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Original article

CPAP effects on atherosclerotic plaques in patients with sleep-disordered breathing and coronary artery disease: The ENTERPRISE trial

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ABSTRACT

Background: Sleep-disordered breathing (SDB) is a novel cardiovascular risk factor. To date, the effects of continuous positive airway pressure (CPAP) on coronary plaque atheroma in SDB patients with coronary artery disease (CAD) have remained unclear. The CPAP Effects on Atherosclerotic Plaques in Patients with Sleep-Disordered Breathing and Coronary Artery Disease (ENTERPRISE) trial was designed to evaluate the effects of CPAP treatment in addition to optimal medical treatment on coronary plaque regression in SDB patients.

Methods: This study is planned as a prospective, randomized, open-label, single-center study. The presence of SDB is defined as a 3% oxygen desaturation index (ODI) of $\geq$15 events/h as measured by nocturnal pulse oximetry. A total of 100 eligible SDB patients undergoing intravascular ultrasound (IVUS)-guided percutaneous coronary intervention will be randomly assigned to either CPAP as add-on therapy or no CPAP for SDB (1:1 ratio for CPAP vs. no CPAP). The intervention will consist of 12 months of CPAP treatment. The primary endpoint will be percentage changes in plaque atheroma volume of the non-culprit lesion segment as measured by IVUS. A specialist sleep cardiology team will carefully monitor patients receiving CPAP treatment in order to quickly detect and resolve problems, and to motivate patients to continue treatment.

Conclusion: This study will provide novel information on the effects of SDB and its treatment with CPAP on coronary plaque stability with regard to secondary prevention of CAD.

Introduction

Sleep-disordered breathing (SDB) is characterized by repetitive nocturnal hypoxia and sleep disturbances, such as snoring, frequent waking, and daytime sleepiness. SDB is reportedly associated with coronary artery disease, stroke, and all-cause death among the general population [1–4]. In addition, epidemiological studies have shown that SDB is present in about 50% of patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) [5,6]. A recent meta-analysis also demonstrated that SDB appears to increase the risk of cardiovascular events, including cardiac death, myocardial infarction (MI), and coronary revascularization in patients undergoing PCI [7]. In patients with coronary atherosclerosis, SDB is associated with an increased burden of coronary plaques as documented by noninva-

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sive coronary computed tomography angiography [8–10]. Several intravascular imaging studies have shown a significant association between severity of SDB and larger coronary atheroma volume, which is a discriminator of plaque vulnerability [11,12].

Continuous positive airway pressure (CPAP) is an established treatment for SDB, significantly decreasing apnea–hypopnea and reducing oxidative stress, sympathetic nerve activity, inflammation, and possibly myocardial ischemia [13,14]. Moreover, a previous report from the largest clinical cohort showed a clinical benefit of CPAP treatment in reducing the risk of cardiovascular events [15]. However, few data have been accumulated regarding the mechanism of reducing clinical events by CPAP treatment, as well as the efficacy of CPAP for plaque modification, including coronary atheroma volume and vulnerability in patients with coronary artery disease. The CPAP Effects on Atherosclerotic Plaques in Patients with Sleep-Disordered Breathing and Coronary Artery Disease (ENTERPRISE) trial was thus designed to evaluate the effects of adding CPAP treatment to optimal medical treatment on coronary plaque in coronary artery disease patients with SDB. We hypothesized that CPAP treatment would regress coronary atheroma volume and improve adverse plaque characteristics.

Methods

Study design

The ENTERPRISE study will be conducted to evaluate the effects of SDB treatment using CPAP therapy on the progression or regression of coronary atherosclerosis. Near-infrared spectroscopy-intravascular ultrasound (NIRS-IVUS) has been selected to evaluate the volume of coronary plaque atheroma and extent of lipid-rich plaque because of the high sensitivity and reproducibility of this imaging modality. Evaluation of the non-culprit lesion segment of the culprit vessel (a non-PCI site), as the primary outcome measure, is conducted at baseline and repeated at the 12-month follow-up. As a secondary measure, the extent of lipid-rich plaque is assessed at the same time points as the primary outcome measure. Other outcomes will include adverse events, such as cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, target lesion revascularization (TLR), non-target lesion target vessel revascularization (non-TL TVR), or hospitalization for congestive heart failure.

Patients will be enrolled between July 2018 and February 2020 or until enrollment has been completed. The planned study duration is from July 2018 to March 2022. This study has been approved by the Institutional Review Board and Independent Ethics Committee of Juntendo University Hospital. The study has been registered with the University Hospital Medical Information Network (UMIN) (UMIN ID: R000036293).

Study population

The ENTERPRISE study will be a prospective, randomized, 12-month, open-label, single-center study. Patients with stable coronary artery disease will be screened for the presence of SDB until hospitalization for planned staged PCI. Thereafter, patients who satisfy all inclusion criteria will be enrolled after having undergone successful PCI under IVUS guidance to treat a culprit lesion and evaluate a non-culprit lesion segment by NIRS-IVUS (Table 1). Exclusion criteria are listed in Table 2. According to these criteria, eligible patients will provide written informed consent and then be randomized to receive either CPAP treatment or no CPAP treatment for SDB by stratified permuted block randomization with two stratification factors [body mass index: $<25\ kg/m^2$ or $\geq 25\ kg/m^2$; 3% oxygen desaturation index (ODI): <30 events/h or ≥ 30 events/h] (Fig. 1).

Table 1
Inclusion criteria.

1. Patients who have been diagnosed with stable coronary heart disease
2. Patients with 3% oxygen desaturation index >15 events/h
3. Successful percutaneous coronary intervention for significant coronary stenotic lesion under intravascular ultrasound (IVUS) guidance
4. Patients having non-calcified plaque with maximal plaque burden >40% of the non-culprit lesion segment detected by IVUS
5. Patients who agree to be enrolled in the trial, providing signed written informed consent

Plaque burden is calculated as plaque and media cross-sectional area (CSA) divided by external elastic membrane CSA.

After randomization, all patients will be treated with medical therapy for secondary prevention of coronary artery disease. If patients have been already treated with antihypertensive and/or lipid-lowering agents, they will maintain those treatments, along with their diet and exercise therapy. Briefly, the physician can decide to start pharmacotherapy or increase the doses of drugs based on the following principle. For all patients, the target serum level for low-density lipoprotein cholesterol (LDL-C) is <100 mg/dL and the target blood pressure is 140/90 mmHg. If patients have diabetes mellitus with comorbidities, the target serum level for LDL-C is <70 mg/dL. For blood pressure control, a calcium channel blocker or renin–angiotensin blockade is recommended as the first-line drug, and a statin is recommended for LDL-C control. All patients will be instructed to measure blood pressure at home in the early morning and evening. The results are reported to the physician-in-charge to detect masked hypertension or hypotension. If morning home blood pressure is greater than 140/90 mmHg at each follow-up visit, patients will be prescribed antihypertensive drugs in steps. For LDL-C control, the dose of statin will be increased until the target LDL-C level is reached. If the target serum level of LDL-C is not reached after administration of high-dose statin, any lipid-lowering medicine can be given. High doses of atorvastatin, pitavastatin, and rosuvastatin are 20 mg, 4 mg, and 10 mg, respectively. If patients have diabetes mellitus and any comorbidity, they will be referred to diabetes specialists in our institute for glycemic control and management of comorbidities from diabetes. All patients will be asked to visit our outpatient clinic every 2 months and blood samples will be taken to measure laboratory data, including lipid profile.

To assess treatment compliance for the CPAP treatment group, the CPAP device registers CPAP usage per night and air pressure, and the physician checks compliance at least every 2 months at the outpatient clinic.

Sleep studies

The presence of SDB will be determined using a wristwatch-type pulse oximeter (PULSOX-Me300; Konica Minolta, Tokyo, Japan). The sampling frequency of this monitor is 1 Hz. Overnight pulse oximetry will be performed during hospitalization for the cardiac catheterization study before PCI. The sensor probe will be

Table 2
Exclusion criteria.

1. Patients treated with continuous positive airway pressure therapy
2. Patients with hypersomnia requiring urgent treatment (defined as an Epworth Sleepiness Scale score ≥ 18)
3. Patients over 75 years of age
4. Patients with New York Heart Association class II, III, or IV heart failure
5. Patients with renal insufficiency (serum creatinine ≥ 2.0 mg/dL)
6. Patients with hemodialysis
7. Patients with malignant disease
8. Patients recognized as unsuitable by attending physician

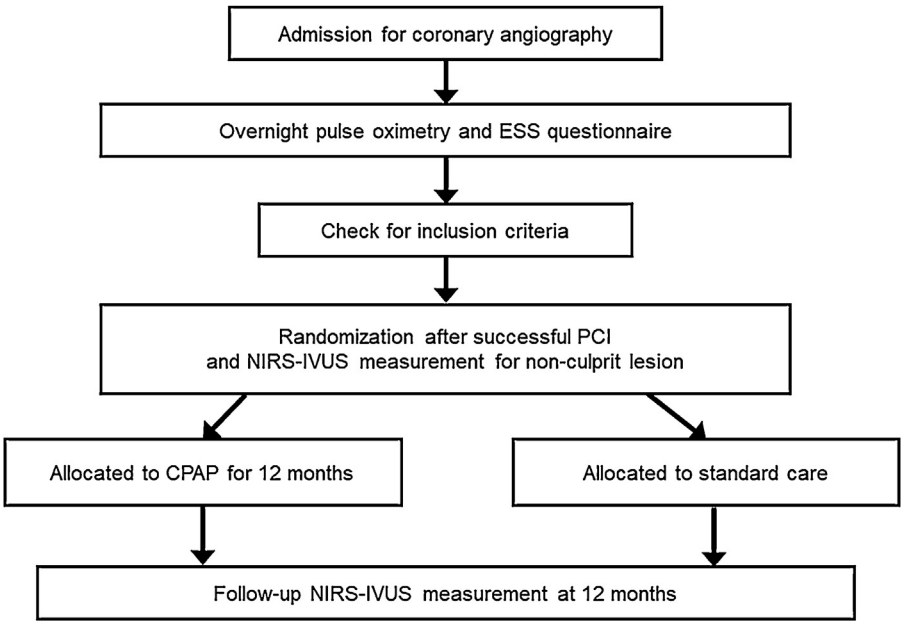

Fig. 1. Flowchart of the ENTERPRISE study. CPAP, continuous positive airway pressure; ESS, Epworth sleepiness scale; PCI, percutaneous coronary intervention; NIRS-IVUS, near-infrared spectroscopy-intravascular ultrasound.

fitted to the second finger and secured with tape or a finger cover to prevent detachment. The internal memory of this device stores the values of arterial blood oxygen saturation (SpO_2). Data will be analyzed using the software supplied with the equipment (DS-Me Ver. 2.1; Konica Minolta). We use the value of the ODI as an indicator of SDB severity. The 3% ODI has been selected as an index of oxygen desaturation, representing the number of events per hour of the recording time in which the patient's blood oxygen level fell by $\geq$3%. The recording time is the time that the patient was in bed. However, this time is often longer than the correct sleep time. Therefore, the patients keep a sleep log to exclude the waking time from analysis and thus minimize potential overestimation of sleep time. In this study, SDB will be defined as a 3% ODI $>$ 15 events/h. We will also record average SpO_2, minimum SpO_2, cumulative time with SpO_2 was $<$95% (expressed as a percentage of total sleep time) and total measurement time for pulse oximetry.

The Epworth sleepiness scale (ESS) will be used to investigate daytime sleepiness. The ESS contains eight questions to evaluate the chance of dozing off under eight scenarios in the past month. Each item is scored from 0 to 3 (0, would never doze; 1, slight chance of dozing; 2, moderate chance of dozing; 3, high chance of dozing). ESS score ranges from 0 to 24. Excessive daytime sleepiness was defined as an ESS score $\geq$10.

NIRS-IVUS acquisition and analysis

Combined NIRS and grayscale IVUS image acquisition will be performed using the commercially available Dualpro™ NIRS-IVUS system with a 50-MHz mechanical transducer ultrasound and a 2.4-Fr Insight™ catheter (Infraredx, Burlington, MA, USA). Before imaging, 0.1–0.2 mg of intracoronary nitroglycerin will be administered. The NIRS-IVUS catheter will be advanced into the PCI or non-PCI vessel as distally as possible and withdrawn at a pullback speed of 0.5 mm/s automatically. NIRS-IVUS images will be recorded onto DVD-R for later offline analysis.

The NIRS analysis allows calculation of lipid core burden index (LCBI). In the present study, maximal LCBI will be estimated in 4-mm and 10-mm pullback compartments for every analyzed lesion ($LCBI_{4mm}$ and $LCBI_{10mm}$). Quantitative grayscale IVUS measurements will be performed using QIvus version 2.1 (Medis, Leiden, the Netherlands) to quantify lumen cross-sectional area (CSA), external elastic membrane (EEM) CSA, plaque and media CSA, plaque burden, and remodeling index (RI). Lesions with RI $\leq$ 0.95 are defined as negatively remodeled, while those with an RI $\geq$ 1.05 are defined as positively remodeled. The target segment to be monitored will be determined in a non-PCI site ($>$5 mm proximal or distal to the PCI site) on the PCI or non-PCI vessel with a reproducible fiduciary index such as side branches, calcifications, or stent edges. All image analyses will be performed offline by the Juntendo University IVUS core laboratory. Images will be analyzed by two experienced medical doctors in the core laboratory blinded to any patient information. IVUS exclusion criteria might include: (1) calcified plaque, (2) any cross-sections with recognizable non-uniform rotation distortion, (3) presence of external elastic membrane out of view, (4) loss of image due to bubbles, or (5) any other artifact preventing complete analysis. Quantitative and qualitative IVUS analysis will be performed according to the criteria of the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies [16].

CPAP intervention and follow-up

CPAP treatment is set up and monitored by a specialist "sleep-cardiology" team. This team exists of two physicians, two nursing practitioners, and two clinical technologists working in the sleep laboratory unit specializing in sleep and breathing disorders.

For patients randomized to receive CPAP treatment, we will use auto-CPAP, because this method is as effective as fixed-pressure CPAP but does not require the presence of a sleep therapist for titration. The auto-CPAP machine (Sleepmate 10 Auto; Resmed, Sydney, Australia) will measure and store information about respiratory events (apneas and hypopneas), patient use (minutes used and nights used), mask leak, and pressure delivered. Before treatment is initiated, a CPAP mask, connecting hose and CPAP device will be set up for each patient. Different masks can be used, from small nasal pillows to a full-face mask, depending on patient preference. Personalized instructions will be given by one of the team members and a written manual for the CPAP device will be

provided. If possible, the partner or a close relative will also be provided with instructions on the use of the CPAP device. Patients will be asked to wear the mask for a short period during the day to become accustomed to using the CPAP device. Auto-CPAP adherence is categorized as no use, any use ($\geq$4 h/night for $<$75% of nights), or acceptable adherence ($\geq$4 h/night for $\geq$75% of nights) [15,17]. Within the first month, CPAP treatment is evaluated together with the patient and CPAP titration is performed using pulse oximetry. The pressure is adjusted until ODI is reduced to normal (ODI $<$ 5 events/h). The CPAP device is provided with a memory card to evaluate the effectiveness of CPAP therapy over time and to monitor CPAP compliance. Treatment with CPAP will be continued for 12 months, during which the patient will have direct contact with the team at all times for clinical problem-solving issues. Medical appointments will be scheduled for all patients (with or without CPAP) at least every 2 months after randomization. After the last medical appointment, after 12 months of CPAP treatment, a repeat NIRS-IVUS procedure will be performed in all patients.

Carotid ultrasonography

Carotid ultrasonography will be performed at baseline and repeated at the 12-month follow-up. The severity of carotid artery atherosclerosis will be evaluated by mean intima-media thickness (IMT) and maximum IMT. Sonography examination is performed using a duplex color-coded ultrasonographic device equipped with a linear-array 7.5-MHz transducer (Aplio CV; Toshiba, Tokyo, Japan). The most stenotic portion of the internal carotid artery is determined using gray-scale and Doppler sonography, as described previously [18]. Plaque morphology and the distribution of the stenotic portion will be evaluated by investigators who are blinded to the clinical information of patients.

Endpoints

The primary endpoint will be the percentage change in coronary atheroma volume of the non-culprit lesion of the culprit vessel measured by IVUS from baseline to 12 months, which will be calculated as follows: percentage atheroma volume (PAV) = Σ(EEM CSA − lumen CSA)/Σ EEM CSA $\times$ 100, where EEM CSA is the cross-sectional area of the external elastic membrane, and lumen CSA is the cross-sectional area of the lumen [19].

Secondary endpoints will be as follows: (1) changes in the extent of lipid-rich plaque in the non-culprit lesion by NIRS analysis from baseline to follow-up; (2) absolute change in atheroma volume of the non-culprit lesion by IVUS analysis from baseline to follow-up; (3) change in IMT by carotid ultrasonography from baseline to follow-up; (4) change in inflammatory markers such as high-sensitivity C-reactive protein from baseline to follow-up; (5) major adverse cardiovascular events (MACE; defined as composite of cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, TLR, non-TL TVR, and hospitalization for congestive heart failure); and (6) all-cause death.

Follow-up data will be collected at every visit to outpatient clinics or, if not feasible, by telephone follow-up and/or a medical questionnaire, carried out by research staff blinded to the allocated treatment. All clinical events will be recorded and assessed by two outcome adjudicators in our hospital (specialist interventional cardiologists), who are blinded to the treatment arm of each patient.

Safety monitoring

For safety evaluation, the numbers and prevalence of adverse events (including abnormal changes in physical values and clinical laboratory values) will be calculated. Adverse events will be summarized by type, severity, causality, and duration of event.

Data management

Patient information, blood samples, and NIRS-IVUS images will be coded with the identification number of this study and the coded number for individual identification will remain blind.

Sample size calculation

The target sample size has been set at 100 patients (50 patients per group). This sample size was selected based on the number of patients deemed capable of being included within the duration of an exploratory clinical study. Several IVUS volumetric studies using statins in Japanese patients with coronary artery disease have been published [20,21]. The standard deviation (SD) for percentage change in atheroma volume in the PRECISE-IVUS trial [21] was 5.55%. The sample size of 100 patients was expected to be statistically significant if detecting a 2.20% difference in the primary endpoint, assuming a SD of 5.55% with 5% type I error for a 2-sided 2-sample *t*-test.

Statistical analysis

Percentage changes in atheroma volume will be summarized by mean, SD, minimum, median, and maximum. Changes in atheroma volume measured by IVUS and changes in extent of lipid-rich plaque measured by NIRS will be evaluated using analysis of covariance, including the baseline measurement as a covariate. The effects of CPAP therapy on each variable will be compared by means of a paired *t*-test or the Mann−Whitney rank-sum test. Percentage changes in each variable after CPAP treatment will also be compared by a paired *t*-test. The correlation between percentage changes in atheroma volume and extent of lipid-rich plaque will be analyzed by linear regression analysis. For safety evaluation, the number and prevalence of adverse events and adverse drug reactions will be calculated.

Discussion

SDB is highly prevalent among coronary artery disease patients. Converging processes by SDB, including increased oxidative stress, proinflammatory responses, and platelet activation, act together to foster the initiation and progression of atherosclerosis. An association between SDB and coronary atherosclerosis and microvascular obstruction has been shown in patients undergoing PCI [11,22]. In addition, recent large registry data have demonstrated the prognostic implications of SDB for patients undergoing PCI [6]. In a randomized trial, 4 months of treatment with CPAP significantly reduced both carotid IMT and arterial stiffness, which was associated with improvements in validated markers of atherosclerosis [23]. In an observational study, Cassar et al. reported that patients with treated SDB who underwent PCI had a significantly lower cardiac mortality than patients with untreated SDB [24]. However, there are insufficient data and surrogate endpoint studies to elucidate the mechanisms underlying the effects of CPAP on coronary artery disease. The ENTERPRISE study will add to the understanding of the mechanisms for CPAP effects as well as the clinical implications of SDB in patients with coronary artery disease.

Furthermore, the low level of awareness of SDB among interventional cardiologists and inadequate treatment compliance with CPAP among patients represent major practical problems. A number of earlier studies investigating the effects of CPAP treatment suffered from low compliance [15,25]. To ensure

treatment compliance within this study, a specialist sleep cardiology team will carefully monitor patients receiving CPAP treatment in order to quickly detect and resolve problems, and motivate patients to continue treatment. We expect that this will enhance treatment compliance.

This study will use high-resolution pulse oximetry, which is a convenient and inexpensive method to detect SDB. However, some limitations are evident. Because this method only measures the change in oxygen saturation and does not monitor nasal flow or respiratory effort, obstructive sleep apnea is not able to be distinguished from central sleep apnea (CSA). CSA is more common among older adults, and patients with congestive heart failure display a higher risk of developing CSA [26]. We are therefore excluding both elderly patients (>75 years old) and patients with symptomatic heart failure, to remove patients with predominantly CSA as much as possible.

Conclusion

The ENTERPRISE study will be the first study performed in a Japanese population using NIRS-IVUS to evaluate the effects of CPAP for SDB in controlling the progression or regression of coronary atherosclerosis. The results of this study will provide new insights into CPAP therapy for SDB and residual risk management in patients with coronary artery disease.

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