**Effect of mandibular advancement therapy on inflammatory and metabolic biomarkers
in patients with severe obstructive sleep apnoea: A randomized controlled trial.**

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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 to the sham device, despite high treatment adherence (6.6 h/night).

Trial registration number: Results, NCT01426607

Key words: obstructive sleep apnoea syndrome; mandibular advancement device; inflammation; cytokines.

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 continuous positive airway pressure (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 randomized 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 supplement 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, randomization 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 supplement. (ClinicalTrials.gov number: NCT01426607, Results).

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 *versus* sham device) were modelled using linear regression (STATA version 13.1; STATA Corp., College Station, TX), adjusting for baseline values and potential covariates. (See online supplement for further details).

Results

Study flow and baseline characteristics

Among 150 randomized 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 randomized patients, patients included and not included in the present analysis (see online supplemental Table E1). As shown in table 1, only gender was significantly different between the effective and the sham device groups (p=0.04).

Table 1: Baseline characteristics of the study population

	All patients	Effective MAD	Sham device	p value
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, mmHg	126.4 (15.1)	127.1 (14.3)	125.8 (16.0)	0.66
DBP, mmHg	77.6 (11.4)	76.6 (12.5)	78.6 (10.2)	0.38

Data are expressed as mean (standard deviation), median [interquartile range] or percentages. Abbreviations: MAD, mandibular advancement device; BMI, body mass index; ESS, Epworth sleepiness score; AHI, apnoea-hypopnoea index; ODI, 3% oxygen desaturation index, SBP, office systolic blood pressure; DBP, office diastolic blood pressure.

Outcomes

In 84 patients with available objective adherence data, mean objective use rate was 6.6 (1.4) h/night in the effective MAD group (n=42) *versus* 6.0 (2.0) h/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). Effective MAD was superior to sham device in reducing the AHI (p<0.001), the oxygen desaturation index (p<0.001), and the micro-arousal index (p=0.009) (see online supplemental Table E2). A complete response (AHI reduced by $\geq 50\%$ to less than 5/h) was obtained in 10% patients, a partial response (AHI reduced by $\geq 50\%$ to but persistent ≥ 5 /h) in 50% of patients and 40% of patients were poor responders with less than 50% reduction in AHI.

As shown in Table 3, 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 2 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 to the sham device group (-118.5 pg/mL [95%CI, -230.9; -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 3: Impact of effective mandibular advancement device (MAD) *versus* sham device on inflammatory, metabolic biomarkers and N-terminal pro-brain natriuretic peptide

	Effective MAD		Sham device		Adjusted intergroup differences *	
	Baseline	Follow-up	Baseline	Follow-up	Mean (95%CI)	p value
CRP, mg/L	3.8 (6.9)	3.6 (7.3)	1.7 (1.4) †	3.6 (8.1)	-0.9 (-3.5;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;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;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;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;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;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;2.6)	0.91
Adiponectin, μ g/mL	18.3 (8.9)	18.2 (9.3)	14.9 (6.8) †	14.3 (6.7)	0.5 (-1.0;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;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;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;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;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;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;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;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;64.9)	0.65

Data are expressed as mean (standard deviation) or mean (95% confidence interval [CI])
Abbreviations: CRP, C-reactive protein; IL-6, interleukin-6; TNF- α , tumour necrosis factor- α ; TNF-R1, tumour necrosis factor receptor 1; TNF-R2, tumour necrosis factor receptor 2; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance index; NT-ProBNP, N- terminal pro-brain natriuretic peptide.

* Adjusted for baseline value, age, gender and body mass index and baseline apnoea-hypopnoea index.

** $p < 0.01$ versus baseline.

† $p < 0.05$ *versus* effective MAD group at baseline.

§ $p < 0.05$ *versus* baseline.

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 randomized 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 randomized 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 randomized trials and a meta-analysis have shown remarkably small effects of CPAP on inflammatory and metabolic biomarkers, even in patients at high cardio-metabolic 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.

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Contributors

SR, J-LP, BV, RA, FC-G, BF, FGou, SL, CM, NM, VB, X-LN, AP, PP, RT, WT, and FGag were substantially involved in the design of the study and critical revision of the paper for important intellectual content.

SR, FGag, J-LP, BV, WT, were substantially involved in drafting the article.

All authors were substantially involved in data acquisition, data analysis, and/or interpretation of data. All authors critically revised the article for important intellectual content.

Competing interests

The authors declare no competing interests.

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Patient consent

Obtained

Ethics approval

Comité de Protection des Personnes (CPP), Ouest II, Angers, France; No. 2010/14

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Legends

Figure 1: Flow diagram showing trial allocation

Abbreviation: MAD, mandibular advancement device

Confidential: For Review Only

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273x210mm (144 x 144 DPI)

Online only supplementary material

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Methods (expanded version)

Study Design and Patients

This randomized, single-blind, parallel-group trial conducted in five French sleep centres was approved by our local ethics committee (Comité de Protection des Personnes, Ouest II, Angers; No. 2010/14), and registered with ClinicalTrial.gov (NCT01426607). Patients with severe obstructive sleep apnoea (OSA; Apnoea-Hypopnoea Index [AHI] > 30), aged 18-70 years, for whom mandibular advancement device (MAD) therapy was considered as second-line therapy because of continuous positive airway pressure (CPAP) intolerance, were assessed for eligibility. Exclusion criteria were body mass index (BMI) greater than or equal to 32 kg/m²; history of cardiovascular disease (CVD) including coronary heart disease, heart failure, arrhythmias, and stroke; coexisting sleep disorders other than OSA; central sleep apnoea defined by a central apnoea index greater than or equal to 5; severe daytime sleepiness defined by an Epworth Sleepiness Scale greater than or equal to 16; and inadequate dental structure or temporomandibular joint disease contraindicating MAD treatment as assessed by a dentist. All patients provided their written informed consent to participate in the study.

Randomization

Patients were randomly assigned to receive 2 months of treatment with either effective MAD or a sham device according to a 1:1 allocation using a computer-generated randomization list stratified by site with permuted blocks of random sizes. The effective MAD was custom-made, consisting of an adjustable two-piece acrylic oral appliance (AMO; Orthosom, Beaucouzé, France) with attachments of various sizes allowing adjustment of mandibular advancement (Figure E1). The sham device consisted of the upper appliance only and did not advance the mandible. As previously described,[1] treatment adherence with the effective MAD and the sham device was objectively measured by a validated embedded microsensor thermometer (TheraMon[®], IFT Handels- und Entwicklungsgesellschaft GmbH,

Handelsagentur Gschladt, Hargelsberg, Austria). With ethics committee approval, patient blinding was achieved by concealing the less effective nature of the sham device.[1,2]

Interventions

At baseline, patients underwent clinical assessment, overnight in-lab polysomnography (PSG) followed by collection of blood samples. All patients underwent a 6-week MAD acclimatization period, during which the mandible was incrementally advanced by 1-mm steps every 1 or 2 weeks until symptom relief or until adverse effects prevented further advancement. Patients were then submitted to a one-week washout period, after which they were allocated to receive 2 months of treatment with either effective MAD or the sham device. Clinical assessment, PSG with effective MAD or sham device, and blood sample collection were repeated after the 2-month treatment period. Objective treatment adherence was also calculated after the 2-month treatment period.

Measurements of inflammatory and metabolic biomarkers

After overnight fasting, blood samples were collected in EDTA tubes (Vacutainers, Becton Dickinson, Le Pont de Claix, France) from a peripheral vein using a 21-gauge needle to minimize platelet activation, and were processed for assays within 2 hours. Samples were centrifuged for 20 minutes at 250 g. Platelet-rich plasma was harvested and centrifuged 20 minutes at 1500 g to obtain platelet-free plasma (PFP). PFP was aliquoted and stored at 80°C for subsequent use.

The assessment of inflammatory biomarkers was performed on PFP with an enzyme-linked immunosorbent assay (ELISA) using MESO QuickPlex SQ 120 assay (MSD, Rockville, Md., USA). Each assay was performed in duplicate in order to verify the intra-assay variability using samples randomly prepared. Then, if the coefficient of variability was less than 10%, the mean of each duplicate was calculated. Measures with a coefficient of variability > 10% were considered as unavailable biological data (n=5). A single assay was used to measure

plasma levels of adiponectin, C-reactive protein (CRP) and leptin. Multiplex assays were used for the assessment of interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), N- terminal pro-brain natriuretic peptide (NT-ProBNP), tumor necrosis factor receptor 1 and 2 (TNF-R1 and TNF-R2) and P-selectin. Both assays depended on the electro chemiluminescent compound SULFO-TAG™ linked to a detection antibody. All the solutions were supplied by MSD and experiments were performed according to manufacturer's protocol.

For single assays, PFP was first 1000-fold diluted for adiponectin and CRP in an assay diluent whereas detection of leptin did not require any dilution. Then, the samples were incubated in 96-wells plate coated by a capture antibody directed against the protein of interest. After 2 hours of incubation at room temperature with vigorous shaking, the plate was washed three times with PBS supplemented with 0.05% of Tween-20. Then, SULFO-TAG-labelled detection antibodies were added for another 2 hours at room temperature with vigorous shaking. At the end, three other washes were performed before addition of a read solution. Then, voltage stimulation of plate electrodes induced chemilumescence read by the instrument (MESO QuickPlex SQ 120, USA). The level of the protein of interest is proportional to the emitted light present in the PFP and is calculated thanks to a calibration curve. The limits of detection (LOD) of CRP, adiponectin and leptin were 1.33 pg/mL, 0.005 ng/mL and 43 pg/mL respectively. None of the measured values were outside of these limits.

For the multiplex assay, samples were 2-fold diluted and then incubated for 2 hours with vigorous shaking in a 96-wells plate. Each well is seeded in 6 distinct spot coated with capture antibody specific of the protein of interest. After three washes with PBS supplemented with 0.05% of Tween-20, SULFO-TAG-labelled detection antibodies were added for another 2 hours at room temperature with vigorous shaking. At the end, three other washes were performed before addition of a read solution. Then, voltage stimulation of plate electrodes induced chemilumescence read by the instrument (MESO QuickPlex SQ 120, USA). The

level of the protein of interest is proportional to the emitted light present in the PFP and is calculated thanks to a calibration curve. The calculated LOD of IL-6, TNF- α , TNF-RI, TNF-RII, P-selectin and NT-proBNP were 0.06 pg/mL, 0.04 pg/mL, 0.569 pg/mL, 0.102 pg/mL, 29.9 pg/mL and 0.311 pg/mL respectively. None of the measured values were outside of these limits.

Plasma glucose, insulin, triglycerides, total serum cholesterol, and high-density lipoprotein serum cholesterol (HDL-c) were directly measured in accredited laboratories using standard techniques. Low-density lipoprotein serum cholesterol (LDL-c) was calculated. The homeostasis model assessment resistance index (HOMA-IR.) was calculated from fasting glucose and insulin concentrations, as follows: $\text{insulin (mIU/l)} * \text{glucose (mmol/l)} / 22.5$.

Statistics

A sample size calculation was performed for the primary endpoints of the main study.[1] In the present ancillary study, we performed a per-protocol analysis including patients with available biomarkers before after 2 months of effective MAD or sham device. Continuous variables were described as mean (SD) or mean (95% confidence interval [CI]) for variables with a normal distribution and as median (interquartile range) for variables with a non-normal distribution. Normality of distribution was assessed using the Kolmogorov–Smirnov test. Normal variables were analysed using an unpaired Student’s t test for intergroup difference and a paired t test for intragroup difference. Linear regression analysis was used to adjust for baseline values and potential covariates. Non-normal variables were analysed using the Mann-Whitney test for intergroup difference and the Wilcoxon signed rank test for intragroup difference. The Chi-square test and Fisher’s exact test were used for categorical variables, as appropriate. All reported p values are two-sided. A p value less than or equal to 0.05 was considered to indicate statistical significance. All analyses were performed using STATA version 13.1 (STATA Corp., College Station, TX).

Results

Table E1: Baseline characteristics of all patients randomized in the main study[1] with patients included and not included in the present ancillary study.

	All randomized patients	Patients included in the ancillary study	Patients not included in ancillary study	p value
n	150	109	41	
Age, years	53.8 (10.2)	53.6 (10.1)	54.7 (10.7)	0.97
BMI, kg/m ²	27.0 (3.2)	27.1 (3.3)	26.56 (2.9)	0.71
Women, %	14.4	12.1	23.1	0.48
Hypertension, %	20.7	20.9	17.8	0.51
Diabetes, %	5.1	5.7	3.6	0.71
Dyslipidemia, %	11.7	11.2	14.3	0.64
ESS	9.3 (4.2)	9.1 (4.2)	9.8 (4.3)	0.76
AHI, n	41.0 [35.0-53.0]	41.0 [34.0-52.0]	42.0 [36.0-53.0]	0.78
ODI, n	31.9 (17.9)	31.7 (17.1)	32.2 (19.9)	0.99
SBP, mmHg	125.7 (14.4)	126.4 (15.1)	123.6 (11.4)	0.66
DBP, mmHg	77.7 (10.9)	77.6 (11.4)	78.21 (9.0)	0.97

Data are expressed as mean (standard deviation), median [IQR] or percentages.

Abbreviations: BMI, body mass index; AHI, apnoea-hypopnoea index; ESS, Epworth sleepiness score; ODI, 3% oxygen desaturation index, SBP, office systolic blood pressure; DBP, office diastolic blood pressure.

Table E2: Impact of effective mandibular advancement device (MAD) *versus* sham device on daytime polysomnographic indices

	Effective MAD		Sham device		Adjusted intergroup differences *
	Baseline	Follow-up	Baseline	Follow-up	Mean (95%CI)
AHI, n	40.0 [34.0-51.0]	17.5 † [11.5-25.0]	44.5 [35.0;56.0]	38.5 † [19.0;51.0]	-17.2 (-23.6;-10.8) ll
ODI, n	30.2 (18.5)	15.2 (10.8) †	33.2 (15.6)	28.0 (17.4)	-11.9 (-17.6;-6.1) ll
TST, min	402.7 (74.4)	397.9 (61.9)	376.2 (67.8)	372.3 (71.2)	14.9 (-11.2;41.0)
N1sleep, min	40.9 (32.8)	32.4 (24.5)	36.6 (30.1)	29.6 (21.8)	0.2 (-7.4;7.8)
N2 sleep, min	200.3 (67.3)	194.9 (46.6)	202.0 (69.9)	196.5 (58.7)	-2.3 (-22.6;18.0)
N3 sleep, min	69.5 (45.7)	78.1 (38.7)	61.4 (43.0)	65.8 (40.7)	11.4 (-2.1;24.9)
REM, min	87.0 (30.7)	91.8 (28.6)	68.2 (36.0)	77.3 (34.7) §	6.0 (-6.3;18.2)
MAI, n	32.7 (16.9)	23.1 (11.9) ‡	36.3 (12.8)	31.9 (13.9) §	-7.2 (-12.5;-1.8) **

Data are expressed as mean (standard deviation), median [interquartile range] or mean (95% confidence interval [CI])

Abbreviations: AHI, apnoea-hypopnoea index; AI, apnoea index; ODI, 3% oxygen desaturation index; TST, total sleep time; REM, rapid eye movement sleep; MAI, micro-arousal index.

* Adjusted for baseline value, age, gender and body mass index

† p<0.001 *versus* baseline; ‡ p<0.01 *versus* baseline; § p<0.05 *versus* baseline

ll p<0.001; ** p<0.01

E References

- 1 Gagnadoux F, Pépin J-L, 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.
- 2 Gotsopoulos H, Kelly JJ, Cistulli PA. Oral appliance therapy reduces blood pressure in obstructive sleep apnea: a randomized, controlled trial. *Sleep* 2004;27:934–41.

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Figure Legends

Figure E1: The effective mandibular advancement device used in the study. Full-coverage acrylic appliances designed to fit onto the upper and lower dental arches are connected by acrylic plates of various sizes allowing adjustment of mandibular advancement. The microsensor thermometer was sealed into the upper arch of the device. The sham device consisted of the upper appliance alone

Figure E1: The effective mandibular advancement device used in the study. Full-coverage acrylic appliances designed to fit onto the upper and lower dental arches are connected by acrylic plates of various sizes allowing adjustment of mandibular advancement. The microsensor thermometer was sealed into the upper arch of the device. The sham device consisted of the upper appliance alone

342x240mm (144 x 144 DPI)