Relationship Between Sodium Intake and Sleep Apnea in Patients With Heart Failure

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Objectives	The purpose of this study was to test the hypothesis that severity of sleep apnea (SA), assessed by frequency of apneas and hypopneas per hour of sleep (apnea-hypopnea index [AHI]), is related to sodium intake in patients with heart failure (HF).
Background	Dependent edema and overnight rostral fluid shift from the legs correlate with the AHI in patients with HF in whom excessive sodium intake can cause fluid retention.
Methods	Sodium intake was estimated by food recordings in 54 HF patients who underwent overnight polysomnography.
Results	Thirty-one of the 54 patients had SA, and their mean sodium intake was higher than that in those without SA (3.0 ± 1.2 g vs. 1.9 ± 0.8 g, $p < 0.001$). There was a significant correlation between the AHI and sodium intake ($r = 0.522$, $p < 0.001$). Multivariate analysis showed that the significant independent correlates of the AHI were sodium intake, male sex, and serum creatinine level.
Conclusions	These findings suggest that in patients with HF, sodium intake plays a role in the pathogenesis of SA. (J Am Coll Cardiol 2011;58:1970–4) © 2011 by the American College of Cardiology Foundation

Sleep apnea (SA), including obstructive sleep apnea (OSA) and central sleep apnea (CSA), occurs in approximately 50% of patients with heart failure (HF), in whom it is associated with increased mortality (1–3). The observation that OSA is more prevalent in patients with edematous states, such as HF, than in the general population, despite lower body weight (1,4,5), raises the possibility that fluid retention may increase the risk for OSA. A recent study suggested that fluid retained in the legs during the day could shift rostrally into the neck when recumbent during sleep, causing peripharyngeal fluid accumulation and upper airway narrowing, thereby predisposing such persons to OSA (6).

CSA also is common in HF patients (1) and is caused by a tendency to hyperventilate resulting from increased chemoreceptor responsiveness and from pulmonary conges-

tion that induces a fall in partial pressure of carbon dioxide below the apnea threshold (7). In HF patients, the degree of overnight rostral fluid displacement from the legs is inversely proportional to partial pressure of carbon dioxide during sleep and is directly related to the severity of CSA, suggesting that some of this fluid is redistributed into the lungs (6). Because fluid retention in the legs in the daytime contributes to rostral redistribution of fluid into the neck and lungs at night, it seems likely that high sodium intake, which can cause fluid retention in HF patients, may play a role in the pathogenesis of both OSA and CSA.

Sodium retention, a hallmark of HF, causes excessive fluid accumulation (8,9). Indeed, we recently demonstrated that high sodium intake is associated with an increased risk of HF exacerbations (10). We therefore tested the hypothesis that in HF patients, sodium intake is related to the severity of SA.

Methods

Subjects. Subjects for this study were originally enrolled in our previous study between 2003 and 2007 (10). Inclusion criteria were HF patients 18 to 85 years of age with left ventricular ejection fraction (LVEF) <35%, with stable medical condition for 3 months or more, and receiving optimal medical HF therapy. Exclusion criteria were a

serum creatinine level of >140 mmol/l and a serum sodium level of <130 mmol/l. Patients consumed a self-selected diet. Among 123 patients enrolled in the original study, 57 (46%) underwent overnight polysomnography as a part of an epidemiological study (n = 45) (1) or as a part of screening for a clinical trial (n = 12) (11). Among them, we excluded 3 patients who had been hospitalized for HF during the interval between dietary assessment and polysomnography, because this may have affected sodium intake. All polysomnograms were obtained within 3 years before or 6 months after the assessment of sodium intake (mean interval: 14.6 months). Demographic characteristics, medications, LVEF, estimated glomerular filtration rate (eGFR), and serum sodium were recorded before the assessment of sodium intake. The study was approved by the local research ethics board, and all subjects provided written informed consent before enrollment.

Assessment of sodium intake. Sodium intake was assessed by 2 3-day food recordings: one at study entry and a second 6 to 12 weeks later. Mean values were used to estimate habitual intake of sodium and other nutrients. This is a valid method to assess dietary intake in HF patients (12) and to capture individual day-to-day variation in sodium consumption (13,14). Further details of this dietary assessment were described previously (10,12).

Polysomnography. Subjects underwent overnight in-laboratory polysomnography using standard techniques and scoring criteria for sleep stages and arousals from sleep and obstructive and central apneas and hypopneas, as previously described (1,15,16). Severity of SA was assessed by the frequency of apneas and hypopneas per hour of sleep (apnea-hypopnea index [AHI]). For purposes of this study, subjects were divided into an SA group (AHI ≥15) and a non-SA group (AHI <15) (1,17) and also into an obstructive-dominant group (i.e., ≥50% obstructive events) and a central-dominant group (i.e., >50% central events).

Statistical analysis. Patient characteristics and dietary intake were compared between the non-SA and SA groups using the *t* test or Mann–Whitney *U* test for continuous variables and the chi-square or Fisher exact test for categorical variables. The best cutoff value for sodium intake predicting the presence of SA was identified by receiver operating characteristic curve at regular intervals as the value that minimized the expression ($[1 - \text{sensitivity}]^2 + [1 - \text{specificity}]^2$). Univariate correlations between AHI and other variables were analyzed. Because the latency between the dietary assessment and polysomnography was long, interactions between the latency period and the correlation between AHI and sodium intake were assessed. Stepwise multiple regression analysis with AHI as the dependent variable and age, sex, body mass index (BMI), use of medications, eGFR, LVEF, and calorie, fluid, potassium, and sodium intake as independent variables was performed. Similar univariate and multiple regression analyses also were performed in the obstructive-dominant and central-

dominant subgroups. A p value <0.05 indicated statistical significance.

Results

Subject characteristics. Of 54 patients, 23 (43%) were in the non-SA group and 31 (57%) were in the SA group (Table 1). Patients with SA were more likely to be male than those without SA. A lower percentage of the SA group was receiving furosemide than those in the non-SA group, whereas a higher percentage of the SA group was receiving spironolactone than those in the non-SA group. The SA group had greater fluid, potassium, protein, and total calorie intake than the non-SA group (Table 2), but there was no significant difference in BMI between them. By definition, the AHI was greater in the SA group than in the non-SA group (Table 3). Compared with the non-SA group, obstructive and central AHIs were higher, minimum arterial oxyhemoglobin saturation was lower, and the arousal index was higher in the SA group.

Abbreviations and Acronyms

AHI = apnea-hypopnea index

BMI = body mass index

CPAP = continuous positive airway pressure

CSA = central sleep apnea

eGFR = estimated glomerular filtration rate

HF = heart failure

LVEF = left ventricular ejection fraction

OSA = obstructive sleep apnea

SA = sleep apnea

Table 1	Characteristics of the Subjects		
	No Sleep Apnea AHI <15/h (n = 23)	Sleep Apnea AHI ≥15/h (n = 31)	p Value
Age, yrs	55 ± 15	62 ± 10	0.085
Male	10 (44)	28 (90.3)	<0.001
BMI, kg/m²	30.4 ± 5.3	30.7 ± 5.7	0.865
NYHA functional class I to II	15 (65)	20 (65)	0.957
NYHA functional class III to IV	8 (35)	11 (35)	
LVEF, %	25 ± 9	26 ± 9	0.873
Systolic BP, mm Hg	116 ± 15	119 ± 17	0.584
Diastolic BP, mm Hg*	70 [10]	70 [10]	0.542
Heart rate, beats/min	71 ± 13	73 ± 16	0.619
Serum sodium, mmol	139 ± 2	139 ± 3	0.328
eGFR, ml/min/1.73 m²	78.9 ± 23.8	68.2 ± 18.4	0.069
Coronary artery disease	8 (35)	13 (42)	0.594
Diabetes	7 (30)	11 (36)	0.697
Hypertension	6 (26)	12 (39)	0.331
Smoker	2 (9)	5 (16)	0.685
Medications			
Furosemide	22 (96)	22 (71)	0.021
Spironolactone	7 (30)	18 (58)	0.044
Beta-blocker	20 (87)	28 (90)	1.000
ACE-I/ARB	22 (96)	30 (97)	1.000

Values are mean ± SD, n (%), or median [interquartile range] as appropriate. *Mann–Whitney *U* test was used for comparison between groups.

ACE-I = angiotensin-converting enzyme inhibitors; AHI = apnea-hypopnea index; ARB = angiotensin II receptor blockers; BMI = body mass index; BP = blood pressure; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Table 2	Dietary Intake		
	No Sleep Apnea AHI <15/h (n = 23)	Sleep Apnea AHI ≥15/h (n = 31)	p Value
Calories, kcal/day	1,758 ± 604	2,152 ± 537	0.017
Carbohydrate, g/day	222 ± 82	266 ± 88	0.069
Protein, g/day	82 ± 26	106 ± 26	0.001
Fat, g/day	59 ± 28	73 ± 25	0.072
Fluid, ml/day	1,923 ± 471	2,404 ± 956	0.031
Ethanol, g/day*	2.9 [4.6]	0 [12.4]	0.589
Potassium, g/day	2.9 ± 0.9	3.4 ± 1.0	0.045
Sodium, g/day	1.9 ± 0.8	3.0 ± 1.2	<0.001

Values are mean ± SD or median [interquartile range] as appropriate. *Mann–Whitney *U* test was used for comparison between groups.

AHI = apnea-hypopnea index.

Sodium intake and SA. The SA group had significantly greater sodium intake than the non-SA group (Table 2). The best cutoff value of sodium intake predicting SA was more than 2.39 g (area under the curve: 0.78; 95% confidence interval: 0.65 to 0.91; p = 0.001; sensitivity: 74.2; specificity: 78.3).
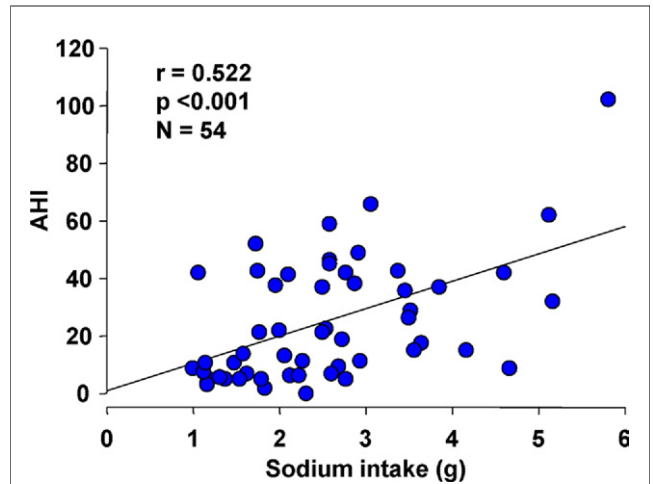
The AHI correlated significantly with sodium intake (Fig. 1). The only other significant correlates of the AHI were calorie intake (coefficient: 0.313; p = 0.021) and male sex (coefficient: 0.522; p < 0.001). Multivariate analysis showed that the only significant independent correlates of the AHI were male sex, eGFR, and sodium intake, which together accounted for 47% of the variability in the AHI (p < 0.001) (Table 4). There was no interaction between the latency period between dietary assessments and polysomnography (over vs. under the mean value) and the correlation between AHI and sodium intake (p = 0.630).

In the obstructive-dominant group (n = 35), there were better correlations between AHI and sodium intake (r = 0.565; p < 0.001) than for the entire group, and multivariate analysis showed that the only significant independent correlates of the AHI were male sex, BMI, and sodium intake (Table 5). In the central-dominant group (n = 19),

Figure 1	Correlation Between Sodium Intake and AHI

Graph showing the correlation between sodium intake and apnea-hypopnea index (AHI).

there was only a nonsignificant tendency for the AHI to correlate with sodium intake (r = 0.422; p = 0.072), but multivariate analysis showed that significant independent correlates of the AHI were BMI, LVEF, and sodium intake (Table 6).

Discussion

Our findings provide novel insights into the pathogenesis of SA in patients with HF. First, we found that the AHI was related independently to sodium intake. Second, we found an inverse relationship between AHI and eGFR. Our findings therefore suggest that high sodium intake and impaired renal function increase the odds for SA in patients with HF.

Among HF patients, excessive sodium intake, renal dysfunction, or both can cause sodium and fluid retention (8,9), whereas fluid distribution is influenced by posture. While sitting, gravity sequesters fluid in the legs (18). In HF, elevated venous pressure further contributes to leg edema (19). Therefore, HF patients with excessive sodium intake, renal dysfunction, or both are prone to accumulate

Table 3	Sleep Study Data		
	No Sleep Apnea AHI <15/h (n = 23)	Sleep Apnea AHI ≥15/h (n = 31)	p Value
Total AHI, n/h of sleep	7.7 ± 3.6	38.2 ± 18.6	<0.001
Obstructive AHI, n/h of sleep	5.9 ± 4.3	21.7 ± 20.3	<0.001
Central AHI, n/h of sleep*	0.4 [2.7]	11.9 [30.8]	<0.001
Mean SaO₂, %	94.9 ± 1.9	94.4 ± 1.9	0.331
Minimum SaO₂, %	86.7 ± 3.8	81.9 ± 10.3	0.038
Total sleep time, min	314.7 ± 74.7	300.7 ± 54.7	0.430
Slow wave sleep, %TST	13.1 ± 9.0	9.0 ± 7.9	0.078
REM sleep, %TST	16.1 ± 5.4	15.8 ± 7.2	0.862
Arousal index, no./h of sleep*	12.4 [9.0]	27.6 [13.0]	<0.001

Values are mean ± SD or median [interquartile range]. *Mann–Whitney *U* test was used for comparison between groups.

AHI = apnea-hypopnea index; REM = rapid eye movement; SaO_2 = arterial oxyhemoglobin saturation; %TST = percentage of total sleep time.

Table 4	Factors Independently Related to the Apnea-Hypopnea Index	
	Partial Correlation Coefficient	p Value
Male	0.444	0.001
eGFR	−0.374	0.006
Sodium intake/day	0.522	<0.001
	Multiple Correlation Coefficient	
Total model	0.687	<0.001

Independent variables included in this multivariate analysis included age, sex, body mass index, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use, beta blocker use, furosemide use, spironolactone use, estimated glomerular filtration rate, left ventricular ejection fraction, calorie intake, fluid intake, potassium intake, and sodium intake.

eGFR = estimated glomerular filtration rate.

fluid in their legs. Our recent study showed that the severity of both OSA and CSA in men with HF is strongly related to the amount of fluid displaced rostrally from the legs overnight (6). The amount of this overnight fluid displacement in turn was related directly to the amount of time spent sitting during the daytime and the degree of leg edema. Therefore, high sodium intake and renal dysfunction likely contributed to SA severity at least partially through fluid retention and increased overnight rostral fluid displacement. Because fluid retention in the legs during the daytime contributes to overnight rostral fluid redistribution to the neck and lungs, it is probable that high sodium intake and renal dysfunction contribute to the pathogenesis of OSA and CSA in HF patients. The observation that sodium intake correlated independently with the AHI in both the obstructive-dominant and central-dominant groups favors this possibility.

In terms of the appropriate level of sodium intake for patients with HF, there is some controversy. Our previous study suggested that the upper limit of sodium intake for HF patients should be similar to that recommended for healthy adults, that is, 2.3 g/day (10). Interestingly, this value is practically identical to the best cutoff value of sodium intake that predicted the presence of SA in the present study. Previous data showed that the presence of SA in HF patients is associated with increased mortality risk (2,3). Because high sodium intake is associated with the presence of SA in HF patients, there may be an interaction between sodium intake and SA that increases the risk of adverse cardiovascular events, possibly via fluid retention. In this context, limitation of sodium intake may be beneficial to HF patients either directly by alleviating pulmonary congestion, or indirectly by alleviating SA and its related adverse effects.

Study limitations. First, because it was observational, the results do not prove a cause-and-effect relationship between sodium intake and SA. One way to determine whether there is a cause-and-effect relationship between sodium intake and sleep apnea would be through a trial of sodium restriction. However, such a trial would not be warranted unless we found a relationship between sodium intake and SA severity. Second, the ability to control for confounders may be limited by the sample size. Third, we did not directly

Table 5	Factors Independently Related to the Apnea-Hypopnea Index in the Obstructive-Dominant Group (n = 35)	
	Partial Correlation Coefficient	**p Value**
Male	0.477	0.005
BMI	0.396	0.022
Sodium intake/day	0.364	0.037
Multiple Correlation Coefficient		
Total model	0.723	<0.001

The same variables described in Table 4 were included.
  BMI = body mass index.

Table 6	Factors Independently Related to the Apnea-Hypopnea Index in the Central-Dominant Group (n = 19)	
	Partial Correlation Coefficient	**p Value**
BMI	−0.689	0.002
LVEF	−0.483	0.049
Sodium intake/day	0.675	0.003
Multiple Correlation Coefficient		
Total model	0.790	0.002

The same variables described in Table 4 were included.
  Abbreviations as in Table 1.

measure the degree of fluid retention and overnight fluid redistribution related to sodium intake. It therefore is possible that other unmeasured factors also might have affected the relationship between sodium intake and SA. Fourth, we did not assess B-type natriuretic peptide concentration, a marker of cardiac volume overload. Finally, during the interval between polysomnography and assessment of sodium intake, the amount of sodium intake could have changed. However, the lack of any interaction between this interval and relationship between sodium intake and AHI suggests that this latency did not affect the results of the relationship between sodium intake and AHI.

Conclusions

We have shown that in HF patients, the severity of SA is related directly to dietary sodium intake and is inversely related to renal function. It is likely that this association is the result of fluid retention secondary to the combined effects of high sodium intake and impaired renal function and to overnight rostral fluid shift from the legs. High sodium intake therefore may play a role in the pathogenesis of SA in HF patients. If so, modulation of sodium intake may be a therapeutic strategy to alleviate SA in HF. Consequently, studies assessing fluid volume and overnight fluid shift and their relationships to both sodium intake and severity of SA, as well as interventional studies to assess the effect of reduced sodium intake on fluid volume and severity of SA, will be required to test our hypotheses.

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