Exercise End-Tidal CO₂ Predicts Central Sleep Apnea in Patients With Heart Failure

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BACKGROUND: Increased CO₂ chemosensitivity and augmented exercise ventilation are characteristic of patients with heart failure (HF) with central sleep apnea (CSA). The aim of this study was to test the hypothesis that decreased end-tidal CO₂ by cardiopulmonary exercise testing predicts CSA in patients with HF.

METHODS: Consecutive ambulatory patients with New York Heart Association II to III HF were prospectively evaluated by CO₂ chemosensitivity by rebreath, cardiopulmonary exercise testing, and polysomnography (PSG). Subjects were classified as having either CSA (n = 20) or no sleep apnea (n = 13) by PSG; a central apnea-hypopnea index (AHI) ≥ 5 was used to define CSA. Subgroups were compared by *t* test or Mann-Whitney test and data summarized as mean ± SD. *P* < .05 was considered significant.

RESULTS: At rest, subjects with CSA had higher central CO₂ chemosensitivity (Δ minute ventilation [$\dot{V}_E$]/ Δ partial pressure of end-tidal CO₂ [PETCO₂], 2.3 ± 1.0 L/min/mm Hg vs 1.6 ± 0.4 L/min/mm Hg, *P* = .02) and $\dot{V}_E$ (15 ± 7 L/min vs 10 ± 3 L/min, *P* = .02) and lower PETCO₂ (31 ± 4 mm Hg vs 35 ± 4 mm Hg, *P* < .01) than control subjects. At peak exercise, the ventilatory equivalents per expired CO₂ ($\dot{V}_E/\dot{V}_{CO_2}$) was higher (43 ± 9 vs 33 ± 6 , *P* < .01) and PETCO₂ lower (29 ± 6 mm Hg vs 36 ± 5 mm Hg, *P* < .01) in subjects with CSA. In addition, CO₂ chemosensitivity, peak exercise $\dot{V}_E/\dot{V}_{CO_2}$, and PETCO₂ were independently correlated with CSA severity as quantified by the AHI (*P* < .05). Peak exercise PETCO₂ was most strongly associated with CSA (OR, 1.29; 95% CI, 1.08-1.54; *P* = .01; area under the curve, 0.88).

CONCLUSIONS: In patients with HF and CSA, ventilatory drive is increased while awake at rest and during exercise and associated with heightened CO₂ chemosensitivity and decreased arterial CO₂ set point.

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ABBREVIATIONS: AHI = apnea-hypopnea index; CSA = central sleep apnea; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PETCO₂ = partial pressure of end-tidal CO₂; PSG = polysomnography; $\dot{V}_E$ = minute ventilation; $\dot{V}_E/\dot{V}_{CO_2}$ = ventilatory equivalents per expired CO₂; VT = tidal volume

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In patients with heart failure (HF), central sleep apnea (CSA) is recognized on polysomnography (PSG) as Cheyne-Stokes respiration characterized by a crescendo-decrescendo breathing pattern with hyperventilation alternating with compensatory apnea.^{1,2} In HF case series, the reported frequency of CSA has ranged from 21% to 50%³⁻⁶ and has been associated with increased mortality.⁷ Despite high pretest probability for sleep apnea, routine PSG for patients with HF has not been endorsed because of cost considerations; an insufficient number of laboratories to accommodate the large number of potential referrals; and lack of controlled, prospective studies demonstrating benefit of intervention for sleep-disordered breathing on cardiovascular outcomes.^{8,9} However, as more effective therapy for CSA emerges,¹⁰⁻¹² improved recognition of patients with HF to refer to PSG for definitive diagnosis may improve outcomes.¹³

An enhanced exercise ventilatory response and augmented CO₂ chemosensitivity are frequently observed

in patients with HF, and each has been shown to correlate with the severity of CSA as measured by the apnea-hypopnea index (AHI).¹⁴⁻²⁰ Patients with HF and CSA breathe more closely to the apneic CO₂ threshold, which predisposes to hypopnea and apnea.¹⁵ Prior investigation demonstrated that hypocapnea detected by arterial blood gas measurement is sensitive and specific for prediction of CSA in patients with HF.¹⁴ This observation suggests that noninvasive estimates of CO₂, including transcutaneous measurement, and the partial pressure of end-tidal CO₂ (PETCO₂) at cardiopulmonary exercise testing also predict CSA, although this has not yet been firmly established.²⁰⁻²²

We hypothesized that PETCO₂ measured during cardiopulmonary exercise testing predicts CSA in patients with HF. Accordingly, the aim of this study was to evaluate the relationship of CO₂ chemosensitivity and exercise ventilation and gas exchange to the presence of CSA in patients with HF.

Materials and Methods

Subject Selection

Subjects were consecutive, clinically stable, symptomatic ambulatory outpatients with HF with no symptom progression, no hospitalization, and no change in HF management in the prior 3 months. Inclusion criteria were left ventricular ejection fraction (LVEF) $\leq 35\%$ and New York Heart Association (NYHA) class II to III symptoms despite > 3 months of optimal pharmacotherapy.²³ Exclusion criteria were unstable symptoms or inability to perform cardiopulmonary exercise testing. All subjects gave written informed consent. This study was conducted in accordance with the Declaration of Helsinki and approved by the Mayo Clinic Institutional Review Board (IRB #1729-03). All procedures followed institutional and Health Insurance Portability and Accountability Act guidelines.

Exercise Testing

All subjects underwent cardiopulmonary exercise testing, including measurement of metabolic gas exchange as previously described.²⁴ Exercise ventilation and gas exchange were assessed by metabolic cart (MGC Diagnostics Corporation); measures included peak oxygen consumption, CO₂ output, PETCO₂, tidal volume (V_T), minute ventilation ($\dot{V}_E$), and breathing frequency. Data were collected continuously and reported as averages obtained over the final 30 s of each workload. Derived measures included the respiratory exchange ratio and ventilatory equivalents per expired CO₂ ($\dot{V}_E/\dot{V}_{CO_2}$). Our group has previously shown that $\dot{V}_E/\dot{V}_{CO_2}$ is highly correlated with the slope of $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}$ at submaximal and peak exercise.²⁵

CO₂ Chemosensitivity

CO₂ chemosensitivity was measured by a modified rebreathe technique as previously described.²⁶ Subjects breathed from a mouthpiece connected to a rebreathing bag, which included 5% CO₂ and balance oxygen at study initiation. PETCO₂ was monitored by mass spectroscopy as were breath-to-breath changes of $\dot{V}_E$ by a pneumotachograph. The slope of $\Delta\dot{V}_E/\Delta\text{PETCO}_2$ was used as an index of central CO₂ chemosen-

sitivity. Three runs were performed per subject and values reported as the mean.

Polysomnography

Full diagnostic PSG was performed in the Mayo Clinic Center for Translational Science Activities. All PSGs were digitally recorded on an E-Series digital PSG acquisition system (Compumedics Limited). Per published guidelines,²⁷ subjects were considered to have CSA if the total AHI (events/h) was > 5 with $> 50\%$ disordered-breathing events of central origin. Subjects were classified into two groups based on PSG findings for comparison: (1) CSA or (2) no sleep apnea. Subjects with OSA or mixed OSA/CSA were excluded from analysis.

Clinical Characteristics

Clinical characteristics were reviewed and recorded for each subject. Characteristics included age, sex, NYHA class, BMI, LVEF, medications, presence or absence of atrial fibrillation, and prior treatment by cardiac resynchronization therapy.

Statistical Analysis

The Shapiro-Wilk test was used to evaluate normality. Comparisons between subjects were made by the Student *t* test and Mann-Whitney *U* test. Differences in proportions were tested by the two-tailed Fisher exact test and statistical dependence by the Spearman rank test. Logarithmic transformation was performed for variables with nonnormal distribution. Multiple regressions were performed after controlling for sex and age for evaluation of log AHI and other parameters for detection of CSA. Multivariate logistic regression was performed after controlling for sex and age to analyze the strength of the association of measured end points with CSA. Decision statistics (2×2 tables) were calculated for several cutoff values of rest and peak PETCO₂ and CO₂ chemosensitivity and for the composite of rest PETCO₂ and CO₂ chemosensitivity. Data are summarized as mean $\pm$ SD. *P* $< .05$ was considered statistically significant. Statistical analysis was done using Statistica 12.0 (StatSoft Inc) and SAS, version 9.3 (SAS Institute Inc) software.

Results

Fifty-six subjects with HF were enrolled in the study. Of these, 11 were given a diagnosis of mixed sleep apnea and 12 with OSA. These subjects were excluded from further analysis. Of the remaining 33 subjects with HF, 20 with CSA (61%) and 13 with no sleep apnea (39%) ($AHI \leq 5$) formed the study cohort. Comparison of the two groups (CSA vs no sleep apnea) demonstrated no differences in age, BMI, LVEF, NYHA class, and mean nocturnal oxygen saturation; subjects with CSA were mostly men (14 [70%]) (Table 1). No significant differences existed between the two groups for medications and frequency of atrial fibrillation, and none of the subjects had undergone cardiac resynchronization therapy.

Subjects with CSA had higher CO_2 chemosensitivity (2.3 ± 1.0 L/min/mm Hg vs 1.6 ± 0.4 L/min/mm Hg, $P = .02$). Cardiopulmonary ventilatory and gas exchange measures at rest demonstrated that subjects with CSA had lower $PETCO_2$ and higher $\dot{V}_E$ and tended to have a higher $\dot{V}_E/\dot{V}CO_2$. Similarly, at 50% peak (ie, submaximal) exercise, subjects with CSA had higher V_T , $\dot{V}_E$, and $\dot{V}_E/\dot{V}CO_2$, and lower $PETCO_2$. At peak exercise, $\dot{V}_E/\dot{V}CO_2$ remained higher and $PETCO_2$ lower in subjects with CSA (Table 2).

The severity of CSA quantified by the AHI was significantly and inversely correlated with $PETCO_2$ at rest and submaximal and peak exercise. The AHI also significantly positively correlated with $\dot{V}_E$ at rest and submaximal exercise, V_T at submaximal and peak exercise, and $\dot{V}_E/\dot{V}CO_2$ at peak exercise. In addition, the AHI significantly correlated with CO_2 chemosensitivity (Table 3).

TABLE 1] Comparison of Clinical Characteristics by Subject Group

Characteristic	CSA (n = 20)	No Sleep Apnea (n = 13)	P Value
AHI	32 ± 17	3 ± 2	$< .01$
Age, y	65 ± 11	59 ± 10	.13
Male (female) sex	14 (6)	4 (9)	.04
Mean nocturnal oxygen saturation, %	94 ± 2	94 ± 2	.29
NYHA class	3 ± 1	2 ± 1	.44
BMI, kg/m ²	27 ± 5	27 ± 4	.86
LVEF, %	21 ± 8	26 ± 8	.12

Data are presented as mean $\pm$ SD unless otherwise indicated. AHI = apnea-hypopnea index; CSA = central sleep apnea; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

TABLE 2] Comparison of Cardiopulmonary Exercise Ventilation by Subject Group

Parameter	CSA (n = 20)	No Sleep Apnea (n = 13)	P Value
Rest			
$\dot{V}_E$, L/min	15 ± 7	10 ± 3	.02
V_T , mL	754 ± 345	561 ± 138	.06
fb, breaths/min	20 ± 7	18 ± 5	.31
$PETCO_2$, mm Hg	31 ± 4	35 ± 4	$< .01$
$\dot{V}_E/\dot{V}CO_2$	46 ± 8	42 ± 5	.16
50% peak exercise			
$\dot{V}_E$, L/min	31 ± 10	22 ± 8	.01
V_T , mL	$1,174 \pm 402$	869 ± 315	$< .01$
fb, breaths/min	28 ± 7	26 ± 7	.32
$PETCO_2$, mm Hg	31 ± 6	36 ± 4	$< .01$
$\dot{V}_E/\dot{V}CO_2$	42 ± 8	36 ± 6	.03
Peak exercise			
$\dot{V}O_2$, mL/min/kg	14.9 ± 4.2	17.5 ± 6	.29
$\dot{V}_E$, L/min	57 ± 20	46 ± 14	.12
V_T , mL	$1,758 \pm 654$	$1,446 \pm 548$	.07
fb, breaths/min	35 ± 8	33 ± 7	.56
$PETCO_2$, mmHg	29 ± 6	36 ± 5	$< .01$
$\dot{V}_E/\dot{V}CO_2$	43 ± 9	33 ± 6	$< .01$
RER	1.14 ± 0.11	1.07 ± 0.16	.17

Data are presented as mean $\pm$ SD. fb = breathing frequency; $PETCO_2$ = partial pressure of end-tidal CO_2 ; RER = respiratory exchange ratio; $\dot{V}_E$ = minute ventilation; $\dot{V}_E/\dot{V}CO_2$ = ventilatory equivalents per expired CO_2 ; $\dot{V}O_2$ = oxygen consumption; V_T = tidal volume. See Table 1 legend for expansion of other abbreviation.

Multiple regression analysis adjusted for potential confounders frequently associated with CSA (age, sex)^{13,28} demonstrated that the AHI remained significantly correlated with CO_2 chemosensitivity, $\dot{V}_E$ at submaximal exercise, $PETCO_2$ at rest and submaximal and peak exercise, and $\dot{V}_E/\dot{V}CO_2$ at peak exercise (Table 3). CO_2 chemosensitivity was also independently associated with submaximal and peak exercise $PETCO_2$ ($b = -0.38$, $F = 1.7$, $P = .04$, and $b = -0.40$, $F = 2.2$, $P = .02$, respectively).

Logistic regression analysis showed that CO_2 chemosensitivity, $PETCO_2$ at rest and submaximal and peak exercise, and $\dot{V}_E/\dot{V}CO_2$ at peak exercise were significantly associated with the presence of CSA (Table 4). Receiver operating characteristic analysis demonstrated that peak exercise $PETCO_2$ was the strongest independent predictor of CSA (area under the curve, 0.88; $P = .01$).

TABLE 3] Spearman Rank Correlation and Multiple Regression for AHI

AHI	Spearman Rank Correlation		Multiple Regression		
	ρ	P Value	β	F Ratio	P Value
Age	0.46	.01	...	...	NS
Rest $\dot{V}_E$	0.43	.01	...	...	NS
50% exercise $\dot{V}_E$	0.50	< .01	0.46	7.3	.01
50% exercise V_T	0.58	< .01	...	...	NS
Peak exercise V_T	0.47	.01	...	...	NS
Rest $PETCO_2$	-0.44	.01	-0.34	6.22	.04
50% exercise $PETCO_2$	-0.35	.05	-0.37	7.11	.01
Peak exercise $PETCO_2$	-0.46	.01	-0.45	9.22	< .01
Peak exercise $\dot{V}_E/\dot{V}CO_2$	0.41	.02	0.38	7.20	.01
$\Delta\dot{V}_E/\Delta PETCO_2$	0.53	< 0.01	0.43	8.60	< 0.01

NS = nonsignificant; $\Delta\dot{V}_E/\Delta PETCO_2$ = central CO_2 chemosensitivity. See Table 1 and 2 legends for expansion of other abbreviations.

The best cutoff value of peak exercise $PETCO_2$ for detection of CSA was 33 mm Hg, which yielded a sensitivity of 80% and specificity of 85% (Table 5). Subjects with peak $PETCO_2$ levels $\leq$ 33 mm Hg ($n = 18$) were highly likely to have CSA with a positive likelihood ratio of 5.2 (95% CI, 1.4-19). By comparison, decision statistics for rest parameters significantly associated with CSA yielded lower sensitivity and specificity, or both. The best rest $PETCO_2$ cutoff value (33 mm Hg) yielded a sensitivity of 80% and a specificity of 62%, whereas the best CO_2 chemosensitivity cutoff value (2 L/min/mm Hg) yielded a sensitivity of 40% and a specificity of 77%.

A composite of these two rest parameters yielded a sensitivity of 88% and a specificity of 67%.

Discussion

The novel observations of this study are that peak exercise $PETCO_2$ is independently associated with the presence and severity of CSA as quantified by the AHI and is the strongest predictor for CSA by receiver operating characteristic analysis. Furthermore, we made, to our knowledge, the unique observations in a single-study cohort that subjects with CSA breathe with significantly higher $\dot{V}_E$ and lower $PETCO_2$ at rest and higher

TABLE 4] Logistic Regression for CSA

Variable	OR	95% CI	AUC	P Value
Cardiopulmonary exercise parameters				
Rest $\dot{V}_E$	0.86	0.70-1.05	0.79	.14
50% exercise $\dot{V}_E$	0.87	0.76-1.01	0.78	.06
Peak exercise $\dot{V}_E$	0.97	0.92-1.03	0.75	.37
Rest V_T	1.00	0.99-1.00	0.76	.21
50% exercise V_T	1.00	0.99-1.00	0.78	.23
Peak exercise V_T	1.00	1.00-1.00	0.72	.72
Rest $PETCO_2$	1.31	1.01-1.71	0.80	.04
50% exercise $PETCO_2$	1.22	1.04-1.44	0.84	.02
Peak exercise $PETCO_2$	1.29	1.08-1.54	0.88	.01
Rest $\dot{V}_E/\dot{V}CO_2$	0.93	0.83-1.05	0.74	.25
50% exercise $\dot{V}_E/\dot{V}CO_2$	0.88	0.78-1.00	0.80	.04
Peak exercise $\dot{V}_E/\dot{V}CO_2$	0.85	0.75-0.97	0.86	.01
CO_2 chemosensitivity				
$\Delta\dot{V}_E/\Delta PETCO_2$	0.07	0.005-0.951	0.87	.05

AUC = area under curve. See Table 1, 2, and 3 legends for expansion of other abbreviations.

TABLE 5] 2 × 2 Decision Statistics: Peak Exercise PETCO₂ for Detection of CSA

PETCO ₂ , mm Hg	Sensitivity, % (95% CI)	Specificity, % (95% CI)	+LR (95% CI)	−LR (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
26	50 (27-73)	92 (64-99)	6.5 (0.9-45)	0.5 (0.3-0.9)	91 (59-98)	55 (32-76)
33	80 (56-94)	85 (55-98)	5.2 (1.4-19)	0.2 (0.1-0.6)	89 (62-98)	73 (45-92)
40	100 (83-100)	15 (2-45)	1.2 (0.9-1.5)	0	65 (45-81)	100 (19-100)

−LR = negative likelihood ratio; +LR = positive likelihood ratio; NPV = negative predictive value; PPV = positive predictive value. See Table 1 and 2 legends for expansion of the other abbreviations.

$\dot{V}_E$, V_T , and $\dot{V}_E/\dot{V}_{CO_2}$ and lower PETCO₂ during submaximal exercise and that each of these measures significantly correlates with the severity of CSA as quantified by AHI.

Javaheri and Corbett¹⁴ demonstrated decreased arterial CO₂ by blood gas analysis in patients with CSA while awake at rest, whereas others have shown lower rest transcutaneous CO₂ or PETCO₂.^{22,29,30} During exercise, Arzt et al¹³ demonstrated $\dot{V}_E/\dot{V}_{CO_2}$ to be independently associated with AHI in subjects with HF and CSA. Similarly, Roche et al²² and Meguro et al²⁰ showed significantly higher $\dot{V}_E/\dot{V}_{CO_2}$ slope, whereas Roche et al²² demonstrated lower rest and peak exercise PETCO₂ in subjects with HF and CSA. However, two subsequent studies did not confirm these observations.^{20,21} In addition, Arzt et al¹³ did not observe decreased PETCO₂ in patients with CSA, whereas Roche et al²² did not demonstrate an independent association of peak PETCO₂ and CSA. Meguro et al²⁰ observed no correlation of $\dot{V}_E/\dot{V}_{CO_2}$ slope and AHI, whereas Koike et al²¹ did not show a significant association between PETCO₂ at rest and peak exercise and AHI. The differences between the present study observations and these prior reports may be attributable to differences in the severity of both HF and CSA because the subjects in the current study may have had more advanced HF with lower LVEF and higher AHI.

An inverse association of exercise PETCO₂ and AHI has not been consistently observed in prior studies of subjects with CSA.^{20,21} Moreover, few previous studies compared rest and exercise ventilatory measures for the detection of CSA.^{13,21,22} In the present subject cohort, we demonstrated that exercise PETCO₂ was more strongly associated with CSA than rest PETCO₂, CO₂ chemosensitivity, or a composite of these two parameters. At peak exercise, the subjects with HF also had a significantly higher $\dot{V}_E/\dot{V}_{CO_2}$ and lower PETCO₂ than patients with no sleep apnea, and these measures significantly correlated with the magnitude of AHI even after adjustment for age and sex.

In contrast to Arzt et al,¹³ PETCO₂ in the present study was more strongly associated with CSA than $\dot{V}_E/\dot{V}_{CO_2}$. Indeed, in the study by Arzt et al,¹³ rest PETCO₂ was not significantly lower in patients with CSA. This apparent discrepancy from the present findings may be explained by more advanced HF in the current subjects or by different inclusion criteria used for the control and study groups.¹³ In the present study, subjects with peak exercise PETCO₂ ≤ 33 mm Hg were more likely to have CSA; a peak exercise PETCO₂ cutoff value of 33 mm Hg yielded a sensitivity of 80% and a specificity of 85%. Especially important is the relatively high specificity (ie, low false-positive findings) that further increases with the lowering of the cutoff value.

In the present study, exercise parameters, especially the peak PETCO₂, were more strongly associated with CSA than the rest parameters. Several prior studies have shown patients with CSA to have more advanced HF.³¹⁻³³ Multiple factors associated with HF may contribute to the increased ventilatory response to exercise, including lung congestion, ergoreflex activation, ventilation/perfusion mismatch, and lactic acidosis.^{34,35} Therefore, heightened ventilatory drive with exercise may identify a subgroup of individuals at increased risk for CSA.

As previously shown by others,^{15,19} we observed that CO₂ chemosensitivity was significantly elevated in subjects with CSA. However, to our knowledge, this study is the first to demonstrate that CO₂ chemosensitivity is independently associated with both the presence and the severity of CSA as well as with submaximal and peak exercise PETCO₂ in patients with HF and CSA. These observations support the concept previously suggested by others that CO₂ chemosensitivity plays an important role in the pathogenesis of CSA.^{19,36}

Because patients with CSA typically do not snore, this diagnosis may not be clinically suspected despite its high frequency in patients with HF. Because adaptive servoventilation may prove superior to CPAP for the treatment of sleep-disordered breathing in patients with HF,^{37,38} recognition of clinical phenotypes associated

with CSA may prove important for patient referral for PSG. For this reason, the present observations regarding the relationship of exercise ventilation to CSA may have clinical implications. Cardiopulmonary exercise testing often is used for assessment of functional capacity and risk stratification in patients with HF. Exclusion of subjects with other types of sleep apnea prevents recommendation of cardiopulmonary exercise testing as a screening method for CSA in patients with HF. However, in the present selected study cohort, we show peak exercise PETCO_2 to be strongly associated with CSA, suggesting that cardiopulmonary exercise testing may promote recognition of patients at increased risk for CSA.

Limitations

The study cohort was small, and there were more men than women in the CSA group, although this sex distribution is consistent with previous reports.⁴ The AHI is the standard measure in clinical practice and was used as the measure of CSA severity; however, loop gain has been shown to quantify the severity of ventilatory instability in both OSA and CSA.³⁹ To characterize the CSA phenotype, the present study cohort was highly selected. In contrast to CSA, OSA is associated with airway obstruction and chronic hypoventilation.⁴⁰ Vulnerability to airway obstruction is also characteristic of mixed sleep apnea.⁴¹ Therefore, subjects with OSA or

mixed sleep apnea were excluded from analysis. The excluded subjects with OSA had significantly lower ventilatory drive, and subjects with mixed sleep apnea tended to hyperventilate less than patients with CSA, although this difference was not significant (data not shown). The present study subjects had moderate to severe HF, and those with CSA appeared to have more advanced HF than control subjects, although the differences were not statistically significant. Multiple prior reports have demonstrated that patients with more advanced HF are more likely to have CSA.³¹⁻³³ The current study design allowed us to describe the CSA phenotype, but it prevents the generalization of these findings to the overall HF population.

Conclusions

Patients with HF and CSA have lower PETCO_2 at rest and both lower PETCO_2 and higher $\dot{V}_E/\dot{V}_{\text{CO}_2}$ at submaximal and peak effort during cardiopulmonary exercise testing compared with patients with HF and no sleep apnea. These findings are consistent with abnormal ventilatory control while awake, including increased ventilatory drive at rest and during exercise as well as during sleep in patients with HF and CSA. These observations suggest that findings at cardiopulmonary exercise testing may promote recognition of the CSA phenotype in patients with HF.

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