The association between endothelial dysfunction and subclinical myocardial injury in male obstructive sleep apnoea patients

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In male OSA patients, endothelial dysfunction appears to be potentially correlated with an increased risk of subclinical myocardial injury, as evidenced by the higher prevalence of detectable hs-cTnI levels https://bit.ly/3zvW1WG

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Abstract

Background Endothelial dysfunction was shown to contribute significantly to the elevated cardiovascular risk observed in the general population. However, the relationship between endothelial dysfunction and subclinical myocardial injury in obstructive sleep apnoea (OSA) patients remains unclear.

Methods This cross-sectional study recruited 165 consecutive male patients diagnosed with OSA. All participants underwent overnight polysomnography to confirm the diagnosis and assess the severity of OSA. Subclinical myocardial injury was evaluated using high-sensitivity cardiac troponin I (hs-cTnI) measurements, while endothelial dysfunction was assessed through the peripheral arterial tonometry.

Results Endothelial dysfunction was present in 80 (48.5%) of the subjects and hs-cTnI was detectable in 147 (89.1%) of the participants. When compared with OSA patients without endothelial dysfunction, those with endothelial dysfunction exhibited significantly lower percentages of hypertension (23.8% *versus* 43.5%, p=0.007) and abdominal obesity (76.3% *versus* 88.2%, p=0.043). Patients with endothelial dysfunction frequently manifest a lower apnoea–hypopnoea index and oxygen desaturation index. Despite comparable median hs-cTnI levels, a higher proportion of subjects with detectable hs-cTnI levels was observed among those with endothelial dysfunction (95% *versus* 83.5%, p=0.018). Logistic regression analysis indicated that endothelial dysfunction was significantly associated with a detectable level of hs-cTnI after adjustment for multiple confounders.

Conclusions In male OSA patients, endothelial dysfunction appears to be potentially correlated with an increased risk of subclinical myocardial injury, as evidenced by the higher prevalence of detectable hs-cTnI levels. Further investigations are warranted to elucidate the role of endothelial dysfunction in predicting future cardiovascular mortality in this population.

Background

Obstructive sleep apnoea (OSA) is a highly prevalent disorder, affecting up to 50% of men and over 20% of women [1], characterised by repetitive obstruction of the upper airway, leading to nocturnal intermittent hypoxia and sleep fragmentation [2]. The diagnosis and severity assessment of OSA primarily rely on the apnoea–hypopnoea index (AHI) in the majority of published literature. OSA has been firmly established as a significant contributor to various conditions, including endothelial dysfunction and cardiovascular diseases (CVDs) [3]. A cross-sectional study revealed a nonlinear relationship between the oxygen desaturation index (ODI), a measure of hypoxia, and endothelial function, observing a threshold effect both above and below a specific ODI level [4]. Furthermore, the study also demonstrated a similar correlation between AHI and endothelial dysfunction. However, there remains a lack of consensus regarding whether intermittent hypoxia in OSA exerts a protective or detrimental effect on endothelial

function. Additionally, given that the pathophysiological hallmarks of OSA encompass sympathetic activation and oxidative stress, both of which have detrimental impacts on the cardiovascular system, OSA has been consistently associated with adverse cardiovascular outcomes [5]. While the precise mechanisms underlying the OSA–CVD association remain incompletely understood, endothelial dysfunction is considered an early and potentially pivotal step in the development of CVD among OSA patients [6].

As one of the intracellular cardiac myofibrillar proteins, cardiac troponin has been recognised as a biomarker reflecting myocardial injury [7]. Compared with traditional assays, high-sensitivity cardiac troponin I (hs-cTnI) or troponin T (hs-cTnT), measured using various assays with a substantially lower detection limit, have demonstrated the ability to predict coronary heart disease and heart failure. A cross-sectional study has asserted that increased OSA severity is independently associated with elevated levels of hs-cTnI, suggesting that intermittent hypoxia in OSA may contribute to subclinical myocardial injury [8]. This finding aligns with another study, which concluded that hs-cTnT was independently related to OSA after adjusting for multiple confounders, and was associated with subsequent risk of mortality and heart failure across all severity groups [9]. However, a large-scale, population-based cohort study investigating the relationship between hs-cTnT and OSA categories found that the association lost statistical significance upon adjustment for confounders [10]. This inconsistency in the literature highlights a gap in understanding the correlation between OSA severity and high-sensitivity cardiac troponin levels. Endothelial dysfunction, stemming from reduced bioavailability of endothelial relaxing factors such as nitric oxide, has been established as a marker of cardiovascular risk in the general population [11]. Nevertheless, there is a paucity of data specifically examining this association in OSA patients, despite the potential implications for understanding the cardiovascular consequences of OSA.

In the present analysis, we investigated the association between endothelial dysfunction, as evaluated by reactive hyperaemia peripheral arterial tonometry (PAT), and subclinical myocardial injury, as indicated by detectable levels of hs-cTnI, in a cohort of OSA patients without overt, pre-existing CVDs.

Methods

Study design and population

We evaluated consecutive adult patients who were referred to the sleep centre of Peking Union Medical College Hospital (PUMCH) from August 2019 to June 2021. Recognising the gender disparity in our centre, with significantly more male than female patients seeking consultation and sleep monitoring, we focused our recruitment efforts exclusively on male patients diagnosed with OSA. Our exclusion criteria were as follows: 1) previous treatment with continuous positive airway pressure; 2) unable to complete questionnaires; 3) pre-existing CVDs including myocardial infarction, strokes and heart failure; 4) comorbidities, including asthma or COPD; and 5) diagnosis of restless leg syndrome, narcolepsy or central sleep apnoea. The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethical committee of PUMCH. Written informed consents were obtained from all participants.

Each participant underwent an overnight polysomnography (PSG; Embla N7000, Natus Medical Incorporated, Orlando, FL, USA) from 23:00 to 06:00. Electroencephalography, electrooculography, electromyography, electrocardiography, thermistor signal of air flow, thoracoabdominal movement, pulse oximetry and sensors for body position were recorded according to standard protocols recommended by the American Academy of Sleep Medicine [12]. Hypopnoea was defined as a 30% reduction in airflow lasting at least 10 s accompanied by oxygen desaturation of ⩾3% or an arousal. Apnoea was identified as cessation of airflow for ⩾10 s. The AHI was calculated as the average number of apnoea and hypopnoea episodes per hour of sleep. OSA was diagnosed according to a previous guideline [12]. OSA was graded as mild (AHI >5, <15 events·h^{-1}), moderate (AHI ⩾15, <30 events·h^{-1}), severe (AHI 30–50 events·h^{-1}) and very severe (AHI >50 events·h^{-1}) [13]. All recordings were scored by a skilled sleep technician based on standard criteria. We also collected metrics, including ODI, time spent with saturation of pulse oxygen (S_{pO_2}) <90% (T90), mean S_{pO_2}, lowest S_{pO_2} and the percentages of sleep stages in the PSG report. Furthermore, a low arousal threshold (ArTH) plays a pivotal role in the pathogenesis of OSA. We operationalised ArTH using PSG parameters, defining a low ArTH score as the sum of one point each for AHI <30 events·h^{-1}, LS_{pO_2} >82.5% and hypopnoea% >58.3%, with a total score of ⩾2 indicating a low ArTH, as previously reported [14].

All patients completed the Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI) questionnaire. Poorer sleep quality was identified as a PSQI ⩾8 [15]. Excessive daytime sleepiness was defined as an ESS score >10 [16]. Data on baseline demographic characteristics, including age, current smoking status, and comorbidities such as hypertension, hyperlipidaemia and diabetes were obtained. Neck, waist and hip circumferences were recorded. A waist–hip ratio >0.90 for males is defined as abdominal obesity [17].

Endothelial function was evaluated in the morning following PSG using PAT (Endo-PAT 2000, Itamar Medical Ltd., Caesarea, Israel) [18]. The standard protocol comprised three consecutive phases: 1) a 5-min baseline recording; 2) inflation of the blood pressure cuff to 60 mmHg above the baseline systolic pressure and exceeding 200 mmHg to occlude the brachial artery for 5 min; and 3) a further 5-min recording after cuff deflation. The reactive hyperaemia index (RHI) was automatically calculated by the Endo-PAT system. Endothelial dysfunction was defined as an RHI value <1.67 [19]. Subsequent fasting blood samples were collected at 07:00 and processed immediately. All plasma were centrally stored at −80°C. hs-cTnI was measured using a highly sensitive assay (Elecsys Troponin I; Abbott Diagnostics, Abbott Park, IL, USA) with a lower limit of detection of 1.0 $ng \cdot L^{-1}$. Lipid profiles and glycated haemoglobin were concurrently measured.

Statistical analysis

Categorical data were presented as frequency (percentage). Quantitative variables were expressed as median (interquartile range, 25th to 75th percentile) or mean±SD depending on whether the data followed a skewed or normal distribution, respectively. Chi-squared/Fisher's exact tests were employed to analyse differences between categorical variables, as appropriate. Quantitative variables were analysed using an independent samples t-test or Mann–Whitney U-test. For patients with an undetectable hs-cTnI level, a concentration of 0.5 $ng \cdot L^{-1}$ was imputed, consistent with the strategy adopted in previous literature [8]. In regression modelling, the presence of detectable hs-cTnI was set as the dependent variable to assess the association between endothelial dysfunction and subclinical myocardial injury. The multivariable model was adjusted for age, smoking status, hyperlipidaemia, hypertension, diabetes, abdominal obesity, OSA severity and excessive daytime sleepiness. To determine the association between OSA and both endothelial dysfunction and myocardial injury, the p-values for trends in rates across groups were examined using the logistic regression models. A test for trend was based on a quasi-continuous variable containing the median value for each group. The nonlinearity between ODI and endothelial dysfunction was assessed using restricted cubic splines with three knots positioned at the 10th, 50th and 90th percentiles to further evaluate their dose–response relationship.

A two-sided p-value <0.05 was considered as statistically significant. Data analyses were conducted with SPSS (version 24.0, Armonk, NY, USA) and GraphPad Prism 9.5.1.

Results

A total of 165 participants were recruited for this study. Among these patients, 80 (48.5%) exhibited endothelial dysfunction. hs-cTnI was detectable in 147 (89.1%) of the participants. The median age of the cohort was 39 years. The baseline characteristics of patients with and without endothelial dysfunction are presented in table 1. Compared with OSA patients without endothelial dysfunction, those with endothelial dysfunction demonstrated significantly lower prevalences of hypertension (23.8% *versus* 43.5%, p=0.007) and abdominal obesity (76.3% *versus* 88.2%, p=0.043). No significant differences were observed between the two groups in terms of age, body mass index (BMI), smoking status, diabetes, excessive daytime sleepiness or sleep quality.

TABLE 1 Comparison of baseline characteristics in OSA patients with and without endothelial dysfunction

Variables	Total (n=165)	Endothelial dysfunction (n=80)	No endothelial dysfunction (n=85)	p-value
Age, years	39 (35–48)	39 (34–46)	40 (36–48)	0.300
BMI, $kg \cdot m^{-2}$	27.8 (25.5–29.7)	27.0 (25.0–29.7)	27.8 (26.0–29.8)	0.206
BMI>25	128 (77.6)	58 (72.5)	70 (82.4)	0.129
BMI>30	36 (21.8)	17 (21.3)	19 (22.4)	0.864
Current smoking	49 (29.7)	23 (28.8)	26 (30.6)	0.796
Diabetes	14 (8.5)	7 (8.8)	7 (8.2)	0.906
Hypertension	56 (33.9)	19 (23.8)	37 (43.5)	0.007
Hyperlipidaemia	122 (73.9)	58 (72.5)	64 (75.3)	0.683
Neck circumference, cm	41 (39–42)	40 (39–42)	41 (39–42)	0.778
Abdominal obesity	136 (82.4)	61 (76.3)	75 (88.2)	0.043
ESS>10	99 (60.0)	50 (62.5)	49 (57.6)	0.525
PSQI⩾8	68 (41.2)	35 (43.8)	33 (38.8)	0.521

Data are presented as n (%) and median (range). OSA: obstructive sleep apnoea; BMI: body mass index; ESS: Epworth sleepiness scale; PSQI: Pittsburgh sleep quality index.

TABLE 2 Comparison of polysomnography data and laboratory tests in OSA patients with and without endothelial dysfunction

Variables	Endothelial dysfunction (n=80)	No endothelial dysfunction (n=85)	p-value
Total sleep time, min	405.5±56.5	405.3±60.9	0.983
Sleep efficiency, %	93.1 (85.3–96.9)	92.8 (83.2–96.9)	0.993
Percentage of N2 sleep	44.5±14.4	45.4±15.8	0.707
Percentage of N3 sleep	22.7±13.2	21.5±13.5	0.580
Percentage of REM sleep	14.8±6.4	14.8±5.7	0.949
Low arousal threshold	36 (45.0)	28 (32.9)	0.112
AHI, events·h^{-1}	35.8 (12.5–54.4)	46.9 (18.6–65.2)	0.049
AHI>15	57 (71.3)	69 (81.2)	0.134
AHI>30	41 (51.3)	53 (62.4)	0.150
ODI, events·h^{-1}	24.5 (10.3–50.4)	39.6 (16.5–65.0)	0.046
T90, %	0.3 (0–2.4)	1.1 (0.1–6.8)	0.012
MS$_{pO_2}$, %	96.2 (94.2–97.7)	95.4 (94.0–97.2)	0.050
LS$_{pO_2}$, %	85.0 (77.3–89.0)	82.0 (74.5–88.0)	0.115
TC >5.7	19 (23.8)	19 (22.4)	0.831
TG >1.7	37 (46.3)	51 (60.0)	0.077
HDLC <0.93	21 (26.3)	30 (35.3)	0.209
LDLC >3.37	35 (43.8)	30 (35.3)	0.267
HbA1c, %	5.5 (5.2–5.7)	5.4 (5.2–5.7)	0.787
Hs-cTnI, ng·L^{-1}	2.0 (1.2–3.0)	2.1 (1.1–3.0)	0.359
Detectable hs-cTnI	76 (95.0)	71 (83.5)	0.018

Data are presented as n (%), mean±SD and median (range). OSA: obstructive sleep apnoea; AHI: apnoea–hypopnoea index; HbA1c: glycated haemoglobin; HDLC: high-density lipoprotein cholesterol; hs-cTnI: high-sensitivity cardiac troponin I; LDLC: low-density lipoprotein cholesterol; LS$_{pO_2}$: lowest oxygen saturation; MS$_{pO_2}$: the mean oxygen saturation; ODI: oxygen desaturation index; REM: rapid eye movement; T90: time spent with oxygen saturation <90% per hour of sleep; TC: total cholesterol; TG: triglyceride.

As illustrated in table 2, patients with endothelial dysfunction had lower AHI (35.8 *versus* 46.9 events·h^{-1}, p=0.049), ODI (24.5 *versus* 39.6 events·h^{-1}) and T90 (0.3% *versus* 1.1%, p=0.012). However, both groups had similar OSA severity based on AHI (⩾15 or ⩾30), as well as comparable lipid profiles, including total cholesterol, triglyceride and low-density lipoprotein cholesterol. Despite comparable median hs-cTnI levels, a higher proportion of participants with endothelial dysfunction had detectable hs-cTnI levels (95% *versus* 83.5%, p=0.018).

Table 3 demonstrates the correlation between OSA severity and both endothelial dysfunction and the presence of detectable hs-cTnI. No significant trend was observed in the proportion of patients exhibiting endothelial dysfunction with escalating OSA severity, as categorised by the AHI (p-value trend=0.181). Similarly, no significant trend was detected for the presence of hs-cTnI with OSA severity (p-value trend=0.825). We also tested the dose–response association between ODI and RHI using a restricted cubic spline model, and found that there was no nonlinear effect of ODI for endothelial dysfunction (p-value for nonlinear=0.829; supplementary figure 1).

TABLE 3 Associations of OSA severity with endothelial dysfunction and detectable hs-cTnI[#]

	Endothelial dysfunction		Detectable hs-cTnI	
OSA severity, AHI, events·h^{-1}	**n/N**	**OR (95% CI)**	**n/N**	**OR (95% CI)**
Mild, 8.4 (5–15)	23/39	1 (ref)	33/39	1 (ref)
Moderate. 20.6 (15–30)	16/32	0.69 (0.26–1.84)	29/32	1.84 (0.38–8.83)
Severe, 42.4 (30–50)	17/31	1.01 (0.37–2.77)	27/31	0.76 (0.18–3.29)
Very severe, 66.9 (>50)	24/63	0.51 (0.21–1.25)	58/63	1.06 (0.26–4.31)
p-value for trend[¶]		0.181		0.825

Data for OSA severity are presented as median (range). AHI: apnoea–hypopnoea index; hs-cTnI: high-sensitivity cardiac troponin I; OSA: obstructive sleep apnoea. [#]: ORs and 95% CI were calculated with the use of the logistical regression models. The models were adjusted for age, smoking, diabetes, hypertension, hyperlipidaemia and abdominal obesity. [¶]: Test for trend was based on variables containing the median value for each group.

Based on multivariable logistic regression analysis (figure 1), endothelial dysfunction was significantly associated with the presence of detectable hs-cTnI (OR 6.28, 95% CI 1.74–22.62). Additionally, baseline hypertension (OR 5.80, 95% CI 1.17–28.81) and hyperlipidaemia (OR 5.09, 95% CI 1.46–17.81) were also identified as risk factors associated with an increased likelihood of detectable hs-cTnI levels.

Discussion

In this cross-sectional study, we conducted a comparative analysis of baseline demographics, sleep metrics and laboratory tests between patients with and without endothelial dysfunction, as assessed noninvasively *via* the measurement of RHI. Patients with endothelial dysfunction displayed a lower prevalence of hypertension and abdominal obesity, a milder degree of intermittent hypoxia and an elevated proportion of detectable hs-cTnI. The present study was the first to explore the correlation between endothelial dysfunction, evaluated using PAT, and subclinical myocardial injury, indicated by the detectable levels of hs-cTnI in OSA patients. After adjusting for multiple confounding variables, a significant and persistent association between these two parameters was observed.

Endothelial dysfunction, an early indicator of atherosclerosis and predictor of cardiovascular events, is associated with OSA. The recurrent hypoxia/re-oxygenation episodes during sleep may underlie this association, adversely affecting the endothelial function through mechanisms including reduced nitric oxide bioavailability, oxidative stress, inflammation and sympathetic hyperactivity. This leads to increased adhesion molecules, vascular damaging microparticles and hypercoagulability. Additionally, diminished endothelial progenitor cells compromise the repair capacity, further contributing to endothelial dysfunction in OSA [20].

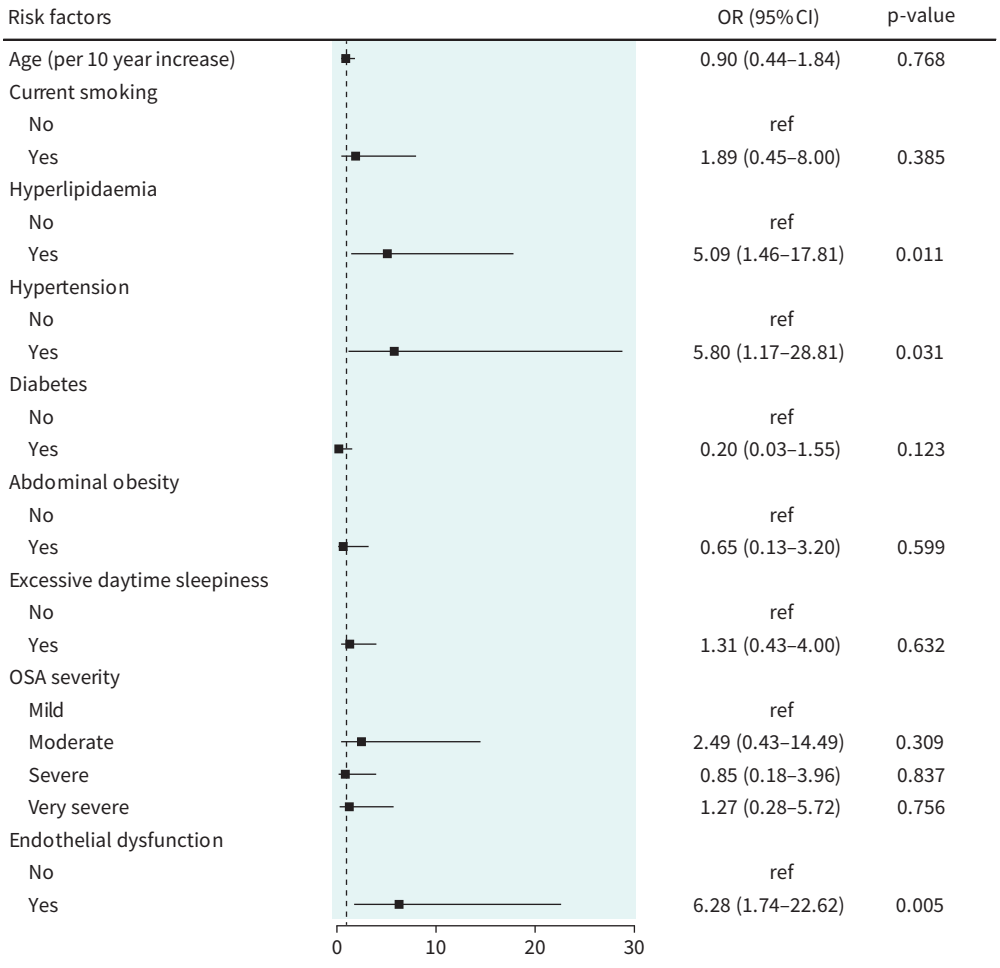

FIGURE 1 Adjusted association of multiple factors with detectable hs-cTnI (high-sensitivity cardiac troponin I) in obstructive sleep apnoea (OSA) patients.

Previous research has yielded diverging results concerning the association between OSA and endothelial dysfunction. Notably, the Framingham part of the Sleep Heart Health Study failed to identify a significant correlation between OSA and endothelial function [21]. The study enrolled participants with predominantly mild OSA (63% of subjects had an AHI of 5–14.9). Similarly, studies in diabetic patients without overt CVD have demonstrated a diminished effect of moderate-to-severe OSA on digital microvascular endothelial function [19]. In contrast, another study showed reduced endothelial function in patients with moderate-to-severe OSA, independent of obesity and other conventional risk factors [22]. A cross-sectional study involving 267 individuals with established CVD or CVD risk factors further examined the relationship between OSA severity (as assessed by AHI or ODI) and endothelial dysfunction measured by PAT [4]. The study revealed an intriguing trend of improved endothelial function at an ODI range of 13.9–24.6, suggesting a potential protective role of moderate intermittent hypoxia. However, a graded decline in endothelial function was also observed with higher levels of intermittent hypoxia. Given such a disparity, it is not surprising that patients in our cohort with endothelial dysfunction exhibited milder intermittent hypoxia, as indicated by sleep parameters, including AHI. Meanwhile, we found no significant trend of an increase in the proportion of patients exhibiting endothelial dysfunction as OSA severity escalated. Given this, we hypothesise that when AHI reaches a critical threshold, such as exceeding 30 events·h^{-1}, indicating severe OSA in our study, further alterations in endothelial function, whether beneficial or detrimental, may be attenuated.

The relationship between OSA and CVD risk is complex, with the prevailing view suggesting that OSA triggers a cascade of detrimental effects within the cardiovascular system, including sympathetic activation, oxidative stress, systemic inflammation and endothelial malfunction, all contributing to the atherosclerotic process and ultimately poorer cardiovascular outcomes [5]. Einvik *et al*. [8] reported in a community-based study of 514 subjects that increased OSA severity is significantly associated with elevated levels of hs-cTnI, which is supported by two additional studies showing a positive correlation between OSA severity and detectable levels of hs-cTnT in patients with comorbid CVDs [23, 24]. This suggests that intermittent hypoxia in OSA may lead to subclinical myocardial injury. A study involving 505 participants demonstrated that hs-cTnT was detectable in 53.2% of all subjects with OSA (AHI⩾5) and in 72.0% of those with severe OSA (AHI⩾30) [10]. In our study, an even higher proportion of OSA patients (almost 89%) had detectable hs-cTnI levels, providing further evidence of OSA-related myocardial injury. However, two studies have unexpectedly proposed that OSA may exhibit a protective influence on CVD under certain conditions through the mechanism of “ischaemic preconditioning” [25, 26], challenging the conventional view of OSA’s detrimental role. While the role of ischaemic preconditioning in OSA with intermittent hypoxia remains controversial, this mechanism has been demonstrated *in vivo* and warrants further investigation in clinical and experimental trials [27]. Additionally, the effect of continuous positive airway pressure therapy for OSA on hs-cTnT levels or the reduction of CVD risk has yet to reach a consensus [28, 29]. The intricate interplay between OSA, endothelial function and cardiac injury necessitates additional research to elucidate the underlying molecular mechanisms.

Although the prevailing consensus in the published literature is that endothelial dysfunction increases the risk of CVD in the general population [30], it remains unclear and difficult to elucidate whether this effect persists or is altered in OSA patients. Furthermore, the role of OSA severity, as measured by AHI or ODI, in modulating this relationship warrants further discussion. Our data support the notion that endothelial dysfunction in OSA patients serves as an indicator of vascular health, providing valuable supplementary information regarding subclinical myocardial injury captured by clinical parameters such as hs-cTnI. Notably, our study found that the presence of OSA did not affect the positive correlation between endothelial dysfunction and low-grade myocardial injury; however, the underlying mechanisms responsible for this consistent association remain poorly understood.

Several limitations should be acknowledged. First, the cross-sectional design, small sample size and the exclusive inclusion of male participants in the present study undoubtedly restrict the extrapolation of our conclusions. Second, the absence of multiple objective measure of cardiac data, such as brain natriuretic peptide levels, echocardiography and magnetic resonance imaging, leads to a relatively incomplete evaluation of cardiac injury. Similarly, endothelial function in the current study was assessed by Endo-PAT technology, a validated surrogate measure that, while informative, does not necessarily provide absolute accuracy. The reactive hyperaemia response, as measured by Endo-PAT, reflects digital pulse amplitude, which is partly mediated by nitric oxide. However, it is expected that nitric oxide mediates approximately 60% of digital artery dilation during reactive hyperaemia, with the remainder attributed to other vasodilator components [31]. Nevertheless, PAT has its advantages, including reduced dependence on operator skill and being a robust measure, and has been utilised in numerous studies. Third, our analysis was limited to patients without overt pre-existing CVD, thus limiting the generalisation of our conclusions to patients with concurrent OSA and CVD.

Conclusion

This study represents the first to investigate the relationship between endothelial dysfunction, as assessed by PAT, and subclinical myocardial injury, reflected by detectable hs-cTnI levels, in patients with OSA. After adjusting for multiple confounders, a persistent and significant association was observed. Our findings underscore the importance of heightened vigilance towards endothelial dysfunction in OSA patients, given the intricate interplay among OSA, endothelial function and cardiac injury, which may have implications for improving cardiovascular outcomes. Urgently needed are larger, multicentre studies to corroborate and extend our observations.

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Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics statement: The study was approved by the Ethics Committee of PUMCH. Written informed consent was obtained from all the participants.

Conflict of interest: The authors have nothing to disclose.

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