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Review

Postoperative cognitive decline: A current problem with a difficult future

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ABSTRACT

The ageing population is both a marvel of civilisation and a huge challenge for healthcare provision. Coupled with surgical and anaesthetic advances, this shift in population distribution has meant that far greater numbers of elderly patients are undergoing surgery than has ever previously been the case. This is a double edged sword as the elderly population are more prone to develop perioperative complications than younger patients.

Postoperative cognitive dysfunction (POCD) is one such complication, and can result in a serious deterioration in quality of life and an increased duration of hospital stay. It may persist for months or even years, and could yet prove to be a harbinger for the development of dementia in later life.

The pathogenesis of POCD is still not yet fully understood, though a number of mechanisms have been postulated and there are several clearly identified risk factor. POCD also does not yet have a standardised diagnostic classification, and this has proven problematic in terms of research progress. Unsurprisingly, the complex relationship between POCD and dementia has also yet to be fully elucidated, though there is considerable overlap in risk factors for the two conditions.

The common theme that runs through the risk factors for POCD is that they all pertain to either a reduction in functional reserve or a propensity to cerebral injury. Many of these risk factors are non-modifiable such as age, genotype, history of cerebrovascular disease and preoperative cognitive function. One exception to this is the development of postoperative delirium, which may also increase the risk of POCD. Postoperative delirium has myriad potential causes, many of which are treatable, if not preventable. This makes postoperative delirium an interesting prospect for study, as if it does contribute to the development of POCD then its early detection and management could produce real improvements in quality of life for many elderly patients.

This review will outline the existing theories as to the pathophysiology underpinning POCD, the problems in defining it and the merits of various methods used in its detection. Risk factors precluding the development of POCD will also be discussed, with a focus placed specifically on age, preoperative cognitive status and the role of postoperative delirium. Common causes of postoperative delirium and their potential as modifiable risk factors will be highlighted and the protective or deleterious roles of common anaesthetic agents, type of surgery and certain individual factors will also be examined. Finally, the authors have offered some general principles of good practice to guide management in lieu of more concrete, targeted recommendations.

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1. Introduction

One of the biggest challenges facing modern medicine is that of an ageing population [1], and this is set to have far-reaching implications across many, if not all areas of medicine. Coupled with surgical and anaesthetic advances, this shift in population means that far greater numbers of elderly patients are undergoing surgery than has ever previously been the case, across a wide range of specialties [2–4]. In spite of these advances, the elderly population are still much more prone to develop perioperative complications than younger patients [5], presumably due to a higher prevalence of comorbidities [1]. Postoperative cognitive dysfunction (POCD) is one such complication, and this can represent a serious deterioration in quality of life and an increased duration of hospital stay [6–8]. It may persist for months or even years, and could yet prove to be a harbinger for the development of dementia in later life [9].

The pathogenesis of POCD is still not yet fully understood, though there a number of mechanisms have been postulated and there are several clearly identified risk factors [6,10]. POCD also does not yet have a standardised diagnostic classification, and this has proven problematic in terms of research progress [6,10,11]. Unsurprisingly, the complex relationship between POCD and dementia has also yet to be fully elucidated, though there is considerable overlap in risk factors for the two conditions [9].

The common theme that runs through the risk factors for POCD is that they all pertain to either a reduction in functional reserve or a propensity to cerebral injury [12–14]. Many of these risk factors are non-modifiable such as age, genotype, history of cerebrovascular disease and preoperative cognitive function [15]. One exception to this is the development of postoperative delirium, which may also increase the risk of POCD [15,16]. Postoperative delirium has myriad potential causes, many of which are treatable, if not preventable [17]. This makes postoperative delirium an interesting prospect for research, as if it does contribute to the development of POCD then its early detection and management could produce real improvements in quality of life for many elderly patients.

This review will outline the existing theories as to the pathophysiology underpinning POCD, the problems in defining it and the merits of various methods used in its detection. Risk factors precluding the development of POCD will also be discussed, with a focus placed specifically on age, preoperative cognitive status and the role of postoperative delirium. Common causes of postoperative delirium and its potential as a modifiable risk factor will be highlighted. The protective or deleterious roles of common anaesthetic agents, type of surgery and certain individual factors will also be examined.

2. Postoperative Cognitive Dysfunction

In the most general terms, POCD can be described as a relative decline in cognitive function that occurs in patients following surgery [6,7,10]. It can affect different aspects of cognition such as memory, comprehension and attention, and this varies on an individual basis [7]. These limitations can constitute a significant handicap in daily life but this functional decline is usually subtle and often may go unrecognised by clinicians [18]. However, there are also more serious ramifications. Alarmingly, one study found that patients with POCD at discharge were more likely to die in the first 3 months after surgery [8]. It should be stressed that this is not a causal link but likely reflects the presence and influence of other comorbidities as in this study, patients who developed POCD were more likely to have a history of stroke and to be of an older age. Importantly however, these patients may also have experienced additional problems such as lack of compliance with medication or loss to follow-up due to poor memory.

POCD is actually a remarkably common occurrence. The 1998 landmark study conducted by the International Study of Postoperative Cognitive Dysfunction (ISPOCD) showed that one week after surgery 25.8% of patients over the age of 60 had POCD at one week, while 9.9% of the cohort had POCD after 3 months [10]. Initial research specifically into POCD focused on cardiac surgery and the purported mechanism of injury was thought to be related to the use of cardiopulmonary bypass (CPB) [19]. We now know this is not the case as POCD can also occur following many other forms of surgery [8,10], and although the aetiology is still not entirely clear there are several prominent hypotheses. It should be noted more generally that long-term cognitive impairment is a serious and surprisingly frequent complication that does not just occur as a consequence of surgery. In survivors of the ICU it has been reported to be as high as 30%, while research has also described it as a phenomenon related to cancer, lupus and obstructive sleep apnoea [20,21].

Putative causes of POCD are diverse. Among those studied are microemboli, cerebrovascular disease, upregulation of inflammatory mediators and neurodegenerative changes [6]. The likelihood is that several pathological mechanisms are probably at play. Microemboli were once thought to be an important consideration as they are common following surgery using CPB [22], however, this theory has to a certain extent been disregarded. Randomised studies comparing cardiac surgery both with and without CPB failed to find any association between avoidance of CPB (and the high likelihood of microemboli) and the incidence of POCD [23,24]. In spite of this, the fact remains that multiple studies demonstrate associations between the presence of cardiovascular disease risk factors (to be discussed) and poor cognition [25–28]. This does hint at cerebrovascular disease playing a role in deteriorating cognition, despite data from the ISPOCD study failing to find an association between many cerebrovascular disease risk factors [10]. This will be discussed in more detail below.

POCD in elderly patients has also been speculated to be the manifestation or the exacerbation of a pre-existing process related to ageing [6] and some evidence suggests that markers of inflammation are upregulated in the ageing brain following surgery, rendering them vulnerable to injury [13]. One study in particular showed that elevated levels of plasma IL-6 and CRP were associated with poorer cognition, both at baseline and at follow-up [29]. This study also showed that those with the highest levels of these inflammatory markers were more likely to develop cognitive decline. Another study [30] found a correlation between abnormalities in cortisol secretion and the onset of POCD, suggesting a potential role of endocrine stress. In further support of an inflammatory mechanism, animal models of POCD have also revealed that neuroinflammation of the hippocampus has been linked to a number of inflammatory mediators including the release of cytokines such as TNF-a, IL-1, IL-1B and IL-6 [31–33]. Once again however, this evidence has not yet been verified using clinical studies. Attempts at perioperative immunomodulation in an attempt to temper the inflammatory response have yielded very mixed results, with decreased complement activation seeming effective in one instance [34] but not in others [35,36].

All of these postulated mechanisms lead to a decrease in cognitive reserve. This leaves the brain vulnerable to injury and loss of function, whether that is permanent or temporary, and this opens up a novel avenue for research. Cognitive reserve is a hypothetical construct which has been coined in an attempt to help describe the impacts of changes in the ageing brain and in response to injury [37]. It represents an important consideration when contemplating the underlying mechanisms of POCD [12]. An interesting research question is this: if decreased cognitive reserve is behind POCD, can this be ameliorated by somehow increasing cognitive reserve preoperatively? If possible, this could help expedite postoperative restoration of function in at risk patients.

In spite of the relative abundance of evidence and potential for further clinical research, it is difficult to draw definitive conclusions when it comes to a unified pathophysiological model of POCD, and this may be due in part to the fact that it is such a multifactorial phenomenon. However, methodological issues have been hampering research for a considerable length of time [11]. One of these is that there is no consensus definition of POCD in the literature; there is no universal diagnostic code with which to classify it [14]. This has given rise to large disparities in the reported incidence of POCD [6]. There has also been a frustrating lack of consistency in terms of the techniques used to assess cognition [11]. The number of tests, when they are performed and the definitions of cognitive decline have not been consistent enough to allow a meta-analysis to be performed. Compounding this, surgical populations are incredibly variant, and factors that are at play in one group may well be absent in others. In order for meaningful progress to be made in this field these significant methodological hurdles will need to be overcome.

3. Assessing and diagnosing POCD

Cognitive assessment is carried out for three primary reasons:

- to screen for possible cognitive impairments
- to produce a differential diagnosis of cause
- to rate the severity of a disorder or monitor its progression.

In the case of POCD the main aim of assessment is to simply qualitatively diagnose the condition. As mentioned above, there is as of yet no recognised diagnostic criteria for POCD, and this has limited the usefulness of research. However, this is not to say that there is not consensus in other areas regarding the detection of POCD.

The ISPOCD has recognised the need for standardisation, and reviewed the effectiveness of various methodologies [38]. They emphasised a need for pre and postoperative testing to establish a baseline of cognitive function. The points at which testing should be carried out had also been far from uniform, although a general consensus seems to have now been reached. Again following ISPOCD recommendations, assessments are usually carried out at baseline (both pre- and postoperatively), 7 days and 3 months postoperatively.

In addition, the ISPOCD group also offered a suitable test battery that could be used in postsurgical patients. The battery evaluates memory, sensorimotor speed, cognitive flexibility and various aspects of motor function. Tests involved include:

- Mini Mental State Examination (MMSE)
- The Visual Verbal Learning Assessment
- The Concept Shifting Task
- The Stroop Colour Word Test
- The Memory Scanning Test
- Letter-Digit Coding.

This battery of tests, while comprehensive, takes around 45 min to perform [10], and this may explain why it has not been widely adopted. This is an acceptable duration for research purposes, but is unlikely to be used by clinicians on a regular basis.

More recently, the Montreal Cognitive Assessment (MoCA) has been shown to have excellent sensitivity (96%) and specificity (95%) in the detection of cognitive impairment [39]. The MoCA has also been validated for use in identifying vascular cognitive impairment [40], vascular dementia [41] and neurodegenerative conditions [42]. Importantly, the MoCA has also been shown to be a feasible tool for use in surgical patients [43], with one study demonstrating that not only is the test acceptable to elderly patients, it also has been shown to be superior in both sensitivity and specificity to other single tests such as the MMSE. In comparison with the ISPOCD's test battery, the MoCA takes less than 10 min to perform [44] and this gives it potential for identifying POCD in a clinical setting.

Beyond choice of test, different definitions for POCD have been created based on how patients perform in cognitive assessments and the subsequent analysis of these performances [38]. This commonly uses either a set threshold score, or alternatively a relative decline in function from preoperative baseline, either individually (e.g. a 20% decline) or as compared to the cohort mean (i.e. using Z-scores) [45]. The ISPOCD recommends the measurement of an individual's variation from baseline for use in research [38], and this is partly why they advocate a battery of tests over a single test, as this removes the floor/ceiling effect which makes use of the MoCA alone less appropriate in a research capacity.

4. Risk factors

As the pathogenesis of PCOD has not yet been delineated, risk factors are important in shedding light on possible ways we can predict POCD and prevent its development. Given the variety of surgical and medical context, most of the risk factors studied are very general so as to be relevant to all patient groups. The most consistently associated factor with POCD is age [8,10,14,46], but where others have been suggested, the evidence has been conflicting. As well as age, early postoperative delirium and poor preoperative cognitive function (especially in the form of diagnosed mild cognitive impairment (MCI)) have also been strongly implicated on multiple occasions [8,10,12,47], and will be discussed below. There is also evidence demonstrating an association between cardiovascular risk factors and poor cognition such as diabetes, hypertension and cardiac disease [48]. A common theme that underpins all of these risk factors is that like the postulated mechanisms of pathogenesis they all constitute either a decrease in cognitive reserve or some kind of traumatic exposure.

4.1. Increasing age

As mentioned, increasing age remains the most consistently associated factor with the development of POCD. This was demonstrated by the ISPOCD study, which showed that age was a constant association across all three surgical procedure groups that they studied: major abdominal, non-cardiac thoracic and orthopaedic [8].

The majority of studies have looked exclusively at elderly patients regarding the development of POCD, so a major finding came when middle-aged patients were the subject of an ISPOCD study [49]. The working hypothesis was that POCD would be present in this demographic but at a lower incidence than the older population, and this was confirmed. In this study POCD had a prevalence of 19.2% at 1 week and 6.2% at 3 months, significantly lower than the ISPOCD's findings for the older age group of those over 60 (25.8% at 1 week; 9.9% at 3 months) [10], using the same assessment techniques.

Despite the consistency with which age is associated with POCD even this relationship is far from straightforward. Age is not a causative factor in itself but is rather a descriptive factor, and so this association is more likely to be related to biological age than chronological, though this is difficult to directly quantify in clinical trials. Cardiovascular comorbidities such as hypertension, history of stroke, diabetes and cardiac abnormalities increase with age [50], and the brain's functional reserve decreases [51]. Any combination of these and other risk factors may come into play with increasing age, and so the fact that there is a relationship between age and POCD does little to help in the development of preventive measures.

4.2. Poor preoperative cognitive function

One study reports that pre-existing cognitive impairment exists in 20% of elderly patients presenting for total hip replacements [46], while this may be as high as 35% in those presenting for coronary artery bypass grafts (CABG) [52], and so this clearly presents relatively commonly. Similarly to age, preoperative cognitive function is a descriptive factor, representing a possible decreased cognitive function and by extension a decreased functional reserve. Surrogate measures of cognitive reserve such as educational and occupational level have been used in an attempt to delineate a relationship with POCD, and indeed a history of a lower educational level has been cited as a risk factor for the development of POCD [8,10,12].

As discussed, POCD may also represent an exacerbation of a pre-existing process related to ageing. This same process could present in patients as impaired cognitive function that simply deteriorates further following surgery. Indeed, POCD does seem to be more likely to occur in individuals who suffer from depression and MCI before their operation [53] and thus pre-existing cognitive impairment is frequently cited as a major risk factor for the development of POCD [8,10,54].

MCI is now widely recognised as a precursor to Alzheimer's disease (AD) [55], which has a prevalence of 7.1% in the UK among the over 65's [56]. MCI itself is thought to be a very common occurrence with reports estimating that prevalence could be as high as 42% amongst older patients [57], although estimates are highly varied [58]. Typically a patient with MCI will have preserved independence and will not struggle with activities of daily living, despite experiencing a subjective memory deficit [59]. It often goes undiagnosed for several years before the condition deteriorates to the point when the patient can present with profound memory loss as frank Alzheimer's [55,60]. In a similar fashion to POCD, failure to complete high school (or equivalent), and thus a low level of educational achievement, has also been associated with an increased risk of developing MCI [47]. The question in this case is whether anaesthesia and surgery exacerbate MCI which may already be present. Animal studies using rats have suggested that there is a functional impairment of memory in rats following exposure to anaesthesia (specifically volatile and gaseous agents) [61], as well as increased production of amyloid. However, there is as yet insufficient evidence to ascertain whether this phenomenon may also occur in humans.

The identification of a link between surgery, anaesthesia, POCD, MCI, and AD would create a novel opportunity to expedite the development of both clinical and pharmacological preventive strategies. This would have an added benefit of early diagnosis of Alzheimer's for the individual.

Unfortunately, similarly to that which was previously mentioned, there is a distinct lack of consistency regarding definitions and assessments of cognitive impairment, preventing significant collaboration between the psychogeriatric and anaesthetic communities. While anaesthetists define pre-existing cognitive impairment (pre-CI) as a decrease of 2 standard deviations from the norm in two or more of 7 or 8 cognitive tests [28,52], MCI is defined as an objective decrease of 1.5 standard deviations on memory testing alone, when coupled with a subjective complaint of memory loss [60]. Unfortunately, as a result of these discrepancies data garnered from large population studies of MCI cannot be applied to individuals in surgery and anaesthesia.

4.3. Postoperative delirium

Delirium is defined as an acutely altered and fluctuating mental status with features of inattention and an altered level of consciousness [20] and so it is a separate entity from POCD in this respect. Delirium is typically classified in terms of motor symptoms: hypoactive, characterised by lethargy, decreased alertness and unawareness; hyperactive, which presents as irritability, restlessness and agitation; or a mixture of the two states [62]. Delirium is one of the most common neuropsychiatric conditions experienced by the elderly [63], and although incidence seems to vary wildly it is thought to affect between 25% and 65% of elderly surgical patients [20]. This wide variation in reported incidence results from discrepancies in population, assessment method and degree of operative stress [64].

There have been a number of studies that have attempted to characterise the relationship between postoperative delirium and POCD. Some of these have found greater decline in cognitive function at follow-up in patients experiencing delirium relative to controls. For example, geriatric hip fracture patients with delirium were shown to be almost twice as likely to have cognitive impairments at a 2-year follow-up [65]. Another study, again commissioned by the ISPOCD [16], found that delirium was associated with an increased incidence of early POCD (adjusted risk ratio 1.6, 95% CI 1.1–2.1), but not long-term POCD (adjusted risk ratio 1.3, 95% CI 0.6–2.4). More generally, hospitalised geriatric medical patients treated in the Emergency Department with delirium were found to have MMSE scores five points lower than those without delirium 1 year after discharge [66]. Unfortunately, despite repeated efforts to recognise an association between POCD and postoperative delirium, the relationship remains unclear.

Postoperative delirium is a quintessentially geriatric complication, and it is associated with poor outcomes such as functional decline, longer hospitalisation, institutionalisation and a higher mortality [67–69]. Patients who develop delirium during hospitalisation have also been shown to have significantly higher mortality at 6 months in comparison to patients who do not develop delirium [70]. Unlike POCD, postoperative delirium can be diagnosed categorically using verified classifications such as the Confusion Assessment Method (CAM) [71] and those found in the Diagnostic and Statistical Manual of Mental Disorders (DSM) [72].

Risk factors for the development of postoperative delirium can be classified by whether they are related to the individual, the procedure or perioperative factors. Commonly measured patient-specific risk factors include older age, history of substance abuse and poor preoperative cognitive function (most commonly quantified using a Mini Mental State Exam) [17]. While these cannot be reversed, risk factors for developing delirium are additive [73], and therefore recognising patients with multiple comorbidities should trigger surgical and anaesthetic teams to implement environmental and supportive measures that have been proven to prevent its onset.

In terms of procedure, the more invasive the surgery and the greater the level of stress placed on the body, the higher the risk is of developing postoperative delirium [74]. For example, minimally invasive cataract surgery carries a 4% incidence of postoperative delirium [75], while vascular surgery came with a much higher incidence of 36% [76]. This could be due to a number of reasons including increased risk of infection, a greater postoperative inflammatory response or possibly the presence of other comorbidities associated with those who need major surgery, such as cardiovascular risk factors [77].

It is thought that between 30% and 40% of cases of postoperative delirium may be preventable [78], and so it is vital that interventions begin in the preoperative period. Perioperative interventions that help protect against the development of postoperative delirium include prevention of sepsis, fluid and electrolyte disturbances, GI bleeds and reduction in alcohol intake [17]. Notably, the perioperative use of sedative and analgesic medications such as benzodiazepines and opioids such as pethidine is also associated with the development of postoperative delirium [79,80]. The fact that there are several common modifiable risk factors means that there is potential for reducing the incidence of postoperative delirium. If postoperative delirium is indeed itself a risk factor for POCD, then it follows that targeting these risk factors could help to prevent the onset of or reduce the severity of POCD.

Perioperative medication choice in particular represents an intriguing target for research. Evidence suggests that benzodiazepines and opioids can contribute to the onset of postoperative delirium [79,81], but as with many other aspects of POCD, evidence for these drugs' role in POCD is ambiguous. The ISPOCD1 study suggested that preoperative benzodiazepines may actually have a protective role against POCD, but this effect was not seen when prescribed postoperatively [10]. As well as this, a subsequent ISPOCD2 study [82] was able to demonstrate that postsurgical blood levels of benzodiazepines and POCD were not related, using a multiple linear regression analysis. Interestingly, one recent study looked at patients who were using anticholinergics and sedative hypnotics such as benzodiazepines prior to surgery, and found that this cohort were at an increased risk of developing POCD [14]. This was the first time this cohort had been studied in relation to POCD, and given the relatively small sample size used it is certainly worth seeing if this can be replicated. More generally, given what is known of the role of benzodiazepines in postoperative delirium and the ambiguity of the relationship between postoperative delirium and POCD, further research is certainly warranted.

4.4. Choice of anaesthetic agent

The relationship between the type of anaesthesia used and the onset of POCD is evolving. A 2011 meta-analysis of 26 randomised controlled trials [83] found that the type of general anaesthesia did not contribute to the development of longstanding POCD. This echoed earlier studies from cataract and hip surgery, which gave no indication of a major advantage for regional over general [84–86]. The ISPOCD also attempted to address this relationship in 2003 by looking at epidural versus general anaesthetic in noncardiac surgery, but unfortunately their study was impeded by many patients not receiving the anaesthetic they were initially allocated [87]. A 2010 meta-analysis of 21 studies asserted that the use of general anaesthesia may increase the risk of developing POCD [88], however their data proved to be marginally non-significant (odds ratio 1.34, 0.93–1.95 with 95% confidence).

In the years since research into anaesthesia's role in POCD began, there has been a great improvement in both peripheral nerve catheters and ultrasound technology [89,90]. This has led to major improvements in terms of clinicians' ability to administer effective continuous peripheral nerve blockade [91]. This has significant potential in reducing the incidence of postoperative delirium, as evidence suggests that perioperative nerve blockade in orthopaedic surgery reduces reliance on benzodiazepines and opioid analgesics for pain relief, and this in turn can reduce the incidence of postoperative delirium by as much as 58% [92,93]. A systematic review [94] also found that the use of continuous peripheral nerve blockade could improve patient outcomes such as improved postoperative sleep and decreased fatigue [95]. This could in part be responsible for the reduction in postoperative delirium.

There is also some evidence suggesting that increased depth of anaesthesia (as measured by EEG) may reduce the incidence of POCD [96,97], and this has been postulated to result from a lowering the metabolic needs of the brain, which is neuroprotective. Animal studies suggested a potential protective role for inhaled anaesthetics such as xenon [98] and sevoflurane [33] as seen by reductions cerebral levels of inflammatory cytokines such as IL-1β.

Unfortunately, these results have not yet translated into clinical findings. Rather, an association between use of sevoflurane and an increased risk of developing POCD has been found [14], while xenon was shown not to be any more beneficial than propofol [99]. Furthermore, other animal studies demonstrated that volatile and gaseous anaesthetic agents can cause a functional impairment [100,101], and both halothane [102] and sevoflurane [61] have been shown to increase levels of beta-amyloid, the pathological protein that underpins AD.

Although the evidence concerning the role of various general anaesthetic agents is conflicting, what is clear is that interventions which reduce the reliance on opiates, such as nerve blockade, have great potential, especially in the field of geriatric orthopaedic surgery, and certainly warrant further research.

4.5. Type of surgery

POCD, as with postoperative delirium, seems to be more common following major surgery than minor surgery. While the incidence of POCD was found to be around 6.8% in minor surgery [103] it can be over 25% following major surgery [10]. This difference was greatly reduced in the same studies at the 3 month interval (6.6%

versus 9.9%) and this suggests that perhaps the extent of surgery exerts a greater impact on shorter term POCD. Indeed, in cardiac patients, it was also found that cognitive impairment was comparable at 6 and 12 months between patients who had major surgery with CPB and those who had percutaneous coronary interventions [23]. This phenomenon could potentially be a reflection of increased oxidative stress, differences in the degree of inflammatory response or even simply a reflection of the patient groups requiring different surgery. It may also turn out after all to reflect differences in anaesthetic duration or choice of agent. It has been observed that the greater the surgical trauma the larger the body's inflammatory response tends to be [104], as represented by serum levels of Interleukin-6. This finding, together with the association between surgical trauma and short term POCD and that which is seen between Il-6 and cognitive impairment [29], gives credence to the idea that there is a subacute inflammatory component of POCD. This may at least partly subside over the months and years following an operation.

The type of patient that requires major surgery and the comorbidities they possess are also important considerations. For example, by definition patients who have multiple cardiovascular risk factors are far more likely to require major cardiac surgery than those who do not, and as discussed above patients who require CABG are also far more likely to have pre-existing cognitive impairment [52]. This implies that in the longer term the invasiveness of surgery may not be as important as other factors that predispose the patient to POCD beforehand.

4.6. Other individual factors

Aside from the major risk factors discussed above, there has been extensive research into a number of other plausible risk factors in the development of POCD. Possession of the APOE4 genotype [14,105,106], high ASA (American Society of Anesthesiologists) status [6] and cardiovascular risk factors [6,8,10] have all been studied and implicated by evidence, and these suggest that individuals with a lack of cognitive reserve are especially vulnerable to the development of POCD.

The ASA physical status classification is a commonly used tool in anaesthetics that is designed to classify the overall severity of an individual's health problems in a preoperative setting, in order to assess risk [107]. A patient is ascribed a number between 1 and 6, depending on their health:

1. No significant health issues
2. Mild systemic disease
3. Severe systemic disease
4. Severe systemic disease that is a constant threat to life
5. A moribund person who is not expected to survive without the operation
6. A declared brain-dead patient whose organs are being removed for donor purposes

It is perhaps not surprising that the higher an individual's ASA status, the more likely they were to develop POCD [8]. This was seen at both discharge and at 3 month follow-up. Given what has previously been discussed around reduced cognitive reserve, it follows that the more systemically unwell a person is, the more vulnerable they are likely to be to develop any sort of complication, including brain injury.

However, while this tool has its uses in estimating risk, given its vague and perhaps subjective parameters, it is not a particularly robust measure for use in research [108,109]. It also clearly cannot account well for those with multiple versus single comorbidities and has no intermediate distinction between mild and severe. Importantly, its reliability has been suggested to be especially limited in the elderly population (over 80 years old), resulting from the fact that most octogenarians have some kind of chronic health problem [110]. Thus it may prove more useful to look at more specific risk factors.

As discussed above, it seems likely that cerebrovascular disease plays some sort of role in the pathogenesis of POCD. Indeed, Monk et al. [8] found that patients with a history of stroke had a higher incidence of POCD at 3 month follow up, and this was even true for those whose stroke had left no residual impairments. Major risk factors for stroke include hypertension, type 2 diabetes, hypercholesterolaemia, smoking status, atrial fibrillation and ischaemic heart disease [111]. There is ample evidence to suggest that these are also involved in the pathogenesis of vascular dementia [26,27], and more generally with cognitive impairment [28] even in middle age [25]. In spite of all this evidence, the 1998 ISPOCD study found no association was seen between any of these and an increased incidence of POCD [10]. This may be partly explained by their stringent exclusion criteria, which left out patients with pre-existing cognitive impairment (MMSE score <23) and also those who had previously undergone neuropsychiatric testing. These patients would have been more likely to have previously had strokes and may have had many of the risk factors mentioned above. Future studies may consider including this group of at risk patients.

In terms of genetic predisposition, patients who carry the apolipoprotein E4 (APOE4) genotype were at more risk of POCD 3 months after major noncardiac surgery (odds ratio 4.74, CI = 1.09–22.19) [14]. This result echoed earlier evidence from studies of cardiac surgery [105] and endarterectomy (106), but contrasted with a prominent earlier multicentre ISPOCD study that failed to find a clear association between APOE4 and POCD [112]. However, although this study had a much larger sample size, it also recruited much younger patients (those aged over 40 versus those aged over 65). The deleterious effects of an APOE4 genotype may not become apparent until older age, and so this may have prevented a significant difference from being identified. Their exclusion criteria also deemed anybody 'not fit enough for testing' and so may have grossly underestimated the incidence of PCOD. It should be noted too that the results of this study did demonstrate that APOE4 carried a 20% increase in risk of POCD, but the sample size would have needed to be greater to know whether this was a true difference.

APOE4 warrants attention as this genotype has also been consistently associated with a 3-fold or greater risk of developing AD [113–115]. In terms of function, APOE is a polymorphic protein associated with plasma lipoproteins, specifically in neural tissues [116]. It has long been known of, and is thought to be involved in the utilisation of cholesterol in the regeneration and maintenance of myelin, both during development or after injury [117,118]. Potential pathological mechanisms which APOE4 could predispose an individual towards include proinflammatory cytokine release [119], increased blood brain barrier permeability, increased amyloid precursor protein metabolism and alterations in platelet function [120,121]. Most promisingly, some evidence suggests that possession of the APOE4 genotype also predisposes both to the development of postoperative delirium [122], and a slower recovery time from delirium [123]. This reinforces hopes of finding a link between POCD, AD and postoperative delirium.

One possible research avenue in terms of preventing POCD is that of nootropic agents, so called 'smart drugs' used to enhance cognition. These are growing in popularity especially amongst student populations [124,125], and there are myriad different drugs available, though this goes far beyond the scope of this review. To take one example, piracetam has been studied for decades in relation to its cognitive enhancement potential [126]. It has long been known to have potential in preventing postoperative delirium [127] and age-related cognitive decline [128], and this may be through a reduction in damage caused by oxidative stress [129]. This drug is neither a stimulant nor a sedative [130], and is thought to work in a complex manner by altering membrane properties through the phospholipid bilayer of neurons [128]. Other agents such as noopept stimulate expression of neurotropic factors such as NGF and BDNF [131]. Although most research has been conducted in animals at this stage, given the promising nature of the results in just one of the many available agents this would certainly be an intriguing area for POCD research in the future to focus.

5. Management

Although there has been a great deal of research into the risk factors, diagnosis and assessment of POCD, there is still a dearth in terms of guidance for managing it when it does appear. However, it is important to keep in mind some general principles of good practice to guide management in lieu of more concrete, targeted recommendations. Four such principles tie in with what has already been discussed:

1. Early identification of patients who are at risk of POCD, based on the risk factors outlined above
2. Preoperative optimisation of at-risk patients (both in terms of cardiovascular risk factors and potentially in terms of cognition)
3. Minimalisation of intraoperative stress, and thus reducing analgesic and anaesthetic requirements
4. Timely, holistic employment of perioperative measures aimed at reducing the incidence of POD

Building on these four principles and relating it to what has previously been discussed around the phenomenology of POCD, the below represents a summary of the authors' recommendations for detecting those at risk and preventing POCD.

5.1. Early identification

- Premorbid patient-specific risk factors such as old age, ongoing cognitive impairment, and multiple cardiovascular comorbidities should all act as prompts for the patient to be recognised as at risk.
- Whether or not they have previously suffered from delirium or have a history of alcohol or drug abuse should also be considered.
- The nature of surgery being performed is also pertinent. For example, more invasive and prolonged surgery can be associated with a higher risk of developing both POCD and POD.

5.2. Preoperative optimisation

- Having identified the at-risk patient, it is important to put measures in place to make sure they are as physiologically prepared for surgery as possible, again following general principles.
- In the case of elective surgery this could begin in primary care, including interventions such as optimising haemoglobin levels, maintaining glycaemic control and managing hypertension.
- Specific to POCD and its associated loss of functional reserve, interventions such as preoperative cognitive training could play a role, as mentioned previously.
- Emerging nootropic agents have been shown to enhance cognitive function. Could these have a role in preoperative optimisation of cognition alongside training?

5.3. Minimalisation of intraoperative stress

- Surgery should be kept as minimally invasive as possible, and this goes hand-in-hand with a reduced anaesthetic and analgesic burden.
- Efforts should be made to prevent oxygen desaturation, fluctuations in blood pressure and hypothermia, and avoidance of crystalloid overload.

5.4. Delirium prevention

- As discussed, POD has many causes and requires a multidisciplinary approach to be adequately addressed.
- Adequate hydration and nutrition needs to be started as early as possible postoperatively, and this should be converted to the oral route as soon as the patient is able.
- Interventions to decrease opioid and benzodiazepine use should be put in place, and this can include the use of peripheral nerve blockade, +/− LA infusions via catheters, in some cases.
- Other key interventions include encouraging a regular circadian sleep pattern, minimising invasive monitoring and NG tubes, regular orientation and noise reduction in ward areas.

6. Conclusion

In this review, POCD has been discussed in terms of its pathophysiology, assessment, diagnosis, management and the major reported risk factors that predispose an individual to it. The pathophysiology of POCD is likely multifactorial, with inflammatory, vascular, neurodegenerative and even genetic components.

At this point, substantial research has also attempted to elucidate the complex relationships between dementia, POCD and postoperative delirium but important and intriguing questions still remain. This could, and perhaps should, represent an important area of study in the future.

Increasing age, poor preoperative cognitive function and type of surgery remain the most consistent risk factors. Whether postoperative delirium and the use of anaesthetic agents such as sevoflurane constitute major iatrogenic risk factors for POCD is still not entirely clear, though current evidence and the potential for therapeutic intervention is sufficient to mandate further research.

Moving forward, given that all major risk factors lead to a reduction in cognitive reserve or represent an insult on the brain, future research investigating whether there are any effective means of improving cognitive reserve in a preoperative setting could be very interesting. Although there is potential here, perhaps for both primary and secondary prevention, until more research is done no interventions that are supported by robust data can be recommended. In the meantime, the authors advocate a common-sense approach based on the principles discussed above. Individuals who are most at risk of POCD need to be identified and where possible, resources directed to reduce the impact of any ensuing decline. Following this, the avoidance of the development of delirium and all that entails should be considered paramount.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tacc.2018.04.002.

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