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Respiratory drive in patients with chronic heart failure and central sleep apnea: Data from the Daunia Heart Failure Registry

Michele Correale [a], Giovanna Elisiana Carpagnano [b], Natale Daniele Brunetti [b,*], Lucia Forte [b], Ilenia Monaco [b], Armando Ferraretti [b], Roberto Sabato [a], Maria Pia Foschino Barbaro [b], Matteo Di Biase [b], Donato Lacedonia [b]

[a] Ospedali Riuniti University Hospital, Foggia, Italy
[b] Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy

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The prevalence of sleep disorders breathing (SDB) in patients with chronic heart failure (CHF) is relevantly high. According to prior studies, SDB is present in about 50% of patients with CHF and, among these, a great part are affected by Cheyne-Stokes Breathing (CSB) [1,2]. The presence of CSB in patients with CHF is considered to be an independent risk factor for increased overall mortality [3]. CSB usually occurs during non-REM sleep when chemical control of breathing predominates and is characterized by oscillations in tidal volume; alterations of respiratory control system are considered as related to decreased PaO_2, increased $PaCO_2$, circulatory delay, and reductions in systemic oxygen transport [4]. Thus, CSB does not simply characterize subjects with severe HF, but modifications of peripheral chemoreceptors consequent to HF seem to be involved in the genesis of this respiratory pattern [5].

However, central response to hypercapnia and the possible role in pathophysiology of CSB has not been fully investigated. There are different methods to measure the respiratory drive (RD) to hypercapnia, although the most commonly used are P0.1, the rebreathing technique, and the combination of both [6,7].

We therefore aimed to assess the possible correlations between RD and CSB in patients with CHF.

Between 1st November 2015 and 15 January 2016, a total of 28 consecutive outpatients with CHF with at least one hospitalization for HF and in stable clinical conditions, enrolled in the Daunia Heart Failure Registry as reported elsewhere [8,9,10,11,12], were assessed by nocturnal poligraphy: their clinical characteristics are given in Table 1.

Medical history, heart rate, systolic blood pressure, Body Mass Index, NYHA class, and medications were recorded.

All patients underwent conventional 2D echocardiography and then cardiopulmonary exercise testing (CPET) in order to evaluate exercise capacity (ramp and constant workload) in ambulatory setting and under resting conditions and then were followed up. In all patients the determination of RD was obtained, measuring by mouth occlusion pressure (P0.1) while breathing room air and during CO_2 rebreathing in ambulatory setting and under resting conditions (see details below).

Ambulatory cardio-respiratory overnight monitoring (Somtè-Compumedics, Australia) was performed, in accordance with standard criteria, during the patient staying at home. Sleep stages were not evaluated while flow by nasal cannula, thoracic and abdominal movement, snoring, sleep position, SaO_2 and heart rate were recorded. The study score was calculated by an expert in sleep medicine, who was unaware of the data relating to the cardiovascular characteristics of the subjects, according to the 2007 AASM (American Academy of Sleep Medicine) [13]. In particular obstructive apnea was scored when airflow was absent or reduced >90% (at least for 10 s) and in the presence of thoracic and/or abdominal movements, while CSA (Central Sleep Apnea) was determined in the absence of both movements. Hypopnea was defined as a flow reduction >30% associated with SaO_2 desaturation ≥4%. CSB was defined as at least three episodes of continuous cycles of waxing and waning tidal volumes with periods of hyperventilation separated by central apneas or hypopneas. The subjects were considered OSA (Obstructive Sleep Apnea) if the number of obstructive events was >50% of the total apnea/hypopnea index (AHI), while when central apnea associated to Cheyne-Stokes breathing was >50% the patients were considered CSB. Percentage of Cheyne-Stokes (%CS) was measured dividing time during patient have a typical CSB by all time of useful registration.

Subjects were seated comfortably, attached to the mouth piece with a nose clip in place. At randomized intervals, and without the subject's knowledge, the inspiratory side of the rebreathing circuit was occluded during late expiration. The pressure generated at 0.1 s after the onset of inspiration was obtained in each subject during several minutes with a minimum of 10 measurements prior to the rebreathing test [14].

* Corresponding author at: Cardiology Section, Department of Medical & Surgical Sciences, University of Foggia, Viale Pinto 1, 71122 Foggia, Italy.
E-mail address: natale.brunetti@unifg.it (N.D. Brunetti).

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Table 1
Population's characteristics and group comparison.

	CSB−		CSB+		
	N = 18 (65%)		N = 10 (35%)		
	Mean	SD	Mean	SD	P value
Age (years)	61	12	54	6	n.s.
Max heart rate (%)	72	16	58	19	n.s.
SBP (mmHg)	137	26	114	26	0.04
Weight (kg)	93	23	84	11	n.s.
Height (cm)	162	25	165.77	4.32	n.s.
BMI (kg/m2)	31.5	4	29.6	2.4	n.s.
Hypertension (%)	13 (76%)		6 (60%)		n.s.
Diabetes (%)	6 (35%)		2 (20%)		n.s.
COPD (%)	7 (41%)		4 (40%)		n.s.
Creatinine(mg/dl)	1.16	1.1	1.27	1.25	n.s.
NYHA III–IV (%)	4 (36.52%)		7 (70%)		0.01
LVEF (%)	42	12	35	8	n.s.
LVEDd (mm)	56	10	60	7	n.s.
LVESd (mm)	45	21	52	0	n.s.
LA diameter (mm)	45.1	5.5	47.7	4.9	n.s.
PAsP (mmHg)	28	11	30	13	n.s.
E (cm/s)	78.3	27.8	88.5	34.8	n.s.
A (cm/s)	84.7	31.5	71.9	26.1	n.s.
E/A	1.58	1.1	1.76	0.86	n.s.
E-DT (ms)	236.1	90.7	234.5	135.6	n.s.
E/E′	14.3	8.1	14.5	4.4	n.s.
ACE-inhibitors (%)	10 (62)		7 (70)		n.s.
ARB (%)	4 (25)		1 (10)		n.s.
Beta-blockers (%)	13 (81)		10 (100)		n.s.
Digoxin (%)	2 (12)		1 (10)		n.s.
Diuretics (%)	13 (77)		10 (100)		n.s.
VO_2 peak (ml/kg/min)	14.9	2.9	14.2	4.1	n.s.
VO_2/WR slope	10.1	2.4	10.0	2.2	n.s.
O_2 pulse	11.71	3.6	14.1	5.6	n.s.
RER	1.57	2.2	1.0	0.1	n.s.
% VE max	45.4	16.2	45.4	14.3	n.s.
VE/VCO_2	30.8	5.8	36.5	4.3	0.02
VE/VCO_2 slope	28.2	6.5	33,07	3.0	0.05
$PETCO_2$@AT	38.4	5.5	34.3	2.8	0.05
$PETCO_2$	38.2	5.2	33.30	3.16	0.02
$PETO_2$	105.5	6.4	111.56	5.85	0.03
VD/VT rest	0.2	0.1	0.3	0.04	n.s.
TiBed (min)	429.3	44.4	435.4	22.8	n.s.
TST90 (%)	6.5	13.6	11.7	16.4	n.s.
ODI (events/h)	16.2	20.0	24.2	16.5	n.s.
Mean SaO_2 (%)	93.8	2.4	93.7	2.1	n.s.
Nadir (%)	82.6	8.9	70.0	28.4	n.s.
AHI (events/h)	18.0	21.8	24.5	16.0	n.s.
Cheyne-Stokes time (%)	1.50	2.3	31.4	28.8	<0.001
P0.1	2.83	1.23	4.71	1.91	0.004
$P01/PetCO_2$ slope	1.78	2.45	1.26	1.42	n.s.
$VE/PetCO_2$ slope	0.67	0.77	0.98	0.78	n.s.

Thereafter, occlusion pressures were measured simultaneously during CO_2 rebreathing at randomized intervals [14,15]. The slope of this curve was used as an index of the RD to hypercapnia (i.e. central chemoreflex drive) and reported as $\Delta P0.1/\Delta PetCO_2$ [14,15].

We used a simple rebreathing technique according to Read's rebreathing technique, which consisted of a rebreathing bag filled with a gas mixture (7% CO_2 and 93% O_2) [16]. In the rebreathing bag, a total volume of approximately twice the measured vital capacity of the patient was used.

Under hyperoxia the ventilatory response to hypercapnia (HCVR) represents the central chemoreflex response only, assuming that the peripheral chemoreflex drive is suppressed by hyperoxia [15,16]. Equilibrium of pressures between CO_2 in cerebral blood and end-tidal PCO_2 exhalation at the mouth ($PetCO_2$) is expected not to occur before recirculation of cerebral blood flow [16]. Respiratory volumes were recorded by a turbine volume measuring device (Oxycon-Pro, Jaeger). The Oxycon Pro was calibrated according to the instruction manual before each test (Oxycon instruction manual ver. 4.5. Erich Jaeger GmbH, Hoechberg, Germany) [17]. Oxygen and CO_2 analyzers were calibrated with room air and certified calibration gases at 180 kPa (16% O_2, 5% CO_2 and 79% N_2). The flow turbine (Triple V, Erich Jaeger GmbH, Hoechberg, Germany) was calibrated with a 3.00 l 5530 series calibration syringe (Hans Rudolph, Inc., Kansas City, USA). Both gas and volume calibration were repeated until the difference between consecutive calibrations was <1%. Therefore, measurements were not considered to be influenced under hyperoxia. Expired gas at the mouth was sampled continuously and analyzed for $PetCO_2$ by a fast-response infrared analyzer. The software calculated tidal volumes, inspiratory and expiratory times, minute ventilation, and $PetCO_2$ on a breath-by-breath basis. The hyperoxic ventilator response to hypercapnia (HCVR) was measured during several minutes after equilibrium between the end-tidal CO_2 and mixed venous CO_2. In this phase, a linear increase in V′E with respect to $PetCO_2$ was observed. The slope of this curve was used as the index of the ventilatory central chemosensitivity and reported as $\Delta V'E/\Delta PetCO_2$ [16].

Incremental CPX was performed on a cycloergometer (Ergometrics Lode Medical Tecnology-Corival, Groningen, The Netherlands) using a ramp protocol that was personalized with the objective of each patient reaching a maximum exercise within 8 to 10 min. After 60 s of unloaded pedaling at 60 rpm, work was continuously increased at a rate of 4 to 10 W/min starting at 0 W. In all cases, breath-by-breath expiratory gases and ventilation analysis were performed (Vmax Spectra 29S, Sensor Medics, Yorba Linda, CA). AT was measured with the V-slope analysis from the plot of VCO_2 vs. VO_2 on equal scales. The AT value was confirmed by ventilatory equivalents and end-tidal pressures of CO_2 and O_2. If no agreement was obtained, the AT was considered not identified. The VO_2/work rate relationship was evaluated throughout the entire exercise. The VE/VCO_2 slope was calculated as the slope of the linear relationship between VE and VCO_2 from 1 min after the beginning of loaded exercise to the end of the isocapnic buffering period. Peak exercise ventilation as % of a predicted value (VE%) was also reported. ECG and heart rate were assessed continuously.

All patients gave an informed consent. The study was approved by local ethical committee and was held according the ethical standards for experiments in human subjects established by the Declaration of Helsinki.

Twenty-eight consecutive outpatients with CHF (60 ± 10 years; 96% male gender, mean LVEF: 41 ± 12%; III–IV NYHA class 37%) were enrolled in the study. 18 subjects (65%) were classified as CSB negative (CSB−) even if among them 10 patients (36% of whole population) presented obstructive sleep apnea (mean AHI 29.7), while in 10 patients (35%) there was a high percentage of central sleep apnea and CSB and were classified ad CSB positive (CSB+). These groups were not different for age, gender, BMI, comorbidities and LVEF (Table 1).

Bidimensional and conventional Doppler echocardiography findings were not different between the two groups. 10 patients with CSB+ were different from CSB− for some cardiopulmonary exercise testing parameters ($PETCO_2$: 33 ± 3 vs 38 ± 5 mmHg, p: 0.02; $PETO_2$: 112 ± 6 vs. 105 ± 6 mmHg, p: 0.03; VE/VCO_2: 36 ± 4 vs. 31 ± 6, p: 0.02; VE/VCO_2 slope: 33 ± 3 vs. 28 ± 6, p: 0.05; $PETCO_2$@AT: 34 ± 3 vs. 38 ± 5 mmHg, p: 0.05) and, by definition, at poly-somnography parameters (CS% 31 ± 29 vs. 1 ± 2% p: <0.001).

Subjects with evidence of CSB were characterized by higher values of resting P0.1 than CSB− patients (4.7 ± 1.9 vs. 2.8 ± 1.2, p = 0.004 Fig. 1). Even if some CSB− patients presented higher response to CO_2 when compared to CBS+, no significantly different values of $P01/PetCO_2$ slope (1.3 ± 1.4 vs. 1.7 ± 2.4, p: 0.54) and $VE/PetCO_2$ slope (1.0 ± 0.8 vs. 0.7 ± 0.8, p: 0.31) were found.

Augmented central chemoreceptor sensitivity has already been demonstrated in clinical settings of CHF. As a result of the effects of chemoreflexes on the circulatory, respiratory and neurohormonal systems, changes in their activity may justify some pathophysiological features of CHF (increased ventilation, abnormal cyclic respiratory pattern and sympathetic overactivity). Despite the real mechanisms are not completely known, CHF patients with abnormally elevated chemosensitivity show an augmented ventilator response to exercise,

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