Clinically Different Phenotypes of Obstructive Sleep Apnea according to 24 Hours Heart Rate Tachogram Pattern

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Background and Objective Heart rate variability (HRV) parameters are altered during sleep in patients with obstructive sleep apnea (OSA). Nondipping of nocturnal heart rate during sleep is characteristic, but not all patients with OSA show this. The aim of this study was to identify differences in OSA patients with or without nocturnal heart rate dipping.

Methods We retrospectively reviewed patients (n = 40) who were confirmed to have OSA [4% Oxygen desaturation index (ODI4) > 5/hr] by a simplified sleep study and underwent a 24 hours Holter electrocardiogram. The OSA patients were compared with control subjects (n = 72), who had been found to have no significant medical diseases.

Results Most HRV parameters were lowered in OSA patients [standard deviation of all normal R-R intervals (SDNN): 99.23 vs. 149.06 ms; $p < 0.0001$]. The OSA patients were divided to two subgroups according to their 24 hours HR tachogram patterns. A HR nondipper subgroup (n = 18) showed a marked decrease in SDNN when compared with a HR dipper subgroup (n = 22) (SDNN 71.72 vs. 121.72 ms; $p < 0.0001$). SDNN was not associated with a severity index of OSA (ODI4) ($r = -0.15$, $p = 0.3619$).

Conclusions In the OSA patients, most HRV parameters (SDNN, standard deviation of the average normal R-R intervals for each 5-min period (SDANN), percentage of adjacent cycles that are > 50 ms apart (pNN50%), root mean square successive differences in milliseconds) were lower than in the control subjects. The OSA patients can be divided to two subgroups according to a 24 hours HR tachogram patterns (HR dipper and nondipper). In HR nondipper OSA subgroup, HRV parameters (SDNN, SDANN), Mean SaO₂ and basal heart rate during sleep were markedly lowered, but were not associated with an OSA severity (ODI4).

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Key Words Obstructive sleep apnea, Heart rate variability, Heart rate dipping, Endophenotype.

INTRODUCTION

The disappearance of nocturnal physiological heart rate dipping has been observed in patients with obstructive sleep apnea (OSA), and this phenomenon might suggest the existence of underlying OSA.¹ Nondipping of nocturnal (that means during sleep) heart rate may be due to disturbed sleep or fragmentation of sleep, which is a characteristic of OSA, but not all OSA patients show this tendency. We therefore attempted to identify clinical differences in OSA patients with or without nocturnal heart rate dipping.

METHODS

We retrospectively reviewed patients (n = 40, male 35, female 5) who were confirmed to have OSA [4% Oxygen desaturation index (ODI4) > 5/hr] by Win-Visi monitoring system (Stowood Scientific Instrument, Oxford, UK) and had undergone 24 hours monitoring with a Holter electrocardiogram (Marquette Series 8000 Holter Scanner, Milwaukee, USA). The patients with OSA and a comparison group of control subjects (n = 72, male 40, female 32) were recruited from medical records of a tertiary general hospital. The control subjects had been found to have no significant medical diseases. The 24 hours heart rate tachogram pattern was

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taken from a Holter electrocardiogram (Marquette Heart Rate Variability Software Version MARS 4.1B). A heart rate dipper pattern was defined as the dipping of nocturnal heart rate more than 10% from baseline level before sleep. Heart rate variability (HRV) parameters were derived from the Holter monitoring data. Comparison of data between patients with OSA, control subjects and OSA subgroups were done with T test using Med-

Calc 11.4 statistical program (Mariakerke, Belgium).

RESULTS

As expected, when we compared the parameters of OSA patients with those of the control subjects, OSA patients showed

Table 1. HRV parameters in OSA and control subjects

	OSA patients (n = 40)		Control subjects (n = 72)		p
	Mean	SD	Mean	SD	
Age	52.60	13.32	50.32	13.46	0.3904
MeanNN	750.28	122.58	833.47	93.60	0.0001
SDNN	99.23	35.46	149.06	36.19	<0.0001
SDANN	87.40	35.85	136.47	35.46	<0.0001
pNN50%	5.21	5.53	9.50	8.45	0.0048
rMSSD	23.30	8.89	30.79	11.80	0.0007
LHR	1.59	0.54	1.61	0.38	0.7687
SHR	72.13	15.88	58.54	8.33	<0.0001

HRV: heart rate variability, OSA: obstructive sleep apnea, MeanNN: mean value of all normal-to-normal interbeat intervals, SDNN: standard deviation of all normal R-R intervals, SDANN: standard deviation of the average normal R-R intervals for each 5-min period, pNN50%: percentage of adjacent cycles that are > 50 ms apart, rMSSD: root mean square successive differences in milliseconds, LHR: ratio of low to high frequency, SHR: basal heart rate during sleep.

Fig. 1. Heart rate nondipper: male 73-year-old, obstructive sleep apnea syndrome, 4% Oxygen desaturation index 29, SDNN 78 ms, sleep heart rate 76 (arrow: Sleep heart rate).

lower HRV values such as mean value of all normal-to-normal interbeat intervals (Mean NN), standard deviation of all normal R-R intervals (SDNN), standard deviation of the average normal R-R intervals for each 5-min period (SDANN), percentage of adjacent cycles that are > 50 ms apart (pNN50%), root mean square successive differences in milliseconds (rMSSD) (Table 1). The basal heart rate during sleep (SHR) taken from the 24 hours heart rate tachogram also showed a marked differ-

ence with the OSA group displaying significantly higher SHR values than the controls (Table 1). When the OSA group was divided into two separate subgroups based on their 24 hours heart rate tachogram pattern (HR nondipper vs dipper) (Figs. 1 and 2),² the HR nondipper subgroup (n = 18) was found to be significantly different from the HR dipper subgroup (n = 22) in SDNN, SDANN, ratio of low to high frequency (LHR), Mean SaO₂, and SHR (Table 2 and 3)(Figs. 3, 4 and 5). The two sub-

Fig. 2. Heart rate dipper: male 47-year-old, Obstructive sleep apnea syndrome, 4% Oxygen desaturation index 38.8, SDNN 111 ms, sleep heart rate 60 (arrow: Sleep heart rate).

Table 2. Differences between HR nondippers (n = 18) and dippers (n = 22)

	HR nondippers		HR dippers		p
	Mean	SD	Mean	SD	
Age	56.22	13.00	49.64	13.13	0.1212
ESS	11.44	4.66	10.18	3.92	0.3577
BMI	29.67	4.51	27.32	3.98	0.0887
NC (inches)	16.51	1.33	16.02	1.28	0.2474
ODI4	28.82	24.01	25.84	20.18	0.6721
PRR	31.67	15.90	38.55	16.65	0.1926
Mean SaO ₂	90.98	4.58	93.58	1.37	0.0158
SHR	81.56	18.39	64.41	7.48	0.0003

HR: heart rate, ESS: Epworth sleepiness scale, BMI: body mass index, NC: neck circumference, ODI4: 4% oxygen desaturation index, PRR: pulse rate rise, SHR: basal heart rate during sleep.

groups did not differ in terms of ODI4, pulse rate rise (PRR) > 6/min, Epworth sleepiness scale, Body mass index, or neck circumference (Table 2 and 3). The results of a correlation analysis are shown in Table 4. In the undifferentiated OSA group, SDNN was found to be significantly related to both SHR and Mean SaO₂, but it was not associated with Mean SaO₂ in the HR dipper subgroup. SHR was related to most HRV parameters (Mean NN, SDNN, SDANN, pNN50%, and rMSSD) in patients with

Fig. 3. Standard deviation of all normal R-R intervals (ms) in heart rate nondipper and dipper (mean + SD)(71.72 + 25.01 vs. 121.73 + 25.48, $p < 0.0001$).

Fig. 4. Sleep heart rate (/min) in HR Nondipper and Dipper (mean + SD)(81.56 + 18.39 vs. 64.41 + 7.48, $p = 0.0003$).

OSA, but in the HR dipper subgroup, it was unrelated to rMSSD, pNN50, ODI4, PRR and Mean SaO₂. In contrast, SHR was significantly associated with ODI4, PRR, Mean SaO₂, MeanNN, SDNN, SDANN, pNN50%, and rMSSD in the HR nondipper subgroup.

DISCUSSION

Almost all energy on earth is derived from the sun. On our planet, biological systems have evolved to develop sophisticated and efficient processes of energy utilization.³⁻⁶ Efficiency of energy utilization is reflected on the interaction of heart and lung, or 'cardiopulmonary coupling'. We can detect and measure the efficiency of cardiopulmonary coupling in many ways. HRV analysis is one well known method of evaluating cardiopulmonary coupling. HRV is known to be decreased in OSA,⁷ but increased HRV in OSA has been reported.^{8,9} The HRV pattern during sleep has revealed pathological, as well as physiological changes. The pathological changes induced by sleep disordered breathing may therefore increase HRV parameters, especially in severe OSA.^{8,9} A daytime decrease in HRV may reflect sympathetic overactivity as a carry-over effect, so the 24 hours HRV pattern is more important than night time HRV. Contrary to a

Fig. 5. Mean SaO₂ in heart rate nondipper and dipper (mean + SD) (90.98 + 4.58 vs. 93.58 + 1.37, $p = 0.0158$).

Table 3. HRV parameters in HR nondippers (n = 18) and dippers (n = 22)

	HR nondippers		HR dippers		P
	Mean	SD	Mean	SD	
MeanNN	744.83	148.93	754.73	99.52	0.8033
SDNN	71.72	25.02	121.73	25.48	<0.0001
SDANN	59.72	20.89	110.05	28.97	<0.0001
pNN50%	5.66	6.06	4.846	4.55	0.6507
rMSSD	23.22	9.90	23.36	8.22	0.9609
LHR	1.38	0.45	1.76	0.55	0.0260

HRV: heart rate variability, MeanNN: mean value of all normal-to-normal interbeat intervals, SDNN: standard deviation of all normal R-R intervals, SDANN: standard deviation of the average normal R-R intervals for each 5-min period, pNN50%: percentage of adjacent cycles that are >50 ms apart, rMSSD: root mean square successive differences in milliseconds, LHR: ratio of low to high frequency.

previous report,⁷ the severity index of OSA (ODI4) was not associated with SDNN, which is the best index of HRV ($r = -0.15$, $p = 0.3619$). Certain other parameters of HRV were not associated with ODI4: these were SDANN, rMSSD, and pNN50%. ODI4 was related only to MeanNN and LHR. The two sub-

groups were different in the association with ODI4 and MeanNN; the relationship held in HR nondipper subgroup ($r = -0.57$, $p = 0.0142$), but not in HR dipper subgroup ($r = -0.11$, $p = 0.6150$). SDNN had significant relationship with Mean SaO₂ ($r = 0.56$, $p = 0.0002$) in the undifferentiated OSA group, wher-

Table 4. Correlations between SDNN, SHR and ODI4 in HR nondipper and dipper subgroups

		OSA patients (n = 40)		HR nondipper OSA (n = 18)		HR dipper OSA (n = 22)	
		r	p	r	p	r	p
SDNN	Age	-0.23	0.1483	-0.05	0.8325	-0.10	0.6444
	ESS	-0.18	0.2548	-0.43	0.0771	0.18	0.4139
	BMI	-0.27	0.0974	-0.33	0.1832	0.09	0.6797
	NC	-0.14	0.3897	-0.15	0.5642	0.10	0.6499
	ODI4	-0.15	0.3619	-0.27	0.2859	-0.02	0.9154
	PRR	0.09	0.5864	-0.23	0.3677	0.02	0.9442
	Mean SaO ₂	0.56	0.0002	0.69	0.0017	0.08	0.7096
	SHR	-0.81	< 0.0001	-0.81	< 0.0001	-0.74	0.0001
SHR	Age	-0.08	0.6333	-0.36	0.1426	-0.14	0.523
	ESS	0.27	0.0921	0.41	0.0937	-0.15	0.4951
	BMI	0.26	0.1115	0.30	0.2233	-0.22	0.3238
	NC	0.14	0.4023	0.20	0.4186	-0.28	0.203
	ODI4	0.35	0.0276	0.56	0.0159	0.00	0.9862
	PRR	0.20	0.2097	0.66	0.0029	-0.02	0.9382
	Mean SaO ₂	-0.70	< 0.0001	-0.73	0.0005	0.03	0.9084
	MeanNN	-0.75	< 0.0001	-0.94	< 0.0001	-0.73	0.0001
	SDNN	-0.81	< 0.0001	-0.81	< 0.0001	-0.74	0.0001
	SDANN	0.76	< 0.0001	-0.75	0.0003	-0.74	0.0001
	pNN50%	-0.34	0.034	-0.51	0.0304	-0.32	0.1482
	rMSSD	-0.44	0.0047	-0.63	0.005	-0.34	0.1232
ODI4	LHR	-0.11	0.5088	0.00	0.9881	0.32	0.1522
	Age	-0.54	0.0003	-0.66	0.0029	-0.50	0.0176
	ESS	0.06	0.7154	0.31	0.2183	-0.24	0.2781
	BMI	0.25	0.1128	0.43	0.072	0.04	0.8582
	NC	0.32	0.042	0.40	0.1005	0.23	0.2928
	PRR	0.76	< 0.0001	0.82	< 0.0001	0.79	< 0.0001
	Mean SaO ₂	-0.40	0.0112	-0.37	0.1343	-0.68	0.0005
	MeanNN	-0.38	0.0155	-0.57	0.0142	-0.11	0.615
	SDNN	-0.15	0.3619	-0.27	0.2859	-0.02	0.9154
	SDANN	-0.13	0.4222	-0.22	0.3895	-0.05	0.8174
	pNN50%	-0.19	0.2362	-0.19	0.4468	-0.21	0.3503
	rMSSD	-0.26	0.1100	-0.26	0.2987	-0.25	0.2549
	LHR	0.42	0.0067	0.40	0.1024	0.56	0.0072
	SHR	0.35	0.0276	0.56	0.0159	0.00	0.9862

SDNN: standard deviation of all normal R-R intervals, SHR: basal heart rate during sleep, ODI4: 4% oxygen desaturation index, HR: heart rate, ESS: Epworth sleepiness scale, BMI: body mass index, NC: neck circumference, PRR: pulse rate rise, MeanNN: mean value of all normal-to-normal interbeat intervals, SDANN: standard deviation of the average normal R-R intervals for each 5-min period, pNN50%: percentage of adjacent cycles that are >50 ms apart, rMSSD: root mean square successive differences in milliseconds, LHR: ratio of low to high frequency, SHR: basal heart rate during sleep.

as this relationship was found in the HR nondipper subgroup ($r = 0.69$, $p = 0.0017$). In the HR dipper subgroup, there was no association with Mean SaO₂ ($r = 0.08$, $p = 0.7096$). This finding may suggest the possibility of different prognoses, but a long term follow study will be necessary to prove this is the case. It may be thought that in the HR dipper subgroup, better SDNN (121.73 vs. 71.72 ms), Mean SaO₂ (93.58 vs. 90.98%) and lower SHR (64.41 vs. 81.56/min) already suggested a more preserved homeostatic condition. SDNN showed the highest association with SHR ($r = -0.81$, $p < 0.0001$) in both the subgroups of HR nondipper and dipper. SDNN is a very sensitive predictor of morbidity and mortality,¹⁰ and resting heart rate is strongly related to the risk of sudden cardiac death.¹¹ It is therefore not surprising that SDNN was closely related to SHR in our study ($r = -0.81$, $p < 0.0001$). This may be deduced from the finding that HR and SDNN have shown reciprocal changes simulating mirror images.¹² The division of OSA patients into HR dipper and nondipper subgroups, which is very simple and easy by 24 hours heart rate tachogram, showed marked differences in SDNN, SDANN, SHR and MeanSaO₂, but no differences in ODI4 and PRR. The nocturnal HR dipping pattern had no association with ODI4 or, PRR. This finding may suggest the possibility that HR dipping during sleep is a kind of endophenotype.¹³

In the long term, many of the HRV parameters (SDNN, SDANN, SHR and Mean SaO₂) are expected to be related to cardiovascular mortality and morbidity, but further studies will be necessary to confirm this. Our study suggest that the 24 hours heart rate tachogram pattern may give clinically significant informations about subgroup differentiation (HR dipper vs. nondipper) and resting basal heart rate (i.e., sleep heart rate: SHR), which showed markedly different HRV pattern.

Limitations. This was not prospective study, and sampling biases are therefore a particular risk. Moreover the diagnosis of OSA was confirmed by a simplified sleep study (Win-Visi monitoring system), and the results of this may be different from those using traditional polysomnography.

Conclusion

In OSA patients, most HRV parameters (SDNN, SDANN, pNN-50%, and rMSSD) showed lower levels than in the control sub-

jects. When OSA patients were divided to two subgroups according to 24 hours HR tachogram patterns (HR dipper vs. nondipper), HRV parameters (SDNN, SDANN, Mean SaO₂, and SHR) in the HR nondipper subgroups were markedly lowered, but were not associated with the OSA severity index of ODI4.

Conflicts of Interest

The authors have no financial conflicts of interest.

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