Association between Obstructive Sleep Apnea and Atrial Fibrillation and Delirium after Cardiac Surgery. Sub-analysis of DECADE Trial

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Trial Registration: The Ancillary Effects of Dexmedetomidine Sedation after Cardiac Surgery (DECADE) trial (NCT02004613 and IRB IRB# 12–1379) is the underlying trials and IRB (IRB #19-1649) the current sub-study.

Declaration of Interest: None

Author contributions:

Eva Rivas: This author helped conceive and design the study, analyze and interpret the data, write and critically revise the manuscript.
Peter Shehata: This author helped analyze and interpret the data, write and critically revise the manuscript.
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Highlights:

- Question: Is preoperative obstructive sleep apnea associated with atrial fibrillation and delirium after cardiac surgery?
- Findings: Obstructive sleep apnea was not associated with atrial fibrillation and delirium after cardiac surgery.
- Meaning: Different mechanisms might contribute to the development of atrial fibrillation and delirium after cardiac surgery.

Abstract

Background: Atrial fibrillation and delirium are common complications after cardiac surgery. Both are associated with increased Intensive Care Unit (ICU) and hospital length of stay, functional decline, 30-day mortality and increase in health care costs. Obstructive Sleep Apnea (OSA) induces deleterious effects in the cardiovascular and nervous systems. We hypothesized that adult patients with preoperative OSA have a higher incidence of postoperative atrial fibrillation and delirium than patients without OSA, after cardiac surgery.

Methods: Sub-analysis of the DECADE trial at Cleveland Clinic hospitals. Our exposure was OSA, defined by STOP-BANG questionnaire score higher than 5 and/or a preoperative diagnosis of OSA. The primary outcome was atrial fibrillation, defined by clinician diagnosis or documented arrhythmia. The secondary outcome was delirium assessed twice during the initial five postoperative days using the Confusion Assessment Method for ICU. We assessed the association between OSA and atrial fibrillation and delirium using a logistic regression model adjusted for confounders using inverse probability of treatment weighting.

Results: 590 patients were included in the final analysis. 133 were diagnosed with OSA and 457 had no OSA with a satisfactory balance between groups with an absolute standardized difference <0.10 for most variables. The incidence of atrial fibrillation was 37% (n=49) in the patients with OSA and 33% (n=150) in the non-OSA. OSA was not associated with atrial fibrillation with an estimated odds ratio of 1.22 (95% CI: 0.75,1.99;p=0.416). The incidence of delirium was 17% (n=22) in patients with OSA and 15% (n=67) in the non-OSA. OSA was not associated with delirium with an estimated odds ratio of 0.93 (95% CI: 0.51,1.69;p=0.800).

Conclusion: In adult patients having cardiac surgery, OSA is not associated with a higher incidence of postoperative atrial fibrillation and delirium. These

results suggest different prominent factors rather than OSA affect the incidence of these postoperative outcomes.

INTRODUCTION

Atrial fibrillation and delirium are common complications after cardiac surgery[1–5] and are associated with increased intensive care unit and hospital length of stay, functional decline, 30-day mortality, and increase in health care costs.[6–13]. Understanding the contributing factors is crucial to prevent these important postoperative complications.

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by upper airway collapse resulting in recurrent episodes of hypoxemia and sleep disturbances. OSA is highly prevalent in patients undergoing cardiac surgery.[14,15] OSA induces deleterious physiological effects in the cardiovascular system leading to autonomic dysfunction and atrial remodeling.[16,17] The repeated episodes of hypoxemia and hypercarbia might lead to autonomic dysfunction and an inflammatory response.[16,17] Moreover, changes in intrathoracic pressure may contribute to deleterious atrial remodeling, predisposing to atrial fibrillation.[18,19]

In the general population, there is evidence that OSA is associated with higher incidence of atrial fibrillation. However, this has not been well established in patients having cardiac surgery. Although some studies have shown association between OSA and postoperative atrial fibrillation,[20–24] others found no such association when adjusting for confounders. [25–28]

In addition, intermittent hypoxia disrupts the brain's microenvironment and synaptic plasticity, and might be associated with poor postoperative cognitive outcomes after cardiac surgery.[29,30] Recently, several prospective studies found that sleep-disordered breathing including OSA might serve as an independent risk factor for postoperative delirium, but these observations are also inconclusive.[29–32] The main limitations of the previous studies are their small sample size, failure to adjust for potential confounding variables, and the difficulty in accurately diagnosing postoperative atrial fibrillation and delirium.

Therefore, we aimed to evaluate the association between OSA and postoperative atrial fibrillation and delirium after cardiac surgery in patients who participated in the *Ancillary effects of dexmedetomidine sedation after cardiac surgery* (DECADE) trial.[33] In this large clinical trial, there was good characterization of OSA using the well validated STOP-BANG score, as well as accurate diagnosis of postoperative atrial fibrillation and delirium. We specifically tested the primary hypothesis that preoperative OSA is associated with higher incidence of atrial fibrillation after cardiac surgery. Secondarily, we tested the hypothesis that preoperative OSA is associated with a higher incidence of delirium after cardiac surgery.

METHODS

Study design

This is a sub-analysis of a multicenter, randomized, double-blind placebo controlled clinical trial, DECADE trial (Clinical Trials NCT 02004613). Briefly, the underlying trial tested whether the use of dexmedetomidine during and after cardiac surgery utilizing cardiopulmonary bypass affects the incidence of postoperative atrial fibrillation and delirium. Eight hundred patients were randomized to dexmedetomidine or placebo infusion before incision up to 24 hours after surgery. The main result showed dexmedetomidine did not decrease the incidence of postoperative atrial fibrillation or delirium after cardiac surgery.[33]

In this sub-analysis, we aimed to evaluate the association between obstructive sleep apnea and postoperative atrial fibrillation and delirium. The current study was designed before the main trial (IRB# 12–1379) analysis was conducted and was also approved by the Cleveland Clinic Institutional Review Board, with waived individual consent (Cleveland Clinic IRB #19-1649).

Study population

We included adult inpatients enrolled in the DECADE trial at the Cleveland Clinic hospitals (main campus, Hillcrest, and Fairview hospitals) who were 18-85 years old and had cardiac surgery from January 2012 through November 2018. Patients were excluded if they had: sick-sinus or Wolff-Parkinson-White syndromes; atrioventricular block; hypersensitivity or known allergy to dexmedetomidine; hepatic disease; atrial fibrillation within 30 days; a permanent pacemaker; amiodarone or dexmedetomidine use within 30 days; ejection fraction <30% or severe heart failure; myocardial infarction within 7 days; body-mass index ≥40 kg/m²; or took clonidine within 48 hours. We also excluded patients with missing data.

Measurements

The exposure, OSA screening, was defined as a STOP-BANG questionnaire score higher than 5 evaluated during the preoperative assessment visit and/or a preoperative diagnosis of OSA (ICD9 codes).[34]

The primary outcome was atrial fibrillation, defined as the presence of any of the following in a patient from the time of ICU admission until the earlier of hospital discharge or five postoperative days. While in ICU, patients' electrocardiogram was continuously monitored. After ICU discharge, patients had twelve-lead electrocardiograms twice daily. Diagnoses of atrial fibrillation were made by clinicians who were masked to original trial's group allocation based on: 1) Documented arrhythmia lasting at least five minutes, or 2) Presence of arrhythmia on ECGs in intermittently monitored patients.

The secondary outcome was delirium, which was prospectively collected by formally trained masked research personnel twice daily in the morning and evening, during the initial five postoperative days. Delirium was assessed using first the Richmond Agitation and Sedation Scale (RASS) to evaluate the level of possible sedation, and then the Confusion Assessment Method for the

ICU (CAM-ICU) for diagnosing delirium. Nurses also assessed delirium with CAM-ICU daily and described patients' mental status in their notes. Patients were considered to have had delirium if one or more CAM-ICU assessments by investigators or nurses were positive, or if there was a clear indication of delirium in written nursing evaluations.[33]

Statistical methods

We aimed to assess the association between OSA and atrial fibrillation (primary outcome) and delirium (secondary outcome). We controlled for observed potential confounding factors shown in **Table 1** using inverse probability of treatment weighting (IPTW). First, we estimated propensity scores using a logistic regression model with OSA as the outcome, and demographic and clinical characteristics (**Table 1**) as the predictors. IPTW weights were then calculated from the propensity score. For each patient, the weight was the inverse of the probability of receiving the treatment that they received.

Balance on important baseline clinical characteristics and demographic variables included in **Table 1** was assessed using absolute standardized difference (ASD) before and after weighting. ASD is roughly defined as the absolute difference between means or proportions divided by the pooled standard deviation. Imbalance was defined as ASD >0.10.

After assessing balance, weighted logistic regression models were fit to estimate the odd ratio (OR) and the associated 95% CI for both outcomes. In these outcome regression models, we also included as covariates any variables on which we failed to achieve balance (*i.e.*, ASD > 0.10) after weighting.

In the primary analysis, one criterion for defining OSA was a STOP-BANG risk score greater than 5 as a proxy for OSA. The STOP-BANG score consists of multiple OSA risk factors such as body mass index (BMI), hypertension, age,

etc. Some of these are also risk factors for atrial fibrillation and were thus adjusted for in the primary analyses. This “double” adjustment (e.g., adjusting for age both in the primary analysis and as part of the STOP-BANG risk score) makes the interpretation of the primary analysis more challenging, and potentially introduces bias. Thus, we conducted a post-hoc sensitivity analysis in which we used only ICD-9 codes to define OSA and evaluated its association with atrial fibrillation. All analyses were carried out using R 4.2.0.

Sample Size

We used a convenience sample, limited by the underlying trial. Initially, we anticipated to have 90% power at the 0.05 significance level to detect an odds ratio of 1.6 between OSA and atrial fibrillation, assuming a baseline atrial fibrillation incidence of 35%, and total sample size of 794 patients. However, our final sample size was lower than planned because data on OSA was available only for the DECADE patients enrolled at the Cleveland Clinic sites (**Figure 1**). Thus, using our actual study sample size of 590 patients and OSA incidence of 23%, we had 90% power at the 0.05 significance level to detect an odds ratio of 1.92 between OSA and atrial fibrillation.

RESULTS

Seven hundred and ninety-four patients from the DECADE trial were eligible for this sub-study. After excluding patients who had missing data, 590 patients were included in the final analysis (**Figure 1).** Of these, 133 (23%) were diagnosed with OSA and 457 (77%) had no OSA. Demographic and clinical characteristics are shown in **Table 1**. After applying propensity score weighting, we achieved satisfactory balance (defined as ASD < 0.10) between groups for most variables except for gender, BMI, hypertension, dyslipidemia, and calcium channel blocker use. (**Table 1 and figure 2**).

The incidence of atrial fibrillation was 37% (n=49) in patients with OSA and 33% (n=150) in the non-OSA patients. The unadjusted OR was 1.19 [95% CI: 0.79, 1.78]. In the analysis using IPTW, we did not find evidence for an association between OSA and atrial fibrillation after adjusting for imbalanced confounding variables, with an estimated odds ratio of 1.22 (95% CI: 0.75, 1.99, p = 0.416). Although the point estimate suggested a higher rate of postoperative atrial fibrillation in patients with OSA, the 95% confidence interval was wide, ranging from 0.75 to 1.99 (**Figure 3**).

The incidence of delirium was 17% (n=22) in patients with OSA and 15% (n=67) in the non-OSA patients. The unadjusted OR was estimated to be 1.15 [95% CI: 0.67, 1.93]. In the adjusted analysis, we did not find evidence of an association between OSA and delirium, with an estimated adjusted odds ratio of 0.93 (95% CI: 0.51, 1.69; p=0.800). Although there was a lower rate of postoperative delirium in patients with OSA, the 95% confidence interval was wide, ranging from 0.51 to 1.69 (**Figure 3**).

The post-hoc sensitivity analysis included 586 patients. Ninety patients (15%) were diagnosed with OSA using the new criteria (i.e., only ICD-9 codes).

There was no evidence for an association between OSA and atrial fibrillation, with estimated adjusted odds ratio of 1.27 (95% CI: 0.73, 2.21; p = 0.394), neither with delirium with estimated odds ratio of 1.24 (95% CI: 0.64 – 2.43; p = 0.517).

DISCUSSION

We did not find evidence of an association between OSA and the incidence of postoperative atrial fibrillation or delirium after adult cardiac surgery. Although there are plausible mechanisms for an association between OSA and postoperative atrial fibrillation, only a few studies aimed to evaluate the relation. Our study adds to the literature describing the lack of association within a real-world prospectively followed cohort.

The lack of association between OSA and atrial fibrillation after cardiac surgery has been previously reported in a small prospective observational study of 190 patients with OSA confirmed by polysomnography. Similar to our results, postoperative atrial fibrillation was not associated with OSA after adjustment for confounders.[28] However, our results are in contrast to several other retrospective and observational studies [20–24], along with a meta-analysis of 7 studies (876 patients) that showed OSA patients, compared to patients without OSA, had 33.3% higher odds of cardiovascular or cerebrovascular events, and a 2-fold higher risk to develop postoperative atrial fibrillation (OR 1.94; 95%CI: 1.13, 3.33; P =0.02) after cardiac surgery.[15] Notwithstanding, it is important to note, that this positive result was driven by one single study,[22] while the other studies were negative or inconclusive (low sample and wide confident interval). Moreover, although the prospective observational studies had a good characterization of OSA with polysomnography[20,21] or validated questionnaires,[22] they included a relatively low number of patients, making the results fragile.[35] Finally, despite large sample sizes, the retrospective studies had a poor characterization of the exposure, since OSA is an often-undiagnosed disease, as well as the end outcome, because new onset of atrial fibrillation may be missed if only evaluated using diagnosis codes.[23-27] Our results are drawn from a post-hoc analysis of a prospective trial whose primary outcome was atrial fibrillation, actively collected by well-trained researchers. Moreover, OSA was defined as

a score higher than 5 in the STOP-BANG questionnaire during the preoperative assessment, which is highly correlated with moderate or severe OSA.[34]

There is even less evidence regarding the association between OSA and postoperative delirium after cardiac surgery. There are only 2 small prospective studies with controversial results.[29,32] While Roggenback et al., in a prospective cohort study of 92 patients demonstrated that OSA was associated with a nearly 6-fold increased risk of postoperative delirium;[32] the results *by* Tafelmeir et al. support our findings and showed no differences in the incidence of delirium between OSA and non-OSA patients after cardiac surgery.[29] Both studies used satisfactory definitions of the exposure and outcome, but the sample size was small (less than 140 patients) in both studies making results once again relatively fragile.[35] One plausible explanation is that the administration of supplemental oxygen during the intraoperative and postoperative period in the ICU affected the effect of this intermittent hypoxemia and reduced its deleterious effects.[36]

Our strengths are the excellent characterization of the primary and secondary outcomes, although it is important to notice that the underlying trial was originally underpowered for delirium. The main limitation of our study is the use of STOP-BANG and ICD-9 codes to define OSA, rather than a definitive test (e.g., poly-somnography). Nonetheless, STOP-BANG questionnaire is an extended preoperative screening tool to assess the probability of having OSA.[34,37] A STOP-BANG score higher than 5 has been associated with high risk of moderate or severe OSA. Although DECADE trial was a multicentric study, we restricted our analysis to Cleveland Clinic Hospitals achieving a satisfactory balance between our study groups. Finally, our study was only powered to find an OR of 1.92 meaning that we don't have power to assess weaker associations. Additionally, our study groups were well-balanced with good adjustment of confounders.

Conclusion

In summary, in adult patients having cardiac surgery, we did not find evidence of an association between OSA and the incidence of postoperative atrial fibrillation and delirium. This suggests different prominent factors contributing to these postoperative outcomes.

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Figure 1. Patient flow chart. We included adult inpatients enrolled in the DECADE trial at the Cleveland Clinic hospitals. We excluded patients with OSA missing data (n=192), as well as patients with ASA Status 2 (n=7) since all were allocated in the non-OSA group. Finally, we excluded 5 patients with "outlier" BMI defined as <10 or >70 kg/m^2 since DECADE excluded patients with BMI>40 kg/m^2 and a BMI<10 kg/m^2 likely indicates error in recording data.

Figure 2. Balance Plot. Absolute standardized difference (ASD) between OSA and non-OSA patients across different confounders, before and after inverse probability of treatment weighting. ASD > 0.10 (dashed line) indicates imbalance.

Figure 3. Forest plot. Association of obstructive sleep apnea with atrial fibrillation and delirium, after adjusting for confounding using inverse probability of treatment weighting.