HHS Public Access

Author manuscript

Med Hypotheses. Author manuscript; available in PMC 2015 July 24.

Published in final edited form as:

Med Hypotheses. 2013 July ; 81(1): 15–20. doi:10.1016/j.mehy.2013.03.033.

Delirium after cardiac surgery: have we overlooked obstructive sleep apnea?

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Abstract

Obstructive sleep apnea is common in patients with cardiovascular disease. It is well known that cardiac surgery is a risk factor for delirium. Researchers have shown that obstructive sleep apnea is an independent risk factor for the occurrence of delirium. In this manuscript we speculate on how obstructive sleep apnea may increase the risk of delirium in patients with cardiac surgery. If this is found to be confirmed, we would have another target through which we can decrease the risk of delirium in this population.

Introduction

Obstructive sleep apnea (OSA) is a common disorder affecting up to 24 % of the US population [1]. OSA is characterized by repetitive complete and/or partial blockage of the upper airways occurring during sleep. It is not just a simple sleep or snoring problem, but rather a disease with systemic features. This notion is supported by the fact that OSA may contribute to the occurrence of cardiovascular and metabolic diseases [2–4] and its treatment may improve the function of several target organs [4]. The association between OSA and comorbid disease may be mediated via a disturbance in fundamental biochemical processes, as well as low grade systemic inflammation and oxidative stress [5].

Delirium is a common adverse outcome in patients after major surgery [6–11] and in medical patients [12]. It is characterized by fluctuating disturbances in attention, memory, orientation, perception, psychomotor behavior and sleep [13–15]. The criteria for delirium,

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Confllct of Interest Statement

None

as described by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, are shown in Table 1.

Delirium tends to be diagnosed based on clinical suspicion and, therefore, may be underdiagnosed [16]. Several clinically validated screening tools are available, which may help clinicians to detect delirium early [17–19]. It is relevant to note that delirium is independently associated with an increase in both short-term and long-term mortality [20].

The incidence of postoperative delirium varies by surgery type. For example, delirium after knee replacement occurs in 20 to 30 % of patients. It is important to note that the incidence of postoperative delirium is higher after cardiac surgery, as demonstrated by several recent studies [21–23].

The major goal of this article was to review the current evidence on delirium after cardiac surgery and why OSA may be an important risk factor. To do so, we first reviewed the basic pathophysiology of delirium. Second, we explored the diagnosis of delirium. We also reviewed the specific risk factors for delirium in patients with cardiac surgery, assessing the epidemiology of OSA in patients with coronary artery disease (CAD) and those undergoing cardiac surgery. Data on the detrimental effects of OSA on neuronal functioning were also explored. Finally, we reviewed published studies on the occurrence of delirium in patients with OSA.

Hypothesis

OSA is very common in patients with cardiovascular and metabolic diseases. Furthermore, OSA may act as an independent risk factor for the incidence of cardiac pathology and related morbidity and mortality. Therefore, OSA may contribute to the progression of cardiovascular disease and resultant increase in cardiac revascularization procedures.

As will be discussed later in the text OSA has been shown to be independent risk factor for the occurrence of delirium in patients with non- cardiac surgery. We will speculate how OSA may mediate an increased risk for delirium in patients with cardiac surgery.

Delirium pathogenesis

The pathogenesis of delirium is not entirely understood. An extensive review of the pathophysiology of delirium is beyond the scope of this article and the interested reader is referred to a review article on this topic [24]. Several potential mechanisms, which are believed to be important for the occurrence of delirium, will be discussed below.

Alterations in the levels of neurotransmitters have been proposed to be a leading pathobiological mechanism for delirium. Hsieh et al. hypothesized that deficient cholinergic neurotransmission is involved in the pathogenesis of delirium and cognitive dysfunction [25]. This is supported by the well-known clinical observation that medications with anticholinergic actions may lead to delirium in susceptible individuals [26]. Other neurotransmitters such as dopamine, serotonin and norepinephrine are also implicated in the pathogenesis of delirium, but the scientific data are less robust [27].

Systemic inflammation has also been shown to contribute to the pathogenesis of delirium. Animal data suggest that an increase in systemic inflammatory cytokines activate neuroglia cells, which further augment damage to central neurons [28]. This inflammatory cell damage may mediate cell death of cholinergic and dopaminergic neurons. Burkhart et al. recently showed that an increase in C-reactive protein (CRP) concentration was independently related to delirium after cardiac surgery [29]. In another study, Macdonald et al. demonstrated that high levels of CRP independently predicted the incidence of delirium [30]. However, White et al. questioned the clinical use of CRP in predicting delirium [31].

Based on the above, multiple simultaneous factors play a role in the pathophysiology of delirium.

Delirium after cardiac surgery: specific risk factors

As mentioned previously, delirium is commonly seen in patients after cardiac surgery. Several pivotal studies performed by a group from Harvard University showed that the incidence of delirium ranges from 43.1 to 52 % [21–23]. Furthermore, delirium is associated with a cognitive deficiency for up to one year after coronary artery bypass graft (CABG) [32] surgery and long-term mortality for up to ten years after cardiac surgery [20]. In a recent large sample study, Martin et al. showed that individuals who developed delirium after cardiac surgery had a greater future risk for stroke and death [33]. Therefore, delirium should be approached as a disorder that may be used as a marker for future pathological events. Biochemical and pathophysiological disturbances associated with delirium may contribute to such a risk.

Common risk factors for the incidence of delirium such as baseline cognitive function, psychiatric comorbidity, the use of certain medications, major medical comorbidities and advanced age are relevant for patients undergoing cardiac surgery [12]. However, cardiac surgery may have specific risk factors for delirium, due to its unique techniques and complications.

Abu-Omar et al. recruited 45 patients who had undergone on-pump CABG, off-pump CABG and open cardiac surgery (15 each) with bilateral continuous transcranial Doppler monitoring [34]. They found that open cardiac surgery, on-pump CABG and off-pump CABG were associated with microembolic events in the descending order according to the transcranial Doppler monitoring. Clark et al. showed that cerebral microembolism was associated with the occurrence of delirium after CABG [35].

Several alterations in hormonal metabolism have been implicated in the pathogenesis of delirium in the setting of CABG. Mu et al. enrolled 243 patients and measured morning serum cortisol levels on post-operative day one to study its potential association with delirium [36]. They observed that higher cortisol levels were associated with an increased incidence of delirium. The authors proposed that increased cortisol concentrations due to stress related to cardiac surgery may detrimentally affect brain functioning. However, the study was unable to adjust cortisol levels for other diseases such as depression and baseline cognitive dysfunction. Plashcke et al. showed that patients who had undergone CABG and developed delirium had greater levels of cortisol and interleukin-6 [37]. Indeed, CABG is

associated with an increased inflammatory response during the early post-operative period [38], activation of white blood cells and a decrease in thyroid hormone levels [39]. A decrease in the levels of iodine-containing thyroid hormones may predispose individuals to cognitive deficits after surgery [40].

It is important to mention the results of a study performed by Schoen et al. who enrolled 231 patients undergoing cardiac surgery and assessed regional pre-operative cerebral oxygen saturation [41]. They found that decreased preoperative cerebral oxygen saturation was related to the occurrence of delirium after cardiac surgery.

Rudolph et al. enrolled patients undergoing cardiac surgery to validate the prediction scale for the occurrence of postoperative delirium [22]. They observed that lower baseline cognitive function, geriatric depression scale score>4, prior cerebrovascular disease and abnormal albumin were linked to the incidence of delirium. Afonso et al. showed that increased age and the duration of cardiac surgery were the only variables independently associated with delirium [42]. Researchers from the Erasmus University, the Netherlands, demonstrated that lower baseline cognitive function assessed by the mini-mental status examination, higher pre-operative creatinine levels and the duration of surgery were associated with the incidence of delirium [43].

Guenther et al. in a recent study showed that a greater age, higher Charlson's comorbidity index, lower mini mental state examination score and length of cardio-pulmonary bypass were predictive of a greater risk of delirium after cardiac surgery [44]. Arensen et al. from the University of Manitoba, Canada in a retrospective study showed that postoperative cerebrovascular disease, prolonged mechanical ventilation, older age 65, concomitant coronary artery bypass grafting and valve surgery, prior benzodiazepine use, a need for any postoperative blood product transfusion, and postoperative renal dysfunction were identified as risk factors for the delirium after cardiac surgery [45].

A summary of the common risk factors for the occurrence of delirium are presented in Table 2.

Epidemiology of OSA in patients with coronary artery disease

CAD is a group of disorders of the cardiac coronary artery circulation ranging from stable angina to myocardial infarction and sudden cardiac death [46]. CAD is the major cause of morbidity and mortality worldwide, with a decreasing incidence in the USA and developed countries, but an increasing one in countries with limited resources [47]. The major CAD risk factors are male gender, family history, age and smoking, as well as comorbid diseases such as hypertension, renal disease, diabetes mellitus and dyslipidemia.

Several treatment options are available for the management of CAD including pharmacological intervention, percutaneous coronary intervention (PCI) and surgical revascularization or CABG [48]. CABG is considered for symptomatic patients on a maximal medical therapy plus unsuitable anatomy for PCI and decreased left ventricular performance.

OSA is associated with an increased risk for cardiovascular diseases independently from traditional risk factors and confounders such as obesity and type 2 diabetes mellitus [49]. Marin et al. enrolled 264 healthy men, 377 snoring individuals without OSA and 1010 people with OSA (403 with untreated mild OSA, 235 with untreated severe disease and 372 with treated OSA) and monitored them for the incidence of new onset vascular events with a median follow up of 10.1 years [50]. Multivariate regression analysis showed that untreated severe OSA was independently associated with the incidence fatal and non-fatal vascular events (OR 2.87 and OR 3.17, respectively).

Punjabi et al. recruited 1047 subjects with OSA and followed them up with an average of 8.2 years to assess mortality from general causes and from CAD [51]. As in a previous study, the presence of OSA was linked to a greater mortality from CAD. Young et al. analyzed data from the Wisconsin Sleep Cohort study to assess the impact of untreated OSA on mortality from general and cardiovascular causes [52]. They found that untreated OSA was associated with a greater all-cause and cardiovascular mortality independently of age, gender and body mass index. Gottlieb et al. recruited 4422 patients with OSA and no baseline cardiovascular disease to study the influence of OSA on the occurrence of cardiovascular disease, with a median follow-up of 8.7 years [53]. After performing multivariate regression analysis, they discovered that men with severe OSA aged<70 years had a greater incidence of new onset CAD compared to those with milder OSA.

Mooe et al. enrolled 142 patients with known CAD undergoing coronary angiography and 50 controls without overt cardiac disease, and screened them with portable sleep monitoring for the presence of sleep-disordered breathing [54]. They found that patients with CAD displayed a greater prevalence of sleep-disordered breathing of 39% compared to 22% among controls. It is interesting to note that patients with OSA may have a family history of premature CAD and CAD-related mortality [55]. Furthermore, patients with OSA and concomitant CAD may be more prone towards nocturnal acute coronary events compared to subjects without OSA [56].

Yumino et al. recruited 89 patients with acute coronary ischemia who had undergone PCI and screened them with polysomnography for the presence of OSA [57]. They found that the presence of OSA was independently associated with greater cardiovascular morbidity and mortality and higher restenosis rates. Cassar et al. showed that treated OSA patients had lower mortality rates from cardiac causes after PCI [58].

Therefore, OSA is common in patients with CAD and may independently contribute to the occurrence of new onset cardiovascular events. Successful OSA treatment may reduce mortality in patients with concomitant CAD.

Epidemiology of OSA in patients undergoing cardiac surgery

From a theoretical point of view, it is very likely that OSA is common in patients undergoing cardiac surgery, particularly CABG. This is based on the fact that OSA is prevalent among patients with CAD and may complicate its course. Thus, OSA may in part contribute to the need for cardiac surgery. However, only a few studies have directly assessed the prevalence of OSA among patients undergoing cardiac surgery.

Bhamma et al. studied 20 patients with OSA undergoing CABG and the results were matched to 65 controls [59]. Patients with OSA were more likely to have a longer stay in the intensive care unit, require tracheostomy and have prolonged ventilation after surgery. These findings were supported by a recently performed meta-analysis by Kaw et al., who showed that patients with OSA had higher rates of post-operative respiratory failure, post-operative cardiac events and transfers to the intensive care unit [60].

Unosawa et al. recruited 89 patients undergoing cardiac surgery and screened them with portable sleep monitoring and 24-hour Holter electrocardiography monitoring [61]. Sleep-disordered breathing was present in 29% of the patients, which was higher than that seen in the general population [1]. Sleep-disordered breathing was independently associated with a greater heart rate and nighttime ventricular premature contractions. An even higher prevalence of OSA among patients undergoing CABG was shown by Danzi-Soares et al. [62]. OSA was diagnosed among 87% of the patients with full night polysomography.

Therefore, OSA is quite common in this group of surgical patients. Healthcare practitioners should routinely screen for the presence of OSA to reduce post-operative morbidity and mortality in this population.

OSA and neuronal damage

Excessive daytime sleepiness, unrefreshing sleep and daytime fatigue are common findings in patients with OSA. These symptoms and decreased daytime vigilance are believed to underlie a greater risk for car accidents in patients with OSA [63]. It is essential to mention that OSA treatment reduces the risk of motor vehicle accidents via resolution of daytime symptoms and fatigue. In this section, we will briefly discuss the data from key studies on the association between OSA and cognitive dysfunction.

Yaffe et al. showed that the presence of OSA was associated with an increased risk for developing cognitive deficits and overt dementia [64]. Oxygen desaturation index and a high rate of apneas or hypopneas per hour of sleep, but not sleep duration or fragmentation, were related to an increased risk of cognitive deficiency.

Aylon et al. showed that patients with OSA had reduced ability for immediate word recall and prolonged reaction time compared with healthy controls, which might be explained by the deleterious effects of OSA on brain cortical function in aging individuals [65]. Kheirandish-Gozal et al. observed that children with OSA had lower immediate and overnight recall performances than controls [66].

However, Quan et al. were unable to find any association between OSA and cognitive impairment after adjustment for gender, ethnic background and level of education [67]. On the other hand, they were able to show that patients with OSA and severe nocturnal oxygen desaturation had worse neurocognitive performance compared with subjects with minimal or absent nocturnal desaturation. It is relevant to note that the studied subjects had minimal daytime symptoms and were enrolled prior to initiation of continuous positive pressure (CPAP) therapy, a standard treatment for OSA.

The importance of early OSA diagnosis and treatment was highlighted in studies by Vernet et al. [68] and Lau et al. [69]. These groups showed that patients with treated OSA and residual daytime symptoms had decreased stage 3 sleep, more nocturnal periodic limb movements, and longer daytime naps.

Several studies provided the anatomical basis for OSA-related cognitive deficiency. Ayalon et al. showed a relationship between OSA and decreased brain activation in multiple cortical areas [70]. They found that increased arousal index, but not OSA severity per se, was associated with abnormal neurocognitive performance.

Macey et al. found that patients with OSA had decreased fractional anisotropy of white matter in multiple areas of the brain as assessed by MRI, which is consistent with neuronal stress [71].

Yaouhi et al. discovered that patients with OSA had brain volume loss and abnormal brain metabolism in cortical areas, as well as in the thalamus and hippocampus [72]. Such brain changes might precede the development of clinically significant neurobehavioral dysfunction in OSA patients. Torelli et al. found that the brain parenchymal fraction and right hippocampal area were smaller in patients with OSA compared to controls [73].

Castronovo et al. noted that untreated patients with OSA who had minimal daytime symptoms had increased activation in the left frontal cortex and hippocampus [74]. Initiation of CPAP therapy resulted in a decrease in neuronal activation in the aforementioned brain areas. They speculated that increased brain activation might be a compensatory mechanism for overcoming OSA-mediated neuronal injury. The same group later showed that patients with OSA had reduced brain parenchymal volume in the left hippocampus and cortical areas, as assessed by brain MRI [75]. CPAP therapy led to an improvement of both clinical and brain imaging parameters, supporting a role for OSA in the development of central neuronal injury.

OSA and delirium after non-cardiac surgery

Several case reports have been published in the medical literature linking OSA to delirium and psychotic diseases. Berritini published a case of acute paranoid psychosis in a patient who was found to have sleep apnea during hospitalization. However, this patient had a prior psychiatric history, which, in addition to other limitations of case reports, makes any speculations on this association difficult [76]. Martin and Lefebvre presented a case report on a boy with mental retardation and psychosis [77]. They reported that surgical correction of OSA resolved his psychotic syndrome. Nevertheless, as in the previous case, a psychiatric comorbidity places extensive limitations on their conclusion.

Whtiney and Gannon published the case of a middle-aged male who developed acute delirium [78]. The authors proposed that OSA was a probable cause of the patient’s delirium because OSA treatment was shown to resolve the delirium. However, alcohol withdrawal syndrome could not be excluded in this case report, nor could the presence of alternative diagnoses such as obesity hypoventilation syndrome.

Lee published a case of recurrent delirium in a morbidly obese patient who exhibited polysomnographic evidence of sleep apnea [79]. Munoz et al. and Lombardi et al. independently published reports linking severe OSA to the occurrence of acute delirium [80, 81]. OSA treatment was shown to be successful in the resolution of delirium in both studies.

It is relevant to note that case reports cannot exclude alternative precipitating factors; thus, it is difficult to draw a definitive conclusion on the relationship between OSA and delirium. Nevertheless, case reports may highlight possible associations between the diseases and stimulate further research.

A retrospective study published in 2001 by Gupta et al. examined the effect of pre-existing OSA on several postoperative complications, including delirium, in 101 patients with OSA and 101 matched controls undergoing knee or hip replacement surgery [82]. Patients with OSA had higher rates of ICU transfer and longer hospital stays, both of which are surrogate markers of postoperative complications. The incidence rate of delirium in OSA patients was almost twice that seen in patients without OSA, but the difference was not statistically significant ($p=0.07$). Since delirium was identified by a chart review, it may have been under-recognized in this study. A systematic screening tool, prospective design, and larger sample might yield a more accurate representation of delirium in the setting of OSA.

Recently, Flink et al. demonstrated an association between OSA and post-operative delirium [83]. This study of 106 elderly patients undergoing elective knee replacement surgery was the first prospective study to identify pre-existing obstructive sleep apnea as an independent predictive risk factor for postoperative delirium (OR 4.3, $p=0.0123$). In this study, 8 (53%) out of 15 patients with OSA experienced delirium versus 19 (20.9%) out of 91 without OSA. Given that the sample size in this study was relatively small and that assessment of sleep apnea was not systematically carried out in all subjects, further research specific to the effect of OSA on delirium is warranted. Since OSA is frequently undiagnosed, there may have been subjects who were categorized as not having OSA when, in fact, they did. These false negatives would have the effect of minimizing the observed effect of OSA on delirium, so the effect of OSA on delirium may be even greater than suggested.

Thus, there is evidence from case reports, one retrospective study and one prospective study that OSA may be associated with an increased risk of delirium. Based on the material reviewed above, we hypothesize that this relationship may be mediated by tissue hypoxia, systemic inflammation, oxidative stress, and the vascular and metabolic abnormalities so commonly observed in OSA.

Implications of the hypothesis

Prospective studies should assess whether treatment of OSA reduce the incidence of the delirium after cardiac surgery. If the hypothesis is found to be correct we will have another target for the prevention of post-operative delirium and would gain an additional knowledge on the delirium pathogenesis.

Conclusion

OSA is a common medical condition and independent risk factor for cardiovascular disease, including CAD. Patients undergoing cardiac surgery and CABG in particular display a greater prevalence of OSA. Research in patients undergoing non-cardiac surgery has shown that OSA is an independent risk factor for the occurrence of post-operative delirium. This association may be explained by a myriad of fundamental biochemical alterations associated with OSA, leading to neurological damage and greater susceptibility to delirium. Future research should address whether OSA is a risk factor for the occurrence of delirium after cardiac surgery and whether OSA management reduces the burden of post-operative delirium in this population.

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Table 1

DSM-IV Criteria for Delirium

A. Disturbance of consciousness with reduced ability to focus, sustain, or shift attention
B. A change in cognition (memory, language, or orientation) or the development of a perceptual disturbance not better accounted for by dementia
C. Disturbance develops over a short period of time and tends to fluctuate during the course of the day
D. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition

Table 2

Common Risk Factors for Delirium

Age>65 years
Male gender
Open cardiac surgery
Major medical comorbidity (infection, anemia, myocardial infarction etc.)
Alcohol withdrawal
Underlying neurological disease (stroke, tumor etc.) and cognitive dysfunction
Sleep deprivation
Iatrogenic (medications, urinary catheterization, dehydration etc.)
Metabolic and nutritional abnormalities
Pain
Fractures (Hip)
Depression and psychological stress