Si tratta del primo lavoro al mondo che dimostra l'efficacia del trattamento occlusale anche sulle complicanze cardiocircolatorie dell'OSAS

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CHEST

Original Research

SLEEP MEDICINE

Autonomic Cardiac Modulation in Obstructive Sleep Apnea*

Effect of an Oral Jaw-Positioning Appliance

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Background: **Patients with obstructive sleep apnea (OSA) are characterized by deranged cardiovascular variability, a well-established marker of cardiovascular risk. While long-term treatment with continuous positive airway pressure leads to a significant improvement of cardiovascular variability, little is known of the possibility of achieving the same results with other therapeutic approaches. The aim of our study was to investigate the responses of autonomic indexes of neural cardiac control to another type of OSA treatment based on an oral jaw-positioning appliance.**

Methods: **In 10 otherwise healthy subjects with OSA (OSA+) and in 10 subjects without OSA (OSA−) we measured heart rate, BP, and indices of autonomic cardiac regulation derived from time-domain and spectral analysis of R-R interval (RRI), before and after 3 months of treatment with the oral device. High-frequency (HF) power of RRI was taken as an index of parasympathetic cardiac modulation, and the ratio between low-frequency (LF) and HF RRI powers as an indirect marker of the balance between sympathetic and parasympathetic cardiac modulation.**

Results: **At baseline, in comparison with OSA− subjects, OSA+ subjects displayed a significantly lower RRI variance ($p < 0.02$) and reduced HF RRI powers ($p < 0.001$). After 3 months of treatment with the oral device, the OSA+ group showed a marked reduction in apnea-hypopnea index ($p < 0.001$), a lengthening in RRI and a significant increase in its variance ($p < 0,02$), an increased HF RRI power (from 134 ± 26 to 502 ± 48 ms^2, $p < 0.001$), and a reduction in LF/HF RRI power ratio (from 3.11 ± 0.8 to 1.5 ± 0.5). As a result of these changes, after the 3-month treatment there were no more significant differences between the two groups in these parameters. In both OSA+ and OSA− groups, body weight, heart rate, and BP did not change over time.**

Conclusions: **Three months of treatment with a specific oral jaw-positioning appliance improves cardiac autonomic modulation in otherwise healthy patients with OSA of mild degree.**

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Key words: autonomic nervous system; cardiovascular prevention; heart rate variability; obstructive sleep apnea; oral device

Abbreviations: AHI = apnea-hypopnea index; CPAP = continuous positive airway pressure; HF = high frequency; LF = low frequency; low O_2 = lowest oxygen saturation; OSA = obstructive sleep apnea; OSA+ = with obstructive sleep apnea; OSA− = without obstructive sleep apnea; OSAS = obstructive sleep apnea syndrome; RRI = R-R interval; SaO_2 = arterial oxygen saturation

Obstructive sleep apnea (OSA) is a common and often neglected disorder[1] that is strongly associated with known cardiovascular risk factors, including obesity, insulin resistance, and dyslipidemia. OSA itself may represent an independent risk factor for hypertension,[2] heart failure,[3] myocardial infarction,[4] and stroke.[5] The mechanisms underlying the association between OSA and cardiovascular disease are not well defined, even though it has been suggested that a deranged cardiovascular variability may represent a pivotal link in this context.[6] An altered cardiovascular variability, reflecting a deranged autonomic cardiovascular regulation, may not only predict morbidity and mortality in patients with

diabetes,[7] heart failure,[8] and myocardial infarction,[9] but also represent an independent risk factor in normal and hypertensive subjects.[10,11] This may be the case also for patients with OSA, who are characterized both at night and during wakefulness by increased plasma levels of norepinephrine,[12] elevated muscle sympathetic nerve activity,[13] and altered heart rate variability.[5,14] Evidence is available that long-term treatment with continuous positive airway pressure (CPAP) results in a significant improvement of these autonomic indices in OSA patients.[15–17] This therapeutic approach, however, if often poorly accepted by patients on a long-term basis. The oral jaw-positioning appliance,[18] known to induce an enlargement of the upper airway, represents an alternative, useful, and well-tolerated treatment for OSA, leading to a significant reduction of breathing disorders during sleep.[19,20] In spite of this, the effects of its application on indexes of neural autonomic cardiac control have not been previously investigated. The aims of our study were to fill this gap and to evaluate the changes induced by treatment with a specific oral device on time-domain and frequency domain parameters of heart rate variability.

Materials and Methods

Subjects

We considered for our study 13 consecutive subjects referred to our laboratory because of symptoms of OSA syndrome (OSAS) for diagnostic polysomnography. All subjects were normotensive, free of any other known disease, and receiving no medications. No subjects smoked cigarettes or chewed tobacco at the time of the study and during the previous 6 months. All subjects were used to drinking no more than two cups of expresso coffee per day, this being the case both at baseline and during treatment. On recruitment, all subjects underwent an orthodontic assessment of jaw posture on the three spatial planes to detect possible jaw deviation from normal occlusion. Three subjects were excluded from the study because they did not have any evidence of significant occlusion defects. As a control group, we included 10 healthy subjects matched for age and body mass index, in which occult OSA was excluded using polysomnography.

Measurements and Protocol

Diagnostic polysomnography was performed with a polysomnographic recorder (StarDust; Respironics; Murrysville, PA). Heart rate (ECG), airflow at the mouth and nose, respiratory effort, and arterial oxygen saturation (SaO_2) were monitored during the night. The polysomnogram was scored manually according to standard criteria.[21] An apnea was defined as cessation of inspiratory airflow for >10 s with or without oxyhemoglobin desaturation. An obstructive apnea was defined as the absence of airflow in the presence of rib cage and/or abdominal excursion. A central apnea was defined as the absence of rib cage and abdominal excursions with absence of airflow. Hypopnea was defined as a discernible reduction of $>50\%$ airflow and a decrease of oxyhemoglobin saturation $\geq 4\%$. To diagnose OSA, a threshold of five events per hour was set.[22]

Measurements of ECG, heart rate, and BP were obtained while subjects were awake, during 20 min of undisturbed supine rest in the same room from 10:00 to 11:00 AM; during the recording, the subjects were asked to avoid sudden changes in respiratory rate, which, in all subjects, remained approximately 12 breaths/min. Studies were conducted 3 h after last meal, and the patients voided before the recordings. These recordings were repeated after a 3-month follow-up in both groups, during which subjects with OSA (OSA+) made use of the oral appliance while no intervention was planned in subjects without OSA (OSA−).

Oral Appliance

An individualized acrylic oral splint was applied to each OSA+ subject (Fig 1). The device (Bernkopf-Bertarini) is endowed with orthodontic hooks that fix it to the teeth of the lower dental arch and can be easily removed by the patient. The device consists of an occlusal bite plane set between the two antagonist dental arcades, which modifies the vertical dimension, and of a "repositioning wall" that works over the vestibular surfaces of the upper incisors and canines. This repositioning wall modifies both

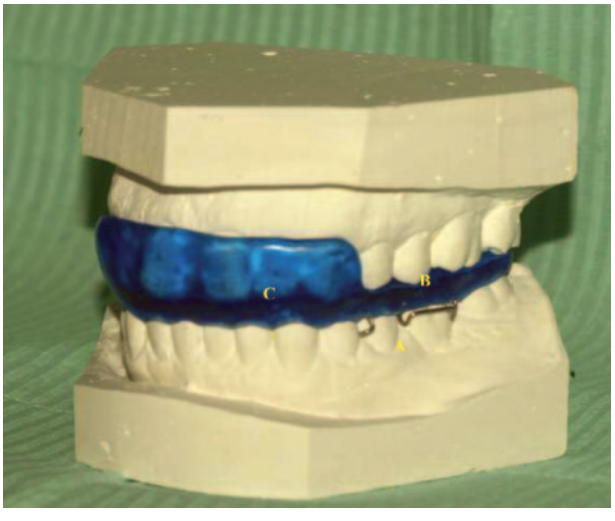

Figure 1. Photograph of the oral jaw-positioning appliance (*C*) and its relation to the upper dental arch (*B*) and lower dental arch (*A*).

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the sagittal and the lateral relationships between the maxilla and the mandible. Each appliance also had a lingual "target" made by an acrylic ring that stimulates the patient's tongue toward its proper position on the palatine folds immediately behind the upper incisors. The above described device is prepared after the dentist has repositioned the mandible, by means of adequate manipulation, into the posture regarded as the correct one when compared with the posture usually assumed by the patient. Patients were required to wear the appliance continuously during sleep, and they were assessed monthly to monitor its proper functioning.

Data Analysis

All the data on cardiac autonomic modulation were obtained during daytime with the patients awake, and were analyzed off-line with a personal computer (MARS 5000; Marquette Hellige; Freiburg, Germany). ECG and respiratory activity were derived, and the resulting tachogram was displayed on a computer screen. All suitable segments from the tachogram, free of ectopic beats and artifacts, were selected for further analysis. A 512-beat length was the minimum period length accepted for analysis. The mean R-R interval (RRI) [measured in milliseconds] and its total variance (milliseconds squared) were calculated. Power spectral analysis was then performed to estimate the powers in the low-frequency (LF) range (0.04 to 0.14 Hz) and in the high-frequency (HF) range (0.15 to 0.50 Hz). To this aim, each RRI series was interpolated and resampled at 2.5 Hz to obtain evenly sampled data. The average RRI spectral power was then integrated in the LF and HF, and the LF/HF ratio was computed accordingly to obtain an indirect marker of the balance between sympathetic and parasympathetic cardiac modulation.[23,24] The LF and HF components were expressed in absolute units (milliseconds squared). BP was measured by an automatic oscillometric sphygmomanometer (SpaceLabs 90207; OSI Systems; Hawthorne, CA). Differences in all parameters between baseline and follow-up were computed.

Statistics

Values are given as means ± SEM, except for demographics of the subjects (means ± SD). Statistical analysis consisted of repeated-measures analysis of variance with time as the within-factor parameter and the difference OSA+/OSA− as the between-factor parameter. Differences were considered to be significant at a level of $p < 0.05$. All subjects were included after giving informed consent. The study was approved by the Ethics Committee of our institution.

Results

The demographic characteristics of the two groups are presented in Table 1.

Table 1—*Demographics of OSA+ and OSA− Subjects

Demographics	OSA−	OSA+
Subjects, No.	10	10
Age, yr	42 ± 8	48 ± 10
Body mass index, kg/m^2	25 ± 2	27 ± 1
Male/female gender, No.	5/5	6/4
Mean arterial pressure, mm Hg	85 ± 10	88 ± 10

*Values are means ± SD unless otherwise indicated.

Baseline

In our OSA+ subjects, mean apnea-hypopnea index (AHI) was 18.2 ± 2/h. As shown in Table 2, RRI was significantly shorter in OSA+ subjects (820 ± 30 ms) than in OSA− subjects (930 ± 50 ms; $p < 0.02$). The variance of RRI was significantly reduced in OSA+ subjects compared to OSA− subjects (980 ± 300 ms^2 vs 3,800 ± 700 ms^2, respectively; $p < 0.02$). In comparison with OSA− subjects, OSA+ subjects showed a decrease in HF RRI powers (134 ± 26 ms vs 470 ± 50 ms, $p < 0.001$) and a tendency toward an increased LF/HF ratio of RRI variability (3.11 ± 0.8 vs 1.27 ± 0.6, p = not significant).

After 3-Month Follow-up

The OSA+ group showed a marked reduction in AHI (from 18 ± 2 to 4 ± 1/h; $p < 0.001$). Polysomnographic indexes quantifying the severity of OSA (such as AHI, Sa_{O_2}, and lowest oxygen saturation [low O_2]) are shown in Table 3. Data obtained at baseline and after 3 months of treatment with the oral appliance are separately shown in OSAS subjects. The corresponding parameters obtained at baseline in normal subjects are also shown. After treatment, RRI and its overall variance were no more significantly different between the two groups. More specifically, the OSA+ group showed an increased HF power of the RRI variability (from 134 ± 26 to 502 ± 48 ms^2, $p < 0.001$) and a tendency to a nonsignificant decrease of LF/HF ratio (from 3.11 ± 0.8 to 1.5 ± 0.5) [Table 4]. In both groups, body weight and arterial BP did not change over time. ECG, heart rate, and BP of the control group did not change during the follow-up period.

Discussion

The novel finding of our study is that treatment with an oral jaw-positioning appliance may improve

Table 2—*RRI Mean Values and Variances and RRI Spectral Parameters Derived by Spectral Analysis Through an Autoregressive Model in OSA− and OSA+ Groups

Variables	OSA−	OSA+
RRI, ms	930 ± 50	820 ± 30‡
RRI variation, ms^2	3,800 ± 700	980 ± 300‡
LF, ms^2	589 ± 102	390 ± 101
LF, NU	50 ± 6	61 ± 5
HF, ms^2	470 ± 50	134 ± 26†
HF, NU	40 ± 7	29 ± 5
LF/HF ratio	1.27 ± 0.6	3.11 ± 0.8

*Values are means ± SEM. NU = normalized units.
†$p < 0.001$.
‡$p < 0.02$.

Table 3—*Polysomnographic Data in OSAS and Control Groups at Baseline and After 3 Months of Therapy*

				OSAS Subjects					
	Control Subjects (Baseline)			Baseline			During Therapy (After 3 mo)		
Subject, No.	AHI, /h	SaO_2, %	Low O_2, %	AHI, /h	SaO_2, %	Low O_2, %	AHI, /h	SaO_2, %	Low O_2, %
1	2	98	96	18.2	92	69	3.2	96	94
2	2.2	97	95	17.3	94	72	4.1	97	95
3	1.5	98	96	17.2	96	71	4.2	98	90
4	2.6	99	95	19.3	95	68	5.2	96	89
5	3	97	95	18.2	96	84	3.8	95	87
6	1.8	98	96	17.4	94	82	3.6	98	84
7	2.7	99	96	19.5	90	88	4.7	94	88
8	3.5	97	95	19	94	90	5.2	95	91
9	4.1	99	97	17.8	90	84	3.9	98	87
10	3.2	98	97	18	93	68	4	95	88
Mean ± SEM	2.6 ± 0.8	98 ± 0.8	95.8 ± 0.8	18.2 ± 0.8	93.4 ± 2.2	77.6 ± 8.8	4.2 ± 0.7	96.2 ± 1.5	89.3 ± 3.6

cardiac autonomic modulation during wakefulness in healthy patients with mild degree of OSA. It has been suggested that cardiovascular variability is altered in patients with moderate-to-severe sleep apnea (AHI $>$ 20/h), even in the absence of arterial hypertension, heart failure, or other overt cardiovascular problems.[6,25] Our data seem to suggest that such an alteration is detectable also in a mild degree of OSA (OSA+, AHI $\leq$ 18/h). This finding may be relevant, since previous studies[10,26] also in normal subjects have demonstrated that impaired cardiovascular variability is involved in determining patient's cardiovascular risk, being associated with insulin resistance condition, left ventricular hypertrophy, and new-onset hypertension. The ability of CPAP treatment[17] not only to improve sleep-related breathing disorders but to normalize alterations in sympathetic activity and cardiovascular variability, has been previously demonstrated in patients with moderate-to-severe sleep apnea, even though, because of frequent side effects, $<$ 50% of patients who are prescribed CPAP treatment are regularly compliant with treatment.[27] Consequently, the availability of other effective, noninvasive, and well-tolerated therapeutic approaches would be highly desirable, particularly in patients with milder forms of OSA. Polysomnography often confirms the beneficial effects of this approach by demonstrating a decrease of snoring frequency, AHI or respiratory disturbance index, and oxygen desaturation frequency and intensity in as many as 50 to 80% of patients.[28,29] Therefore, polysomnography should always be conducted in patients treated with an oral appliance, because an increased AHI after therapy with oral devices has been reported in approximately 13% of patients; while in other cases, a gradual decline in treatment effect either in the short and long term, or an unsatisfactory change in the number of breathing events in patients otherwise reporting a subjective improvement, have been described.[30–32] Although no guidelines on the applicability of oral devices are available, it has been suggested that this therapy might be less effective in severe OSAS, even if other studies[33,34] postulate that severity should not

Table 4—*RRI, Its Variance, and Power Spectral Analysis of RRI Variability in OSA+ and OSA− Groups**

	OSA+		OSA−	
Variables	Before	Oral Device (After 3 mo)	Before	After 3 mo
RRI, ms	820 ± 30	930 ± 60‡	930 ± 50	940 ± 50
RRI variation, ms^2	980 ± 300	3,200 ± 600‡	3,800 ± 700	3,600 ± 650
LF, ms^2	390 ± 101	559 ± 53	589 ± 102	580 ± 98
LF, NU	61 ± 5	57 ± 4	50 ± 6	52 ± 7
HF, ms^2	134 ± 26	502 ± 48†	470 ± 50	467 ± 48
HF, NU	30 ± 5	34 ± 6	40 ± 7	38 ± 5
LF/HF ratio	3.11 ± 0.8	1.5 ± 0.5	1.27 ± 0.6	1.4 ± 0.5

*Values are means ± SEM. See Table 2 for expansion of abbreviation.

†$p < 0.001$.

‡$p < 0.02$, statistical significance of differences between baseline and oral device in OSA+ subjects.

be a reason to exclude patients from oral appliance treatment. Magnetic resonance index and cephalometric variables are also debatable indices to guide a therapeutic choice; indices apparently associated with favorable response to oral devices include a cranial position of the hyoid bone, a smaller mandibular plane angle, a reduced lower anterior face height, a longer anterior cranial base, an increased maxillary length, a shorter soft palate, and a "normal" airway diameter.[35,36] Given that mandibular advancement is the most commonly acknowledged factor responsible for a symptomatic improvement with oral devices, this approach may be particularly indicated for those patients with a retruded mandibular posture, belonging to class II in the orthodontic classification proposed by Angle,[37] even though treatment success has also been associated with a lower body mass index, smaller neck circumference, and younger age, and it is more likely reported in patients with posture (supine)-dependent airway obstruction.[38]

Most of the devices used until now in adults may induce their effect by increasing the anteroposterior pharyngeal diameter, resulting in a forced nonphysiologic dental malocclusion.[39] A large number of complications such as jaw joint pain, facial muscle pain, tooth pain, and xerostomia may consequently follow.[40] On the contrary, the oral appliance used in our study allows a physiologic jaw repositioning toward a lingual target, which stimulates the tongue to keep it in its proper position on palatine folds immediately behind the upper incisors. A repositioning wall, on the vestibular surface of the upper canine teeth, obliged the patient to modify the habitual jaw position in favor of a more appropriate one. In this way, we obtained an enlarging of the retrolingual space and a change from oral to nasal breathing. Our jaw-repositioning appliance was effective in inducing a significant reduction of nightly apneas and an improvement of the altered RRI variability. The precise mechanisms underlying the improvement in autonomic cardiac modulation after 3 months of treatment with our oral appliance were not explored in our study, even though it is likely that an attenuation of the apneic events leading to a decreased chemoreflex sensitivity with a consequent decrease in sympathetic activity played a role.[41] Increased production of nitric oxide and systemic release of other vasoactive substances, mediated by restoration of a correct nasal ventilation, may also be involved.[42] A number of clinical studies[43,44] have assessed the possible association between the application of treatment in OSAS and a prolonged arterial BP reduction; in several cases, they have provided conflicting evidence: CPAP being reported either to contribute to the BP reduction or to have no effect at all; unfortunately, these studies were affected by methodologic problems, the most important ones being the lack of proper control groups with placebo and inadequate BP measurement techniques. In contrast with the discouraging results of studies using oral preparations as placebo, in two analyses[45,46] in which CPAP at subtherapeutic pressures was used as a physical placebo in control groups, significant BP reductions have been demonstrated in active treatment groups, also when considering daytime BP; the average reductions of BP induced by effective CPAP in one of these studies,[46] characterized by a particularly long treatment time (9 weeks), were 10.0 mm Hg at daytime and 10.3 mm Hg at nighttime; similarly, controversies have been reported also on the BP-lowering effects of OSAS treatment by an oral device, mainly in relation with the duration of follow-up.[47,48] Thus, we cannot exclude that also in our study, in which no BP reduction was seen after 3 months, some BP effect might become evident over a longer follow-up period. A few favorable aspects of our study deserve to be emphasized. First, since our subjects were free of any disease other than OSA and were receiving no medications, possible confounding effects of concomitant drug treatments on cardiac autonomic modulation could be excluded. Second, OSA patients and control subjects were matched by age and body mass index, thereby ruling out any potential influence of differences in these important confounders on the parameters under evaluation. Third, while treatment-induced changes of respiratory parameters in OSA are usually evaluated during sleep, this being the case also for cardiovascular variability in a few articles,[49] our data were obtained during daytime with the patients awake in the absence of either apneas, hypopneas, or hypoxemia. This allowed us to obtain information on the persisting effects of OSA and of its treatment by an oral appliance on autonomic cardiac control also during wakefulness. In conclusion, our study shows that a personalized oral jaw-positioning appliance is not only well tolerated but is also effective in reducing sleep-related respiratory disorders and in inducing an improvement of cardiac autonomic modulation, as reflected by changes in heart rate variability. This effect may have favorable implications for the prevention of cardiovascular disease even in subjects with milder degrees of OSA, an issue that deserves to be explored by longitudinal studies.

References

1 Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002; 165:1217–1239
2 Kales A, Bixler EO, Cadieux RJ, et al. Sleep apnoea in a hypertensive population. Lancet 1984; 2:1005–1008
3 Bradley TD, Floras JS. Sleep apnea and heart failure: part 1; Obstructive sleep apnea. Circulation 2003; 107:1671–1678
4 Hung J, Whitford EG, Parsons RW, et al. Association of sleep apnoea with myocardial infarction in men. Lancet 1990; 336:261–264
5 Dyken ME, Somers VK, Yamada T, et al. Investigating the relationship between stroke and obstructive sleep apnea. Stroke 1996; 27:401–4077
6 Narkiewicz K, Montano N, Cogliati C, et al. Altered cardiovascular variability in obstructive sleep apnea. Circulation 1998; 98:1071–1077
7 Kataoka M, Ito C, Sasaki H, et al. Low heart rate variability is a risk factor for sudden cardiac death in type 2 diabetes. Diabetes Res Clin Pract 2004; 64:51–58
8 Hadase M, Azuma A, Zen K, et al. Very low frequency power of heart rate variability is a powerful predictor of clinical prognosis in patients with congestive heart failure. Circ J 2004; 68:343–347
9 Kleiger RE, Miller JP, Bigger JT Jr, et al. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987; 59:256–262
10 Palatini P, Julius S. Heart rate and cardiovascular risk. J Hypertens 1997; 15:3–17
11 Coruzzi P, Parati G, Brambilla L, et al. Effects of salt sensitivity on neural cardiovascular regulation in essential hypertension. Hypertension 2005; 46:1321–1326
12 Dimsdale JE, Coy T, Ziegler MG, et al. The effect of sleep apnea on plasma and urinary catecholamines. Sleep 1995; 18:377–381
13 Somers VK, Dyken ME, Clary MP, et al. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 1995; 96:1897–1904
14 Pagani M, Lombardi F, Guzzetti S, et al. Power spectral analysis of heart rate and arterial pressure variability as a marker of simpatho-vagal interaction in man and conscious dog. Circ Res 1986; 59:178–193
15 Bonsignore MR, Parati G, Insalaco G, et al. Continuous positive airway pressure treatment improves baroreflex control of heart rate during sleep in severe obstructive sleep apnea syndrome. Am J Respir Crit Care Med 2002; 166:279–286
16 Hedner J, Darpo B, Ejnell H, et al. Reduction in sympathetic activity after long-term CPAP treatment in sleep apnoea: cardiovascular implications. Eur Respir J 1995; 8:222–229
17 Narkiewicz K, Kato M, Phillips BG, et al. Nocturnal continuous airway pressure decreases daytime sympathetic traffic in obstructive sleep apnea. Circulation 1999; 100:2332–2335
18 Kato J, Isono S, Tanaka A, et al. Dose-dependent effects of mandibular advancement on pharyngeal mechanics and nocturnal oxygenation in patients with sleep-disordered breathing. Chest 2000; 117:1065–1072
19 Villa MP, Bernkopf E, Pagani J, et al. Randomized controlled study of an oral jaw-positioning appliance for the treatment of obstructive sleep apnea in children with malocclusion. Am J Respir Crit Care Med 2002; 165:123–127
20 Ferguson KA, Ono T, Lowe AA, et al. A short-term controlled trial of an adjustable oral appliance for the treatment of mild to moderate obstructive sleep apnoea. Thorax 1997; 52:362–368
21 Thorpy MJ, for the Diagnostic Classification Steering Committee. The international classification of sleep disorders: diagnostic and coding manual. Rochester, MN: American Sleep Disorders Association, 1990; 52–58
22 Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993; 17:1230–1235
23 Akselrod S, Gordon D, Ubel FA, et al. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981; 213:220–222
24 Cooley JW, Tukey JW. An algorithm for the machine computation of the complex Fourier series. Math Comput 1965; 19:297–301
25 Carlson JT, Hedner J, Elam M, et al. Augmented resting sympathetic activity in awake patients with obstructive sleep apnea. Chest 1993; 103:1763–1768
26 Singh JP, Larson MG, Tsuji H, et al. Reduced heart rate variability and new-onset hypertension: insights into pathogenesis of hypertension; the Framingham Heart Study. Hypertension 1998; 32:293–297
27 Krieger J. Long-term compliance with nasal continuous positive airway pressure (CPAP) in obstructive sleep apnea patients and nonapneic snorers. Sleep 1992; 15:42–46
28 Ferguson KA, Cartwright R, Rogers R, et al. Oral appliances for snoring and obstructive sleep apnea: a review. Sleep 2006; 29:244–262
29 Engleman HM, McDonald JP, Graham D, et al. Randomized crossover trial of two treatments for sleep apnea/hypopnea syndrome: continuous positive airway pressure and mandibular repositioning splint. Am J Respir Crit Care Med 2002; 166:855–859
30 Schmidt-Nowara W, Lowe A, Wiegand L, et al. Oral appliances for the treatment of snoring and obstructive sleep apnea: a review. Sleep 1995; 18:501–510
31 Randerath WJ, Heise M, Hinz R, et al. An individually adjustable oral appliance vs continuous positive airway pressure in mild-to-moderate obstructive sleep apnea syndrome. Chest 2002; 122:569–575
32 Walker-Engstrom ML, Tegelberg A, Wilhelmsson B, et al. Four-year follow-up of treatment with dental appliance or uvulopalatopharyngoplasty in patients with obstructive sleep apnea: a randomized study. Chest 2002; 121:739–746
33 Liu Y, Zeng X, Fu M, et al. Effects of a mandibular repositioner on obstructive sleep apnea. Am J Orthod Dentofacial Orthop 2000; 118:248–256
34 Henke KG, Frantz DE, Kuna ST. An oral elastic mandibular advancement device for obstructive sleep apnea. Am J Respir Crit Care Med 2000; 161:420–425
35 Gao XM, Zeng XL, Fu MK, et al. Magnetic resonance imaging of the upper airway in obstructive sleep apnea before and after oral appliance therapy. Chin J Dent Res 1999; 2:27–35
36 Skinner MA, Robertson CJ, Kingshott RN, et al. The efficacy of a mandibular advancement splint in relation to cephalometric variables. Sleep Breath 2002; 6:115–124
37 Angle, EH. Classification of malocclusion. Dental Cosmos 1899; XLI:248–244, 350–357
38 Liu Y, Lowe AA, Fleetham JA, et al. Cephalometric and physiologic predictors of the efficacy of an adjustable oral appliance for treating obstructive sleep apnea. Am J Orthod Dentofacial Orthop 2001; 120:639–647
39 Pitsis AJ, Darendeliler MA, Gotsopoulos H, et al. Effect of vertical dimension on efficacy of oral appliance therapy in obstructive sleep apnea. Am J Respir Crit Care Med 2002; 15(6 Suppl):S42–S46
40 Neill A, Whyman R, Bannan S, et al. Mandibular advance-

ment splint improves indices of obstructive sleep apnoea and snoring but side effects are common. N Z Med J 2002; 115:289–292
41 Kara T, Narkiewicz K, Somers VK. Chemoreflexes physiology and clinical implications. Acta Physiol Scand 2003; 177:377–384
42 Haight JS, Djupesland PG. Nitric oxide (NO) and obstructive sleep apnea (OSA). Sleep Breath 2003; 7:53–62
43 Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. BMJ 2000; 320:479–482
44 Fletcher EC. Cardiovascular effects of continuous positive airway pressure in obstructive sleep apnea. Sleep 2000; 23(suppl 4):S154–S157
45 Dimsdale JE, Loredo JS, Profant J. Effect of continuous positive airway pressure on blood pressure. Hypertension 2000; 35:144–147
46 Becker HF, Jerrentrup A, Ploch T, et al. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. Circulation 2003; 107:68–73
47 Yoshida K. Effect on blood pressure of oral appliance therapy for sleep apnea syndrome. Int J Prosthodont 2006; 19:61–66
48 Otsuka R, Ribeiro de Almeida F, Lowe AA, et al. The effect of oral appliance therapy on blood pressure in patients with obstructive sleep apnea. Sleep Breath 2006; 10:29–36
49 Brown TE, Beightol LA, Koh J, et al. Important influence of respiration on human R-R interval power spectra is largely ignored. J Appl Physiol 1993; 75:2310–2317