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Assessment of atherosclerotic plaque activity in patients with sleep apnea using hybrid positron emission tomography/magnetic resonance imaging (PET/MRI): a feasibility study

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Abstract

Purpose—Evidence suggests that the inflammatory state of an atherosclerotic plaque is important in predicting future risk of plaque rupture. This study aims to investigate the feasibility of measuring plaque inflammation in patients with obstructive sleep apnea (OSA) utilizing advanced vascular imaging — hybrid positron-emission tomography/magnetic resonance imaging (PET/ MRI) with fluorodeoxyglucose (FDG) tracer—before and after continuous positive airway pressure (CPAP).

Methods—Patients with newly diagnosed moderate to severe OSA underwent baseline PET/MRI for assessment of vascular inflammation of the carotid arteries and thoracic aorta prior to initiation of CPAP. Those adherent to CPAP returned for repeat imaging after 3–6 months of CPAP use. Atherosclerotic plaque activity, as measured by arterial wall FDG uptake, was calculated using target-to-background ratios (TBR) before and after CPAP.

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of Icahn School of Medicine at Mount Sinai and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Results—Five patients were recruited as part of a focused project. Mean age was 52 years (80% male), and mean apnea-hypopnea index (AHI) was 33. Three patients were objectively adherent with CPAP. In the pre-CPAP phase, all patients had focal FDG uptake in the carotid arteries and aorta. After CPAP, there was an average reduction in TBR of 5.5% (TBR_{mean}) and 6.2% (TBR_{max}) in carotid and aortic plaque inflammation, similar in magnitude to the reduction observed with statin therapy alone in non-OSA patients (previously reported by others).

Conclusions—We demonstrate the feasibility of using hybrid PET/MRI to assess atherosclerotic plaque inflammation in patients with OSA before and after CPAP. Use of the vascular PET/MRI platform in patients with OSA may provide better insight into the role of OSA and its treatment in reducing atherosclerotic inflammation.

Keywords

Obstructive sleep apnea; CPAP; Atherosclerosis; Plaque; Inflammation; PET/MRI

Introduction

Sleep apnea (SA) affects millions of Americans, with substantial increases in its prevalence over the last two decades [1]. Obstructive sleep apnea (OSA) is characterized by repetitive breathing pauses secondary to upper airway obstruction and has been associated with atherosclerosis and cardiovascular disease (CVD) [2–6]. Atherosclerosis is a complex disease initiated by the deposition of low-density lipoprotein within the arterial intima. Recurrent asphyxia and arousals from OSA culminating in intermittent hypoxia and sympathetic activation lead to oxidative stress and endothelial dysfunction, which are some of the direct mechanisms linking OSA to atherosclerosis [4].

Evidence suggests that the biologic composition and inflammatory state of an atherosclerotic plaque are important in predicting future risk of rupture [7, 8]. Plaque inflammatory activity can be measured using Positron Emission Tomography (PET), an imaging modality that is widely used in conjunction with ^{18}F -fluorodeoxyglucose (FDG) tracer in oncologic imaging. ^{18}F -FDG is a radioactive tracer and a glucose analog useful in detecting accumulation of cholesterol-engorged macrophages. These pro-inflammatory macrophages have an elevated glycolytic rate, avidly accumulate FDG and are implicated in atherosclerosis [9–14]. FDG-PET has been used in research studies looking at vascular inflammation to detect and quantify atherosclerosis and subsequent plaque destabilization [15]. Studies have shown that arterial FDG uptake correlates with symptomatic, unstable plaque, and macrophage burden [12, 16] and has proven to be a useful prognostic imaging tool to identify patients most at risk for early CVD recurrence [17–20]. Importantly, statin therapy produces dose-dependent reductions in atherosclerotic FDG uptake which may represent respective changes in plaque inflammation [21–23]. Hence, this modality may be useful as a surrogate end-point in clinical trials detecting early treatment effects of anti-atherosclerotic activities in patients with atherosclerosis.

Utilizing imaging modalities aiming at detection of plaque activity/inflammation has shown that morphologically similar appearing plaques can be metabolically quite different, i.e., either active (inflamed) or inactive (Fig. 1). However, meta-bolically active plaques can

better predict vulnerability and risk of rupture vs. metabolically inactive plaque [16]. Therefore, assessing vascular inflammation/plaque activity is crucial in SA patients to better understand the link between SA and vascular events. We are not aware of any studies that have measured the inflammatory state of atherosclerotic plaques in OSA patients, using ^{18}F -FDG PET signal as a marker of plaque vulnerability to help identify individuals at risk of clinical vascular events. Therefore, in this pilot study, we utilize state-of-the-art vascular multi-modality imaging technology — hybrid PET/magnetic resonance imaging (MRI) with FDG—to determine the feasibility of measuring vascular atherosclerotic plaque activity in the carotid and thoracic aortic vascular beds in patients with OSA before and after continuous positive airway pressure (CPAP) therapy. We hypothesized that short-term OSA treatment with CPAP can reduce atherosclerotic plaque activity in the carotid and aortic vessels (Fig. 2).

Methods

Study population

A Focused Project Award by the American Sleep Medicine Foundation funded our study. We recruited five ambulatory care patients from pulmonary and sleep clinics at the Mount Sinai Hospital (New York, NY) who were screened via the electronic health record (EHR). Inclusion criteria were age ≥ 21 years, moderate to severe OSA as defined by an apnea-hypopnea index (AHI) ≥ 15 events per hour of sleep or recording time (diagnosed by an in-lab polysomnography [PSG] or portable sleep test), OSA treatment naive, with stable cardiovascular risk factors including but not limited to hypertension (HTN), hyperlipidemia (HLD), diabetes, and smoking. Exclusion criteria are noted in Table 1. Patients who met the inclusion criteria were enrolled into the study using informed written consent. Our study was approved by our local Institutional Review Board (IRB).

Baseline assessment

Data on demographic characteristics included age, sex, and baseline body mass index (BMI), obtained from the EHR. Covariates included HTN, HLD, diabetes, and smoking (former or current). These were either identified based on EHR diagnosis or the use of antihypertensive medications, lipid lowering agents other than statins, and diabetic medications other than insulin. Excessive daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS), which is a validated measure of daytime sleepiness [24].

Polysomnography

We identified patients who had received a diagnosis of OSA based on nocturnal in-lab PSG or portable sleep testing performed between August 1, 2015, and September 1, 2016, and were CPAP-naïve prior to patient recruitment and consent for imaging. In-lab diagnostic PSG and CPAP titrations were conducted in an American Academy of Sleep Medicine (AASM) accredited sleep center, and the data was acquired and scored in accordance with the recommended standards and specifications as outlined in the AASM Manual for the Scoring of Sleep and Associated Events 2.3 [25, 26]. The recording montage comprised of frontal, central, and occipital electroencephalogram channels, left and right electrooculogram channels, chin electromyogram, airflow from nasal pressure transducer

and oronasal thermistor, body position, thoracoabdominal efforts channels, pulse oximetry, electrocardiogram channel, and left and right leg electromyogram. An apnea was defined as a 90% reduction in airflow lasting at least 10 seconds, and a hypopnea was defined as 30% reduction in airflow, lasting at least 10 seconds with an associated desaturation of 3% or more. The apnea-hypopnea index (AHI) was defined as all apneas and hypopneas divided by recording or sleep time. An AHI ≥ 15 per hour of sleep was used to define moderate OSA, and an AHI of ≥ 30 per hour of sleep was used to define severe OSA in order to meet inclusion criteria. AHI, total sleep time, and lowest oxygen saturation are reported for patients compliant with CPAP therapy. Portable sleep studies were conducted using two monitors, WatchPAT (Itamar Medical) and Embletta portable diagnostic system (PDS, Medcare, Reykjavik, Iceland). The WatchPAT is an FDA-approved device that identifies respiratory events by monitoring changes in the peripheral artery tone using a finger probe. It also detects body position and snoring. The Embletta portable system measures the following signals: airflow via a nasal cannula connected to a pressure transducer, body-position, effort, or actigraphy.

PET/MRI imaging

Image acquisition and analysis were conducted at the Translational and Molecular Imaging Institute (TMII) at the Icahn School of Medicine at Mount Sinai. Vascular intraplaque inflammation was quantified using state-of-the-art hybrid PET/MR imaging techniques, carried out by leading experts in vascular PET imaging [27, 28]. This was piloted in SA patients before and after CPAP, using imaging metrics that have previously been utilized to quantify the anti-inflammatory effects of statins [23]. Each patient underwent two imaging studies, one at baseline, and the second after 3 to 6 months of OSA treatment with CPAP therapy (if they demonstrated adherence).

Imaging workflow

The participants' glomerular filtration rate (GFR) and glucose levels were checked prior to imaging. After overnight fasting, ^{18}F -FDG tracer (10 mCi [milliecurie]) was injected 90 minutes prior to imaging. The circulation time was based on prior studies to obtain optimal target to background FDG uptake ratio [29]. The PET and MRI data were acquired simultaneously by a hybrid PET/MRI scanner (Siemens BiographTM 3 T mMR scanner) for a total period of 60 min. See Fig. 3 for details of the study visit.

Image analysis

Image co-registration—For analyzing the carotid and aortic PET images, we combined vascular MRI and PET images to co-register morphological features of atherosclerotic plaques with quantitative assessments of plaque inflammation, respectively. All acquired PET list-mode data were histogrammed into a single data frame and later reconstructed with an Ordinary Poisson-Ordered Subsets Expectation Maximization (OP-OSEM) algorithm (three iterations, 21 subsets) to derive the respective ^{18}F -FDG 3D PET images. We utilized the co-registered 3D time-of-flight MRI images to assist with the accurate delineation of the PET regions of interest (ROIs) for calculation of FDG uptake. The PET/MRI images were aligned and analyzed using the OsiriX image processing application. The selected PET ROIs

for this study were the left and right carotid arterial walls at the carotid bifurcations, as well as the descending thoracic aortic wall. One observer independently analyzed slice by slice all the studies in each subject. Occasional slices had to be excluded because of poor image quality.

Measurement of FDG uptake—Arterial FDG uptake was measured using target-to-background ratio (TBR) calculations along the axial segments of the carotid arteries and thoracic aorta (whole vessel TBR_{mean} and TBR_{max}); a validated method of measuring global vascular inflammation [30, 31].

To calculate TBR, we drew circular target ROIs fitted to the artery wall on the axial plane of the target vessels. Coronal and sagittal views were used to ensure that the FDG uptake was from the artery. For the right and left carotid arteries, we started 2 cm below the bifurcation and made measurements every 3 mm superiorly up until we were 2 cm into the internal carotid artery. The background right and left carotid ROIs were drawn from a bottom arterial lumen section of the respective right and left common carotid arteries. For the thoracic aorta, we drew 3D ellipsoid target and background ROIs at a descending aortic wall section and the neighboring aortic lumen region, respectively. The arterial standardized uptake values (SUV) metrics for FDG were calculated for every voxel of the PET images as a decay-corrected tissue radioactivity divided by the ratio of the dose to body weight. Then, the mean and maximum SUV (SUV_{mean} , SUV_{max}) for FDG was recorded for each target ROI on the axial slice along the vessel length. The SUV_{mean} value was normalized to the blood pool SUV_{mean} value, as measured from the carotid or aortic arterial lumen background ROIs, to correct for blood pool uptake.

The result was the mean arterial TBR (TBR_{mean}), a reflection of arterial FDG normalized-to-blood mean uptake [12, 30]. We also calculated maximum arterial TBR (TBR_{max}) as the ratio of SUV_{max} measured in the target ROIs of the arterial vessel walls, normalized to the arterial blood pool SUV_{mean} value [30]. Previous analysis has demonstrated high intraobserver (0.93 and 0.98) and interobserver (0.90 to 0.97) agreement for these image metrics in vessel wall regions [29, 31].

Follow-up

Once the baseline-imaging exam was completed, the patient received a CPAP device as per clinical indication. The PAP device was either a fixed-pressure derived from an in-lab CPAP titration, or auto-set CPAP, depending on the prescribing physician's order. It was capable of being continuously monitored for adherence via the secure digital (SD) card. Adherence data were available for download wirelessly to the study investigators. All participants were contacted periodically by the research team to inquire about and encourage CPAP adherence. Subjects who were adherent to OSA treatment (use of CPAP for at least 4 hours or more per night for 70% of the nights in the monitored period) [32] were asked to return for a second imaging study after at least 3 months and up to 6 months of initiating CPAP therapy. We were interested in determining the anti-atherosclerotic effects of CPAP, and therefore, suboptimal CPAP users were not invited for repeat-imaging (a priori decision).

Statistical analysis

TBR_{mean} and TBR_{max} scores were calculated for all ROIs before and after CPAP treatment to make quantitative assessments of plaque inflammation in the carotid arteries and descending thoracic aorta. Continuous variables are reported as medians and categorical variables as counts and percentages. We report two measurements for each ROI, TBR_{mean} and TBR_{max}, before and after CPAP. We also report the mean percent change in TBR_{mean} and TBR_{max} for each ROI after CPAP.

Results

We recruited five patients (See Table 2 for baseline characteristics). Majority were middle-aged males, with a median AHI of 31 (ranging from 16 to 54). The patients had a low to moderate Framingham Risk Score (FRS) [33, 34], which is equivalent to a < 20% 10-year risk of coronary heart disease (CHD). Three patients were diagnosed with an in-lab PSG and two using portable sleep testing. Two underwent fixed pressure in-lab CPAP titration, and the remaining were prescribed auto-set CPAP. All patients underwent a baseline PET/MRI scan before CPAP initiation. Three out of the five patients were adherent with CPAP as per our predefined adherence criteria, two out of five declined CPAP use and refused to return for follow-up imaging. The three patients adherent to CPAP had a mean residual AHI of 2.3 on therapy demonstrating good efficacy of treatment and completed the follow-up imaging study after > 3 months of CPAP therapy. In the time period between the two scans, the subjects were not initiated on statins or additional antihypertensive agents. One subject had a 20-lb weight gain from baseline within this time, and this same individual had persistently elevated BP and was not consistently compliant with his antihypertensive medications.

Qualitative reductions in FDG uptake in the carotid arteries and aorta before and after CPAP using PET/MRI are shown in Fig. 4. Quantitative analysis of FDG uptake before and after CPAP, as measured by TBR, is depicted in Table 3 and Fig. 5. In the pre-CPAP phase, all patients had focal elevation of FDG signal in the aorta and carotid arteries. After CPAP, there was an average decrease in plaque activity by 6.1% and 3.8% in the right and left carotid arteries as determined by TBR_{mean} and an average decrease in TBR_{max} by 5.4% and 5.2%, respectively. Quantitative analysis of aortic atherosclerotic plaques after CPAP therapy revealed an average decrease in TBR_{mean} and TBR_{max} of 6.5% and 7.9% (Table 3).

Discussion

Our study measured vascular atherosclerotic plaque activity in patients with moderate to severe OSA using hybrid PET/MRI technology with ¹⁸F-FDG tracer. We demonstrated the feasibility of using this technique for quantitative analysis of vascular plaque inflammation in this patient population before and after CPAP therapy. There was an average reduction of 5.5% (TBR_{mean}) and 6.2% (TBR_{max}) in carotid and aortic plaque inflammation as measured by TBR after 3–6 months of CPAP therapy. This reduction in plaque inflammation is similar to the magnitude of reduction observed with statin therapy alone in non-OSA patients. Tawakol et al. demonstrated that 12 weeks of 80 mg of atorvastatin therapy showed a 6.7% reduction in TBR from baseline (using FDG Positron Emission Tomography/Computed Tomography [PET/CT]) in the carotid arteries and ascending aorta [23]. Therefore, a

reduction in TBR seen in patients with OSA post CPAP therapy may represent a reduction in vascular inflammation similar in magnitude to statin therapy.

Evidence suggests that patients with OSA have early signs of atherosclerosis. In one study, Drager et al. found that patients with OSA have increased arterial stiffness as measured by pulse-wave velocity (PWV) and increased carotid wall intima-media thickness (CIMT) measured by ultrasonography [3, 4]. Additionally, the same group demonstrated that effective treatment with CPAP therapy improves validated markers of atherosclerosis including arterial stiffness and CIMT [2]. However, a larger, more recent study examining the effects of OSA and CPAP on carotid atherosclerosis did not show an increase in CIMT in patients with OSA vs controls and did not show a change in CIMT after PAP therapy [35]. It is important to note that while there are several studies evaluating CIMT in OSA, carotid *plaque* burden or *activity* was not measured in these studies. Although CIMT is a surrogate measure of atherosclerosis associated with cardiovascular risk factors [36], carotid plaque burden, compared to presence of CIMT, had a higher diagnostic accuracy for the prediction of future CV events [37]. Furthermore, the presence of plaque on ultrasound in addition to CIMT improved CVD-risk prediction when added to traditional risk factors [38], and regression of CIMT alone, induced by CV drug therapies, did not reflect a reduction in CV events [39]. Therefore, we believe PWV and CIMT alone may be markers of arterial stiffening, and assessment of plaque burden and activity may be a better marker for ongoing atherosclerosis and risk of CVD. Kylintireas et al. used cardiovascular magnetic resonance of the carotid arteries and aorta in patients with and without OSA to assess plaque morphology and characterize carotid atheroma. The investigators found an increased atheroma burden with advanced, high-risk plaque features in patients with OSA [40]. However, they did not assess plaque morphology post-CPAP or utilize FDG-PET to measure plaque *activity*.

Ours is the first study to measure atherosclerotic *plaque activity* using *hybrid* PET/MRI with FDG tracer in patients with OSA before and after CPAP. Vascular MRI offers superior soft tissue contrast at the luminal borders and has the ability to provide detailed information with respect to plaque morphology when compared to CT. Additionally, *hybrid* PET/MRI allows for accurate motion correction by obtaining continuous and synchronized PET and MR data, thus improving data quality and PET quantification of small-volume carotid plaques [27]. Measuring plaque FDG activity provides important information on intraplaque inflammation, which is a crucial mediator of plaque rupture and thromboembolism [19]. FDG, a radioactive tracer and a glucose analog, is taken up by cellular glucose transporters, which are upregulated during atherogenesis due to hypoxia within the core of the atherosclerotic plaques [15, 41]. The fate of an atherosclerotic plaque is by and large determined by the actions of macrophages, as macrophages are found in increased density in unstable coronary lesions [9–11]. FDG signal indicates increased pro-inflammatory macrophage activity resulting in inflammation within high-risk atherosclerotic plaques [9]. We know that in recently symptomatic carotid stenosis, inflammation-related FDG uptake (as measured by SUV) is associated with early stroke recurrence, independent of the degree of stenosis [17]. It has also been shown to improve incident CVD prediction independent of traditional risk factors [20]. With this in mind, imaging of extracranial carotid arteries in

determining plaque composition, stability, and risk of rupture in patients with OSA can provide more insight into CV risk prediction for this patient population.

We observed several novel findings in this pilot study. All patients with OSA demonstrated arterial FDG uptake and vascular inflammation at baseline as measured by TBR. Our patients had a low to moderate FRS, with no history of overt CHD. The FRS is an algorithm used to predict the 10-year CHD risk in a given individual, accounting for age, gender, smoking status, cholesterol, and systolic blood pressure. A low to intermediate FRS confers a < 20% 10-year risk of CHD [33, 34]. CPAP was the the main systematically modified variable in the study prior to repeat imaging (although dietary recall and physical activity were not assessed for this time period). The reduction in TBR values post-CPAP therapy was similar in magnitude to that observed with statin therapy [23], observed even in a patient who had a 25-lb weight gain from baseline. However, we recognize that the established pleiotropic effects of statins on atherosclerosis and CV outcomes represent more than just their affect on atherosclerotic plaque inflammation [42].

Although *prospective* clinical trials showing an association between a reduction in arterial FDG uptake/TBR and improved CV events after a study intervention may be lacking, there is strong evidence that FDG-PET is an excellent surrogate marker for vascular plaque instability, rupture, and risk of adverse CV events. Therefore, reduction in TBR values of this magnitude following CPAP therapy in patients with OSA is a novel finding and an important one. FDG-PET has been used in research studies looking at vascular inflammation to detect and quantify atherosclerosis and subsequent plaque destabilization [15]. Studies have shown that arterial FDG uptake correlates with symptomatic, unstable plaque, and macrophage burden [12, 16] and has proven to be a useful prognostic imaging tool to identify patients most at risk for CVD occurrence [17–20]. Additionally, TBR values measured in the larger arteries on PET/CT (among individuals undergoing cancer surveillance) have been shown to predict subsequent CV events independent of traditional risk factors, even after adjustment for coronary calcium score [18–20]. Incorporation of TBR values in incident cardiovascular risk prediction also improved CVD-risk prediction beyond the FRS [20]. Therefore, our preliminary findings indicating a reduction in vascular inflammation following CPAP therapy merit further investigation in appropriately powered studies.

Although there are several potential mechanisms by which CPAP therapy may reduce vascular inflammation, the exact mechanism remains unclear. Acute physiological consequences of OSA, such as intermittent hypoxia, swings in intrathoracic pressures, and repetitive arousals leading to sympathetic activation are some of the proposed mechanisms by which OSA may contribute to an accelerated rate of endothelial dysfunction, oxidative stress, and atherosclerosis over time [43]. Exposure to chronic snoring vibrations may also trigger an inflammatory cascade leading to endothelial damage, thus contributing to early development of atherosclerosis [44–47]. By relieving some of the acute physiologic consequences of OSA, CPAP therapy may thereby eliminate some of the triggers leading to accelerated atherosclerosis and vascular inflammation overtime.

Limitations

Several methodological limitations should be considered in the interpretation of our study results. First, the sample size was small, and the study was not designed or powered to detect a statistically significant difference in vascular inflammation before and after CPAP therapy. Nonetheless, this pilot study demonstrates the feasibility of using simultaneous PET/MR imaging to evaluate the effect of CPAP on arterial atherosclerotic plaque activity in larger scale studies in the future. Second, the patients were diagnosed with OSA using variable sleep study methods (nocturnal PSG and portable sleep testing) and treated with either fixed-pressure or auto-set CPAP. This was done at the discretion of the ordering sleep physician, taking into account each individual patient's indications for in-lab versus portable testing and the pre-test probability of having moderate to severe OSA. A more standardized diagnostic approach (i.e., using only patients diagnosed with nocturnal PSG) in future larger studies may provide homogeneity in sleep apnea diagnostic and treatment methodology. However, all our patients had at least moderate to severe OSA with a median AHI of 31 events per hour, and were therefore less likely to be influenced by choice of home vs. in-lab testing. With respect to fixed vs. auto-CPAP, all patients were found to have efficacious OSA treatment as demonstrated by residual AHI on their CPAP compliance download data. Furthermore, home diagnosis using portable sleep testing and treatment of OSA with auto-titrating CPAP has been shown to be non-inferior to the traditional approach of in-lab PSG with fixed-pressure CPAP [48–50]. Therefore, it is unlikely that this may have affected our results. Third, the observer was not blinded to the patient scans, which may have introduced observer bias in the TBR measurements of vascular inflammation before and after CPAP therapy. However, the high inter- and intra-observer agreement for TBR measurement approaches reduces the risk of measurement error. Additionally, the TBR values calculated for the index vessels seem to be within the physiologic threshold of FDG uptake in the arterial wall [51]. However, studies have shown that there is substantial overlap in FDG uptake between healthy controls and patients at risk for CVD as measured by TBR, and it has yet to be proven that lower levels of inflammation are not associated with an increased cardiovascular risk [30, 51].

Lifestyle changes or pharmacotherapy-related modifications during follow-up could have impacted our study findings. However, in this study, we try to limit the influence of these factors by assessing for weight change on follow-up visits and monitoring for initiation of cholesterol/lipidlowering medications or those used to reduce blood pressure (antihypertensives). We did not, however, collect dietary recall or measure physical activity during the follow-up period of our study, changes in which could theoretically affect vascular inflammatory activity in these patients. Nevertheless, we chose to assess short-term effects of CPAP therapy (weeks to months vs. years) on vascular inflammation, which reduces the influence of factors such as major lifestyle changes, dietary habits, and physical activity on vascular inflammation. Such changes are less likely to materialize in a few weeks — especially without any evidence of significant weight loss during follow-up, which none of our study participants experienced. (In fact, one patient was noted to gain weight upon follow up.) Therefore, they are less likely to have impacted our outcome measure. Finally, we did not assess plaque activity in the patients who were non-adherent to CPAP therapy.

Although this group may have served as a control group in the study, our goal was to demonstrate *feasibility* of quantifying vascular inflammation in patients with OSA, as well as the effect of CPAP on the same; therefore, we chose to include only those adherent to therapy. Additionally, individuals who are non-adherent to CPAP are also more likely to be non-adherent to their CVD medications, diet, etc., which may affect vascular inflammation and therefore may not serve as true controls.

The application of this molecular imaging modality is important in OSA and CVD research, where randomized controlled trials (SAVE) have failed to show a beneficial effect of OSA treatment on vascular event rates [52]. The use of robust and well-established surrogate endpoints for CV events such as atherosclerotic plaque inflammation, measured using hybrid PET/MRI with FDG, may be essential in identifying OSA phenotypes that may respond to OSA treatment. Furthermore, such an end-point would aid in characterizing the effect of OSA and its treatment on molecular atherosclerotic mechanisms, which remain largely unknown. Future large randomized studies will be valuable to assess the effect and efficacy of CPAP on vascular inflammation utilizing the PET/MRI platform.

Conclusion

We apply state-of-the-art vascular PET/MR imaging techniques to image and quantify intraplaque inflammation on OSA patients. Furthermore, we quantify the anti-inflammatory actions of CPAP using imaging metrics that have already been successfully utilized to quantify the anti-inflammatory effects of statins [21–23], demonstrating possible early anti-atherosclerotic treatment effects of CPAP at a molecular level. Use of the vascular PET/MRI platform in future larger studies could allow us to better understand the impact of OSA and its treatment on the risk of vascular inflammation and, ultimately, clinical CVD events.

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Fig. 1.
Atherosclerotic plaque activity. Pictorial of inflammatory/active and inactive atherosclerotic plaque in arterial vessel walls

Fig. 2.
Pictorial of study hypothesis: Short-term treatment with CPAP reduces atherosclerotic plaque inflammation as measured by PET/MRI before and after CPAP

Fig. 3.

Imaging work-flow. Upon patient arrival, point-of-care glucose and renal function testing was done. FDG tracer was then injected to allow 90 minutes of circulation time, following which PET/MRI data were acquired simultaneously for a total of 60 minutes

Reductions in arterial wall FDG uptake in the carotid arteries and aorta after CPAP

Fig. 4. Reduction in FDG uptake after CPAP therapy. Bq (Becquerel), CPAP (continuous positive airway pressure), FDG (fluorodeoxyglucose), PET/MR (positron emission tomography/ magnetic resonance), RC (right carotid), and LC (left carotid)

Fig. 5. Carotid inflammation before and after CPAP. TBR (target-to-background ratio) and CPAP (continuous positive airway pressure). Average reductions in arterial wall FDG uptake as measured by TBRmax in the right and left carotid arteries after CPAP

Table 1

Study exclusion criteria

1	History of cerebrovascular disease, i.e., stroke, carotid stent placement, or endarterectomy; myocardial infarction, coronary artery bypass graft surgery, insulin-dependent diabetes, or pre-scan glucose of ≥ 200 mg/dl
2	Presence of ferromagnetic implants (e.g., aneurysm clip, defibrillator, pacemaker, etc.) or a condition that may be contraindicated for the MRI procedure (e.g., claustrophobia)
3	Actively receiving SA treatment with positive airway pressure therapy (PAP), oral appliance, etc.
4	$GFR < 60$ mg/ml/1.73m ²
5	Pregnancy
6	Allergic to gadolinium
7	On statin medications

GFR glomerular filtration rate, *MRI* magnetic resonance imaging, *SA* sleep apnea

Table 2

Baseline characteristics—demographics, CV-risk factors, sleep study indices, and CPAP adherence data

Demographics	
Subjects (<i>n</i>)	5
Median age (years)	41 (40–69)
Male	4 (80%)
Female	1 (20%)
Median BMI (kg/m ²)	33 (26–40)
Framingham risk score category	
• Low risk	3 (60%)
• Intermediate risk	2 (40%)
Diagnosis of HTN	4 (80%)
Diagnosis of HLD	1 (20%)
Smoking history	3 (60%)
Median ESS	7 (0–18)
In-lab PSG	3 (60%)
Portable study	2 (40%)
Median AHI (range)	31 (16–54)
Mean TST (minutes)	378
Mean lowest O ₂ saturation (%)	82
Median duration of CPAP prior to follow-up imaging (weeks) (<i>n</i> = 3)	17 (15–19)
Mean CPAP usage (hours/day) (<i>n</i> = 3)	6
Mean AHI on CPAP (<i>n</i> = 3)	2.3

AHI apnea-hypopnea index, *BMI* Body Mass Index, *CPAP* continuous positive airway pressure, *CV* cardiovascular, *ESS* Epworth Sleepiness Score based on a scale of 1–24, *HLD* hyperlipidemia, *HTN* hypertension, *PSG* polysomnography, *TST* total sleep time

Table 3

Quantitative analysis of carotid and aortic FDG uptake before and after CPAP ($n = 3$)

ROI	Average TBR _{mean}		Average TBR _{max}		Percent change	Percent change
	Pre-CPAP	Post-CPAP	Pre-CPAP	Post-CPAP		
Right carotid	1.19	1.12	1.39	1.32	- 6.10%	- 5.42%
Left carotid	1.23	1.18	1.43	1.36	- 3.80%	- 5.23%
Aortic wall	1.36	1.27	1.69	1.56	- 6.48%	- 7.89%
Average of ROIs	1.26	1.19	1.26	1.41	- 5.46%	- 6.18%

CPAP continuous positive airway pressure therapy, FDG 18F-fluorodeoxyglucose, ROI region of interest, TBR_{mean} mean target-to-background ratio, TBR_{max} maximum target-to-background ratio