






Inverse relationship of subjective daytime sleepiness to mortality in heart failure patients with sleep apnoea

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Abstract

Aims Patients with sleep apnoea (SA) and heart failure (HF) are less sleepy than SA patients without HF. HF and SA both increase sympathetic nervous system activity (SNA). SNA can augment alertness. We previously showed that in HF patients, the degree of daytime sleepiness was not related to the severity of SA but was inversely related to SNA. Elevated SNA is associated with increased mortality in HF. Therefore, we hypothesized that in HF patients with SA, the degree of daytime sleepiness will be inversely related to mortality.

Methods and results In a prospective cohort study, 218 consecutive patients with systolic HF had overnight polysomnography. Among them, 80 subjects with SA (apnoea–hypopnoea index ≥ 15) were followed for a mean of 28 months to determine all-cause mortality rate. Subjective daytime sleepiness was assessed by the Epworth Sleepiness Scale (ESS). During follow-up, 20 patients died. The 5 year death rate in patients with ESS less than 6 (i.e. less sleepy) was significantly higher than in patients with an ESS at or above the median of 6 (i.e. sleeper) [21.3 deaths/100 patient-years vs. 6.2 deaths/100 patient-years, unadjusted hazard ratio (HR) 2.94, 95% confidence interval (CI) 1.20 to 7.20, $P = 0.018$]. After adjusting for confounding factors that included sex, history of hypertension, and mean arterial oxyhaemoglobin saturation, compared with the sleeper patients, less sleepy patients had greater risk of mortality (HR 2.56, 95% CI 1.01 to 6.47, $P = 0.047$). As a continuous variable, ESS scores were inversely related to mortality risk (HR 0.86, 95% CI 0.75 to 0.98, $P = 0.022$).

Conclusions In patients with HF and SA, the degree of subjective daytime sleepiness is inversely related to the mortality risk, suggesting that among HF patients with SA, those with the least daytime sleepiness are at greater risk of death. They may therefore have greater potential for mortality benefit from therapy of SA than those with greater daytime sleepiness.

Keywords Apnoea–hypopnoea index; Epworth Sleepiness Scale; Sympathetic nervous system activity; Therapy

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Introduction

Previous studies have shown that many patients with heart failure (HF) with reduced ejection fraction and sleep apnoea (SA) do not complain of excessive daytime sleepiness and thus lack the principal clinical indication for the latter's treatment.^{1,2} In one study, HF patients had lower Epworth Sleepiness Scale (ESS) scores for any degree of obstructive sleep apnoea (OSA) severity than a community sample

without HF, despite on average, sleeping 1 h and 20 min less.¹ In another study in HF patients,² only 30% of central sleep apnoea (CSA) patients complained of excessive daytime sleepiness. The prevalence of this symptom did not differ from HF patients without SA.

The lack of sleepiness suggests up-regulation, by its substantial adrenergic inputs, of central neural arousal networks promoting daytime wakefulness.³ These pathways could be stimulated by both HF and SA. HF is characterized by

heightened subcortical norepinephrine turnover, internal jugular epinephrine and norepinephrine spillover, and efferent sympathetic nerve firing rates^{4–8}; co-existing SA elicits further upward resetting of sympathetic discharge during wakefulness that can be reversed by its specific treatment.^{6,7,9,10} Whereas sleep fragmentation by repetitive apnoeas and arousals could promote daytime sleepiness, such an effect might be counteracted by increased sympathetic nervous system activity (SNA). Indeed, in healthy individuals, without SA, muscle sympathetic nerve activity (MSNA) during wakefulness relates inversely to frequency of micro-arousals during sleep.¹¹

Activation of the sympathetic nervous system and diminished heart rate variability predict, independently, mortality in HF.^{7,8} In our previous investigations involving HF patients with SA, we found that daytime sleepiness, as assessed by the ESS score, was inversely related to MSNA measured while awake and to heart rate variability indices of SNA during sleep.^{12,13} In those studies, we divided participants into two groups based on a median ESS score of 6: those with an ESS score <6 and those with an ESS score ≥6. The less sleepy group had higher MSNA than the sleepier group.¹² We therefore hypothesized that in HF patients with SA, the degree of daytime sleepiness as assessed by ESS scores (<6 or ≥6) also relates inversely to mortality.

Methods

Subjects

We prospectively enrolled, as part of an epidemiologic study, consecutive patients with HF newly referred to the Heart Failure Clinic of the Mount Sinai Hospital in Toronto between 1 September 1997 and 1 December 2004 regardless of symptoms or signs of sleep disorders, who met the following inclusion criteria: (i) men and women at least 18 years of age; (ii) HF due to ischaemic, nonischaemic, or hypertensive dilated cardiomyopathy for at least 6 months; (iii) left ventricular systolic dysfunction [left ventricular ejection fraction (LVEF) ≤45% at rest by radionuclide angiography or echocardiography performed within 3 months before polysomnography]; (iv) New York Heart Association (NYHA) class II–IV after optimization of medical treatment; and (v) stable clinical status with optimal medical treatment for >1 month before entry. Exclusion criteria were (i) unstable angina, myocardial infarction, or cardiac surgery within the previous 3 months; (ii) pregnancy; and (iii) prior history of SA. The investigation conforms with the principles outlined in the *Declaration of Helsinki* and was approved by the institution's research ethics board. All subjects provided written informed consent before entry.

Baseline assessment

Baseline patient characteristics, NYHA class, and medications were recorded at study entry. LVEF was measured <3 months before polysomnography. Body mass index was calculated from height and weight data acquired before starting overnight polysomnography. Atrial fibrillation was identified by electrocardiographic recording during polysomnography.

Polysomnography

Overnight polysomnography was performed using standard techniques and criteria for scoring sleep stages and arousals.^{14,15} Thoracoabdominal movements were measured by respiratory inductance plethysmography, and oxyhaemoglobin saturation (SaO₂) was monitored by oximetry. Apnoea and hypopnoea were defined as a >90% or a 50–90% relative reduction in airflow from baseline, respectively, assessed from the sum channel of the respiratory inductance plethysmograph, for ≥10 s.^{16,17} Apnoea was classified as obstructive or central in the presence or absence of thoracoabdominal motion, respectively.^{16,17} Hypopnoea was classified as obstructive or central in the presence or absence of out-of-phase thoracoabdominal motion, respectively.^{16,17} Mean and lowest SaO₂ were assessed. All signals were recorded and analysed on a computerized sleep recording system (Sandman; Nellcor Puritan Bennett, Ltd., Ottawa, Ontario, Canada).

For the purposes of this study, patients were considered to have SA if the frequency of apnoeas and hypopnoeas per hour of sleep [i.e. apnoea–hypopnoea index (AHI)] was ≥15. Patients with an AHI <15 were excluded from further analyses. An AHI cut-off point of 15 was used in order to conform to that used in our previous studies.^{17–20} Patients with SA were subclassified into those with CSA, in whom >50% of apnoeas and hypopnoeas were central, or OSA, in whom ≥50% were obstructive. Treated OSA was defined as initiation of continuous positive airway pressure (CPAP) treatment, followed by documentation at a routine assessment in the sleep disorders clinic 3 months later of continued use at that time.¹⁷ Patients were considered to have untreated OSA if they did not start CPAP or if they started CPAP but abandoned treatment before this 3 month follow-up assessment. Patients with treated OSA were excluded from this analysis because in a previous study we showed that CPAP treatment was associated with a strong tendency to reduced mortality compared with those with untreated OSA.¹⁷ With respect to patients with CSA, we showed in the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnoea and Heart Failure (CANPAP) trial²⁰ that use of CPAP to treat CSA had no effect on overall mortality in patients with HF. Therefore, in this study, patients with CSA who received CPAP treatment were not excluded from the prospective

analysis. Technicians who were blinded to the patients' baseline clinical characteristics analysed the sleep studies.

Daytime sleepiness

To assess the degree of subjective daytime sleepiness, the ESS questionnaire was administered to all participants the evening before polysomnography. An ESS score of ≥ 11 is considered the cut-off for the definition of excessive daytime sleepiness for the general population.²¹ However, as indicated in the Introduction section, patients with HF seldom have an ESS score ≥ 11 ,¹ and we therefore divided the subjects into two groups, based on our previous studies,^{12,13} according to the median ESS score of 6: one group with an ESS score of < 6 (less sleepy group) and a second group with an ESS score ≥ 6 (sleepier group).

Outcomes

The study outcome was the cumulative rate of death from any cause from the date of the diagnostic sleep study until 1 January 2005. Follow-up data were obtained by HF clinic personnel from telephone interviews with the patients or, if the patients had died or were not available, their family members, by review of the patients' hospital or HF clinic records, or by personal communication with the patients' primary physicians, including the date and cause of death. The present analysis forms part of a larger study, using this same database, elements of which have been published previously.^{17,19}

Statistical analysis

Comparisons between the sleepier and less sleepy groups were performed using Student's *t*-tests for continuous variables that were normally distributed and Mann–Whitney *U* tests for variables that were not normally distributed. Chi-square or Fisher's exact tests were used to compare nominal variables.

Cumulative probabilities of event curves were estimated using the Kaplan–Meier method. To evaluate the association between ESS scores, either as categorical variable or as continuous variable or other baseline characteristics and death from any cause, Cox proportional hazards models were used. On multivariate analysis, variables were included if they conferred at least a 10% change in the hazard ratio (HR) for death when added to the model.²² Independent variables were introduced into the model one at a time and included age, sex, body mass index, NYHA class, LVEF, ischaemic origin of HF, atrial fibrillation, history of hypertension, hyperlipidaemia, diabetes, OSA or CSA, medications, and

polysomnographic variables (including total sleep time, sleep efficiency, AHI, arousal index, mean SaO₂, and lowest SaO₂).

Data are presented as mean \pm standard deviation or as frequencies. A *P* value < 0.05 was considered statistically significant. All analyses were performed using SPSS version 11.0 (SPSS Inc., Chicago, IL).

Results

Of the 242 eligible patients, 218 (90%) agreed to undergo sleep studies. Among them, 117 (54%) patients had an AHI < 15 and were excluded from further analysis. The remaining 101 (46%) patients had SA. Patients were followed up prospectively for mean and maximum durations of 32 and 88 months, respectively. Seven patients were lost to follow-up, and 14 patients whose OSA was treated with CPAP were excluded from further analysis. Thus, complete follow-up data were available in 80 subjects, 37 with OSA and 43 with CSA, and were included in the final analysis. *Figure 1* illustrates the flow of patients through the study.

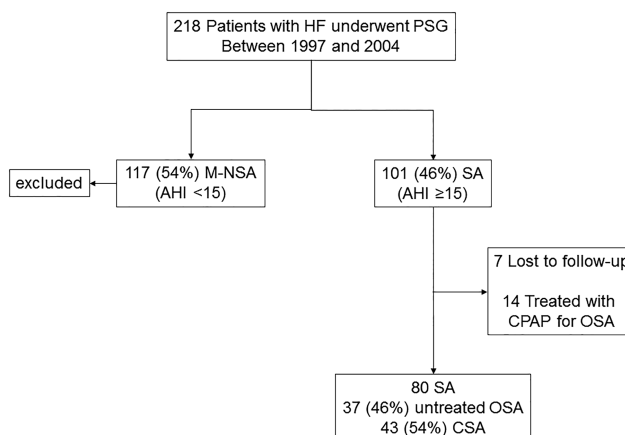
Of patients with SA, 53 (66%) were sleepier and 27 (34%) were less sleepy. ESS scores ranged from 0 to 18 for all subjects. *Table 1* lists the baseline characteristics of the subjects. There was a non-significant trend for a higher proportion of less sleepy patients to be treated with angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers than sleepier patients. There were no significant differences in other baseline characteristics.

Polysomnographic characteristics of the patients with SA are listed in *Table 2*. There were no significant differences in percentage of obstructive events and proportion of OSA between the less sleepy and sleepier patients. Sleepier patients had a significantly higher AHI than less sleepy patients. Less sleepy patients had a non-significant trend towards a higher frequency of periodic leg movements than sleepier patients. There were no differences in other polysomnographic characteristics between the two groups.

Outcomes

During the follow-up period, there were 20 deaths (25%). Death rates were higher in the less sleepy than in the sleepier patients (44% or 12 deaths vs. 15% or 8 deaths, *P* = 0.010). *Figure 2* shows the Kaplan–Meier plots of the time to death. The 5 year death rate in the less sleepy subjects was significantly higher than in the sleepier patients [21.3 deaths/100 patient-years vs. 6.2 deaths/100 patient-years, unadjusted HR 2.94, 95% confidence interval (CI) 1.20 to 7.20, *P* = 0.018]. After adjusting for significant confounding factors that included sex, history of hypertension, and mean SaO₂, less sleepy patients had a significantly higher independent risk for death (HR 2.56, 95% CI 1.01 to 6.47, *P* = 0.047). As

FIGURE 1 Progress of the cohort through the study. AHI, apnoea–hypopnoea index; CPAP, continuous positive airway pressure; CSA, central sleep apnoea; HF, heart failure; M-NSA, mild or no sleep apnoea; OSA, obstructive sleep apnoea; PSG, polysomnography; SA, sleep apnoea.



a continuous variable, ESS score was a significant inverse risk factor for death (HR 0.86, 95% CI 0.75 to 0.98, $P = 0.022$), without adjustments for other variables because none of them conferred at least a 10% change in the HR when added to the model.

Discussion

The present study provides novel insights into the relationship between SA and subjective daytime sleepiness in

patients with HF. First, we made the observation that in patients with HF and SA, those who were less sleepy, defined as an ESS score <6 , had increased mortality risk than those who were sleepier, defined as an ESS ≥ 6 , independently of other risk factors. Second, we found an inverse dose–response relationships between ESS score as a continuous variable and mortality risk in patients with SA. These findings suggest that in HF patients with SA, lower ESS values or lack of subjective sleepiness suggest poor prognosis.

It is well known that the ascending reticular activating system that involves the brainstem, posterior hypothalamus, thalamus, and forebrain plays an important role in promoting

Table 1 Characteristics of the patients

Variable	Sleepier (ESS ≥ 6) ($n = 53$)	Less sleepy (ESS < 6) ($n = 27$)	P
Age (years)	58.4 \pm 10.9	61.0 \pm 9.3	0.288
Male, n (%)	44 (77)	26 (96)	0.180
BMI (kg/m ²)	29.4 \pm 6.0	28.0 \pm 3.8	0.253
LVEF (%)	23.3 \pm 9.4	23.6 \pm 9.6	0.910
NYHA class III + IV, n (%)	29 (51)	14 (48)	0.995
Atrial fibrillation, n (%)	7 (12)	6 (21)	0.476
Ischaemic cardiomyopathy, n (%)	24 (42)	15 (52)	0.527
History of hypertension, n (%)	27 (47)	11 (38)	0.530
History of hyperlipidaemia, n (%)	26 (49)	8 (30)	0.155
History of diabetes mellitus, n (%)	17 (30)	9 (31)	1.000
Epworth Sleepiness Scale score	9.7 \pm 3.2	3.7 \pm 1.5	<0.001
Medications			
Diuretics, n (%)	51 (90)	24 (83)	0.329
ACE inhibitors and/or ARBs, n (%)	45 (79)	27 (93)	0.083
Beta-blockers, n (%)	41 (72)	20 (69)	0.961
Spironolactone, n (%)	12 (21)	2 (7)	0.166

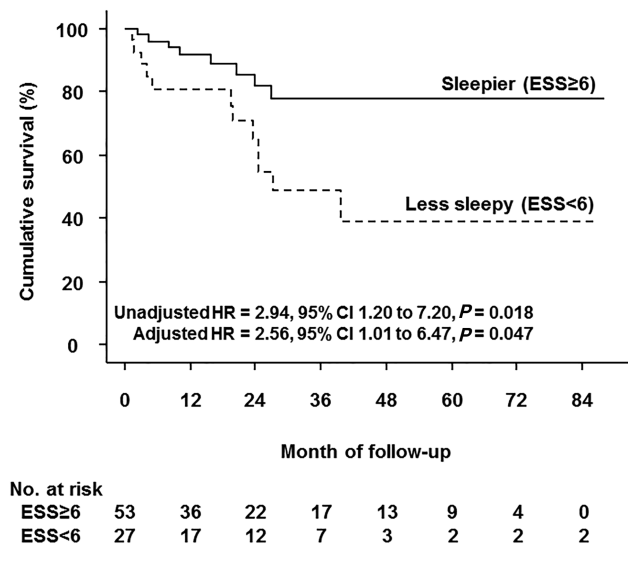
Values are expressed as mean \pm standard deviation unless indicated otherwise. ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BMI, body mass index; eGFR, estimated glomerular filtration rate; ESS, Epworth Sleepiness Scale; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Table 2 Polysomnography data of patients

Variable	Sleepier ESS ≥ 6 ($n = 53$)	Less sleepy ESS < 6 ($n = 27$)	P
Total sleep time (min)	287.2 \pm 79.2	307.0 \pm 81.4	0.298
Slow-wave sleep (% of total sleep time)	9.3 \pm 7.5	7.5 \pm 6.7	0.327
REM sleep (% of total sleep time)	12.8 \pm 9.6	13.6 \pm 7.1	0.365
Sleep latency (min)	22.3 \pm 31.1	22.0 \pm 28.5	0.611
Sleep efficiency (%)	68.7 \pm 17.9	74.2 \pm 16.0	0.179
AHI (no/h of sleep)	36.0 \pm 14.4	29.0 \pm 14.5	0.043
Obstructive events (%)	50.9 \pm 38.6	49.4 \pm 38.7	0.839
Obstructive sleep apnoea, n (%)	25 (47)	12 (44)	1.000
Central sleep apnoea, n (%)	28 (53)	15 (56)	1.000
Arousals (no/h of sleep)	33.1 \pm 14.4	29.3 \pm 11.7	0.238
Mean SaO ₂ (%)	94.3 \pm 2.6	94.9 \pm 1.8	0.244
Minimum SaO ₂ (%)	83.1 \pm 9.4	84.5 \pm 4.9	0.467
Periodic leg movements (no/h of sleep)	17.3 \pm 38.0	24.9 \pm 34.0	0.074

Values are expressed as mean \pm standard deviation unless indicated otherwise. AHI, apnoea–hypopnoea index; ESS, Epworth Sleepiness Scale; REM, rapid eye movement.

FIGURE 2 Kaplan–Meier plots comparing survival between sleepier and less sleepy subjects. *Adjusted HR for significant confounding factors included sex, history of hypertension, and mean SaO₂. CI, confidence interval; ESS, Epworth Sleepiness Scale; HR, hazard ratio.



wakefulness.²³ In particular, a specific group of nuclei in the brainstem appears to be essential for the control of sleep and wake states.²³ Neurons in the brainstem reticular formation receive inputs from the sensory systems and project upwards to the thalamus, hypothalamus, and basal forebrain. Firing of neurons projecting from those areas to the cortex produces cortical activation and increases the level of alertness.^{23,24}

The solitary tract nucleus in the brainstem is a point of convergence of many autonomic neural afferents, including inputs from both the arterial baroreceptors in the carotid sinus and peripheral chemoreceptors in the carotid body.²⁵ The recurrent cycles of hypoxia and re-oxygenation characteristic of SA sensitize carotid body chemoreceptors.²⁶ Enhanced neural input to solitary tract nuclei with projections to cortical autonomic regions augments efferent sympathetic discharge²⁷ and elicits a potent alerting response via the locus coeruleus in the ascending reticular activating system. When HF and SA co-exist, these independently and additively reset upwards resting efferent sympathetic discharge during wakefulness, suggesting the concurrent induction of hyper-arousal.^{6,7,13} Chronically, such hyper-arousal could manifest as lack of objective and subjective excessive daytime sleepiness, in spite of less time spent asleep.²⁸ Therefore, although sleep fragmentation by repetitive apnoeas and arousals in SA patients without HF could promote daytime sleepiness, such an effect might be counteracted centrally, in patients with both conditions, by markedly increased SNA. Indeed, we recently reported

that in HF patients with OSA, the degree of daytime sleepiness as assessed by the ESS scores was inversely related to muscle SNA during wakefulness and the degree of very low frequency heart rate variability, an index of SNA, during sleep such that the greater the SNA, the less sleepy the patient.^{12,13} Elevated SNA is associated with increased mortality in patients with HF.^{7,8} Taken together, in patients with both HF and SA, it is possible that less sleepy patients have a higher risk of mortality than sleepier patients through such increases in SNA.

In patients without HF, SA can provoke sleepiness and increase SNA, but presumably, in most instances, the soporific effect of SA outweighs the alerting effect of increased SNA. Thus, in the non-HF population, sleepiness can simply be an indicator of the severity of SA and the degree of sleep fragmentation by repetitive apnoeas and arousals. In that case, because the degree of subjective sleepiness reflects severity of SA, sleepier patients may have a poorer prognosis than less sleepy SA patients. Indeed, it was reported that in a non-HF population, SA patients with excessive daytime sleepiness had significantly greater mortality risk than SA patients without excessive daytime sleepiness.²⁹

Because we would require relatively high mortality rates to detect differences between relatively small patient groups, in the present study, an AHI cut-off point of 15 was used because in three previous studies of patients with HF and reduced LVEF, we showed that for both OSA and CSA, this AHI was a level above which mortality increased and was higher than in those with an AHI of <15.^{17–19} In addition, we included CSA patients who received CPAP treatment because results from the CANPAP trial,²⁰ CPAP for CSA, revealed no effect on mortality.

Our observations are subject to some limitations. First, we assessed sleepiness by the ESS score, a subjective scale that correlates significantly but modestly with objective measures of sleepiness. Nevertheless, objective measurement of sleepiness by the Multiple Sleep Latency Test does not correlate any better with the AHI or other indices of SA severity than does the ESS.³⁰ From the clinical viewpoint, decisions about treatment of patients with SA are most often made on the basis of a subjective perception of excessive daytime sleepiness, often in conjunction with the ESS score, so that our findings should be clinically applicable. Second, we did not have any direct measure of SNA. Thus, we cannot be certain whether increased mortality risk observed in the present study was due to increased SNA. However, we have previously shown that ESS scores are inversely related to direct measures of SNA (i.e. muscle SNA).¹² Third, subjective sleepiness and mortality risk could be influenced by medical therapy acting on both the central nervous and cardiovascular systems. However, there were no differences in use of any of the medications between the less sleepy and sleepier groups in patients with SA, and no confounding effects of use of any of these

drugs on relationship between subjective sleepiness and mortality risk were observed.

In conclusion, this study demonstrates that in HF patients with SA, the degree of subjective daytime sleepiness is inversely related to mortality risk. In general, excessive daytime sleepiness is the main indication for therapy of SA in patients with and without HF. Indeed, in patients with SA but without HF, several randomized trials demonstrated that treatment of sleepy (ESS score >10) patients reduces subjective sleepiness and improves quality of life and neurocognitive function³¹ whereas treatment for non-sleepy patients (ESS scores of ≤10) does not improve these outcomes.^{32,33} Thus, in patients without HF, sleepy patients derive greater clinical benefits through treating their SA than non-sleepy patients. On the other hand, even though an observational study among patients with HF who lacked excessive daytime sleepiness showed that patients often refused CPAP therapy or discontinued its use soon after starting it,¹⁷ other randomized trials demonstrated that in such patients, treating SA, even in patients without excessive daytime sleepiness, increases LVEF and lowers SNA over 1 month.¹⁰ These data suggest, paradoxically, that among HF patients with SA, those with less daytime sleepiness may have greater potential for mortality benefit from therapy of SA than those with more daytime sleepiness. Therefore, our findings add further impetus to perform large-scale long-term randomized trials to determine whether treating SA in non-sleepy patients with HF improves cardiovascular outcomes, even if it does not improve symptoms of SA. Indeed, such a trial, the ADVENT-HF trial, is presently underway, and its results should shed light on this issue.³⁴

Conflict of interest

None declared.

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