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Left Atrial Size, Chemosensitivity, and Central Sleep Apnea in Heart Failure

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BACKGROUND: Central sleep apnea (CSA) is common among patients with heart failure (HF) and is promoted by elevated CO_2 chemosensitivity. Left atrial size is a marker of the hemodynamic severity of HF. The aim of this study was to determine if left atrial size predicts chemosensitivity to CO_2 and CSA in patients with HF.

METHODS: Patients with HF with left ventricular ejection fraction $\leq 35\%$ underwent polysomnography for detection of CSA, echocardiography, and measurement of CO_2 chemosensitivity. CSA was defined as an apnea-hypopnea index (AHI) ≥ 15/h with $\geq 50\%$ central apneic events. The relation of clinical and echocardiographic parameters to chemosensitivity and CSA were evaluated by linear regression, estimation of ORs, and receiver operator characteristics.

RESULTS: Of 46 subjects without OSA who had complete data for analysis, 25 had CSA. The only parameter that significantly correlated with chemosensitivity was left atrial volume index (LAVI) ($r = 0.40$, $P < .01$). LAVI was greater in those with CSA than those without CSA (59.2 mL/m² vs 36.4 mL/m², $P < .001$) and significantly correlated with log-transformed AHI ($r = 0.46$, $P = .001$). LAVI was the best predictor of CSA (area under the curve = 0.83). A LAVI ≤ 33 mL/m² was associated with 22% risk for CSA, while LAVI ≥ 53 mL/m² was associated with 92% risk for CSA.

CONCLUSIONS: Increased LAVI is associated with heightened CO_2 chemosensitivity and greater frequency of CSA. LAVI may be useful to guide referral for polysomnography for detection of CSA in patients with HF. CHEST 2014; 146(1):96-103

Heart failure (HF) is common, affecting 1% to 2% of the adult population.[1] As many as 50% of patients with HF may have sleep-disordered breathing, most frequently central sleep apnea (CSA).[2,3] CSA is associated with adverse prognosis,[4,5] and treatment improves sleep architecture, cardiac function,[6] exercise capacity, HF symptoms,[7-13] and may improve survival.[6,13,14] However, diagnosis requires polysomnography (PSG), which is expensive and not always readily available. Some have advocated formal sleep testing for all patients with HF,[15] although current guidelines do not recommend routine testing or screening for CSA.[16-18] History, physical examination, and symptoms are of limited usefulness for screening for CSA.[19] Moreover, no method has been endorsed for routine application in patients with HF as a screening tool for CSA.[20,21] Hence, the development of a simple screening strategy for CSA in patients with HF potentially would have wide utility.

CSA is associated with elevated pulmonary capillary wedge pressure.[22-24] It has been shown that pulmonary congestion promotes lung J-receptor stretch with increased reflex ventilatory response to CO_2[25,26] and hyperventilation.[22,27,28] Indeed, in patients with HF, CSA is manifested as cyclic hyperventilation with compensatory apnea and considered secondary to increased cardiac filling pressures.[22]

Central apnea frequency is related not only to pulmonary capillary wedge pressure but also to left atrial size,[29] as patients with HF with CSA have greater left atrial dimension than patients with HF who do not have CSA.[3,30,31] Assessment of left atrial size is a routine part of a comprehensive echocardiographic examination,[32] a test that is widely recommended in the evaluation of patients with HF.[16-18] However, to our knowledge no previous study has reported whether left atrial size is predictive of CSA or chemosensitivity to CO_2, which may promote CSA. The purpose of this study was to determine if left atrial size predicts chemosensitivity to CO_2 and CSA in patients with HF. We hypothesized that left atrial size is sensitive and specific for the detection of CSA and associated with augmented CO_2 chemosensitivity. Accordingly, our specific aims were to quantify left atrial volume by echocardiography in patients with HF who underwent measurement of CO_2 chemosensitivity and PSG.

Materials and Methods

This study was conducted in accordance with the amended Declaration of Helsinki and approved by the Mayo Clinic Institutional Review Board (IRB#923-02). Written informed consent was obtained from all participants. Consecutive ambulatory outpatients were prospectively enrolled from the Mayo Clinic Heart Failure Clinic for participation in this study, which included laboratory-based, overnight, attended PSG; echocardiography; neurohormonal measurement; and assessment of chemosensitivity in all subjects. Patients were required to have stable HF with no changes of optimized medical therapy in the preceding 3 months and left ventricular ejection fraction (LVEF) $\leq$ 35% measured by echocardiography. New York Heart Association (NYHA) function class was assessed[18]; those with NYHA III-IV HF were defined as having "advanced heart failure." BMI was computed as weight in kilograms divided by body surface area in square meters.

Echocardiography

All subjects underwent comprehensive transthoracic echocardiography. Measured parameters included LVEF, left ventricular end diastolic diameter (LVEDD), right ventricular systolic pressure (RVSP), mitral regurgitation (defined as moderate or more in severity by proximal isovelocity surface area), left atrial volume index (LAVI) (defined as left atrial volume to body surface area in mL/m² by biplane two-dimensional echocardiography consistent with current guidelines[32]), mitral deceleration time, mitral E velocity, and the ratio of mitral E velocity to medial anulus e′ velocity (E/e′).

Measurement of Neurohormones

Concentration of brain natriuretic peptide (BNP) was measured from serum drawn on the evening of PSG. Measurement of BNP was evaluated by either the Shionogi immunoradiometric assay (Shionogi & Co, Ltd) or DxI 800 immunoassay (Beckman Coulter Inc). The coefficient of variation of these two BNP assays was > 0.99.

Measurement of Chemosensitivity

CO_2 chemosensitivity was measured by a modified rebreathing method as previously described.[33] Subjects breathed from a mouthpiece connected to a 6-L rebreathing bag; the bag included 5% CO_2 with balance oxygen. Ventilation was measured by a pneumotachograph. End-tidal oxygen and end-tidal CO_2 ($PETCO_2$) were monitored by mass spectrometry for comparison with changes in minute ventilation ($\dot{V}E$). As the subject rebreathes, inspired CO_2 in the rebreathing bag increases and the oxygen level falls. However, inspired oxygen levels do not fall below 500 mm Hg (approximately 70% oxygen). Rebreathing continues until $PETCO_2$ values reach 50 to 55 mm Hg (or about 8% CO_2 requiring approximately 4 min). The slope of the plot of $\dot{V}E$ vs $PETCO_2$ is used as an index of CO_2 chemosensitivity ($\Delta\dot{V}E/\Delta PETCO_2$). Three runs were performed for each subject, and values were reported as the mean.

Sleep Evaluation

Diagnostic PSG was performed in the Center for Translational Science Activity Sleep Core facility of the Clinical Research Unit and digitally recorded on Dimensions software (Network Concepts Inc) or PSG Online2 E-Series (Compumedics Ltd) and scored using Uniquant (Thermo Fisher Scientific Inc) or Profusion2 software (Compumedics USA Inc). Recorded parameters included three-channel EEGs, two-channel electrooculograms, oronasal airflow by pressure transducer and thermocouple sensors, submental and limb electromyograms, one-channel ECG, transcutaneous pulse oximetry (Ohmeda 3740; General Electric Co) and integrated pulse oximetry (Compumedics USA Inc), thoracic and abdominal respiratory effort by inductance plethysmography, snoring by tracheal microphone or piezo crystal sensor, and body position by closed-circuit video monitoring. Disordered breathing events were classified as apneas or hypopneas and as either obstructive or central. Apneas were defined as a cessation of airflow or > 90% reduction in airflow from baseline for > 10 s with

an oxygen desaturation $\geq 4\%$. Hypopneas were defined as a $\geq 50\%$ reduction in airflow with an oxygen desaturation $\geq 4\%$. Events were classified as central when the airflow criteria were met in the absence of respiratory effort as recorded by thoracic and abdominal inductance plethysmography and as obstructive when airflow criteria were met despite continued or increased respiratory effort. Per published guidelines, patients were considered to have CSA if the total apnea-hypopnea index (AHI) was $\geq 15/h$ with $\geq 50\%$ disordered breathing events of central origin regardless of the presence or absence of respiratory periodicity.[34] Subjects found to have OSA or mixed apneas in which $\geq 50\%$ of disordered breathing events were obstructive were excluded from analysis.

Statistical Analysis

Differences among group means were tested for differences by two-sided t tests or Wilcoxon rank-sum tests, depending on distribution. Differences in proportions were tested by the χ^2 or Fisher exact tests. The relationship of $\Delta\dot{V}E/\Delta P ETCO_2$ slope to continuous clinical variables was compared by linear regression and summarized using Pearson correlation coefficients. The primary analysis was logistic regression assessing clinical and echocardiographic variables for association with CSA, with results expressed as the ORs with 95% CIs. Variables associated with CSA were evaluated by receiver operator characteristic (ROC) analysis, with results presented as area under the curve (AUC) and 95% CIs derived by the Mann-Whitney statistic. Sensitivity, specificity, and positive and negative predictive values were used to estimate 2×2 decision statistics, and positive and negative likelihood ratios were calculated for several cutoff values of LAVI. Given the greater prevalence of CSA among men,[19,35] we conducted a separate ROC analysis restricted to men to assess whether test performance characteristics differed by sex. Analyses were performed with JMP, version 8, and SAS, version 9.2 (SAS Institute Inc). For all comparisons, a two-tailed P value $< .05$ was considered significant.

Results

Of the 62 consecutive subjects with HF who were studied by PSG, 29 (47%) had CSA and seven (four men, three women) were found to have OSA or mixed apneas and were excluded. Of these 55 subjects without OSA, 46 had complete data available for analysis; 25 of these had CSA. Median time between PSG and echocardiography was 16 days (interquartile range, 0-41 days).

Men were significantly more likely to have CSA than women (65% vs 25%, $P = .02$), and subjects with CSA were older (68.5 years vs 59.3 years, $P = .001$). BNP concentration was significantly higher in those with CSA than in those without CSA (1,184 pg/mL vs 346 pg/mL, $P < .001$). No statistical differences in the proportion of patients with ischemic cardiomyopathy, atrial fibrillation, or in HF medications were observed on comparison of subjects with HF and CSA compared with those with HF and without CSA. By definition, subjects with CSA had significantly higher AHI (37.9/h vs 4.7/h, $P < .01$). As expected, mean oxygen saturation during sleep was lower in those with CSA, and those with CSA spent a greater proportion of sleep time with oxygen saturation $< 90\%$ (18.2% vs 1.3%, $P < .001$) (Table 1).

CO_2 chemosensitivity ($\Delta\dot{V}E/\Delta P ETCO_2$ slope) was significantly greater in patients with HF with CSA than those without CSA (2.67 vs 1.83, respectively; $P = .03$) but not different in those with advanced HF (ie, NYHA III-IV) compared with those with nonadvanced HF (ie, NYHA I-II) (2.36 vs 2.00, respectively; $P = .17$). A nonsignificant difference in $\Delta\dot{V}E/\Delta P ETCO_2$ slope was seen between men and women (2.34 vs 2.09, respectively; $P = .45$). In addition, age ($r = 0.29$, $P = .06$) and BNP ($r = 0.06$, $P = .69$) concentration did not significantly correlate with $\Delta\dot{V}E/\Delta P ETCO_2$ slope. The only echocardiographic parameter that significantly correlated with $\Delta\dot{V}E/\Delta P ETCO_2$ slope was LAVI ($r = 0.40$, $P = .006$) (Table 2).

Subjects with CSA had more hemodynamically severe HF, as evidenced by lower LVEF (21.1% vs 25.3%, $P = .03$), higher RVSP (49.0 mm Hg vs 37.8 mm Hg, $P = .02$), higher LAVI (59.2 mL/m² vs 36.4 mL/m², $P < .01$), shorter mitral deceleration time (172.3 milliseconds vs 232.9 milliseconds, $P = .03$), lower medial anulus e′ velocity (e′) (0.04 vs 0.05, $P = .02$), and higher E/e′ (27.2 vs 16.7, $P = .02$). No significant difference in LVEDD or the proportion of subjects with mitral regurgitation was seen in the two study groups (Table 3).

After adjusting for LAVI, no other echocardiographic parameter was significantly associated with the presence of CSA, and the association between LAVI and CSA persisted even after controlling for age, sex, and BNP concentration (OR, 1.08 per mL/m²; $P = .03$) (Table 4). LAVI also significantly correlated with log-AHI ($r = 0.46$, $P = .001$).

ROC analysis showed that the best predictor of CSA was LAVI (AUC = 0.83), although BNP (AUC = 0.79) and age (AUC = 0.77) performed similarly. A LAVI cutoff of 44 mL/m² yielded a sensitivity of 80% and specificity of 81% (Table 5). Test performance was similar when the analysis was restricted to just men compared with the overall group in univariate analysis (AUC = 0.88 [95% CI, 0.74-1.00] vs AUC = 0.83 [95% CI, 0.70-0.95]) and in multivariate analysis adjusting

TABLE 1] Subject Characteristics

Characteristic	HF Without CSA	HF With CSA	P Value
Subjects, No.	21	25	...
Demographics			
Male sex	12 (57)	22 (88)	.02
Age, y	59.3 ± 9.9	68.5 ± 8.1	.001
BMI, kg/m²	27.7 ± 3.5	29.0 ± 5.5	.32
Heart failure class			
NYHA I-II	7 (33)	4 (16)	.17
NYHA III-IV	14 (66)	21 (84)	...
Ischemic	10 (48)	13 (52)	.77
Atrial fibrillation	1 (5)	5 (20)	.20
BNP concentration, pg/mL	345.7 ± 433.6	1,184.0 ± 1,588.4	.02
Medications			
β-Blocker	18 (86)	22 (88)	.82
ACE/ARB	21 (100)	24 (96)	1.00
Aldosterone antagonist	5 (24)	8 (32)	.54
Diuretics	14 (67)	19 (76)	.48
Digitalis	14 (67)	15 (60)	.64
Nitrates	1 (5)	1 (4)	1.0
Sleep parameters			
AHI, events/h	4.7 ± 4.2	37.9 ± 15.5	<.001
Mean Sao_2, %	93.6 ± 3.6	92.2 ± 2.6	.01
T90%	1.3 ± 2.2	18.2 ± 19.4	<.001

Data given as mean ± SD or No. (%) unless otherwise specified. ACE/ARB = angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; AHI = apnea-hyponea index; BNP = brain natriuretic peptide; CSA = central sleep apnea; HF = heart failure; NYHA = New York Heart Association; Sao_2 = oxygen saturation of arterial blood hemoglobin; T90% = time with arterial oxygen saturation <90%.

for sex (AUC = 0.88 [95% CI, 0.76-1.00] vs AUC = 0.88 [95% CI 0.79-0.98]). Risk for CSA by LAVI cutoff values is shown in Figure 1.

TABLE 2] Correlations Between Clinical Variables and CO_2 Chemosensitivity

Characteristic	Correlation (r)	P Value
Age	0.29	.06
BNP, pg/mL	−0.06	.69
LVEF, %	−0.13	.39
LVEDD, mm	−0.02	.88
RVSP, mm Hg	0.26	.08
LAVI, mL/m²	0.40	<.01
Mitral deceleration time, ms	−0.28	.10
e′, medial annulus, m/s	−0.18	.26
E/e′, medial annulus	0.22	.16

e′ = medial anulus e′ velocity; E/e′ = ratio of mitral E velocity to medial anulus e′ velocity; LAVI = left atrial volume index; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; RVSP = right ventricular systolic pressure. See Table 1 legend for expansion of other abbreviation.

Discussion

The novel findings of this study were that LAVI is associated with enhanced CO_2 chemosensitivity and the presence of CSA and may be useful as a screening tool for detection of CSA in patients with HF.

LAVI and CO_2 Chemosensitivity

Enhanced CO_2 chemosensitivity occurs in HF[36] and correlates with sympathetic activation[37] and natriuretic peptide elevation[38,39] as well as HF mortality.[38] Augmented chemosensitivity also promotes hyperventilation with reduction of CO_2 concentration below the apneic threshold, thereby causing compensatory and cyclic hypopnea or apnea characteristic of CSA.[25,26,40,41] Consistent with prior studies,[25,26,40] we observed that CO_2 chemosensitivity is augmented in patients with HF with CSA. To our knowledge, this is the first report to demonstrate a significant correlation between left atrial volume and CO_2 chemosensitivity. Our findings may support a link between left atrial dimension; chronic

TABLE 3] Echocardiographic Findings

Characteristic	HF Without CSA	HF With CSA	P Value
LVEF, %	25.3 ± 6.5	21.1 ± 6.3	.03
LVEDD, mm	70.0 ± 6.8	71.2 ± 9.0	.60
RVSP, mm Hg	37.8 ± 14.9	49.0 ± 15.9	.02
Mitral regurgitation, %	23.8	48.0	.13
LAVI, mL/m²	36.4 ± 9.7	59.2 ± 23.4	<.001
Mitral deceleration time, ms	232.9 ± 93.9	172.3 ± 48.5	.03
e', medial annulus, m/s	0.05 ± 0.03	0.04 ± 0.01	.02
E/e', medial annulus	16.7 ± 8.4	27.2 ± 18.1	.02

Data given as mean ± SD unless otherwise indicated. See Table 1 and 2 legends for expansion of abbreviations.

pulmonary venous hypertension, which can promote pulmonary J-receptor stretch; and enhanced CO_2 chemosensitivity and CSA in patients with HF.[25,26] However, the modest correlation suggests that other factors are also likely important in affecting CO_2 chemosensitivity and sleep-disordered breathing in patients with HF.

LAVI as a Screening Tool for CSA

Our study may have practical implications regarding the management of patients with HF. Multiple guidelines recommend consideration of sleep-disordered breathing as a comorbidity in HF.[15-18] However, diagnosis requires PSG, which is expensive, time consuming,

TABLE 4] Multivariate Predictors of CSA

Parameter	OR	95% CI	P Value
Model 1: AUC = 0.88 (0.79, 0.98)			
Age, per y	1.12	1.01-1.25	.03
LAVI, per mL/m²	1.10	1.03-1.18	.005
Model 2: AUC = 0.89 (0.80, 0.98)			
Age, per y	1.11	0.99-1.25	.07
Male sex	1.51	0.19-12.09	.70
LAVI, per mL/m²	1.09	1.02-1.17	.01
Model 3: AUC = 0.90 (0.81, 0.99)			
Age, per y	1.12	0.99-1.28	.08
Male sex	2.07	0.21-20.81	.54
LAVI, per mL/m²	1.08	1.01-1.16	.03
BNP, per 200 pg/mL	2.35	0.95-1.91	.09

Data given as mean ± SD. AUC = area under the curve. See Table 1 and 2 legends for expansion of other abbreviations.

and not always readily available. Herein we have shown that increased LAVI is predictive of CSA. Of all the clinical parameters considered, including age and sex, we found that LAVI most strongly correlated with the presence of CSA, with patients with LAVI ≥ 44 mL/m² having a fourfold increased risk.

As this study included consecutive, nonselected, ambulatory patients from a HF clinic, the assessment of positive and negative predictive values likely approximates the post-test probability of CSA in similar populations. A LAVI ≤ 33 mL/m², a value at approximately the 25th percentile of our study population, was associated with 22% risk for CSA. Whether this is considered an acceptably low risk for CSA to defer PSG is unclear and would likely depend on the clinical situation and the perceived benefits of treatment. By comparison, LAVI ≥ 53 mL/m², a value at approximately the 75th percentile of our study cohort, was associated with 92% risk for CSA. Thus, the main utility of assessment of left atrial size would seem to be in selecting those most at risk for CSA.

Limitations

The sample size was modest and included only patients with LVEF ≤ 35%, the majority of whom had advanced HF. These findings need to be confirmed in a larger study with a broader spectrum of disease severity. The subject population had a high prevalence of CSA, likely because the majority of subjects had advanced HF. Whether our findings apply to those with less advanced HF is unclear, although the prevalence of CSA also appears high in other studies.[3,35] We excluded subjects with HF who had OSA or mixed apnea with a significant obstructive component, which may limit the generalizability of our findings to the overall HF population in which obstructive events are not rare.[3,35] In nine subjects enrolled in the study, datasets were

Characteristic	Sensitivity	Specificity	PPV	NPV	LR+	LR−
LAVI, mL/m²						
33	92 (75-98)	33 (17-55)	62 (46-76)	78 (45-94)	1.38 (1.00-1.91)	0.24 (0.06-1.03)
44	80 (61-91)	81 (60-92)	83 (64-93)	77 (57-90)	4.20 (1.70-10.36)	0.25 (0.11-0.56)
53	52 (34-70)	95 (77-99)	93 (69-99)	63 (45-77)	10.92 (1.55-76.71)	0.50 (0.33-0.77)
BNP, pg/mL						
148	92 (75-98)	43 (25-64)	66 (49-79)	82 (52-95)	1.61 (1.09-2.37)	0.19 (0.05-0.77)
336	84 (65-94)	71 (50-86)	78 (59-89)	79 (57-92)	2.94 (1.46-5.91)	0.22 (0.09-0.57)
1,149	36 (20-56)	91 (71-97)	82 (52-95)	54 (38-70)	3.78 (0.92-15.61)	0.71 (0.51-0.98)
Age, y						
59	92 (75-98)	38 (21-59)	64 (48-78)	80 (49-94)	1.49 (1.04-2.12)	0.21 (0.05-0.88)
62	88 (70-96)	57 (37-76)	71 (53-84)	80 (55-93)	2.05 (1.23-3.44)	0.21 (0.07-0.65)
71	44 (27-63)	91 (71-97)	85 (58-96)	58 (41-73)	4.62 (1.15-18.56)	0.62 (0.43-0.90)
$\dot{V}E/P_{ETCO_2}$ slope						
1.36	92 (74-98)	10 (3-29)	54 (39-68)	50 (15-85)	1.01 (0.84-1.22)	0.88 (0.14-5.68)
1.76	88 (69-96)	52 (32-72)	68 (50-81)	79 (52-92)	1.84 (1.15-2.95)	0.24 (0.07-0.74)
2.38	42 (25-61)	91 (71-97)	83 (55-95)	58 (41-73)	4.38 (1.08-17.75)	0.65 (0.45-0.93)
Sex						
Male	88 (70-96)	43 (25-64)	65 (48-79)	75 (47-91)	1.54 (1.04-2.29)	0.28 (0.09-0.90)

Data are given as AUC (95% CI) unless otherwise indicated. LR− = negative likelihood ratio; LR+ = positive likelihood ratio; NPV = negative predictive value; PPV = positive predictive value; $\dot{V}E/P_{ETCO_2}$ = CO_2 chemosensitivity. See Table 1, 2, and 4 legends for expansion of other abbreviations.

incomplete due to either inability to quantify left atrial volume (n = 4) or no BNP measurement performed on the day of PSG (n = 5). Of these nine subjects, four had CSA, and five did not have CSA or OSA. Including these nine subjects in the overall analyses did not cause
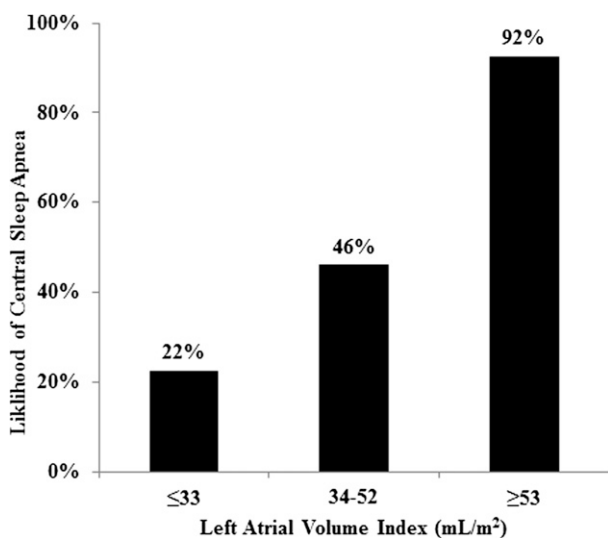

Figure 1 – Risk of central sleep apnea (CSA) was best predicted by the left atrial volume index (LAVI). Risk for CSA for those with LAVI ≤ 33 mL/m² was 22% (95% CI, 3%-60%); with LAVI 34 to 52 mL/m², 46% (95% CI, 26%-67%); and with LAVI ≥ 53 mL/m², was 92% (95% CI, 64%-100%).

changes in the significance of the outcomes as summarized in Tables 1-5.

Variation in LAVI or PSG findings may have influenced our results, though this seems unlikely as the majority of subjects underwent echocardiography within 30 days of PSG and all were clinically stable and on optimized medical therapy for > 3 months. While we found LAVI to be related to risk for CSA independent of sex, the degree to which our results apply to women is unclear, as our study included few women. However, prior research has suggested that risk factors for CSA and their relative importance are similar between men and women,[19] and our estimates of the utility of LAVI for detection of CSA were similar when the analysis was restricted to men. It is also unclear if these findings apply to other groups of patients without HF where CSA may be present. Finally, the study design was observational and not designed to evaluate the specific physiologic and molecular mechanisms that may link left atrial volume increase to augmented CO_2 chemosensitivity and CSA. In conclusion, these data show that left atrial size is significantly associated with elevated CO_2 chemosensitivity and CSA in patients with HF and that left atrial dimension may be useful to guide referral for definitive diagnosis of CSA by PSG.

Acknowledgments

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