CORE
Metadata, citation and similar papers at core.ac.uk
Provided by Elsevier - Publisher Connector

Respiratory Medicine (2010) **104**, 911–916

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Effects of CPAP therapy on the sympathovagal balance and arterial stiffness in obstructive sleep apnea

Kazuki Shiina, Hirofumi Tomiyama*, Yoshifumi Takata, Masanobu Yoshida, Kota Kato, Hirokazu Saruhara, Yuki Hashimura, Chisa Matsumoto, Kihiro Asano, Yasuhiro Usui, Akira Yamashina

Department of Cardiology, Tokyo Medical University, 6-7-1 Nishi-Shinjuku, Shinjuku-ku, Tokyo 160-0023, Japan

Received 8 August 2009; accepted 13 January 2010
Available online 6 February 2010

KEYWORDS
Sleep apnea;
Arterial stiffness;
Autonomic nervous system;
Continuous positive airway pressure

Summary
Objective: Increased arterial stiffness and sympathovagal imbalance are noted in patients with obstructive sleep apnea (OSA). It has been thought that continuous positive airway pressure (CPAP) therapy can have beneficial effects on the vascular function in such cases. However, it is not yet clear whether the improvement of sympathovagal balance by CPAP might be related to reduction of the arterial stiffness, independent of changes in the blood pressure.
Methods: In 50 consecutive eligible patients with OSA (apnea–hypopnea index $\geq$ 20/hour) receiving CPAP therapy, the brachial-ankle pulse wave velocity (baPWV), heart rate variability (LF, HF and LF/HF ratio), baroreceptor sensitivity (BRS), plasma levels of C-reactive protein (CRP), and endothelial function as assessed by changes in the forearm blood flow before and after reactive hyperemia (END) were measured before and after 3-months' CPAP therapy.
Results: Significant decrease of the LF/HF ratio, plasma levels of CRP, baPWV and heart rate were observed after 3 months' CPAP therapy. The change in the baPWV following 3-months' CPAP therapy was significantly correlated with the change in the LF/HF ratio and mean blood pressure (MBP), but not with that of the BRS, CRP or END after the therapy. Multivariate linear regression analysis demonstrated a significant correlation between the change in the LF/HF ratio and that in the baPWV (beta = 0.305, $p = 0.041$), independent of the changes in the MBP, plasma CRP levels and heart rate.
Conclusions: Improvement of the sympathovagal balance by CPAP therapy may be significantly related to decreased stiffness of the central to middle-sized arteries, independent of the changes in the blood pressure and vascular endothelial status.
© 2010 Elsevier Ltd. All rights reserved.

* Corresponding author. Tel.: +81 3 3342 6111; fax: +81 3 3342 4820.
E-mail address: tomiyama@tokyo-med.ac.jp (H. Tomiyama).

0954-6111/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2010.01.010

Introduction

Obstructive sleep apnea (OSA) has been reported to be an independent risk factor for cardiovascular disease.[1,2] Abnormal vascular functions such as increased arterial stiffness and endothelial dysfunction have been demonstrated in patients with OSA, and it has been suggested that the increase in cardiovascular risk in these patients may be related to these abnormalities.[3,4] Increased arterial stiffness is an independent determinant of the cardiovascular risk. Continuous positive airway pressure (CPAP) therapy, an established treatment for OSA, has been shown to exert beneficial effects on the vascular functions.[5,6] We showed increased stiffness of the central to middle-sized arteries in patients with OSA in a previous study,[3] and another study reported a reduction of the arterial stiffness following CPAP therapy in OSA patients.[6] This reduction of the arterial stiffness following CPAP therapy is considered to be attributable, at least in part, to improvements of the oxidative stress and/or inflammation by CPAP therapy.[1,2,7,8] Furthermore, abnormal sympathovagal balance has been noted frequently in OSA patients, and this imbalance may directly elevate the blood pressure.[9,10] While sympathovagal balance is well known to affect the vascular tone,[11,12] it is not clear whether improvement of the sympathovagal balance by CPAP therapy might also be associated with a reduction of the arterial stiffness.

The present study was conducted to clarify whether improvement of the sympathovagal balance by CPAP therapy may also be associated with a reduction of the stiffness of the central to middle-sized arteries in patients with OSA, independent of the changes in the blood pressure.

Materials and methods

Patients and study protocol (Fig. 1)

Consecutive eligible patients were admitted to our institution between November 2006 and June 2007 for diagnostic assessment of sleep disorders.

Among the 76 consecutive participants, 54 were diagnosed as having moderate to severe OSA {which is considered as an indication for CPAP therapy; apnea–hypopnea index (AHI) $\geq$ 20/hour}[13–15] and 50 of these patients were entered in the present study protocol (1 patient was excluded because of coronary heart disease, 1 patient because he was under treatment with insulin injections and 2 patients because they were under treatment with beta-blockers) and followed up at our hospital. Before the patients were initiated on CPAP therapy, assessments of the vascular functions {measurement of the brachial-ankle pulse wave velocity (brachial-ankle PWV), assessment of changes in the forearm blood flow before and after reactive hyperemia by strain-gauge plethysmography} and heart rate variability were conducted, and blood examination was performed. After 3 months of CPAP therapy, the same examinations were repeated again. During this 3-month treatment period, no changes were made in the prescribed medications. The study was conducted with the approval of the Ethics Committee of Tokyo Medical University, and the study was performed in accordance with the guidelines of the latest version of the Declaration of Helsinki. Written informed consent was obtained from each of the patients prior to his/her participation in the study.

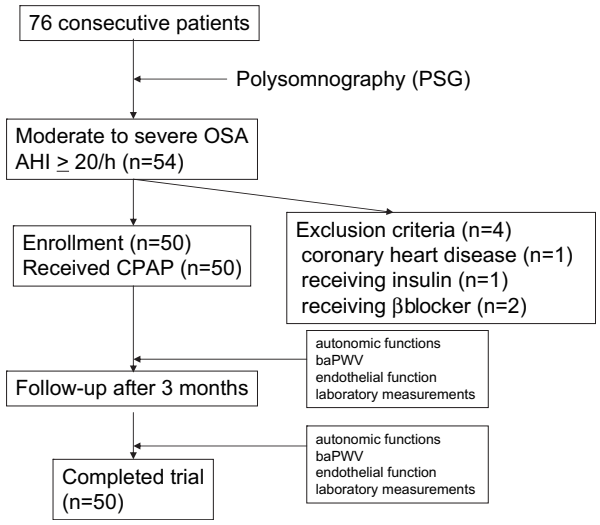

Figure 1 Study protocol of patients examined in the sleep laboratory between November 2006 and June 2007. Abbreviations: OSA = obstructive sleep apnea; AHI = apnea–hypopnea index; CPAP = continuous positive airway pressure therapy; baPWV = brachial-ankle pulse wave velocity.

Sleep study

Overnight fully-attended polysomnographic monitoring was performed with the Alice 4 Sleep System™ (Respironics, Inc; Murrysville, PA) in the sleep laboratory. Apnea, hypopnea, sleep stages, and electroencephalographic arousal were scored according to standard criteria.[13–15] AHI was defined as the number of apnea–hypopnea episodes per hour, and was calculated as the total number of apnea–hypopnea episodes per hour of sleep. The severity of OSA was classified according the criteria of the American Academy of Sleep Medicine.[14]

After the diagnostic polysomnography, the OSA patients with an AHI of $\geq$20/h underwent overnight CPAP titration (REMStar Auto; Respironics, Inc; Murrysville, PA). The CPAP level was increased until respiratory events, snores and oxygen desaturation were eliminated during all stages of sleep in the supine position. Each patient visited our outpatient clinic once a month and was encouraged to use the CPAP device every night. At every visit to our hospital, the average usage time of CPAP and the AHI under CPAP treatment were calculated using the software package included with the CPAP device (Encore Pro, Respironics). After 3 months of optimal CPAP therapy, the experimental assessments were repeated.

Measurement of the autonomic functions, brachial-ankle pulse wave velocity and endothelial function as assessed by reactive hyperemia

On the morning of the measurement day, the prescribed drugs were taken by the subjects with a small amount of

water. The patients were allowed to rest in the sitting position in a quiet, dark, air-conditioned room (22 °C to 25 °C) for 5 min. Then, the blood pressure and heart rate were determined by oscillometric methods (Omron Colin, Kyoto, Japan). After this measurement, the patients were allowed to rest in the supine position in the same room. Then, after the patients had rested for at least 15 min, the following measurements were conducted; the patients were instructed to fast for at least 8 h and to abstain from alcohol, smoking, caffeine and antioxidant vitamins for at least 12 h prior to the measurements.

The systolic blood pressure and heart rate were recorded for 10 min in the supine position using arterial tonometry and electrocardiography (Jentow-7700, Omron Colin, Kyoto, Japan). These measurements were not controlled for the respiratory phase. The spontaneous baroreceptor sensitivity (BRS) and heart rate variability were determined from these samples using a commercial software (GMview II, Signalysis, Tokyo, Japan).[16] In relation to the assessment of the BRS, all of the patients exhibited a correlation coefficient of $\geq$0.85 between the systolic blood pressure and the R-R interval. From the samples of the R-R intervals, the high-frequency power (HF) component, low-frequency power (LF) component and the ratio of the LF to HF (LF/HF ratio) were calculated.

After assessment of the autonomic functions, the brachial-ankle PWV was measured (FORM, Omron Colin, Kyoto, Japan). The details of the measurement have been described in a previous report by the authors.[17] Briefly, electrocardiographic electrodes were placed on both wrists, and a microphone for the phonocardiogram was attached to the left chest. Electrocardiograms and phonocardiograms were used to provide timing markers for the device. Occlusion cuffs, which were connected to both the plethysmographic and oscillometric sensors, were tied around both the upper arms and ankles while the patients lay in the supine position. The brachial and post-tibial arterial pressures were measured by the oscillometric sensor. The brachial and post-tibial arterial pressure waveforms determined by the plethysmographic sensor and recorded for 10 sec were stored. The measurements were conducted after the subjects had rested for at least 5 min in the supine position.

Then, forearm blood flow was measured by strain-gauge plethysmography (model EC5R, DE Hokanson, Inc. Bellevue, WA, USA). A mercury-in-silastic strain gauge that was electrically calibrated was placed on the thickest part of the right forearm. A wrist cuff was inflated to 30 mm Hg above the systolic blood pressure to exclude the hand circulation from the measurements obtained 1 min before measurement of the forearm blood flow. The upper arm-congesting cuff was inflated to 40 mm Hg. The forearm blood flow was recorded for 7 s and expressed as mL of blood flow per minute per 100 mL of forearm blood volume. The forearm vasodilatory response to reactive hyperemia was evaluated using previously established methods.[18] After obtaining the average baseline forearm blood flow from 2 measurements, the upper arm was compressed by inflation of a pneumatic tourniquet at a pressure of 30 mm Hg over the systolic blood pressure for 4.5 min.[18] Then, the forearm blood flow was measured until 120 s after the cuff deflation; the measurements were taken 30, 60, 90 and 120 s after the cuff deflation. The reactive hyperemia ratio was calculated as reactive hyperemia divided by the baseline forearm blood flow: i.e. reactive hyperemia ratio = sum of the forearm blood flow obtained at 30, 60, 90 and 120 s after cuff deflation/basal forearm blood flow. In 22 volunteers, the intra-class correlation coefficient of reproducibility of the forearm blood flow response to reactive hyperemia was 0.86.

Laboratory measurements

The serum levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides and creatinine, and the plasma level of glucose were measured enzymatically in the subjects after they had fasted overnight. The plasma levels of high-sensitive C-reactive protein (CRP) were measured by immunonephelometry using a validated assay method (Dade Boehring Holding GmbH, Liederbach, Germany).

Statistical analysis

All the data, including those presented in the tables, were expressed as means $\pm$ SD. The significances of the differences in the variables measured between the start of the study and after 3 months of CPAP therapy were determined using Wilcoxon's *t* test for paired variables. The differences in the values before and after 3 months of CPAP therapy were calculated as the percent delta changes: (values after 3 months of CPAP therapy minus those before CPAP therapy) divided by the values before CPAP therapy x 100. Correlations among the variables were assessed by both univariate linear regression analysis and multivariate linear regression analyses. *P* values of less than 0.05 were considered to denote statistically significant differences. The statistical analyses were performed using the SPSS software package (SPSS Inc., J11.0, Chicago, IL).

Results

A total of 50 patients entered into the present study protocol. Table 1 shows the changes in the variables before and after 3 months of CPAP therapy. CPAP therapy for 3 months was followed by a significant decrease of the LF/HF ratio, plasma level of CRP, brachial-ankle PWV and the heart rate. In the univariate linear regression analysis performed to assess the relationship of the percent delta change of the brachial-ankle PWV following 3-months' CPAP therapy with the changes in the other variables, a significant positive correlation was found between the percent delta change of the brachial-ankle PWV and that of the LF/HF ratio ($r = 0.33$, $p = 0.02$) and mean blood pressure ($r = 0.66$, $p < 0.01$), but not those of other variables. Multivariate linear regression analysis demonstrated that the percent delta change of the brachial-ankle PWV after 3 months of CPAP therapy was significantly related to that of the LF/HF, independent of the change of the mean blood pressure (Table 2).

Discussion

To the best of our knowledge, the present study is the first to evaluate the correlation between the change in the sympathovagal balance and that of the stiffness of the

Table 1 Changes in the clinical characteristics after 3-months' CPAP therapy.

Variables	Baseline	After 3 months of CPAP	*P* value
No. of subjects	50		
Age, yr	54 ± 10		
Gender (male/female)	45/5		
BMI, kg/m^2	27.4 ± 3.4	27.5 ± 3.6	0.53
Smokers {n (%)}	25 (50)	25 (50)	
SBP (mmHg)	129 ± 14	129 ± 16	0.78
DBP (mmHg)	80 ± 11	80 ± 10	0.63
HR (beats/min)	75 ± 13	66 ± 9	<0.001
AHI (events/h)	53.6 ± 22.1		
Lowest SpO_2 (%)	77 ± 9		
ESS	10 ± 4		
TC (mg/dL)	204 ± 32	203 ± 30	0.44
TG (mg/dL)	199 ± 161	208 ± 167	0.06
HDL (mg/dL)	48 ± 12	50 ± 12	0.13
FPG (mg/dL)	100 ± 25	99 ± 23	0.25
Crnn (mg/dL)	0.81 ± 0.18	0.79 ± 0.17	0.06
CRP (mg/L)	1.1 ± 1.5	0.8 ± 0.8	0.036
baPWV (m/sec)	15.4 ± 0.3	14.5 ± 0.3	0.001
END	15.7 ± 3.6	16.5 ± 6.2	0.36
LF (ms^2)	474 ± 485	522 ± 598	0.82
HF (ms^2)	210 ± 280	256 ± 372	0.83
LF/HF	4.6 ± 3.9	3.4 ± 2.4	0.036
BRS (msec/mmHg)	8.1 ± 4.3	9.7 ± 4.5	0.15
Medication			
CCB	14	14	
ARB	7	7	
ACEi	13	13	
Diuretics	2	2	
Statin	12	12	
Med for DM	5	5	

Abbreviations: BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; AHI = apnea–hypopnea index; ESS = Epworth sleepiness scale; TC = serum total cholesterol; HDL = serum high density lipoprotein cholesterol; TG = serum triglycerides; FPG = fasting plasma glucose; Crnn = serum levels of creatinine; CRP = plasma levels of C-reactive protein; baPWV = brachial-ankle pulse wave velocity; END = endothelial function assessed by changes in the forearm blood flow before and after reactive hyperemia; LF = low-frequency power component of the heart rate variability; HF = high-frequency power component of heart rate variability; LF/HF = low-frequency power component/high-frequency power component ratio of heart rate variability; BRS = baroreceptor sensitivity; Medication = number of patients on medication; CCB = calcium channel blocker; ARB = angiotensin II receptor blocker; ACEi = angiotensin-converting enzyme inhibitor; Med for DM = oral medication for diabetes mellitus.

central to middle-sized arteries following CPAP therapy in patients with moderate to severe OSA.

Arterial stiffness has been classified as functional stiffness and structural stiffness.[19,20] The former is mainly derived from the arterial wall tension and arterial wall tone.[11,19–21] Blood pressure affects the arterial wall tension, and vasoactive substances and sympathovagal activity influence the arterial wall tone.[11,19–21] On the other hand, the latter is mainly derived from degenerative changes of the arterial wall, such as the degradation of elastin fibers, proliferation of collagen fibers and vascular smooth muscle cell hypertrophy.[19,20] A relatively short period of CPAP therapy (less than 4 months) has been shown to improve the carotid-femoral PWV,[22] a marker of central arterial stiffness, as well as the brachial-ankle PWV[6]; therefore, it was considered that this therapy might also improve functional arterial stiffness. While CPAP therapy decreases the blood pressure level,[23] Kitahara et al. demonstrated that this therapy decreased the brachial-ankle PWV without affecting the blood pressure.[6] Even so, the precise mechanisms underlying the pressure-independent reduction of the stiffness of the central to middle-sized arteries brought about after CPAP therapy still remain unclear.

Blood pressure has been demonstrated as one of the major determinants of arterial stiffness,[17,19,20] therefore, the change of the brachial-ankle PWV following CPAP therapy would be expected to be significantly correlated with the change of the mean blood pressure. However, in the present study, CPAP therapy was followed by a reduction of the brachial-ankle PWV without any significant reduction of the blood pressure. These findings suggest a pressure-independent effect of CPAP therapy on the arterial stiffness, and one of the plausible mechanisms underlying such an effect might be reduction of the arterial tone. Thus, the autonomic nervous system (i.e., sympathovagal balance) may have some major roles in the regulation of arterial stiffness.[11,21] In the present study, the sympathovagal balance was assessed by assessment of the heart rate variability. In the analysis of heart rate variability, the LF component is mainly correlated with the sympathetic efferent activity, the HF component is mainly correlated with the vagal activity, and the LF/HF ratio serves as an index of the sympathovagal balance.[24–26] Huang et al demonstrated increase of the LF/HF ratio by hypoxia,[27] therefore, the value of the LF/HF ratio in the present study subjects was higher than that in healthy subjects[28–30]; the results of the present study wherein CPAP therapy decreased the LF/HF ratio was consistent with this. Similar findings have been demonstrated in another study.[29] Then, in the present study, multivariate linear regression analysis demonstrated that the changes in the LF/HF ratio by CPAP therapy were positively correlated with the changes in brachial-ankle PWV, independent of the changes in the mean blood pressure. Therefore, the changes of the sympathovagal balance occurring following CPAP therapy might be correlated, at least in part, with the reduction of arterial stiffness of the central to middle-sized arteries in patients with OSA.

Endothelial function affects the arterial stiffness via various endothelium-derived vasoactive substances.[19,20] In the present study, endothelial function was assessed by the changes in the forearm blood flow response to reactive hyperemia, and nitric oxide (NO), endothelium-derived hyperpolarization factors (EDHF) and/or adenosine are thought to affect this response.[31,32] In addition, we measured the plasma levels of CRP as a marker of vascular endothelial inflammation.[33] While CPAP therapy significantly reduced the plasma levels of CRP in the present study, it did not improve the endothelial function. The

Table 2 Multivariate Linear Regression Analysis to Assess the Relationship of Percent Delta Changes by CPAP Therapy in brachial-ankle PWV with those in LF/HF and MBP. Dependent variable = Percent delta changes in brachial-ankle pulse wave velocity by continuous positive airway pressure therapy. Total *R*-square = 0.483.

Independent variable	Non-standardization coefficient (SE)	Standardization coefficient	*t*-Value	*p*-Value
perdl LF/HF	4.333×10^{-2} (0.020)	0.305	2.124	0.041
perdl MBP	57.148 (16.356)	0.501	3.494	0.001
perdl CRP	4.881×10^{-3} (0.006)	0.104	0.825	0.415
perdl HR	4.965×10^{-2} (0.100)	−0.065	−0.497	0.622

Abbreviations: SE = standard error; perdl = percent delta changes before and after 3 months of CPAP therapy; MBP = mean blood pressure.

changes in the plasma levels of CRP following CPAP therapy showed no significant relationship with the changes in the brachial-ankle PWV following the therapy. Thus, the present study results suggested that the improvement of the vascular endothelial status by CPAP therapy was not a major determinant of the stiffness of the central to middle-sized arteries.

Study limitations

The present study had some study limitations: 1. Increased arterial stiffness, especially of the central artery, is an independent risk factor for cardiovascular disease.[19,20] While several studies have demonstrated that sympathetic activation increases the central arterial stiffness,[34,35] we did not clarify the independent correlation of the change of the sympathovagal balance following CPAP therapy to that of the carotid-femoral PWV, a gold standard for assessment of the central arterial stiffness in the present study[36]; 2. The relationships between oxidative stress and arterial stiffness are controversial,[37] and we did not evaluate the effect of CPAP therapy on this relationship in this study; 3. In the present study protocol, nitroglycerine forearm blood flow response was not obtained and the respiration was not controlled for measurement of the autonomic nervous function; 4. At our institution, OSA patients with coronary heart disease and/or heart failure are managed at the outpatients department for coronary heart disease or heart failure. Therefore, none of the present study subjects had clinical manifestations of cardiovascular disease. Confirmation of the relationship between the changes in the sympathovagal balance and those of the arterial stiffness following CPAP therapy in subjects with clinical manifestations of cardiovascular disease is proposed.

Conclusions

In patients with OSA, CPAP therapy exerted beneficial effects on parameters of the heart rate variability and on the brachial-ankle PWV. Furthermore, the improvements in both parameters were significantly correlated, independent of the changes in the blood pressure, endothelial function and plasma levels of CRP. Thus, the change of the sympathovagal balance by CPAP therapy may be significantly correlated with the decreased stiffness of the central to middle-sized arteries, independent of the changes in the blood pressure and vascular endothelial status.

Conflict of interest statement

The authors have no conflict of interests to declare.

Acknowledgement

The authors are indebted to Professor J. Patrick Barron of the International Medical Communications Center of Tokyo Medical University for his review of this manuscript.

References

1. Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. *JAMA* 2003;**290**:1906—14.
2. Lattimore JD, Celermajer DS, Wilcox I. Obstructive sleep apnea and cardiovascular disease. *J Am Coll Cardiol* 2003;**41**:1429—37.
3. Shiina K, Tomiyama H, Takata Y, et al. Concurrent presence of metabolic syndrome in obstructive sleep apnea syndrome exacerbates the cardiovascular risk: a sleep clinic cohort study. *Hypertens Res* 2006;**29**:433—41.
4. Kohler M, Craig S, Nicoll D, Leeson P, Davies RJ, Stradling JR. Endothelial function and arterial stiffness in minimally symptomatic obstructive sleep apnea. *Am J Respir Crit Care Med* 2008;**178**:984—8.
5. Cross MD, Mills NL, Al-Abri M, et al. Continuous positive airway pressure improves vascular function in obstructive sleep apnoea/hypopnoea syndrome: a randomised controlled trial. *Thorax* 2008;**63**:578—83.
6. Kitahara Y, Hattori N, Yokoyama A, Nakajima M, Kohno N. Effect of CPAP on brachial-ankle pulse wave velocity in patients with OSAHS: an open-labelled study. *Respir Med* 2006;**100**:2160—9.
7. Jelic S, Padeletti M, Kawut SM, et al. Inflammation, oxidative stress, and repair capacity of the vascular endothelium in obstructive sleep apnea. *Circulation* 2008;**117**:2270—8.
8. Noda A, Nakata S, Koike Y, et al. Continuous positive airway pressure improves daytime baroreflex sensitivity and nitric oxide production in patients with moderate to severe obstructive sleep apnea syndrome. *Hypertens Res* 2007;**30**:669—76.
9. Ziegler MG, Mills PJ, Loredo JS, Ancoli-Israel S, Dimsdale JE. Effect of continuous positive airway pressure and placebo treatment on sympathetic nervous activity in patients with obstructive sleep apnea. *Chest* 2001;**120**:887—93.
10. Brooks D, Horner RL, Kozar LF, Render-Teixeira CL, Phillipson EA. Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. *J Clin Invest* 1997;**99**:106—9.
11. Karita K, Izumi H. Effect of baseline vascular tone on vasomotor responses in cat lip. *J Physiol* 1995;**482**:679—85.

12. Egan B, Panis R, Hinderliter A, Schork N, Julius S. Mechanism of increased alpha-adrenergic vasoconstriction in human essential hypertension. *J Clin Invest* 1987;**80**:812—7.
13. Rechtschaffen A, Kales A. *A manual of standardized terminology, techniques and scoring systems for sleep stages of human subjects*. Los Angeles: UCLA Brain Information Service/Brain Research Institute; 1968.
14. American Sleep Disorders Association. EEG arousals: scoring rules and examples. *Sleep* 1992;**15**:173—84.
15. The Report of an AASM task force: sleep-related breathing disorders in adults: recommendations syndrome definition and measurement techniques in clinical research. *Sleep* 1999;**22**: 667—89.
16. Yamada J, Tomiyama H, Matsumoto C, Yoshida M, Shiina K, Yamashina A. Effects of azelnidipine on the autonomic functions and its influence on arterial stiffness and endothelial functions. *J Cardiol* 2008;**51**:114—20.
17. Yamashina A, Tomiyama H, Takeda K, et al. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 2002; **25**:359—64.
18. Tomiyama H, Motobe K, Zaydun G, et al. Insulin sensitivity and endothelial function in hypertension: a comparison of temocapril and candesartan. *Am J Hypertens* 2005;**18**:178—82.
19. Safar ME, Levy BI, Struijker-Boudier H. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. *Circulation* 2003;**107**:2864—9.
20. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol* 2005;**25**:932—43.
21. Dampney RA, Horiuchi J, Tagawa T, Fontes MA, Potts PD, Polson JW. Medullary and supramedullary mechanisms regulating sympathetic vasomotor tone. *Acta Physiol Scand* 2003; **177**:209—18.
22. Drager LF, Bortolotto LA, Figueiredo AC, Krieger EM, Lorenzi GF. Effects of continuous positive airway pressure on early signs of atherosclerosis in obstructive sleep apnea. *Am J Respir Crit Care Med* 2007;**176**:706—12.
23. Bazzano LA, Khan Z, Reynolds K, He J. Effect of nocturnal nasal continuous positive airway pressure on blood pressure in obstructive sleep apnea. *Hypertension* 2007;**50**:417—23.
24. Zaza A, Lombardi F. Autonomic indexes based on the analysis of heart rate variability: a view from the sinus node. *Cardiovasc Res*. 2001;**50**:434—42.
25. Perini R, Veicsteinas A. Heart rate variability and autonomic activity at rest and during exercise in various physiological conditions. *Eur J Appl Physiol* 2003;**90**:317—25.
26. Parati G, Saul JP, Di Rienzo M, Mancia G. Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation. A critical appraisal. *Hypertension* 1995; **25**:1276—86.
27. Huang SC, Wong MK, Wang JS. Systemic hypoxia affects cardiac autonomic activity and vascular hemodynamic control modulated by physical stimulation. *Eur J Appl Physiol* 2009;**106**: 31—40.
28. Park SB, Lee BC, Jeong KS. Standardized tests of heart rate variability for autonomic function tests in healthy Koreans. *Int J Neurosci* 2007;**117**:1707—17.
29. Roche F, Court-Fortune I, Pichot V, Duverney D, Costes F, Emonot A, Vergnon JM, Geyssant A, Lacour JR, Barthélémy JC. Reduced cardiac sympathetic autonomic tone after long-term nasal continuous positive airway pressure in obstructive sleep apnoea syndrome. *Clin Physiol* 1999;**19**:127—34.
30. Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK. Altered cardiovascular variability in obstructive sleep apnea. *Circulation* 1998;**98**:1071—7.
31. Tousoulis D, Antoniades C, Stefanadis C. Evaluating endothelial function in humans: a guide to invasive and non-invasive techniques. *Heart* 2005;**91**:553—8.
32. Tagawa T, Imaizumi T, Endo T, Shiramoto M, Harasawa Y, Takeshita A. Role of nitric oxide in reactive hyperemia in human forearm vessels. *Circulation* 1994;**90**:2285—90.
33. Paffen E, DeMaat MP. C-reactive protein in atherosclerosis: a causal factor? *Cardiovasc Res* 2006;**71**:30—9.
34. Mahmud A, Feely J. Acute effect of caffeine on arterial stiffness and aortic pressure waveform. *Hypertension* 2001;**38**:227—31.
35. Yildiz M, Sahin B, Sahin A. Acute effects of oral melatonin administration on arterial distensibility, as determined by carotid-femoral pulse wave velocity, in healthy young men. *Exp Clin Cardiol* 2006;**11**:311—3.
36. 2007 Guidelines for the Management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007;**25**:1105—87.
37. Plantinga Y, Ghiadoni L, Magagna A, et al. Supplementation with vitamins C and E improves arterial stiffness and endothelial function in essential hypertensive patients. *Am J Hypertens* 2007;**20**:392—7.