





ORIGINAL RESEARCH

# Central Apneas Are More Detrimental in Female Than in Male Patients With Heart Failure

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**BACKGROUND:** Central apneas (CA) are a frequent comorbidity in patients with heart failure (HF) and are associated with worse prognosis. The clinical and prognostic relevance of CA in each sex is unknown.

**METHODS AND RESULTS:** Consecutive outpatients with HF with either reduced or mildly reduced left ventricular ejection fraction ( $n=550$ , age  $65\pm 12$  years, left ventricular ejection fraction  $32\pm 9\%$ , 21% women) underwent a 24-hour ambulatory polygraphy to evaluate CA burden and were followed up for the composite end point of cardiac death, appropriate implantable cardioverter-defibrillator shock, or first HF hospitalization. Compared with men, women were younger, had higher left ventricular ejection fraction, had lower prevalence of ischemic etiology and of atrial fibrillation, and showed lower apnea-hypopnea index (expressed as median [interquartile range]) at daytime (3 [0–9] versus 10 [3–20] events/hour) and nighttime (10 [3–21] versus 23 [11–36] events/hour) (all  $P<0.001$ ), despite similar neurohormonal activation and HF therapy. Increased chemoreflex sensitivity to either hypoxia or hypercapnia (evaluated in 356 patients, 65%, by a rebreathing test) was less frequent in women ( $P<0.001$ ), but chemoreflex sensitivity to hypercapnia was a predictor of apnea-hypopnea index in both sexes. At adjusted survival analysis, daytime apnea-hypopnea index  $\geq 15$  events/hour (hazard ratio [HR], 2.70; 95% CI, 1.06–7.34;  $P=0.037$ ), nighttime apnea-hypopnea index  $\geq 15$  events/hour (HR, 2.84; 95% CI, 1.28–6.32;  $P=0.010$ ), and nighttime CA index  $\geq 10$  events/hour (HR, 5.01; 95% CI, 1.88–13.4;  $P=0.001$ ) were independent predictors of the primary end point in women but not in men (all  $P>0.05$ ), also after matching women and men for possible confounders.

**CONCLUSIONS:** In chronic HF, CA are associated with a greater risk of adverse events in women than in men.

**Key Words:** central apneas ■ chemoreflex ■ Cheyne-Stokes breathing ■ chronic heart failure ■ prognosis ■ sex difference ■ women

Sleep-disordered breathing is an extremely common comorbidity in patients with heart failure (HF), traditionally encompassing obstructive apneas (characterized by upper airways obstruction and increased respiratory effort) and/or central apneas (CA, neurally mediated interruption of respiratory muscle activation).<sup>1,2</sup> Although obstructive apneas are frequently reported in the general population and

constitute a recognized risk factor for cardiovascular diseases, CA are more frequently observed in heart failure (HF), affecting up to 70% patients with systolic dysfunction.<sup>1–6</sup> Both phenomena have been linked to higher mortality in patients with HF.<sup>7–9</sup> Although obstructive apneas usually occur at sleep time and thus are called obstructive sleep apneas (OSA), CA may be observed also in awake individuals,<sup>10–13</sup> yielding to a

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## CLINICAL PERSPECTIVE

### What Is New?

- In heart failure, central apneas are less prevalent but seem more detrimental in women than in men.
- Although a few sex-specific predictors of central apneas may be identified, increased chemoreflex sensitivity to hypercapnia remains a strong determinant of the apnea burden in both sexes.

### What Are the Clinical Implications?

- Women with heart failure and central apneas should be closely followed up because they may represent a subgroup at a higher risk of adverse cardiovascular events.
- Future studies should investigate more tailored strategies to treat central apneas in heart failure, shifting the focus on female patients, largely underrepresented in previous clinical trials
- The possibility to target the chemoreflex system seems a promising therapeutic option for heart failure related central apneas in both men and women.

## Nonstandard Abbreviations and Acronyms

<b>AHI</b>	apnea-hypopnea index
<b>CA</b>	central apneas
<b>CAI</b>	central apnea index

further increase in the risk of adverse events,<sup>4</sup> in particular when persisting in the upright position.<sup>14</sup>

The prevalence of CA is known to be higher in male patients with HF, and male sex has been identified as an independent predictor of CA severity.<sup>3,5,15</sup> Although a few studies in healthy controls have documented that sex hormones may influence the apneic threshold,<sup>16–18</sup> the reasons behind the different CA burden, as well as the possible clinical and prognostic implications of CA in female versus male patients with HF, have never been investigated. Furthermore, the impact of sex on the response to treatments developed for CA is currently unknown. Women have been extremely underrepresented in the CANPAP (Continuous Positive Airway Pressure for Central Sleep Apnea and Heart Failure, women ~5%)<sup>19</sup> and SERVE-HF (Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure, women ~10%)<sup>20</sup> trials, which yielded neutral or negative results, and they were not enrolled in some small pharmacological trials using acetazolamide<sup>21</sup> or buspirone.<sup>22</sup> In this respect, understanding

the differences related to sex in the pathophysiology and prognostic impact of CA in HF would help not only to close gaps in the care of women with CA and HF but also to properly design future studies based on a patient-tailored therapeutic approach.

Therefore, in the present work, we aimed to assess, for the first time, the sex-related differences in predictors, clinical, and prognostic significance of CA in chronic HF.

## METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

### Study Population and Design

Consecutive outpatients with chronic HF with either reduced left ventricular ejection fraction (LVEF  $\leq 40\%$ ) or mildly reduced (LVEF 41%–49%) LVEF in stable clinical conditions were prospectively enrolled from February 2010 to December 2020. Severe physical and/or cognitive impairment, severe pulmonary disease, current treatment with any therapy influencing respiratory control (eg, morphine, theophylline, acetazolamide, oxygen  $-O_2-$  continuous positive airway pressure), as well as acute coronary syndromes, history of OSA, cardiac surgery, or resynchronization therapy within the previous 3 months were considered as exclusion criteria.

Each patient underwent 2D echocardiography (model IE33 ultrasound machine with X5-1 transducer; Philips Medical Systems, Palo Alto, CA)<sup>23</sup>; 24-hour ECG recording (Elamedical, Paris; signals digitized at a sampling rate of 250 Hz) including measurements of heart rate variability in the time domain in patients in sinus rhythm (expressed as the SD of the mean of normal-to-normal RR intervals, the SD of the mean of averaged normal-to-normal intervals 5 minute periods segments, the root mean square of the successive difference between normal heartbeats, and the number of pairs of successive normal-to-normal intervals that differ more than 50 milliseconds divided by the total number of normal-to-normal intervals)<sup>24</sup>; cardiopulmonary exercise test on a cycle ergometer (VMAX, Sensormedics, Conshohocken, PA); neurohormonal characterization; 24-hour cardiorespiratory monitoring, as detailed subsequently. A subset of patients also underwent chemoreflex sensitivity assessment to hypoxia and hypercapnia, measured by the rebreathing technique and expressed as hypoxic ventilatory response (normocapnic hypoxia down to  $O_2$  saturation of 75%, n.v.  $<0.77$  L/min per % $SaO_2$ ) and hypercapnic ventilatory response (normoxic hypercapnia up to  $etCO_2$  of 50 mm Hg, n.v.  $<0.79$  L/min per mm Hg), as previously described.<sup>25,26</sup>

Before enrollment, all patients provided informed consent for the study, which was approved by the Institutional Review Board Committee of the Fondazione Toscana G. Monasterio and conducted in accordance with the Declaration of Helsinki of the World Medical Association.

All patients were followed at the hospital outpatient clinic until April 30, 2021, and the outcome status was determined from the medical records or telephone interviews with patients, patients' families, or general practitioners. The primary end point was a composite of cardiac death (including death from HF progression, sudden cardiac death, fatal myocardial infarction), life-threatening ventricular tachyarrhythmia requiring appropriate implantable cardioverter-defibrillator shock, or first hospitalization for HF.

### Twenty-Four-Hour Ambulatory Polygraphic Cardiorespiratory Recording

All patients underwent a 24-hour continuous polygraphic recording, including, according to the guidelines,<sup>27</sup> nasal airflow by nasal pressure probes, chest and abdominal respiratory movements by inductance plethysmography belts, and O<sub>2</sub> saturation (Somté PSG2; Compumedics, Victoria, Australia). Apneas were defined as a cessation of airflow for  $\geq 10$  seconds and classified as either obstructive or central based upon the presence/absence of thoracic and abdominal movements, respectively. Hypopneas were defined as a reduction in airflow  $\geq 50\%$ , lasting for  $\geq 10$  seconds, with a corresponding reduction in O<sub>2</sub> saturation  $\geq 4\%$ . Apnea severity was then quantified by the apnea-hypopnea index (AHI), and the incidence of either CA or OSA per hour was reported as the central apnea index (CAI) and the obstructive apnea index, respectively. The values of AHI, CAI, and obstructive apnea index were computed for the whole 24-hour period, with daytime hours defined between 7:00 AM and 9:59 PM and nighttime hours between 10:00 PM and 6:59 AM.<sup>4</sup> As previously specified, apneic events during the daytime were considered only in the setting of a clear periodicity (cycle time  $>30$  seconds), thus excluding pauses due to speaking, drinking, or eating.<sup>4</sup> Finally, the burden of oxygen desaturation was calculated as the time spent with a saturation  $<90\%$  (T-90).<sup>9</sup> All records were reviewed by experienced sleep technicians and then revised by a physician with specific clinical and research experience in the field (A.G., M.E., and C.P.).

### Statistical Analysis

First, the data were divided to compare women and men. Quantitative values were presented as mean $\pm$ SD, or median (interquartile interval) (for values with non-normal distribution) and qualitative values as numbers

or percentages. Mean differences among groups were evaluated through the unpaired Student *t* or Mann-Whitney *U* test, analysis of variance, or Kruskal-Wallis, with Bonferroni post hoc correction, when appropriate. Discrete variables were compared by the chi-square test with Yates's correction or the Fisher exact test. Linear regression was used to identify the predictors of daytime, nighttime, and 24-hour AHI in women and men. Skewed variables were ln-transformed before entering regression models. Kaplan-Meier method and log-rank statistics (Mantel-Cox) were used to estimate event-free survival according to the daytime and nighttime AHI/CAI. At this purpose, patients were dichotomized for AHI values  $<15$  or  $\geq 15$  events/hours and for CAI values  $<10$  or  $\geq 10$  events/hour (ie, moderate-to-severe disease), as previously proposed.<sup>20</sup> Cox-regression analysis was used to estimate the independent prognostic significance of daytime and nighttime AHI/CAI and of T-90 in women and men, adjusting the models for other predictors of poor outcome in similar populations such as patient's age, New York Heart Association class III to IV, LVEF, estimated glomerular filtration rate (eGFR), and N-terminal pro-B-type natriuretic peptide, and taking into account the number of events within each subgroup to avoid model overfitting.

Finally, in light of the lower proportion of women in the study population and to account for some differences among the baseline clinical features that could have unevenly influenced the prevalence and the prognostic significance of CA in women and men, a propensity score was calculated using a logistic regression analysis including patient's age ( $\pm 2$  years), ischemic etiology of HF, atrial fibrillation (AF), and LVEF ( $\pm 2\%$ ), obtaining, by the greedy nearest neighbor matching algorithm,<sup>28</sup> a 1:1 matched-pairs cohort of women and men. The sex differences in CA prevalence and prognostic significance were then assessed also in the matched cohort.

Statistical analysis was performed by using SPSS (version 25.0, 2017, IBM Statistics, Armonk, NY), R statistical software (version 3.4.0, The R Foundation for Statistical Computing, Vienna, Austria), and the related graphical user interface EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan)<sup>29</sup>; a 2-tailed *P* value  $\leq 0.05$  was considered significant.

## RESULTS

### Study Population

Finally, 550 patients were recruited (age  $65\pm 12$  years, LVEF  $32\%\pm 9\%$ , 21% women). As reported in Table 1 and Figure 1, women were younger compared with men (age  $62\pm 15$  years versus  $66\pm 11$  years,  $P=0.007$ ), had less frequently an ischemic etiology of HF (28%

**Table 1. Characteristics of the Study Population According to Sex**

Variables	All patients n=550	Unmatched subgroups			Matched subgroups*		
		Women n=118 (21%)	Men n=432 (79%)	P value	Women n=113 (50%)	Men n=113 (50%)	P value
Clinical features							
Age, y	65±12	62±15	66±11	<0.001†	64±13	65±12	0.357
Body mass index, kg/m <sup>2</sup>	27±5	27±6	27±5	0.123	27±6	28±5	0.080
BSA, m <sup>2</sup>	1.9±0.2	1.8±0.2	2.0±0.2	<0.001†	1.8±0.2	2.0±0.2	<0.001†
Ischemic etiology, n (%)	233 (42)	33 (28)	200 (46)	<0.001†	33 (29)	34 (30)	1.000
New York Heart Association III to IV, n (%)	106 (19)	19 (16)	87 (20)	0.428	19 (17)	16 (14)	0.714
Atrial fibrillation, n (%)	116 (21)	10 (9)	106 (25)	<0.001†	10 (9)	8 (7)	0.807
Biohumoral data							
Hemoglobin, g/dL	13.2±1.5	12.5±1.3	13.5±1.7	<0.001†	13.1±1.3	13.9±1.7	<0.001†
Anemia, n (%)	175 (32)	35 (29)	140 (32)	0.264	32 (28)	26 (26)	0.765
Estimated glomerular filtration rate, mL/min per 1.73 m <sup>2</sup>	74 (55–93)	83 (57–103)	72 (54–90)	0.001†	83 (61–103)	72 (54–90)	0.004†
N-terminal pro-B-type natriuretic peptide, ng/L	409 (271–580)	933 (416–2083)	1263 (518–2870)	0.094	960 (443–2333)	940 (403–1618)	0.377
Norepinephrine, ng/L	1233 (510–2791)	387 (269–568)	413 (276–604)	0.566	390 (269–569)	396 (232–618)	0.991
Echocardiography							
Left atrial diameter/BSA, mm/m <sup>2</sup>	24±4	24±4	24±4	0.365	24±4	23±4	0.283
Severe mitral regurgitation, n (%)	99 (18)	20 (17)	79 (18)	0.788	20 (18)	19 (17)	1.000
Diastolic dysfunction III, n (%)	139 (29)	19 (17)	120 (32)	0.004†	19 (18)	35 (35)	0.007†
E/e' average	14 (9–18)	12 (9–16)	13 (9–20)	0.023†	12 (9–16)	13 (8–19)	0.220
Left ventricular end-diastolic diameter/BSA, mm/m <sup>2</sup>	32±8	33±6	32±5	0.150	33±6	31±4	0.002†
Left ventricular end-systolic diameter/BSA, mm/m <sup>2</sup>	27±6	27±6	27±5	0.565	27±6	26±5	0.014†
Left ventricular ejection fraction, %	32±9	34±9	31±9	<0.001†	34±9	34±9	0.912
HFrEF/HFmrEF, n (%)	464/86 (84/16)	91/27 (77/23)	373/59 (86/14)	0.021†	90/23 (80/20)	92/21 (81/19)	0.867
Right ventricular diameter/BSA, mm/m <sup>2</sup>	15±3	15±2	15±3	0.655	15±2	15±3	0.536
Tricuspid annular plane systolic excursion, mm	18±5	19±5	18±5	0.733	19±5	19±5	0.176
Systolic pulmonary arterial pressure, mm Hg	38 (30–47)	33 (28–42)	40 (32–49)	0.004†	33 (28–42)	41 (34–53)	0.001†
Cardiopulmonary exercise test parameters							
Workload, Watts	80 (61–109)	70 (50–82)	85 (65–113)	<0.001†	70 (50–81)	87 (70–110)	<0.001†
Peak oxygen consumption/kg, mL/kg per min	15±6	14±5	15±6	0.116	13±5	16±9	0.030†
Ventilation-to-carbon dioxide output slope	33 (29–40)	32 (30–39)	34 (29–40)	0.542	33 (30–40)	35 (29–41)	0.589
Exertional oscillatory ventilation, n (%)	99 (30)	13 (19)	86 (32)	0.050†	12 (19)	22 (29)	0.236
Treatment							
Beta blockers, n (%)	519 (95)	112 (96)	407 (95)	1.000	108 (96)	108 (96)	1.000
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, n (%)	484 (89)	105 (90)	379 (89)	0.869	101 (89)	100 (80)	1.000
Angiotensin receptor-nepilysin inhibitors, n (%)	20 (4)	3 (3)	17 (4)	0.589	3 (3)	5 (4)	0.722

(Continued)

**Table 1. Continued**

Variables	All patients n=550	Unmatched subgroups			Matched subgroups*		
		Women n=118 (21%)	Men n=432 (79%)	P value	Women n=113 (50%)	Men n=113 (50%)	P value
Mineralocorticoid receptor antagonists, n (%)	405 (74)	84 (71)	321 (75)	0.476	81 (72)	81 (72)	1.000
Furosemide, n (%)	379 (70)	73 (62)	306 (72)	0.069	72 (64)	77 (68)	0.575
Implantable cardioverter-defibrillator, n (%)	112 (20)	17 (14)	95 (22)	0.072	17 (15)	24 (21)	0.300
Cardiac resynchronization therapy, n (%)	94 (17)	11 (9)	83 (19)	0.012 <sup>†</sup>	11 (10)	20 (18)	0.121

BSA indicates body surface area.

\*1:1 pairs of patients matched for age, ischemic etiology of heart failure, atrial fibrillation, and left ventricular ejection fraction. Values are mean±SD, median (interquartile interval), or n (%).

<sup>†</sup>Statistically significant (ie,  $P$  value  $\leq 0.05$ ).

versus 46%,  $P < 0.001$ ), a diagnosis of AF (9% versus 25%,  $P < 0.001$ ), and showed a greater LVEF ( $34\% \pm 9\%$  versus  $31\% \pm 9\%$ ,  $P < 0.001$ ). Women and men did not differ in terms of body mass index, New York Heart Association class, and neurohormonal activation (expressed as circulating levels of N-terminal pro-B-type natriuretic peptide and norepinephrine) (all  $P > 0.05$ ), and women showed higher eGFR than men ( $P < 0.001$ ). At echocardiography, women had a milder diastolic dysfunction and lower systolic pulmonary arterial pressure than men (all  $P < 0.05$ ). During the cardiopulmonary exercise test, women reached lower workload than men ( $P < 0.001$ ), whereas peak oxygen consumption ( $\text{VO}_2/\text{kg}$ ) and  $\text{VE}/\text{VCO}_2$  were similar between sexes (both  $P > 0.05$ ). At the time of recruitment, most patients were on guideline recommended medical therapy (>90% on beta blockers, >90% on angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers or angiotensin-receptor neprilysin-inhibitor, and >70% on mineralocorticoid antagonists), with no significant difference between sexes.

### Twenty-Four-Hour ECG Recording, Cardiorespiratory Monitoring, and Chemoreflex Sensitivity

As reported in Table 2, women showed a higher heart rate variability, expressed as the root mean square of the successive difference between normal heartbeats ( $P = 0.013$ ), and a lower incidence of nonsustained ventricular tachycardia ( $P < 0.001$ ).

During cardiorespiratory monitoring, women showed a significantly lower burden of CA compared with men both at daytime (AHI 3 [0–9] versus 10 [3–20] events/hour) and at nighttime (AHI 10 [3–21] versus 23 [11–36] events/hour) (both  $P < 0.001$ ). Also, the prevalence of moderate-to-severe disease (ie, AHI  $\geq 15$  events/hour) was lower in women than in men at

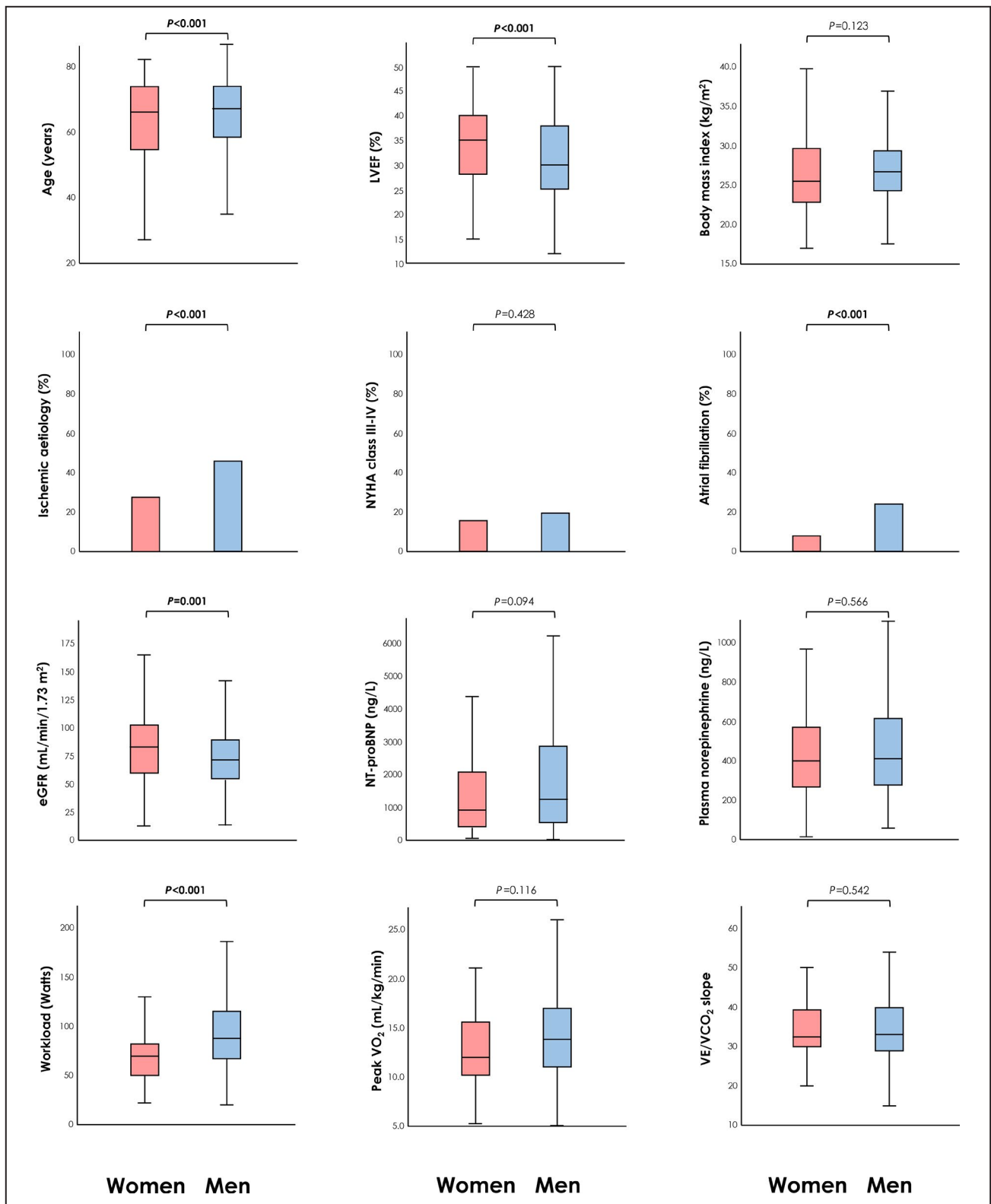
daytime (12% versus 36%) and at nighttime (37% versus 68%). Similarly, when considering the CAI, women showed a lower burden of CA compared with men both at daytime (0 [0–1] versus 2 [0–9] events/hour) and at nighttime (0 [0–4] versus 5 [1–19] events/hour) (both  $P < 0.001$ ). Again, the prevalence of moderate-to-severe disease (ie, CAI  $\geq 10$  events/hour) was lower in women than in men at daytime (2% versus 23%) and at nighttime (15% versus 38%) (Figure 2). As for T-90, no significant difference was observed between sexes (4 [2–11] versus 6 [1–14] minutes,  $P = 0.299$ ).

Chemoreflex sensitivity data were collected in 356 patients (65%). Chemoreflex sensitivity to hypoxia (0.34 [0.15–0.58] versus 0.5 [0.30–0.87] L/min per %SaO<sub>2</sub>,  $P < 0.001$ ) and to hypercapnia (0.82 [0.52–1.23] versus 1 [0.71–1.46] L/min per mm Hg,  $P = 0.014$ ) was lower in women than in men. Further, women showed less frequently a combined increased in chemoreflex sensitivity to both hypoxia and hypercapnia compared with men (23% versus 5%,  $P < 0.001$ ) (Table 2 and Figure 3).

### Predictors and Clinical Significance of Central Apneas in Women Versus Men

LVEF, diastolic dysfunction, left atrial dimension, and hypercapnic ventilatory response were predictors of daytime AHI in both sexes, whereas age, body mass index, AF, eGFR, and tricuspid annular plane systolic excursion were predictors of daytime AHI only in men (Table S1). AHI, age, body mass index, left atrial dimension, LVEF and hypercapnic ventilatory response were predictors of nighttime AHI in both sexes. Diastolic dysfunction was a predictor of nighttime AHI only in women, whereas ischemic etiology, eGFR, and hypoxic ventilatory response were predictors of nighttime AHI only in men (Table S2).

When stratifying patients according to the presence of moderate-to-severe CA (AHI  $\geq 15$  vs  $< 15$  events/hour)



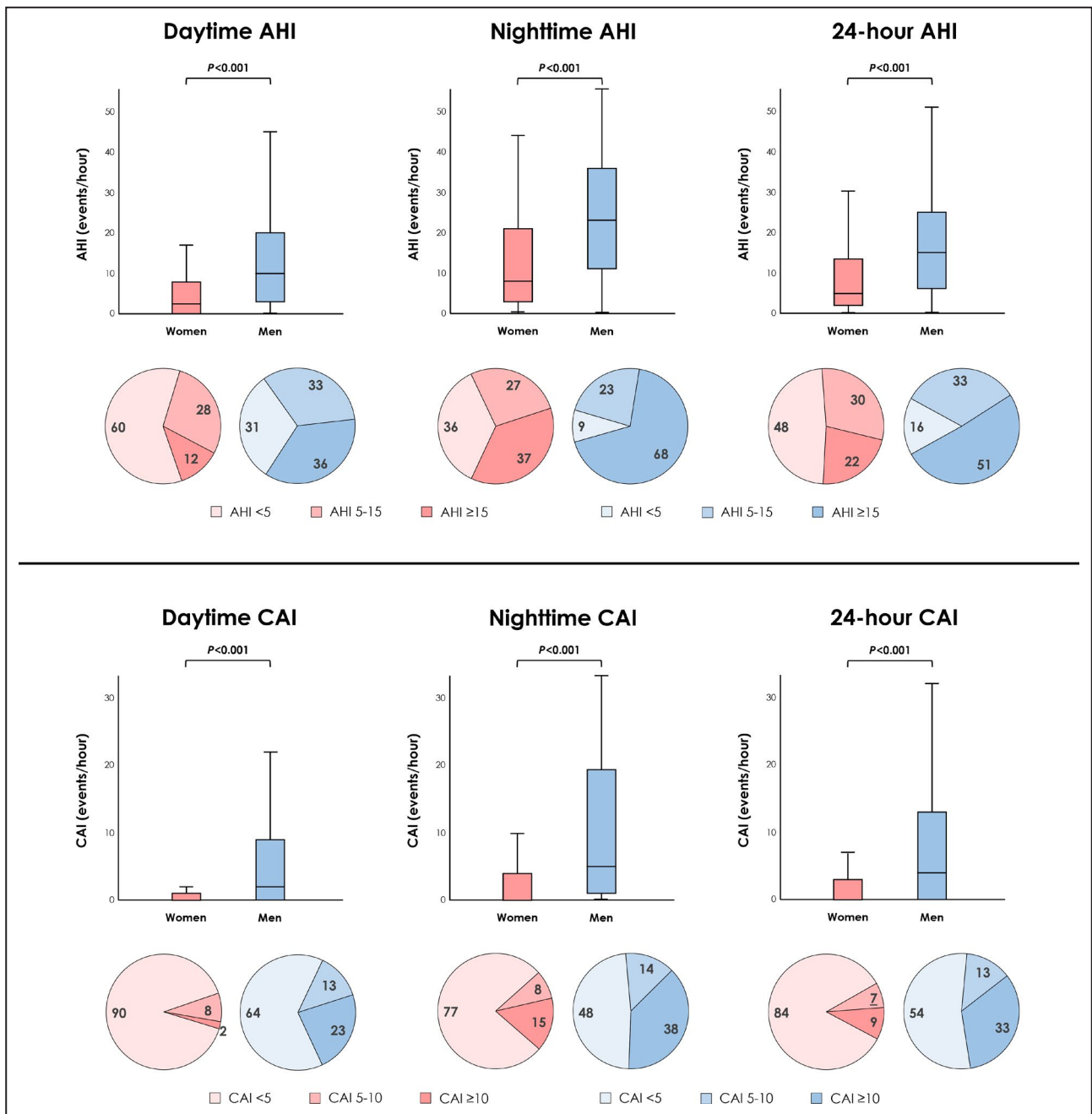
**Figure 1. Clinical characteristics of the study population according to sex.**

In the whole study population, compared with men, women were younger, had higher LVEF, lower prevalence of ischemic heart failure and atrial fibrillation, better renal function, and performed worse on cardiopulmonary exercise test. No sex differences were observed as for body-mass index, NYHA class, and neurohormonal activation. eGFR indicates estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; VE/VCO<sub>2</sub>, ventilation-to-carbon dioxide output; and VO<sub>2</sub>, oxygen consumption.

**Table 2. Twenty-Four-Hour ECG Recording, Cardiorespiratory Monitoring, and Chemoreflex Sensitivity According to Sex**

Variables	All patients n=550	Unmatched subgroups		P value	Matched subgroups†		P value
		Women n=118 (21%)	Men n=432 (79%)		Women n=113 (50%)	Men n=113 (50%)	
Holter monitoring							
Mean heart rate, bpm	68±10	70±11	68±10	0.029†	70.21±10.62	66.66±10.13	0.012†
SD of the mean of normal-to-normal intervals, ms	100 (75–137)	100 (82–126)	100 (72–141)	0.850	99 (81.5–126)	99.50 (74.5–128)	0.700
SD of the mean of averaged normal-to-normal intervals 5-min periods segments, ms	72 (53–92)	78 (60–93)	69 (50–92)	0.013†	77 (60–91.50)	67 (55–93.50)	0.192
Number of pairs of successive normal-to-normal intervals that differ more than 50 ms divided by the total number of normal-to-normal intervals, %	8 (2–26)	6 (2–20)	8 (2–28)	0.228	6 (2–20.25)	6 (2–17.25)	0.871
Root mean square of the successive difference between normal heartbeats, ms	43 (27–94)	40 (28–69)	43 (27–109)	0.159	39 (27–69)	42 (27–69.50)	0.822
Nonsustained ventricular tachycardia, n (%)	269 (51)	41 (35)	228 (55)	<0.001†	39 (85.1)	57 (52.3)	0.014†
Cardiorespiratory monitoring							
Daytime AHI, event/h	8 (2–17)	3 (0–9)	10 (3–20)	<0.001†	3 (0–9)	12 (4–22)	<0.001†
Nighttime AHI, event/h	20 (8–33)	10 (3–21)	23 (11–36)	<0.001†	10 (3–21)	25 (14–39)	<0.001†
24-h AHI, event/h	13 (5–23)	5 (2–14)	15 (7–25)	<0.001†	6 (2–14)	18 (10–31)	<0.001†
Daytime CAI, event/h	1 (0–7)	0 (0–1)	2 (0–9)	<0.001†	0 (0–1)	3 (0–11)	<0.001†
Nighttime CAI, event/h	3 (0–15)	0 (0–4)	5 (1–19)	<0.001†	0 (0–4)	8 (1–28)	<0.001†
24-h CAI, event/h	2 (0–10)	0 (0–3)	4 (0–13)	<0.001†	0 (0–3)	7 (1–17)	<0.001†
Nighttime obstructive apnea index, event/h	0 (0–2)	0 (0–1)	0 (0–2)	0.173	0 (0–1)	0 (0–3)	0.143
Percentage of time asleep with SaO <sub>2</sub> <90%, min	5 (1–12)	4 (2–11)	6 (1–14)	0.299	4 (2–12)	6 (1–12)	0.489
Chemoreflex sensitivity	n=356	n=67	n=289		n=66	n=109	
HVR-slope, L/min per %SaO <sub>2</sub>	0.46 (0.30–0.83)	0.34 (0.15–0.58)	0.50 (0.30–0.87)	<0.001†	0.35 (0.15–0.58)	0.82 (0.32–1.00)	<0.001†
HCVR-slope, L/min per mm Hg	0.97 (0.66–1.40)	0.82 (0.52–1.23)	1.00 (0.71–1.46)	0.014†	0.82 (0.52–1.23)	1.25 (0.95–1.63)	<0.001†
Isolated increased HVR, n (%)	30 (8)	4 (6)	26 (9)	0.108	4 (6)	6 (6)	0.654
Isolated increased HCVR, n (%)	155 (43)	30 (45)	125 (43)	0.150	30 (45)	43 (39)	0.060
Increased HVR and HCVR, n (%)	68 (19)	3 (6)	65 (23)	<0.001†	3 (5)	54 (50)	<0.001†

AHI indicates apnea-hypopnea index; CAI, central apnea index; HCVR, hypercapnic ventilatory response; and HVR, hypoxic ventilatory response. \*1:1 pairs of patients matched for age, ischemic etiology of heart failure, atrial fibrillation, and left ventricular ejection fraction. Values are mean±SD, median (interquartile interval), or n (%). †P≤0.05.



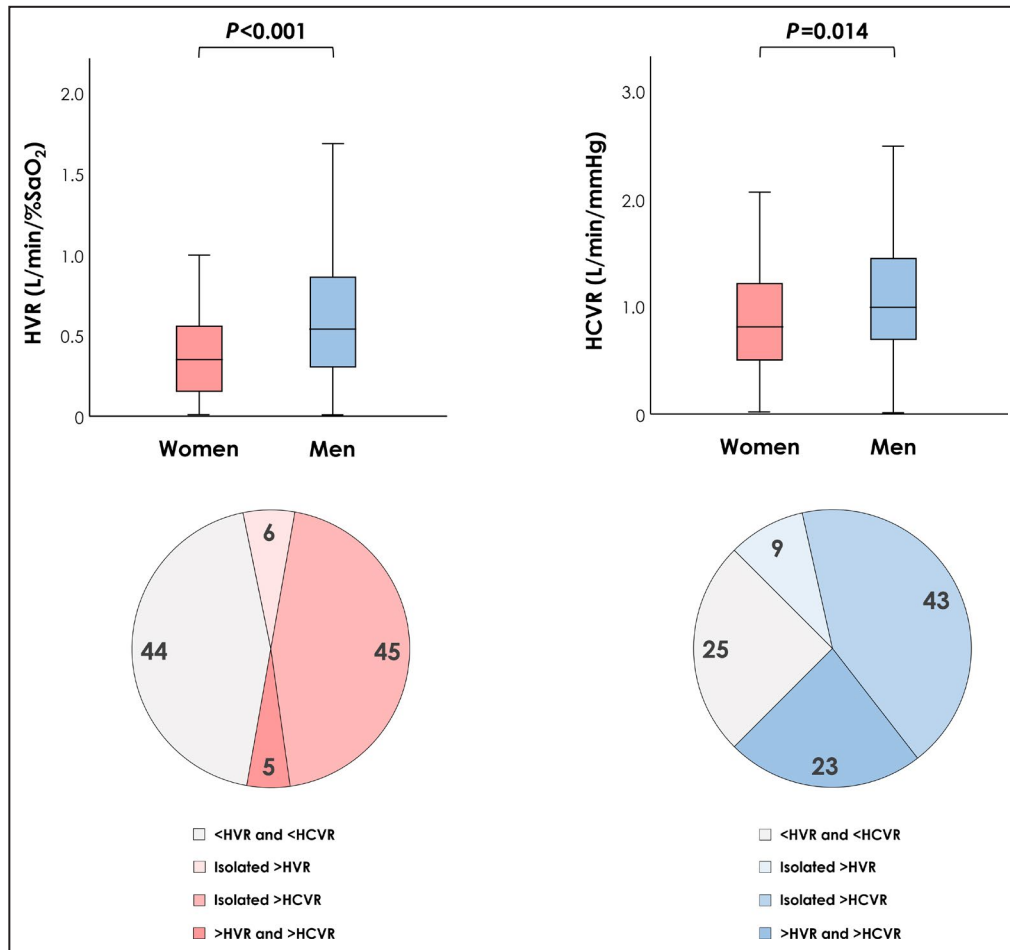
**Figure 2.** Sex-related differences in central apneas burden. AHI indicates apnea-hypopnea index; and CAI, central apnea index.

either at daytime or nighttime, higher plasma values of N-terminal pro-B-type natriuretic peptide and norepinephrine levels, and higher hypercapnic ventilatory response were observed in both sexes (all  $P < 0.05$ ) (Table S3). Men with moderate-to-severe CA showed a worse performance during cardiopulmonary exercise test compared with those with  $AHI < 15$  events/hour, whereas no significant difference was observed in women (Table S3).

### Survival Analysis

During a median follow-up of 36 (13–79) months, 199 (37%) patients met the primary composite end point: there were 154 deaths (29%), 92 (17%) cardiac deaths, 22 appropriate implantable cardioverter-defibrillator shocks, and 130 first hospitalizations for HF. The incidence of the primary end point was significantly higher in men than in women (40% versus 26%; log-rank=6.86,  $P=0.009$ ). Similarly,





**Figure 3. Sex-related differences in chemoreflex sensitivity.** HCVR indicates hypercapnic ventilatory response; and HVR, hypoxic ventilatory response.

both the incidence of all-cause death (31% versus 18%; log-rank=9.95,  $P=0.002$ ) and of cardiac death (18% versus 11%, log-rank=4.79,  $P=0.029$ ) were higher in men.

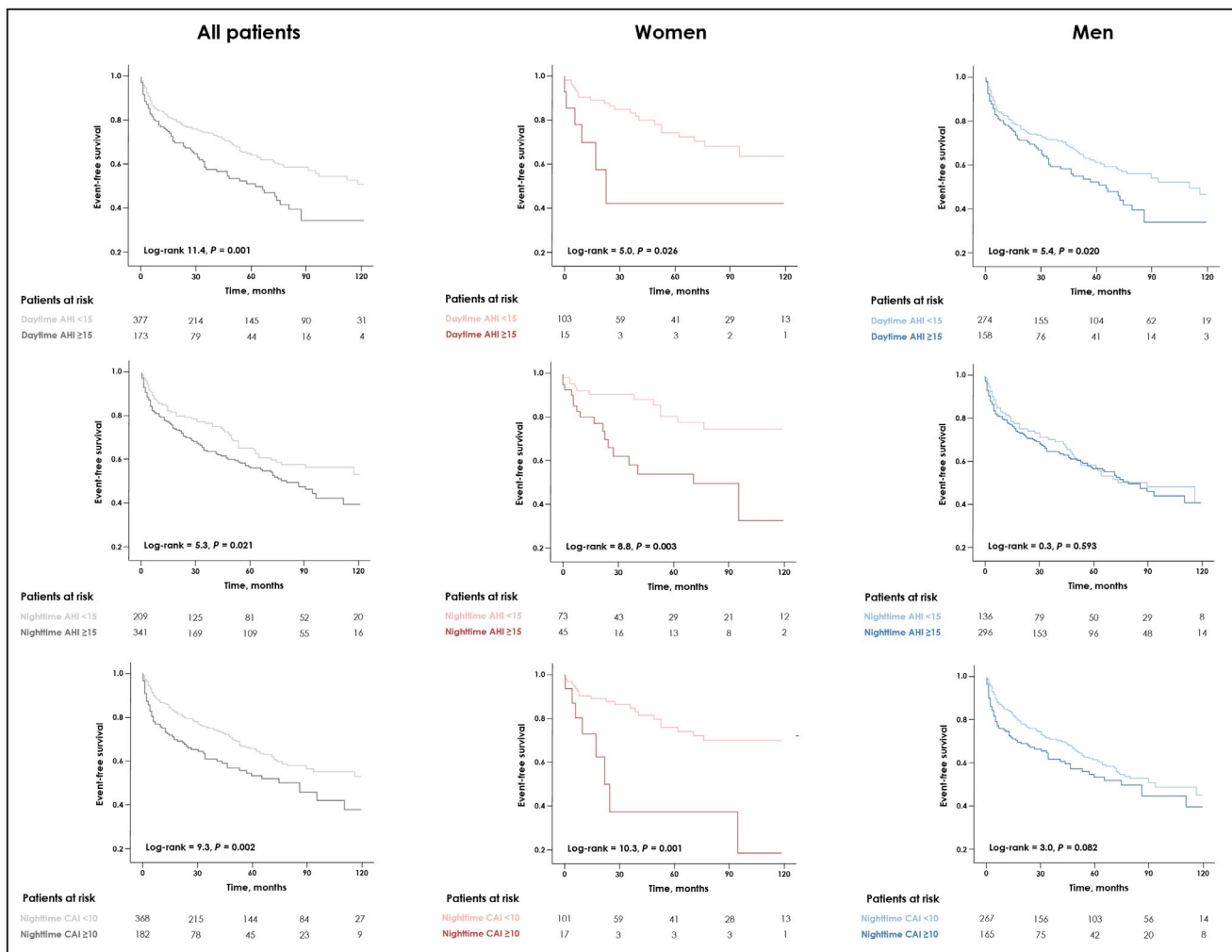
When stratifying the overall population (without considering sex) according to the apneic burden, a lower event-free survival was observed in patients with a daytime and nighttime AHI  $\geq 15$  events/hour ( $P=0.001$  and  $0.021$ , respectively) (Figure 4). Similar results were observed when considering stratifying patients according to a CAI  $\geq 10$  events/hour.

After dividing the study population into sex subgroups, a daytime AHI  $\geq 15$  events/hour was associated with a lower event-free survival in both women ( $P=0.026$ ) and men ( $P=0.020$ ), and a nighttime AHI  $\geq 15$  events/hour was associated with a lower event-free survival only in women ( $P=0.003$ ), not in men ( $P=0.593$ ). Similarly, a nighttime CAI  $\geq 10$  events/hour was associated with lower event-free survival in women ( $P=0.001$ ) but not in men ( $P=0.082$ ) (Figure 4). Considering the very low prevalence of daytime CAI  $\geq 10$  events/hour in women (ie, 2%), this was not considered for survival analysis to avoid model overfitting.

At multivariable Cox-regression analysis, considering the whole study population, a daytime AHI  $\geq 15$  events/hour and T-90 were independent predictors of the primary end point independently of sex ( $P$  for interaction=0.193 and =0.727, respectively), whereas a nighttime AHI  $\geq 15$  events/hour and a nighttime CAI  $\geq 10$  events/hour were independent predictors of the primary end point in women but not in men ( $P$  for interaction=0.013 and =0.030, respectively) (Figure 5). When considering the 2 sexes separately, a daytime AHI  $\geq 15$  events/hour (HR, 2.70; 95% CI, 1.06–7.34;  $P=0.037$ ), a nighttime AHI  $\geq 15$  events/hour (HR, 2.84; 95% CI, 1.28–6.32;  $P=0.010$ ), and a nighttime CAI  $\geq 10$  events/hour (HR, 5.01; 95% CI, 1.88–13.4;  $P=0.001$ ) remained independent predictors of the primary composite end point only in women (Table 3).

### Propensity-Score Matching Analysis

After propensity-score matching, 226 patients were selected (113 women, 50%). Baseline characteristic of matched female and male patient cohorts are reported in Table 1. As expected, after matching,



**Figure 4.** Kaplan-Meier curves for the primary combined end point of cardiac death, appropriate ICD shock, or first hospitalization for HF according to daytime AHI, nighttime AHI, and nighttime CAI in the study population and according to sex. AHI indicates apnea-hypopnea index; CAI, central apnea index; HF, heart failure; and ICD, implantable cardioverter-defibrillator.

women and men no longer differed in age, LVEF, ischemic etiology, and prevalence of AF (all  $P > 0.05$ ) (Figure S1). Even after propensity-score matching, women showed a lower prevalence of CA at daytime and at nighttime and a lower chemoreflex sensitivity to both hypoxia and hypercapnia (all  $P < 0.001$ ) (Table 2 and Figure S2 and S3).

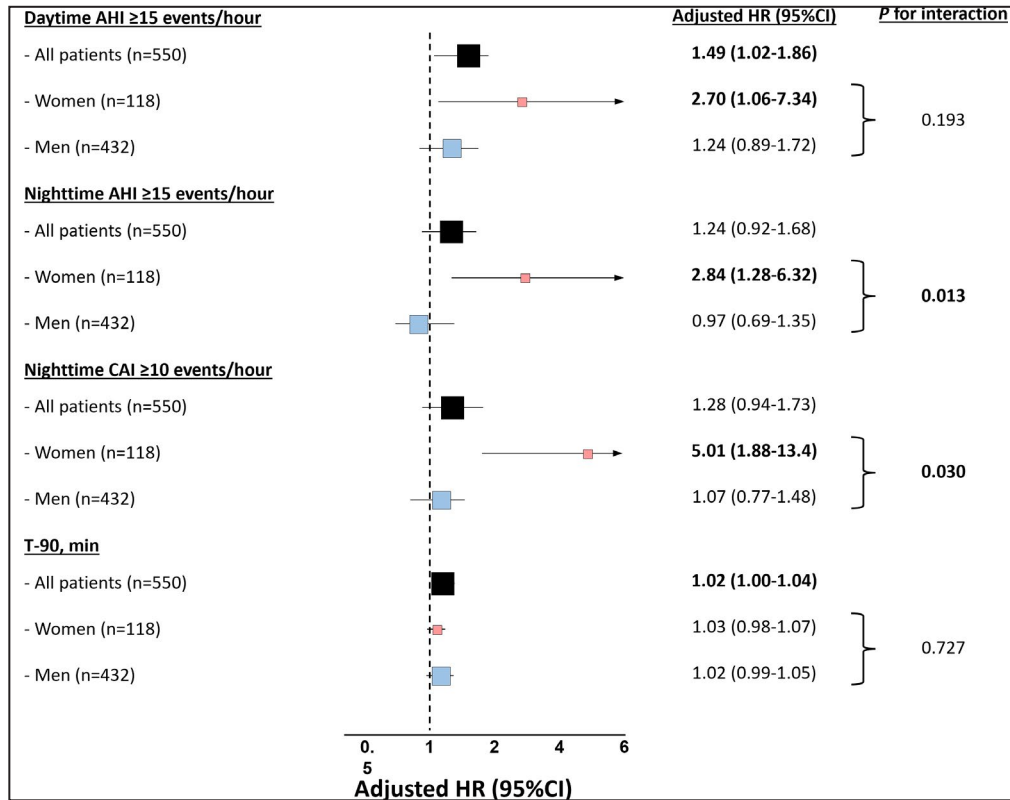
At survival analysis, the incidence of the primary end point was significantly higher in men than in women in the matched cohort (45% versus 26%;  $P = 0.010$ ) (Figure S4). Considering all patients of the matched cohort, both daytime and nighttime AHI  $\geq 15$  events/hour were associated with a lower event-free survival (both  $P < 0.05$ ). However, when considering the 2 sexes separately, a daytime ( $P = 0.03$ ) and a nighttime ( $P = 0.009$ ) AHI  $\geq 15$  events/hour, as well as nighttime CAI  $\geq 10$  events/hour ( $P = 0.007$ ) were associated with lower event-free survival only in women, not in men ( $P = 0.237, 0.081, \text{ and } 0.060$ , respectively) (Figure S5).

## DISCUSSION

This is the first study to specifically investigate the influence of sex on predictors and clinical and prognostic significance of CA in patients with HF (Figure 6). Compared with men, women showed a lower burden of CA across the 24-hour period, even when accounting for possible confounders such as age, ischemic etiology of HF, AF, and LVEF. Moderate-to-severe CA were associated with lower event-free survival in the overall population, but when considering sex categories separately, such relation was present only in women, even after propensity-score matching.

### Prevalence and Predictors of Central Apneas in Women Versus Men

Breathing disorders are frequently observed in patients with HF, and CA represent the most common



**Figure 5. Independent prognostic significance of central apneas in the whole study population and in either women or men with HF.**

In the whole study population, a daytime AHI ≥15 events/hour and the T-90 were predictors of the composite end point of cardiac death, appropriate implantable ICD shock, or first hospitalization for HF independently of sex (*P* for interaction=0.193 and 0.727, respectively). On the other hand, a nighttime AHI ≥15 events/hour and a nighttime CAI ≥10 events/hour were independent predictors of the composite end point in women but not in men (*P* for interaction=0.013 and 0.030, respectively). AHI indicates apnea-hypopnea index; CAI, central apnea index; HF, heart failure; ICD, implantable cardioverter-defibrillator; and T-90, percentage of time asleep with SaO<sub>2</sub> <90%.

phenotype in patients with LV systolic dysfunction, affecting from 30% to 70% of patients in different clinical series.<sup>3-6</sup> Male sex has been consistently related to a higher prevalence of CA: in a population of 700 patients with symptomatic systolic HF, women represent only 15% of patients with nighttime CA.<sup>15</sup> Similar findings have been also reported in different studies,<sup>3,4,8,30-32</sup> in which women also showed a lower severity of apneic events.<sup>4,8,31,32</sup>

Accordingly, male sex has been identified as an independent risk factor for breathing disorders, particularly of CA. In the work by Yumino et al., male sex was associated with a 5-fold and an 8-fold greater risk of having either OSA or nighttime CA, respectively.<sup>30</sup> Similarly, in a study from our group including 700 outpatients with chronic HF (including patients with reduced, mildly reduced, and preserved ejection fraction), male sex was an independent predictor of CA both at daytime (odds ratio [OR], 5; 95% CI, 2-11; *P*<0.001) and at nighttime (OR, 11; 95% CI, 3-42; *P*<0.001).<sup>3</sup>

In the present study, beyond confirming the higher prevalence and severity of CA in men than in women across the 24-hour period, we observed, for the first time, that such differences may persist even after excluding possible confounders through propensity-score matching (ie, age, ischemic etiology of HF, AF, and LVEF).

**Potential Mechanisms Behind Sex-Related Difference in Central Apneas**

To date, the possible mechanisms linking male sex to CA have been poorly investigated. In a multicenter registry including 6876 patients with HF (1448, 36% women), sleep-disordered breathing increased with age in both sexes, but more markedly in women (from 16% in patients 18 to 50 years old, up to 47% in patients >80 years old).<sup>32</sup> Authors reported no sex-related difference in the predictors of apneas evaluated in the study (obesity, severe LV systolic dysfunction, higher

**Table 3. Univariable and Multivariable Cox-Regression Analysis for the Primary Composite End Point of Cardiac Death, Appropriate ICD Shock, or First Hospitalization for HF in Women and Men in the Whole Study Population**

Variables	Women			Men		
	Univariable model		Multivariable model*	Univariable model		Multivariable model*
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Daytime AHI ≥15 events/h	2.68 (1.09–6.61)	0.033†	2.70 (1.06–7.34)	0.037†	1.44 (1.06–1.95)	0.021†
Nighttime AHI ≥15 events/h	2.87 (1.39–5.96)	0.005†	2.84 (1.28–6.32)	0.010†	1.09 (0.79–1.51)	0.596
Nighttime central apnea index ≥10 events/h	3.51 (1.54–7.98)	0.003†	5.01 (1.88–13.4)	0.001†	1.31 (0.96–1.79)	0.084
Percentage of time asleep with SaO <sub>2</sub> <90%, min	1.04 (1.01–1.08)	0.031†	1.03 (0.98–1.07)	0.235	1.03 (1.01–1.05)	0.014†

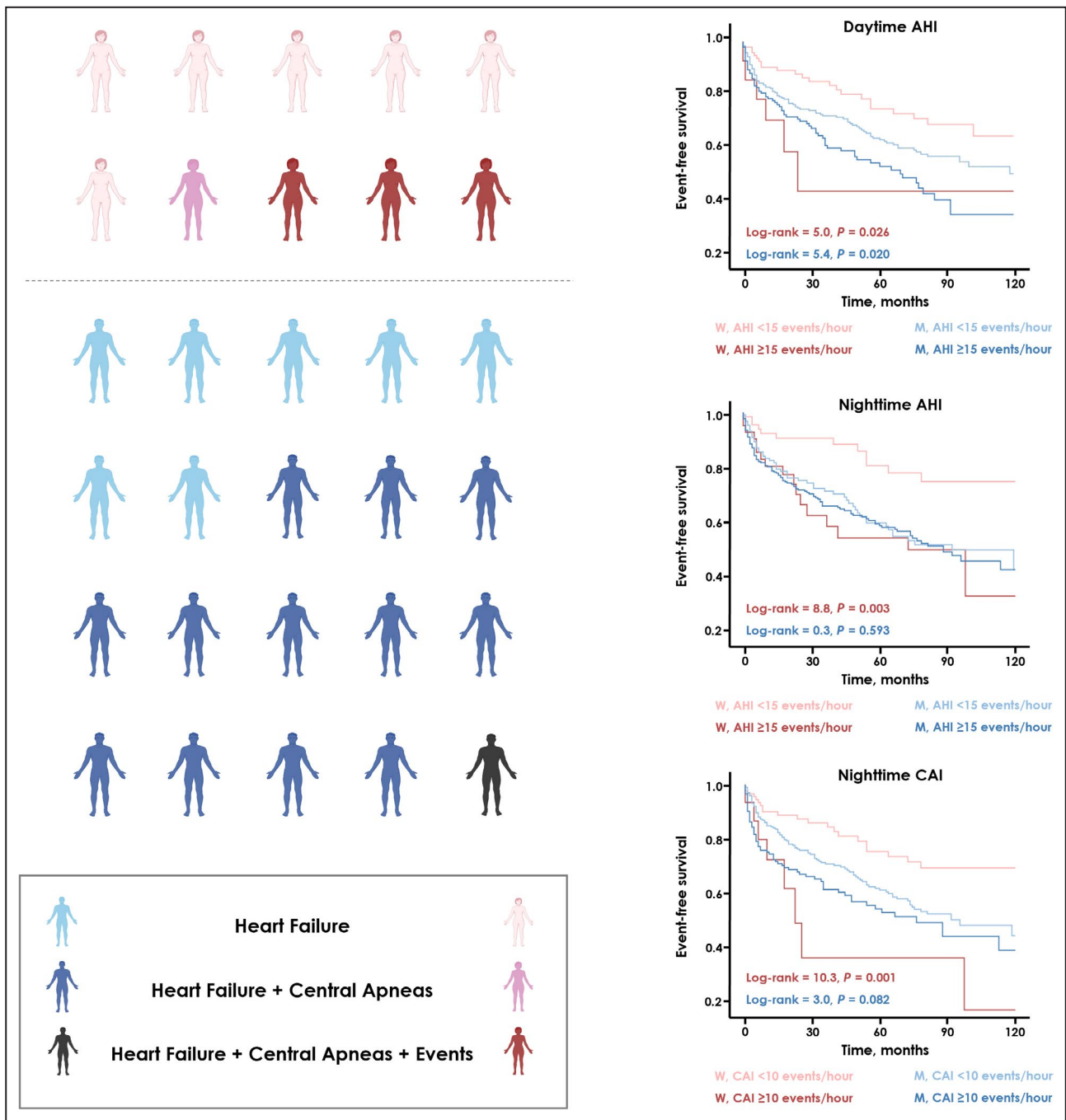
AHI indicates apnea-hypopnea index; HF, heart failure; HR, hazard ratio; and ICD, implantable cardioverter-defibrillator.  
 \*Multivariable models have been adjusted for patients' age, left ventricular ejection fraction, New York Heart Association class III–V, estimated glomerular filtration rate, and plasma N-terminal pro-B-type natriuretic peptide.  
 †P<0.05.

New York Heart Association class, and AF).<sup>32</sup> Some shared predictors of CA severity were identified in both men and women also in our study, such as LVEF, atrial dimension, and chemoreflex sensitivity to hypercapnia, in line with previous studies.<sup>3,15,26,32,33</sup> On the contrary, some sex-specific predictors have been evidenced in the current study (ie, ischemic etiology, eGFR, and chemoreflex sensitivity to hypoxia in men and diastolic dysfunction in women).

A possible influence of sex-hormones on respiratory control has been proposed to explain the higher propensity of male subjects to develop CA, because inhibition of testosterone-related pathways seemed effective in stabilizing breathing in patients with centrally mediated apneas/hypopneas.<sup>16–18</sup> In line with this hypothesis, in the present study we compared chemoreflex sensitivity in female and male patients, observing higher values of chemoreflex sensitivity to hypoxia and hypercapnia in men. Interestingly, although chemoreflex sensitivity to hypoxia was a predictor of nighttime AHI only in men, chemoreflex sensitivity to hypercapnia was a consistent predictor of breathing instability across the 24-hour period in both sexes, highlighting once more the key role of carbon dioxide sensing as pathophysiological substrate of CA<sup>14,26,27,34</sup> and the potential of central chemoreceptors (major determinants of the chemoreflex sensitivity to hypercapnia) as a therapeutic targets for CA in chronic HF.<sup>22</sup> It is notwithstanding possible that other predictors of ventilatory instability, such as the plant gain (lung contribution)<sup>27</sup> or the mixing gain (circulation time)<sup>35</sup> may exert some role and explain, at least in part, sex-specific differences in the epidemiology and clinical significance of CA in HF.

### Clinical and Prognostic Significance of Central Apneas in Women Versus Men

Contrary to OSA, CA are less often associated with specific symptoms, but some patients may report poor sleep quality, paroxysmal nocturnal dyspnea, and nocturia.<sup>1</sup> However, in accordance with previous studies,<sup>8,31</sup> we did not observe any difference in New York Heart Association functional class in patients with or without CA, although both women and men with moderate-to-severe CA showed greater neuro-hormonal activation, as pointed out by higher plasma levels of N-terminal pro-B-type natriuretic peptide and of norepinephrine. Thus, the possible reasons behind such a discrepancy remain to be clarified and may be related to a different level of chemoreflex activation and/or central gating/processing of visceral peripheral inputs driving to aversive reaction to apneas/hyperventilation. As for cardiopulmonary exercise test parameters, CA were associated with lower exercise capacity and worse ventilatory efficiency only in men, possibly a result from the higher chemoreflex response



**Figure 6. Sex-related differences in burden and prognostic significance of central apneas in HF patients.** AHI indicates apnea-hypopnea index; CAI, central apnea index; and HF, heart failure.

to gas changes during exercise.<sup>36,37</sup> Again, future studies are expected to clarify the impact of patients' sex on the relation between breathing disorders and exercise tolerance and performance and the related clinical consequences.

Although CA have been consistently associated with poor outcomes in patients with HF,<sup>4,8,14,31</sup> the possible influence of sex on such relation has never been specifically addressed before this study. Although patients

with moderate-to-severe CA showed lower event-free survival considering the whole population, such negative and independent prognostic impact of CA was confirmed only in women but not in men, both in the unmatched and the matched populations. This surprising result is particularly evident with regard to nighttime apneas. Indeed, whereas some smaller difference in survival curves is still perceptible in men considering daytime apneas (at least at Kaplan-Meier analysis), at

night the difference between men with or without CA is completely negligible at least in the unmatched population. When considering the matched population, the difference in the prognostic significance of nighttime events between women and men is less striking but still present, unmasking some HF-related CA cofactors in women that may lead to a worse prognostic trajectory. Anyway, neither AHI or CAI did stratify prognosis in men across the 24-hour period at multivariable Cox-proportionate analysis, making the results more consistent and reliable.

The possible mechanisms behind such findings remain to be clarified. A different effect of intermittent hypoxia on cardiac myocytes in either men or women could be hypothesized, according to a different neurohormonal/inflammatory response and/or susceptibility of the myocardial substrate in the 2 sexes. In a large cohort of middle-aged individuals ( $n=1652$ , 893 women) with OSA, the severity of apneas was independently associated with ongoing cardiac damage, as indicated by elevated high sensitivity-troponin T, and incident HF in women but not in men, suggesting different sex-related pathophysiological mechanisms.<sup>38</sup> Despite the several differences between CA and OSA, a greater sex-specific susceptibility of women to hypoxia and/or sympathetic surges and/or intrapleural swings related with apneas can be hypothesized.<sup>38</sup> Future studies should be specifically designed to clarify sex-related differences in the pathophysiological consequences of CA in chronic HF.

Finally, the different prognostic impact of CA in female and male patients with HF seems relevant when looking at the design of future therapeutic approaches. Indeed, the potential prognostic benefit of treating CA in women is unknown, because female patients have been extremely underrepresented in the 2 main clinical trials conducted so far to test the effects of noninvasive ventilation on the outcome of patients with HF and CA (ie, the CANPAP and the SERVE-HF).<sup>19,20</sup> Of note, although both continuous positive airway pressure and adaptive servoventilation had been effective in reducing the severity of CA during follow-up, the 2 studies failed to demonstrate any reduction in their primary end points (ie, transplant-free survival for the CANPAP, and a composite of death from any cause, lifesaving cardiovascular intervention, or unplanned hospitalization for worsening HF for the SERVE-HF), calling into question the prognostic significance of CA.<sup>19,20</sup> On the contrary, considering the results of the present work, the treatment of CA would be more likely to yield prognostic benefits in women than in men with chronic HF. Therefore, whether these observations should be confirmed in different and larger populations, future studies on the treatment of CA in chronic HF should be tailored shifting the focus on female patients rather than partly or completely excluding them.

## Limitations

Ambulatory cardiorespiratory monitoring was used to assess AHI and CAI instead of attended in-hospital polysomnography; therefore the lack of electroencephalographic recording did not allow the evaluation of arousals and sleep stages. However, avoiding hospital admission may reduce patients' discomfort and related costs, and the evaluation of breathing disorders across the entire 24 hours may yield further information of potential clinical interest.<sup>4,10-14</sup> As previously suggested,<sup>39</sup> hypopneas were considered as either central or obstructive following the more prevalent type of apneas. However, the exclusion of patients with history of OSA from the analysis and the very low obstructive apnea index in our population makes misclassification of hypopneas rather unlikely. Nonetheless, we have also considered beyond the AHI the CAI and have obtained comparable and consistent results. Chemoreflex sensitivity was assessed only in a subset of the study population, not allowing powered comparisons between smaller subgroups or further survival analyses. However, the higher values of chemoreflex sensitivity in men, as well as the prevalent role of chemoreflex sensitivity to hypercapnia as a predictor of CA severity are in line with previous observations,<sup>14,18</sup> promoting future studies aimed to clarify whether chemoreceptors might be considered a valuable therapeutic target<sup>22</sup> in both sexes or not. Women constituted only a minority of the whole study population (ie, 21%) and had fewer events during follow-up compared with men. Although the main findings of this work were confirmed when the 2 sexes were equally represented and harmonized for possible confounders, through propensity-score matching analysis, larger confirmatory studies with a higher proportion of women and longer follow-up are desirable. Despite a similar body mass index, body surface area (as expected) was lower in women than in men even after matching and might potentially explain the different prevalence and clinical significance of CA between the 2 sexes. Considering that CA are neurally mediated, we believe that the effect of body surface area is presumably less important in this clinical scenario (CA in HF), as compared with the influence of body mass index in the pathophysiology of OSA.

Because an LVEF <50% constituted an inclusion criterion for the present study, both patients with HF with reduced left ventricular ejection fraction and HF with mildly reduced left ventricular ejection fraction were enrolled. However, similar findings were observed when considering only patients with HF with reduced left ventricular ejection fraction (Table S4). Furthermore, survival analysis was adjusted for LVEF. Finally, as acknowledged within the recently released universal definition of HF,<sup>40</sup> there is a growing body of evidence that standard therapy for HF with reduced left ventricular

ejection fraction may be effective and extended to select patients with HF with mildly reduced left ventricular ejection fraction.

## CONCLUSIONS

Central apneas are a common comorbidity in patients with chronic HF despite an optimal-medical therapy and are more prevalent in men than in women, independently of possible confounders. Similar predictors of CA severity may be identified in women and men, confirming a key role of increased chemoreflex sensitivity in both sexes. Although moderate-to-severe CA is associated with poor prognosis in patients with chronic HF, their prognostic role is independent from other established predictors only in women, not in men, especially considering nighttime apneas. In light of such findings, alongside the disappointing results of the main clinical trial conducted so far in which women were largely underrepresented,<sup>19,20</sup> the investigation of sex-tailored therapeutic strategies for CA in chronic HF may then be warranted.

## ARTICLE INFORMATION

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### Disclosures

None.

### Supplemental Material

Tables S1–S4  
Figures S1–S5

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# **SUPPLEMENTAL MATERIAL**

**Table S1. Predictors of daytime AHI in women and men of the study population.**

Variables	Women		Men	
	$\beta$ coefficient (95%CI)	p	$\beta$ coefficient (95%CI)	p
Age, years	0.09 (-0.01-0.19)	0.083	0.16 (0.06-0.26)	<b>0.002</b>
BMI, kg/m <sup>2</sup>	0.24 (-0.01-0.49)	0.059	0.29 (0.05-0.53)	<b>0.018</b>
Ischemic etiology	2.18 (-1.07-5.43)	0.186	1.26 (-1.09-3.61)	0.304
Atrial fibrillation	0.85 (-4.42-6.12)	0.883	2.72 (0.01-5.43)	<b>0.022</b>
eGFR, ml/min/1.73 m <sup>2</sup>	-2.29 (-5.74-1.15)	0.189	-3.29 (-6.49-(-0.10))	<b>0.019</b>
LADi, mm/m <sup>2</sup>	0.39 (0.20-0.58)	<b>0.043</b>	0.42 (0.11-0.73)	<b>0.007</b>
Severe MR	0.91 (-2.98-4.80)	0.708	2.42 (-0.61-5.45)	0.116
Diastolic dysfunction III	3.94 (0.01-8.00)	<b>0.050</b>	2.76 (0.08-5.44)	<b>0.042</b>
LVEF, %	-0.21 (-0.35-(0.06))	<b>0.008</b>	-0.14 (-0.28-(-0.02))	<b>0.010</b>
TAPSE, mm	-0.07 (-0.16-1.19)	0.656	-0.41 (-0.65-(0.16))	<b>0.001</b>
HVR, L/min/%SaO <sub>2</sub>	1.63 (-6.11-9.39)	0.688	0.18 (-3.87-3.49)	0.888
HCVR, L/min/mmHg	5.52 (1.29-9.76)	<b>0.011</b>	3.83 (1.37-6.09)	<b>0.001</b>

Skewed variables were ln-transformed before entering regression models. AHI: apnea-hypopnea index; BMI: body mass index; eGFR: estimated glomerular filtration rate; HCVR: hypercapnia-ventilatory response; HVR: hypoxia-ventilatory response; LADi: left atrium diameter/body-surface area; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; TAPSE: tricuspid annular plane systolic excursion.

**Table S2. Predictors of nighttime AHI in women and men of the study population.**

Variables	Women		Men	
	$\beta$ coefficient (95%CI)	p	$\beta$ coefficient (95%CI)	p
Age, years	0.22 (0.05-0.40)	<b>0.011</b>	0.16 (0.03-0.29)	<b>0.014</b>
BMI, kg/m <sup>2</sup>	0.50 (0.07-0.93)	<b>0.023</b>	0.72 (0.41-1.02)	<b>&lt;0.001</b>
Ischemic etiology	3.86 (-1.83-9.54)	0.182	3.04 (0.03-6.04)	<b>0.048</b>
Atrial fibrillation	0.25 (-8.98-9.48)	0.957	0.56 (-2.94-4.06)	0.755
eGFR, ml/min/1.73 m <sup>2</sup>	-3.39 (-9.41-2.63)	0.267	-4.85 (-8.96-(-0.74))	<b>0.021</b>
LADi, mm/m <sup>2</sup>	0.22 (0.03-0.73)	<b>0.042</b>	0.39 (0.10-0.79)	<b>0.022</b>
Severe MR	1.05 (-7.88-5.79)	0.763	2.13 (-1.76-6.02)	0.283
Diastolic dysfunction III	8.52 (1.48-15.5)	<b>0.018</b>	2.87 (-0.62-6.35)	0.107
LVEF, %	-0.22 (-0.41-(0.04))	<b>0.020</b>	-0.16 (-0.29-(-0.02))	<b>0.023</b>
TAPSE, mm	-0.38 (-0.95-0.18)	0.181	-0.23 (-0.53-0.08)	0.151
HVR, L/min/%SaO <sub>2</sub>	4.31 (-10.1-18.6)	0.549	5.06 (0.19-9.93)	<b>0.042</b>
HCVR, L/min/mmHg	12.8 (5.25-20.4)	<b>0.001</b>	5.39 (2.49-8.31)	<b>&lt;0.001</b>

AHI: apnea-hypopnea index; BMI: body mass index; eGFR: estimated glomerular filtration rate; HCVR: hypercapnia-ventilatory response; HVR: hypoxia-ventilatory response; LADi: left atrium diameter/body-surface area; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; TAPSE: tricuspid annular plane systolic excursion. Skewed variables were ln-transformed before entering regression models.

**Table S3. Clinical significance of central apneas in women and men.**

Variables	Women (n=118)			Men (n=432)		
	Daytime AHI <15 events/h (n=103, 87%)	Daytime AHI ≥15 events/h (n=15, 13%)	p	Daytime AHI <15 events/h (n=274, 63%)	Daytime AHI ≥15 events/h (n=158, 37%)	p
Age, years	62 ± 15	64 ± 14	0.595	64 ± 12	68 ± 10	<0.001
BMI, kg/m <sup>2</sup>	26 ± 6	27 ± 5	0.541	27 ± 5	28 ± 5	0.320
Ischemic etiology, n (%)	27 (27)	6 (40)	0.357	123 (45)	77 (49)	0.483
NYHA III-IV, n (%)	17 (17)	2 (13)	0.999	48 (18)	39 (24)	0.082
Atrial fibrillation, n (%)	8 (8)	2 (13)	0.615	55 (20)	51 (32)	<b>0.005</b>
eGFR, mL/min/1.73 m <sup>2</sup>	84 (58-106)	75 (59-89)	0.163	75 (56-93)	68 (50-86)	<b>0.031</b>
NT-proBNP, ng/L	836 (382-1764)	2416 (1126-4174)	<b>0.010</b>	942 (391-2401)	1645 (932-3540)	<0.001
Norepinephrine, ng/L	368 (259-538)	552 (382-714)	<b>0.016</b>	376 (231-518)	497 (321-725)	<0.001
Severe MR, n (%)	17 (17)	3 (20)	0.718	46 (17)	33 (21)	0.303
Diastolic dysfunction, n (%)	15 (16)	4 (27)	0.293	180 (73)	78 (59)	<b>0.006</b>
LVEF, %	35 ± 10	29 ± 7	<b>0.013</b>	32 ± 8	30 ± 9	<b>0.024</b>
TAPSE, mm	19 ± 5	17 ± 5	0.262	19 ± 5	18 ± 5	<b>0.017</b>
sPAP, mmHg	33 (29-41)	35 (28-44)	0.603	38 (30-48)	43 (33-51)	<b>0.036</b>
Workload, Watts	70 (51-81)	63 (36-88)	0.518	90 (67-122)	79 (60-98)	<b>0.002</b>
Peak VO <sub>2</sub> /kg, mL/kg/min	14 ± 5	13 ± 4	0.679	16 ± 7	13 ± 3	<b>0.004</b>
VE/VCO <sub>2</sub> slope	33 (29-40)	31 (30-36)	0.494	33 (28-39)	35 (30-42)	0.098
HVR-slope, L/min/SaO <sub>2</sub>	0.35 (0.15-0.58)	0.32 (0.15-0.56)	0.816	0.50 (0.30-0.84)	0.57 (0.26-0.90)	0.900
HCVR-slope, L/min/mmHg	0.79 (0.52-1.21)	0.95 (0.91-1.38)	<b>0.050</b>	0.94 (0.61-1.33)	1.17 (0.82-1.69)	<b>0.001</b>
	Nighttime AHI <15 events/h (n=73, 62%)	Nighttime AHI ≥15 events/h (n=45, 38%)	p	Nighttime AHI <15 events/h (n=136, 31%)	Nighttime AHI ≥15 events/h (n=296, 69%)	p
Age, years	60 ± 16	65 ± 12	0.078	63 ± 12	67 ± 11	<b>0.004</b>
BMI, kg/m <sup>2</sup>	26 ± 6	28 ± 6	0.062	26 ± 4	28 ± 5	<0.001
Ischemic etiology, n (%)	16 (22)	17 (38)	0.073	54 (40)	146 (49)	0.077
NYHA III-IV, n (%)	13 (18)	6 (13)	0.610	27 (20)	60 (20)	0.999
Atrial fibrillation, n (%)	8 (11)	2 (4)	0.313	107 (79)	219 (74)	0.336
eGFR, mL/min/1.73 m <sup>2</sup>	88 (60-108)	78 (58-95)	0.131	78 (56-97)	70 (53-88)	<b>0.011</b>
NT-proBNP, ng/L	802 (381-1576)	1636 (496-3809)	<b>0.020</b>	907 (391-2453)	1439 (651-3036)	<0.001
Norepinephrine, ng/L	327 (229-519)	504 (370-699)	<0.001	345 (219-475)	455 (298-697)	<b>0.010</b>
Severe MR, n (%)	10 (14)	10 (22)	0.312	22 (16)	57 (19)	0.504
Diastolic dysfunction, n (%)	8 (12)	11 (36)	0.078	33 (27)	87 (34)	0.195
LVEF, %	36 ± 9	32 ± 10	<b>0.032</b>	32 ± 9	31 ± 9	0.129
TAPSE, mm	19 ± 5	18 ± 5	0.283	19 ± 5	18 ± 5	0.540
sPAP, mmHg	31 (28-35)	35 (30-44)	0.129	34 (28-46)	42 (32-51)	<b>0.019</b>
Workload, Watts	70 (54-81)	70 (45-83)	0.629	89 (64-127)	83 (66-110)	0.335
Peak VO <sub>2</sub> /kg, mL/kg/min	14 ± 5	12 ± 4	0.103	16 ± 9	14 ± 4	<b>0.033</b>
VE/VCO <sub>2</sub> slope	33 (27-39)	32 (30-38)	0.518	33 (27-38)	34 (30-41)	<b>0.012</b>
HVR-slope, L/min/SaO <sub>2</sub>	0.34 (0.14-0.47)	0.38 (0.15-0.61)	0.619	0.40 (0.25-0.84)	0.55 (0.30-0.87)	0.102
HCVR-slope, L/min/mmHg	0.74 (0.51-1.01)	0.96 (0.65-1.39)	<b>0.045</b>	0.92 (0.59-1.25)	1.08 (0.77-1.50)	<b>0.007</b>

AHI: apnea-hypopnea index; BMI: body mass index; eGFR: estimated glomerular filtration rate; HCVR: hypercapnia-ventilatory response; HVR: hypoxia-ventilatory response; LAD: left atrial diameter; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; sPAP: systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion; VE/VCO<sub>2</sub>: ventilation-to-carbon dioxide output; VO<sub>2</sub>: oxygen consumption.

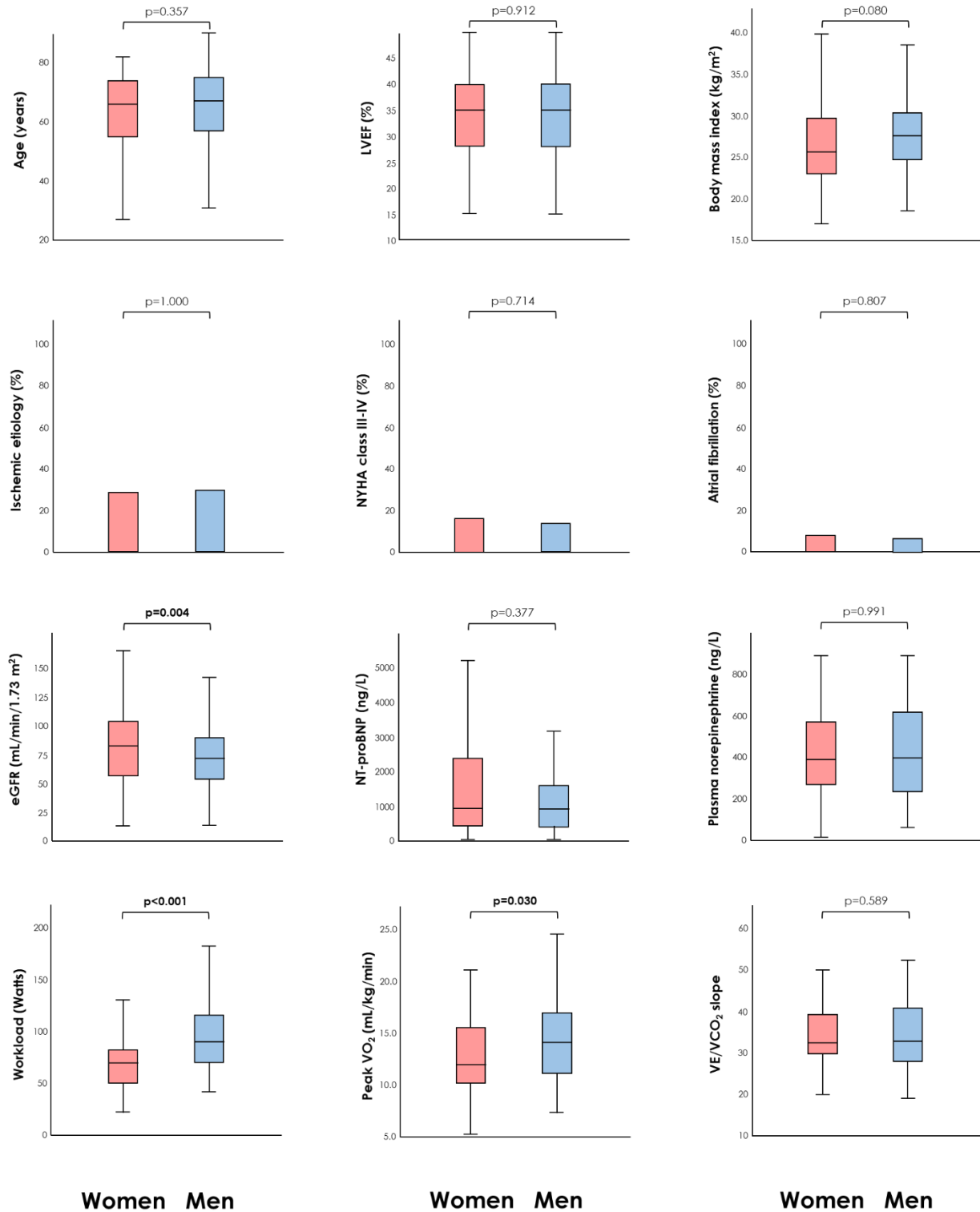
**Table S4. Cardiorespiratory monitoring, and chemoreflex sensitivity according to sex in patients with heart failure and reduced ejection fraction (HF<sub>r</sub>EF).**

<b>Variables</b>	<b>Women n=91</b>	<b>Men n=373</b>	<b>p</b>
<b>Cardiorespiratory monitoring</b>			
Daytime AHI, event/h	3 (0-11)	11 (3-20)	<b>&lt;0.001</b>
Nighttime AHI, event/h	10 (3-22)	24 (11-36)	<b>&lt;0.001</b>
24-h AHI, event/h	6 (2-16)	16 (8-26)	<b>&lt;0.001</b>
Daytime CAI, event/h	0 (0-2)	2 (0-9)	<b>&lt;0.001</b>
Nighttime CAI, event/h	0 (0-5)	6 (0-22)	<b>&lt;0.001</b>
24-h CAI, event/h	0 (0-3)	4 (0-15)	<b>&lt;0.001</b>
Nighttime OAI, event/h	0 (0-1)	0 (0-2)	0.173
T-90, min	4 (2-10)	6 (2-14)	0.249
<b>Chemoreflex sensitivity</b>			
	<b>n=54</b>	<b>n=245</b>	
HVR-slope, L/min/%SaO <sub>2</sub>	0.40 (0.16-0.59)	0.50 (0.30-0.87)	<b>0.002</b>
HCVR-slope, L/min/mmHg	0.80 (0.50-1.21)	1.00 (0.73-1.49)	<b>0.009</b>
Isolated increased HVR, n (%)	2 (4)	23 (9)	0.112
Isolated increased HCVR, n (%)	23 (43)	108 (44)	0.163
Increased HVR and HCVR, n (%)	3 (6)	57 (23)	<b>&lt;0.001</b>

Values are median (interquartile interval), or n (%). AHI: apnea-hypopnea index; CAI: central apnea index; HCVR: hypercapnic ventilatory response; HVR: hypoxic ventilatory response; OAI: obstructive apnea index; T-90: percentage of time asleep with SaO<sub>2</sub> <90%.

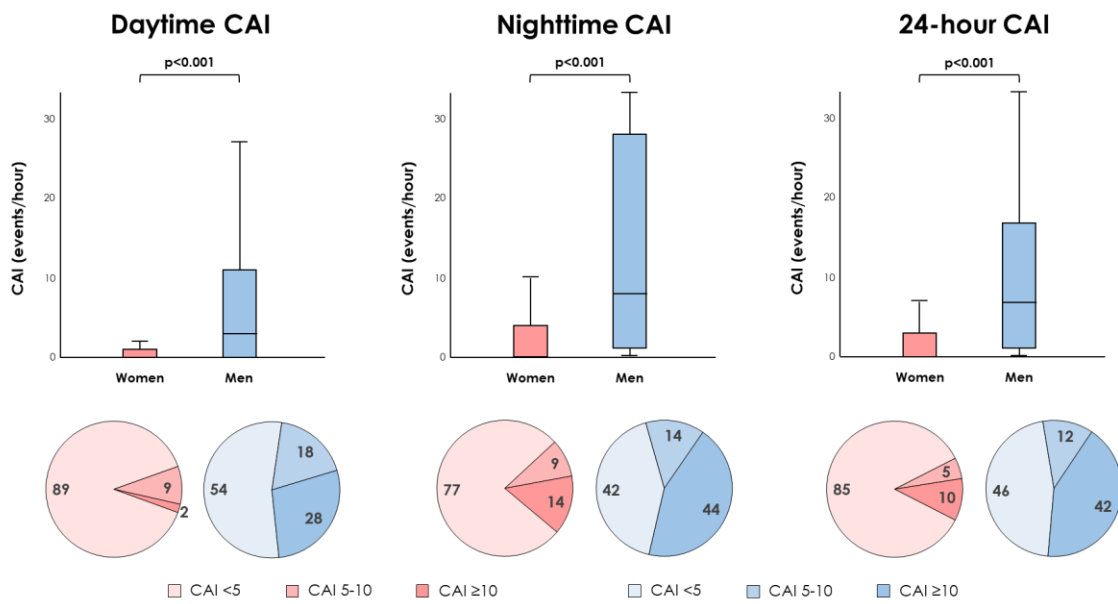
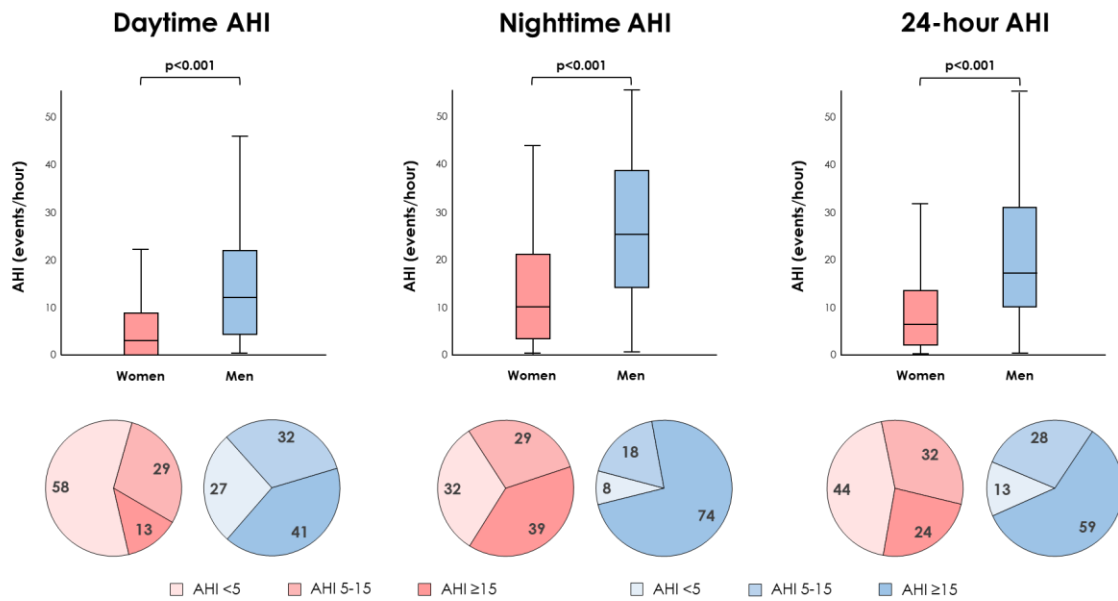
**Figure S1. Clinical characteristics of the study population according to sex after propensity-score matching.**

eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; VE/VCO<sub>2</sub>: ventilation-to-carbon dioxide output; VO<sub>2</sub>: oxygen consumption.



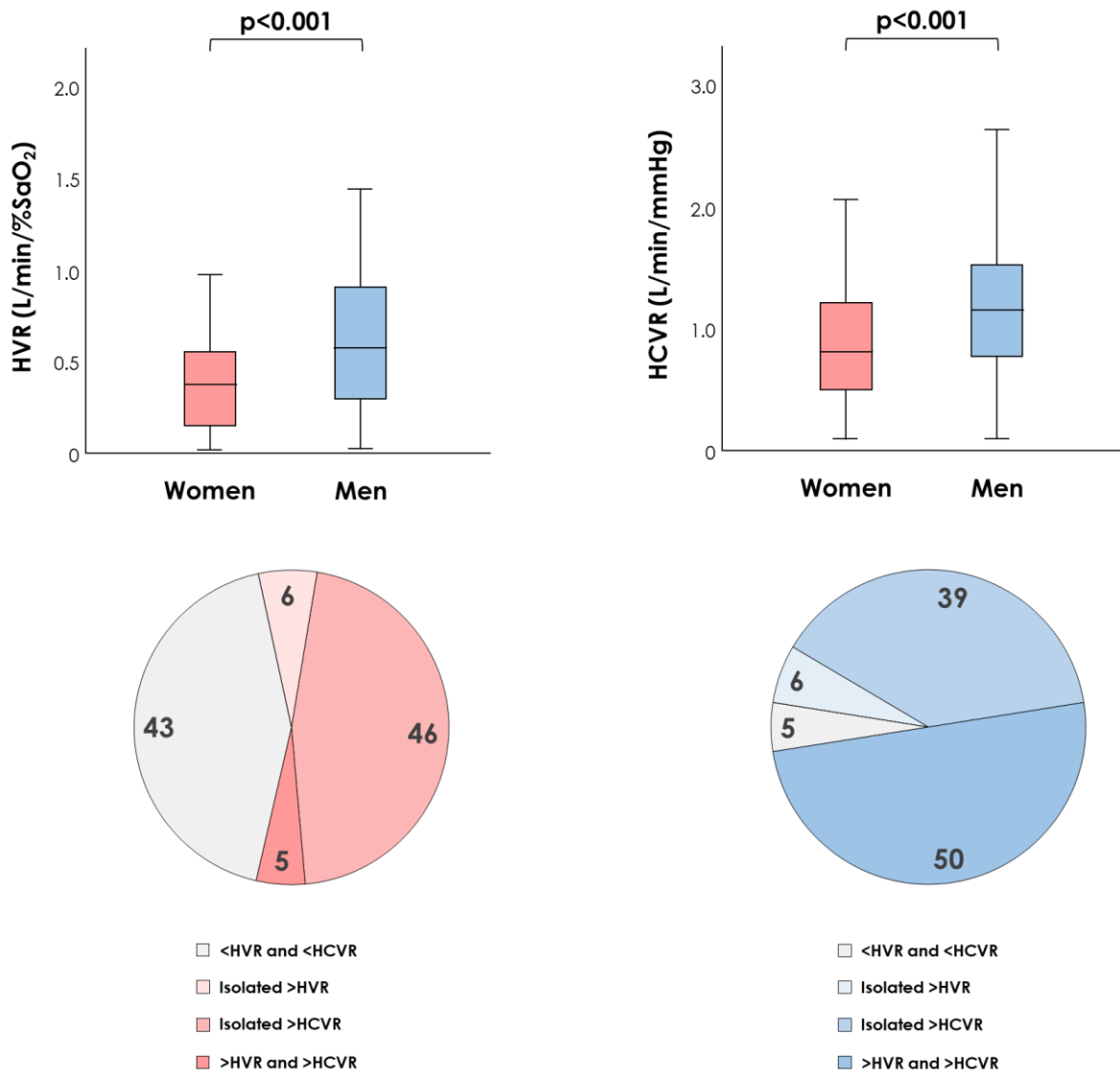
**Figure S2. Sex-related differences in central apneas burden after propensity-score matching.**

AHI: apnea-hypopnea index; CAI: central apnea index.



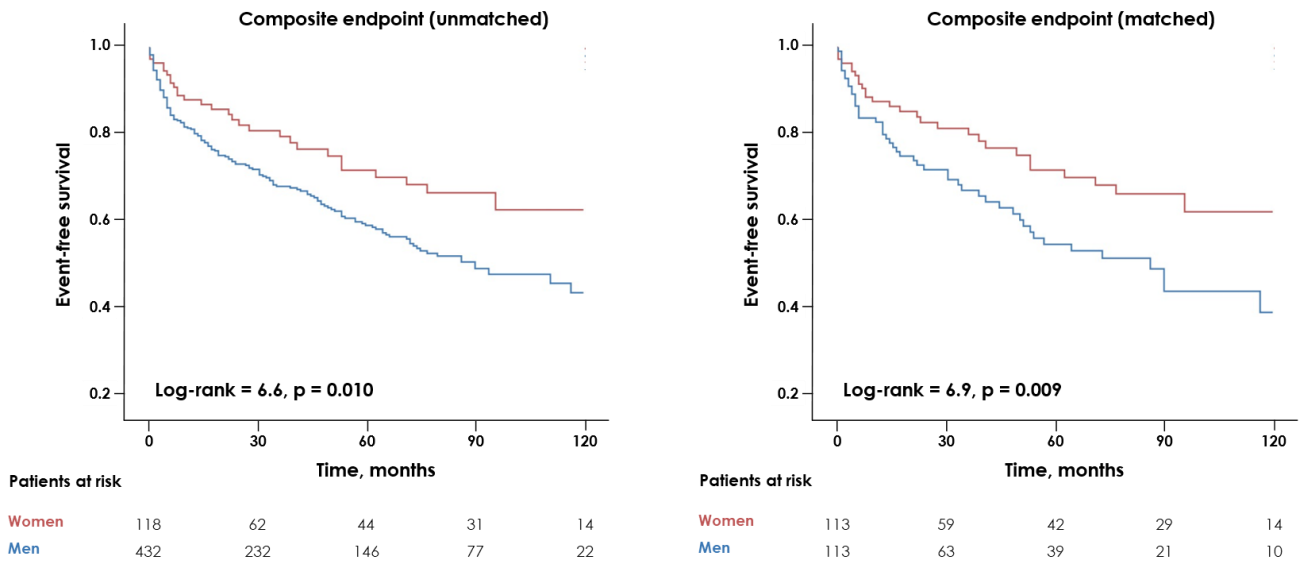
**Figure S3. Sex-related differences in chemoreflex sensitivity after propensity-score matching.**

HCVR: hypercapnic ventilatory response; HVR: hypoxic ventilatory response.





**Figure S4. Kaplan-Meier curves for the primary endpoint according to sex before and after propensity-score matching.**



**Figure S5. Kaplan-Meier curves for the primary combined endpoint of cardiac death, appropriate ICD-shock, or first hospitalization for HF according to daytime AHI, nighttime AHI, and nighttime CAI in the study population and according to sex after propensity-score matching.**

AHI: apnea-hypopnea index; CAI: central apnea index; HF: heart failure; ICD: implantable cardioverter-defibrillator.

