

BMJ Open Postoperative vascular complications in unrecognised Obstructive Sleep apnoea (POSA) study protocol: an observational cohort study in moderate-to-high risk patients undergoing non-cardiac surgery

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ABSTRACT

Introduction: Emerging epidemiological data suggest that obstructive sleep apnoea (OSA) is common in the general surgical population. Unfortunately, the majority of these patients are unrecognised and untreated at the time of surgery. There is substantial biological rationale to indicate that patients with unrecognised OSA are at a higher risk of postoperative vascular events. However, the extent of this morbidity is currently unknown. We have initiated the postoperative vascular complications in the unrecognised obstructive sleep apnoea (POSA) study to determine the associations between OSA, nocturnal hypoxia and major postoperative vascular events in 1200 moderate-to-high risk patients undergoing major non-cardiac surgery.

Methods and analysis: The POSA study is an international prospective observational cohort study. Using a type 3 portable sleep monitoring device and ambulatory oximetry, we will quantify the severity of OSA. The primary outcome is a composite of vascular death, myocardial infarction; non-fatal cardiac arrest; stroke; pulmonary embolism; congestive heart failure and new arrhythmia within 30 days of surgery. As of November 2013, we have recruited over 700 patients from nine centres in six countries. The mean age is 68 years, the mean body mass index is 27 kg/m² and 55% of patients are men. 27.9% of patients have known coronary artery disease, over 76% have diabetes. The majority of patients underwent orthopaedic surgery (28%) and colorectal resection (18.5%).

Ethics and dissemination: The POSA study has received ethics approval from all study sites before patient recruitment. Informed consent will be obtained from all patients. The POSA study will determine the risk of unrecognised OSA in major non-cardiac surgery. We will publish these findings in peer-reviewed journals.

Trial Registration: ClinicalTrials.gov Identifier: NCT01494181

Obstructive sleep apnoea (OSA) is the most common sleep disordered breathing affecting 17% of men and 9% of women aged between 50 and 70 years.¹ In the general population, unrecognised, and therefore untreated, OSA is associated with higher risks of vascular death, myocardial infarction, stroke, heart failure and arrhythmia.^{2–7} This is commonly attributed to the frequent episodes of nocturnal apnoea and hypopnea that lead to oxyhaemoglobin desaturation and surges of sympathetic activity.⁸ In addition, OSA can increase systemic inflammation, endothelial dysfunction and platelet aggregation,^{9 10} which may also contribute to adverse vascular events.

General *anaesthetics* and potent opioid analgesics are powerful respiratory depressants. They reduce pharyngeal muscle tone and depress ventilatory response to *hypoxaemia* and hypercapnia.¹¹ It is therefore not surprising that OSA might aggravate postoperative adverse cardiac events. Few studies have reported the impact of OSA on cardiac morbidity after surgery. Earlier prospective cohort studies were small trials with limited number of events.¹² Subsequent analyses of several large databases, however, showed mixed results. Depending on the outcome definition, the risk of postoperative morbidity and mortality was either increased,^{13 14} unchanged¹⁵ or even paradoxically reduced in patients who were known to have or at risk for OSA.¹⁶ Interpretation of these findings is difficult because it is not clear what percentage of patients labelled as non-OSA actually had undiagnosed disease. In this regard, over 50% of patients with moderate-to-severe OSA were undiagnosed at the time of

surgery,^{17 18} and hence the results could have been biased because of group misclassification. In addition, perioperative treatment, such as non-invasive ventilation, may have also obscured the effect of OSA on the perioperative outcome.

Taken together, there is currently a lack of data documenting the extent of postoperative vascular morbidity in patients with unrecognised OSA. Therefore, a prospective observational study that accurately evaluates the presence and severity of OSA in a large group of patients, in whom a substantial number of adverse vascular events is expected to occur, will be required to establish the associations between OSA and perioperative risk. These data are important to facilitate informed decision-making about the risks of surgery and to guide perioperative management in patients with OSA. Interestingly, a clinical study to determine the associations between OSA and perioperative risk has been rated as one of the high priority areas in OSA research.^{19 20}

METHODS

Study design

We have initiated the *postoperative complications in the unrecognised obstructive sleep apnoea (POSA) study*—an international prospective, observational study in 1200 patients with known, or at risk of, atherosclerotic disease undergoing major non-cardiac surgery to determine the association between OSA and postoperative vascular events. We hypothesised that patients with unrecognised OSA had a higher rate of postoperative vascular events than those who did not.

Study population

Institutional research ethics committee approval was obtained from each of the participating centres. We approach patients undergoing major elective non-cardiac surgery for consideration of the study, and we recruit patients who are at moderate-to-high risk for postoperative vascular events. Box 1 shows the inclusion and exclusion criteria of the study. We excluded patients undergoing tonsillectomy, septoplasty, uvuloplasty, pharyngoplasty, tracheostomy or prolonged (>2 days) mechanical ventilation of the lungs because these interventions are likely to prevent or at least modify the severity of OSA.

Overnight portable sleep monitoring and pulse oximetry

Research staff in each participating site identifies eligible patients from the daily attendance list in the preoperative clinic and the routine surgical lists for the next day. Following patient consent, all patients undergo overnight recording in the hospital surgical ward, the night before surgery, using a type 3 portable sleep monitoring device (ApneaLink, ResMed, San Diego, California, USA). Patients who are admitted on the day of surgery will have sleep monitoring performed at home in the week prior

Box 1 Inclusion and exclusion criteria of the POSA study

Patients are eligible for the study if they are:

1. Adult males and females.
2. Age ≥ 45 years.
3. Undergoing major elective non-cardiac surgery that is expected to require a hospital stay of more than three nights.
4. At increased risk for postoperative vascular events, defined as having at least one of the following risk factors:
 - A. High-risk surgery (intraoperative, major orthopaedic or vascular surgery);
 - B. History of coronary artery disease;
 - C. History of congestive heart failure;
 - D. History of stroke or transient ischaemic attack;
 - E. Diabetes requiring insulin therapy;
 - F. Serum creatinine $>175 \mu\text{mol/L}$.

Patients will be excluded if:

1. They have a previous diagnosis of obstructive sleep apnoea or any sleep-related breathing disorder.
2. They are unwilling or physically unavailable for portable sleep monitoring within the week prior to surgery.
3. Their surgery include tonsillectomy, septoplasty, uvuloplasty, pharyngoplasty, tracheostomy or prolonged (>2 days) mechanical ventilation of the lungs is anticipated after surgery.

to surgery. At bedtime, research personnel attach the device to the patient. ApneaLink contains a nasal pressure transducer to measure flow limitation and snoring. It is battery powered and records on a 16-bit signal processor, with a sampling rate of 100 Hz. The preset internal memory is 15 MB, and thus allows continuous recording for 10 h. In addition, we monitor oxyhaemoglobin saturation (SpO_2) using a high-resolution pulse oximeter wristwatch (PULSOX-300i, Konica Minolta Sensing, Inc, Osaka, Japan). The sampling frequency is set as 1 Hz with an averaging duration of 3 s. The resolution of the pulse oximetry is 0.1%. All patients breathe room air during preoperative recording.

Research staff retrieves the devices the following morning and processes the polysomnography (PSG) and oximetry data using the ApneaLink and Profox (Profox Associates, Escondido, California, USA) software, respectively. Both devices have been found to be highly sensitive and specific in determining the apnoea hypopnoea index (AHI) when compared with in-laboratory or portable PSG in patients with moderate-to-severe OSA.^{21–25}

Apnoea is defined as a decrease in airflow $\geq 90\%$ of baseline for >10 s and hypopnoea as a reduction of airflow of $\geq 50\%$ of baseline for >10 s and was associated with $\geq 3\%$ decrease in SpO_2 . The AHI is determined based on the recording time (≥ 4 h), and is the average number of apnoea and hypopnoea episodes per hour. We also calculate the oxygen desaturation index (ODI) which is defined as the average number per hour of episodes of desaturation $\geq 4\%$ from baseline and >10 s.²⁵ OSA is diagnosed when AHI is ≥ 5 , moderate OSA is defined as AHI of 15–30 and severe OSA is when AHI >30 .²⁶

Perioperative care

Before surgery, research staff interviews, examines and reviews the hospital charts of all patients to obtain information on patient characteristics. Specifically, we record data that are potential risk predictors for major perioperative vascular events according to a recently developed VISION risk model.²⁷ Site investigators review and approve the data collected before submission to the database. In addition, we assess the patients' risk for OSA using the STOP-Bang screening tool.²⁸

Anaesthesia and surgery are performed according to routine standard of care at each site. In order to reflect usual clinical practice and maximise generalisability, we do not control the use of postoperative analgesia, fluid management and other aspects of patient care. However, drugs used during anaesthesia, postoperative analgesia, haemodynamic data and supplemental oxygen, if required, are recorded.

Patient follow-up

During their stay in the hospital, patients are followed daily, and outcomes are recorded until discharge. After surgery, ECG and venous blood samples are collected for the measurement of plasma cardiac troponin concentrations at 6–12 h and daily during the first 3 days. Additional tests, such as echocardiograms and lung scans, are ordered if clinically indicated. During the first three nights after surgery, we monitor and record SpO₂ using the Pulsox 300i device. Patients discharged home are contacted by phone at 30 days to ascertain whether they have experienced any adverse outcomes. If detected, we will arrange further testing and contact their hospitals and physicians-in-charge to acquire the appropriate documentation.

Study outcomes

The primary endpoint is postoperative vascular events at 30 days after surgery. It is a composite of vascular death, myocardial infarction, myocardial injury after non-cardiac surgery, non-fatal cardiac arrest, revascularisation procedure, pulmonary embolism, deep venous thrombosis, new atrial fibrillation, stroke and congestive heart failure.

Secondary endpoints include the following: (1) tracheal intubation and mechanical ventilation (including use of continuous positive airway pressure ventilation) after surgery; (2) unplanned admission to the intensive care unit; (3) duration of stay in hospital and intensive care unit; (4) pneumonia and (5) infection and/or sepsis. Individual outcome definitions are listed in table 1.

Outcome adjudication

All outcomes are verified by a team of three experienced perioperative clinicians who are blinded to the AHI and STOP-Bang data collected. Only adjudicated outcomes are used for statistical analysis.

Bias control and ethical considerations

Patients and research staff who collect outcome data will be blinded to the AHI findings, STOP-Bang questionnaire and oximetry readings. Patients, attending surgeons and physicians will be given a summary report of their portable sleep study and STOP-Bang questionnaire 30 days after surgery. During this period, all patients will receive local standard of care and monitoring. Patients with abnormal AHI results will be referred to their local sleep clinic for further treatment after the conclusion of the study. This arrangement is considered appropriate and has been approved by the ethics committee in the POSA study.

Statistical considerations

We will report the proportion of patients with OSA based on their AHI findings and separately according to the severity. We will conduct a logistic regression model to examine the independent association between OSA and postoperative vascular events. The dependent variable is postoperative vascular complication within 30 days of surgery, and the independent variables are the ethnicity the VISION risk model score (a composite score of age ≥ 75 years, history of coronary artery disease, stroke, chronic obstructive pulmonary disease, peripheral vascular disease, undergoing cancer surgery, urgent/emergent surgery and neurosurgery)^{27 29} and the presence of OSA (according to its severity with non-OSA as reference). In addition, we test whether a clinical screening tool, such as STOP-Bang questionnaire, could be used to predict postoperative vascular outcome. In this regression model, we replace AHI values with STOP-Bang risk score. Reliability will be determined by bootstrapping. The effect of nocturnal hypoxia (expressed as ODI) on the timing to postoperative vascular events will be determined using the Cox proportional hazard function model.

Sample size

The sample size is estimated for the logistic model, because it requires the largest number of patients to ensure model stability. Previous simulation study has demonstrated that at least 12 events per independent variable are required to produce stable estimates in logistic regression.³⁰ Based on the findings in the VISION study,^{27 29} we expect a 6% event rate for postoperative vascular event in this study. Hence, at least 800 patients will be required to ensure a stable regression model. We propose to study 1200 patients to account for a Hawthorne effect where event rate may be decreased by as much as a third from 6% to 4%.

Study organisation and funding

The POSA study is coordinated by the Department of Anaesthesia and Intensive Care at the Chinese University of Hong Kong. Site investigators of the trial are listed in the online supplementary appendix. ResMed has supplied the ApneaLink devices and

Table 1 Outcome definitions

Outcome	Definition
Vascular death	Death attributable to a vascular cause including deaths following myocardial infarction, cardiac arrest, revascularisation procedure, pulmonary embolism, deep venous or arterial thrombosis, arrhythmias, stroke and congestive heart failure or deaths due to an unknown cause
Myocardial infarction ³³	The diagnosis of myocardial infarction requires any one of the following criterion: <ol style="list-style-type: none"> 1. Detection of a rise and/or fall of cardiac troponin values with at least one value above the 99th centile upper reference limit and with at least one of the following: <ol style="list-style-type: none"> A. Symptoms of ischaemia B. New or presumed new significant ST-T changes or new left bundle branch block C. Development of pathological Q waves in the ECG D. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality E. Identification of an intracoronary thrombus by angiography or autopsy 2. Pathological Q waves with or without symptoms in the absence of non-ischaemic causes 3. Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause 4. Pathological findings of a prior myocardial infarction
Myocardial injury after non-cardiac surgery	This is an elevated cardiac troponin value within 30 days after surgery without evidence of a non-ischaemic aetiology, such as pulmonary embolism, sepsis, cardioversion or known persistent elevated cardiac troponin values)
Non-fatal cardiac arrest	Non-fatal cardiac arrest is defined as successful resuscitation from ventricular fibrillation, ventricular tachycardia, asystole or pulseless electrical activity
Revascularisation procedure	This is defined as percutaneous coronary intervention or coronary artery bypass graft surgery
Pulmonary embolus	Any one of the following: <ol style="list-style-type: none"> 1. A high probability ventilation/perfusion lung scan 2. An intraluminal filling defect of segmental or larger artery on a helical CT scan 3. An intraluminal filling defect on pulmonary angiography 4. A positive diagnostic test for deep venous thrombosis (eg, positive compression ultrasound) with either one of the following: <ol style="list-style-type: none"> A. Low or intermediate probability ventilation/perfusion lung scan B. Subsegmental defects or technically inadequate study helical CT scan
Deep venous thrombosis	Any one of the following: <ol style="list-style-type: none"> 1. Non-compressibility of one or more venous segments on B mode compression ultrasonography 2. Intraluminal filling defect on contrast-enhanced CT 3. Persistent intraluminal filling defect on contrast venography
New atrial fibrillation	Atrial fibrillation (or flutter) occurred after surgery
Stroke	Stroke is defined as a new focal neurological deficit thought to be vascular in origin with signs or symptoms that last >24 h or is leading to death
Congestive heart failure	Any one of the clinical signs: elevated jugular venous pressure, respiratory crackles, or presence of S3 At least one of radiographic features: vascular redistribution, interstitial oedema or alveolar pulmonary oedema
Pneumonia	Either crackles on physical examinations of chest with one of the followings <ol style="list-style-type: none"> 1. Purulent sputum or change in sputum characteristics 2. Positive blood culture or isolation of pathogen from transtracheal aspirate, bronchial brushing or biopsy or chest radiography showing new or progressive infiltrate, consolidation, cavitation, or pleural effusion and any of the following: <ol style="list-style-type: none"> 1. Purulent sputum or change in sputum characteristics 2. Positive blood culture or isolation of pathogen from transtracheal aspirate, bronchial brushing or biopsy 3. Isolation of virus or detection of viral antigen from respiratory secretions 4. Diagnostic single antibody titre or fourfold increase in paired serum samples for pathogen 5. Histopathological evidence of pneumonia
Infection/sepsis	Invasion of pathogenic organisms isolated from normally sterile tissue (including wound) or fluid or body cavity Sepsis is defined by the presence of an infection and a systemic inflammatory response

ST-T, ST-segment-T wave.

PULSOX-300i oximeter wristwatch in all sites as an unrestricted loan. These will be returned at the end of the study.

Potential limitations of the POSA study

Given the resource constraints, it is impractical to perform standard in-laboratory attended PSG for all patients in the POSA study. We have therefore resorted to use a type 3 portable sleep monitoring device. It is known that these devices may underestimate AHI values especially in patients with mild OSA.³¹ Therefore, these patients may be erroneously classified as non-OSA. Nevertheless, ApneaLink measurements appeared to correlate with standard PSG. At AHI value of 5, the sensitivity and specificity ranged between 85.4–100% and 50–100%, respectively.^{21–24} It should be noted that we do not measure electroencephalogram in our sleep monitoring, and hence we cannot track whether the patient is asleep during measurement. We therefore standardised recordings by processing the data collected between 23:00 and 06:00, even though the patients may be awake during the period.

CURRENT STATUS OF THE STUDY

The POSA study is currently enrolling patients from nine centres in six countries. As of November 2013, we have screened 998 patients who fulfilled the POSA eligibility criteria. Among these patients, 294 were not enrolled to the study because 265 patients did not consent or their surgeons did not approve their participation. In addition, 29 patients were excluded because ApneaLink was not available (n=2) or preoperative recording was not successful (n=27). Currently, 704 patients are included in the POSA study and over 650 patients have completed the 30-day follow-up. Table 2 summarises the baseline characteristics and type of surgery among the first 567 patients enrolled to the study. The mean age of patients was 68 years, 55% were male, 27.9% had a history of known coronary artery disease and 75.8% had three risk factors for atherosclerosis. The majority of patients underwent orthopaedic (28%), general (31%), urological (8.6%) and vascular (6.9%) surgery.

DISCUSSION

OSA is a common condition that is often unrecognised, undiagnosed and associated with significant morbidity and mortality. The POSA study will inform clinicians about the magnitude and severity of unrecognised OSA in the surgical population in different countries. More importantly, it will determine the risks of postoperative vascular events in patients with unrecognised and untreated OSA. Specifically, it will facilitate surgeons and patients in making decisions and will guide perioperative patient management. Furthermore, the findings will provide insights into the possible harmful effect of nocturnal hypoxia. This knowledge will inform the possible mechanisms of postoperative vascular events and should

Table 2 Baseline characteristics

Variables	Values
Number of patients	567
Age (year)	68±10
Weight (kg)	70±16
Height (cm)	161±10
BMI (kg/m ²)	27.0±5.5
Male, n (%)	312 (55)
Ethnicity, n (%)	
Chinese	272 (48.1)
Malay/Indian	187 (32.9)
Caucasian	108 (18.9)
ASA physical status, n (%)	
ASA II	336 (59.3)
ASA III	217 (38.3)
ASA IV	14 (2.4)
Comorbidity, n (%)	
Hypertension	487 (85.9)
Coronary artery disease	158 (27.9)
Congestive heart failure	21 (3.7)
Peripheral vascular disease	51 (9)
Cerebrovascular disease	96 (16.9)
Diabetes mellitus	435 (76.7)
Renal impairment	51 (9)
Current smokers	198 (34.9)
Surgical types, n (%)	
Colorectal surgery	105 (18.5)
Liver surgery	71 (12.5)
Genitourinary surgery	49 (8.6)
Orthopaedics	159 (28)
Spine	34 (6)
Vascular surgery	39 (6.9)
Others	110 (19.4)
Minimally invasive surgery, n (%)	101 (17.8)
Duration of surgery (hours)	2.25±2.39

Values are number (%) or mean±SDs.

ASA, American Society of Anaesthesiologists; BMI, body mass index.

stimulate future research into the prevention of this harm. Over 200 million patients undergo surgery each year,³² many of them have significant OSA, we believe any improvement in postoperative outcome should have major implications for healthcare delivery.

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