Continuous positive airway pressure improves blood pressure and serum cardiovascular biomarkers in obstructive sleep apnoea and hypertension

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In subjects with moderate-to-severe OSA and receiving three or more antihypertensive drugs, continuous positive airway pressure for treatment of OSA improves blood pressure control, and may alleviate subclinical myocardial injury and strain https://bit.ly/3u6DsAe

Cite this article as: Lui MM-S, Tse H-F, Lam DC-L, *et al*. Continuous positive airway pressure improves blood pressure and serum cardiovascular biomarkers in obstructive sleep apnoea and hypertension. *Eur Respir J* 2021; 58: 2003687 [DOI: 10.1183/13993003.03687-2020].

This article has supplementary material available from erj.ersjournals.com

Received: 30 Sept 2020
Accepted: 23 March 2021

Abstract

Background The impact of treatment for obstructive sleep apnoea (OSA) on reduction of cardiovascular risk is unclear. This study aimed to examine the effect of continuous positive airway pressure (CPAP) on ambulatory blood pressure (BP) and subclinical myocardial injury in subjects with OSA and hypertension.

Methods This was a parallel-group randomised controlled trial. Subjects with hypertension requiring at least three antihypertensive medications and moderate-to-severe OSA were enrolled. Eligible subjects were randomised (1:1) to receive either CPAP treatment or control (no CPAP) for 8 weeks. Changes in ambulatory BP and serum biomarkers were compared. Stratified analysis according to circadian BP pattern was performed.

Results 92 subjects (75% male; mean±SD age 51±8 years and apnoea–hypopnoea index 40±8 events·h^{-1}, taking an average of 3.4 (range 3–6) antihypertensive drugs) were randomised. The group on CPAP treatment, compared with the control group, demonstrated a significant reduction in 24-h systolic BP (−4.4 (95% CI −8.7–−0.1) mmHg; p=0.046), 24-h diastolic BP (−2.9 (95% CI −5.5–−0.2) mmHg; p=0.032), daytime systolic BP (−5.4 (95% CI −9.7–−1.0) mmHg; p=0.016) and daytime diastolic BP (−3.4 (95% CI −6.1–−0.8) mmHg; p=0.012). CPAP treatment was associated with significant BP lowering only in nondippers, but not in dippers. Serum troponin I (mean difference −1.74 (95% CI −2.97–−0.50) pg·mL^{-1}; p=0.006) and brain natriuretic peptide (−9.1 (95% CI −17.6–−0.6) pg·mL^{-1}; p=0.036) were significantly reduced in CPAP compared with the control group.

Conclusions In a cohort with OSA and multiple cardiovascular risk factors including difficult-to-control hypertension, short-term CPAP treatment improved ambulatory BP, and alleviated subclinical myocardial injury and strain.

Introduction

Both hypertension and obstructive sleep apnoea (OSA) are highly prevalent medical conditions, each affecting 1 billion adults worldwide [1, 2]. Notably, OSA is estimated to be present in 25–50% of the hypertensive population [2]. In hypertensive subjects with concomitant untreated OSA, blood pressure (BP) is typically more difficult to control [2]. In our previous cross-sectional study, 50% of subjects with difficult-to-control hypertension, defined as requiring three or more antihypertensive drugs, had severe OSA that was asymptomatic and unrecognised, highlighting the burden of the condition [3]. Meta-analyses have demonstrated a modest benefit of continuous positive airway pressure (CPAP) treatment for OSA on BP reduction of ∼2 mmHg [4–6]. However, significant heterogeneity in BP response was present among

the included studies, and certain phenotypes such as younger age, uncontrolled BP and more severe sleep apnoea predicted better BP response to treatment of comorbid OSA [7].

Hypertension is a major driver of end-organ injury and cardiovascular diseases (CVDs). Suboptimal BP control contributes to left ventricular strain and atherosclerotic coronary artery disease [2]. Other than hypertension, OSA also gives rise to multiple downstream pathogenic mechanisms which may potentially generate cardiovascular injury [8]. However, evidence regarding the impact of OSA treatment on prevention of major cardiovascular events and end-organ damage remains conflicting [9]. Given the close association between untreated OSA, hypertension and CVD, it is worthwhile to examine the relationship between OSA treatment, BP control and surrogate biomarkers robustly associated with cardiovascular prognosis. This randomised controlled trial (RCT) aimed to investigate the effects of short-term CPAP treatment on ambulatory BP control and serum biomarkers of subclinical cardiovascular impairment, in subjects with moderate-to-severe OSA and requiring multiple drugs for hypertension.

Materials and methods

Study design and participants

This was a parallel-group RCT (1:1) conducted at the Ho Ting Sik Sleep Disorder Centre at Queen Mary Hospital in Hong Kong. Consecutive subjects admitted for in-laboratory polysomnography were screened for eligibility, and recruited between July 2010 and March 2019. Subjects were considered eligible if they were aged 18–65 years, had hypertension on at least three antihypertensive medications and had moderate-to-severe OSA defined as apnoea–hypopnoea index (AHI) $\geqslant$15 events·h^{-1}. Exclusion criteria included moderate renal impairment (estimated glomerular filtration rate (eGFR) <30 mL·min^{-1}·1.73 m^{-2} body surface area), presence of other causes of secondary hypertension, previously diagnosed OSA with or without treatment, unstable medical conditions such as congestive heart failure, regular use of other drugs that affected BP (*e.g.* nonsteroidal anti-inflammatory drugs or steroids), noncompliance with antihypertensive medications (by interview), change in antihypertensive regimen within 2 months, occupations or routines that warranted early CPAP treatment (*e.g.* occupational/regular drivers and machine operators) and inability to sign an informed consent. Subjects with no occupational risks were invited to participate in the study irrespective of their degree of daytime sleepiness.

The study was approved by the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong (UW 09-051). The study was in compliance with the Declaration of Helsinki. All participants gave written informed consent. The study is registered at ClinicalTrials.gov with identifier number NCT00881985.

Study procedures

Baseline demographic documentation, polysomnography, blood sampling and assay of serum biomarkers, and ambulatory BP monitoring (ABPM) were performed as described in the supplementary material. Staff performing these measurements were completely blinded to the study intervention status of the subjects. History of coronary artery disease with or without interventions, arrhythmia, congestive heart failure or ventricular hypertrophy was determined from questionnaires and electronic medical records, and indicated the presence of cardiac dysfunction. Eligible subjects were randomised to either the CPAP or control group according to a computer-generated sequence (www.randomization.com). Investigators who enrolled the subjects were not involved in the randomisation or allocation of study groups. An auto-titrating positive airway pressure device (S8 AutoSet; ResMed, San Diego, CA, USA) with a built-in compliance monitor was provided to each subject randomised to the CPAP arm. The control group was assigned to usual care without CPAP. All subjects were educated on sleep hygiene measures, and advised to maintain their usual exercise habits and to report any change in their medication regimen upon reassessment.

Satisfactory CPAP adherence was defined as an average nightly CPAP usage of >4 h during the study period. The primary outcome was the change in 24-h mean systolic BP (SBP) between baseline and the eighth week. Secondary outcomes were changes in 24-h mean diastolic BP (DBP), mean SBP and DBP during daytime or night-time, serum high-sensitivity troponin I, brain natriuretic peptide (BNP), high-sensitivity C-reactive protein (CRP), heart-type fatty acid binding protein (HFABP), and plasma advanced oxidation protein products (AOPPs). All the outcomes were reassessed at the eighth week.

Sample size estimation and statistical analysis

In previous studies, CPAP treatment for 3 weeks to 6 months was accompanied by ~2–3 mmHg reduction in 24-h SBP [7]. Assuming a common standard deviation of 3 mmHg for both groups and a difference in change of SBP of 2 mmHg between the two groups, a minimum of 33 subjects was required in each group with a power of 80% to detect the difference between the two groups at a significance level of 5%. From

our past experience of clinical trials on OSA subjects newly initiated on CPAP [10], ~40% of the subjects might be noncompliant with CPAP or study assessments, or dropout from the clinical trial. The target sample size was set to be 46 in each arm, in order to achieve adequate statistical power.

The two-group comparisons in baseline characteristics were performed using the Chi-squared test for categorical variables, the paired t-test for normally distributed continuous data or the Mann–Whitney U-test for data not in normal distribution. Between-group comparisons of the change in BP and other parameters over the 8-week study period were performed using ANCOVA with adjustment for confounders. An intention-to-treat approach was adopted. A two-sided p-value <0.05 was taken as statistically significant. Analyses were performed using SPSS version 20.0 (IBM, Armonk, NY, USA).

Results

Figure 1 shows the flowchart of subject recruitment. 92 subjects were recruited and randomised to either the CPAP (n=46) or control group (n=46), with mean±SD age 53.2±8.7 years and body mass index (BMI) 30.9±5.1 kg·m^{-2}; 77% were male. The median (interquartile range) AHI was 44.4 (33.5–64.3) events·h^{-1}. In the CPAP group, five subjects did not return for reassessment at the eighth week and one subject refused reassessment ABPM. In the control group, four subjects were lost to follow-up and one subject refused reassessment ABPM. All subjects were included in the intention-to-treat analysis.

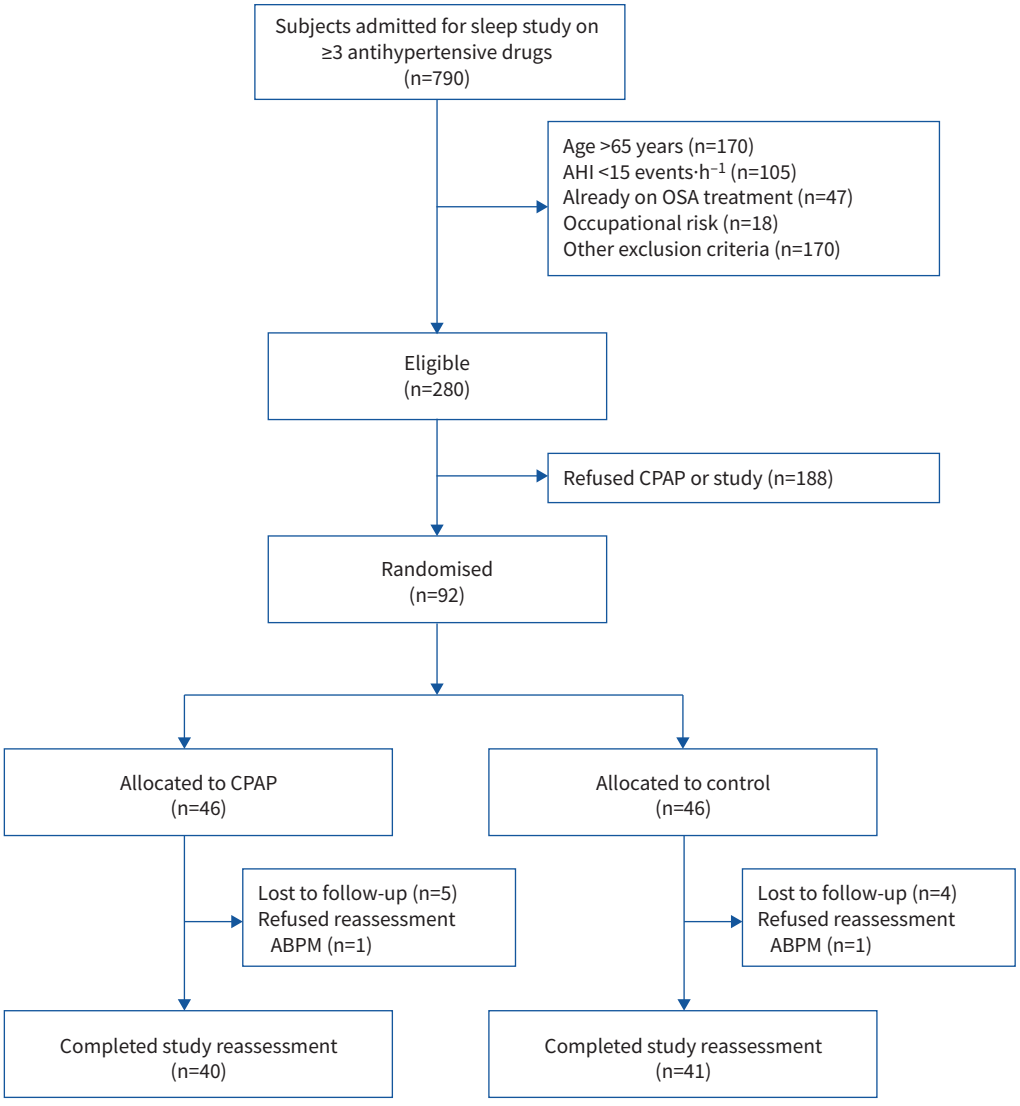

FIGURE 1 Flowchart showing subject identification. AHI: apnoea–hypopnoea index; OSA: obstructive sleep apnoea; CPAP: continuous positive airway pressure; ABPM: ambulatory blood pressure monitoring.

Table 1 shows the baseline characteristics of the recruited subjects. The two groups had significant differences in baseline Epworth Sleepiness Scale (ESS) and eGFR. The two groups were similar in terms of the constituents of their antihypertensive drug regimen (supplementary table S1). None had any change in number or dosage of their medications during the study period. At the end of the study, mean±SD CPAP usage over 8 weeks was 3.1±2.5 h·night^{-1} among the treatment group, with residual AHI 4.9±4.2 events·h^{-1}. 23 out of 41 (56%) subjects had satisfactory CPAP adherence and their mean±SD CPAP usage was 5.3±1.3 h·night^{-1}. No significant change in BMI, waist circumference and neck circumference in either group was detected over the study period.

TABLE 1 Baseline characteristics of the study subjects

	CPAP group	Control group
Subjects	46	46
Age years	52.5±9.0	53.9±8.4
Male	36 (78.3)	35 (76.1)
BMI kg·m^{-2}	30.9±5.1	31.0±5.2
Waist circumference cm	101.0±10.9	100.7±9.7
ESS*	8.4±5.5	6.0±3.9
ESS ⩾10*	16 (34.8)	6 (13.0)
Excessively sleepy during the day#	14 (30.4)	10 (21.7)
Nonsmoker	36 (78.3)	27 (58.7)
Nondrinker	36 (78.3)	33 (71.7)
History of cardiac diseases		
Arrhythmia	0	3 (6.5)
Coronary artery disease	11 (23.9)	10 (21.7)
Heart failure/left ventricular hypertrophy	3 (6.5)	5 (10.9)
History of cerebrovascular accident	3 (6.5)	8 (17.4)
Presence of metabolic syndrome	44 (95.7)	42 (91.3)
eGFR* mL·min^{-1}·1.73 m^{-2}	80.6±13.6	71.3±16.6
Ambulatory BP parameters		
24-h SBP mmHg	130.8±14.0	128.2±16.9
24-h DBP mmHg	79.8±9.1	79.1±8.8
Daytime SBP (7:30–23:30)	133.0±14.5	129.8±16.7
Daytime DBP (7:30–23:30)	81.2±9.5	80.3±8.6
Night-time SBP (23:30–7:30)	123.5±15.1	122.5±21.8
Night-time DBP (23:30–7:30)	75.5±9.8	75.1±12.3
⩾4 drugs or 3 drugs with BP ⩾130/80 mmHg¶	34 (73.9)	33 (71.7)
⩾4 drugs or 3 drugs with BP ⩾120/80 mmHg	43 (93.4)	42 (91.6)
Nondipper	29 (63.0)	31 (67.4)
Sleep parameters		
TST min	385 (337–424)	384 (336–431)
AHI events·h^{-1}	45.4 (31.8–71.3)	41.6 (34.2–61.2)
ODI events·h^{-1}	42.2 (24.3–69.9)	39.2 (29.5–59.0)
Minimum oxygen saturation %	76 (64–81)	75 (67–80)
Oxygen saturation <90% min	27.6 (10.9–66.8)	34.3 (12.1–90.1)
Arousal index events·h^{-1}	22.2 (13.8–42.3)	20.4 (15.3–36.4)
Biomarker parameters		
Troponin I pg·mL^{-1}	4.0 (2.5–6.7)	5.0 (3.2–8.7)
BNP pg·mL^{-1}	19.4 (10.9–37.8)	19.4 (10.1–33.8)
CRP ng·mL^{-1}	5.4 (1.6–8.9)	4.2 (1.5–8.7)
HFABP ng·mL^{-1}	5.5 (2.4–33.4)	4.1 (2.6–8.2)
AOPPs μM	130 (39–495)	270 (34–519)

Data are presented as n, mean±SD, n (%) or median (interquartile range). CPAP: continuous positive airway pressure; BMI: body mass index; ESS: Epworth Sleepiness Scale; eGFR: estimated glomerular filtration rate; BP: blood pressure; SBP: systolic BP; DBP: diastolic BP; TST: total sleep time; AHI: apnoea–hypopnoea index; ODI: oxygen desaturation index; BNP: brain natriuretic peptide; CRP: C-reactive protein; HFABP: heart-type fatty acid binding protein; AOPP: advanced oxidation protein product. #: positive response was considered when feeling excessively sleepy during the day occurred >4 times per month. ¶: definition of resistant hypertension in the 2018 European Society of Cardiology/European Society of Hypertension guidelines [11]. *: p<0.05 between the treatment and control groups.

TABLE 2 Comparison of changes in the continuous positive airway pressure (CPAP) and control groups (intention-to-treat analysis)

	CPAP group[#]		Control group[¶]		Intergroup difference between changes in CPAP and control	
	Baseline	After 8 weeks	Baseline	After 8 weeks	Adjusted mean difference	p-value
24-h SBP mmHg	131 (127–135)	128 (124–132)	128 (123–133)	131 (126–135)	−4.4 (−8.7–−0.1)	0.046*
24-h DBP mmHg	80 (77–83)	78 (75–81)	79 (76–82)	80 (78–83)	−2.9 (−5.5–−0.2)	0.032*
Daytime SBP mmHg	133 (129–137)	130 (125–134)	130 (125–135)	133 (128–137)	−5.4 (−9.7–−1.0)	0.016*
Daytime DBP mmHg	81 (78–84)	79 (76–82)	80 (78–83)	82 (79–85)	−3.4 (−6.1–−0.8)	0.012*
Night-time SBP mmHg	123 (119–128)	122 (118–125)	123 (116–129)	124 (119–129)	−2.0 (−7.8–3.8)	0.495
Night-time DBP mmHg	76 (73–78)	75 (72–77)	75 (71–79)	76 (73–79)	−1.3 (−5.0–2.4)	0.491
Troponin I pg·mL^{-1}	5.6 (3.9–7.4)	4.8 (3.3–6.2)	7.9 (5.4–10.4)	8.5 (5.4–11.5)	−1.74 (−2.97–−0.50)	0.006*
BNP pg·mL^{-1}	30.7 (21.1–40.3)	20.3 (15.3–25.4)	24.6 (18.3–30.8)	22.7 (17.9–27.6)	−9.1 (−17.6–−0.6)	0.036*
CRP µg·mL^{-1}	8.0 (4.1–11.8)	5.4 (3.1–7.7)	4.8 (3.5–6.1)	5.6 (1.7–9.5)	−2.3 (−5.7–1.0)	0.172
HFABP ng·mL^{-1}	29.4 (1.2–57.6)	26.8 (−2.2–55.9)	40.5 (−2.0–83.0)	43.6 (9.1–78.1)	−16.9 (−58.7–24.9)	0.424
AOPPs µM	308 (200–416)	340 (241–440)	414 (239–589)	307 (218–396)	47.0 (−95.8–189.7)	0.514

Data are presented as adjusted mean (95% confidence interval). SBP: systolic blood pressure; DBP: diastolic blood pressure; BNP: brain natriuretic peptide; CRP: C-reactive protein; HFABP: heart-type fatty acid binding protein; AOPP: advanced oxidation protein product. [#]: n=46; [¶]: n=46. Intergroup comparisons were performed using ANCOVA with adjustment for baseline age, gender, apnoea–hypopnoea index, estimated glomerular filtration rate and Epworth Sleepiness Scale. *: p<0.05.

By intention-to-treat analysis and comparison with the control group, the CPAP group showed a significant reduction in 24-h SBP (intergroup difference −4.4 (95% CI −8.7–−0.1) mmHg; p=0.046), 24-h DBP (−2.9 (95% CI −5.5–−0.2) mmHg; p=0.032), daytime SBP (−5.4 (95% CI −9.7–−1.0) mmHg; p=0.016) and daytime DBP (−3.4 (95% CI −6.1–−0.8) mmHg; p=0.012) upon reassessment at the eighth week (table 2). There was no significant difference in nocturnal SBP or DBP. In the per-protocol analysis comparing CPAP compliant or noncompliant groups with controls, the benefits of CPAP on BP were attenuated in the CPAP compliant group and became nonsignificant in the noncompliant group, partly related to the lowered numbers of subjects (supplementary table S2).

Both troponin I (intergroup difference −1.74 (95% CI −2.97–−0.50) pg·mL^{-1}; p=0.006) and BNP (−9.1 (95% CI −17.6–−0.6) pg·mL^{-1}; p=0.036) levels were significantly reduced in the CPAP treatment group compared with the control group, while there was no significant difference in CRP, HFABP or AOPPs (table 2). When only those without a history of cardiac dysfunction were analysed (n=33 in the CPAP group and n=32 in the control group), a significant reduction in troponin I level was present comparing the CPAP group with the control group (−1.25 (95% CI −2.21–−0.29) pg·mL^{-1}; p=0.012), while BNP reduction was no longer significantly different (supplementary table S3). In the analysis on the subgroup with resistant hypertension as defined in the 2018 European Society of Cardiology and European Society of Hypertension guidelines [11], a significant reduction in troponin I and BNP was achieved after CPAP treatment for 8 weeks compared with controls, in addition to lowering of daytime SBP and DBP (supplementary table S4).

Pearson correlation analysis of the entire study cohort (n=92) showed that the changes in troponin I level were correlated with the changes in nocturnal SBP (r=0.26, p=0.014) and not other BP variables. There was no correlation between changes in BNP level with that of any BP parameters.

Subgroup analyses of nocturnal BP dippers (n=32) and nondippers (n=60) were performed. 15 (46.9%) dippers and 31 (51.7%) nondippers received CPAP treatment. There was no significant difference in demographic characteristics between dippers and nondippers at baseline (table 3). Nondippers in the CPAP group, compared with those in the control group, achieved a significant reduction in 24-h SBP (intergroup difference −6.2 (95% CI −11.7–−0.7) mmHg; p=0.028), 24-h DBP (−4.3 (95% CI −7.8–−0.9) mmHg; p=0.016), daytime SBP (−7.1 (95% CI −12.5–−1.6) mmHg; p=0.012) and daytime DBP (−4.5 (95% CI −8.0–−1.0) mmHg; p=0.013). Such BP changes were not observed among dippers (figure 2).

Discussion

This RCT confirmed the BP-lowering effect of CPAP therapy for moderate-to-severe OSA in subjects with difficult-to-control hypertension. A nondipping BP pattern was identified to drive the response. In addition, for the first time, beneficial effects of CPAP therapy of OSA on subclinical myocardial injury and strain were demonstrated as significant lowering of troponin I and BNP levels, respectively.

TABLE 3 Baseline characteristics of nondippers and dippers

	Nondipper	Dipper
Subjects	60	32
Randomised to CPAP group	31 (51.7)	15 (46.9)
Age years	52.8±8.8	53.9±8.6
Male	45 (75.0)	26 (81.3)
BMI kg·m^{-2}	31.1±4.8	30.6±5.8
Waist cm	101.4±9.4	99.7±11.7
ESS	7.3±5.1	7.1±4.7
Nonsmoker	39 (65.0)	24 (75.0)
Nondrinker	45 (75.0)	24 (75.0)
Presence of cardiac dysfunction	17 (28.3)	10 (31.3)
Presence of metabolic syndrome	56 (93.3)	30 (93.8)
BP parameters		
BP above goal	42 (70.0)	26 (81.3)
24-h SBP mmHg	128.4±16.3	131.5±14.0
24-h DBP mmHg	79.8±9.1	78.9±7.5
Daytime SBP mmHg	129.0±15.9	136.0±14.3
Daytime DBP mmHg	80.1±9.7	81.9±7.8
Night-time SBP mmHg	126.9±19.6	115.7±14.4
Night-time DBP mmHg	78.9±11.0	68.5±7.6
Sleep parameters		
TST min	384 (328–428)	385 (347–430)
AHI events·h^{-1}	45.6 (33.6–66.8)	39.3 (33.0–63.1)
ODI events·h^{-1}	42.2 (30.2–61.4)	37.9 (24.4–68.6)
Minimum oxygen saturation %	78 (67–82)	73 (64–81)
Oxygen saturation <90% min	31.5 (11.6–69.3)	27.2 (9.3–101.0)
Arousal index events·h^{-1}	20.4 (14.6–40.1)	23.9 (15.9–40.3)

Data are presented as n, n (%), mean±SD or median (interquartile range). CPAP: continuous positive airway pressure; BMI: body mass index; BP: blood pressure; SBP: systolic BP; DBP: diastolic BP; ESS: Epworth Sleepiness Scale; TST: total sleep time; AHI: apnoea–hypopnoea index; ODI: oxygen desaturation index. No significant difference in baseline characteristics between dippers and nondippers.

Hypertension remains a very common and important risk factor worldwide for morbidity and mortality due to its end-organ damage resulting in CVDs and cerebrovascular diseases. However, the optimal BP for attaining CVD risk reduction, and even definitions for "normal" BP levels, are subject to debate and evolution in the light of new knowledge [2, 11, 12]. In a recent multicentre randomised trial, an intensive pharmacological strategy to lower SBP to a target of <120 mmHg, compared with the standard goal of <140 mmHg, resulted in a 25% reduction in fatal and nonfatal cardiovascular events (acute coronary syndrome, stroke and heart failure) [13]. However, intensive drug regimens lead to more drug-related side-effects.

Several meta-analyses have suggested a modest benefit of CPAP treatment of OSA in reducing ambulatory BP by 2–3 mmHg in general hypertension [4–6, 14–17]. In OSA subjects with treatment-naïve hypertension, antihypertensive medication (valsartan) achieved a greater decrement of BP than CPAP [18]. A meta-analysis summarising the findings of four RCTs in resistant hypertension (n=224) suggested that CPAP treatment, for 3 weeks to 6 months, achieved a mean reduction in 24-h SBP and DBP of 6.7 and 5.9 mmHg, respectively [14]. Another sham-CPAP controlled study reported that 8 weeks of CPAP could produce a significant decrement in 24-h SBP [19]. However, a subsequent large single-centre RCT in Brazil did not find any significant change in BP with CPAP treatment for 6 months, in patients on a mean of five antihypertensive drugs and moderate-to-severe OSA [17].

We further identified a predilection for a BP-lowering effect among nondippers in this group of subjects with drug-resistant hypertension. This has been similarly demonstrated in OSA subjects with drug-naïve hypertension, in whom a nondipping BP pattern was found to be a predictor of favourable BP response to CPAP therapy [20]. A nondipping BP pattern has been commonly identified among OSA subjects with or without hypertension [21], and this pattern predicted stroke, heart failure and mortality [22].

The reduction in 24-h ambulatory BP was driven by significant decrement of daytime BP, while nocturnal BP only showed a trend of reduction. This prominence of daytime BP improvement after CPAP treatment

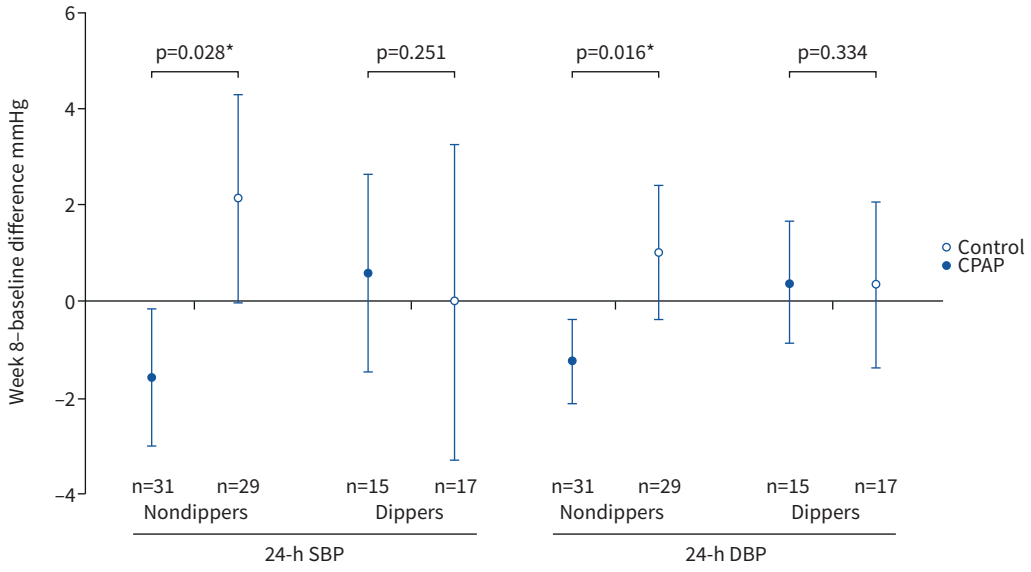

FIGURE 2 Changes in 24-h ambulatory blood pressure (BP) of CPAP treatment *versus* control in the dipper and nondipper subgroups: systolic BP (SBP) and diastolic BP (DBP) at baseline and after 8 weeks of treatment according to the circadian pattern. Data are presented as means with standard error. Comparisons were performed using ANCOVA with adjustment for baseline age, gender, apnoea–hypopnoea index, estimated glomerular filtration rate and Epworth Sleepiness Scale. *: p<0.05.

directed at nocturnal sleep disordered breathing appears counter-intuitive, but similar findings of daytime BP responding more readily to CPAP have been reported [15, 23]. Daytime BP is subject to surges from various external stimuli, especially against a high baseline sympathetic tone. An observational study found that CPAP for 6 months reduced daytime diastolic BP and norepinephrine, but not night-time BP and epinephrine, indicating that daytime sympathetic tone may respond first to CPAP treatment [23]. Likewise, CPAP treatment for 2 months suppressed daytime peripheral chemosensitivity among those with day–night sustained hypertension, as opposed to night-time chemosensitivity in those with isolated nocturnal hypertension [24].

Troponin, BNP and CRP are widely utilised in the clinical setting, with established diagnostic and prognostic values [25, 26]. Troponin is a protein present in myocardial cells and its spillage into the circulation indicates myocardial injury. There is growing evidence that modest elevations in its level which are below the clinical diagnostic threshold for acute myocardial insult indicate chronic myocardial injury [27]. Such elevated levels of high-sensitivity troponin T and N-terminal pro-BNP predicted 10-year incident cardiovascular events in individuals with hypertension not currently recommended for medications [28]. In two studies of large community cohorts without CVD, an elevated level of high-sensitivity troponin at baseline [27] or its subsequent increment [29] correlated with incident coronary events, heart failure, ischaemic stroke and mortality over follow-up of >10 years.

Our group has previously reported on the association of high-sensitivity troponin I and OSA severity (AHI), independent of BP control, in an observational study [3]. Data on the effect of CPAP treatment for OSA on troponin are scarce. Only one crossover RCT, which comprised 37 OSA subjects without known cardiac diseases and only 25% of whom had hypertension, found no change in high-sensitivity troponin T level after CPAP for 8 weeks [30]. High-sensitivity troponin T has been reported to be less sensitive than high-sensitivity troponin I in detecting subclinical myocardial injury. The use of high-sensitivity troponin I and the target OSA sample with a much higher background cardiovascular risk in the present study could be factors accounting for the reduction in troponin levels after CPAP treatment.

BNP is released from cardiac muscle cells in response to increased ventricular wall stress from volume expansion. It is clinically used in the diagnosis of heart failure and values in the range below diagnosis of acute events have been shown to be reliable measures of the degree of cardiac strain [31]. OSA has been consistently reported to be independently associated with left ventricular diastolic dysfunction [32] and CPAP treatment of OSA might revert cardiac dysfunction or prevent its progression [33]. The association

between BNP and OSA is inconsistent [34–36], and the impact of CPAP treatment of OSA on BNP or its metabolites remains controversial [30, 37]. Compared with a negative randomised study on the effect of CPAP on BNP and other aspects of cardiac function [38], our study subjects had more severe OSA and more cardiovascular background risks, making them more responsive to the effect of CPAP on reducing right ventricular pre-load, pulmonary congestion and hence ventricular strain.

This study has a number of caveats. This was a single-centre study of patients with moderate-to-severe OSA and hypertension that required multiple drugs for treatment, so the results are not generalisable to other populations. Adult patients of middle-age range (<65 years old) were included in the study, and thus the effects of CPAP on BP and biomarkers in the elderly would require further study. The compliance to antihypertensive drugs was evaluated by interview, which might not be precise. Patients having three or more medications regardless of their clinic BP were recruited in the study, and 27% (table 1) had ambulatory 24-h BP control within the goal and did not fulfil the definition of resistant hypertension (supplementary material) [11]. Our study used controls without CPAP treatment as the comparison group rather than sham-CPAP, in view of the likelihood of poor adherence to sham-CPAP and its lack of a genuine effect on blinding [39]. Follow-up of participants on CPAP has not been extended for further measurements of biomarkers or the occurrence of cardiovascular events. Troponin and BNP were secondary outcomes, and the study could be underpowered for evaluation of these biomarkers.

In summary, in this RCT targeting a specific subset of our sleep centre referrals that had a high baseline cardiovascular risk at relatively young age, CPAP treatment of OSA provided further control of ambulatory BP despite the use of multiple antihypertensive medications, and might alleviate subclinical myocardial injury and strain. In the light of contradictory results of OSA treatment on cardiovascular protection, our findings provide support that certain clinical subsets among the heterogeneous OSA patient population may derive more treatment benefit [7]. Further clinical trials with longer follow-up duration on the treatment outcome from CPAP in defined OSA populations will be highly desirable.

Acknowledgement: The authors would like to thank Peony Chong (Dept of Medicine, The University of Hong Kong, Hong Kong) for collection of data, dataset management and statistical support; Helen Zhi (Biostatistics and Clinical Research Methodology Unit, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong) for professional statistical advice; Michelle Cheong (Dept of Medicine, The University of Hong Kong, Hong Kong) for manual scoring; S.L. Choi and the nursing team (Ho Ting Sik Sleep Disorder Center, Queen Mary Hospital, Hong Kong) for clinical care of recruited subjects; Victor Hui, Christopher Hui and Terence Tam (Dept of Medicine, Queen Mary Hospital, Hong Kong) for assistance in subject recruitment; and Judith Mak (Dept of Medicine, Queen Mary Hospital, Hong Kong) for her professional advice on biomarker assays.

This study is registered at ClinicalTrials.gov with identifier number NCT00881985. All the individual participant data collected during the trial, after de-identification, will be shared; the study protocol, statistical analysis plan, informed consent form, clinical study report and analytic code will be available. Data will be available 1 year following full publication and ending 5 years following article publication, to researchers who provide a methodologically sound proposal. Data will be provided to achieve the aims in the approved proposal. Proposals should be directed to the corresponding author. To gain access, data requestors will need to sign a data access agreement.

Author contributions: Study design: M.S-M. Ip and M.M-S. Lui. Study subject recruitment and data acquisition: M.M-S. Lui, K-K. Lau, D.C-L. Lam, C.W-S. Chan, H-F. Tse and M.S-M. Ip. Data analysis and interpretation: M.M-S. Lui, M.S-M. Ip, H-F. Tse, D.C-L. Lam and C.W-S. Chan. Manuscript preparation: M.M-S. Lui, M.S-M. Ip, H-F. Tse and D.C-L. Lam. All authors contributed towards and approved the final version to be submitted. M.S-M. Ip has full access to the data.

Conflict of interest: M.M-S. Lui has nothing to disclose. H-F. Tse has nothing to disclose. D.C-L. Lam has nothing to disclose. K-K. Lau reports grants, personal fees and nonfinancial support from Boehringer Ingelheim, grants and nonfinancial support from Pfizer, grants from Sanofi and Amgen, nonfinancial support from Eisai, outside the submitted work. C.W-S. Chan has nothing to disclose. M.S-M. Ip has nothing to disclose.

Support statement: This study was supported by the Ho Ting Sik Donation Fund for Sleep Research. The donor has no role in the scientific conduct of the study. Funding information for this article has been deposited with the Crossref Funder Registry.

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