Silent Brain Injury After Cardiac Surgery: A Review

Cognitive Dysfunction and Magnetic Resonance Imaging Diffusion-Weighted Imaging Findings

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The appearance of cognitive dysfunction after cardiac surgery in the absence of focal neurologic signs, a poorly understood but potentially devastating complication, almost certainly results from procedure-related brain injury. Confirmation of the occurrence of perioperative silent brain injury has been developed through advances in magnetic resonance imaging (MRI) techniques. These techniques detect new brain lesions in 25% to 50% of patients after both coronary artery bypass graft and valve surgery. Use of post-operative cognitive dysfunction as a marker of brain injury is problematic because of potential difficulties in ascertainment. It can be hypothesized that post-operative appearance of MRI lesions may serve as a more objective marker of brain injury in research efforts. If MRI examination can be used in this way, then 2 vitally important questions can be addressed. 1) What is the frequency of important, but silent, brain injury during cardiac surgery? 2) Does long-term cognitive impairment ensue? This review briefly discusses clinical features of post-operative cognitive dysfunction and reviews the evidence supporting a possible association with MRI evidence of perioperative brain injury and its potential for long-term dementia. We conclude that this association is plausible, but not yet firmly established.

Focal neurologic deficits (FND) appear in up to 3% of cardiac surgical patients in the early post-operative period (1). However, many more patients without FND manifest cognitive dysfunction or evidence of brain injury on magnetic resonance imaging (MRI) without FND. We review the current understanding of this silent brain injury after cardiac surgery.

Incidence. Cognitive dysfunction is the most common clinical evidence of brain injury after cardiac surgery. It can be detected only with careful neuropsychological testing by a trained and experienced examiner. A meticulous look for characteristic disturbances in memory, psychomotor speed, executive function, visuo-constructional ability, and ability to concentrate is required. According to published studies in which such testing is used systematically before hospital discharge after cardiac surgery, post-operative cognitive dysfunction (POCD) may be detected in 14% to 48% (2–7) of patients. Moreover, impairment continues to be detectable in at least 30% for 6 weeks and in 25% for 6 months (2–5).

These estimates of early and persistent POCD must be regarded as rough approximations for several reasons. First, determination of the true incidence requires documentation that cognitive impairment was not present before surgery but appeared after surgery. To meet this requirement, the same level of testing must have been used at both time points. All of the studies cited can be criticized for either the comparability or the timing of testing. Second, the individual studies cited generally include only a small number of patients. Third, important interstudy variations exist with regard to important patient characteristics, to the timing and methodology of testing cognitive function, and to the nature and frequency of surgical procedures. Between studies there also exists potentially important variability in the post-operative surgical environment (8). The heterogeneity of these case series makes a pooled analysis of dubious accuracy.

Cause and pathogenesis. It has long been assumed that cerebral embolism associated with cardiopulmonary bypass or triggered by intracardiac and intra-aortic manipulation accounts for both post-operative stroke and POCD. Indeed, transcranial Doppler monitoring consistently demonstrates showers of small particulate or air emboli during all cardiac and cerebrovascular manipulations (9,10).

Skeptics point out that there are alternative explanations (e.g., procedure-associated cerebral hypoperfusion or the effects of perioperative drug therapy) (11). They further note that if embolization explained some, or all, of POCD, then it should occur more frequently after intracardiac surgery than after coronary artery bypass graft (CABG) surgery because of the greater risk of embolization in the former. Evidence does not support this connection. There is a similar incidence of POCD in patients undergoing valve surgery or combined coronary and valve surgery as compared with those undergoing CABG surgery alone (12,13).
It also seems plausible that, apart from embolization, adverse effects of cardiopulmonary bypass could result in cerebral injury, but both randomized trials (14) and a compilation of observational studies (15) contradict this possibility. Perhaps most telling are the observations that indicate that POCD can be detected in one third of patients after major noncardiac surgery (16,17).

Thus, despite years of study, many facets of the incidence, pathogenesis, and consequences of silent brain injury remain to be clarified. Much of the lack of clarity can be attributed to the complexity of the neuropsychological testing necessary to identify the presence of the cognitive dysfunction. Thus, neuropsychological testing has limited usefulness as an end point for study of these issues.

**POCD and chronic dementia.** Of perhaps even more importance is the possibility that temporary perioperative brain injury may trigger chronic or progressive dementia. An association between short-term POCD and long-term cognitive deficits was found by Newman et al. (4) and others (18), who reported that after initial recovery from POCD, late deterioration could be found when subjects were retested at 5 years.

These observations, however, lack a control population. Some historical comparisons are available. Comparisons have been made between the results of serial neuropsychological testing of patients after cardiac surgery and those of subjects with comparable demographic and clinical characteristics who had never undergone cardiac surgery. The frequency of progressive cognitive dysfunction at 1, 3, 5, and 6 years of follow-up was similar (19–24). Thus, the observed progression in patients with POCD simply may represent ongoing progression of a pre-operative process.

### Magnetic Resonance Brain Imaging

MRI examination of the brain provides a means of identifying and quantifying brain injury even in the absence of clinical signs (25–29). A variety of imaging techniques are applied to identify markers of such injury, including diffusion-weighted imaging (DWI) (26,27), fluid attenuated inversion recovery sequencing (28,29), proton density-weighted imaging, and T2 sequences. Examples of typical fluid attenuated inversion recovery sequencing lesions are shown in Figure 1. Once developed, these findings are present indefinitely. Thus, with these techniques, a pre-operative study must be available to confirm that a lesion present after cardiac surgery appeared during the perioperative period. Bright lesions identified by DWI (26,27) obviate this need. DWI lesions typically appear within 2 hours of the event and resolve by approximately 2 weeks of age (Fig. 2). In this paper, lesions appearing in the postoperative period are referred to as new when they were identified as new in comparison with a pre-operative study or when DWI was used to identify post-operative brain injury. The general term MRI lesions is used otherwise.

Large- and small-vessel occlusions associated with cardiac surgery can cause brain infarction and may or may not be associated with FND or POCD. Although commonly associated with FND, large-vessel occlusions may not be. Chronic obstructions of small, subcortical arteries (30–36) are recognized on conventional MRI studies as lacunar infarcts, leukoaraiosis, or both. On necropsy examination, lacunar infarcts are seen as small, empty spaces in subcortical brain tissue and are believed to reflect infarction attributable to occlusion of a single penetrating artery. Such occlusions may
be embolic or may be a consequence of arteriosclerotic changes that are especially common in hypertensive subjects. Leukoaraiosis, also known as hyperintensity lesions of white matter, has been associated with concentric hyaline arterial wall thickening. Some investigators believe that this process may eventuate in widespread, incomplete infarction and diffuse areas of reduced myelination. Not surprisingly, in view of their presumptive common origin in obstruction of small subcortical arterial branches, lacunar infarcts and leukoaraiosis often coexist and share the same risk factors (30–36).

Silent Infarctions in Asymptomatic Populations

MRI evidence of chronic brain infarction has been detected in putatively normal subjects as young as 30 years of age. The frequency of such lesions increases with age. By 70 years of age, they have been detected in up to 50% of healthy, elderly individuals who undergo MRI examinations as part of population-based studies (31–39). Further, they are even more frequent in participants in such studies with vascular risk factors (31,40–42). In these apparently healthy individuals, the presence of MRI lesions is associated with a greater risk of subsequent stroke and with a doubling of the risk of dementia (43–45). Despite the association of MRI lesions and vascular risk factors, the appearance of overt brain dysfunction seems to be independent of such risk factors.

Silent Infarctions and Cognitive Dysfunction

In population-based studies, a strong association has been found between MRI lesions and prevalent cognitive dysfunction and dementia (31–45). Such an association could be predicted based on the location of the lesions. The frontal lobe, a common location, plays an important role in executive function, social behavior, and motivational status. Moreover, MRI lesions are positioned so as to affect cortical areas important for language, praxis, and self-awareness. It therefore is plausible that accumulating silent lesions, in the absence of overt stroke, may contribute to impairment of cognitive function and to difficulties in mental flexibility, language, and short-term and working memory (35,38,46–51).

Beyond the mere presence of these lesions, the extent of changes in white matter has been found to be associated with cognitive decline. The more extensive the MRI lesions, the more severe is the observed cognitive impairment (43,52–54). Furthermore, it seems that the greater the volume of the MRI abnormality, the more likely it is that progression in its size will occur. Data supporting this assertion may be found in several longitudinal, population-based studies (44,45,53,55).

Importantly, in addition to the volume of lesions at baseline, the presence of vascular risk factors (e.g., diabetes, hypercholesterolemia, hypertension, obesity, atrial fibrillation, or a history of stroke) also predicts more rapid progression. Taken together, these observations can be construed as supporting an association between the presence of MRI lesions and cognitive dysfunction or frank dementia in the general population. Further, there seems to be a potential for progression of the process after it has been initiated.

Silent Infarctions and Cardiac Surgery

Bendszus and Stoll (25), in a recent review, highlighted the frequency with which MRI-identified silent infarctions appear after a variety of cardiovascular procedures. They suggested that they represent embolic phenomena and as such are “fingerprints of invasive medical procedures.” Importantly, before this assertion can be confirmed, however, a control population is necessary. Healthy subjects belonging to the same age groups as cardiac surgical patients often have evidence of silent infarctions. Therefore, pre-existing lesions must be disregarded and only reports describing lesions appearing in the post-operative period logically can be ascribed to the cardiac procedure. Because new DWI
lesions become invisible within 2 weeks of their appearance, their detection in the post-operative period is a valuable marker of periprocedural brain injury.

Table 1 includes 13 published reports (8,56–67) in which DWI examination was used. Of 446 patients included in these studies, 127 (29%) had DWI (new) lesions on post-operative imaging. Characteristically, these lesions are multiple and very small (1 to 10 mm in diameter and 32 to 750 mm³ in volume). They were located in all cerebrovascular territories, but more frequently in frontal and watershed border zones. Few were associated with overt clinical signs of stroke. The imaging was conducted an average of 5 days after surgery.

The frequency of the appearance of new lesions was not remarkably different with regard to the type of surgery undertaken. Notably, lesions appeared even when cardiopulmonary bypass was not required. Two studies of off-pump surgery provide conflicting data. In one (62), DWI lesions were found in 5 (31%) of 16 patients undergoing off-pump CABG. In the other (64), none were found. Additional studies also have shown that new lesions can be detected with T2 and proton density-weighted imaging studies after cardiac surgery (68,69).

Many important questions regarding the appearance of new lesions remain to be answered. Some of this uncertainty reflects the clinical environment after cardiac surgery. It may be difficult consistently to obtain an appropriately timed MRI examination. Moreover, the observed incidence of new lesions may be affected by the timing of the MRI examination. Few serial post-operative studies have been reported. Consequently, little is known about whether the timing of the appearance or the stability of post-operative lesions. Indeed, regression has been demonstrated particularly when the degree of injury is mild or when there is reason to believe that early reperfusion has occurred (57,70). Thus, a later image may not accurately reflect the number visible more acutely.

Observations as to the risk factors for the development of new lesions are conflicting. Some have found their appearance to be associated with advancing age (56,59,60), pre-existing cerebrovascular disease (56), pre-existing silent lesions (56,63), atheromatous disease (56,59,63), atrial fibrillation, and hyperlipidemia. Indeed, Restrepo et al. (57) found a history of hypertension and post-operative atrial fibrillation to be present in all patients who had DWI lesions after surgery. In contrast, several investigators have reported no correlation between their appearance and either pre-operative clinical characteristics (58,61,62,64) or procedural variables (58,60,61,64).

Not only are the risk factors for the appearance of new lesions unclear, the pathogenetic mechanisms are equally obscure. The pattern of distribution suggests an embolic basis; therefore, microthrombotic and air embolism long have been assumed to play a prominent role. This assumption recently was questioned by Kruis et al. (11) based on their review of the literature on this topic. Moreover, the association between the development of new small, silent lesions, advancing age, and pre-existing silent or overt cerebral vascular disease raises the possibility that underlying disease in the cerebral circulation (71) may increase susceptibility to whatever processes the surgical procedure initiates.

### Silent Infarctions and POCD

The frequent coexistence of MRI lesions and cognitive dysfunction in population-based studies suggests the possi-

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**Table 1**

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>n</th>
<th>New Lesions</th>
<th>POCD</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendzus et al. (56)</td>
<td>35</td>
<td>9 (26%)</td>
<td>No</td>
<td>On-pump CABG</td>
</tr>
<tr>
<td>Restrepo et al. (67)</td>
<td>13</td>
<td>4 (31%)</td>
<td>Yes + 1 overt CVA</td>
<td>On-pump CABG</td>
</tr>
<tr>
<td>Kripp et al. (58)</td>
<td>29</td>
<td>13 (45%)</td>
<td>Yes (resolved at 3 months)</td>
<td>On-pump CABG</td>
</tr>
<tr>
<td>Djaihani et al. (590)</td>
<td>50</td>
<td>8 (16%)</td>
<td>Confusion (resolved by 5 days)</td>
<td>On-pump CABG</td>
</tr>
<tr>
<td>Stolz et al. (60)</td>
<td>37</td>
<td>14 (38%)</td>
<td>No</td>
<td>AVR</td>
</tr>
<tr>
<td>Kripp et al. (61)</td>
<td>30</td>
<td>14 (47%)</td>
<td>Yes (resolved by 4 months)</td>
<td>Valve</td>
</tr>
<tr>
<td>Friday et al. (62)</td>
<td>16</td>
<td>5 (31%)</td>
<td>Yes</td>
<td>Off-pump CABG</td>
</tr>
<tr>
<td>Floyd et al. (63)</td>
<td>34</td>
<td>6 (18%)</td>
<td>Not reported</td>
<td>Valve surgery and CABG</td>
</tr>
<tr>
<td>Dijaihani et al. (64)</td>
<td>13 on-pump</td>
<td>8 (61%)</td>
<td>Confusion 2 (resolved by 6 days)</td>
<td>CABG</td>
</tr>
<tr>
<td></td>
<td>13 off-pump</td>
<td>0</td>
<td>Confusion 2 (resolved by 6 days)</td>
<td>CABG</td>
</tr>
<tr>
<td>Cook et al. (65)</td>
<td>50</td>
<td>16 (32%)</td>
<td>30% POCD unrelated to new lesions</td>
<td>Valve surgery and CABG</td>
</tr>
<tr>
<td>Barber et al. (66)</td>
<td>40</td>
<td>17 (43%)</td>
<td>Yes</td>
<td>Valve surgery and CABG</td>
</tr>
<tr>
<td>Gerriets et al. (8)</td>
<td>86</td>
<td>13 (15%)</td>
<td>Yes, correlated with new lesion early but not at 3 months</td>
<td>Most complete cognitive testing, on-pump CABG</td>
</tr>
<tr>
<td>Knipp et al. (67)</td>
<td>39</td>
<td>20 (51%)</td>
<td>Early improvement after surgery, but declined at between 3 months and 1 yr; not associated with new lesions</td>
<td>CABG</td>
</tr>
</tbody>
</table>

Total: 446  127 (29%)

AVR = aortic valve replacement; CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; POCD = postoperative cognitive dysfunction.
bility of a common pathogenetic mechanism. Thus, a similar connection between the appearance of new lesions after cardiac surgery and POCD is plausible (58,60,63,65). In the 13 studies (8,56–67) in which the investigators reported the appearance of new DWI lesions after cardiac surgery (Table 1), neuropsychological assessment for POCD was conducted in 12 studies. A standardized or mildly modified battery of neuropsychological tests was performed in 10 of these 13 studies (8,56–58,60–62,65–67). Unfortunately, the minor variations in the methodology of these assessments and in the timing of the imaging inhibit any firm conclusions regarding the nature of the interrelationship. In 11 studies in which both pre- and postoperative neurological assessment for POCD were performed at 2 to 7 days before surgery, 1 day to 4 months after surgery (8,56–62,64,65), and 3 to 12 months after surgery (67). Many, if not most, patients have some degree of cognitive dysfunction in the immediate post-operative period. Such a nearly universal occurrence is clearly not an appropriate marker of POCD as the phenomenon has been viewed. Only after this period has passed can objective assessment of the patient’s cognition be performed. Unfortunately, the duration of altered cognition after operation required to define POCD has not been defined clearly.

Two studies with serial MRI and neuropsychological examinations conducted both before and after surgery provide conflicting results. One included 86 patients in whom an association between new DWI lesions and cognitive dysfunction was found in the early post-operative period, but the relationship was lost by 3 months (8). In the other, new lesions were found in 51% of 39 patients. Scores from cognitive testing demonstrated a biphasic pattern (67). They improved modestly between discharge and 3 months, but then deteriorated between 3 months and 3 years. In the latter, no association between persistence of cognitive impairment and new lesions was found.

Factors affecting neurocognitive test performance during first week after surgery are multiple confounders resulting from treatment of post-operative pain, sedation, and other clinical recovery issues. It is difficult to evaluate the very dynamic, transient imaging and clinical course early while the hemodynamic stability is the priority. Consequently, reports of case series of POCD neuropsychological examinations have been conducted at different times during the post-operative period.

In addition to the complexity involved with detailed neurocognitive testing and the obstacles to relevant imaging in the early post-operative period, a correlation between DWI examination and POCD is complicated by other, more subtle issues. For example, the total volume of new lesions in the post-operative period or their location may be more significant than simply their appearance. Further, the brain has intrinsic compensatory mechanisms that may change the relationship between imaging defects and cognitive function. With these limitations in mind, one must conclude that no convincing association between new silent lesions and POCD has been demonstrated yet.

**Silent Infarctions and Long-Term Cognitive Dysfunction**

It is plausible that brain injury sustained in the perioperative period may initiate a series of processes in endothelial cells, astrocytes, neurons, or the vasculature that may take years to become manifest. It is also possible that brain injury incurred perioperatively could combine with the effects of aging and lead to chronic dementia, stroke, or Alzheimer’s disease.

Observations from longitudinal, population-based studies (31,32,44,72) support the notion that brain injury from whatever cause, although initially silent, may be followed by progressive brain dysfunction. In them, imaging evidence of silent brain injury does progress over time. The greater the volume of such lesions on baseline examination, the greater is the likelihood of progression in the number or the size of such abnormalities (44,45,53,55). As is the case in serial imaging in putatively healthy populations, the presence of vascular risk factors (e.g., diabetes, hypercholesterolemia, hypertension, obesity, atrial fibrillation, or a history of stroke) also predict more rapid progression (72).

Knopman et al. (73) investigated the possibility that prior cardiac surgery constitutes a risk factor for chronic cognitive impairment. In a case-control study, they observed 1,114 patients for 5.5 years. No increase in the incidence of dementia was demonstrated by patients who had undergone cardiac surgery. Using a similar approach, Lee et al. (74) reported conflicting results. In 9,710 veterans, they compared the incidence of Alzheimer’s disease in the 5 years after CABG with the incidence in those who underwent percutaneous coronary intervention. After adjusting for age, length of hospital stay, and number of procedures, they found a slightly higher incidence of Alzheimer’s disease among those undergoing CABG (p = 0.04). Although the difference is statistically significant, the absolute difference in risk was quite small.

**Conclusions**

This review was undertaken to highlight the paucity and conflicting nature of available information regarding the clinical details and the pathogenetic basis for silent perioperative brain injury. This arguably may reflect the use of POCD as the marker of silent brain injury. The accuracy of the ascertainment of POCD can be questioned because of inherent weakness in the reproducibility and objectivity of tests for its presence. MRI potentially reduces or eliminates the problem of accurate ascertainment of perioperative silent brain injury. We propose that systematic study of post-surgical brain injury by this means may open the way for productive investigation into the predictive factors, incidence, and persistence of silent brain injury and, most importantly, its prevention.
REFERENCES


Key Words: cardiac surgery • cognitive dysfunction • magnetic resonance imaging diffusion-weighted imaging • silent brain injury.