POCD & cardiac surgery

Rony Al Nawwar
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A review of postoperative cognitive dysfunction and neuroinflammation associated with cardiac surgery and anaesthesia

A. E. van Harten, T. W. L. Scheeren and A. R. Absalom

1 Research Fellow, 2 Professor, Department of Anesthesiology, University Medical Centre Groningen, University of Groningen, The Netherlands
Medline-based search of all literature published up to June 2011 using the following keywords:
cardiac surgery; coronary artery bypass grafting; CABG; coronary revascularization; postoperative cognitive dysfunction; POCD; cognitive decline; cardiopulmonary bypass; inflammation; neuro-inflammation; and cerebral inflammation

To limit the number of references, articles for inclusion were selected based on a combination of the strength of the evidence and the time since publication
Diagnosis of POCD

The incidence of POCD is highly dependent on:
--the number and types of cognitive tests used
--the statistical analysis used to define a significant change in cognitive function

The reported incidences of POCD vary widely, and part of the reason for this is that there are no standard, universally accepted diagnostic criteria.
Possible causes of POCD related to surgery
Altered cerebral perfusion and oxygenation
CBF: normally independent of perfusion pressure when the CPP is within the physiological range (60–140 mmHg)

$$\text{CPP} = \text{MAP} - \left( \text{the greater of CVP or ICP} \right)$$

CBF may become pressure-dependent when auto-regulation fails, and/or when the CPP is outside the physiological range, making the brain susceptible to harmful levels of *ischemia* or *hyperemia* & cerebral edema when perfusion pressures are low or high, respectively
Why autoregulation may be impaired during surgery?
During CPB

BP ≈ 60 mmHg

normal people: adequate

HTN: < lower limit of autoregulation → reset threshold for autoregulation
During off-pump

Heart Manipulations (to facilitate distal anastomoses on the posterior surface)

- CO impaired
- BP & CBF reduced
Cerebral Edema

HF $\rightarrow$ cerebral edema $\rightarrow$ ICP $\uparrow$ $\rightarrow$ CPP $\downarrow$ to below the threshold for autoregulation $\rightarrow$ cerebral perfusion & oxygenation impaired
Hypothermia

Decrease the metabolic rate of the brain
Decrease susceptibility to ischemic and hypoxic injury

Fast re-warming $\rightarrow$ cerebral hyperthermia $\rightarrow$ cerebral autoregulation impaired
Maintaining perfusion pressure at more physiological levels during CPB (80–90 mmHg) is associated with less early POCD and delirium.

Intra-operative decline in MAP of > 32 mmHg from the preoperative baseline is associated with lower mini-mental state examination scores postoperatively.
Overall, the evidence that impaired deranged cerebral hemodynamics is associated with neurological injury is weak and sometimes conflicting.
A study using single photon positron-emission computed tomography (SPECT) failed to show significant correlations between changes in regional and global CBF and POCD.
The hypothesis that a pulsatile flow pattern in the CPB circuit would improve outcomes has also been opposed by several studies that found no beneficial effect of pulsatile flow compared with constant pump flow on cognitive outcomes 2 months after surgery.
2 cohort studies have failed to show an effect of temperature management during CPB on postoperative cerebral edema and a large blinded randomized controlled trial showed no effect on cognitive function
At present, it is not possible to measure intraoperative CBF or perfusion directly.
It is, however, possible to perform real-time assessment of regional (frontal) cortical oxygenation using near-infrared spectroscopy.

Brain tissue oxygen Hb saturation reflects the balance between oxygen delivery and utilization.

Low saturation levels provide an indication of a mismatch between cerebral perfusion or oxygen delivery and oxygen requirements.
Cerebral microemboli
The CPB circuit and the surgical field in cardiac surgery are a potential source of a variety of embolic particles such as:

- Thrombi
- Fat
- Gas bubbles
- Disruption of aortic atherosclerotic plaques by aortic manipulation and cannulation
Diffusion-weighted MRI techniques indicate that about 50% of patients undergoing on-pump CABG develop discrete lesions suggestive of microembolic infarcts.

Transcranial doppler ultrasonography indicate that on-pump surgery is associated with larger numbers of microemboli than off-pump surgery.
Several studies have failed to show a correlation between embolic load (transcranial doppler), or infarct load (diffusion-weighted MRI) and POCD or delirium after CABG.
Inflammation
Pros

On-pump cardiac surgery:
- contact between blood and artificial materials of the bypass circuit
- ischemia-reperfusion injuries of the heart, lungs and kidneys

→ Activation of the immune system

→ Widespread inflammatory response

In the presence of BBB injury or disruption, it follows that systemic inflammation induced by CPB might also cause cerebral inflammation
Cons

No significant difference in systemic inflammatory markers between patients randomized to on-pump or off-pump surgery.

These findings suggest that there is no direct relationship between CPB, systemic and cerebral inflammation, and POCD.
Possible causes of POCD related to anesthesia
Temporary deactivation or depression of cerebral functions is intrinsic to the functioning of anesthetic agents.
Hypnotic or anesthetic agents could amplify the effects of the insults associated with cardiac surgery and cause long-term cognitive deficits or even permanent structural changes in the brain.
There is no convincing evidence that anesthetic agents cause inflammation resulting in POCD
Volatile agents may enhance the susceptibility of neurons to apoptosis, and may enhance neurodegenerative processes.

There is no evidence that volatile agents are associated with POCD.

There might even be a protective effect of inhalational anesthesia.
Patient-related factors
Normal ageing is associated with structural cerebral changes:

- Reduction in grey matter volume and myelinated axon length
- Loss of neuronal dendrites, spines and myelin
- Alterations in synaptic transmission and receptors

→ normal decline in cognitive function
Association between old age and impaired baseline pre-operative cognitive function, with worse early cognitive outcomes after surgery
Possible explanations for an exaggerated response to cerebral injury in elderly and vulnerable patients include immune priming caused by pre-existing low-grade inflammatory states associated with:

- ageing
- neurodegeneration
- other chronic inflammatory disorders
A common factor

the inflammatory response
Any tissue damage is generally followed by an inflammatory reaction associated with activation of the immune system, that can result in repair and healing, but can also result in further damage.
Severe systemic inflammatory response can cause multi-organ failure, that can include the brain, leading to a range of clinical consequences including delirium and ‘septic encephalopathy’, with symptoms ranging from subtle cognitive deficit to coma with suppression of EEG activity.
One might speculate that systemic inflammation known to be associated with cardiac surgery and to cause dysfunction of several organ systems via inflammatory effects also results in neuronal inflammation and cognitive dysfunction
To date, there is very little direct evidence that POCD is the result of cerebral inflammation caused by neuronal injuries, systemic inflammation, or a combination of the two
In the search for causative factors of POCD after cardiac surgery, the focus of research is moving from surgery-related factors to patient-related risk factors.
The systemic inflammatory reaction that occurs after cardiac surgery may be associated with POCD

This inflammatory reaction was previously attributed to the CPB circuit, but increasing evidence shows inflammation to be of equal severity in off-pump surgery
A low-grade baseline state of systemic and neuronal inflammation is likely in groups of patients at risk of POCD, such as the *elderly* and those affected by neurodegenerative disease or atherosclerosis.
These known risk factors may contribute to the development of POCD by priming the neuronal inflammatory system, and therefore lead to an exaggerated inflammatory response to CPB and cardiac surgery.