

# Endocrine responses during CPAP withdrawal in obstructive sleep apnoea: data from two randomised controlled trials

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## ABSTRACT

The aim of this investigation was to elucidate the effect of CPAP withdrawal on neurometabolic and cardiometabolic markers in patients with obstructive sleep apnoea. We evaluated 70 patients (mean age 61±10 years, 82% men) treated with CPAP in two 2-week, parallel, randomised controlled trials. CPAP withdrawal resulted in elevated 3,4-dihydroxyphenylglycol, norepinephrine and cortisol after 2 weeks of CPAP withdrawal; however, no statistically significant changes of the renin–angiotensin–aldosterone system (RAAS) determinants were documented. In summary, CPAP withdrawal may be more prominently linked to short-term increases in sympathetic activation than hypothalamic–pituitary–adrenal axis or RAAS activation. ClinicalTrials.gov Identifier: NCT02493673 and NCT02050425.

## INTRODUCTION

Obstructive sleep apnoea (OSA) is a sleep-related breathing disorder with an estimated prevalence as high as 23%–50% in the middle-aged population.<sup>1</sup> Several pathways were identified to play a role in the pathogenesis of hypertension present in patients with OSA, such as activation of the renin–angiotensin–aldosterone system (RAAS), increased sympathetic nervous system activity and endothelial dysfunction.<sup>2</sup> Furthermore, repeated arousals and subsequent activation of the hypothalamic–pituitary–adrenal (HPA) axis resulted in increased cortisol levels, which has been suggested to contribute to the development of cardiovascular disease in patients with OSA.<sup>3</sup> OSA is associated with therapy-resistant hypertension, which together with increased cortisol and blood pressure (BP) maintenance may contribute to an increased cardiovascular risk.<sup>2,4</sup> The pathophysiological aspects of OSA, such as causes, consequences or markers of neurometabolic and cardiometabolic dysfunction, are under investigation, and several key metabolites, including cortisol, catecholamines and members of the RAAS, have been implicated in OSA.<sup>4</sup> Thus, treatment of OSA represents an important strategy to reduce metabolic risk. However, the role of CPAP in treating cardiovascular consequences is a matter of debate and a recent meta-analysis of randomised controlled trials in adults with cardiovascular disease under CPAP therapy suggested that CPAP therapy does not significantly improve survival or prevent major cardiovascular events.<sup>5</sup>

We hypothesised that CPAP withdrawal would result in changes in catecholamine levels, cortisol metabolism and metabolites of the RAAS. Therefore, our aim was to further investigate the link between OSA and its metabolic consequences to determine the mechanisms that underlie the observed increase in daytime BP due to CPAP withdrawal.

## METHODS

### Trial design

Combined data from two 2-week, parallel, randomised controlled trials, conducted in the University Hospital Zurich (Switzerland), were designed to address whether CPAP withdrawal for 2 weeks affects cerebral vascular reactivity and exhaled breath patterns in patients with moderate and severe OSA.<sup>6,7</sup> The study design and more detailed eligibility criteria have been reported elsewhere.<sup>6,7</sup> The main outcome of interest was the change in blood catecholamine levels as well as metabolites of the HPA axis and RAAS.

### Participants

Participants were eligible for the trials if they were treated with CPAP for 1 year with high compliance (ie, >4 hours per day, >80% of all days within the last year) prior to commencement and met the following inclusion criteria: (1) age between 20 and 75 years, (2) apnoea–hypopnoea index (AHI) and/or 4% oxygen desaturation index (ODI<sub>4%</sub>) ≥20/h in their in-laboratory sleep study at the time of diagnosis, and (3) an ODI<sub>4%</sub> ≥15/h in a current nocturnal pulse oximetry during a 4–5 night period off CPAP treatment. All procedures were performed in accordance to Good Clinical Practice guidelines. Details on the analytics and statistical methods can be found in online supplementary file.

## RESULTS

Recruitment started in February 2014 and the last patient's follow-up was completed in December 2017. A trial flow chart can be found in online supplementary file (figure 1). Baseline characteristics and baseline values of all analysed blood markers are provided in tables 1 and 2, respectively.

3,4-Dihydroxyphenylglycol (DHPG), norepinephrine (NE) and cortisol showed statistically significant (p<0.005) or suggestive (p=0.05 to 0.005) increases after 2 weeks of CPAP withdrawal,



even after adjusting for baseline values, age, sex, body mass index (BMI) and presence of hypertension (mean difference in change DHPG between groups, +123.32 pg/mL, 95% CI +32.28 to +214.37,  $p=0.009$ ; mean change NE, +76.37 pg/mL, 95% CI +22.48 to +130.27,  $p=0.006$ ; mean change cortisol, +24.19 ng/mL, 95% CI +2.55 to +45.84,  $p=0.029$ ). No statistically significant treatment effects in any of the metabolites of the RAAS were observed. Results from all investigated metabolites are shown in [figure 1](#).

The recurrence of OSA in the CPAP-withdrawal group was well documented with a significant increase in AHI (mean change AHI, 31.8 events/h, 95% CI +22.8 to +40.6,  $p<0.001$ ) and ODI (mean change ODI, 31.5 events/h, 95% CI +22.4 to +40.5,  $p<0.001$ ). A detailed table is featured in online supplementary file.

## DISCUSSION

After adjusting for sex, age, BMI and presence of hypertension, DHPG levels were significantly increased in patients with OSA after 2 weeks of CPAP withdrawal with a similar trend to increased NE and cortisol levels. No significant changes to other adrenal steroids or to other hormones associated with the RAAS system were noted.

In line with our results, the majority of previous randomised controlled trials confirmed significantly reduced catecholamines and/or catecholamine metabolites in blood or urine after CPAP treatment, or increases in these markers following CPAP withdrawal.<sup>4</sup>

While plasma epinephrine levels primarily reflect adrenomedullary secretion of the hormone, plasma NE stems mainly from the exocytotic release of NE from sympathetic noradrenergic nerves.<sup>8</sup> DHPG, the main intraneuronal metabolite of NE, is a marker of NE reuptake. Based on animal studies, intraneuronally generated DHPG (different from NE that underwent rapid metabolic transformation) traverses the cell membrane readily and enters the circulation. An increased underlying sympathetic activity in patients with OSA and subsequent NE turnover is better reflected by plasma DHPG than by plasma NE concentrations.<sup>9</sup>

Stressors such as the tilt-table test and drugs such as yohimbine can produce increased plasma levels of both NE and DHPG, providing clinical information about sympathetic function.<sup>8,10</sup> Thus, elevated NE and DHPG but normal epinephrine levels in OSA emphasise the relevance of sympathetic activation to high BP levels and long-term cardiovascular risks.<sup>10</sup>

In our study, short-term CPAP withdrawal did not result in significant changes to the RAAS metabolites and HPA axis, despite concomitant secondary causes for hypertension, such as primary hyperaldosteronism in patients with OSA.<sup>11</sup> There is evidence from rodent studies that artificial hypoxemia and sympathetic activation result in carotid body-dependent short-term RAAS activation.<sup>12</sup> However, these isolated models might not be comparable with natural OSA in humans due to the involvement of anaesthetics, mechanical ventilation and the lack of adequate oxygen saturation monitoring. In humans, there are findings suggesting that OSA-related changes of RAAS metabolites occur in specific patient populations or those with certain BP profiles.<sup>2</sup> In our data, there was only a non-significant trend towards higher cortisol levels; however, in contrast to other studies, our representative OSA population (ie, old, already hypertensive, average BMI of  $33.6\pm 6.2$  kg/m<sup>2</sup>) might have influenced these results, as obesity and hypertension is known to be a HPA axis and RAAS modulator. In contrast,

an investigation in a non-obese and normotensive OSA population over a 2-month period showed significant increases of cortisol levels during CPAP withdrawal.<sup>3</sup>

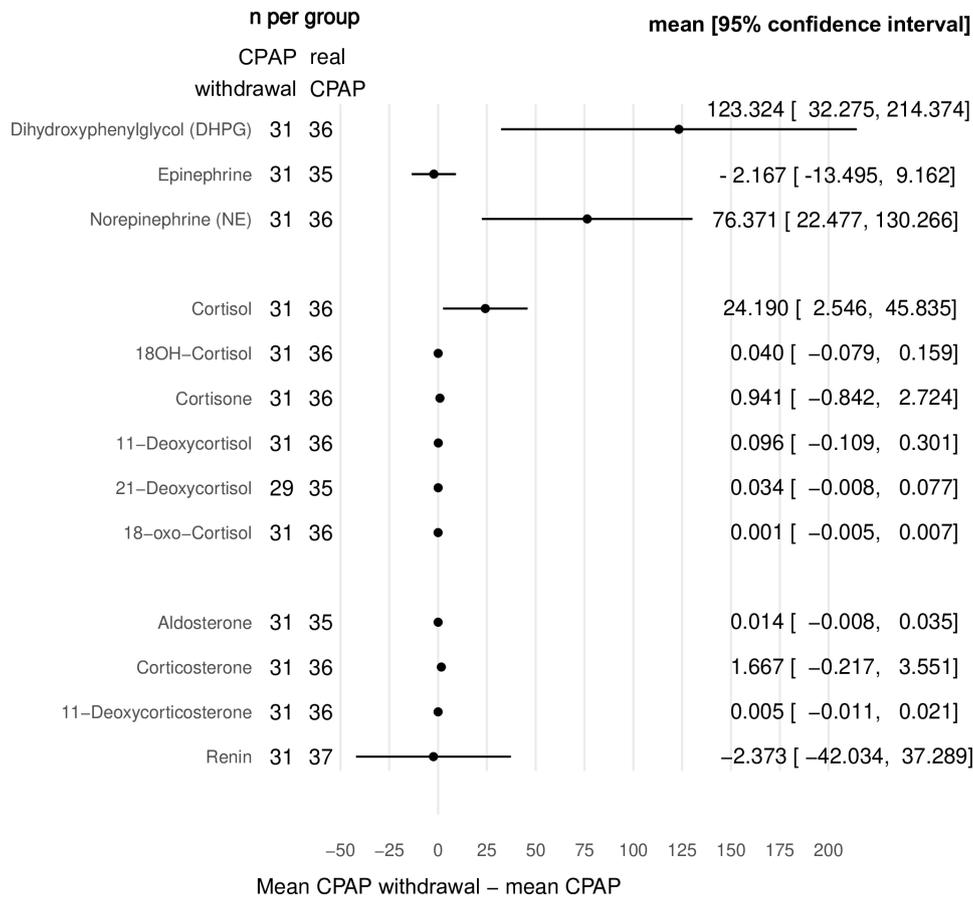
Our study features some limitations. First of all, this was a subanalysis of two randomised controlled trials investigating cerebral vascular reactivity and breath patterns in patients with OSA, therefore being of descriptive nature. We included patients taking antihypertensive medication, which could have confounded our results. Cortisol is a hormone that follows a clear circadian rhythm, and its levels are determined by an individual's sleep schedule. Therefore, sampling patients at different time points might have resulted in more robust data. In addition, a few additional factors should be considered while interpreting our results. Investigation of CPAP-adherent patients with moderate to severe OSA limits the generalisability of the findings. Moreover, acute CPAP withdrawal (ie, 2 weeks) may not reflect the natural history of untreated OSA or reflect long-term changes.

In summary, CPAP withdrawal may be more prominently linked to short-term increases in sympathetic activation than HPA axis or RAAS activation.

**Table 1** Baseline characteristics of the study participants

	Therapeutic CPAP (n=37)	CPAP withdrawal (n=33)
<b>Anthropometrics</b>		
Age, years	62.0±10.6	60.9±10.8
Sex, male (%)	31 (83.8%)	27 (81.8%)
Height, cm	174±9	173±8
Weight, kg	98±19	104±19
BMI, kg/m <sup>2</sup>	32.7±6.5	34.6±5.8
Neck circumference, cm	43.7±3.8	43.6±3.7
Waist circumference, cm	114.8±13.1	117.6±9.9
Hip circumference, cm	113.3±11.6	117.94±10.9
Waist:hip ratio	1.0±0.1	1.0±0.1
<b>Comorbidities</b>		
Active smoker, n (%)	4 (10.8%)	4 (12.1%)
Ex-smoker, n (%)	14 (37.8%)	14 (42.4%)
Pack years, py	14.4±18.5	14.9±19.6
Hypertension, n (%)	19 (51.4%)	20 (60.6%)
Diabetes, n (%)	9 (24.3%)	9 (27.3%)
Coronary artery disease, n (%)	7 (18.9%)	3 (9.1%)
Heart failure, n (%)	1 (2.7%)	0 (0.0%)
Dyslipidemia, n (%)	10 (27.0%)	7 (21.2%)
Obesity, n (%)	22 (59.5%)	24 (72.7%)
<b>OSA characteristics</b>		
OSA diagnosis since, years	8.4±4.1	7.2±5.4
AHI at time of diagnosis, events per hour	51.8±20.0	50.6±24.9
ODI at time of diagnosis, events per hour	50.0±19.3	49.4±25.1
Epworth Sleepiness Scale, points	7.0±3.5	7.5±3.4
CPAP usage, % days of last year	94±7	93±8
Residual AHI under CPAP therapy, events per hour	2.9±2.6	2.6±1.9

AHI, apnoea-hypopnoea index; BMI, body mass index; CPAP, continuous positive airway pressure; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea.



**Figure 1** Adjusted effects of the intervention (ie, CPAP withdrawal) for the primary outcomes. Haemolytic blood samples or samples with an above-average noise ratio ( $\pm 2$  SD) were excluded from the analysis. The effects were adjusted for sex, body mass index, age and presence of hypertension.

**Table 2** Changes in hormones during the intervention by study group

	Therapeutic CPAP (n=37)			CPAP withdrawal (n=33)			P value*
	Baseline	Follow-up	Delta follow-up minus baseline	Baseline	Follow-up	Delta follow-up minus baseline	
Dihydroxyphenylglycol, ng/mL	719.75 $\pm$ 178.81	731.66 $\pm$ 205.78	+11.91 $\pm$ 167.97	754.92 $\pm$ 234.63	857.50 $\pm$ 261.41	+105.28 $\pm$ 203.70	0.0087
Epinephrine, ng/mL	36.06 $\pm$ 26.16	36.35 $\pm$ 24.77	+0.29 $\pm$ 22.89	27.37 $\pm$ 20.46	31.09 $\pm$ 27.81	3.72 $\pm$ 23.95	0.7026
Norepinephrine, ng/mL	294.11 $\pm$ 113.74	299.92 $\pm$ 106.54	+5.81 $\pm$ 104.83	337.32 $\pm$ 154.59	374.80 $\pm$ 132.52	37.48 $\pm$ 150.03	0.0062
Cortisol, pg/mL	142.33 $\pm$ 51.67	136.50 $\pm$ 47.25	-5.83 $\pm$ 50.89	140.32 $\pm$ 49.47	160.33 $\pm$ 45.71	20.01 $\pm$ 57.63	0.0289
18OH-Cortisol, pg/mL	0.63 $\pm$ 0.27	0.64 $\pm$ 0.25	+0.01 $\pm$ 0.29	0.61 $\pm$ 0.32	0.68 $\pm$ 0.29	0.07 $\pm$ 0.25	0.5069
Cortisone, pg/mL	19.63 $\pm$ 4.25	20.16 $\pm$ 3.79	+0.53 $\pm$ 5.07	19.29 $\pm$ 5.13	21.35 $\pm$ 3.67	2.06 $\pm$ 5.47	0.2949
11-Deoxycortisol, pg/mL	0.57 $\pm$ 0.43	0.50 $\pm$ 0.42	-0.07 $\pm$ 0.44	0.59 $\pm$ 0.59	0.61 $\pm$ 0.43	+0.02 $\pm$ 0.67	0.3514
21-Deoxycortisol, pg/mL	0.08 $\pm$ 0.13	0.06 $\pm$ 0.11	+0.02 $\pm$ 0.09	0.05 $\pm$ 0.06	0.07 $\pm$ 0.10	+0.02 $\pm$ 0.10	0.1093
18-oxo-Cortisol, pg/mL	0.02 $\pm$ 0.01	0.02 $\pm$ 0.01	0 $\pm$ 0.01	0.02 $\pm$ 0.01	0.02 $\pm$ 0.01	0 $\pm$ 0.01	0.6712
Aldosterone, pg/mL	0.08 $\pm$ 0.05	0.08 $\pm$ 0.05	0 $\pm$ 0.04	0.07 $\pm$ 0.05	0.09 $\pm$ 0.05	0.02 $\pm$ 0.04	0.2023
Corticosterone, pg/mL	4.13 $\pm$ 4.06	3.51 $\pm$ 4.33	-0.62 $\pm$ 3.42	4.51 $\pm$ 3.94	5.39 $\pm$ 3.89	+0.88 $\pm$ 4.44	0.8125
11-Deoxycorticosterone, pg/mL	0.05 $\pm$ 0.04	0.04 $\pm$ 0.04	-0.01 $\pm$ 0.03	0.06 $\pm$ 0.06	0.05 $\pm$ 0.04	-0.01 $\pm$ 0.06	0.3514
Renin, pg/mL	32.66 $\pm$ 60.63	41.32 $\pm$ 73.76	+8.66 $\pm$ 97.31	49.20 $\pm$ 96.09	50.75 $\pm$ 94.53	+1.55 $\pm$ 113.36	0.9051

\*Adjusted for sex, body mass index, age and presence of hypertension. Treatment effects are shown in figure 1.

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#### REFERENCES

- 1 Heinzer R, Vat S, Marques-Vidal P, *et al*. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med* 2015;3:310–8.
- 2 Casitas R, Martínez-Cerón E, Galera R, *et al*. The effect of treatment for sleep apnoea on determinants of blood pressure control. *Eur Respir J* 2017;50.
- 3 Kritikou I, Basta M, Vgontzas AN, *et al*. Sleep apnoea and the hypothalamic–pituitary–adrenal axis in men and women: effects of continuous positive airway pressure. *Eur Respir J* 2016;47:531–40.
- 4 Jullian-Desayes I, Joyeux-Faure M, Tamisier R, *et al*. Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: a systematic review from sham CPAP randomized controlled trials. *Sleep Med Rev* 2015;21:23–38.
- 5 da Silva Paulitsch F, Zhang L. Continuous positive airway pressure for adults with obstructive sleep apnea and cardiovascular disease: a meta-analysis of randomized trials. *Sleep Med* 2019;54:28–34.
- 6 Thiel S, Lettau F, Rejmer P, *et al*. Effects of short-term continuous positive airway pressure withdrawal on cerebral vascular reactivity measured by blood oxygen level-dependent magnetic resonance imaging in obstructive sleep apnoea: a randomised controlled trial. *Eur Respir J* 2019;53.
- 7 Schwarz EI, Martínez-Lozano Sinues P, Bregy L, *et al*. Effects of CPAP therapy withdrawal on exhaled breath pattern in obstructive sleep apnoea. *Thorax* 2016;71:110–7.
- 8 Goldstein DS, Eisenhofer G, Stull R, *et al*. Plasma dihydroxyphenylglycol and the intraneuronal disposition of norepinephrine in humans. *J Clin Invest* 1988;81:213–20.
- 9 Cabassi A, Vinci S, Quartieri F, *et al*. Norepinephrine reuptake is impaired in skeletal muscle of hypertensive rats in vivo. *Hypertension* 2001;37:698–702.
- 10 Goldstein DS, Cheshire WP. Roles of catechol neurochemistry in autonomic function testing. *Clin Auton Res* 2018;28:273–88.
- 11 Di Murro A, Petramala L, Cotesta D, *et al*. Renin–angiotensin–aldosterone system in patients with sleep apnoea: prevalence of primary aldosteronism. *J Renin Angiotensin Aldosterone Syst* 2010;11:165–72.
- 12 Kim SJ, Fong AY, Pilowsky PM, *et al*. Sympathoexcitation following intermittent hypoxia in rat is mediated by circulating angiotensin II acting at the carotid body and subfornical organ. *J Physiol* 2018;596:3217–32.