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Cheyne-Stokes respiration related oscillations in cardiopulmonary hemodynamics in patients with heart failure☆

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ABSTRACT

Background: Although Cheyne-Stokes respiration (CSR) is an oscillatory phenomenon, the direct effects of cyclical hyperventilation and apnea on cardiopulmonary hemodynamics have been poorly investigated. The aim of the study was to examine the echocardiographic changes associated with CSR phases in a group of patients with systolic heart failure (HF) and daytime CSR.

Methods: 14 HF patients (age 70 ± 9 years, LVEF 24 ± 5) underwent a thorough clinical evaluation, 24-h respiratory polygraphy, chemoreflex evaluation by rebreathing technique and neuro-hormonal assessment. Furthermore, they received a simultaneous echocardiographic and respiratory monitoring embedding the respiratory signal in the echocardiographic machine.

Results: All patients had daytime CSR (diurnal apnea-hypopnea index, AHI: 18.5, interquartile range: 15.3–39.5 events/h). Systolic pulmonary artery pressure and pulmonary vascular resistances (PVR) increased from hyperventilation to apnea (H 45.3 ± 11.4 vs A 52.4 ± 13.8 mmHg, $p = 0.004$, and H 3.3 ± 2.5 vs A 5.1 ± 3.2 Wood units, $p = 0.0003$, respectively), while acceleration time of the pulmonary artery decreased (H 110.1 ± 19.8 vs A 92.0 ± 19.9 ms, $p = 0.001$). During apnea a reduction of right and left ventricular outflow tract VTI (H 12.8 ± 4.9 versus A 9.9 ± 3.1, $p = 0.002$ and H 26.9 ± 8.8 versus A 22.8 ± 7.9 mm, $p = 0.006$, respectively), and a reduction in tricuspid annular plane systolic excursion (H 15.9 ± 4.4 versus A 14.4 ± 4.1 mm, $p = 0.005$) were also observed. Notably, PVR variation strongly correlated with chemosensitivity to hypercapnia ($R = 0.89$, $p = 0.0004$) and plasma norepinephrine level ($R = 0.78$, $p = 0.003$).

Conclusions: In HF patients with CSR, an increase in pulmonary pressure and pulmonary vascular resistances was observed during apnea. Pulmonary vasoconstriction strongly correlated with chemosensitivity to hypercapnia and indexes of adrenergic activation.

1. Introduction

Patients with chronic heart failure (HF) often present with Cheyne-Stokes respiration (CSR), a kind of periodic breathing characterized by a crescendo-decrescendo pattern, with alternating cycles of hyperventilation and central apnea, associated with phasic oscillations in respiratory gases [1]. CSR is present throughout the 24-h period, being observed in up to 60% of patients during the nighttime, and in 30% during the daytime [2]. While in some patients CSR has been viewed as compensatory [2], in a subset of patients with HF (depending on CSR severity and background triggers) CSR has been considered as a potential determinant of negative outcome, due to either increased arrhythmic risk or worsening hemodynamics [2], facilitated by increased sympathetic activation [3,4], despite neurohormonal drug antagonism including beta-blockers. Although CSR is an oscillatory phenomenon, its periodic nature has been often overlooked. Nonetheless, oscillations in respiratory gases and chemoreflex outflow actually occur during CSR cycles. In particular, during central apneas the undesirable coincident presence of hypercapnia and hypoxia does occur, with hypoxia also extending during early hyperventilation, at an extent depending on individual circulatory delay. While in the systemic circulation those

Abbreviations: AHI, apnea-hypopnea index; CAI, central apnea index; CSR, Cheyne-Stokes respiration; FAC, fractional area change; HCVR, hypercapnic ventilatory response; HF, heart failure; HVR, hypoxic ventilatory response; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal fraction of proB-type natriuretic peptide; PVR, pulmonary vascular resistances; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; T-90, time spent with oxygen saturation < 90%.

☆ These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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gas variations cause vasodilation, in the pulmonary circulation they induce vasoconstriction [5]. Furthermore, hypoxia and hypercapnia may also increase the adrenergic outflow to the pulmonary circulation via chemoreflex stimulation [6,7]. This supplementary adrenergic vasoconstrictive drive is indeed physiologically plausible considering the deep ramification of the sympathetic system throughout the pulmonary vascular tree in humans [8] and the relevant increase of the chemoreflex gain in patients with HF and CSR [6,7,9]. On the other hand, during hyperventilation recovery of respiratory gases realizes and may at least partially reverse, what happens during apnea [2].

While the influence of the periodic nature of CSR on blood gases and autonomic function has been studied, the direct effects of cyclical hyperventilation and apnea on cardiopulmonary hemodynamics have been poorly investigated. We aimed at: a) assessing potential changes in cardiopulmonary haemodynamics during different phases of CSR; b) correlating them with the background chemoreflex gain and with measures of adrenergic activity, by analyzing prolonged simultaneous echocardiographic and respiratory recordings during stable diurnal CSR.

2. Methods

2.1. Subjects and study design

Outpatients diagnosed with chronic HF and CSR during the daytime were prospectively recruited at the Fondazione Toscana Gabriele Monasterio, Pisa, Italy. Inclusion criteria were: echocardiographic evidence of left ventricular ejection fraction (LVEF) <50%; tricuspid regurgitation, allowing a reliable determination of systolic pulmonary artery pressure (SPAP); a diurnal apnea-hypopnea index (AHI) ≥15 events/h.

Exclusion criteria were: New York Heart Association (NYHA) class IV or impossibility of comfortably lying in a recumbent position, acute coronary syndrome, episodes of acute HF or cardiac resynchronization therapy within 6 months before examination, severe renal dysfunction (i.e. estimated glomerular filtration rate, eGFR <30 ml·min^{-1}), severe pulmonary disease as assessed by standard spirometry (vital capacity and total lung capacity <50% of predicted value, FEV1 < 50% of predicted value, and FEV1/FVC < 70%), obstructive sleep apnea (OSA), and treatment with drugs affecting ventilation such as morphine or derivatives, theophylline, oxygen, benzodiazepines or acetazolamide or with noninvasive positive pressure ventilation.

The study design, completed within 3 days, included a thorough clinical evaluation, complete 2-dimensional (2D) Doppler echocardiography with simultaneus assessment of respiration via inductance plethysmography, 24-h cardiorespiratory monitoring (Somtè, Compumedics, Abbotsford, Australia) for CSR detection, as previously described [3,10], evaluation of the chemosensitivity to hypoxia and hypercapnia, by assessment of the individual hypoxic-normocapnic (HVR) and normoxic-hypercapnic ventilatory response (HCVR), by rebreathing technique as previously described [6,7]; neuro-hormonal evaluation including natriuretic peptides, norepinephrine, direct plasma renin and aldosterone, with plasma blood samples withdrawn at 8 am from an antecubital vein after a 30-min rest in supine position [11] and 24-h electrocardiographic recording.

Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

2.2. Simultaneous respiratory and echocardiographic assessment

Echocardiographic images were obtained using a Philips IE33 Ultrasound machine, with S5–1 transducer (Philips Medical Systems, Palo Alto, California, USA).

A pre-protocol screening 2D echocardiography was performed to identify patients with suitable echocardiographic windows. Parameters of left ventricular (LV) chamber dimension, systolic and diastolic function, right ventricular (RV) chamber dimension and function and continuous wave, pulsed wave and tissue Doppler measures were sampled and analyzed according to guidelines recommendations [12,13,14].

After a baseline recording, a prolonged echocardiography was performed embedding in the echocardiography machine a respiratory signal obtained by inductance plethysmography. Patients were asked to remain awake during the echocardiographic recording. To correct for random variation in the echocardiographic signals a prolonged scanning was performed, with each parameter sampled for at least one complete CSR cycle (60 s on average). To allow this long continuous recording, the echocardiographic screen was duplicated through a visual system (Virtual Dub, Version 1.10.4, Avery Lee, GNU General Public License) on a second personal computer. The video frame of interest was then analyzed off-line, after measure calibration using a dedicated software (Sobox Image Viewer, Version 2.3.0.1) by two independent operators (VR and CT), obtaining 9 measures for each variable in each CSR phase (3 measures for early, mid and late apnea and 3 measures for early, mid and late hyperpnea), which were then averaged to correct for potential sampling inconsistencies. Considering that some variability was also present between inspiration and expiration, for hyperpnea only, each of the 9 samples was obtained by averaging values recorded at peak expiration and peak inspiration (18 samples).

2.3. Statistical analysis

Statistical analysis was performed using SPSS 21.0 program (1989–2012, IBM Corporation, USA). Values are presented as mean ± standard deviation (SD) for variable with normal distribution or median and interquartile range (IR) for variables with skewed distribution. Mean differences between groups were evaluated through paired *t*-test or Wilcoxon signed-rank test, when appropriate. The Pearson correlation coefficient was used to describe the correlation between different numerical variables, after logarithmic transformation for variables with a skewed distribution. From pilot data, we calculated (G Power 3.1 version) a sample size of 12 patients in order to detect (Wilcoxon signed-rank test) significant differences (p value of 0.05 and a power of 80%) in SPAP between apnea and hyperventilation. To ensure robustness of our findings we then recruited 14 patients.

3. Results

Fourteen patients finally matched our entry criteria and were enrolled in the study (Table 1). Patients were more frequently male and had a higher prevalence of ischemic etiology. All patients presented with severe LV systolic dysfunction, pulmonary hypertension and RV impairment. The majority of them also showed severe diastolic dysfunction, while only one third of them also showed severe mitral regurgitation or atrial fibrillation. All patients had moderate-severe CSR throughout the 24 h and increased chemoreflex sensitivity, associated with relevant neurohormonal activity, mainly expressed by high norepinephrine and natriuretic peptide plasma levels, despite optimal neurohormonal drug antagonism and device therapy.

3.1. CSR phase-related changes in cardiopulmonary haemodynamics

The variations of echocardiographic parameters during the different phases of CSR are summarized in Table 2. The typical behavior of echocardiographic variables is shown in the Fig. 1.

In the transition from hyperventilation to apnea, an average 16% increase in SPAP was observed (Fig. 2, panel a). The increase in SPAP was mirrored by a coherent reduction in the acceleration time of the pulmonary artery during apnea (Fig. 2, panel b). Considering the observed reduction in the right ventricular outflow tract velocity time integral (VTI) during apnea (Fig. 2, panel d), the increase in SPAP was largely driven by an average 55% increase in pulmonary vascular resistances (PVR) (Fig. 2, panel c). SPAP during phases of stable breathing (observed in only 10 subjects due to entry criteria) was lower than SPAP during apneas (42.9 ± 13.3 vs 51.5 ± 15.9, p = 0.003) and similar SPAP during hyperventilation (42.9 ± 13.3 vs 43.1 ± 12.5, p = 0.95).

Focusing on right chambers, a slight reduction in the tricuspid annular plane systolic excursion was found during apnea, while no significant variation in right ventricular diameters, areas and fractional area change was observed (Table 2). With regard to the left heart, a reduction atrial area (Fig. 2, panel e), in E wave velocity (Fig. 2, panel f) and in left ventricular outflow tract VTI (Fig. 2, panel h), left ventricular stroke volumes and cardiac index (Table 2) was found during apnea. On the contrary, no significant change in left ventricular diameters, volumes and LVEF (Fig. 2, panel g) was observed during different CSR phases (Table 2, all p > 0.05).

The PVR variation, observed in the shift from hyperventilation to apnea, strongly and directly correlated with chemosensitivity to hypercapnia (R = 0.89, p = 0.0004, Supplemental Fig. 1, panel a). Chemosensitivity was calculated only in 10 subjects, due to the persistence of CSR in 4 patients during the rebreathing tests, despite the hypoxic and hypercapnic stimuli. Likewise, PVR variation also correlated with norepinephrine levels (R = 0.78, p = 0.003, Supplemental Fig. 1, panel c). The chemosensitivity to hypercapnia also correlated with SPAP variation (R = 0.7, p = 0.018, Supplemental Fig. 1, panel b) and with norepinephrine plasma levels (R = 0.60, p = 0.04, Supplemental Fig. 1, panel d). In patients with sinus rhythm (n = 9), the PVR variation also inversely correlated with the 24-h heart rate standard deviation from Holter 24-h recording (R = -0.89, p = 0.015). On the contrary, neither PVR variation nor SPAP variation

Table 1
Clinical characteristics of the study population (n = 14).

	HF patients with CSR
Number	14
Age (years)	69.9 ± 9.3
Male (%)	93
BMI (kg/m^2)	28.3 ± 5.6
Creatinine (mg/dl)	1.6 ± 0.6
Ischaemic/idiopathic (%)	64/36
NYHA class III (%)	50
Atrial fibrillation (%)	36
NSVT (%)	29
Heart rate SD (ms)	72 ± 27
LVEF (%)	24.4 ± 4.9
Diastolic dysfunction, grade 1–2/3 (%)	29/71
Mitral regurgitation, grade 0–2/3 (%)	71/29
SPAP (mmHg)	48.2 ± 16.0
PVR (mmHg/L/min)	4.4 ± 2.4
RV parasternal diameter (mm)	31.9 ± 5.2
TAPSE (mm)	14.8 ± 4.6
FAC (%)	24.8 ± 6.2
Norepinephrine (ng/L)	874.5 (722.3–1071.3)
Direct plasma renin (μU/mL)	291.4 (36.0–422.0)
Aldosterone (ng/L)	106.5 (50.8–147.0)
NT-proBNP (ng/L)	5081.5 (2097.0–9911.8)
pH	7.46 (7.43–7.47)
pO2 (mmHg)	83.0 (74.0–93.0)
pCO2 (mmHg)	34.0 (30.0–37.0)
HVR (L/min/%)	0.68 ± 0.32
HCVR (L/min/mmHg)	1.55 ± 0.47
Diurnal AHI (events/h)	18.5 (15.3–39.5)
Nocturnal AHI (events/h)	33.0 (23.5–38.0)
24-h AHI (events/h)	25 (17.5–39.0)
Diurnal CAI (events/h)	9.0 (4.5–22.0)
Nocturnal CAI (events/h)	30.0 (11.5–35.0)
24-h CAI (events/h)	16.0 (11.0–28.0)
Diurnal OAI (events/h)	0 (0–0)
Nocturnal OAI (events/h)	0 (0–0.6)
24-h OAI (events/h)	0 (0–0.2)
Maximal apnea duration (sec)	38.5 (27.8–48.0)
SaO2 min (%)	83.0 (78.0–85)
T-90 (min)	13.0 (7.0–17.0)
Beta-blockers (%)	100
ACE inhibitors-ARBs (%)	78
Mineralocorticoid receptor antagonists (%)	86
Diuretics (%)	93
Digoxin (%)	17
CRT-ICD (%)	67

AHI: apnea-hypopnea index; ACE: angiotensin converting enzyme; ARBs: angiotensin receptor blockers; AHI: apnea hypopnea index; BMI: body mass index; CAI: central apnea index; CRT: cardiac resynchronization therapy; FAC: fractional area change; HCVR: hypercapnic ventilatory response; HVR: hypoxic ventilatory response; ICD: implantable cardioverter defibrillators; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; NT-proBNP: amino terminal prohormon of brain natriuretic peptide; PVR: pulmonary vascular resistances; RV: right ventricle; SD: standard deviation; TAPSE: tricuspid annular plane systolic excursion; T90: time spent with oxygen saturation < 90%; NSVT: nonsustained ventricular tachycardia.

correlated with the chemosensitivity to hypoxia, diurnal, nocturnal and 24-h AHI, diurnal, nocturnal as well as with 24-h CAI, minimal SaO2 and T-90 (all $p > 0.05$). Likewise, no correlation was found between PVR/SPAP variation and hyperpnea, apnea and cycle length durations (all $p > 0.05$).

4. Discussion

In this study we first report the phase-related oscillatory changes in cardiopulmonary hemodynamics throughout CSR cycle in patients with HF. In the transition from hyperventilation to central apneas, a 16% increase in SPAP occurs, related to a 55% increase in PVR, even considering the decrease in cardiac output associated with the loss of respiratory mechanical support to circulation observed during apnea. Indeed, during apnea a decrease in the VTI of the right ventricle was observed. Focusing on left chambers, a reduction in left atrial and ventricular filling, as well as in stroke volume and cardiac index was observed. Notably, a strong correlation between the variation in pulmonary vascular resistances and both chemosensitivity to hypercapnia and indexes of increased adrenergic outflow was observed.

4.1. CSR, hemodynamics and prognosis in HF

It is estimated that one HF patient out of 2 experiences CSR during the night and one out of 3 also during the day [2], as in the original description made by Cheyne and Stokes [15]. The phenomenon has been associated with higher adrenergic activity, even in patients on beta-blocker therapy [16], so that CSR has been suggested as a major cause of "adrenergic escape" in HF and as a risk factor for sudden death [17] or aborted sudden death in ICD recipients [18]. This hypothesis has been argued by the study of Mansfield and colleagues, in which apneas (central/obstructive) were no more independently associated with sympathetic nerve activity at multivariate analysis, when incorporating mean pulmonary pressure [19]. In Mansfield study, pulmonary pressure was related to HF severity, neglecting the potential influence of CSR on pulmonary pressure and sympathetic activation was evaluated by norepinephrine spillover, a static measure not reflecting oscillations of adrenergic discharge, which are likely to happen during CSR.

Nonetheless, in several studies CSR has been indeed associated with increased mortality in HF [3,20,21,22]. A recent study in a population on guideline recommended treatment reports that up to 82% of deaths in systolic HF patients with CSR are due to HF progression, while 10% are due to sudden death [3], similarly to previous reports, showing HF progression related death (21 to 82%) being prevalent over sudden death in this clinical scenario (3 to 57%) [3,19,20,21,22]. In this respect, in patients with CSR not only pulmonary hypertension [9], but also RV dilation and dysfunction [19,22] are frequently observed. In the current study, 79% of patients presented with RV dilation and 66% with RV dysfunction (Table 1), a known mortality risk factor in HF [22]. This may partly justify the potential harm of treatments negatively impacting on right ventricular preload and function, such as assisted support ventilation as in the SERVE-HF trial [23,24].

4.2. Incresed chemoreflex gain, the culprit bystander

In patients with HF, it is now well acknowledged that CSR is mainly caused by an increased chemosensitivity to both hypoxia and hypercapnia [6,7,25]. Other CSR determinants are chemoreflex delay, related to increased circulatory time [27], and increased plant gain, the latter so far only mathematically hypothesized [25,28]. It is generally believed, that the higher is the chemoreflex gain the wider is the ventilatory overshoot, while the larger is the chemoreflex delay the longer is the CSR duration [6,26]. Therefore, it is possible that in patients with very low cardiac output (as in our patients) the increased cycle length might paradoxically decrease the AHI (i.e. the longer the cycle, the lesser the number of cycles per minute), partially impacting on its potential to stratify CSR severity. On the contrary, the level of background chemoreflex gain may not only drive to CSR, but also mediate, beyond ventilation, the level of adrenergic discharge for each apneic event [6,7,29]. It is therefore, not surprising that in our population only the chemoreflex sensitivity to hypercapnia, but not the AHI, correlated with norepinephrine levels and with the PVR and SPAP variation observed during apnea.

More surprisingly, neither the chemosensitivity to hypoxia, nor indexes related to oxygen desaturation correlated with PVR/SPAP variation. This might be related to the choice of comparing the whole hyperpnea phase, with the whole apnea phase. It is known that the nadir in oxygen levels is indeed achieved with some delay after apnea, depending on circulatory delay and lung oxygen stores [1]. It is therefore likely that hypoxia and the chemosensitivity to hypoxia would exert their effects during the first phase of hyperventilation.

Table 2
Echocardiographic changes associated with different phases of CSR.

	Hyperventilation	Apnea	Absolute change	P value
SPAP (mmHg)	45.3 ± 11.4	52.4 ± 13.8	7.1 (2.7/11.5)	0.004
RV outflow VTI (mm)	12.8 ± 4.6	10.1 ± 3.1	−2.7 (−1.2/−4.3)	0.002
PVR (mmHg/L/min)	3.3 ± 2.5	5.1 ± 3.2	1.9 (1.1/5.2)	0.0002
Pulmonary artery AT (ms)	110.1 ± 19.8	92.0 ± 19.7	−18.1 (−9.5/−26.6)	0.001
Right atrial area (cm^2)	31.3 ± 6.5	31.6 ± 7.1	0.3 (−1.4/2.0)	0.73
RV diameter (mm)	32.2 ± 5.3	33.2 ± 6.5	0.0 (−1.3/1.2)	0.99
RVEDA (cm^2)	25.9 ± 4.4	26.8 ± 5.7	0.9 (−1.4/3.4)	0.42
RVESA (cm^2)	18.4 ± 4.5	19.3 ± 5.3	0.9 (−1.2/2.9)	0.37
TAPSE (mm)	15.8 ± 4.3	14.4 ± 3.9	−1.3 (−0.5/−2.2)	0.004
FAC (%)	28.9 ± 9.0	28.0 ± 10.9	−0.9 (−4.3/2.6)	0.61
Left atrial area (cm^2)	34.8 ± 7.8	32.4 ± 6.7	−2.4 (−0.7/4.1)	0.01
E velocity (cm/s)	96.2 ± 36.3	90.1 ± 31.6	−6.7 (−0.4/11.7)	0.038
Mitral DT (ms)	190.8 ± 38.6	204.6 ± 60.9	13.9 (−6.7/34.6)	0.169
A velocity (cm/s)	43.2 ± 18.3	42.6 ± 17.8	−0.5 (−5.1/3.8)	0.76
E/A ratio	2.4 ± 1.6	2.5 ± 1.7	0.1 (−0.3/0.3)	0.82
Mean E'	6.5 ± 1.6	6.7 ± 1.7	0.2 (−0.1/0.6)	0.13
E/E' ratio	13.9 ± 4.7	13.4 ± 4.9	−0.4 (−1.5/0.6)	0.37
LVDV (ml)	268.4 ± 77.3	276.8 ± 74.6	8.4 (−6.6/23.6)	0.25
LVSV (ml)	203.8 ± 72.4	208.8 ± 72.3	5.0 (−5.6/15.7)	0.32
LVEF (%)	25.9 ± 6.3	26.3 ± 6.7	0.4 (−1.3/2.0)	0.65
LV outflow VTI (mm)	26.1 ± 8.8	22.2 ± 7.9	−3.8 (−1.4/−6.3)	0.005
LV stroke volume (ml)	69.2 ± 15.8	59.0 ± 16.3	−10.2 (−4.2/−16.1)	0.003
Cardiac index (L/min/m^2)	2.29 ± 0.53	1.98 ± 0.56	−0.29 (−0.09/−0.51)	0.009

DT: deceleration time; FAC: fractional area change; LV: left ventricle; LVDV left ventricular diastolic volume; LVEF: left ventricular ejection fraction; LVSV: left ventricular systolic volume; PVR: pulmonary vascular resistances; RV: right ventricle; RVEDA: right ventricular end diastolic area; RVESA: right ventricular end systolic area; SPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion; VTI: velocity time integral.
Absolute change in echocardiographic variables was expressed as mean (95% confidence interval).

4.3. Respiration, feedbacks and pulmonary vascular resistances

Left heart disease and in particular HF is the most common cause of pulmonary hypertension, being identified as group II by ESC guidelines [30]. In patients with HF the elevation of left atrial pressure drives to hydrostatic passive increase in pulmonary vascular pressure [31]. In some patients, a superimposed active component caused by pulmonary arterial vasoconstriction leads to "combined precapillary and postcapillary" pulmonary hypertension [30,31], and subsequently to right ventricular afterload and right ventricular failure [31].

Apneas are not currently considered among the pathophysiological mechanisms [29] leading to combined precapillary and postcapillary PH. However, a dynamic increase in pulmonary artery pressure, has been described during obstructive sleep apneas (OSA) [30], recorded either during echocardiography or right heart catheterization. Further, an increasing drift in average pulmonary pressure has been observed in patients with OSA during nighttime, beyond those dynamic changes [30].

In a study by Maze et al. [31], performed before the wide use of neurohormonal drug antagonism, a comparison of LV inflow and outflow was performed in HF patients with CSR, comparing only late hyperventilation and late apnea. A decrease in LV filling (reduction in E velocity) and LV outflow tract VTI was found during apnea, as in our study. Authors hypothesized that those findings could be related to a CSR induced variation in either LV diastolic function or, as we found, in pulmonary pressure and resistances.

Considering that central apneas are present also during the day (with a presumably higher total number of events throughout the 24-h period) [2], and that the background level of chemoreflex sensitivity is higher in central apneas than OSA [1,6,7], the degree of PVR variation increase is presumably higher in CSR (55% increase in the current study) than in OSA. On the other hand, due to the persistence of intrathoracic pressure swings during OSA, a lower decrease in RV stroke volume and a higher flow mediated support of pulmonary pressure is likely to occur during obstructive events [30].

It is currently unknown, whether the dynamic variation in PVR associated with CSR may also cause a stable drift in pulmonary pressure as in OSA. In a previous retrospective study from our group, we observed that patients with central apneas (24-h AHI ≥ 15 events/h) had higher average SPAP levels as compared with patients with stable breathing [9], as well as right ventricular dimensions and thickness. In this study, it seems that during CSR, SPAP would oscillate slightly above the average values observed during phases of normal breathing. Long-term recordings using a Swan Ganz catheter left in place for 24 h and comparing phases of CSR with phases of normal respiration in the same patient may help to unravel this important pathophysiological question in the future. Similarly, recording of muscle sympathetic nerve activity in humans and/or pulmonary sympathetic nerve activity in animals would also allow us to better understand whether CSR is always detrimental or compensatory [2].

During hyperventilation we found a decrease in PVR and SPAP and a positive increase in cardiac output. In this respect, our findings are coherent with a previous observation made by Oldenburg and coworkers [32], in which hyperventilation was shown to cause an increase in cardiac output, measured noninvasively in healthy volunteers (n = 15) and invasively in HF patients (n = 20). On the contrary, Yumino and colleagues found a decrease in cardiac output during hyperventilation in HF patients with central apneas [33]. However, they only compared the last 5 s of hyperventilation with the last 5 s of apnea and they derived cardiac output from digital photoplethysmography. In the peripheral circulation, the complex interaction between direct and indirect vascular effects of hypoxia-hypercapnia (causing vasodilation) and the chemoreflex (causing vasoconstriction) may justify the discrepancy between the work of Yumino and what observed in our study and in the study of Maze [31], based on echo-Doppler estimation of cardiac output and Oldenburg [32], based on cardiac catheterization.

The activation of chemoreceptors, driving to sympathetic activation, may also increase systemic vascular resistances, which were not measured in our study due to the lack of an acknowledged echocardiographic method. In previous studies based on different methods, systemic blood pressure was found to peak at the transition from late apnea to early hyperventilation [34,35]. This may be explained by the fact that the peak in adrenergic discharge, which is known to occur during central apnea [35], is likely to be sensed with some delay by finger-arterial blood pressure as compared to the central circulation

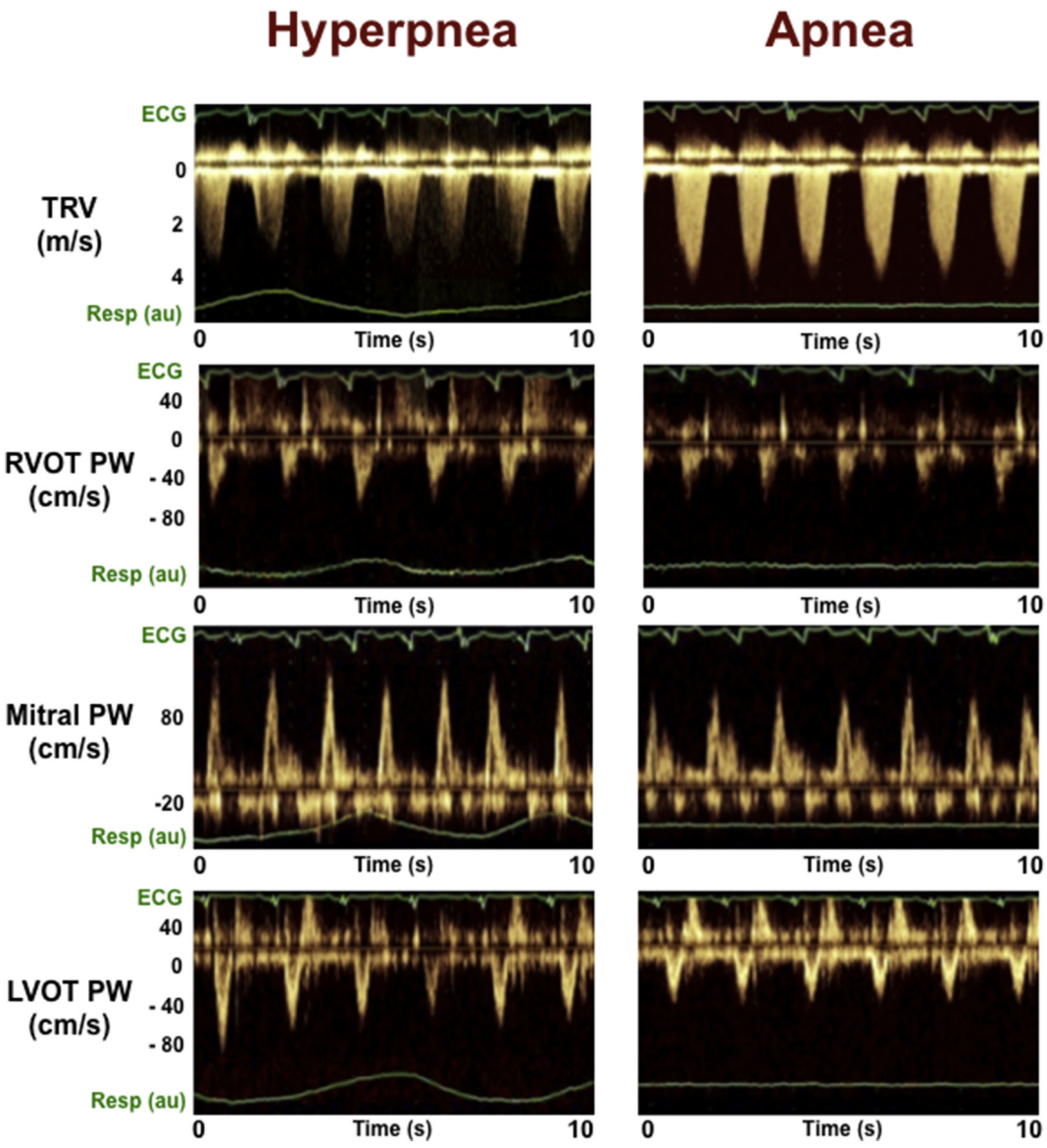

Fig. 1. Simultaneous echocardiographic and respiratory recording in different CSR phases. Simultaneous echocardiographic and respiratory recording in one sample patients showing the variation observed in echocardiographic variables from hyperventilation (right panels) to apnea (left panels). From top to bottom it was shown the CSR phase-related change in: tricuspid regurgitation velocity (TVR); right ventricular tract pulse wave Doppler (RVOT PW); mitral E velocity; left ventricular tract pulse wave Doppler (LVOT PW). The electrocardiogram (ECG) and respiratory traces (Resp) are shown in the upper and lower part of each panel.

[34], and smoothed by the vasodilatory effects of hypercapnia and hypoxia in the peripheral circulation. Nonetheless, future analyses concerning transitions between phases and involving both pulmonary and systemic circulation would be ideal.

4.4. Study limitations

This was a pilot study, in which we used an indirect echo estimation of cardiopulmonary hemodynamics. Therefore, data provided should be obviously confirmed by invasive right heart catheterization. However, the possibility to simultaneusly evaluate volumes, areas, pressures, flows and indexes of contractility and relaxation has suggested us to use echocardiography as the optimal exploratory methodology. In this respect, we should acknowledge that strain measures, especially of the left atrium and RV, might have provided further pieces of information. Nonetheless, we chose to use a visual system to allow a long recording to easily track CSR and to obtain repeated sampling for each variable throughout the whole CSR cycle, favouring reproducibility and consistency over sensitivity. The average of 9 samples for each variable in each CSR phase was helpful to correct for random variations, especially in patients with atrial fibrillation (36% of our population). Nonetheless, our results are in line with those of Oldenburg et al. showing at right heart catheterization an increase in cardiac output and a decrease in pulmonary vascular resistance in HF patients performing voluntary hyperventilation [32].

Finally, we only have a single respiratory signal embedded in the echo machine and thus we could not track respiratory gas variations during the recording. It is possible that, part of the haemodynamic response observed is directly caused by changes in oxygen and carbon dioxide at vascular level, beyond chemoreflex response. While the behavior of carbon dioxide is linear and foreseeable during apneas, the shape of oxygen variation can be less predictable. On the other hand, we can infer it from the 24-h cardiorespiratory monitoring in which we can follow oxygen saturation during the daytime, as a reliable approximation of what happens during the echocardiographic recording.

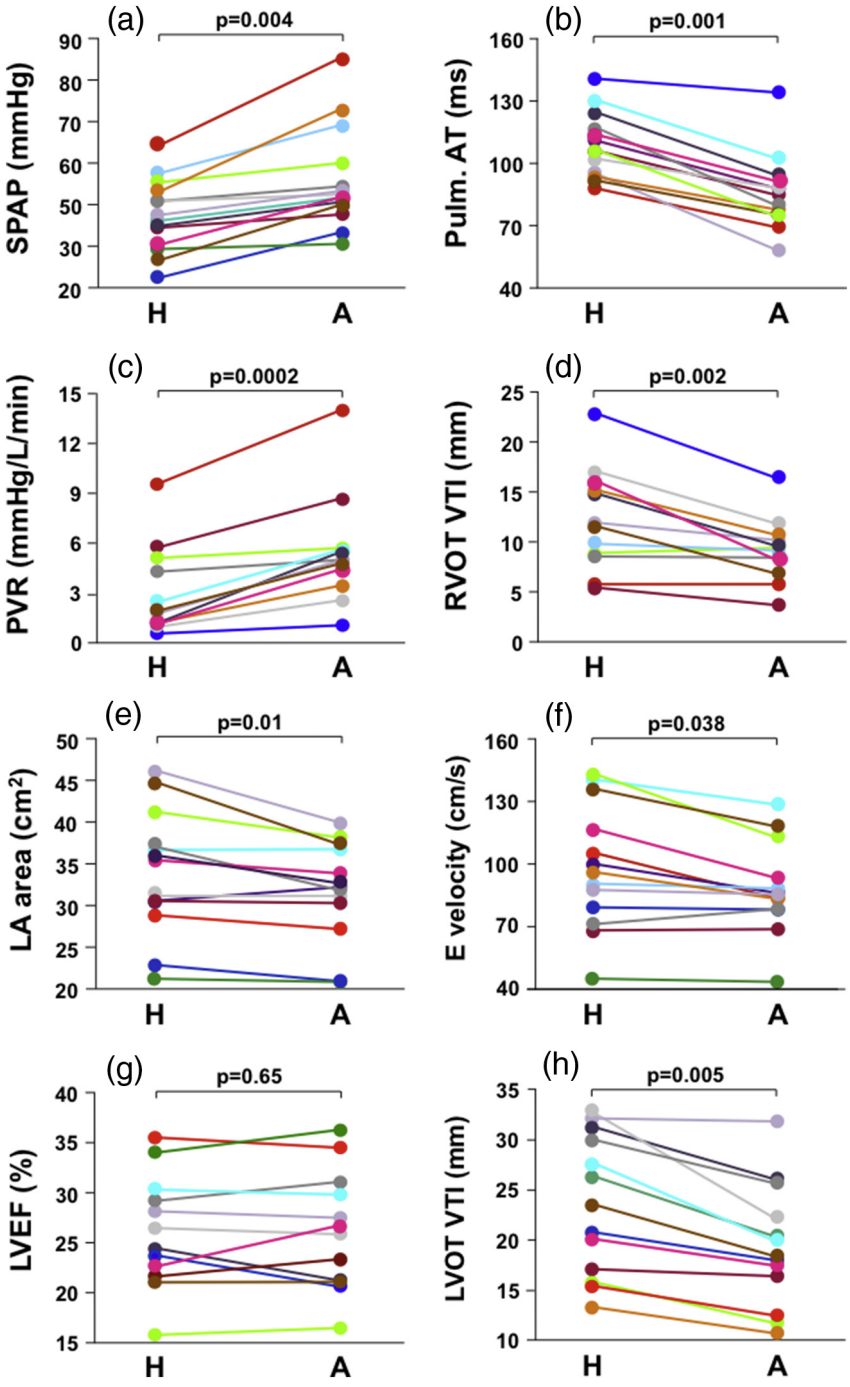

Fig. 2. CSR-related variations in right and left chamber variables. In the transition from hyperventilation (H) to apnea (A) a significant (16%) increase in systolic pulmonary artery variation (SPAP) was found (panel a) and was confirmed by a coherent decrease in the acceleration time (AT) of the pulmonary (pulm.) artery (panel b). The increase in SPAP was related to a relevant (55%) increase in pulmonary vascular resistances (PVR, panel c), considering the drop in right ventricular outflow tract velocity time integral (RVOT VTI, panel d). A decrease in left atrial (LA) area (panel e) and in the mitral E velocity (panel f) was observed in the transition from H to A, denoting a reduction in left ventricular preload. Despite similar left ventricular ejection fraction in the two CSR phases (panel g), a reduction of left ventricular stroke volume was testified by the decrease in left ventricular outflow tract velocity time integral (LVOT VTI, panel h).

Likewise, the apneas recorded during echocardiography were truly central, since the patients were awake during the daytime and no obstructive events were recorded at the 24-h respiratory recordings (daytime, nighttime and 24-h obstructive apnea index = 0 events/h, data not reported).

5. Conclusions

This was the first report to show the dynamic variation in cardiopulmonary hemodynamic during the different phases of CSR cycle. Pulmonary vascular resistances almost doubles during the apnea phase and strongly correlates with chemosensitivity to hypercapnia and adrenergic indexes. The prevalence of CSR in HF (50% of patients), its 24-h extent and the background chemoreflex/adrenergic overactivation makes it a potential contributor to reactive pulmonary hypertension, which deserve to be explored in future studies. Considering the significant variation in echocardiographic variables during CSR, this study also suggests the need to evaluate respiration beyond (and potentially through) electrocardiography during echocardiography, at least in patients with HF.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.03.033.

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Conflict of interest

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