Reducing confusion about post-cardiotomy delirium

Daryl Jones, Carol L Hodgson, Yahya Shehabi and Michael C Reade

Cardiac surgery is one of the most common reasons for elective admission to the intensive care unit in Australia and New Zealand. Post-operative delirium (POD) is a common complication after cardiac surgery and is associated with prolonged mechanical ventilation,[1-3] increased ICU[4,5] and hospital lengths of stay,[6,7] and possibly long-term cognitive and functional decline.[8]

We review the definition, possible mechanisms, risk factors and barriers to the diagnosis of POD. We contend that delirium could be considered conceptually as an acute brain dysfunction, similar to other organ dysfunctions associated with critical illness. Finally, we suggest strategies for improving understanding of POD after cardiac surgery, and implications for its prevention and treatment.

What is delirium?

Delirium is a disturbance of cognitive function that develops over a short period and fluctuates over the course of a day.[9] Importantly for ICU clinicians, new diagnostic criteria for delirium have de-emphasised the importance of altered conscious state (which is particularly relevant in an environment in which conscious state is readily manipulated by pharmacotherapy) and emphasised the importance of problems in sustaining or shifting attention and concentration, disturbance of memory, perceptual disturbance (such as hallucinations), psychomotor retardation or agitation, and altered sleep–wake cycle (Table 1).[9] Such changes must be attributed to the physiological consequences of an underlying general condition or the effects of intoxication or medications.[9] The changes *cannot* be attributable to coma.[9]

Delirium can be classified as hypoactive, hyperactive or mixed, according to the level of motor activity and agitation. In a study of 506 patients, 77.5% were reported to have the hypoactive form of delirium.[10]

What are the causes of post-cardiotomy delirium?

The precise aetiology of POD after cardiotomy is unclear, but a variety of mechanisms have been proposed, including vascular insufficiency, inflammation (systemic inflammation and inflammation involving glial cells within the brain), metabolic causes, and imbalances of neurotransmitters (especially acetylcholine, norepinephrine and dopamine) (Table 2).[11-14] Cardiopulmonary bypass, hypotension, cerebral micro-emboli, anaesthetic agents and variable depth of anaesthesia may be contributing factors. Animal experiments strongly suggest that activation of cerebral microglia is an important pathway in systemic inflammatory conditions.[15]

What clinical factors increase the risk of post-cardiotomy delirium?

Multiple studies have been performed to identify pre- and post-operative associations with the development of POD.[16] However, many of these studies are small, single-centre, poorly designed and fail to adjust for confounding factors. Four of the most consistently reported pre-operative factors associated with POD after cardiac surgery are increasing age, prior stroke, psychiatric illness (especially major depression) and cognitive decline.[17] Surprisingly, the association between prolonged cardio-pulmonary bypass time and development of POD is inconsistently observed.[16]

Table 1. DSM-5 criteria for diagnosis of delirium

A. There is disturbance in:
   a. attention (decreased ability to direct, focus, sustain and shift attention); and
   b. awareness (decreased orientation to the environment).

B. The disturbance:
   a. develops over a short period of time (usually hours to a few days);
   b. represents an acute change from baseline attention and awareness; and
   c. tends to fluctuate in severity during the course of a day.

C. There is also disturbance in cognition (memory deficit, disorientation, language, visuospatial ability or perception).

D. The disturbances in Criteria A and C:
   a. are not better explained by a pre-existing, established or evolving neurocognitive disorder; and
   b. do not occur in the context of a severely reduced level of arousal such as coma.

E. There is evidence from the history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of:
   a. another medical condition;
   b. substance intoxication or withdrawal (ie, due to a drug of abuse or to a medication); or
   c. exposure to a toxin; or
   d. is due to multiple aetiologies.

DSM-5 = Diagnostic and statistical manual of mental disorders, fifth edition.

Table 2. Risk factors associated with development of post-cardiotomy delirium

	Risk factor relative to time of surgery		
Risk factor group	Pre-operative	Intra-operative	Post-operative
Vascular insufficiency and hypoxaemia	Prior stroke Carotid artery disease Poor cardiac function	Prolonged hypotension Aortic cross clamp time Hypoxaemia Anaemia Micro-emboli and air emboli	Cardiogenic shock Hypoxaemia
Inflammation		Duration of cardiopulmonary bypass Intraoperative transfusion	Sepsis Blood transfusion
Genetic pre-disposition	Dopamine transporter gene	Inflammatory response	Predisposition to sepsis
Medication-related	SSRI Benzodiazepines	Anticholinergic Benzodiazepines Anaesthetic agent	Benzodiazepines
Metabolic	Renal dysfunction	Hyponatraemia	Hypo- or hypernatraemia
Other	Increasing age Cognitive decline Major depression		Duration of mechanical ventilation

SSRI = selective serotonin reuptake inhibitor.

Why is delirium after cardiotomy important?

Delirium after cardiac surgery is important for several reasons. First, it is common. Although reported estimates range from 3.0% to 55.2%, the typical reported incidence is about 20%.[13,18] The large variations in the estimations of frequency are likely to relate to the different tools used for diagnosis, variable study design (particularly exclusion criteria), the timing and frequency of measurement, whether patients are assessed in the ICU or on the ward after ICU discharge, and the population studied.[19,20] The increasing age and comorbidity of cardiac surgical patients are likely to increase the importance of delirium in the future.

Short-term associations with POD after cardiotomy include prolonged mechanical ventilation[1-3] and increased ICU[4,5] and hospital lengths of stay.[6,7] Traditionally, delirium in hospitalised patients was thought to be an acute and reversible condition. However, a single study has shown an independent association between post-cardiotomy delirium and mortality within 6 months after hospital discharge.[8] The same study found that patients who had POD were more likely to be dependent in mobility and had higher total cognitive failure scores at 6 months.[8] However, worsening of cognitive function was not confirmed in two other studies.[21,22] Longer term morbidity, including cognitive decline in survivors of critical illness, has been reported in more heterogeneous (non-cardiotomy) populations.[23]

The Australian Commission on Safety and Quality in Health Care has also emphasised the need to improve the recognition of, and response to, changes in mental status.[24] Thus, the diagnosis and treatment of delirium is likely to be increasingly important in emerging quality and safety initiatives for hospitalised patients.

The challenges of diagnosing post-cardiotomy delirium

There are several challenges to the consistent detection and recognition of delirium after cardiac surgery. First, by definition, the condition fluctuates with time.[9] Thus, detection relies on regular and repeated testing, which can be time consuming. Second, hypoactive delirium, which is the more common form, is often underappreciated,[10] and psychomotor retardation and impaired concentration may be confused with the features of pre-operative mood disorders or cognitive impairment.[25] Third, delirium is, by definition, an acute condition, and pre-operative cognitive function may not be routinely assessed. Fourth, disturbance of the sleep–wake cycle is common in patients in the ICU and is not ubiquitously associated with delirium.

Is delirium simply acute brain dysfunction?

In many respects, the pathogenesis, risk factors and consequences of delirium mimic those of other organ dysfunctions in the critically ill. Thus, ICU patients with acute renal dysfunction are more likely to have pre-existing chronic kidney disease and more likely to have a subsequent decline in their renal function.[26] Regardless of the aetiology, acute renal dysfunction manifests as oliguria, hyperkalaemia and uraemia.

Similarly, patients with delirium are more likely to be older and have chronic disorders of the brain, such as cognitive decline and cerebrovascular disease.[16,17,27] In addition, while most patients with POD recover, a minority subsequently develop cognitive and functional decline.[8] Thus, in a manner analogous to renal dysfunction, some patients are likely to develop delirium due to overwhelming inflammatory and circulatory insults, and to subsequently recover (ie, acute brain dysfunction). On the other hand, some patients may develop delirium as a consequence of acute-on-chronic brain dysfunction. In other ICU populations, pre-existing co-morbidities such as stroke and dementia increase the risk of cognitive decline and worse functional recovery.[28]

Clarifying post-cardiotomy delirium

Several questions must be answered to improve understanding of the causes and consequences of delirium after cardiac surgery (Table 3). First, there is a need to better explore the frequency of cognitive impairment in the pre-operative period. This would require the administration of a valid and reliable cognitive screening test in the pre-admission clinic, such as the Mini-Mental State Examination or an equivalent tool.

There is also a need to identify the optimal diagnostic tool in the ICU. The Confusion Assessment Method for the ICU (CAM-ICU) is often used for this in research studies, but it assesses a single point in time and includes altered conscious state in the diagnostic criteria.

The next important step is to decipher the nature of the association between post-operative complications and the occurrence of delirium. For example, there is an observed association between prolonged mechanical ventilation in the ICU and POD.[1-3] This association might be due to a confounding factor such as cardiogenic shock, bleeding or a need to return to the operating theatre that results in prolonged mechanical ventilation and delirium.

Alternatively, the association may be causal, in that early-onset delirium leads to an increased need for sedation and prolonged mechanical ventilation. Finally, the association may be due to reverse causation, in that prolonged mechanical ventilation leads to later-onset delirium. Similar arguments could be made for observed associations with post-operative sepsis, increased ICU length of stay and increased hospital length of stay. Studies that attempt to adjust for severity of illness typically use the Acute Physiology and Chronic Health Evaluation score (or equivalent) assessed at the time of admission to the ICU, which is likely to be less relevant than severity of illness at the time delirium manifests.

Table 3. Questions to improve understanding of causes and consequences of post-operative delirium (POD)

1. How common is cognitive decline in patients before cardiac surgery?
2. What is the optimal timing of commencement and frequency of assessment of POD?
3. What are the most appropriate tools for diagnosis of POD?
4. How can the features of delirium be distinguished from the consequences of pre-existing cognitive decline or psychiatric conditions?
5. What is the relationship between post-operative complications and the occurrence of delirium?
6. What associations with delirium can be avoided or modified?
7. What are the most appropriate medical and non-medical therapies for the prevention and treatment of POD?

Implications for prevention and treatment

Delirium may be a non-specific response to multiple different aetiologies and initiating factors. It is possible that the characteristics and outcomes of patients with delirium may fall into different categories based on the nature and extent of pre-existing cerebral dysfunction, whether the delirium is hyperactive or hypoactive, and the nature of the insult(s) precipitating delirium. These concepts may have important implications for approaches to prevention and treatment of POD after cardiac surgery.

Conclusions

Delirium after cardiac surgery appears to be common, particularly in patients who are older and have pre-existing cerebral dysfunction. Several pre-operative and intra-operative associations with POD have been identified, but to what extent modification of these factors can reduce POD remains largely unknown. There is a need to standardise the timing and frequency of assessment for POD, enhance diagnosis of hypoactive delirium, and improve the understanding of the causal relationship between delirium and post-operative complications. Quality improvement initiatives and prospective trials are needed to minimise the incidence and consequences of post-cardiotomy delirium.

Competing interests

None declared.

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