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FULL RESEARCH PAPER
Heart failure and cardiomyopathies

Clinical and prognostic significance of central and obstructive apnoeas in patients with transthyretin cardiac amyloidosis

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Aims Central apnoea (CA) and obstructive apnoea (OA) are highly prevalent in patients with chronic heart failure (HF), and transthyretin cardiac amyloidosis (ATTR-CA) is an increasingly recognized HF aetiology. This study aims to investigate the prevalence and impact of CA and OA in patients with ATTR-CA.

Methods and results Consecutive patients with ATTR-CA who underwent 24 h ambulatory cardiorespiratory monitoring were enlisted for an evaluation of the prevalence and severity of breathing disorders. The severity of these disorders was quantified using the apnoea–hypopnoea index (AHI). Accordingly, the patients were categorized as having normal breathing (NB, AHI <5 events/h), OA (AHI ≥5 events/h with >50% being obstructive), or CA (AHI >5 events/h with ≥50% being central). The primary endpoint at follow-up was all-cause mortality. Out of 142 patients enrolled ($n = 142$, aged 77 ± 7 years, 91% males, 96% wild-type ATTR-CA), considering the 24 h monitoring, 20% had NB (39% at daytime and 8% at nighttime), 35% had CA (45% at daytime and 39% at nighttime), and 45% had OA (25% at daytime and 54% at nighttime). After a median 2.3-year (1.4–3.3 years) follow-up, 24 h, daytime, and nighttime AHIs were higher in non-survivors vs. survivors (all $P < 0.05$), independently of the prevalent apnoea type ($P = 0.64$). At multivariable regression analysis (adjusted for the possible clinical, echocardiographic, and biohumoral confounders), nighttime AHI ≥30 events/h {hazard ratio 2.37 [95% confidence interval (CI) 1.07–5.23], $P = 0.033$} and high-sensitivity troponin T [hazard ratio 2.43 (95% CI 1.42–4.17), $P = 0.001$] were predictors of mortality.

Conclusion Both CA and OA are highly prevalent, both at daytime and nighttime, in patients with ATTR-CA and are associated with higher mortality.

Lay summary This study investigated the prevalence and prognostic significance of central apnoea (CA) and obstructive apnoea (OA) in 142 patients with transthyretin cardiac amyloidosis.

Both CA and OA were highly prevalent during the whole 24 h period, with only 20% were classified as having normal breathing [meant as an apnoea–hypopnoea index (AHI) <5 events/h during the 24 h period]. Obstructive apnoea was more frequent than CA, particularly during the night, while the prevalence of CA increased with worsening left ventricular systolic and diastolic dysfunctions.

At follow-up, 24 h, daytime, and nighttime AHIs were higher in non-survivors vs. survivors, independently of the prevalent apnoea type, and at multivariable regression analysis (adjusted for the possible clinical, echocardiographic, and biohumoral confounders), nighttime AHI ≥30 events/h was an independent predictor of mortality.

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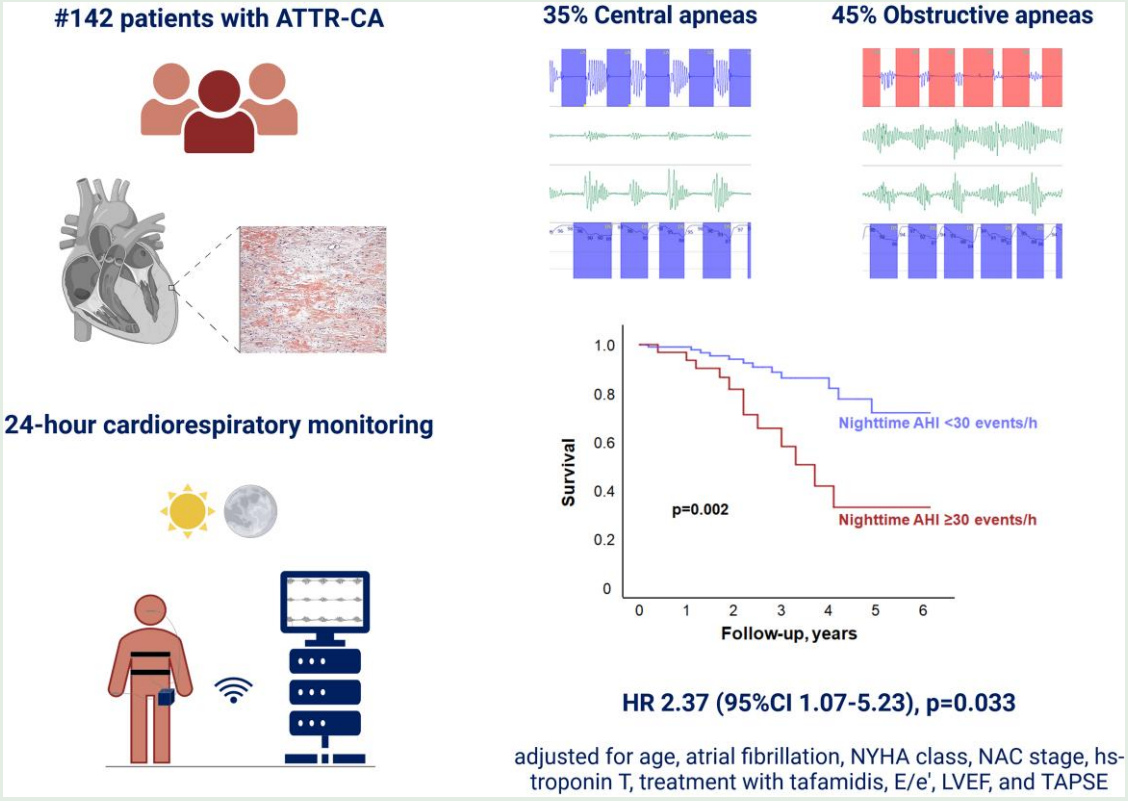
Graphical Abstract



Clinical and prognostic significance of central and obstructive apnoeas in patients with transthyretin cardiac amyloidosis. Central and obstructive apnoeas are highly prevalent in patients with transthyretin cardiac amyloidosis, and a severe apnoea/hypopnoea burden is associated with increased mortality. ATTR-CA, transthyretin cardiac amyloidosis; HR, hazard ratio; LVEF, left ventricular ejection fraction; NAC, National Amyloidosis Centre; NYHA, New York Heart Association; TAPSE, tricuspid annular plane systolic excursion.

Keywords Cardiac amyloidosis • Central apnoeas • Obstructive apnoeas • Periodic breathing • Cheyne–Stokes respiration

Introduction

Cardiac amyloidosis is a group of infiltrative cardiomyopathies secondary to the extracellular deposition of misfolded proteins.[1] Transthyretin cardiac amyloidosis (ATTR-CA) and immunoglobulin light-chain cardiac amyloidosis (AL-CA) are the two most common forms of cardiac amyloidosis.[1,2]

Cardiac amyloidosis has been classified among restrictive cardiomyopathies, as it is characterized by wall stiffness and diastolic dysfunction secondary to amyloid infiltration and myocardial pseudohypertrophy.[3] However, left ventricular (LV) systolic dysfunction often coexists.[4] Accordingly, while cardiac amyloidosis is an increasingly recognized cause of heart failure (HF) with preserved LV ejection fraction (LVEF) (HFpEF, ≥50%),[5] it may also present as or evolve into HF with mildly reduced LVEF (HFmrEF, 41–49%) or reduced LVEF (HFrEF, ≤40%).[6]

Following recent advances in diagnostic and therapeutic tools,[7] ATTR-CA is increasingly diagnosed in the cardiovascular setting and is no longer considered a rare disease, as recently confirmed in a screening study, showing a 0.46% prevalence of ATTR-CA in subjects ≥65 years.[8] A deeper understanding of the pathophysiological mechanisms and prognostic drivers of the disease is hence warranted to improve risk stratification and offer tailored therapies for patients with ATTR-CA.

Breathing disorders are highly prevalent in patients with HF and are associated with higher morbidity and mortality irrespective of LVEF.[9] While obstructive apnoeas (OAs) are sleep-related phenomena, secondary to the collapse of the upper airways,[10] central apnoeas (CAs) occur also in awake[11] and upright patients with HF,[12] elicited by increased chemoreflex sensitivity, plant gain, and circulatory delay.[13] Furthermore, OAs are more frequently observed in HFpEF, while the prevalence and severity of CA increase with worsening LV systolic and diastolic dysfunctions.[14]

Because the clinical significance of breathing disorders has been scarcely investigated in patients with ATTR-CA,[15] this study aimed to assess the prevalence, correlates, and prognostic impact of either daytime or nighttime breathing disorders in a contemporary cohort of patients with ATTR-CA.

Methods

Subjects and study design

Consecutive patients with a diagnosis of ATTR-CA referred to the outpatient clinic of the Fondazione Monasterio (Pisa, Italy) between April

2016 and June 2023 were prospectively enrolled to undergo cardiorespiratory monitoring to investigate the prevalence and severity of breathing disorders (as detailed in the following). Severe physical and/or cognitive impairment, severe pulmonary disease, and treatment with therapies potentially influencing breathing control [e.g. opioids, theophylline, oxygen, and continuous positive airway pressure (CPAP)] were considered as exclusion criteria.

As mentioned previously, 24 h ambulatory cardiorespiratory monitoring (Somté PSG2; Compumedics, Abbotsford, VIC, Australia) was used in the study and included nasal airflow, chest and abdominal respiratory movements by inductance plethysmography belts, and oxygen saturation by a pulse oximeter.[16] As recommended by guidelines,[17] apnoeas were defined as the cessation of airflow for ≥10 s and classified as either obstructive or central based on the presence/absence of respiratory movements. Hypopnoeas were defined as a reduction in airflow ≥50%, lasting for ≥10 s, with a reduction in oxygen saturation ≥4%. The severity of breathing disorders was quantified through the apnoea–hypopnoea index (AHI) for the whole 24 h period, with daytime defined as the period between 7:00 a.m. and 9:59 p.m. and nighttime as the period between 10:00 p.m. and 6:59 a.m..[16,17] Apnoeic events during the daytime were considered only in the setting of periodicity, excluding pauses due to speaking, drinking, or eating. Patients with a 24 h AHI <5 event/h were classified as having normal breathing (NB), while patients with a 24 h AHI ≥5 event/h were classified as having either CA or OA according to the prevalent phenotype (>50% of events being obstructive or central, respectively). As recommended,[17] a severe apnoea burden was considered as an AHI ≥30 events/h. Finally, the burden of oxygen desaturation was calculated as the time spent with a saturation <90% (T-90, minutes).

Beyond the cardiorespiratory monitoring, at enrolment, all patients underwent a standard transthoracic echocardiography (IE33 or Epiq7; Philips Medical Systems, Palo Alto, CA, USA) to assess chamber dimension and systolic and diastolic functions, according to intersociety guidelines.[18] For biohumoral analysis, haemoglobin, estimated glomerular filtration rate (eGFR, CKD-EPI formula), N-terminal pro-B-type natriuretic peptide (NT-proBNP; Roche Diagnostics assay), and high-sensitivity troponin T (hs-troponin T; Roche Diagnostics assay) were collected from all patients. According to the eGFR and NT-proBNP values, patients were classified into three severity stages [i.e. National Amyloidosis Center (NAC) stages], as proposed by Gillmore *et al.*[19]

All patients were followed up at the outpatient clinic of Fondazione Monasterio until 31 December 2023 for the endpoint of all-cause death. The outcome status was determined from the medical records or telephone interviews with patients, relatives, or general practitioners.

Before enrolment, an informed consent was obtained from all patients involved in this study, which was approved by the Institutional Review Board Committee of Fondazione Monasterio and conducted in accordance with the Declaration of Helsinki of the World Medical Association.

Statistical analysis

Quantitative values were presented as mean ± standard deviation or median [inter-quartile range (IQR)] according to distribution, while qualitative values as numbers and/or percentages.

Clinical, biohumoral, echocardiographic, and cardiorespiratory monitoring parameters were compared among patients classified as having NB, CA, or OA. The mean differences were compared by a one-way analysis of variance or Kruskal–Wallis test as appropriate, with a Bonferroni *post hoc* correction. Discrete variables were compared by the χ^2 test with Yates's correction. A Pearson's correlation analysis was performed to identify the clinical characteristics associated with a severity of breathing disorders.

For survival analysis, patients were dichotomized according to the presence of severe breathing disorders (i.e. AHI ≥30 events/h) during the whole 24 h period, at daytime, or at nighttime. Accordingly, the Kaplan–Meier method with log-rank statistics was used to estimate survival. The prognostic significance of CA vs. OA was compared as well.

The independent prognostic values of 24 h, daytime, and nighttime AHI were determined by a stepwise multivariable Cox proportional hazards model, adjusted for other well-known risk predictors in patients with ATTR-CA, namely patient age, atrial fibrillation, New York Heart Association (NYHA) class, NAC stage, hs-troponin T, treatment with tafamidis or continuous positive airway pressure (CPAP), *E*/*e'* average, LVEF, and tricuspid annular plane systolic excursion (TAPSE). Significant univariable predictors ($P < 0.05$) were considered as possible confounders and included in the multivariable analysis, while non-significant variables were omitted in a stepwise fashion, according to the *P*-values. Non-normally distributed variables were log-transformed before entering regressions.

A statistical analysis was performed by using R statistical software (version 3.4.0, The R Foundation for Statistical Computing, Vienna, Austria). A two-tailed *P*-value <0.05 was considered significant.

Results

Study population

The study population consisted of 142 patients (mean age 77 ± 7 years, 91% males, 96% with wild-type ATTR-CA, and 4% with hereditary ATTR-CA). Most patients complained of dyspnoea, 23, 53, and 24% being classified as NYHA Classes I, II, and III, respectively. The mean LVEF was 51% (9%), with 62, 19, and 19% classified as HFpEF, HFmrEF, and HFrEF, respectively. The mean eGFR was 62 (18) mL/min/1.73 m^2, and the median NT-proBNP was 2203 (IQR 850–4853) ng/L. Accordingly, 78 (55%), 45 (32%), and 19 (13%) patients were classified as having NAC Stages I, II, and III, respectively. Most patients had diastolic dysfunction, classified as Grades II and III in 37 and 34% patients, respectively, while 36 (25%) patients had atrial fibrillation at the time of examination. At enrolment, 19 (13%) patients were treated with tafamidis for a median of 7-month period (range 1–32 months).

Prevalence, severity, and clinical correlates of breathing disorders

During the 24 h period, breathing disorders were highly prevalent in the study population, with only 20% of patients (39% at daytime and 8% at nighttime) identified as having NB (*Figure 1*). While OA was the most common phenotype during the 24 h period (45%), the prevalence of CA (35%) increased with worsening LV systolic and diastolic functions (*Figure 1*). Furthermore, while OAs were more prevalent and severe at nighttime (53%, with 29% of patients having an AHI ≥15 events/h), the prevalence of CA was similar at daytime (36%, with 17% of patients having an AHI ≥15 events/h) and at nighttime (39%, with 27% of patients having an AHI ≥15 events/h; *Figure 2*). No significant differences were observed among groups as for clinical features and therapies (*Table 1*), though patients with CA had more dilated left atria and LV and lower LVEF than patients with OA (*Table 2*). Compared with patients with OA, those with CA had a higher AHI at both daytime and nighttime and a higher T-90 (*Table 2*). Detailed data about the number of apnoea/hypopnoea events at daytime, at nighttime, and during the 24 h period and about oxygen saturation are reported in Supplementary material online, *Table S1*. As reported in Supplementary material online, *Table S2*, no significant differences were observed when comparing the prevalence and severity of breathing disorders among patients with a different Perugini scoring system at nuclear imaging.

Daytime AHI was associated with worse symptoms, higher biomarker levels, worsening LV systolic and diastolic functions, and mitral regurgitation severity (*Table 3*), whereas nighttime AHI was significantly

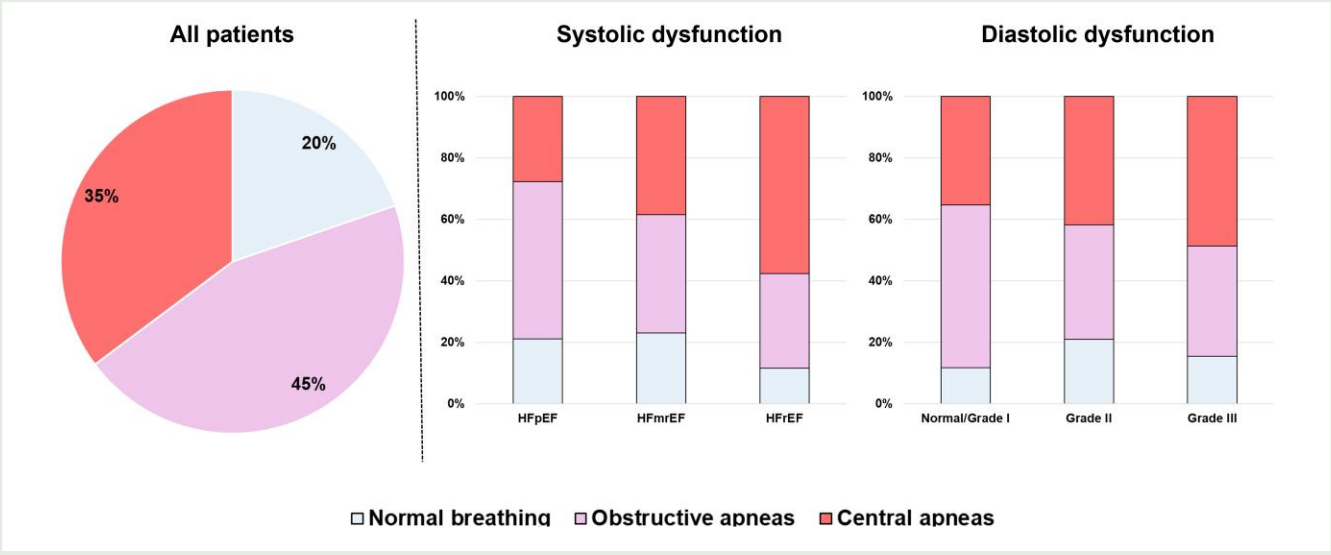


Figure 1 Prevalence of breathing disorders in patients with transthyretin cardiac amyloidosis according to the severity of either systolic or diastolic dysfunction. Patients with transthyretin cardiac amyloidosis show high prevalence of breathing disorders during the 24 h period. Notably, the prevalence of central apnoeas increases with worsening left ventricle systolic and diastolic dysfunctions.

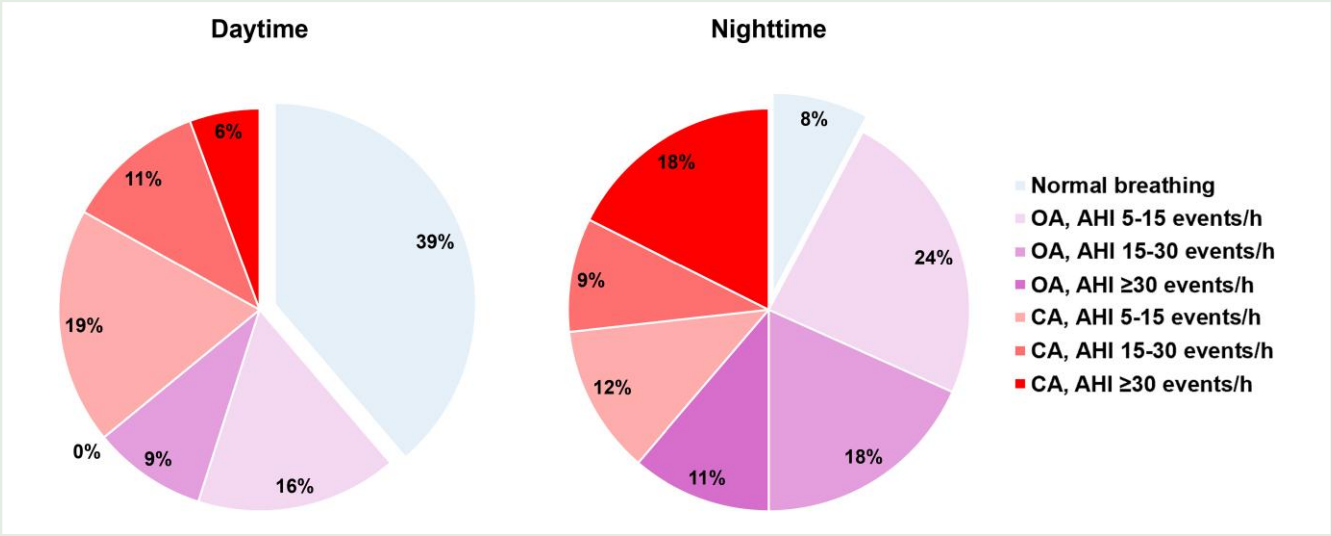


Figure 2 Severity of breathing disorders at daytime and at nighttime in patients with transthyretin cardiac amyloidosis. In patients with transthyretin cardiac amyloidosis, both central apnoea and obstructive apnoea were observed during the 24 h period, although they were more prevalent and severe at nighttime.

associated with NT-proBNP and hs-troponin T levels and mitral regurgitation severity (*Table 3*).

Prognostic significance of breathing disorders

During a median 2.3-year (IQR 1.4–3.3 years) follow-up, 27 (19%) patients died. Compared with survivors, non-survivors had a significantly higher AHI at daytime, at nighttime, and during the 24 h period (*Figure 3*). As shown in the Kaplan–Meier curves in *Figure 4*, severe breathing disorders during the whole 24 h period, at daytime, or at nighttime were significantly associated with a higher mortality. No difference was observed when comparing patients with CA vs. OA according to the prevalent apnoea phenotype (log-rank 0.22, $P = 0.64$).

At adjusted regression analysis, only nighttime AHI ≥30 events/h {hazard ratio 2.37 [95% confidence interval (CI) 1.07–5.23], $P = 0.033$} and log-transformed hs-troponin T [hazard ratio 2.43 (95%CI 1.42–4.17), $P = 0.001$] remained as independent predictors of mortality.

Discussion

The prevalence and clinical significance of daytime and nighttime breathing disorders in patients with ATTR-CA were investigated for

Table 1 Characteristics of the study population according to the breathing patterns

Variables	All patients ($n = 142$)	Normal breathing ($n = 28$) (20%)	Obstructive apnoeas ($n = 64$) (45%)	Central apnoeas ($n = 50$) (35%)
Clinical features				
Age, years	77 ± 7	77 ± 6	77 ± 6	77 ± 8
Men, *n* (%)	129 (91)	23 (82)	59 (92)	47 (94)
BMI, kg/m^2	28 ± 4	27 ± 3	28 ± 4	28 ± 4
NYHA III, *n* (%)	32 (24)	7 (25)	14 (23)	11 (24)
Atrial fibrillation, *n* (%)	36 (28)	9 (38)	13 (22)	14 (32)
NT-proBNP, ng/L	2203 (850–4853)	1969 (719–3579)	2203 (1057–4550)	2262 (884–5780)
eGFR, mL/min/1.73 m^2 (SD)	62 ± 18	63 ± 19	61 ± 18	62 ± 20
NAC Stage I, *n* (%)	78 (55)	17 (61)	37 (58)	24 (48)
NAC Stage II, *n* (%)	45 (32)	6 (21)	21 (33)	(18 36)
NAC Stage III, *n* (%)	13 (19)	5 (18)	6 (9)	8 (16)
Hs-troponin T, ng/L	44 (32–66)	36 (27–53)	48 (33–71)	45 (32–62)
Comorbidities				
Hypertension, *n* (%)	87 (61)	14 (50)	42 (66)	31 (62)
Diabetes, *n* (%)	25 (18)	6 (21)	10 (16)	9 (18)
CAD, *n* (%)	34 (24)	4 (14)	17 (27)	13 (26)
COPD, *n* (%)	15 (11)	1 (4)	9 (14)	5 (10)
Hb, g/dL (SD)	14 (2)	13 (2)	14 (2)	14 (2)
Baseline treatment				
Tafamidis, *n* (%)	19 (13)	3 (11)	12 (19)	4 (8)
Beta-blockers, *n* (%)	92 (79)	22 (85)	35 (59)	35 (75)
ACEi/ARB, *n* (%)	71 (54)	15 (58)	30 (51)	26 (55)
ARNI, *n* (%)	6 (5)	1 (4)	2 (3)	3 (6)
MRA, *n* (%)	38 (29)	9 (35)	17 (29)	12 (26)
SGLT2i, *n* (%)	13 (10)	4 (15)	5 (9)	4 (9)
Furosemide, *n* (%)	85 (64)	16 (62)	37 (63)	32 (68)
PM, *n* (%)	9 (7)	2 (7)	3 (5)	4 (8)
ICD, *n* (%)	7 (5)	4 (14)	1 (2)	2 (4)
CRT, *n* (%)	1 (1)	0 (0)	0 (0)	1 (2)

Values are mean ± SD, median (inter-quartile range), or *n* (%).
ACEi, angiotensin converting-enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; ICD, implantable cardioverter–defibrillator; MRA, mineralocorticoid receptor antagonists; NAC, National Amyloidosis Center; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PM, pacemaker; SGLT2i, sodium–glucose cotransporter-2 inhibitors.

the first time. Both CA and OA were highly prevalent in this subset, and similar to other HF cohorts, a severe apnoea/hypopnoea burden was a predictor of mortality independent of possible confounders.

To the best of our knowledge, only a single study has been previously reported on sleep-disordered breathing in patients with cardiac amyloidosis, which included 39 patients with ATTR-CA (22 mutated and 17 wild-type) and 31 patients with AL-CA who underwent an overnight unattended polygraphy.[15] Conversely, our study predominantly focused on patients with wild-type ATTR-CA undergoing 24 h cardiorespiratory monitoring. Indeed, considering the clinical and prognostic differences between patients with ATTR-CA and those with AL-CA, including both groups may have influenced survival analysis. Despite these differences, in both populations OAs were more prevalent than CAs and the prevalence of nighttime breathing disorders (90%) in the previous study[15] was very close to the 92% observed in our larger cohort. In this respect, the epidemiological characteristics of breathing disorders in patients with ATTR-CA do not seem to be different from those reported in patients with HF across the LVEF spectrum.[9] Indeed, at least during nighttime, OAs were more frequent in patients with HFpEF, while the prevalence of CA increased with worsening LVEF in line with previous findings in a large population ($n = 700$) of patients with HF.[14] This is not surprising considering that LV systolic dysfunction directly affects circulation time, which is a key pathophysiological determinant of CA.[20] Furthermore, in the present study, diastolic dysfunction and left atrium enlargement were associated with a higher prevalence of CA. Chemoreflex sensitization, secondary to increased filling pressure, may be, in this case, a potential mechanism, as it has been demonstrated in HF.[21]

A higher AHI was an independent predictor of outcomes in this population, consistent with previous studies in populations with HF.[11,22–24] Conversely, oxygen desaturation, as expressed by the T-90, was not a predictor of mortality in the current study. This finding seems contradictory to what was observed in the study by Bodez *et al.*,[15] in which nocturnal desaturation, but not AHI, was an independent predictor of outcomes in patients with either AL-CA or ATTR-CA. However, as noted by the same authors, including patients with AL-CA

Table 2 Echocardiographic and cardiorespiratory monitoring parameters of the study population according to the breathing pattern

Variables	All patients, $n = 142$	Normal breathing, $n = 28$ (20%)	Obstructive apnoeas, $n = 64$ (35%)	Central apnoeas, $n = 50$ (45%)
Echocardiography				
LAVi, mL/m^2	41 ± 9	40 ± 9	39 ± 8	44 ± 11 †
Severe MR, *n* (%)	4 (3)	0 (0)	1 (2)	3 (6)
E/e'	17 ± 6	16 ± 5	17 ± 7	18 ± 7
LVEDVi, mm/m^2	55 ± 18	52 ± 13	51 ± 20	60 ± 18 †
LVMI, g/m^2	168 ± 43	165 ± 45	167 ± 39	170 ± 45
LVEF, %	51 ± 10	52 ± 8	52 ± 9	48 ± 11 †
HFpEF, *n* (%)	90 (62)	19 (68)	46 (72)	25 (50) †
HFmrEF, *n* (%)	26 (19)	6 (21)	10 (16)	10 (20)
HFrEF, *n* (%)	26 (19)	3 (11)	8 (12)	15 (30) †
TAPSE, mm	18 ± 5	18 ± 5	18 ± 4	17 ± 5
sPAP, mmHg	40 ± 9	40 ± 10	40 ± 9	41 ± 9
Cardiorespiratory monitoring				
24-h AHI, events/h	12 (5–22)	3 (2–4)	12 (8–17) *	21 (11–31) *,†
Daytime AHI, events/h	7 (3–15)	1 (1–2)	8 (4–13) *	14 (7–22) *,†
Nighttime AHI, events/h	17 (9–31)	6 (4–9)	19 (13–29) *	29 (16–42) *,†
T90, min	20 (12–43)	11 (7–23)	20 (13–42)	28 (14–65) *,†

Values are mean ± SD, median (inter-quartile range), or *n* (%).
AHI, apnoea–hypopnoea index; CAI, central apnoea index; LAVI, left atrial volume index diameter; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MR, mitral regurgitation; RVD, right ventricular diameter; sPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; T-90, percentage of time asleep with $SaO_2 < 90\%$.
*$P < 0.05$ vs. normal breathing; †$P < 0.05$ vs. obstructive apnoeas.

may have influenced this result. Indeed, these patients, characterized by poorer outcomes at follow-up, had a substantially higher T-90 (almost double that of patients with ATTR-CA) despite a lower AHI.[15] It is possible that mechanisms other than apnoeas or hypopnoeas contributed to the desaturation burden in these patients, including more severe lung congestion (as suggested by higher NT-proBNP values and worse NYHA class), pulmonary hypertension, or other pulmonary comorbidities. Conversely, it can be hypothesized that different mechanisms contribute to the detrimental effects of breathing disorders in patients with ATTR-CA. Among these, the haemodynamic consequences of apnoea- and hyperventilation-related thoracic pressure swings may be particularly harmful in the case of restrictive cardiac physiology.[25] Additionally, sympathetic surges resulting from intermittent chemoreflex stimulation due to recurrent hypoxia and hypercapnia may contribute to adverse cardiac remodelling and increase the risk of life-threatening arrhythmias.[26,27] Given these different findings, further studies investigating the pathophysiological consequences of breathing disorders in patients with ATTR-CA are necessary.

Similar to previous observations in HF,[11,12,28] CAs were not only a sleep-related phenomenon in patients with ATTR-CA, but also a daytime occurrence, with at least moderate (AHI ≥15 events/h) CA breathing disorders documented in 17% of the patients. Importantly, daytime AHI was associated with worse symptoms (higher NYHA class), greater neurohormonal activation, and ongoing cardiac damage, as indicated by higher plasma levels of NT-proBNP and hs-troponin T, as well as worse LV systolic and diastolic dysfunctions. These findings further underscored the importance of screening for breathing disorders not only during sleep time but also during the whole 24 h period in patients with HF secondary to different aetiologies, including ATTR-CA. However, contrary to previous reports in patients with HFrEF,[11,12] daytime AHI was not an independent predictor of mortality in the current study. The low prevalence of severe forms (only 6% of patients had a daytime AHI ≥30 events/h) might have underpowered the prognostic analysis for daytime AHI. Nevertheless, as chronically reduced cardiac output contributes to the sensitization of chemoreceptors, chemoreflex sensitivity may be lower in patients with ATTR-CA, whose LV systolic function is generally preserved. Considering that cardiac output is usually higher during the day,[29] this may contribute to the lower severity and prognostic value of daytime AHI. Conversely, the sleep-related reduction in cardiac output and increased filling pressure secondary to rostral fluid shift may exert opposing effects during the night in this subset, increasing circulatory delay and chemoreflex stimulation.[21] This may explain the stronger association between nighttime AHI and mortality. Considering the possible therapeutic implications (as discussed in the following), further studies evaluating the determinants of daytime and nighttime CA in patients with ATTR-CA are needed.

While no studies have investigated the benefits of treating breathing disorders in ATTR-CA, different strategies have been tested in patients with HF.[30,31] Although reducing the apnoea burden, mask-based ventilation systems failed to improve hard outcomes.[32–34] Accordingly, in the latest ADVENT-HF trial, enrolling 731 patients with chronic HF (LVEF ≤45%) and an AHI ≥15 events/h, the adaptive servo-ventilation system did not affect the primary outcome (a composite of mortality, cardiovascular hospitalization, new onset atrial fibrillation or flutter, and appropriate cardioverter–defibrillator shock), irrespective of the prevailing apnoea type (CA or OA).[34] Alternative options are emerging

Table 3 Clinical, humoral, and echocardiographic correlates of breathing disorders in patients with transthyretin cardiac amyloidosis

	24 h AHI		Daytime AHI		Nighttime AHI	
Variables	**ρ coefficient (95% CI)**	***P***	**ρ coefficient (95% CI)**	***P***	**ρ coefficient (95% CI)**	***P***
Age	0.12 (−0.04–0.29)	0.127	0.14 (−0.02–0.29)	0.095	0.11 (−0.05–0.27)	0.184
BMI	0.07 (−0.12–0.25)	0.471	−0.02 (−0.20–0.17)	0.847	0.09 (−0.09–0.27)	0.346
NYHA class	0.19 (0.02–0.35)	**0.025**	0.22 (0.05–0.38)	**0.008**	0.12 (−0.05–0.29)	0.153
Atrial fibrillation	−0.09 (−0.25–0.09)	0.360	−0.06 (−0.23–0.19)	0.531	−0.10 (−0.28–0.07)	0.222
eGFR, mL/min/1.73 m^2	−0.18 (−0.36–0.01)	0.053	−0.20 (−0.37–(−0.01))	**0.034**	−0.16 (−0.34–0.02)	0.086
NT-proBNP, ng/L	0.30 (0.14–0.44)	**<0.001**	0.42 (0.26–0.56)	**<0.001**	0.17 (0.01–0.33)	**0.042**
NAC stage	0.18 (0.02–0.34)	**0.029**	0.25 (0.09–0.39)	**0.003**	0.11 (−0.06–0.27)	0.208
hs-troponin T, ng/L	0.25 (0.07–0.42)	**0.008**	0.28 (0.09–0.45)	**0.003**	0.19 (0.00–0.37)	**0.047**
Tafamidis	−0.09 (−0.25–0.08)	0.286	−0.11 (−0.27–0.05)	0.182	−0.04 (−0.21–0.12)	0.625
Beta-blockers	−0.10 (−0.07–0.27)	0.247	−0.08 (−0.08–0.26)	0.316	−0.08 (−0.09–0.25)	0.352
ACEi/ARB	−0.06 (−0.23–0.11)	0.452	−0.05 (−0.22–0.12)	0.585	−0.08 (−0.25–0.09)	0.368
MRA	0.01 (−0.16–0.18)	0.904	−0.02 (−0.19–0.15)	0.804	0.06 (−0.11–0.23)	0.501
SGLT2i	−0.05 (−0.22–0.12)	0.552	0.04 (−0.13–0.21)	0.657	−0.08 (−0.25–0.09)	0.334
LAVi, mL/m^2	0.15 (−0.02–0.33)	0.084	0.21 (0.04–0.37)	**0.018**	0.05 (−0.11–0.21)	0.539
MR severity	0.29 (0.13–0.44)	**<0.001**	0.35 (0.19–0.49)	**<0.001**	0.19 (0.02–0.35)	**0.029**
E/e'	0.14 (−0.03–0.33)	0.113	0.19 (0.02–0.36)	**0.030**	0.12 (−0.04–0.27)	0.139
LVMI	0.05 (−0.13–0.22)	0.601	0.12 (−0.05–0.29)	0.162	0.03 (−0.21–0.14)	0.706
LVEF, %	−0.22 (−0.38–(−0.06))	**0.009**	−0.18 (−0.34–(−0.01))	**0.034**	−0.16 (−0.32–0.01)	0.065
TAPSE, mm	−0.12 (−0.28–0.06)	0.172	−0.16 (−0.32–0.01)	0.056	0.03 (−0.15–0.20)	0.761
sPAP, mmHg	0.10 (−0.08–0.27)	0.267	0.09 (−0.08–0.27)	0.299	0.10 (−0.08–0.27)	0.267

Abbreviations as in *Tables 1* and *2*.

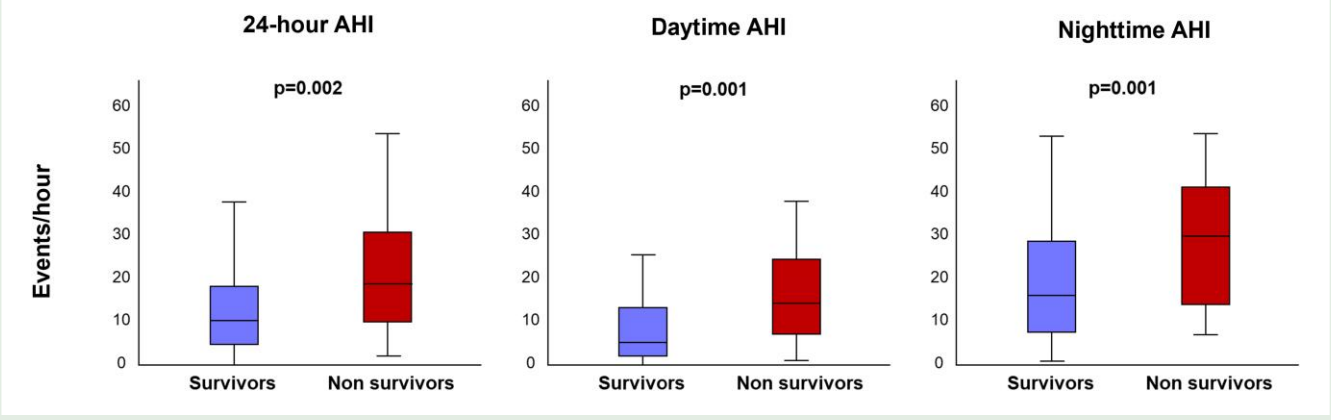


Figure 3 Severity of breathing disorders in survivors vs. non-survivors among patients with transthyretin cardiac amyloidosis. The severity of breathing disorders—expressed as the apnoea–hypopnoea index across the whole 24 h period, at daytime, or at nighttime—was higher in survivors vs. non-survivors.

to treat breathing disorders in a more rational and pathophysiology-based fashion. As regards OA, mandibular advancement devices seem promising to improve patient compliance,[35] while novel bioelectronic and pharmacological approaches are under investigation.[31] As regards CA, while optimizing HF drug treatment should always represent the first step,[36] the pharmacological modulation of the overactive chemoreflex seems an intriguing opportunity, also considering its pathophysiological and independent prognostic role.[26,27,37]

Study limitations

Considering the cross-sectional design of the study, the longitudinal changes in apnoea prevalence and severity over time remain to be investigated in patients with ATTR-CA, particularly in response to disease-modifying therapies (e.g. tafamidis) or tailored treatments (e.g. continuous positive airway pressure or oxygen). Within the study population, 16 patients with a nighttime AHI ≥30 events/h and prevalent OA were referred for pulmonological evaluation to determine the

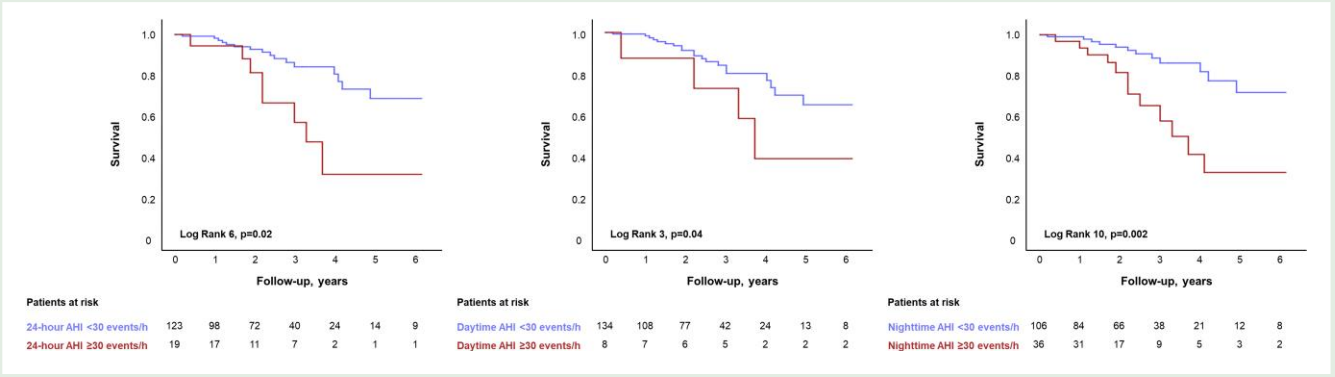


Figure 4 Prognostic value of severe breathing disorders in patients with transthyretin cardiac amyloidosis. In patients with transthyretin cardiac amyloidosis, a higher apnoea–hypopnoea index across the whole 24 h period, at daytime, and at nighttime was associated with a higher risk of all-cause death during follow-up.

appropriateness of specific therapeutic interventions. A domestic CPAP therapy was recommended to eight of these patients, with five initiating the treatment. However, the CPAP therapy was not a significant predictor of mortality at regression analysis. While this is likely due to the small number of patients treated, considering the findings of this study, the inclusion of patients with ATTR-CA should be considered in future studies on the treatment of breathing disorders. In the present study, unattended cardiorespiratory monitoring was used instead of in-hospital polysomnography. Nonetheless, although the use of this method did not allow for the assessment of arousal and sleep stages, it reduces costs and discomfort for the patients and provides data about the whole 24 h period, which could be of potential interest.[11,12,16] Male sex, increased body mass index, and anatomical features of the neck and upper airways are the main determinants of OA in the general population,[10] while increased chemoreflex gain, plant gain, and circulatory delay are the main determinants of CA in patients with HF.[13] Although no substantial difference in sex distribution and body mass index was observed in our population among the groups, future dedicated studies are expected to investigate the pathophysiological determinants of breathing disorders in patients with ATTR-CA. In patients with HFmrEF and HFrEF, the prognostic impact of CA seems higher in female patients than in male patients.[16] As in the present study, the majority of patients (91%) were male, and the existence of sex-related differences was not addressed and remains to be investigated in this subset. In this study, reflecting a contemporary real-life cohort, most of the patients had wild-type ATTR-CA; therefore, no comparison between wild-type and hereditary ATTR-CA was drawn. Considering that hereditary ATTR is a heterogeneous syndrome with a broad spectrum of clinical manifestations (cardiac, neurological, and mixed),[38] future studies should assess the prevalence and clinical significance of apnoeas in these patients. Because of the retrospective design of the study and the absence of a dedicated registry, the precise cause and time of death of the patients could not be retrieved. Considering the chronobiological features of breathing disorders and their link with life-threatening cardiovascular events, this analysis should be addressed by future prospective studies.

Conclusions

Breathing disorders including CA and OA are highly prevalent in patients with ATTR-CA, both at daytime and nighttime, likely contributing to disease severity and poor outcome.

The findings of this study should therefore stimulate future research towards the following: (i) screen patients with ATTR-CA for breathing disorders to improve clinical severity characterization and risk prediction; (ii) evaluate the pathophysiological determinants of CA and OA in these patients and assess the effects of disease-modifying therapies on their prevalence, severity, and prognostic impact; and (iii) consider the inclusion of patients with ATTR-CA when designing future studies investigating the potential benefit of targeting breathing disorders through tailored interventions.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Author contribution

F.G., A.G., M.E., G.V., and C.P. contributed to the conception or design of the work. A.A., V.C., F.B., G.I., and E.D. contributed to the acquisition, analysis, or interpretation of data for the work. F.G., A.A., and V.C. drafted the article. A.G., M.E., G.V., and C.P. critically revised the article. All authors gave their final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Data availability

The data underlying this article are available upon reasonable request to the corresponding author.

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