Effect of mandibular advancement therapy on inflammatory and metabolic biomarkers in patients with severe obstructive sleep apnoea: a randomised controlled trial

Sylvain Recoquillon,[1] Jean-Louis Pépin,[2,3] Bruno Vielle,[4] Ramaroson Andriantsitohaina,[1] Vanessa Bironneau,[5] Frédérique Chouet-Girard,[6] Bernard Fleury,[7] François Goupil,[8] Sandrine Launois,[7] M Carmen Martinez,[1] Nicole Meslier,[1,9] Xuan-Lan Nguyen,[7] Audrey Paris,[8] Pascaline Priou,[1,9] Renaud Tamisier,[2,3] Wojciech Trzepizur,[1,9] Frédéric Gagnadoux[1,9]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2018-212609).

[1]Université d'Angers, INSERM UMR 1063, Angers, France
[2]HP2, INSERM UMR 1042, Université Grenoble Alpes, Grenoble, France
[3]Laboratoire EFCR, Clinique Universitaire de Physiologie, CHU de Grenoble, Grenoble, France
[4]Centre de Recherche Clinique, CHU d'Angers, Angers, France
[5]Service de Pneumologie, Université de Poitiers, CHU, Poitiers, France
[6]Service de Chirurgie Maxillo-faciale et Stomatologie, Centre Hospitalier, Le Mans, France
[7]Unité de Sommeil, Université Paris VI, Hôpital Saint-Antoine, Paris, France
[8]Service de Pneumologie, Centre Hospitalier, Le Mans, France
[9]Département de Pneumologie, CHU d'Angers, Angers, France

Correspondence to
Prof. Frédéric Gagnadoux, Département de Pneumologie, CHU, Angers 49100, France; FrGagnadoux@chu-angers.fr

Received 16 September 2018
Accepted 1 October 2018

To cite: Recoquillon S, Pépin J-L, Vielle B, *et al*. *Thorax* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/thoraxjnl-2018-212609

ABSTRACT

Systemic inflammation and metabolic disorders are among the mechanisms linking obstructive sleep apnoea (OSA) and cardiovascular disease (CVD). In 109 patients with severe OSA and no overt CVD, biomarkers of inflammation (C reactive protein, interleukin-6, tumour necrosis factor-α and its receptors, adiponectin, leptin and P-selectin), glucose and lipid metabolism, and N-terminal pro-brain natriuretic peptide, were measured before and after 2 months of treatment with a mandibular advancement device (MAD) (n=55) or a sham device (n=54). MAD reduced the Apnoea–Hypopnoea Index (p<0.001) but had no effect on circulating biomarkers compared with the sham device, despite high treatment adherence (6.6 hour/night).

Trial registration number NCT01426607.

INTRODUCTION

Systemic inflammation and metabolic disorders are among the intermediary mechanisms linking obstructive sleep apnoea (OSA) with cardiovascular diseases (CVD).[1] Even still debated owing to confounding factors, many studies have established an association between inflammatory cytokines and indices of OSA severity.[2] Exposure of rodents to intermittent hypoxia, a hallmark of OSA, stimulates inflammatory pathways and leads to cardiovascular or metabolic disorders.[3]

Mandibular advancement devices (MAD) have emerged as the main therapeutic alternative to CPAP for OSA. Despite the superior efficacy of CPAP in reducing OSA severity, most trials comparing MAD and CPAP have reported similar health outcomes.[4 5] In a recent multicentre randomised controlled trial, our group evaluated the impact of 2 months of effective MAD therapy versus a sham device on endothelial function in patients with severe OSA.[6] The aim of the present ancillary study was to investigate the effects of MAD therapy on circulating levels of inflammatory and metabolic biomarkers.

METHODS

Study design and interventions

As described previously,[6] patients with severe OSA (Apnoea–Hypopnoea Index (AHI)>30) and no overt CVD were randomly assigned to receive 2 months of treatment with either a custom-made effective MAD or a sham device with objective measurement of treatment adherence by an embedded microsensor (see online supplementary figure E1). Overnight in-lab polysomnography and blood sample collections were performed at baseline and after the 2-month treatment period. Additional details regarding patient recruitment, randomisation procedure, interventions and the laboratory techniques that were used for measuring circulating biomarkers of inflammation, metabolism and N-terminal pro-brain natriuretic peptide (NT-ProBNP) are described in the online supplementary.

Statistics

A sample size calculation was performed for the primary endpoints of the main study.[6] Only patients with available biomarkers before and after the 2-month intervention were included in the present per-protocol analysis. Treatment effects (effective MAD vs sham device) were modelled using linear regression (STATA V.13.1; STATA Corp.), adjusting for baseline values and potential covariates (see online supplementary for further details).

RESULTS

Study flow and baseline characteristics

Among 150 randomised patients, 109 had available biomarkers before and after 2 months of effective MAD (n=55) or sham device (n=54), and were included in the analysis (figure 1). There were no differences between baseline characteristics of all randomised patients, patients included and not included in the present analysis (see online supplementary table E1).

As shown in table 1, only gender was significantly different between the effective and the sham device groups (p=0.04).

Outcomes

In 84 patients with available objective adherence data, mean objective use rate was 6.6 (1.4) hours/night in the effective MAD group (n=42) versus 6.0

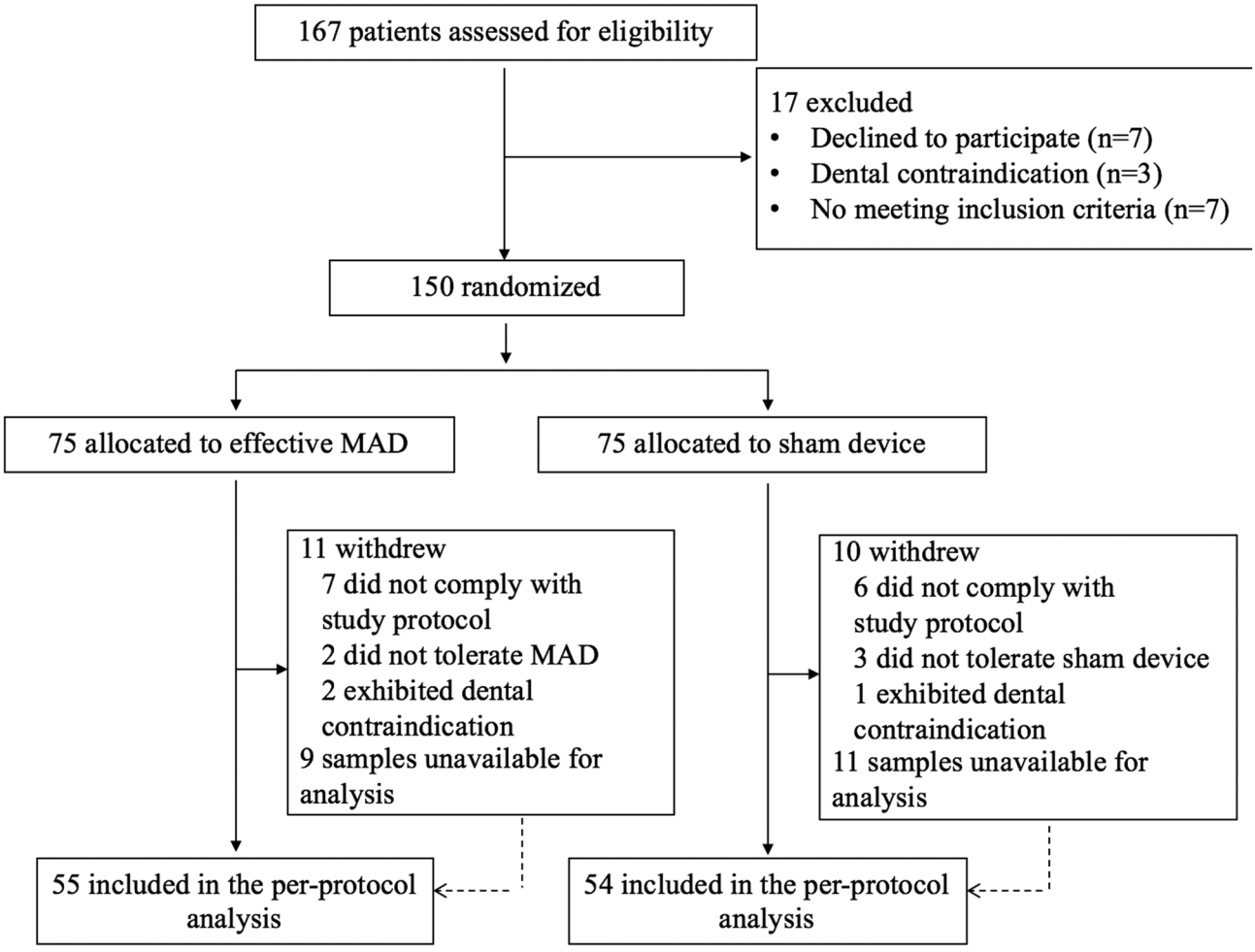

Figure 1 Flow diagram showing trial allocation. MAD, mandibular advancement device.

(2.0) hours/night in the sham device group (n=42) (p=0.10). Only minor changes in body weight were observed during intervention with no significant intergroup differences (p=0.9).

Table 1 Baseline characteristics of the study population

	All patients	Effective MAD	Sham device	P values
N	109	55	54	–
Age, years	53.6 (10.1)	54.2 (10.1)	53.0 (10.2)	0.56
BMI, kg/m^2	27.1 (3.3)	27.0 (3.1)	27.2 (3.4)	0.78
Women, %	12.1	18.5	5.7	0.04
Hypertension, %	20.9	21.1	20.7	0.96
Diabetes, %	5.7	3.8	7.5	0.68
Dyslipidaemia, %	11.2	13.0	9.4	0.56
Current smoker, %	21.1	13.7	28.3	0.07
ESS	9.1 (4.2)	9.0 (4.1)	9.2 (4.3)	0.81
AHI, n	41.0 (34.0–52.0)	40.0 (34.0–51.0)	44.5 (35.0–56.0)	0.27
ODI, n	31.7 (17.1)	30.2 (18.5)	33.2 (15.6)	0.39
SBP, mm Hg	126.4 (15.1)	127.1 (14.3)	125.8 (16.0)	0.66
DBP, mm Hg	77.6 (11.4)	76.6 (12.5)	78.6 (10.2)	0.38

Data are expressed as mean (SD), median (IQR) or percentages.
AHI, Apnoea–Hypopnoea Index; BMI, body mass index; DBP, office diastolic blood pressure; ESS, Epworth Sleepiness Score; MAD, mandibular advancement device; ODI, 3% Oxygen Desaturation Index; SBP, office systolic blood pressure.

Effective MAD was superior to sham device in reducing the AHI (p<0.001), the Oxygen Desaturation Index (p<0.001), and the Microarousal Index (p=0.009) (see online supplementary table E2). A complete response (AHI reduced by ≥50% to less than 5/hours) was obtained in 10% patients, a partial response (AHI reduced by ≥50% to but persistent ≥5/hours) in 50% of patients and 40% of patients were poor responders with less than 50% reduction in AHI.

As shown in table 2, we observed a decrease in tumour necrosis factor-α (TNF-α) in the sham device group (p=0.01), an increase in leptin levels in the two groups (p=0.01) and an increase in triglyceride levels in the effective MAD group (p=0.009). However, after adjustment for baseline value, age, gender, body mass index and baseline AHI, no significant intergroup differences were observed for the outcome of inflammatory, metabolic biomarkers and NT-ProBNP.

As effective and sham device groups were not well balanced for gender, we performed a post-hoc analysis restricted to male patients. No significant intergroup differences in biomarker outcomes were observed in the male population, except for a significant decrease in TNF-α receptor 1 (TNF-R1) levels with effective MAD compared with the sham device group (−118.5 pg/mL (95% CI −230.9 to −6.2), p=0.04). No significant intergroup differences in biomarkers outcome were observed when the analysis was restricted to complete and partial responders to effective MAD.

Table 2 Impact of effective mandibular advancement device (MAD) versus sham device on inflammatory, metabolic biomarkers and N-terminal pro-brain natriuretic peptide (NT-proBNP)

	Effective MAD		Sham device		Adjusted intergroup differences*	
	Baseline	Follow-up	Baseline	Follow-up	Mean (95% CI)	P values
CRP, mg/L	3.8 (6.9)	3.6 (7.3)	1.7 (1.4) †	3.6 (8.1)	−0.9 (−3.5 to 1.7)	0.49
IL-6, pg/mL	1.1 (0.5)	1.3 (1.2)	1.1 (0.8)	1.3 (2.0)	0.3 (0.0 to 0.7)	0.07
TNF-α, pg/mL	6.7 (2.5)	6.4 (2.4)	8.1 (3.6) †	6.7 (3.3) ‡	0.2 (−0.9 to 1.3)	0.71
P-selectin, pg/mL	72.8 (31.2)	71.8 (26.6)	76.0 (34.4)	79.2 (45.4)	−6.7 (−21.1 to 7.7)	0.36
TNF-R1, pg/mL	1859.3 (485.6)	1831.5 (487.9)	1824.1 (507.5)	1909.8 (550.1)	−80.7 (−184.2 to 22.9)	0.12
TNF-R2, pg/mL	4119.6 (1501.1)	4139.3 (1793.6)	3985.2 (1406.3)	3941.2 (1265.6)	108.2 (−368.9 to 585.3)	0.65
Leptin, pg/mL	14.0 (12.8)	16.3 (15.2) ‡	11.4 (8.3)	13.4 (9.2) ‡	0.1 (−2.3 to 2.6)	0.91
Adiponectin, µg/mL	18.3 (8.9)	18.2 (9.3)	14.9 (6.8) †	14.3 (6.7)	0.5 (−1.0 to 2.0)	0.47
Triglycerides, mmol/L	1.4 (0.6)	1.6 (0.9) §	1.5 (0.7)	1.5 (0.6)	0.3 (0.0 to 0.6)	0.05
Cholesterol, mmol/L	5.3 (0.8)	5.4 (1.0)	5.3 (0.8)	5.2 (0.8)	0.2 (−0.1 to 0.4)	0.23
HDL-c, mmol/L	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	0.0 (0.0 to 0.1)	0.30
LDL-c, mmol/L	3.4 (0.7)	3.4 (0.9)	3.3 (0.8)	3.3 (0.8)	0.0 (-0.2 to 0.3)	0.73
Glucose, mmol/L	5.2 (1.3)	5.4 (1.0)	5.4 (1.0)	5.6 (1.4)	0.0 (−0.2 to 0.3)	0.81
Insulin, mU/L	10.4 (7.4)	11.6 (8.3)	11.7 (9.3)	11.7 (8.3)	0.7 (−2.1 to 3.5)	0.60
HOMA-IR	2.6 (3.2)	3.0 (3.3)	3.0 (3.0)	3.2 (3.0)	0.4 (−0.4 to 1.1)	0.31
NT-ProBNP, pg/mL	296.8 (401.6)	252.5 (301.0)	189.8 (173.5)	184.3 (177.8)	12.0 (−40.9 to 64.9)	0.65

Data are expressed as mean (SD) or mean (95% CI).
*Adjusted for baseline value, age, gender and body mass index and baseline Apnoea–Hypopnoea Index.
†P<0.05 versus effective MAD group at baseline.
‡P<0.05 versus baseline.
§P<0.01 versus baseline.
CRP, C reactive protein; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, Homeostasis Model Assessment-Insulin Resistance Index; IL-6, interleukin-6; LDL-c, low-density lipoprotein cholesterol; TNF-R1, tumour necrosis factor receptor 1; TNF-R2, tumour necrosis factor receptor 2; TNF-α, tumour necrosis factor-α.

DISCUSSION

Only few studies flawed by small sample sizes and the absence of placebo group have evaluated the impact of MAD therapy on circulating biomarkers, and reported discrepant findings.[7–9] In this randomised controlled trial, 2 months of effective MAD therapy had no effect on inflammatory and metabolic biomarkers in patients with severe OSA and no overt CVD, despite high objective device adherence and a significant reduction in OSA severity.

As expected, the mean reduction in AHI obtained in the effective MAD group (about 53%) was lower than that is usually obtained with CPAP.[4] However, the hypothesis of an insufficient reduction of AHI with MAD is unlikely, as no significant changes in biomarkers were observed when the analysis was restricted to complete and partial responders. It also cannot be formally excluded that the 2-month intervention was too short. Previous studies have reported improvements of inflammatory and metabolic profiles after 3 months to 1 year of MAD therapy, but these studies were uncontrolled with no sham device group.[7–9] Conversely, recent randomised trials showed no impact of 6 months to 1 year of CPAP therapy on biomarkers despite a complete suppression of apneic events.[10 11] We observed a higher proportion of women in the effective MAD group. It has been reported that female patients with OSA exhibit a less severe inflammatory profile than men.[2] Interestingly, we found that effective MAD therapy was associated with a significant improvement of TNF-R1 levels only in male patients. Between-group differences were also observed for baseline levels of adiponectin, C reactive protein and TNF-α, but adjustments for baseline values were performed to mitigate this potential bias.

We acknowledge that our ancillary study may have been underpowered to detect small changes in biomarkers, as the sample size was based on endothelial function, the primary outcome of the main study.[6] Furthermore, our study population presented several characteristics that may have contributed to a lower cardiovascular response and/or a floor effect of the intervention, including a relatively small proportion of metabolic disorders, no overt CVD and moderate daytime sleepiness at baseline. Further studies are required to determine whether MAD therapy for OSA can improve circulating biomarkers in patients who exhibit more severe inflammatory and metabolic dysfunction at baseline. However, recent randomised trials and a meta-analysis have shown remarkably small effects of CPAP on inflammatory and metabolic biomarkers, even in patients at high cardiometabolic risk.[10–12]

CONCLUSION

Two months of MAD therapy in patients with severe OSA reduced OSA severity, but had no effect on inflammatory and metabolic biomarkers despite high treatment adherence.

Acknowledgements The authors thank Jean-Marie Chrétien, Sonia Dias Domingo, Caroline Erignoux, Anaïg le Cam, Mathieu Lelay and Marie Peeters for their help with trial administration, monitoring and coordination, as well as data management.

Contributors SR, J-LP, BV, RA, FC-G, BF, FG, SL, CM, NM, VB, X-LN, AP, PP, RT, WT and FG were substantially involved in the design of the study and critical revision of the paper for important intellectual content. SR, FG, J-LP, BV and WT were substantially involved in drafting the article. All authors were substantially involved in data acquisition, data analysis and/or interpretation of data. They critically revised the article for important intellectual content.

Funding This study was supported by a grant from the French Ministry of Health (PHRC-I 2010-06). J-LP and RT are supported by the French National Research Agency in the framework of the 'Investissements d'avenir' programme (ANR-15-IDEX-02).

Competing interests None declared.

Patient consent Obtained.

Ethics approval Comité de Protection des Personnes, Ouest II, Angers, France; No. 2010/14.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Drager LF, McEvoy RD, Barbe F, *et al*. Sleep apnea and cardiovascular disease: lessons from recent trials and need for team science. *Circulation* 2017;136:1840–50.
2 Gaines J, Vgontzas AN, Fernandez-Mendoza J, *et al*. Gender differences in the association of sleep apnea and inflammation. *Brain Behav Immun* 2015;47:211–7.
3 Unnikrishnan D, Jun J, Polotsky V. Inflammation in sleep apnea: an update. *Rev Endocr Metab Disord* 2015;16:25–34.
4 Sharples LD, Clutterbuck-James AL, Glover MJ, *et al*. Meta-analysis of randomised controlled trials of oral mandibular advancement devices and continuous positive airway pressure for obstructive sleep apnoea-hypopnoea. *Sleep Med Rev* 2016;27:108–24.
5 Bratton DJ, Gaisl T, Wons AM, *et al*. CPAP vs Mandibular advancement devices and blood pressure in patients with obstructive sleep apnea: a systematic review and meta-analysis. *JAMA* 2015;314:2280–93.
6 Gagnadoux F, Pépin JL, Vielle B, *et al*. Impact of mandibular advancement therapy on endothelial function in severe obstructive sleep apnea. *Am J Respir Crit Care Med* 2017;195:1244–52.
7 Galic T, Bozic J, Ivkovic N, *et al*. Effects of mandibular advancement device treatment on arterial stiffness and glucose metabolism in patients with mild to moderate obstructive sleep apnea: a prospective 1 year study. *Sleep Breath* 2016;20:69–77.
8 Nižankowska-Jędrzejczyk A, Almeida FR, Lowe AA, *et al*. Modulation of inflammatory and hemostatic markers in obstructive sleep apnea patients treated with mandibular advancement splints: a parallel, controlled trial. *J Clin Sleep Med* 2014;10:255–62.
9 Yalamanchali S, Salapatas AM, Hwang MS, *et al*. Impact of mandibular advancement devices on C-reactive protein levels in patients with obstructive sleep apnea. *Laryngoscope* 2015;125:1733–6.
10 Chirinos JA, Gurubhagavatula I, Teff K, *et al*. CPAP, weight loss, or both for obstructive sleep apnea. *N Engl J Med* 2014;370:2265–75.
11 Thunström E, Glantz H, Yucel-Lindberg T, *et al*. CPAP does not reduce inflammatory biomarkers in patients with coronary artery disease and nonsleepy obstructive sleep apnea: a randomized controlled trial. *Sleep* 2017;40:40.
12 Ning Y, Zhang TS, Wen WW, *et al*. Effects of continuous positive airway pressure on cardiovascular biomarkers in patients with obstructive sleep apnea: a meta-analysis of randomized controlled trials. *Sleep Breath* 2018 [Epub ahead of print 22 Apr 2018].