Relationship of Heart Rate Variability to Sleepiness in Patients with Obstructive Sleep Apnea with and without Heart Failure

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Background: Many patients with severe obstructive sleep apnea (OSA) do not complain of excessive daytime sleepiness (EDS), possibly due to increased sympathetic nervous activity (SNA) and accompanying heightened alertness. We hypothesized that in patients with OSA, those without subjective EDS (Epworth Sleepiness Scale, ESS score < 11) would have higher very low frequency (VLF) heart rate variability (HRV) during sleep, reflecting greater sympathetic heart rate modulation than patients with an ESS score ≥ 11.

Methods: Patients with severe OSA (AHI ≥ 30: 26 with and 65 without heart failure) were divided into those with and without EDS. Heart rate (HR) signals were acquired in stage 2 sleep during periods of recurrent apneas and hypopneas and submitted to coarse graining spectral analysis, which extracts harmonic, neurally mediated contributions to HRV from total spectral power. Because the apnea-hyperpnea cycle entrains muscle SNA at VLF (0 to 0.04 Hz), VLF power was our principal between-group comparison.

Results: Subjects without EDS had higher harmonic VLF power (944 ± 839 vs 447 ± 461 msec², $p = 0.003$) than those with EDS, irrespective of the presence or absence of heart failure (1218 ± 944 vs 426 ± 299 msec², $p = 0.043$, and 1029 ± 873 vs 503 ± 533 msec², $p = 0.003$, respectively). ESS scores correlated inversely with VLF power in all ($r = -0.294$, $p = 0.005$) and in heart failure subjects ($r = -0.468$, $p = 0.016$).

Conclusions: Patients with severe OSA but without EDS have higher VLF-HRV than those with EDS. This finding suggests that patients with severe OSA but without EDS have greater sympathetic modulation of HRV than those with EDS that may reflect elevated adrenergically mediated alertness.

Keywords: Sleepiness, obstructive sleep apnea, heart rate variability, sympathetic activity

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Repetitive obstructive apneas lead to periodic hypoxemia, hypercapnia, and arousals from sleep that stimulate peripheral and central chemoreceptors. These cause cyclic oscillations in sympathetic and parasympathetic nervous system activity that drive oscillations in blood pressure and heart rate with each apnea-hyperpnea cycle.¹

Heart rate (HR) can be modulated by the interaction at the sinoatrial node between the neurotransmitters released by the efferent limbs of the sympathetic and parasympathetic nervous systems. Spectral analysis of HR variability (HRV) can provide information concerning autonomic cardiovascular function during sleep.² Normally, breathing influences vagal HR modulation within the high frequency (HF) range (0.15 to 0.5 Hz) of tidal breathing, i.e., respiratory sinus arrhythmia.³ Sympathetic nervous activity (SNA) exerts its influence over HR at lower frequencies, mainly in the low frequency (LF) range (0.04 to 0.15 Hz).⁴ During repetitive apnea-hyperpnea cycles in patients with obstructive sleep apnea (OSA) or central sleep apnea, breathing shifts the predominant HRV spectral power peak from the LF range into the very low frequency (VLF) range (0.004 to 0.05 Hz) of the apnea-hyperpnea cycle.^{5,6}

In some patients with OSA, frequent apnea-induced arousals from sleep contribute to the development of excessive daytime sleepiness (EDS), which is the commonest symptom causing

BRIEF SUMMARY

Current Knowledge/Study Rationale: Many patients with severe obstructive sleep apnea (OSA) do not complain of excessive daytime sleepiness (EDS), but the reason for this is not well understood. Since OSA causes elevation of sympathetic nervous system activity (SNA) that could increase alertness, we sought to determine whether among patients with severe OSA, sympathetic nervous system activity (SNA) at night, as assessed by very low frequency heart rate variability (VLF-HRV) during polysomnography, would be higher in those without, than in those with EDS.

Study Impact: We found that subjects with severe OSA but without EDS (Epworth Score of < 11) had higher VLF-HRV than those with EDS (Epworth Score ≥ 11). These findings shed light on lack of EDS in some patients with severe OSA by showing that they have higher SNA during sleep than those without EDS probably due to the alertness-inducing effects of excessive SNA.

patients with OSA to seek medical attention.⁷ The Epworth Sleepiness Scale (ESS) is widely used to assess subjective sleepiness and to guide diagnosis and treatment of OSA.⁸

Among subjects in the Sleep Heart Health Study, the ESS score increased with increasing severity of OSA,^{9,10} as assessed by the frequencies of apneas and hypopneas per hour of sleep (apnea-hypopnea index [AHI]), yet the majority of participants with moderate-to-severe OSA in this and other epidemiologic studies did not report subjective EDS.^{7,10,11} Moreover,

among heart failure patients, there is no significant relationship between ESS scores and AHI, and ESS scores are lower than in a sample of the general population for any degree of OSA severity, despite a lower total sleep time.¹²

Recently, in a group of patients with heart failure and OSA, we found an inverse relationship during wakefulness between the ESS score and muscle sympathetic nerve activity (MSNA).¹³ This finding suggested that the lack of EDS in heart failure patients with OSA was at least partially related to a concurrent increase in daytime SNA, since SNA is an intrinsic part of the arousal system that heightens alertness. Thus sympathetic overactivation could lead to an uncoupling of sleepiness from OSA-induced sleep fragmentation. However, it has yet to be determined whether lack of EDS in patients with OSA but without heart failure is also related to SNA, and whether indices of SNA during sleep are related to lack of EDS. Because of the technical difficulty in securing stable MSNA recordings during sleep, a noninvasive means of assessing autonomic state during sleep, such as HRV analysis, might capture some of the underlying differences in autonomic state between sleepy and non-sleepy patients with OSA. The aim of this study, therefore, was to test the hypothesis that among patients with severe OSA either with or without heart failure, those who have less subjective sleepiness have greater sympathetic modulation of HRV during sleep than those who are sleepier. Because the apnea-hyperpnea cycles entrain muscle SNA and HR,¹ we focused our attention on VLF spectral power as our principal between-group comparison. Importantly, harmonic contributions to HRV, mediated by oscillations in autonomic nervous system input and in breathing, are superimposed on broadband non-harmonic noise that is fractal in nature and concentrated primarily within the VLF range of specific interest.¹⁴ To quantify specifically the harmonic contributions to HRV, the heart rate signal was submitted to coarse graining spectral analysis (CGSA), which extracts non-harmonic from total spectral power to provide more precise residual estimates of harmonic contributions to VLF, LF, and HF spectral power.¹⁵

METHODS

Subjects

Study subjects were patients referred because of a history suggestive of sleep apnea and found to have severe OSA, defined as AHI ≥ 30 events/h on an overnight polysomnogram (PSG). None of the patients had been treated for OSA prior to enrolling in this study. Excluded were subjects with: (1) drug or ethanol abuse or consumption of central nervous system stimulants or depressants at the time of the PSG, (2) paced cardiac rhythm, (3) unstable angina, myocardial infarction, or cardiac surgery within the previous 3 months, (4) atrial fibrillation, and (5) $> 10\%$ ectopic heart beats on the overnight electrocardiographic (ECG) recording. The protocol was approved by the Research Ethics Board of the Toronto Rehabilitation Institute. All subjects provided written consent prior to participation.

Subjects were divided into two groups: (1) those without heart failure and (2) those with a clinical history of heart failure and left ventricular ejection fraction $< 45\%$ as determined by 2-dimensional echocardiography or radionuclide angiography.

Assessment of Daytime Sleepiness

To assess the degree of subjective daytime sleepiness, the ESS was administered to all participants immediately before the PSG.⁸ Patients were divided into 2 groups: those with an ESS score of ≥ 11 (EDS group), and those with an ESS score < 11 (non-EDS group).

Polysomnography

Sleep stages and arousals from sleep were scored according to standard criteria.¹⁶ The frequency of arousals per hour of sleep was expressed as the arousal index. Thoracoabdominal movements were monitored by respiratory inductance plethysmography (Respitrace; Ambulatory Monitoring; White Plains, NY). Airflow was measured by nasal pressure cannulae (Binaps model 5500, Salter Labs, Arvin, CA). Arterial oxygen saturation (SaO_2) was measured by pulse oximetry. Mean SaO_2 during sleep was derived as previously described.¹⁷ Obstructive apneas were defined as $> 90\%$ reduction in tidal volume (V_T) derived from the sum channel of the respiratory inductance plethysmograph ≥ 10 sec associated with out-of-phase thoracoabdominal movements. Obstructive hypopneas were defined as 50% to 90% reduction in V_T from baseline, lasting ≥ 10 sec accompanied by out-of phase thoracoabdominal movements or flow limitation on the nasal pressure. The AHI was calculated. Data analysis was restricted to stage 2 NREM sleep (N2) because (1) this was invariably the predominant sleep stage with the greatest number of apneas and hypopneas, (2) the cardiovascular and respiratory systems are subject to minimal behavioral influences during this stage, and (3) to avoid the potential confounding effects of sleep state on breathing and heart rate.¹⁸ PSG signals were continuously recorded by a computerized sleep acquisition and analysis system (Sandman Elite; Ottawa, ON).

Heart Rate Variability

ECG data from lead 1 were acquired by the PSG program and submitted to CGSA to derive power spectral density across the VLF (0.00-0.04 Hz) range of the apnea-hyperpnea cycle, as well as the LF (0.04-0.15 Hz) and HF (0.15-0.50 Hz) ranges by a customized computer program (Lab VIEW; National Instruments, Austin, TX).

The coherence between respiratory effort signals and HRV was calculated to determine the specific frequency ranges over which breathing influenced HRV during sleep.¹⁹ Details about HRV analysis technique and coherence evaluation can be found in the supplemental material.

Because vagal discharge is the principal source of HF power,²⁰ HF power has been used to estimate parasympathetic heart rate modulation. Harmonic power within the VLF and LF ranges is derived principally from oscillations in cardiac sympathetic discharge. As heart failure progresses, sympathetic discharge, in the absence of sleep apnea, becomes monotonic, and sinoatrial β -adrenergic responsiveness to norepinephrine is attenuated, causing a profound loss of LF spectral power.²¹ Because the principal objective of this study was to assess the impact of the longer cycle length of the apnea-hyperpnea cycle, which entrains sympathetic nerve discharge within the VLF range,¹ we focused on VLF harmonic power as an index of sympathetic heart rate modulation. In addition, we calculated

Table 1—Characteristics of all subjects, subjects without heart failure, and subjects with heart failure

	All subjects			Subjects without heart failure			Subjects with heart failure		
	Non-EDS (N = 60)	EDS (N = 31)	p	Non-EDS (N = 42)	EDS (N = 23)	p	Non-EDS (N = 18)	EDS (N = 8)	p
ESS score	5.8 ± 2.6	13.0 ± 2.2	< 0.001	5.2 ± 2.6	14.0 ± 2.3	< 0.001	6.9 ± 2.2	12.8 ± 1.4	< 0.001
Age, yrs	57.5 ± 13.0	54.7 ± 12.0	0.328	59.4 ± 13.4	52.8 ± 10.8	0.049	52.9 ± 11.4	60.0 ± 14.2	0.179
Body mass index, kg/m ²	33.1 ± 6.1	31.0 ± 5.8	0.117	33.6 ± 5.9	31.3 ± 5.9	0.363	33.1 ± 6.2	29.2 ± 5.4	0.130
Male, n (%)	45 (75)	26 (83)	0.427	28 (67)	18 (78)	0.401	17 (94)	8 (100)	1.0
Cardiovascular medications, n (%)									
Diuretic	33 (55)	12 (39)	0.185	20 (48)	5 (21)	0.062	13 (72)	7 (88)	0.628
Spironolactone	4 (7)	3 (10)	0.686	0	0	1.000	4 (22)	3 (38)	0.635
Digoxin	6 (10)	3 (10)	1.000	0	0	1.000	6 (33)	3 (38)	1.000
β-blocker	29 (48)	10 (32)	0.182	15 (36)	3 (13)	0.080	14 (78)	7 (88)	1.000
ACEI or ARB	36 (60)	15 (48)	0.374	23 (55)	7 (30)	0.073	13 (72)	8 (100)	0.285

EDS, excessive daytime sleepiness; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2—Polysomnographic data of all subjects, subjects without heart failure, and subjects with heart failure

	All subjects			Subjects without heart failure			Subjects with heart failure		
	Non-EDS (N = 60)	EDS (N = 31)	p	Non-EDS (N = 42)	EDS (N = 23)	p	Non-EDS (N = 18)	EDS (N = 8)	p
Sleep Onset Latency, min	15.4 ± 15.6	12.1 ± 14.1	0.326	16 ± 18	11 ± 12	0.185	13 ± 9	16 ± 19	0.644
TST, min	304.2 ± 76.7	295.0 ± 67.5	0.578	311 ± 76	298 ± 73	0.497	288 ± 77	285 ± 47	0.939
N1, %TST	12.7 ± 7.5	15.7 ± 10.0	0.112	11.6 ± 7.0	14.2 ± 8.2	0.193	15.3 ± 8.3	20.3 ± 13.6	0.306
N2, %TST	65.1 ± 11.6	61.2 ± 14.0	0.161	63.5 ± 11.4	62.5 ± 11.8	0.725	69.4 ± 11.6	57.5 ± 19.6	0.075
N3, %TST	9.4 ± 7.8	11.1 ± 9.9	0.365	10.4 ± 7.9	11.1 ± 10.6	0.772	6.8 ± 7.3	11.0 ± 9.0	0.204
Rapid eye movement, %TST	12.7 ± 7.3	12.9 ± 5.7	0.878	14.6 ± 7.3	12.7 ± 6.0	0.300	8.4 ± 5.4	13.7 ± 5.3	0.035
Sleep efficiency, %TST	73.5 ± 16.6	72.7 ± 14.5	0.827	74.8 ± 16.9	73.7 ± 16.2	0.799	70.3 ± 13.0	69.3 ± 6.2	0.872
Arousal index, events/hours of sleep	50.6 ± 19.1	41.4 ± 15.2	0.022	51 ± 19	43 ± 17	0.105	50 ± 21	36 ± 11	0.085
Apnea hypopnea index, events/hours of sleep	56.7 ± 19.9	46.9 ± 15.2	0.018	57 ± 21	49 ± 17	0.163	57 ± 18	39 ± 7	0.012
Mean apnea-hyperpnea cycle length (sec)	40.9 ± 9.4	43.4 ± 11.1	0.38	44.5 ± 12.0	43.6 ± 16.3	0.800	43.3 ± 9.6	50.0 ± 9.6	0.116
Mean SaO ₂ %	93.4 ± 2.5	94.6 ± 2.1	0.021	93.4 ± 2.6	94.5 ± 1.7	0.067	93.3 ± 2.5	94.9 ± 3.1	0.172
Minimum SaO ₂ %	75.5 ± 11.5	78.5 ± 9.1	0.208	74.7 ± 12.0	76.2 ± 9.0	0.608	77.3 ± 8.9	85.0 ± 5.4	0.033

EDS, excessive daytime sleepiness; TST, total sleep time; N1, N2 and N3: NREM sleep stages 1, 2 and 3; TIB, time in bed after lights out; SaO₂, arterial oxygen saturation.

LF harmonic power and the LF/HF ratio as conventional indices of sympathetic heart rate modulation.²⁰

Statistical Analysis

HF, LF, and VLF harmonic power were expressed both in absolute units (ms²) and as a percentage of total spectral power (including the fractal component). Continuous variables were compared using 2-tailed, unpaired *t*-tests for variables with normally distributed data, and Mann-Whitney rank-sum test for variables with non-normally distributed data. Fisher exact test was used to compare categorical data between different groups of subjects. Relationships among variables were analyzed using linear regression where appropriate. A 2-tailed *p*-value < 0.05 was considered statistically significant. Data are expressed as mean ± SD. Statistical analyses were performed using SPSS 18.0 (SPSS; Chicago, IL) and Graph Pad Prism 5.0 (MacKiev Software, Boston, MA).

RESULTS

All Subjects

Ninety-one patients (71 men and 20 women) met study inclusion criteria (**Table 1**). Of these, 31 were categorized as having EDS on the basis of their ESS score. There were no significant differences in terms of age, BMI, sex distribution, or medication use between the 2 groups. The non-EDS group had a higher AHI and arousal index and lower mean SaO₂ than the EDS group (**Table 2**).

There was high coherence between ILV and both HF and VLF spectral power (**Table 3**). Coherence between ILV and VLF power was greater (*p* = 0.003) in the non-EDS group, whereas there was no between-group difference with respect to coherence between ILV and HF power. Compared to the EDS group, the non-EDS group had higher VLF power in

Table 3—Coherence and coarse graining spectral analysis of heart rate variability in all subjects, subjects without heart failure, and subjects with heart failure

Coherence and coarse graining spectral analysis	All subjects			Subjects without heart failure			Subjects with heart failure		
	Non-EDS (N = 60)	EDS (N = 31)	p	Non-EDS (n = 42)	EDS (n = 23)	p	Non-EDS (N = 18)	EDS (N = 8)	p
Coherence between ILV and HF-HRV	0.74 ± 0.20	0.79 ± 0.14	0.157	0.75 ± 0.18	0.83 ± 0.14	0.075	0.71 ± 0.24	0.71 ± 0.14	0.950
Coherence between ILV and VLF-HRV	0.87 ± 0.11	0.78 ± 0.17	0.003	0.87 ± 0.12	0.76 ± 0.18	0.006	0.87 ± 0.11	0.82 ± 0.13	0.280
Total power including fractal	2862 ± 1944	2057 ± 1973	0.067	3036 ± 1940	2302 ± 2190	0.169	2410 ± 1935	1191 ± 864	0.129
HF harmonic power, msec ²	129 ± 148	173 ± 177	0.209	151 ± 174	199 ± 174	0.264	102 ± 103	98 ± 178	0.304
HF harmonic power, %total	4.7 ± 4.0	8.8 ± 7.2	0.001	5.1 ± 4.3	9.7 ± 7.0	0.002	4.2 ± 4.0	5.7 ± 7.2	0.476
LF harmonic power, msec ²	270 ± 339	154 ± 246	0.095	197 ± 272	142 ± 238	0.361	147 ± 260	37 ± 60	0.032
LF harmonic power, %total	9 ± 10	8 ± 9	0.467	6.4 ± 7.9	6.0 ± 7.8	0.843	5.1 ± 5.4	3.1 ± 5.5	0.393
LF/HF	4.0 ± 6.2	1.7 ± 2.9	0.067	2.6 ± 4.4	1.2 ± 1.8	0.176	2.0 ± 3.1	0.6 ± 0.7	0.293
VLF harmonic power, msec ²	944 ± 839	447 ± 461	0.003	1029 ± 873	503 ± 533	0.003	1218 ± 944	426 ± 299	0.043
VLF harmonic power, %total	33 ± 18	24 ± 16	0.016	34.2 ± 16.3	24.8 ± 16	0.019	46.5 ± 17.2	34.0 ± 15.8	0.092
Fractal power, % total	52.3 ± 16.0	59.3 ± 17.5	0.061	54.3 ± 15.1	60.2 ± 17.4	0.156	44.2 ± 15.1	57.2 ± 18.8	0.073

EDS, excessive daytime sleepiness; ILV, instantaneous lung volume; HRV, heart rate variability; HF, high frequency; LF, low frequency; VLF, very low frequency.

Figure 1—This plot demonstrates a significant inverse relationship between very low frequency (VLF) harmonic power and Epworth Sleepiness Scale (ESS) scores in all subjects.

both absolute terms ($p = 0.003$) and as a percentage of total power ($p = 0.016$, **Table 3**). ESS scores were inversely related to absolute VLF harmonic power (**Figure 1**). There was no significant difference in absolute HF harmonic power between the EDS and non-EDS groups, but HF power as a percentage of total power was significantly lower in the non-EDS group ($p = 0.002$). There was no significant difference between the 2 groups in LF harmonic power either in absolute terms or as a % of total power.

Patients without Heart Failure

We studied 65 patients (48 men and 17 women) without heart failure. The mean ESS score for the EDS group ($n = 23$) was by definition significantly higher than the non-EDS group ($n = 42$,

Table 4—Cardiovascular comorbidities in patients without heart failure

	Non-EDS (N = 42)	EDS (N = 23)	p
Hypertension, n (%)	25 (60)	9 (13)	0.129
Coronary artery disease, n (%)	6 (14)	1 (4)	0.406
Stroke, n (%)	4 (10)	2 (9)	1.000

Table 5—Clinical characteristics of patients with heart failure

Clinical characteristics	Non-EDS (N = 18)	EDS (N = 8)	p
Cause of heart failure, n (%)			
Ischemic cardiomyopathy	11 (62)	6 (75)	1.000
Dilated cardiomyopathy	6 (33)	2 (25)	1.000
Hypertrophic cardiomyopathy	1 (5)	0	1.000
Left ventricular ejection fraction (%)	32.2 ± 11.2	30.3 ± 11.6	0.694

$p < 0.001$, **Table 1**). Patients with EDS were younger than patients without EDS ($p = 0.049$), but there were no significant differences in BMI, sex distribution, medication use, or cardiovascular comorbidities between the 2 groups (**Tables 1, 4**). PSG data revealed no significant difference in sleep architecture, AHI, mean or lowest SaO_2 between the 2 groups (**Table 2**).

Table 3 demonstrates high coherences between ILV and both HF and VLF harmonic power. Compared to the EDS group, there was no significant difference in coherence between ILV and HF harmonic power in the non-EDS group, but coherence between ILV and VLF harmonic power was greater ($p = 0.006$). Although there was no significant difference in absolute HF harmonic power between the EDS and non-EDS groups, HF power as a % of total power was significantly lower in the non-EDS group ($p = 0.002$). There was no significant difference between the 2 groups in LF power either in absolute terms or as a % of total power. However, compared to the EDS group, the non-EDS

group had higher VLF harmonic power both in absolute terms ($p = 0.003$) and as a % of total power ($p = 0.019$, **Table 3**). There was an inverse correlation between ESS and VLF harmonic power of borderline significance ($r = -0.263$, $p = 0.054$).

Patients with Heart Failure

We studied 26 patients (25 men and 1 woman) with heart failure. The mean ESS score for the EDS group ($n = 8$) was by definition significantly higher than the non-EDS group ($n = 18$, $p < 0.001$, **Table 1**). There was no significant difference in age, BMI, sex distribution, cause of heart failure, left ventricular ejection fraction, or medication use between the 2 groups (**Table 1**). As shown in **Table 2**, compared to the EDS group, the non-EDS group had a lower percentage of REM sleep ($p = 0.035$), a higher AHI ($p = 0.012$), and lower minimum SaO_2 ($p = 0.033$).

As shown in **Table 3**, there were high coherences between ILV and both HF and VLF harmonic power. However, there was no significant difference in coherence between ILV and either HF or VLF harmonic power. There was no significant difference in HF harmonic power in either absolute terms or as a % of total power between the 2 groups. However, compared to the EDS group, the non-EDS group had higher absolute LF ($p = 0.032$) and VLF ($p = 0.043$) harmonic power. In addition, ESS scores were inversely related to absolute VLF harmonic power ($r = -0.468$, $p = 0.016$). However, there were no differences in VLF, LF, or HF harmonic power as a percentage of total power between the EDS and the non-EDS groups.

DISCUSSION

This is the first time to our knowledge that CGSA of HRV during sleep has been employed to compare subjectively sleepy and non-sleepy patients with severe OSA with or without heart failure. Our study has given rise to several novel observations regarding factors contributing to lack of subjective EDS in patients with OSA.

The first important finding was that in the non-heart failure group, those without EDS had greater harmonic HRV power in the VLF range, both in absolute terms and as a percentage of total power, than those with EDS. Second, among patients with heart failure, those without EDS had greater harmonic HRV power in both the LF and VLF ranges in absolute terms compared to those with EDS. Among the whole group, those without EDS had greater harmonic HRV power in the VLF range, both in absolute terms and as a percentage of total power, than those with EDS. The difference in VLF power expressed as percentage of total power in the whole group was driven mainly by the non-heart failure group. Finally, among the whole group and those with heart failure, ESS scores were inversely related to VLF harmonic power.

It has been shown that apnea-hyperpnea cycles generated voluntarily during wakefulness by healthy subjects can entrain heart rate and blood pressure oscillations at the same VLF.⁵ Similar entrainment between HRV and apnea-hyperpnea cycle during OSA are mediated by oscillations of autonomic nervous system activity. During repetitive obstructive apneas, the peak of spectral power normally seen in the LF range appears to be shifted to the left into the VLF range, because sympathetic discharge is entrained by the longer apnea-hyperpnea

cycle as demonstrated by MSNA recordings.¹ Somers et al. demonstrated, in patients with OSA, that MSNA progressively increases during obstructive apneas, reaches a peak just after apnea termination and then falls during the remainder of the hyperpnea, such that it oscillates at the VLF of the apnea-hyperpnea cycle, and that elevated MSNA persists into the daytime.¹ Reversal of OSA by CPAP abolishes VLF cyclic oscillations of heart rate during sleep in association with reductions in MSNA.² In addition, Usui et al. demonstrated in a randomized trial that reversal of OSA by CPAP in patients with heart failure reduced daytime MSNA.²² Taken together, these observations indicate that OSA is a cause of these nocturnal VLF oscillations in HR as well as elevations in nocturnal and daytime MSNA.

In a previous study, Szollosi and coworkers found that, in heart failure patients with OSA, the transition from stable breathing to obstructive apneas during sleep was accompanied by increased VLF spectral power of HRV, which they interpreted as a sign of increased sympathetic modulation of HR.²³ Indeed, in heart failure patients, VLF harmonic power during sleep could be a more reliable index of sympathetic modulation of HR than the usual indices such as LF/HF and LF power, since in the presence of increased direct indices of sympathetic activation, such as muscle sympathetic nerve activity, LF, HRV, and LF/HF are reduced.²¹ In this regard, OSA appears to be a stimulus potent enough to entrain sympathetic discharge in the VLF range of the apnea-hyperpnea cycle.^{1,23}

We previously demonstrated in heart failure patients with severe OSA, that subjective sleepiness assessed by the ESS was inversely proportional to MSNA measured while awake.¹³ We concluded that lack of sleepiness in such patients is at least partly related to heightened sympathetic nerve traffic. Such elevated SNA may have counteracted the sleep-inducing effects of sleep fragmentation by OSA through sympathetic stimulation of the reticular activating system. This could lead to a state of heightened arousal that has also been described in some forms of insomnia.²⁴ However, in that study, we neither investigated patients without heart failure nor factors during sleep that might contribute to a lack of EDS.

In the heart failure group, we found an inverse relationship between VLF-HRV power during sleep and ESS score that may be analogous to the above-described inverse relationship between MSNA measured while awake and ESS,¹³ suggesting that marked cyclic elevations of SNA could be a cause of an increased VLF harmonic power. In the whole group of subjects, there was also an inverse relationship between VLF-HRV power during sleep and ESS score that was driven mainly by the heart failure group.

In the present study, we found that among the patients with heart failure, the non-EDS group had a lower percentage of REM sleep than the EDS group. This reduction in REM sleep might be related to the higher AHI of the non-EDS group, which may have prevented sleep consolidation. In addition, the non-EDS group had lower mean and minimum SaO_2 than the EDS group. These findings support our hypothesis because it has been shown in heart failure patients that SNA is proportional to AHI and degree of nocturnal oxygen desaturation.²⁵ In the non-heart failure group, patients with EDS were younger and had higher HF harmonic power as a percentage of total power than the non-EDS group, suggesting that alertness was associated with relatively less cardiac vagal tone.

Our study was subject to some limitations. First, we did not have any direct measure of SNA to compare with VLF harmonic power. Thus, we cannot be certain that high VLF power was due to high SNA. However, since we have previously shown that ESS scores are inversely related to direct measures of MSNA,¹³ and since others have shown that recurrent obstructive apneas give rise to cyclic surges in MSNA, HR, and blood pressure at the same VLF frequency as the apnea-hyperpnea cycle,¹ it is very likely that increased VLF power of HRV is related to increased SNA during sleep. Second, we did not employ any objective measure of sleepiness such as multiple sleep latency test with which to compare HRV indices. However, from the clinical viewpoint, decisions about treatment of patients with OSA are most often made on the basis of a subjective perception of EDS, often in conjunction with the ESS score, so that our findings should be clinically applicable.

In conclusion, in this study we describe a novel relationship between subjective sleepiness assessed by the ESS score and indices of HRV during sleep in patients with severe OSA either with or without heart failure. These findings extend those of our previous study¹³ in two important ways. First, in patients with severe OSA and coexisting heart failure, not only is the ESS inversely related to MSNA during wakefulness, it is also inversely related to HRV indices of SNA during sleep. Such VLF harmonic power is readily derived from electrocardiographic signals during routine PSG that are technically much easier to obtain than MSNA recordings, and are therefore more clinically relevant. Second, we show that elevated VLF indices of SNA during sleep are also related to a lack of EDS in patients with severe OSA but without heart failure, so that our findings appear to be generally applicable to the OSA population. Accordingly, our study provides further evidence that lack of subjective daytime sleepiness in patients with severe OSA is at least partially explained by increased indices of SNA that probably counteract the sleepiness-inducing effects of sleep fragmentation by OSA. Our findings further suggest that in patients with severe OSA but without EDS, factors other than sleepiness, such as cardiac autonomic function and cardiovascular event rates, should be employed as outcome measures in clinical trials to establish whether treating OSA in such patients provides any clinically important benefit.

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SUPPLEMENTAL MATERIAL

Heart rate variability analysis and coherence function

Electrocardiographic (ECG) data from lead I were acquired by the polysomnographic (PSG) program and analyzed offline by a customized computer program (Lab VIEW; National Instruments, Austin, TX). Each R wave was confirmed visually by an investigator. R-wave to R-wave (RR) intervals of all sinus beats occurring over a 20 minute segment of N2 sleep were sampled at 256 Hz. No sleep stage change occurred during the 20 minutes we used for heart rate variability (HRV) analysis, even though recurrent apneas and hyperpneas were present. Ectopic beats were removed because their variability is not mediated by the autonomic nervous system; thus their inclusion would add randomness to the results that would detract from the ability to derive meaningful information about the influence of autonomic activity on HRV. We employed an algorithm to identify premature beats by the degree of prematurity (RR interval more than 50 msec shorter than the preceding RR interval). Once identified, premature beats were removed and the RR signal was corrected by linear interpolation.¹ Afterwards, coarse grain spectral analysis (CGSA) was used to quantify the fractal and harmonic components of HRV.² Only data in which $\geq 95\%$ of the R-waves series consisted of normal beats were used.³

Kobayashi and Saul demonstrated that long-term HRV is characterized by a broadband Fourier spectrum known as the

fractal component.^{4,5} This type of spectrum is inversely related to the frequency (f) and for this reason is also known as the $1/f$ spectrum. Harmonic variations (the series of sinusoids that characterize the variations of the heart rate (HR) signal used to derive indices of parasympathetic and sympathetic nervous system influence on HR) are superimposed on a fractal component in both short- and long-term data collections. An important property of a fractal component is that of being scale invariant, whereas the harmonic component is not.¹ That is, when examined over different time scales, the basic fractal pattern of HRV can appear to be approximately the same. It is this property that permits CGSA to extract the harmonic and non-harmonic ($1/f$ or fractal) components from HRV. In CGSA, the original data are rescaled by taking every second data point, and also by doubling every data point to obtain two new, rescaled data sets. These rescaled data sets are cross-correlated with the original data set, and ensemble averages are derived.² From the harmonic component, the integrated power of the very low frequency (VLF), low frequency (LF), and high frequency (HF) regions was calculated.

To determine whether respiration influences HRV at any frequency range, we examined the coherence between respiration and HR (**Figure S1**). Using instantaneous lung volume (ILV) derived from the respiratory inductance plethysmograph sum signal as the input variable and R-wave to R-wave (RR)

Figure S1—Time (left) and frequency (right) domain data during consecutive apnea-hyperpnea cycles of one subject with heart failure.

RR intervals fluctuate in time with ventilation (instantaneous lung volume, ILV) so that the maximum heart rate (trough in RR interval) occurs during the hyperpnea and the minimum heart rate (peak in the RR interval) occurs during the apnea. The power spectrum shows distinct peaks in both respiration and heart rate variability occurring at the same frequency in the VLF and HF domains with high coherence.

interval as the output variable, coherence was calculated at the HF of tidal breathing, at the VLF of obstructive apneas and hypopneas, and at LF during 20 minutes of stable N2 sleep. Coherence is a measure of the linear correlation between input and output signals, expressed as a number between 0 and 1. Significant coherence (> 0.5) implies a strong relationship between two signals at the frequency of interest.⁶

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