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INTRODUCTION

Obstructive sleep apnea (OSA) is a common condition among overweight and obese individuals. About half of patients with OSA have hypertension, and about half of patients with hypertension have OSA. Causal link between OSA and hypertension is complex and remains debatable, but hypertension may in part arise from increased sympathetic nerve activity induced by hypoxic stress. OAS is associated with a number of secondary health complications, most notably cardiovascular disease, and co-existing cardiometabolic risk factors such as dyslipidemia.
endothelial dysfunction, deranged inflammatory responses, and insulin resistance; all of which are associated with obesity.

The main treatment for OSA is continuous positive airway pressure (CPAP). Meta-analyses have shown CPAP slightly reduces arterial blood pressure. However, studies on the impact of CPAP treatment on sympathetic activity markers such as catecholamines have drawn conflicting conclusions. There is a lack of meta-analyses on large numbers of participants recording the effects of CPAP in the same individuals on both changes in catecholamine levels and blood pressure. This information is important as it provides evidence of sympathetic activity as a mediator of OSA-related stress and hypertension.

We therefore conducted a meta-analysis of published data to document changes in the levels of catecholamines and their inactive metabolites [metadrenalines], as well as blood pressure in response to CPAP treatment of OSA.

2 | METHODS

2.1 | Search criteria

Two investigators followed PRISMA and Cochrane guidelines, and performed independently a literature search of MEDLINE and Google Scholar up to May 2020 using the key terms (British or US usage and abbreviations, eg, CPAP and OSA): obstructive sleep apnea, continuous positive airway pressure, urinary or plasma catecholamines, adrenaline (epinephrine), noradrenaline (norepinephrine), 3-methoxytyramine, metanephrines, normetanephrine, metanephrine and dopamine, and hypertension. No filters for language or data were used. The Boolean operators “AND” and “OR” were used to combine search terms. Relevant studies were hand-searched within these references.

2.2 | Selection criteria

Studies examining the effect of CPAP on catecholamines in the OSA population were included irrespective of age, sex, race, comorbidities, duration of CPAP, and treatment. Studies that fit the inclusion criteria were randomized control trials (RCTs) and prospective cohort studies (PCS). Studies were excluded if they did not present numerical data for catecholamines at baseline and end point.

2.3 | Outcome measures

24-hour urinary or plasma catecholamines: dopamine, adrenaline and noradrenaline, or their products metadrenalines (metanephrines): 3-methoxytyramine, normetadrenaline (normetanephrine) and metadrenaline (metanephrine) and blood pressure were the outcomes used for the comparison analysis.

2.4 | Risk of bias

The quality of the reports was evaluated using the risk of bias assessed using Cochrane Collaboration’s tool for RCTs and risk of bias in non-randomized studies of interventions (ROBINS-I) tool for PCS. The risk of bias for each report was rated independently from low, moderate, serious, or critical by two authors, and any discrepancies were resolved by reciprocal discussion.

FIGURE 1 QUOROM (quality of reporting of meta-analyses) flow chart of literature search
| Study | N   | Mean Age (years) | BMI (kg/m²) | SBP (mmHg) | DBP (mmHg) | Duration |
|-------|-----|-----------------|-------------|------------|------------|----------|
| **RCT (CPAP group)** | | | | | | |
| Arias et al (2008)a | 30/0 | 52 ± 13 | 30.5 ± 4.0 | 121.5 ± 11.4 | 74.5 ± 7.8 | 3 mo |
| Casitas et al (2017)b | 26/6 | 56 ± 11.2 | 29.2 ± 5.6 | 131.5 ± 12.0 | 78.8 ± 8.5 | 12 wk |
| Comondore et al (2009)b | 9/4 | 55 ± 7.1 | 31.1 | 138.4 | 83.8 | 4 wk |
| de Araújo et al (2013)c | 8 (Both) | 43 ± 12 | 28 ± 4 | 112 ± 12 | 67 ± 8 | 1 night |
| Drager et al (2007)d | 12/0 | 44 ± 7 | 29.9 ± 3.0 | 123 ± 12 | 73 ± 10 | 4 mo |
| Kohler et al (2008)e | 51/0 | 48.1 ± 9.5 | 35.8 ± 7.3 | 131.3 ± 13.9 | 83.9 ± 9.3 | 4 wk |
| Lam et al (2010)f | 31/0 | 46.5 ± 10.8 | 27.8 ± 3.7 | 130.8 ± 14.7 | 80.1 ± 10.8 | 4 wk |
| Mansfield et al (2004)g | 28/0 | 57.2 ± 9 | 33.5 ± 4.8 | 99 ± 15.9h | 105 ± 15.9h | 3 mo |
| Mills et al (2006)i | 15/2 | 47.6 ± 10.7 | 31.7 ± 5.8 | 155.2 ± 18.6 | 84.2 ± 10.7 | 2 wk |
| Phillips et al (2011)j | 35/3 | 49 ± 13 | 32.1 ± 4.3 | - | - | 2 mo |
| Rubinsztajn et al (2006)k | 15/0 | 50.6 ± 10.0 | 31.5 ± 6.3 | 130.1 ± 17.8 | 87.3 ± 13.5 | 8 mo |
| Ruzicka et al (2020)l | 7/0 | 59 (58-67)c | 33 (31-35) c | 140 (136-165)c | 73 (66-85)c | 6 wk |
| Ryan et al (2005)m | 9/1 | 57.6 ± 7 | 28.3 ± 4.1 | 120.7 ± 17.1 | 64.6 ± 9.5 | 1 mo |
| Thunstrom et al (2016)n | 15/9 | 58 ± 6.7 | 27.7 ± 3.2 | 164.9 ± 16.2 | 96.5 ± 10.9 | 6 wk |
| **RCT (control group)** | | | | | | |
| Arias et al (2008)a | 30/0 | 52 ± 13 | 30.5 ± 4.0 | 121.5 ± 11.4 | 74.5 ± 7.8 | 3 mo |
| Casitas et al (2017)b | 26/6 | 56 ± 11.2 | 29.2 ± 5.6 | 131.5 ± 12.0 | 78.8 ± 8.5 | 12 wk |
| Comondore et al (2009)b | 9/4 | 55 ± 7.1 | 31.1 | 138.4 | 83.8 | 4 wk |
| de Araújo et al (2013)c | 8 (Both) | 43 ± 12 | 28 ± 4 | 112 ± 12 | 67 ± 8 | 1 night |
| Drager et al (2007)d | 12/0 | 47 ± 6 | 29.7 ± 2.9 | 123 ± 12 | 73 ± 10 | 4 mo |
| Kohler et al (2008)e | 51/0 | 48.7 ± 10.6 | 34.5 ± 5.0 | 138.9 ± 20.8 | 88.3 ± 8.1 | 4 wk |
| Lam et al (2010)f | 30/0 | 46.1 ± 9.8 | 27.2 ± 3.7 | 129.5 ± 16.5 | 82.0 ± 11.6 | 4 wk |
| Mansfield et al (2004)g | 24/3 | 57.5 ± 8.3 | 34.6 ± 6.2 | 99 ± 15.9h | 105 ± 15.9 | 3 mo |
| Mills et al (2006)i | 13/3 | 49 ± 10.4 | 32.2 ± 6.8 | 149 ± 23.2 | 83.6 ± 13.6 | 2 wk |
| Phillips et al (2011)j | 35/3 | 49 ± 13 | 32.1 ± 4.3 | - | - | 2 mo |
| Rubinsztajn et al (2006)k | 10/0 | 45.4 ± 16.5 | 27.6 ± 3.1 | 126.7 ± 12.3 | 84.2 ± 10.0 | 8 mo |
| Ruzicka et al (2020)l | 6/0 | 63 (55-71)c | 34 (33-36)c | 138 (127-143)c | 71 (62-81.5)c | 6 wk |
| Ryan et al (2005)m | 7/1 | 60.3 ± 11.6 | 35.1 ± 10.5 | 139 ± 15.6 | 69.9 ± 12.2 | 1 mo |
| Thunstrom et al (2016)n | 17/6 | 59 ± 3.7 | 27.6 ± 4.1 | 164.9 ± 16.2 | 96.5 ± 10.9 | 6 wk |
| **Prospective cohort studies** | | | | | | |
| Baruzzi et al (1991)m | 6/0 | 41.3 ± 12.9 | 36 ± 6 | - | - | 1 night |
| Bischof et al (2019)n | 18/0 | 55.8 ± 9.5 | 35.5 ± 3.8 | 133.2 ± 14.1 | 80.2 ± 10.6 | 6 mo |
| Bratel et al (1999) o | 18/0 | 51.3 ± 10.8 | 32.0 ± 5.6 | 143.8 ± 17.2 | 87.5 ± 10 | 7 mo |
| Burioka et al (2008)p | 8/0 | 45.9 ± 12.2 | 25.9 ± 1.7 | - | - | 3 mo |
| Castro-Grattoni et al (2017)q | 48/12 | 52.3 ± 9.56 | 30.7 ± 4.2 | 122.7 ± 9.9 | 77.2 ± 7.7 | 6 mo |
| Donadio et al (2007)r | 10/0 | 50 ± 9.5 | 32 ± 6.3 | 144 ± 6.3 | 98 ± 3.2 | 6 mo |
| Fares et al (2014)s | 6/3 | 56.0 ± 15.6 | - | - | - | 1 y |
| Ferrier et al (2008) t | 16/3 | 58.5 ± 11.2 | 30.2 ± 6.7 | 132 ± 16 | 80 ± 9 | 6 mo |
| Grimpel et al (2000)u | 26/3 | 56.9 ± 8.6 | 29.5 ± 3.8 | 98.4 ± 2.7v | 98.4 ± 2.7v | 14 mo² |
| Heitmann et al (2000)x | 18 (Both) | 50.0 ± 10.4 | 29.7 ± 3.7 | 136.8 ± 15.7 | 84.9 ± 12.5 | 42 d³ |
| Jennum et al (1989)y | 13/1 | 42 (36-66)c | 26.13 ± 3.5 | 147.5 ± 5.2 | 122.4 ± 4.3 | 1 wk |
| Kita et al (1998)z | 12/2 | 53 ± 14.5 | 29.9 ± 4.9 | 127.6 ± 19.8 | 77.8 ± 11.6 | 1 night |
| Krieger et al (1989) | 20/1 | 51 ± 10.1 | 32.0 ± 1.3 | - | - | 1 night |

(Continues)
Meta-analysis was performed using Review Manager (RevMan, Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014). The standardized mean difference (SMD) was used to determine the effect size on catecholamines to accommodate for a variety of ways they were measured. The SMD expresses the size of the intervention effect in each study relative to the variability observed in that study. The mean difference (MD) used on the original scale of measurement to determine the effect size on blood pressure. Pooled estimates of each outcome for each treatment were obtained via the DerSimonian and Laird method using a random-effects model. Statistical significance threshold was accepted as $P < .05$. The $I^2$ statistic was used to assess heterogeneity of trial results used to construct pooled estimates of effect.

**RESULTS**

A total of 38 studies met the above search criteria: 14 RCTs including a total of 576 participants (295 in treatment groups and 281 controls) and 24 PCS totaling 547 participants (Figure 1). The mean age ranged between 41 and 62 yr and body mass index between 27.2 and 35.1 kg/m$^2$ (Table 1). The remaining baseline parameters including heart rate, sleep study characteristics, and noradrenaline levels are shown in Table S1. The duration of CPAP treatment ranged from one day to eight months in RCTs and one day to a year in PCS. Most studies used 24-hour urinary noradrenaline as outcome measure, including nine RCTs and 13 PCS. A fewer RCTs and PCS, respectively, reported 24-hour urinary adrenaline ($n = 6$ and 7), normetadrenaline ($n = 3$ and 0) and metadrenaline ($n = 2$ and 0), or plasma noradrenaline ($n = 5$ and 13) and adrenaline ($n = 3$ and 6) (Table 2). Subsequently, data from studies on 24-hour urinary noradrenaline are presented herein while the remaining data on other methods of measurement of catecholamines and their metabolites are shown in Figures S1 and S2.
CPAP treatment reduced the levels of 24-hour urinary noradrenaline levels both in RCT: $SMD = -1.1$ (95%CI = $-1.63$ to $-0.56$) (Figure 2A) and in PCS: $SMD = 0.38$ (95%CI = $0.24$ to $0.53$) (Figure 2B). Inter-study heterogeneity was high among RCT ($I^2 = 81\%$) but low among PCS ($I^2 = 0\%$).

Blood pressure as study outcome measure was reported in ten RCTs totaling 407 participants and ten PCS containing 297 participants (Table 2). CPAP treatment led to a blood pressure reduction. With RCT, mean reductions of SBP were 4.8 mmHg (95%CI = $2.0$-$7.7$ mmHg) (Figure 3A) and of DBP were 3.0 mmHg (95%CI = $1.4$-$4.6$ mmHg) (Figure 3B). With PCS, mean reductions of SBP were 7.5 mmHg (95%CI = $3.3$ to $11.7$ mmHg) (Figure 3C) and of DBP were 5.1 mmHg (95%CI = $2.3$-$8.0$ mmHg) (Figure 3D). There was evidence of substantial inter-study heterogeneity both in RCTs ($I^2 = 84\%$ and $62\%$, respectively, in SBP and DBP analyses) and in PCS ($I^2 = 71\%$ and $64\%$, respectively, in SBP and DBP analyses).

We have also observed that CPAP had similar impact on the reduction of other catecholamines and their metabolites (Results not shown).

Risk of bias for the RCT assessed by random sequence generation (Figure 4A) showed a high risk in three studies since they were not double-blinded. All of the studies used intention-to-treat analysis or did not have any dropouts, to minimize risk of incomplete outcome data. All of the studies lacked information of selective reporting bias as they did not mention the study protocol. There were confounding factors in one study due to all of the patients undergoing surgery and in another where patients were undergoing heart failure treatment.

Risk of bias for PCS was evaluated using the risk of bias in non-randomized studies of interventions (ROBINS-I) tool (Figure 4B). Bias due to confounding factors was seen in five studies, but in only three was there a moderate risk of overall bias. Patients in one study had previously been receiving CPAP therapy for at least three months. Bias in selection of participants was seen in one study: There was no reimbursement for CPAP usage in Brazil. Missing data were assessed to cause a moderate risk of bias in three studies. None of the studies had bias in measurement of outcomes. There was insufficient information from any of the studies for assessing bias in selection of the reported result.

3 | DISCUSSION

In this meta-analysis of data from over a thousand patients with OSA, it was observed that CPAP treatment significantly reduced
**FIGURE 3** Changes in systolic (A) and diastolic (B) blood pressure in RCT and systolic (C) and diastolic (D) blood pressure in PCS by CPAP treatment
urinary or plasma catecholamines, and their metabolites, as well as blood pressure. This suggests that a reduction of OSA-related stress by CPAP decreases sympathetic activity (catecholamines) and consequently blood pressure. These findings lend further support for the intermediary role of sympathetic activity in the relationship between OSA-related stress and hypertension.

The impact of CPAP both on catecholamines and blood pressure has previously been debatable due to inconsistent findings. Forest plots in this analysis revealed high inter-study heterogeneity which may be explained by a variation in study designs and patient characteristics. For example, inclusion criteria of baseline blood pressure or severity of OSA may differ and other factors such as antihypertensive medications and duration of CPAP treatment are also likely to vary between studies.

The reduction in blood pressure observed in this analysis is consistent with findings from previous meta-analyses on CPAP and blood pressure. Although the reduction of systolic blood pressure is relatively small (about 5-7.5 mmHg), this is clinically relevant in reducing stroke incidence.

We found studies from existing literature reported a variety of methods of measurements, either urinary or plasma and catecholamines or their metabolites, but the majority reported urinary noradrenaline. The application of urinary catecholamines and metadrenalines or plasma metadrenaline depends on the degree of risk of an individual to have catecholamine-secreting tumor; urinary method which has high specificity (98%) is suggested for testing low-risk patients, while plasma method (high sensitivity: 97%) is suggested for high-risk patients. Albeit, we found that CPAP had very similar effects on the reduction of all catecholamines and their metabolites.

In this study, we analyzed both RCTs and PCS and observed CPAP to have overall effects both on the reduction of catecholamine levels and blood pressure, which is consistent with observations made by Benson and Hartz. We observed that reductions in blood pressure appear to be higher in PCS than those in RCTs but not able to clarify the underlying reasons for these differences, but bias in selection of participants and CPAP treatment regimen may contribute.

It would be of interest to examine the effects of CPAP on heart rate in response to the reduction of catecholamines. However, only 15 studies reported heart rate at baseline (Appendix S1) and only one studied changes in heart rate in relation to CPAP treatment. Heart rate was therefore not included as an outcome measure in our study.

There are certain limitations identified in this study, as expected for a meta-analysis. These include different methods of measuring catecholamines and their metabolites. There were also varying methods applied to control groups in the RCTs, and some received no treatment while other received sham CPAP treatment. This may introduce a risk of bias since sham CPAP treatment has been shown to have greater influences on the results than non-treatment, which may underestimate the effect of CPAP on catecholamines and blood pressure. Further bias may also arise from the inability to disguise sham CPAP from patients in RCTs; about two-thirds of patients are able to determine whether they were receiving sham CPAP or therapeutic CPAP. The numbers of participants also vary widely between studies, while CPAP treatment duration ranges from one night to one year which would contribute to significant inter-study heterogeneity. There was a low representation of female participants relative to the overall prevalence of women with OSA; thus, the findings from this study should be interpreted cautiously in the female population.

**CONCLUSIONS**

CPAP treatment in patients with OSA reduces catecholamines levels and blood pressure suggesting sympathetic activity plays an
intermediary role in the relationship between OSA-related stress and hypertension.

CONFLICT OF INTEREST
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

AUTHOR CONTRIBUTION
TSH created the study concept and design. TSH and GK-D reviewed the literature. MG performed data collection and data analysis under the guidance of TSH and GK-D. TSH wrote the first draft of the manuscript and edited subsequent versions. DF, CS, PS, and CHF commented on the manuscript. All authors checked, interpreted the results, and approved the final manuscript.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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