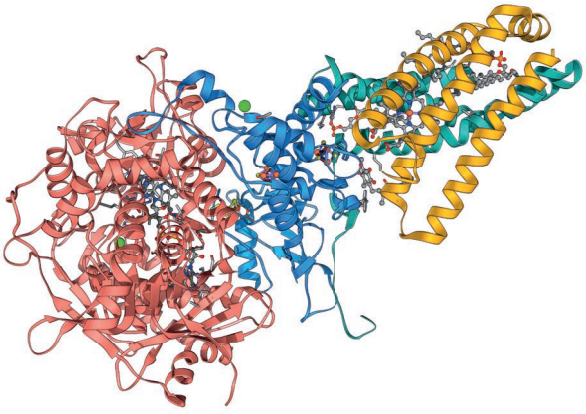
Paragangliomas: Clinical Picture

Niemeijer, N.D.

Chapter 5

Sleep-mediated heart rate variability after bilateral carotid body tumor resection

Nicolasine D. Niemeijer, Eleonora P.M. Corssmit, Robert H.A.M. Reijntjes,
Gert Jan Lammers, J. Gert van Dijk, Roland D. Thijs



Sleep 2015 Apr 1;38:633-639

Abstract

Study Objectives: The carotid bodies are thought to play an important role in sleep-dependent autonomic changes. Patients who underwent resection of bilateral carotid body tumors have chronically attenuated baroreflex sensitivity. These subjects provide a unique opportunity to investigate the role of the baroreflex during sleep.

Design: One-night ambulatory polysomnography (PSG) recording.

Setting: At participants' homes.

Participants: Nine patients with bilateral carotid body tumor resection (bCBR) (four women, mean age 50.4 ±7.2 years) and nine controls matched for age, gender and body mass index.

Interventions: N/A

Measurements: Sleep parameters were obtained from PSG. Heart rate (HR) and its variability were calculated using 30-s epochs.

Results: In bCBR patients, HR was slightly but not significantly increased during wake and all sleep stages. The effect of sleep on HR was similar for patients and controls. Low frequency (LF) power of the heart rate variability spectrum was significantly lower in bCBR patients in active wakefulness, sleep stage 1 and rapid eye movement (REM) sleep. No differences were found between patients and controls for high frequency (HF) power and the LF/HF ratio.

Conclusions: bCBR is associated with decreased LF power during sleep, suggesting impaired baroreflex function. Despite this, sleep-related HR changes were similar between bCBR patients and controls. These findings suggest that the effects of sleep on HR are predominantly generated through central, non-baroreflex mediated pathways.

Keywords: Heart rate variability, carotid body tumor, paraganglioma, sleep, baroreflex

Introduction

Physiological sleep-dependent autonomic changes result from a complex interaction of peripheral cardiovascular reflexes and central modulation.[1,2] The baroreflex arc, with arterial baroreceptors mainly located in the carotid sinuses and aortic arch, is considered to be the critical relay in this complex integration.[3] Baroreflex sensitivity is continuously modulated and differs markedly between behavioral and physiological conditions, including sleep.[1,3,4] During non-rapid eye movement (non-REM) sleep, a progressive decrease is seen in peripheral sympathetic nerve activity and blood pressure (BP), together with a decrease in heart rate (HR).[1,2,5,6] The latter sign suggests increased parasympathic vagal activity. Conversely, a net increase of HR and BP has been reported during rapid eye movement (REM) sleep.[1,2,5,6] This increase is accompanied by irregular changes in autonomic activity.[1]
Paragangliomas are rare neuroendocrine tumors of paraganglia, which are neural-crest derived chromaffin tissues associated with the autonomic nervous system.[7] Paragangliomas in the head and neck region can arise from the carotid body, vagal body or jugulotympanic tissue (i.e. paraganglioma of the temporal bone).[8,9] Due to their location in close proximity to important neurovascular structures, tumor growth may lead to serious morbidity and cranial nerve impairment. These tumors can be removed without recurrence.[10] However, branches of the carotid sinus nerves may not be spared. Bilateral carotid body tumor resection (bCBR) may thus result in arterial baroreflex dysfunction.[11] Patients with bCBR are known to have significant lower baroreflex sensitivity compared with controls, i.e., a less marked heart rate response to a given rise or fall in blood pressure.[11] Baroreflex failure, whether from carotid endarteriectomy,[12] head and neck irradiation,[13,14] mixed cranial nerve neuroma,[15] neurosarcoidosis,[16] or brain stem stroke,[17] is associated with changes in heart rate variability (HRV). Notably, these patients have little 'low frequency' (LF) power, an index of baroreflex-mediated HR control.[18,19] This parallels findings in mouse models, where carotid sinus denervation resulted in lower values of LF power and baroreflex sensitivity.[20] So far, no data are available on the effects of sleep on HRV following bCBR. These patients provide a unique opportunity to study the role of the baroreflex in sleep. We therefore monitored HR and HRV during nocturnal sleep in bCBR patients and compared them with controls matched for age, gender, and body mass index (BMI).

Methods

Subjects

We included nine patients who had previously been treated with bCBR. These patients were recruited from the outpatient clinics of the departments of Endocrinology, Otorhinolaryngology and Surgery of the Leiden University Medical Center and through

an advertisement on the website of the Dutch paraganglioma patient network. For each patient we recruited a healthy control subject matched for gender, age (+/- 5 years), and BMI (+/- 3 kg/m^2).

Exclusion criteria were the presence of a pheochromocytoma, extra-adrenal paraganglioma, history of a psychiatric disorder, history of a diagnosed sleep disorder, or the use of sleep medication.

The Medical Ethics Committee of the Leiden University Medical Center approved the study protocol. All subjects provided written informed consent prior to the study.

Study Design

Polysomnography

Sleep was recorded at home using a portable polysomnography recorder (Somnologica Version 5.1.1, Embla, CO, USA). The measurement started at 16:00 and lasted for 24 hours. Duration of 'active wakefulness', sleep stages 1-3, and REM sleep were assessed. Active wakefulness was defined as all wake epochs occurring between the period from 16:00 until 20 minutes before onset of nocturnal sleep, and the period from 20 minutes after awakening in the morning until the end of the measurement.

Sleep stages and apnea/hypopnea events were manually scored in 30-s epochs by an experienced sleep technician, according to the guidelines of the American Academy of Sleep Medicine.[21] The polysomnography were analysed by a technician who was blinded to the diagnosis of the subject. The autonomic parameters were analyzed automatically.

Respiration was monitored with a nasal pressure sensor and two elastic bands (thorax and abdomen). Oxygen saturation was assessed continuously with a pulse oximeter attached to the index finger. Apneas were defined as a drop in the peak thermal sensor excursion by ≥90 % of baseline for longer than 10 s. Hypopneas were defined as a drop in the nasal pressure signal excursion by ≥30 % of baseline for longer than 10 s, with a ≥4 % desaturation from the pre-event baseline.

Electrocardiography and respiration

A continuous wavelet transform was implemented in Matlab (Version 13.1, Mathworks, MA, USA) to detect R-peaks in the electrocardiogram.[22] A filter was used to exclude outliers, with outliers defined as values that differed > 25 beats/min from the previous or next sample. The signal was resampled at 5 Hz.

R-peak detection resulted in a series of consecutive R-R intervals, split into consecutive 30-s epochs for analysis. For each epoch the mean HR was calculated and a frequency spectrum by creating time-frequency domains through fast Fourier transform. From the frequency spectrum, the LF (0.04-0.15 Hz) and high frequency (HF) (0.15-0.4 Hz) power component

were calculated. The HF component is considered to represent vagal activity, and the LF component to reflect baroreflex-mediated sympathetic activity.[18,23] LF/HF ratio was computed as a reflection of the sympathovagal balance.

Autonomic parameters

LF power and HR were selected as main outcome parameters. Secondary outcome measures included HF and LF/HF ratio.

Selection of epochs

All epochs of sleep following onset of nocturnal sleep and prior to awakening in the morning were included in our analysis. For active wakefulness, a selection of epochs was made, as the length of the active wakefulness period proved to exceed those of the sleep states considerably, which could affect the results. We therefore nullified this effect by limiting the number of epochs of active wakefulness to that of stage 2 epochs for each subject. The wake epochs were selected in a random fashion. To account for the effects of arousals, we labeled every epoch following a transition from sleep stage 3 to stage 2 or 1 and sleep stage 2 to stage 1. We defined these epochs as 'arousal transitions'. In addition, we identified all epochs that coincided with either an apnea or a hypopnea to study the autonomic effects of respiratory arousals.

Statistical Analysis

Overall we included an average total number of 1269 epochs per subject. For each epoch the autonomic parameters, sleep/wake stage, subject number, beta-blocker use, presence of bCBR, arousal transitions and apnea/hypopnea (Figure 1) were recorded and entered into our model. For each autonomic parameter a linear mixed effects regression model was formed to describe the effect of sleep stages and bCBR on the autonomic parameters. To obtain a normal distribution of the residuals of the models, a natural logarithm-transformation was applied. Sleep stage, beta-blocker use, apneas/hypopneas, arousal transitions and the interaction between bCBR and sleep stages were entered as fixed and subjects as random effects to the model. Because of expected differences in variability between sleep stages and between patients and controls, the random subject effects were stratified for sleep stage/wakefulness (5 levels) and patient status (2 levels).

Outliers with a standardized residual at a distance greater than 2.5 standard deviations from 0 were excluded from the linear mixed effects regression model.

P-values below 0.05 were considered to be significant. All statistical analyses were performed using R (Version 3.0.0, R).

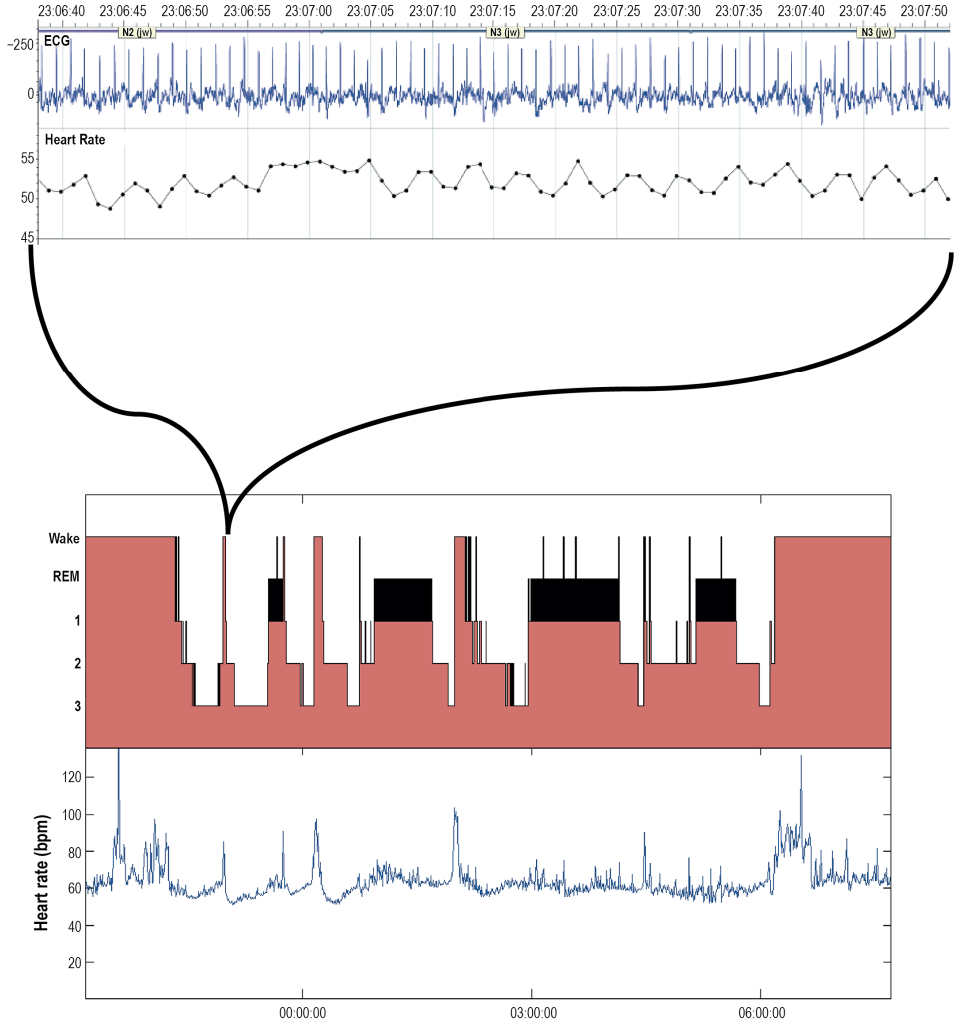


Figure 1. Schematic diagram illustrating our data analysis. For each subject, we analysed the heart rate data during overnight sleep and a random selection of active wakefulness (lower part of the figure). Overall we included an average total number of 1269 epochs per subject. The upper part of the figure zooms in on a representative one-minute segment illustrating how the heart rate was calculated from the one-channel ECG data. For each epoch the autonomic parameters, sleep/wake stage, subject number, beta-blocker use, presence of bCBR, arousal transitions and apnea/hypopnea were recorded and entered into our model.

Results

Participant characteristics

The bCBR group comprised 6 patients with a mutation in subunit D of the *SDH* gene (*SDHD*), one obligate *SDHD* mutation carrier, one patient tested negative for germline mutations in *SDH* genes and one patient had not been genetically tested (Table 1). In the bCBR patients, resection of the first carotid body tumor (CBT) was performed 12.5±7.6 years (range 2.2–25.2 years) and resection of the second CBT 8.9±6.8 years (range 1.2–21.5 years) prior to current study. Three patients had additional head and neck paragangliomas. Two patients had a vagal body tumor and one patient had a jugular foramen tumor. Two patients used beta-blockers (bisoprolol 2.5 mg once daily and propranolol, unknown dosage). None of the participants were shift-workers or were known to have arrhythmias.

Table 1. Clinical characteristics of nine patients with bilateral carotid body tumor resection (bCBR) and their matched healthy controls

Characteristics	bCBR n=9	Controls n=9
Age (year)	50.4 ± 7.2	51.0 ± 8.2
Gender (n)		
Male	5	5
Female	4	4
BMI (kg/m2)	25.7 ± 2.8	25.0 ± 4.2
First CBR		
Time since (yrs; range)	12.5 ± 7.6 (2.2- 25.2)	-
Second CBR		
Time since (yrs; range)	8.9 ± 6.8 (1.2-21.5)	-

bCBR bilateral carotid body tumor resection; *BMI* body mass index; *CBR* carotid body tumor resection.
Data are shown as mean values ± standard deviation.

Sleep parameters

bCBR patients spent significantly more time in sleep stage 1 than controls (12.6% versus 7.5%; $p<0.05$). Apart from this difference, polysomnography parameters were similar between groups. As reported previously, no significant differences in apnea/hypopnea index between patients and controls were found (Table 2).[24]

Autonomic parameters

In bCBR patients, HR was slightly but not significantly increased during wake and all sleep stages (Table 3, Figure 2). The effect of sleep on HR was similar for patients and controls. LF power of the HRV spectrum was significantly lower in bCBR patients during active wakefulness ($p<0.05$), sleep stage 1 ($p<0.01$) and REM sleep ($p<0.05$). (Table 3, Figure 2). No differences were found between bCBR patients and controls for HF power and the LF/HF ratio.

Table 2. Polysomnography results of nine patients with bilateral carotid body tumor resection (bCBR) and their matched healthy controls

Polysomnography	bCBR n=9	Controls n=9
Total sleep time (min)	416.4 ± 52.2	441.8 ± 30.0
Sleep latency (min)	8.0 ± 4.3	4.8 ± 1.8
Sleep efficiency (%)	91.1 ± 3.7	91.8 ± 3.2
% Sleep stage 1	12.6 ± 6.0*	7.5 ± 2.0*
% Sleep stage 2	38.3 ± 8.6	38.4 ± 6.5
% Sleep stage 3	24.8 ± 6.3	27.4 ± 6.5
% REM sleep	24.3 ± 7.6	26.7 ± 3.7
Awakenings (/h)	1.8 ± 0.7	1.9 ± 0.8
AHI (/h)	4.0 ± 4.3	3.3 ± 3.8
AI (/h)	1.2 ± 1.1	1.7 ± 3.0
Hypopnea index (/h)	2.9 ± 3.8	1.6 ± 1.4
Oxygen desaturation events (/h)	4.2 ± 3.9	3.1 ± 3.2

Data are shown as mean values ± standard deviation.
bCBR bilateral carotid body tumor resection; *REM* rapid eye movement; *AHI* apnea hypopnea index; *AI* apnea index.
* p<0.05.

Table 3. Regression coefficients derived from the linear mixed effects model with the effects of sleep on cardiovascular parameters

Model Parameters	HR (bpm)	ln(LF)	ln(HF)	ln(LF/HF)
	β / S.E.	β / S.E.	β / S.E.	β / S.E.
intercept (active wakefulness)	74/3	1/0.2	-0.3/0.4	1/0.3
stage 1	-12/2***	-0.4/0.2*	-0.3/0.2	-0.1/0.2
stage 2	-16/2***	-1/0.2***	-0.6/0.2**	-0.4/0.2*
stage 3	-13/2***	-1/0.3***	-0.6/0.2*	-0.8/0.2**
stage REM	-13/2***	-0.9/0.2***	-0.9/0.2**	-0.1/0.2
beta-blocker	-7/9	-0.4/0.6	-1/1	0.4/0.9
apnea/hypopnea	0.2/0.2	0.5/0.0***	0.2/0.0***	0.3/0.0***
arousal transitions#	1/0.3**	0.5/0.0***	0.1/0.0***	0.3/0.0***
stage active:bCBR	6/6	-0.9/0.3*	-0.2/0.7	-0.6/0.5
stage 1:bCBR	7/5	-1/0.3**	-0.3/0.6	-0.7/0.5
stage 2:bCBR	8/5	-0.6/0.4	-0.0/0.6	-0.5/0.5
stage 3:bCBR	7/5	-0.6/0.4	-0.1/0.7	-0.5/0.5
stage REM:bCBR	7/5	-1/0.4*	-0.4/0.7	-0.6/0.5

Abbreviations: *HR* heart rate; *bpm* beats per minute; *ln* natural log-transformed; *LF* low frequency; *HF* high frequency; β regression coefficient; *S.E.* standard error of the regression; *REM* rapid eye movement; *bCBR* bilateral carotid body tumor resection.

* p <0.05; ** p<0.01; *** p<0.001; # defined as transitions from sleep stage 2 to 1 and from sleep stage 3 to 2 or 1.

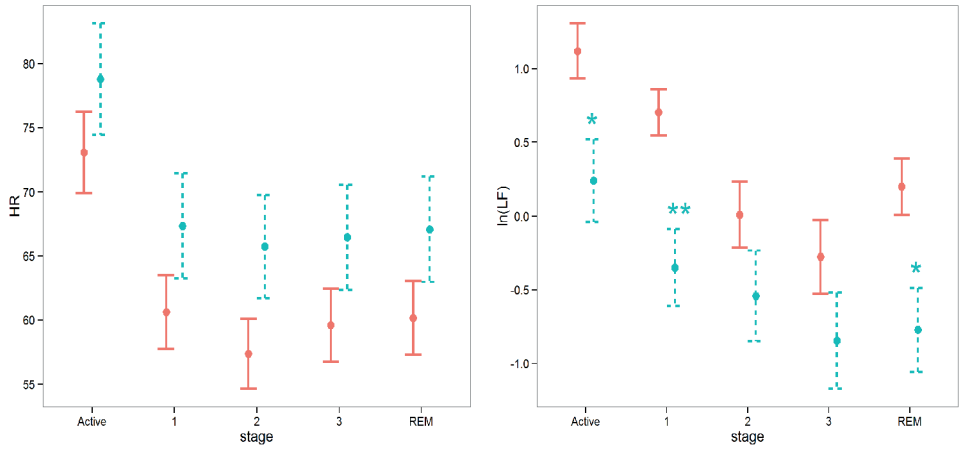


Figure 2. Effects of sleep on heart rate (HR) and low frequency (LF) power of heart rate variability in nine patients with bilateral carotid body tumor resection (dashed, blue lines) and their matched healthy controls (solid, red lines). * p <0.05; ** p<0.01. Bars represent standard error of the mean.

Abbreviations: *HR* heart rate; *REM* rapid eye movement; *ln* natural logarithm; *LF* low frequency power; *Active* active wakefulness.

Discussion

We found that the LF component of HRV was significantly lower during active wakefulness, sleep stage 1, and REM sleep in bCBR patients compared to controls, reflecting baroreflex dysfunction. Interestingly, in spite of these signs of baroreflex dysfunction, the effect of sleep on HR was similar in bCBR patients and their matched controls. These findings suggest that the sleep-related HR decrease primarily results from non-baroreflex mediated pathways.

Sleep studies

Patients with bCBR spent significantly more time than controls in sleep stage 1. This increase in light sleep could not be explained by an increased prevalence of sleep-disordered breathing.[24] Whether these findings are of clinical importance is disputable, as no differences were found in measures of daytime sleepiness between bCBR patients and controls.[24]

Baroreflex and sleep

As in previous daytime studies, bCBR patients had a lower LF indicating baroreflex failure.[12-17] Differences in LF power during sleep between bCBR patients and controls were most apparent in sleep stage 1 and during REM sleep. During deeper sleep (sleep stages 2 and 3), this difference was less marked. This contrast could not be attributed to an *increase* in LF during deeper sleep in the bCBR patients: only minimal LF changes were seen throughout

sleep stages (Figure 2). Instead, the healthy controls appeared to have a marked *decrease* in LF activity during sleep stages 2 and 3 compared to sleep stage 1 and REM sleep. Accordingly, previous work indicated that sleep stages 2 and 3 are associated with the lowest values of sympathetic outflow in healthy controls[1,5,6,25] The absence of significant differences in LF power between patients and controls during sleep stages 2 and 3 is thus explained by the transient suppression of baroreflex function during normal deep sleep. Baroreflex function is thus state-dependent, meaning that it is differently modulated by central influences in the different sleep phases and by wake adaptive behaviours.[1,3,26]

In spite of the marked contrasts in baroreflex function during sleep stage 1 and REM sleep in bCBR patients, sleep-related HR changes were similar for bCBR patients and controls. Notably, the relative higher LF values of the controls seen during sleep stage 1 and REM compared to the bCBR patients, did not translate to more marked HR contrasts in these sleep stages (Figure 2). Also, within the healthy controls we found that sleep stage 3 was associated with lowest LF values, while HR was similar between both sleep stage 2 and 3. This confirms previous work on sleep-related sympathetic outflow: sleep stage 3 was associated with a consistently lower value in muscle sympathetic nerve activity whereas HR remained stable between both sleep stages 2 and 3.[1,5,6,25] Taken together, these findings suggest that the sleep-related HR changes primarily result from non-baroreflex mediated pathways. Which alternative pathways should be considered? It could be argued that the HR decrease during sleep results from inactivity. However, the gradual decrease of HR seen in different non-REM sleep stages and the contrasting effects in REM sleep favor central modulation. Accordingly, overnight infusion of vasopressive drugs (phenylephrine) in healthy subjects results in a sustained decrease in blood pressure the following morning, thus suggesting that overnight blood pressure increases are counteracted by central mechanisms.[27,28] Thus, while inactivity may, of course, in part contribute, this cannot explain the complex dynamics between sleep stages. Diurnal contrasts in autonomic control could also result from neuroendocrine changes, e.g., circadian rhythms in adrenocorticotropic activity and the renin-angiotensin-aldosterone system (RAAS). Clear circadian patterns have been identified for HR and its variability.[29] The overall effects of these circadian effects, however, appear to be modest and can only partly explain the sleep-related HR changes. Supporting this view, the blood pressure dipping pattern has shown to be primarily related to sleep-wake phases rather than endogeneous circadian oscillators.[26] The close correlation between HR and sleep stages argues for direct effects of the sleep-wake cycle on the central autonomic network. Sympathetic outflow decreases and baroreflex sensitivity increases along with the depth of non-REM sleep.[1,5,6,25] Sleep-related autonomic alterations may thus well fit in the general concept of sleep as a state of adaptive inactivity.[30] The central autonomic network during non-REM sleep may involve the hypothalamic ventrolateral preoptic area, central thermoregulatory and central baroreflex pathways, and command neurons in the pons

and midbrain.[26,31] The intact sleep-related HR decrease in bCBR patients suggest that the peripheral baroreceptors play a minor role in the cardiovagal modulation during sleep. We speculate that the balance of neuronal autonomic control changes throughout the sleep-wake cycle. While awake, baroreceptors have an important role in buffering circulatory oscillations induced by activity and mental stress. During non-REM sleep, these oscillations decrease. Consequently, the influence of the baroreceptors gradually declines and autonomic outflow is predominantly driven by the central autonomic network[26,32] (Figure 3). During REM sleep, both pathways are likely equally important: centrally induced transient augmentations of sympathetic outflow cause an increase in baroreceptor activity.[1,2,5,6]

Limitations

We did not quantify baroreflex function as we lacked continuous blood pressure measurements and did not perform daytime standardized baroreflex tests. The low LF values in our bCBR patients are however a clear indication of baroreflex dysfunction.[18,19] Accordingly, a previous small study in eight bCBR subjects confirmed that bCBR causes chronic impairment of baroreflex control of both heart rate and sympathetic nerve activity.[11] Also, ideally given the complex nature of the autonomic nervous system measurements should be multimodal (e.g., including muscle sympathetic nervous activity, sympathetic skin response, pulse arterial tonometry (PAT)) to account for regional differences.

The small sample size of our study was inevitable in view of the extremely low prevalence of paragangliomas. The study did not have enough power to detect small differences. Therefore we were not willing to correct for multiple testing; this may have caused a type I error. However, we believe that our conclusions are valid, as the direction of the results were consistent and in line with previous daytime studies.[12-17] Again, because of the small number of subjects we included two patients who were using beta-blockers. To overcome this limitation, we corrected for beta-blocker use in our mixed effects model, but no significant effects were observed. Another limitation is the lack of measurements of leg movements. We are not aware of an increased prevalence of periodic leg movements in bCBR patients. Even if such a difference would have been the case, the effects on our outcome parameters would be likely minimal as leg movements only have short-term effects: autonomic parameters did not differ between patients with periodic leg movements and controls if the periodic leg movements epochs were excluded.[33]

Conclusion

In conclusion, the arterial baroreceptors are a critical relay in the autonomic network modulating both the peripheral and the central autonomic outflow. Our small study in patients with probable baroreflex failure, however, indicates that the sleep-related HR decrease predominantly results from non-baroreflex mediated, central mechanisms.

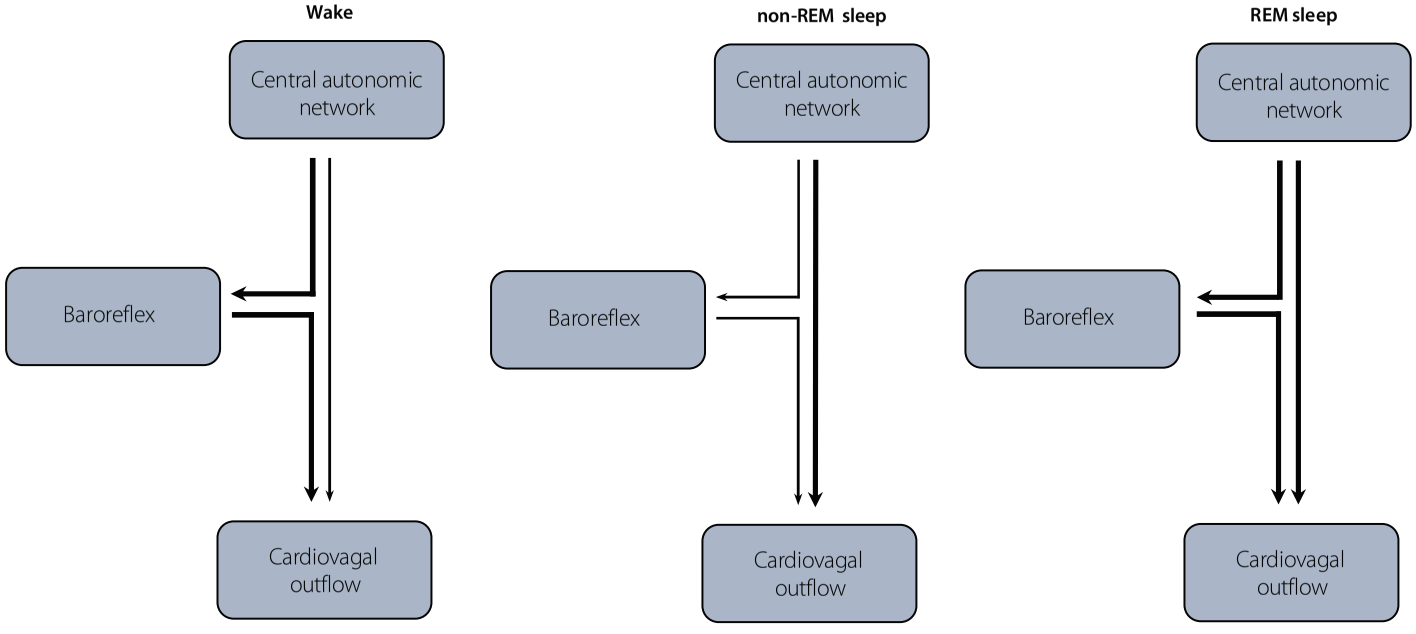


Figure 3. Simplified schematic diagram illustrating the major changes in neuronal autonomic control throughout the sleep/wake cycle. While awake, cardiovagal outflow is predominantly controlled by peripheral baroreceptors, whereas during non-REM sleep the central autonomic network becomes the driving force. During REM sleep, both pathways are likely equally important: central induced transient increases of sympathetic outflow cause an increase in baroreceptor activity.

Abbreviations

bCBR	bilateral carotid body tumor resection
BMI	body mass index
BP	blood pressure
BPM	beats per minute
EEG	electroencephalographic
HF	high frequency
HR	heart rate
HRV	heart rate variability
LF	low frequency
non-REM	non rapid eye movement
PLMS	periodic leg movements
REM	rapid eye movement
SDHD	succinate dehydrogenase subunit D

References

1. Cortelli P, Lombardi C, Montagna P, Parati G. Baroreflex modulation during sleep and in obstructive sleep apnea syndrome. Auton Neurosci 2012;169:7-11.
2. Stein PK, Pu Y. Heart rate variability, sleep and sleep disorders. Sleep Med Rev 2012;16:47-66.
3. Silvani A. Physiological sleep-dependent changes in arterial blood pressure: central autonomic commands and baroreflex control. Clin Exp Pharmacol Physiol 2008;35:987- 994.
4. Di Rienzo M, Parati G, Radaelli A, Castiglioni P. Baroreflex contribution to blood pressure and heart rate oscillations: time scales, time-variant characteristics and nonlinearities. Philos Trans A Math Phys Eng Sci 2009;367:1301-1318.
5. Hornyak M, Cejnar M, Elam M, Matousek M, Wallin BG. Sympathetic muscle nerve activity during sleep in man. Brain 1991;114:1281-1295.
6. Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. New Engl J Med 1993;328:303-307.
7. De Lellis RA, Lloyd RV, Heitz PU, Eng C. World Health Organization classification of tumours, Pathology and Genetics of Tumours of Endocrine Organs. FARC, Lyon 2004.
8. Lack EE, Cubilla AL, Woodruff JM, Farr HW. Paragangliomas of the head and neck region: a clinical study of 69 patients. Cancer 1977;39:397-409.
9. Papaspyrou K, Mewes T, Rossmann H, et al. Head and neck paragangliomas: Report of 175 patients (1989-2010). Head Neck 2012;34:632-637.
10. van Hulsteijn LT, Corssmit EP, Coremans IE, Smit JW, Jansen JC, Dekkers OM. Regression and local control rates after radiotherapy for jugulotympanic paragangliomas: systematic review and meta-analysis. Radiother Oncol 2013;106:161-168.
11. Timmers HJ, Karemaker JM, Wieling W, Marres HA, Folgering HT, Lenders JW. Baroreflex and chemoreflex function after bilateral carotid body tumor resection. J Hypertens 2003;21:591-599.
12. Timmers HJ, Buskens FG, Wieling W, Karemaker JM, Lenders JW. Long-term effects of unilateral carotid endarterectomy on arterial baroreflex function. Clin Auton Res 2004;14:72-79.
13. Timmers HJ, Karemaker JM, Lenders JW, Wieling W. Baroreflex failure following radiation therapy for nasopharyngeal carcinoma. Clin Auton Res 1999;9:317-324.
14. Sharabi Y, Dendi R, Holmes C, Goldstein DS. Baroreflex failure as a late sequela of neck irradiation. Hypertension 2003;42:110-116.
15. Guasti L, Mainardi LT, Baselli G, et al. Components of arterial systolic pressure and RR- interval oscillation spectra in a case of baroreflex failure, a human open-loop model of vascular control. J Hum Hypertens 2010;24:417-426.
16. Jardine DL, Melton IC, Bennett SI, Crozier IG, Donaldson IM, Ikram H. Baroreceptor denervation presenting as part of a vagal mononeuropathy. Clin Auton Res 2000;10:69- 75.
17. Phillips AM, Jardine DL, Parkin PJ, Hughes T, Ikram H. Brain stem stroke causing baroreflex failure and paroxysmal hypertension. Stroke 2000;31:1997-2001.
18. Goldstein DS, Bentho O, Park MY, Sharabi Y. Low-frequency power of heart rate variability is not a measure of cardiac sympathetic tone but may be a measure of modulation of cardiac autonomic outflows by baroreflexes. Exp Physiol 2011;96:1255- 1261.

19. Rahman F, Pechnik S, Gross D, Sewell L, Goldstein DS. Low frequency power of heart rate variability reflects baroreflex function, not cardiac sympathetic innervation. Clin Auton Res 2011;21:133-141.

20. Rodrigues FL, de Oliveira M, Salgado HC, Fazan R, Jr. Effect of baroreceptor denervation on the autonomic control of arterial pressure in conscious mice. Exp Physiol 2011;96:853-862.

21. Iber C, Ancoli-Israel S, Chesson A, Quan SF. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. American Academy of Sleep Medicine, Westchester 2007.

22. Legarreta I, Addison P, Reed M, et al. Continuous wavelet transform modulus maxima analysis of the electrocardiogram: Beat characterisation and beat-to-beat measurement. Int J Wavelets Multi 2005;3:19-42.

23. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J 1996;17:354-381.

24. van Hulsteijn LT, van Duinen N, Ninaber MK, et al. Carotid body tumors are not associated with an increased risk for sleep-disordered breathing. Sleep Breath 2014;18:103-109.

25. Okada H, Iwase S, Mano T, Sugiyama Y, Watanabe T. Changes in muscle sympathetic nerve activity during sleep in humans. Neurology 1991;41:1961-1966.

26. Silvani A, Dampney RA. Central control of cardiovascular function during sleep. Am J Physiol Heart Circ Physiol 2013;305:H1683-692.

27. Sayk F, Becker C, Teckentrup C, et al. To dip or not to dip: on the physiology of blood pressure decrease during nocturnal sleep in healthy humans. Hypertension 2007;49:1070-1076.

28. Iellamo F, Placidi F, Marciani MG, et al. Baroreflex buffering of sympathetic activation during sleep: evidence from autonomic assessment of sleep macroarchitecture and microarchitecture. Hypertension 2004;43:814-819.

29. Boudreau P, Yeh WH, Dumont GA, Boivin DB. Circadian variation of heart rate variability across sleep stages. Sleep 2013;36:919-928.

30. Siegel JM. Sleep viewed as a state of adaptive inactivity. Nat Rev Neurosci 2009;10:747- 753.

31. Paton JFR, Spyer KM. Central nervous control of the cardiovascular system. In: Mathias CJ, Bannister R. Autonomic Failure. 5th ed. United Kingdom: Oxford University Press, 2013:35-51.

32. Palma JA, Benarroch EE. Neural control of the heart: Recent concepts and clinical correlations. Neurology 2014;83:261-271.

33. Palma JA, Alegre M, Valencia M, Artieda J, Iriarte J, Urrestarazu E. Basal cardiac autonomic tone is normal in patients with periodic leg movements during sleep. J Neural Transm 2014;121:385-390.