemiologic investigation. Prolongation of hospital stay, inability to participate in rehabilitation, and new or increased disability may result from POCD.<sup>9</sup> Adverse cerebral effects following surgery and anesthesia have been reported since the 1950s. Cognitive dysfunction, ranging from transient decline in attention and concentration, memory, and/or speed of mental processing to frank dementia, is a possible complication following cardiopulmonary bypass.

While a number of studies over the past two decades have shown that patients experience cognitive changes such as memory loss, poor concentration, and problem-solving difficulties after cardiac surgery,<sup>1,10,11</sup> the focus was mainly on short-term cognitive changes, evaluated days or weeks after the surgery. Recent long-term studies offer more con-

clusive evidence that long-term cognitive decline after CABG can be significant in some patients.<sup>12-15</sup> These studies will be reviewed in detail in the following sections.

### Short-term POCD

The most common complaint in the first few weeks following CABG relates to memory. The recognition of such cognitive changes by patients, families, and physicians led to a series of studies in which different areas of cognitive performance were tested before and at varying times after CABG. Rates of POCD vary considerably in these reports, from 33% to as much as 83%.<sup>1</sup> van Dijk et al<sup>16</sup> conducted a systematic review of studies of neurocognitive dysfunction following CABG. Using pooled data from all studies, the authors reported that 22.5% (95% confidence interval, 18.7% to 26.4%) of patients had presented with a cognitive deficit 2 months after the operation. The cognitive domain with the highest frequency of decline in most studies was memory.

Some of the discrepancies in estimating the rate of impairment are due to the use of different assessment tools and the assessment of diverse study populations.<sup>2</sup> More importantly, most studies of outcomes after CABG are limited by lack of appropriate control groups.<sup>17</sup> Thus, although cognitive changes are well documented, deciding whether they are specifically related to the procedure itself, or whether other surgical procedures would produce similar postoperative cognitive changes, has been difficult.

In 1995, Williams-Russo and colleagues<sup>18</sup> presented the first adequately powered, prospective, randomized study of POCD in noncardiac patients that employed standard neuropsychological instruments. This study compared the effect of epidural versus general anesthesia on the incidence of POCD in patients undergoing elective unilateral total knee replacement. Neurocognitive assessment was performed 1 to 7 days preoperatively (n=262), and 1 week and 6 months (n=231) postoperatively. Overall, 5% of patients exhibited a decline in cognitive function 6 months following surgery, but no statistically significant differences were found between the anesthesia groups.

In the largest prospective study of cognitive function following noncardiac surgery thus far (the International Study of POCD—IPOCD) thirteen hospitals in eight European countries and the USA recruited 1218 patients.<sup>19</sup> One hundred and seventy-six age-matched volunteers from the UK were recruited as controls. To ensure that controls were representative of all national-

ities, 145 national controls were also recruited. The study evaluated changes in both patients and controls in memory, executive functions, and processing speed. Cognitive dysfunction was reported in about 25.8% of patients 1 week after surgery and in about 10% of patients 3 months after surgery—compared with 3.4% and 2.8% of controls after 1 week and 3 months, respectively. These findings suggest that some of the short-term cognitive changes after CABG may not be specific to this procedure, but may also accompany other surgical procedures.

### Long-term POCD

Longer-term complaints of CABG patients are often more subtle. For instance, the patient may have difficulty in following directions, playing chess, or making calculations. Such changes are sometimes described nonspecifically as “I’m just not quite the same.”<sup>20</sup> It should be noted, however, that due to difficulties in following up patients, there are only a few studies that extended the follow-up period to 1 year and beyond. We will therefore review these studies in detail.

Newman and colleagues<sup>12</sup> initially evaluated 261 patients, 172 of whom were still available at the 5-year follow-up. This study evaluated changes in four cognitive domains: verbal memory, visual memory, attention and psychomotor speed, and abstraction. The authors reported that 53% of patients showed a cognitive decline to below their baseline at discharge, but showed some recovery during the next two testing periods (36% and 24% of patients showed cognitive decline at 6 weeks and 6 months, respectively). At 5 years, long-term decline was apparent in 42% of patients. Postoperative cognitive deficits at discharge were a significant predictor of long-term cognitive decline, even when the effects of age, educational level, and baseline score were controlled for. This study had several strengths, including a large sample size, a diverse test battery, neurocognitive assessment prior to surgery, and a long follow-up period. There were also potential limitations, especially the lack of a control group with which to compare changes over time, and potential practice effects.

Selnes and colleagues<sup>14</sup> followed 102 CABG patients over a 5-year period. Their battery of tests assessed eight cognitive domains: attention, language, verbal memory, visual memory, visuoconstruction, executive function, psychomotor speed, and motor speed. The researchers found that cognitive function improved in all of the domains, except for visuoconstruction during the base-

# Clinical research

line to 1-year period. This was followed by a statistically significant decline in mean scores for six of the eight domains during the 1- to 5-year time period. In determining the final baseline-to-5-year change, the group found that the combined initial increase and the later decline in cognitive function resulted in no significant change between baseline and 5 years in most of the domains except visuoconstruction and psychomotor speed, which both showed significant declines.

Although few differences between baseline and 5 years postsurgery were observed, the results suggested a trend of late decline similar to that found in the Newman et al study.<sup>13</sup> None of the covariates measured, including age, sex, race, medical history, and operative and postoperative variables, was found to be statistically significant across many cognitive domains.

Although this study had a large sample size and a comprehensive assessment of different cognitive functions, it also lacked a control group. In a later study, Selnes and colleagues<sup>20</sup> used a group of nonsurgical coronary artery disease patients as a control, with a 1-year follow-up. Interestingly, the study found no significant cognitive test differences between the CABG group and control subjects at 3 months and 1 year, indicating that perhaps certain levels of cognitive change are equally prevalent among all groups with risks for coronary artery disease, and that surgical procedures might not have any effect on cognitive decline.

In a follow-up study of the ISPOCD, 336 patients from the original cohort were re-examined 1 to 2 years postoperatively. Forty-seven nonhospitalized volunteers from the control group were tested at the same intervals. The authors<sup>15</sup> reported that 1 to 2 years after surgery, 35 out of 336 patients (10.4%) had cognitive dysfunction. Of the 47 normal controls, (10.6%) fulfilled the criteria for cognitive dysfunction 1 to 2 years after initial testing, ie, a similar incidence of age-related cognitive impairment as among patients. Three patients (0.9%) had POCD at all three postoperative test sessions. Age, early POCD, and infection within the first 3 postoperative months appeared to be significant risk factors for long-term cognitive dysfunction.

## Genetic factors in POCD

Tardiff and colleagues<sup>21</sup> examined the role of the apolipoprotein E4 allele (*ApoE4*), a known genetic marker for Alzheimer's disease, in the development of

POCD. This allele of the *ApoE4* variant was associated with a decline in cognitive function at hospital discharge and at 6 weeks after surgery in four of nine cognitive measures. The authors argued that some individuals have a decline in cognitive function owing to genetically determined factors. In contrast, Steed et al,<sup>22</sup> using a larger sample of patients, found no association between the presence of the *ApoE4* allele and cognitive decline after POCD. Further studies are required to confirm this hypothesis.

## Anesthesia, surgical procedures, and POCD

Many authors have hypothesized that the changes in cognition may be due to anesthesia or surgical methods, especially, off- or on-pump procedure. There is currently no evidence that the type of anesthesia affects POCD outcome: In a study in 438 elderly patients aimed at evaluating the effects of anesthesia on cognitive dysfunction following surgery, no significant difference was found in the incidence of cognitive dysfunction 3 months after either general or regional anesthesia in elderly patients.<sup>23</sup> Van Dijk and colleagues<sup>2</sup> compared cognitive outcomes after off-pump and on-pump CABG over a 12-month period. The rates of cognitive decline were similar in the two groups at 3 months: 21% of the off-pump patients and 29% of the on-pump patients. Rates of cognitive decline were similar at the 12-month follow-up as well, suggesting that surgical insult from on-pump surgery is not the only contributing factor to cognitive deficiencies after CABG.

## Explaining discrepancies between studies of long-term POCD

The extent to which postoperative cognitive dysfunction is detected will depend on measurement techniques, timing of the assessment, and statistical methods, as well as on the characteristics of the patients selected for studies. One issue concerns the selection of neuropsychological tests.<sup>1</sup> Because the cognitive changes may arise from more than one etiological mechanism, a procedure that assesses all major cognitive domains is recommended. If the test battery does not include assessment of, for example, frontal-lobe functions such as planning and abstraction, or parietal-lobe functions such as spatial and constructional abilities, abnormalities in these areas will be overlooked. Because of the limited time available for neurobehavioral testing preoperatively, few studies have



included tests that cover all major cognitive domains. Second, criteria for what constitutes a cognitive impairment have also varied between studies. Another issue, relatively unexplored until now, is preoperative baseline performance.<sup>1,17</sup> There is substantial variability in neuropsychological performance at baseline, with some patients performing at expected age-adjusted and education-adjusted levels and others performing significantly below expected levels. Some of the POCD cases are interpreted as pre-existing dementia exacerbated by (or even detected for the first time after) anesthesia and surgery. A decline secondary to CABG in patients who are already impaired at baseline may be underestimated. European patient populations undergoing CABG are likely to be younger than their American counterparts and have fewer comorbid health problems.<sup>17</sup> Also, as Selnes and McKhann<sup>24</sup> indicate, only a few of the short-term or long-term follow-up studies included a control group, and even fewer included control groups with similar cardiovascular characteristics, making it difficult to determine whether the late cognitive decline is a consequence of the surgical procedure, worsening cerebrovascular disease, other age-related conditions, or simple practice effects common on repeated administration of the same cognitive tests.

## Depression

High rates of depression are observed in patients with hypertension, diabetes, and coronary artery disease and depression often develops after stroke.<sup>25</sup> This led to the hypothesis that among older persons with major depression, there is a subgroup of individuals with what has been termed “vascular depression.”<sup>26</sup>

There is evidence to suggest that cerebrovascular disease, especially ischemic small-vessel disease, may be a factor in the pathogenesis of late-onset geriatric major depression. Several studies reported frequent occurrence of white-matter hyperintensities in late-onset depression.<sup>27,28</sup> Fujikawa et al<sup>29</sup> described the finding of “silent stroke” in

94% of patients with late-onset major depression, notably, in the absence of family history or psychosocial stressors. The hyperintensities occur mainly in subcortical structures and their frontal projections.<sup>30,31</sup>

Patients with “vascular depression” also exhibit cognitive impairments: Executive functions are most severely impaired in such patients.<sup>31,32</sup> The relationship between depression, cardiovascular disease, and cognitive impairments have led to the hypothesis that depression may be a causal factor in the development of POCD.<sup>1</sup>

Depression is commonly reported after most cardiac surgery procedures, with a frequency of up to 25%.<sup>1</sup> Most of the reports, however, do not take into account the pre-operative mood of the patient. Recent studies<sup>13,32</sup> indicate that newly acquired depression after surgery is uncommon, and that preoperative mood is the best predictor of postoperative depression. It is worth noting that, whereas executive functions are severely impaired in patients with this form of depression,<sup>33,34</sup> a recent study suggested relative sparing of memory functions.<sup>34</sup> As indicated above, memory impairments are a dominant observation in POCD patients. Studies indicate that depression is also not predictive of the presence of POCD.<sup>13</sup>

## Summary and conclusions

This paper has reviewed the evidence for adverse neurological, psychiatric, and neuropsychological outcomes in surgical patients. Adverse neuropsychiatric and neurological outcomes are common, and are not limited to cardiovascular procedures. Of the adverse outcomes, the etiology of POCD remains largely unknown. Several demographic characteristics, as well as clinical conditions such as cerebrovascular disease, genetic susceptibility, and anesthetic technique, have all been associated with POCD. However, no clear etiological model has been defined. POCD may likely be of multifactorial etiology, with many factors contributing small effects to the added risk. Future studies will hopefully shed light on these factors and their interactions. □

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# Clinical research

## Consecuencias neuropsiquiátricas de la cirugía cardiovascular y no cardiovascular

Este artículo revisa los hallazgos relacionados con las consecuencias neuropsiquiátricas a corto y a largo plazo de la cirugía de *by pass* coronario (CBPC) y de la cirugía no cardíaca. El accidente vascular encefálico es potencialmente la complicación más seria de la CBPC, pero hay estudios que han identificado algunos factores de riesgo tanto demográficos como médicos. Los déficits neuropsicológicos a corto plazo son comunes después de la CBPC, pero éstos también han sido documentados en pacientes con cirugía no cardíaca, y pueden por lo tanto no ser específicos de este procedimiento. Sin embargo, los déficits neuropsicológicos en algunas áreas cognitivas pueden persistir a lo largo del tiempo. Los pacientes con depresión antes de la cirugía tendrán mayor probabilidad de continuar con una depresión persistente post cirugía. Además, la depresión no da cuenta del déficit cognitivo después de la CBPC. Se presentan y discuten hallazgos contradictorios y se sugieren las posibles limitaciones metodológicas de los más recientes estudios publicados.

## Conséquences neuropsychiatriques de la chirurgie cardiovasculaire et non cardiovasculaire

Cet article effectue une revue de la littérature sur les conséquences neuropsychiatriques à court et à long terme du pontage aortocoronaire (PAC) et de la chirurgie non cardiaque. L'AVC est la complication potentiellement la plus sérieuse du PAC, mais des études ont identifié des facteurs de risque médicaux et démographiques. Des déficits neuropsychologiques à court terme sont courants après le PAC, mais ont aussi été retrouvés en chirurgie non cardiaque, et ne semblent donc pas spécifiques à cette technique. Certaines altérations cognitives peuvent tout de même persister. Les patients déprimés avant l'intervention ont plus de risque de souffrir de dépression après. La dépression n'explique néanmoins pas le déclin cognitif après le PAC. Des résultats discordants sont présentés et discutés et les éventuelles limites méthodologiques des études actuellement publiées sont évoquées.

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