ORIGINAL RESEARCH

Contribution of the Lung to the Genesis of Cheyne-Stokes Respiration in Heart Failure: Plant Gain Beyond Chemoreflex Gain and Circulation Time

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***Background*—**The contribution of the lung or the plant gain (PG; ie, change in blood gases per unit change in ventilation) to Cheyne-Stokes respiration (CSR) in heart failure has only been hypothesized by mathematical models, but never been directly evaluated.

***Methods and Results*—**Twenty patients with systolic heart failure (age, 72.4±6.4 years; left ventricular ejection fraction, 31.5±5.8%), 10 with relevant CSR (24-hour apnea-hypopnea index [AHI] ≥10 events/h) and 10 without (AHI <10 events/h) at 24-hour cardiorespiratory monitoring underwent evaluation of chemoreflex gain (CG) to hypoxia (CG_{O_2}) and hypercapnia (CG_{CO_2}) by rebreathing technique, lung-to-finger circulation time, and PG assessment through a visual system. PG test was feasible and reproducible (intraclass correlation coefficient, 0.98; 95% CI, 0.91–0.99); the best-fitting curve to express the PG was a hyperbola (R^2≥0.98). Patients with CSR showed increased PG, CG_{CO_2} (but not CG_{O_2}), and lung-to-finger circulation time, compared with patients without CSR (all P<0.05). PG was the only predictor of the daytime AHI (R=0.56, P=0.01) and together with the CG_{CO_2} also predicted the nighttime AHI (R=0.81, P=0.0003) and the 24-hour AHI (R=0.71, P=0.001). Lung-to-finger circulation time was the only predictor of CSR cycle length (R=0.82, P=0.00006).

***Conclusions*—**PG is a powerful contributor of CSR and should be evaluated together with the CG and circulation time to individualize treatments aimed at stabilizing breathing in heart failure. **(*J Am Heart Assoc*. 2019;8:e012419. DOI: 10.1161/JAHA.119.012419.)**

Key Words: chemoreceptor • chronic heart failure • circulation • lung • sleep apnea

Cheyne-Stokes respiration (CSR) is a form of periodic breathing characterized by alternating phases of hyperventilation and central apneas, typical of severe chronic conditions, such as congestive heart failure (HF).[1] This breathing pattern results in numerous repetitive fluctuations in blood gases and hemodynamics,[1] causes chronic sympathetic overactivation,[2] impedes exercise capacity,[3] precipitates ventricular arrhythmias,[4] and increases mortality in HF.[5,6] Current treatments of CSR have rarely considered its complex pathogenesis in HF or tried to interfere with its pathophysiological triggers, with consequent disappointing results of major clinical trials based on positive pressure ventilation.[7,8]

In the past decades, different mathematical models have been proposed to describe the pathophysiology of CSR.[9–12] The overall accepted hypothesis is that the respiratory system could be seen as a closed-loop system, with a certain transit time in the feedback loop.[13] The loop gain (LG) can be defined as the ratio between the power of the response to a disturbance/the disturbance itself. Generally, the system reacts vigorously to each perturbation with a high LG, and with weaker effect when the LG is low.[13] The main determinants of LG are the controller gain and the plant gain (PG).

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An accompanying Video S1 is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012419

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Clinical Perspective

What Is New?

- This is the first study to explore the contribution of the lung or the plant gain in the genesis of central apneas in patients with heart failure.

What Are the Clinical Implications?

- Understanding the plant gain may help to predict Cheyne-Stokes respiration severity and to refine pathophysiological treatments aimed at stabilizing breathing in heart failure.

The controller within the respiratory system is represented by the chemoreflex gain (CG; change in ventilation per unit change in P_{CO_2} or P_{O_2}), whereas the PG is represented by the lungs (change in P_{CO_2} or P_{O_2} per unit change in ventilation). The connection between the controller and the plant is represented by the blood circulating between the lung and the chemoreceptors.[14] If the LG is <1, the response to any respiratory disturbance does not overshoot by more than the size of the original disturbance, so that ventilation slowly returns to steady state. Conversely, if LG is ≥1, any respiratory disturbance produces a response, which is even larger, leading to growing cycles of oscillation.[13]

With these premises, the chemoreflex has been thoroughly evaluated in patients with HF and CSR.[15–17] Increased CG is associated with CSR,[16,17] adrenergic overactivation,[16,17] and arrhythmias[16,17] and has independent prognostic significance in HF.[18,19] However, there is extensive overlap in CG between patients with and without CSR.[15]

Although a few studies have also evaluated the role of circulation time (Ct), showing mainly an association with CSR cycle length rather than CSR severity,[20] the role of PG has never been investigated.

We hypothesized that full evaluation of the global LG, including the CG, the PG, and the Ct, might increase the capability to correctly predict respiratory stability and to design future rational and effective strategies to stabilize breathing, on the basis of tailored pathophysiological approaches acting on CSR triggers. Therefore, we developed a novel method for direct evaluation of PG, and we tested it in healthy subjects and in patients with HF with and without CSR, beyond the evaluation of both the CG and the Ct.

Methods

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

Study Population

Consecutive outpatients with chronic systolic HF (left ventricular ejection fraction <50%) on stable (by 3 months) and optimal guideline-recommended medical and device treatment were enrolled in the study.[21] Exclusion criteria were as follows: chronic obstructive pulmonary disease or respiratory failure[22]; obstructive sleep apnea syndrome; and therapy with drug-influencing ventilation.

The study was approved by our Institutional Review Committee, and all subjects gave informed consent.

All patients underwent the following: 2-dimensional echocardiography[23–25]; neurohormonal characterization, including plasma norepinephrine, renin, aldosterone, and B-type natriuretic peptides[26]; arterial blood gas analysis; spirometry and diffusing lung capacity for carbon monoxide; 24-hour cardiorespiratory monitoring (Somtè; Compumedics, Abbotsford, Australia),[6,27] from which the apnea-hypopnea index (AHI), the central apnea index (CAI), the obstructive apnea index, the minimal oxygen saturation (SaO_2), time spent with SaO_2 <90%, and the lung-to-finger Ct (LFCt) were calculated, as previously described[28,29]; chemoreflex sensitivity to hypoxia (CG_{O_2}) and hypercapnia (CG_{CO_2}), by the rebreathing technique[17,18,30,31] (as explained below); and PG assessment (as explained below).

On the basis of pilot analysis (4 patients with CSR [PG mean, 2.2 mm Hg/L per minute; SD, 0.6 mm Hg/L per minute] and 4 patients without CSR [PG mean, 1.4 mm Hg/L per minute; SD, 0.5 mm Hg/L per minute]) using PG as the target variable and using a 1-sided Mann-Whitney *U* test (calculated effect size of 1.45) to obtain a $P<0.05$ and a power of 80%, we calculated a sample size of 7 subjects per group. To ensure robustness of our findings, we decided to recruit 10 subjects for each group. Considering that we evaluated CSR over the 24 hours and that the 24-hour AHI has an independent prognostic value in HF,[6] we used a threshold of 24-hour AHI ≥10 events/h to differentiate patients with relevant CSR (n=10; 24-hour AHI ≥10 events/h) from those without (n=10; AHI <10 events/h) in this series. A group of 10 healthy controls matched for age, sex, body mass index, and body surface area was also recruited and underwent PG and CG assessment.

CG Assessment

Chemoreflex sensitivity was assessed using the rebreathing technique, as previously explained.[17,18] In summary, subjects were examined in standardized conditions, while seated and connected to a rebreathing circuit through a mouthpiece. ECG, airway flow, and respiratory gases were recorded continuously through a breath-by-breath gas analyzer (Vmax;

Sensormedics, CA), and SaO_2 was recorded through a pulse oximeter (SET Radical; Masimo).

A 4-minute baseline recording was performed during spontaneous breathing. Then, the CG_{O_2} and the CG_{CO_2} were performed in a random order.

In the CG_{O_2}, an isocapnic hypoxia trial was done (from resting SaO_2 values to 70%–80%, according to individual tolerance), with end-tidal CO_2 ($etCO_2$) kept constant through a scrubbing circuit; the CG_{O_2} was then expressed by the linear regression slope between minute ventilation and SaO_2.

In the CG_{CO_2}, a progressive normoxic hypercapnic trial was done (from resting $etCO_2$ values until 50 mm Hg or an increase >10 mm Hg from the basal values, according to individual tolerance), with inspired partial pressure of oxygen kept at the baseline value by adding oxygen to the circuit; the CG_{CO_2} was expressed by the linear regression slope between minute ventilation and the end-tidal pressure of CO_2.

PG Assessment

To estimate the PG, we developed a new test to guide and monitor patient's breath-by-breath imposed variations in minute ventilation and consequent changes in $etCO_2$.

It was possible to refer the $etCO_2$ to the invasive arterial measure, excluding from the study pulmonary diseases with different alveolar emptying constants.

To enable subjects to change ventilation to a predetermined value, the subject's signal from the pneumotachograph (Vmax) was monitored online by a dedicated computer, running custom-designed software. The system was programmed to change subject's ventilation as a percentage of resting ventilation, increasing/decreasing tidal volume and respiratory rate by the same proportion.

The system displayed a moving bar controlled by the subject's inspiration, which should reach a tidal volume target

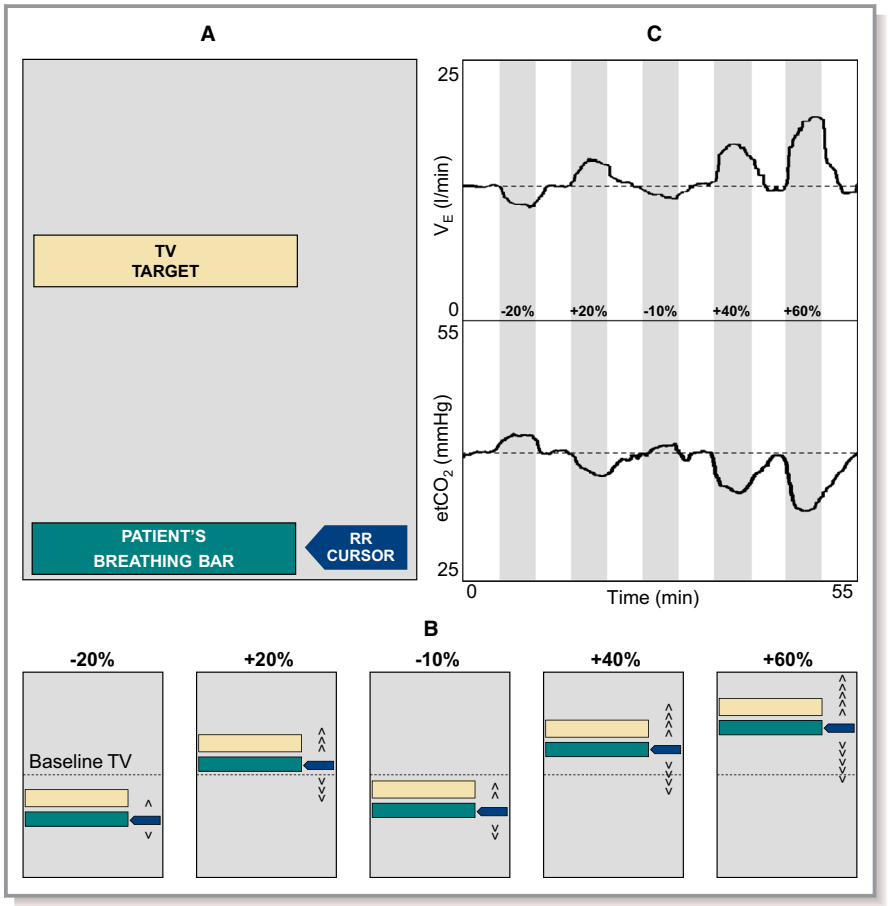

Figure 1. Schematic representation of plant gain assessment. **A**, The patient/software interface showing patient's inspiratory bar, target tidal volume (TV), and respiratory rate (RR) dynamic cursor. **B**, TV target is moved away from resting TV and RR cursor changes velocity across the different respiratory maneuvers, to obtain a prefixed percentage change in baseline ventilation. **C**, The postprocessing software interface allows us to reliably select a 20-second plateau in the end-tidal CO_2 ($etCO_2$) signal, following imposed changes in minute ventilation (V_E).

Table 1. Clinical Features of Patients With HF With or Without CSR

Feature	Patients With HF	Patients With HF With 24-h AHI <10 events/h	Patients With HF With 24-h AHI ≥10 events/h
Total no.	20	10	10
Age, y	72.4±6.4	71.4±7.3	73.4±5.6
Men	19 (95)	9 (90)	10 (100)
BMI, kg/m^2	26.3±3.3	26.1±4.1	26.6±2.5
BSA, m^2	1.97±0.17	1.97±0.18	1.98±0.16
Plasma creatinine, mg/dL	1.12±0.37	1.17±0.48	1.07±0.22
eGFR, mL/min per 1.73 m^2	67.7±20.6	67±23.5	66.5±18.1
Hemoglobin, g/dL	13.8±1.3	13.9±0.8	13.4±1.7
Ischemic/idiopathic	9/11 (45/55)	5/5 (50/50)	4/6 (40/60)
NYHA class I/II/III	6/12/2 (30/60/10)	4/5/1 (40/50/10)	2/7/1 (20/70/10)
Atrial fibrillation	11 (55)	5 (50)	6 (60)
Ejection fraction, %	31.5±5.8	32.9±6.1	30.2±5.5
Diastolic disfunction II–III	10 (50)	5 (50)	5 (50)
Moderate-to-severe MR	8 (40)	3 (30)	5 (50)
sPAP, mm Hg	40.4±10.0	41.9±6.4	39.2±12.4
FAC, %	40.1±9.0	36.3±7.4	43±9.5
HS-troponin T, ng/L	18.4 (10.2–26.4)	13.7 (8.7–25.3)	21.5 (16.6–31.5)
Norepinephrine, ng/L	431.5 (326.8–690.5)	400 (290.5–513.0)	561 (352.0–804.8)
Renin, μU/mL	39.1 (11.7–81.6)	42.1 (14.4–95.2)	30.4 (4.1–77.0)
Aldosterone, ng/L	82.9 (56.2–127.0)	82.3 (55.1–82.3)	92.5 (67.0–127.0)
BNP, ng/L	240.0 (142.0–659.0)	219.0 (80.0–303.0)	449.5 (164.3–824.0)
NT-proBNP, ng/L	981 (484.8–2353.5)	580 (265.0–1187.8)	1340 (772.3–3494.3)*
β Blockers	20 (100)	10 (100)	10 (100)
ACEi-ARB	14 (70)	7 (70)	7 (70)
ARNI	6 (30)	3 (30)	3 (30)
MRA	17 (85)	7 (70)	10 (100)
Furosemide	11 (55)	6 (60)	5 (50)
Digoxin	1 (5)	1 (10)	0 (0)
CRT-D	7 (35)	4 (40)	3 (30)
CRT-P	1 (5)	0 (0)	1 (10)
ICD	1 (5)	0 (0)	1 (10)

Data are given as mean±SD, number (percentage), or median (interquartile range). ACEi indicates angiotensin-converting enzyme inhibitor; AHI, apnea-hypopnea index; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; BMI, body mass index; BNP, brain natriuretic peptide; BSA, body surface area; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, CRT-pacemaker; CSR, Cheyne-Stokes respiration; eGFR, estimated glomerular filtration rate by Modification of Diet in Renal Disease equation; FAC, fractional area change; HF, heart failure; HS, high sensitivity; ICD, implantable cardioverter-defibrillator; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; sPAP, systolic pulmonary artery pressure.
*P<0.05 vs patients with HF with 24-h AHI <10 events/h.

at a respiratory rate rhythm given by a dynamic cursor (Figure 1A and Video S1).

The study subject was first trained to familiarize with the software interface. After a 5-minute baseline recording to obtain resting ventilation and $etCO_2$, each subject was asked to perform 5 maneuvers in random order: 2 hypoventilation maneuvers (a −20% and −10% decrease from baseline ventilation) and 3 hyperventilation maneuvers (a 20%, 40%, 60% increase from baseline ventilation) (Figure 1B).

Each step was maintained for at least 5 minutes, until a plateau in $etCO_2$ had been achieved and maintained for ≥20 seconds. Each step was separated by the following one by 5 minutes of recovery (Figure 1B). Data were then analyzed (Figure 1C).

Table 2. Respiratory Profile of Patients With HF With or Without CSR

Variable	Patients With HF	Patients With HF With 24-h AHI <10 events/h	Patients With HF With 24-h AHI ≥10 events/h
Daytime AHI, events/h	5 (2.0–14.5)	2 (0.8–5.3)	13 (4.8–27.0)*
Nighttime AHI, events/h	18 (5–31)	5 (2.8–11.8)	31 (22.8–36.8)*
24-h AHI, events/h	9 (4.3–17.8)	4.5 (2.8–7.0)	19.5 (15.8–31.3)*
Daytime CAI, events/h	0 (0–3)	0 (0–0)	3 (1.8–18.8)*
Nighttime CAI, events/h	2.5 (0–14.5)	0 (0–1)	14 (7.0–21.3)*
24-h CAI, events/h	1.5 (0–8)	0 (0–0)	7.5 (3.8–17.3)*
Daytime OAI, events/h	0	0	0 (0–1)
Nighttime OAI, events/h	1 (0–2)	0 (0–2)	2 (0.8–2.5)
24-h OAI, events/h	0.5 (0–1)	0 (0–1)	1 (0–1.3)
Cycle length, s	59.8±10.7	53.1±7.7	66.5±9.1*
Apnea length, s	20.3±3.8	17.4±2.9	23.2±1.8*
Hyperpnea length, s	39.6±7.9	35.8±6.2	43.4±7.8*
SaO_2 min, %	86.1±3.3	86.7±3.8	85.5±2.7
T-90, min	5 (2–12)	4 (0.8–11)	9 (2–13)*

Data are given as median (interquartile range) or mean±SD. AHI indicates apnea-hypopnea index; CAI, central apnea index; CSR, Cheyne-Stokes respiration; HF, heart failure; OAI, obstructive apnea index; SaO_2, oxygen saturation; T-90, time spent with SaO_2 <90%.
*P<0.05 vs patients with HF with 24-h AHI <10 events/h.

PG was calculated as the ratio between the variances of $etCO_2$ and minute ventilation across the different respiratory maneuvers (Equation 1).

$$PG = \frac{\sigma^2(etCo_2)}{\sigma^2(ventilation)} \quad (1)$$

The PG repeatability was assessed in 5 volunteers on 2 consecutive days.

Statistical Analysis

Statistical analysis was performed using SPSS (IBM Statistics, version 25.0; 2017). A 2-tailed P<0.05 was considered significant. Values were expressed as mean±SD or median and interquartile range, according to a normal or skewed distribution, evaluated by Kolmogorov-Smirnov test; or as percentages for categorical data. The χ^2 goodness-of-fit test for modified hyperbolic function was used to verify the shape of the PG relationship, using GraphPad Prism, version 7.04 for Windows.

For quantitative variables, comparison between 2 groups was performed using Mann-Whitney U test, whereas comparison among >2 groups was performed using the Kruskal-Wallis test, with Dunn post hoc correction. For qualitative variables, a χ^2 or Fisher exact test was used.

Before regression analysis, variables with a skewed distribution were logarithmically corrected. Univariable and multivariable linear regression analyses were implemented to identify predictors of CSR severity and CSR cycle length (dependent variables), entering the CG, the PG, and the LFCt (independent variables) into the multivariable regression only if they resulted in predictors at univariable analysis with P≤0.05; multicollinearity was excluded by calculation of variance inflation factor, considering a low risk of multicollinearity if the variance inflation factor was <10. Repeatability was measured with the intraclass correlation coefficient and its 95% confidence interval.

Results

The clinical characteristics of the HF population are shown in Table 1. Patients were mainly men, with mild symptoms (90% in New York Heart Association class I/II) confirming clinical stability, despite moderate-severe left ventricular systolic and diastolic dysfunction and presence of relevant mitral regurgitation and atrial fibrillation in 50% and 40%, respectively. All patients were receiving optimal medical and device treatment. According to matching criteria, patients and healthy controls were similar ages (72.4±6.4 versus 69.2±2.7 years; P=0.14), had a similar proportion of men (95% versus 90%; P=0.28), and had a similar body mass index (26.3±3.3 versus 25.9±3.7 kg/m^2; P=0.76) and body surface area (1.97±0.17 versus 1.90±0.18 m^2; P=0.10).

Patients with CSR showed a higher plasma value of NT-proBNP (N-terminal pro-B-type natriuretic peptide; P=0.03) compared with patients without CSR (Table 1). No differences

Table 3. CG, PG, and Ct Measurement in the Study Population

Variable	Healthy Controls (n=10)	Patients With HF With 24-h AHI <10 events/h (n=10)	Patients With HF With 24-h AHI ≥10 events/h (n=10)
CG			
Baseline V_E, L/min	11.9±2.0	11.9±2.4	11.3±2.4
Baseline $etCO_2$, mm Hg	33.6±3.4	31.9±3.2	31.8±3.4
Baseline SaO_2, %	95.7±1.1	95.9±1.6	95.4±1.5
CG_{O_2} $etCO_2$, mm Hg	32.5±5.7	31.5±3.1	31.4±3.5
CG_{O_2} SaO_2, %	78.2±1.4	81.5±4.8	81.6±4.7
CG_{O_2} V_E, L/min	19.6±8.0	17.6±5.1	22.6±7.7
CG_{O_2}, L/min per %SaO_2	0.19 (0.06–0.69)	0.29 (0.14–0.60)	0.42 (0.23–0.67)
CG_{CO_2} $etCO_2$, mm Hg	47.3±4.6	47.5±3.1	48.0±3.6
CG_{CO_2} SaO_2, %	95.8±1.2	95.5±1.4	96.3±1.2
CG_{CO_2} V_E, L/min	24.1±9.1	26.2±5.4	36.1±11.1†
CG_{CO_2}, L/min per mm Hg	0.82 (0.15–1.13)	0.89 (0.48–1.01)	1.45 (0.99–2.26)*†
PG			
Baseline V_E, L/min	11.9±2.0	11.9±2.4	11.3±2.4
−10% V_E, L/min	10.3±3.9	10.6±2.2	9.9±2.2
−20% V_E, L/min	9.5±2.0	9.8±2.4	8.6±1.8
20% V_E, L/min	14.2±2.0	14.7±3.1	13.9±2.4
40% V_E, L/min	17.3±2.3	17.3±3.2	16.2±2.1
60% V_E, L/min	20.3±2.6	19.9±3.7	18.9±2.9
Baseline $etCO_2$, mm Hg	33.8±3.5	31.4±3.4	32.2±3.1
−10% $etCO_2$, mm Hg	34.2±3.3	32.7±3.2	33.7±2.9
−20% $etCO_2$, mm Hg	35.2±3.4	32.8±3.0	35.3±3.2
20% $etCO_2$, mm Hg	29.7±3.3	28.1±3.1	27.9±3.6
40% $etCO_2$, mm Hg	26.6±3.4	25.2±2.5	24.5±2.3
60% $etCO_2$, mm Hg	24.2±3.1	22.3±2.5	20.9±2.4†
PG, mm Hg/L per min	1.15 (0.83–2.06)	1.37 (1.09–1.88)	2.19 (1.44–2.81)*†
Ct			
Daytime LFCt, s	…	26.7±2.8	33.4±6.9‡
Nighttime LFCt, s	…	26.1±3.1	32.9±6.4*
24-h LFCt, s	…	26.4±3.6	34.0±6.2‡

Data are given as mean±SD or median (interquartile range).CG_{O_2} and CG_{CO_2} $etCO_2$, SaO_2, and V_E are the values recorded and averaged in the last 10 seconds of the CG_{O_2} and CG_{CO_2} maneuvers. AHI indicates apnea-hypopnea index; CG, chemoreflex gain; CG_{CO_2}, CG to hypercapnia; CG_{O_2}, CG to hypoxia; Ct, circulation time; $etCO_2$, end-tidal CO_2; HF, heart failure; LFCt, lung-to-finger Ct; PG, plant gain; SaO_2, oxygen saturation; V_E, minute ventilation.

*P<0.05 vs HF with 24-hour AHI <10 events/h.

†P<0.05 vs healthy controls.

‡P<0.01 vs HF with 24-hour AHI <10 events/h.

in age, body mass index, body surface area, New York Heart Association class, renal function, left ventricular systolic and diastolic function, systolic pulmonary pressure, and right ventricular function were observed between patients with or without CSR (Table 1).

Because of patient allocation, patients with CSR showed increased AHI and CAI at daytime, nighttime, and over 24 hours, as well as increased CSR cycle length, apnea and hyperpnea length, and time spent with SaO_2 <90%, whereas no difference was found in the obstructive apnea index (Table 2).

Chemoreflex Sensitivity, PG, and Ct

Patients with CSR showed higher CG_{CO_2} compared with both patients without CSR (P=0.02) and healthy controls (P=0.01,

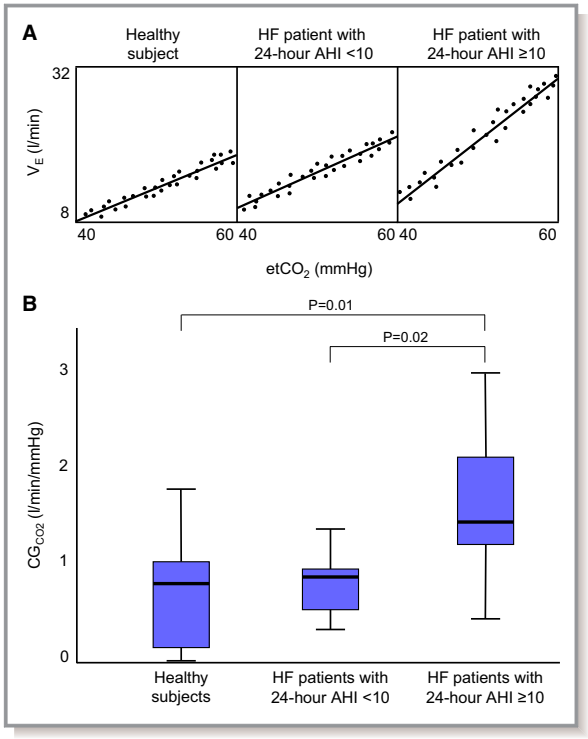

Figure 2. Chemoreflex gain to hypercapnia in healthy subjects and in patients with and without Cheyne-Stokes respiration (CSR). **A**, Linear regression slopes expressing the chemoreflex gain to hypercapnia (CG_{CO_2}) in a sample subject of each study group. **B**, CG_{CO_2} was increased in a patient with heart failure (HF) with CSR compared with patients with HF without CSR and healthy subjects. AHI indicates apnea-hypopnea index; $etCO_2$, end-tidal CO_2; V_E, minute ventilation.

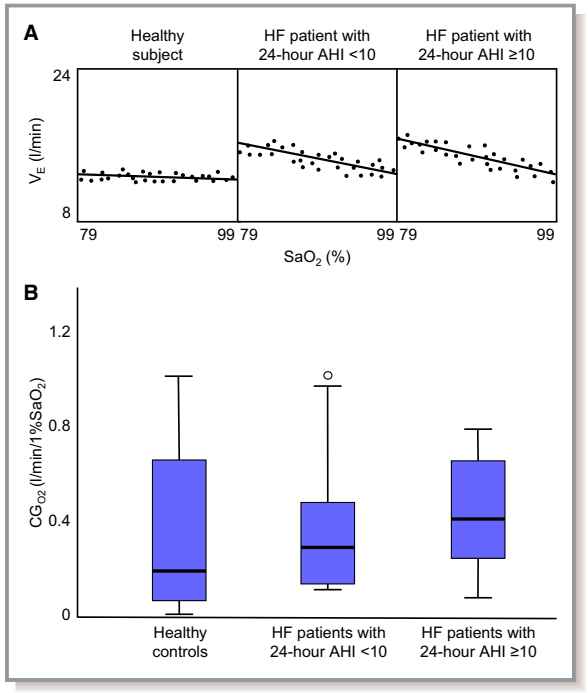

Figure 3. Chemoreflex gain to hypoxia in healthy subjects and in patients with and without Cheyne-Stokes respiration (CSR). **A**, Linear regression slopes expressing the chemoreflex gain to hypoxia (CG_{O_2}) in a sample subject of each study group. **B**, No difference was found among healthy subjects and patients with heart failure (HF) with or without CSR in terms of CG_{O_2}. AHI indicates apnea-hypopnea index; SaO_2, oxygen saturation; V_E, minute ventilation.

Table 3 and Figure 2). Conversely, no difference was found in CG_{O_2} among the different groups (Table 3 and Figure 3). No difference in both CG_{O_2} and CG_{CO_2} was found between patients without CSR and healthy controls.

Both healthy subjects and patients with HF were able to perform the PG test correctly (Table 3), with little deviation from target ventilation (3.1±1.4% in the whole population, 2.7±2.9% in healthy subjects, 2.9±1.4% in those with HF without CSR, and 3.6±1.1% in those with HF with CSR). The PG test showed a high repeatability: intraclass correlation coefficient, 0.98 (95% CI, 0.91–0.99). The best-fitting curve to express the relationship between induced changes in $etCO_2$ and changes in ventilation was a hyperbola (R^2=0.99 for patients without CSR and healthy controls, and R^2=0.98 for patients with CSR) (Figure 4A).

PG was higher in patients with CSR than in patients without CSR (P=0.02) and healthy controls (P=0.01, Table 3 and Figure 4B). No difference in PG was found between patients without CSR and healthy controls. No significant difference in spirometry, lung diffusion, and blood gas analysis was found between patients with normal and increased PG, apart from a trend toward an increase in the forced expiratory volume in the first second (P=0.06) and in the total lung capacity (% predicted; P=0.09) in patients with increased PG (Table 4).

The 24-hour, daytime, and nighttime LFCt values were all increased in patients with CSR compared with patients without CSR (all P<0.05, Figure 5). No significant differences were observed in the LFCt calculated at different time windows (daytime, nighttime, and 24-hour period), within the same group of patients.

CG_{CO_2} and LFCt were correlated (ρ=0.64, P=0.004), whereas no correlation was found between PG and CG_{CO_2} or PG and LFCt.

Prediction of CSR Severity and CSR Cycle Length

The univariable and multivariable predictors of CSR severity in patients with HF are shown in Table 5, whereas linear regression plots (for each CSR predictor) are shown in Figure 6.

At multivariable analysis, CG_{CO_2} and PG were independent predictors of both the 24-hour AHI (Figure 7A) and the nighttime AHI (Figure 7B), whereas PG was the only

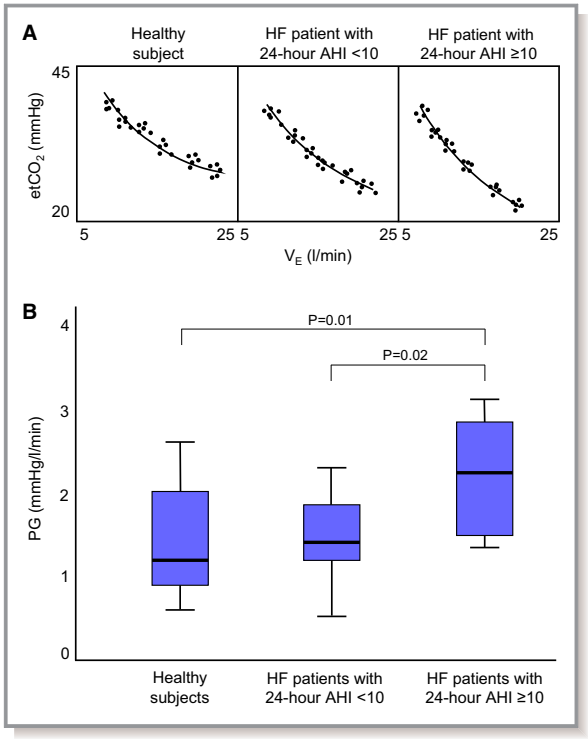

Figure 4. Plant gain (PG) in healthy subjects and in patients with and without Cheyne-Stokes respiration (CSR). **A**, PG respiratory hyperbola in a sample subject of each study group. **B**, PG was increased in a patient with heart failure (HF) with CSR compared with patients with HF without CSR and healthy subjects. AHI indicates apnea-hypopnea index; $etCO_2$, end-tidal CO_2; V_E, minute ventilation.

independent predictor of the daytime AHI (Figure 7C). LFCt was only a univariable predictor of nighttime AHI, but it lost its predictive value at multivariable analysis. Using CAI as the target variable, PG was the only predictor of 24-hour (R=0.55, P=0.01) and daytime (R=0.59, P=0.006) CAI, whereas CG_{CO_2} was the only predictor of nighttime CAI (R=0.56, P=0.01).

On the other hand, the LFCt was an independent predictor of CSR cycle length (Figure 8A), as well as of hyperventilation length (Figure 8B). Apnea length was predicted by both LFCt and the CG_{CO_2}, with LFCt remaining the only independent predictor at multivariable analysis (Figure 8C).

Discussion

This was the first study to assess the PG in patients with HF with and without CSR. Assessing the PG, instead of only CG and the Ct, allowed us to comprehensively test the instability loop hypothesis (Figure 9).[13] Higher CG_{CO_2}, PG, and Ct values were found in patients with CSR. Notably, both CG and PG were able to predict CSR severity during the 24-hour period and at nighttime, whereas only PG was able to predict CSR severity at daytime. Ct showed no role in CSR severity prediction, but was strongly related to CSR cycle length and to hyperpnea and apnea length.

The Instability Loop Hypothesis

The pathophysiological characteristics of CSR in HF are complex and multifactorial. Despite much theoretical and experimental work, a thorough understanding of the mechanisms involved and their interactions has not been achieved. The strength of the pathophysiological model is key to guide experiments designed to challenge the model's assumption and to provide optimal treatments for patients with a disease.[32] On the other hand, if a treatment is not strongly pathophysiologically based and referred to a solid model, the randomized controlled trial is likely to fail, as happened to mask-based therapies based on positive airway pressure, derived from the treatment of obstructive apneas and applied to central apneas of HF.[7,8]

In this setting, a great contribution was provided by the use of mathematical models. Currently, the most accepted hypothesis is that the respiratory control system could be seen as a closed-loop system, constituted by a controller (ie, the chemoreflex) and the plant (ie, the lung), with a transit time in the feedback loop (ie, Ct). In principle, therefore, increased CG, increased PG, and increased Ct have theoretical potential to increase the global LG and cause CSR.

Testing the Instability Loop Hypothesis: CG

Alteration in the gain of the chemoreceptors has been well documented in both experimental[33] and clinical settings.[15–19] The original observation by Javaheri[15] that CG_{CO_2} was strongly correlated with CSR severity was later confirmed by different research groups.[16–19,34] In the current study, the CG_{CO_2} was again confirmed to play a key role in the prediction of CSR severity. By contrast, no significant difference in the CG_{O_2} was found between patients with or without CSR, highlighting once more that CO_2, rather than hypoxia, is the main driver of ventilation, especially at night when ventilation is under chemical control. Recent lines of evidence have shown that in animals with HF, the CG remains high throughout the 24 hours, including the biological night, differently from healthy animals in which the CG is known to decrease during the inactive phase.[35] This may also justify why the difference between the eupneic CO_2 and the CO_2 at anaerobic threshold is decreased at night in patients with HF and CSR compared with patients with stable breathing.[36] The reasons for this persistent overactivity of the CG at night is still unknown, but key differences in the chronobiological characteristics of neurohormonal activity and in cardiac hemodynamics

Table 4. Blood Gas Analysis, Spirometry, and Pulmonary Diffusion in Patients With HF With Low or High PG, According to Its Median Value (1.63 mm Hg/L per Minute)

Variable	Patients With HF (n=20)	Patients With Low PG (n=10)	Patients With High PG (n=10)
Blood gas analysis			
P_{O_2}, mm Hg	80.8±8.3	82.0±7.4	79.9±9.4
P_{CO_2}, mm Hg	36.8±3.4	37.6±4.4	36.1±2.6
pH	7.43±0.04	7.42±0.03	7.44±0.04
HCO_3^-, mmol/L	25.2±2.1	24.8±1.0	25.5±2.6
SaO_2, %	97.7±1.3	97.6±1.8	97.9±1.0
Spirometry			
FEV1, L	2.99±0.48	2.76±0.35	3.2±0.50
FEV1, % predicted	106.8±18.0	99.3±19.9	113.4±14.0
FEV1/FVC, %	70.7±5.6	71.3±7.6	70.1±3.4
FEV1/VC, % predicted	92.0±8.5	92.6±11.3	91.5±5.6
TLC, L	6.4±1.0	6.0±1.0	6.8±0.9
TLC, % predicted	97.4±13.7	90.9±12.6	103.2±12.5
RV/TLC, %	33.7±6.9	36.3±5.3	31.4±7.7
DS/TV	0.16±0.06	0.16±0.06	0.17±0.05
Pulmonary diffusion			
DLCO, mL/min per mm Hg	23.8±5.4	22.6±5.2	24.9±5.6
DLCO, % predicted	88.5±27.4	77.3±32.5	98.6±18.5
AV, L	6.2±0.9	5.8±0.4	6.7±0.9
AV, % predicted	95.7±12.6	89.1±11.4	101.6±11.0
KCO, mL min^{-1} mm Hg^{-1} L^{-1}	3.8±0.7	3.9±0.8	3.8±0.6
KCO, % predicted	99.1±17.8	101.0±20.6	97.3±16.0

Data are given as mean±SD. AV indicates alveolar volume; DLCO, diffusion capacity of the lungs for CO; DS, dead space; FEV1, forced expiratory volume in the first second; FVC, forced VC; HF, heart failure; KCO, DLCO divided by AV; PG, plant gain; SaO_2, oxygen saturation; RV, residual volume; TLC, total lung capacity; TV, tidal volume; VC, vital capacity.

(decreased cardiac output and increased filling pressure), together with a decrease in cerebrovascular reactivity to increased CO_2 (decreased CO_2 washout from chemoreceptors),[37] at night might be involved.

Testing the Instability Loop Hypothesis: PG

Before this study, the PG had been only mathematically hypothesized[9–12] and evaluated in a single study by Miyamoto et al in healthy volunteers,[38] but not in patients with HF. Similar to Miyamoto et al, we also used a visual system to drive subjects during PG execution, but we performed shorter ventilatory maneuvers, to increase the feasibility in patients with HF. Moreover, we calculated the PG as a ratio between the variances of $etCO_2$ and ventilation, rather than using a linear slope obtained at the equilibrium set point,[38] to more reliably express the PG behavior far from stationary conditions.

The feasibility of the test was demonstrated by the reassuringly small discrepancy (<5%) between the target and recorded ventilation in each respiratory maneuver, not only in healthy subjects, but even in patients with HF with or without CSR. Furthermore, as predicted by mathematical models, the relationship between changes in ventilation and the resulting changes in $etCO_2$ fitted a hyperbola (R^2=0.99 for patients without CSR and healthy controls, and R^2=0.98 for patients with CSR).

Notably, we first observed that the PG is increased in patients with HF with CSR, being ≈60% higher than in patients with HF without CSR. Moreover, the PG was the only predictor of CSR severity at daytime, where the chemical control is overdriven by different stimuli, especially cortical influences. Furthermore, adding PG to CG resulted in a more accurate prediction of CSR severity at night ($PG+CG_{CO_2}$ R=0.81 versus CG_{CO_2} alone R=0.61). To put into practice, this means that in patients with a high PG, whatever stimulus is able to change ventilation can make the system oscillate and cause CSR, such as exercise or a mental stress when the patient is awake or an arousal when the patient is sleeping. This should be accounted for when

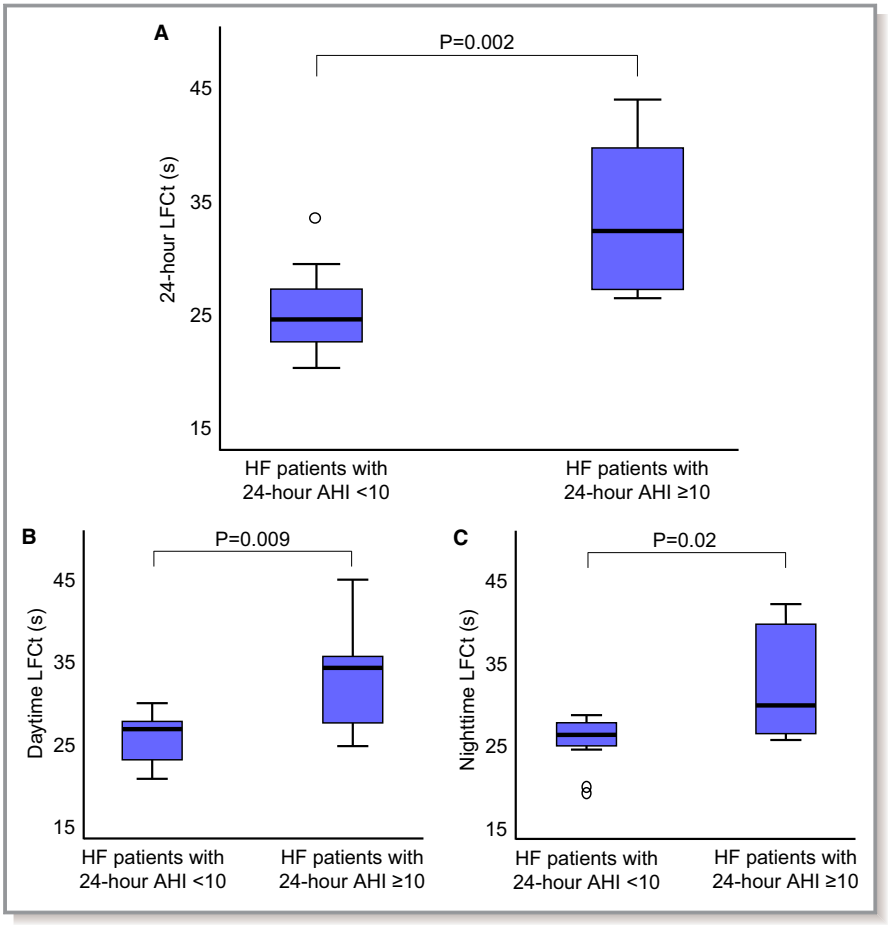

Figure 5. Lung-to-finger circulation time (LFCt) in patients with and without Cheyne-Stokes respiration (CSR). The LFCt was increased in patients with heart failure (HF) with Cheyne-Stokes respiration (CSR) compared with patients without CSR, over the 24-hour period (**A**), at daytime (**B**), and at nighttime (**C**). AHI indicates apnea-hypopnea index.

Table 5. Univariable and Multivariable Models for Prediction of 24-Hour AHI, Nighttime AHI, and Daytime AHI

	Univariable Model				Multivariable Model					
Variable	β, Mean±SD	*R*	R^2	*P* Value	β, Mean±SD	*R*	R^2	R^2-Penalized	*P* Value	VIF
Prediction of 24-h AHI										
CG_{CO_2}	6.9±3.3	0.46	0.21	0.04	8.3±2.7	0.71	0.51	0.44	0.008	1.03
PG	8.3±3.1	0.54	0.29	0.02	8.9±2.9				0.009	1.03
LFCt	0.7±0.4	0.38	0.14	0.10	…					
Prediction of nighttime AHI										
CG_{CO_2}	11.4±3.7	0.61	0.36	0.007	10.4±3.3	0.81	0.65	0.57	0.007	1.24
PG	8.5±4.1	0.44	0.19	0.04	8.1±3.3				0.03	1.06
LFCt	1.1±0.5	0.49	0.24	0.03	…					
Prediction of daytime AHI										
CG_{CO_2}	3.9±3.4	0.26	0.07	0.29	…					
PG	8.3±2.8	0.56	0.32	0.01						
LFCt	0.41±0.38	0.25	0.06	0.29						

AHI indicates apnea-hypopnea index; CG_{CO_2}, chemoreflex gain to hypercapnia; LFCt, lung-to-finger circulation time; PG, plant gain; VIF, variance inflation factor.

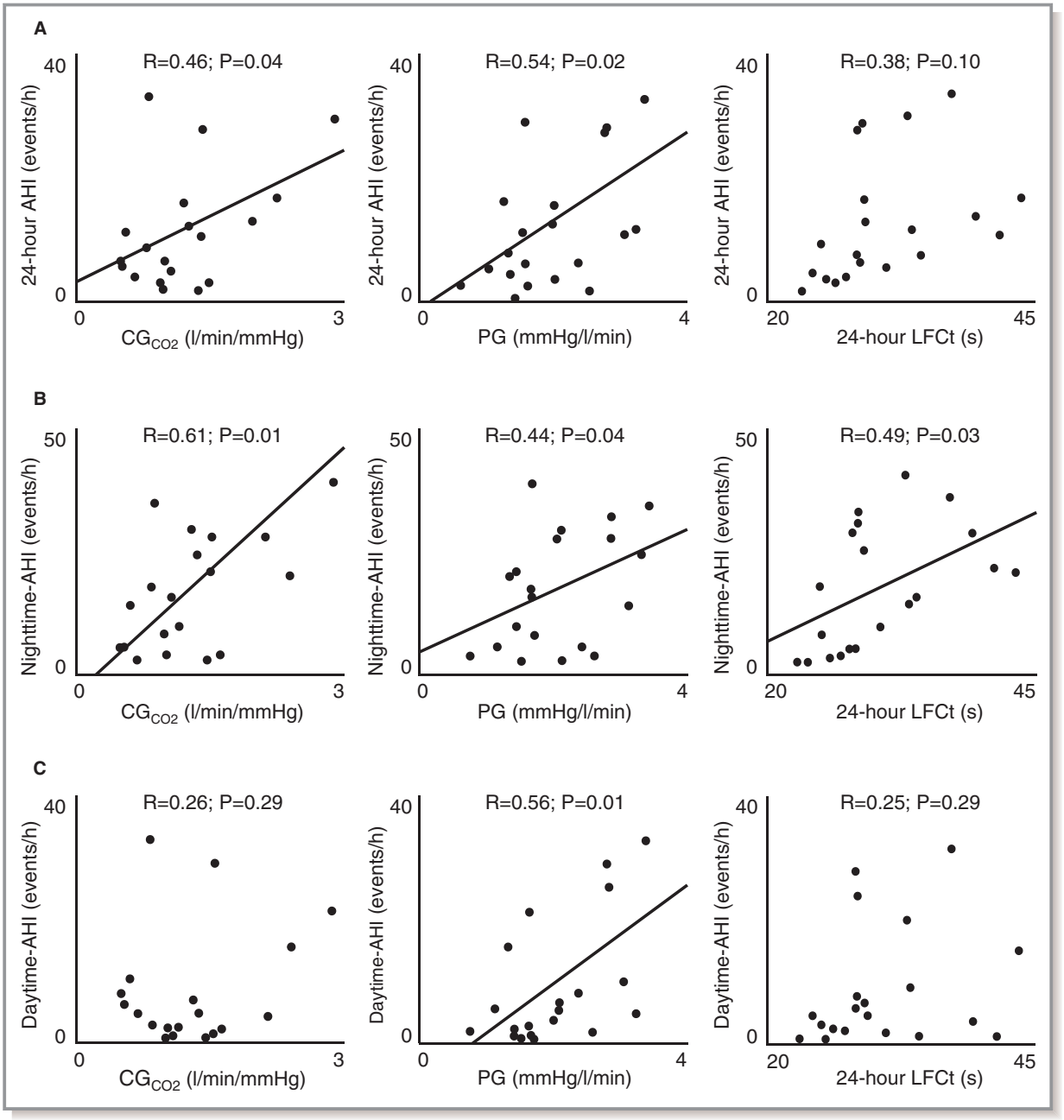

Figure 6. Linear regression plots relating loop gain components and Cheyne-Stokes respiration (CSR) severity in different time windows. Linear regression plots relating chemoreflex gain to hypercapnia (CG_{CO_2}), plant gain (PG), and lung-to-finger (LF) circulation time (LFCt) with CSR severity, as expressed by the apnea-hypopnea index (AHI), over the 24-hour period (**A**), at nighttime (**B**), and at daytime (**C**).

designing and testing novel treatments aimed at stabilizing breathing.

Indeed, several therapeutic approaches have been thought to act on the PG to obtain ventilatory stability, such as CO_2 administration (by increasing lung CO_2 reserve),[39,40] increase of death space (thus decreasing the washout of CO_2 from the lung),[41] acetazolamide administration (causing a shift in the ventilatory equilibrium at a different set point),[42,43] and positive pressure ventilation (by altering lung anatomical characteristics and/or mechanics).[12] The PG was recently measured in patients with obstructive sleep apnea (n=8) and matched controls (n=7), by using a pseudorandom binary stimulation (63 breaths alternating between room air and 4% CO_2, switching frequencies of between 1 and 6 consecutive breaths of CO_2).[44] No difference was found between patients with obstructive sleep apnea and controls, and no effect on

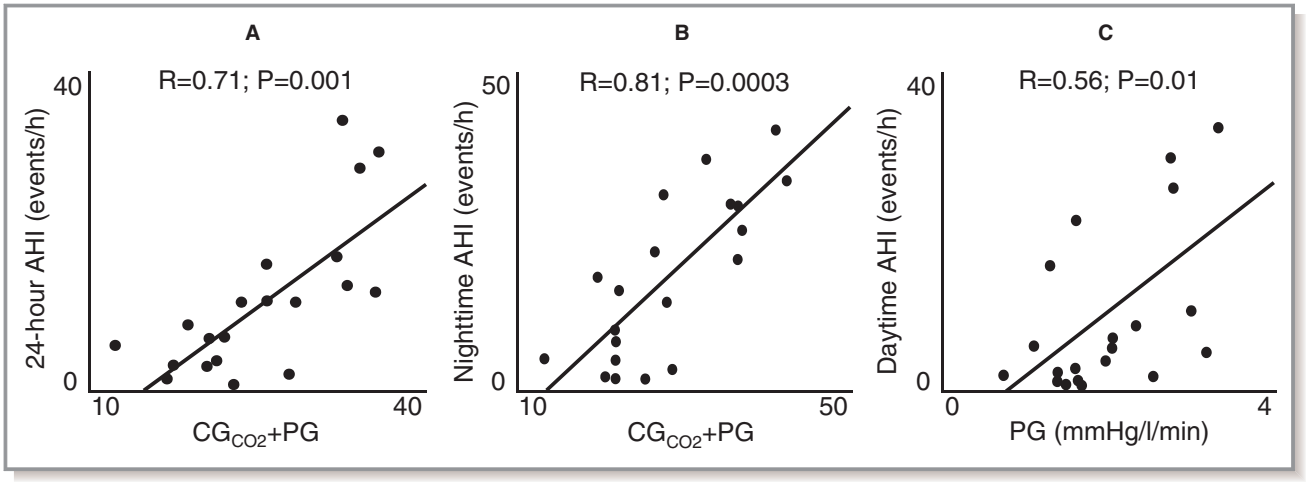

Figure 7. Regression plots showing predictors of Cheyne-Stokes respiration severity in different time windows. Chemoreflex gain to hypercapnia (CG_{CO_2}) and plant gain (PG) were independent predictors of apnea-hypopnea index (AHI) over the 24-hour period (**A**) and at nighttime (**B**), whereas only PG was an independent predictor of AHI at daytime (**C**).

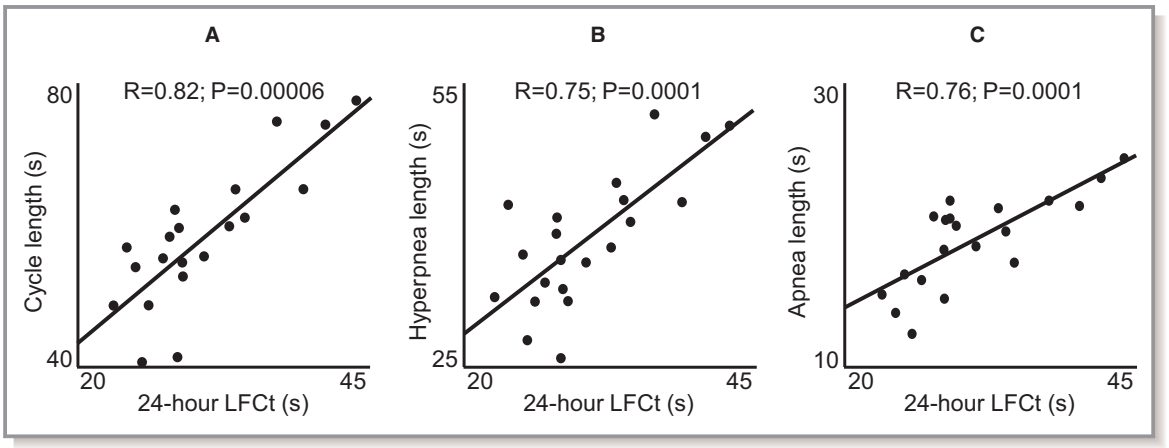

Figure 8. Regression plots showing predictors of Cheyne-Stokes respiration (CSR) cycle and hyperpnea and apnea lengths. The lung-to-finger circulation time (LFCt) was the only independent predictor of CSR cycle length (**A**), hyperventilation length (**B**), and apnea length (**C**).

the PG was observed after 6 week of continuous positive airway pressure treatment.

The main determinants of the PG remained still unknown. In contrast to the hypothesis that lung congestion and the gas-diffusion impairment may increase the PG,[45] in our population, no significant difference in spirometry, lung diffusion, and blood gas analysis parameters was found between patients with high PG (PG above the median) and low PG (Table 4). The only exception was a trend toward an increase in forced expiratory volume in the first second (P=0.06) and total lung capacity (P=0.09) in patients with high PG. These results should be interpreted with caution, and further investigations in a larger population are needed to address this key pathophysiological issue.

Testing the Instability Loop Hypothesis: Ct

The pathophysiological role of Ct delay in determining respiratory instability was supposed by mathematical modeling[9–12] and experimentally demonstrated in dogs by Crowell and coworkers already in 1956.[14] However, the increase in Ct needed to make ventilation unstable in anesthetized dogs[14] was much higher (from 40 seconds to 5 minutes) than that observed in patients with HF.[20] Subsequent studies in humans have highlighted that Ct delay seems to be mainly associated with CSR cycle length and hyperventilation length, rather than CSR onset or severity.[20]

In our population and differently from previous studies, the LFCt, besides cycle length and hyperpnea length, also predicted the apnea duration. This difference may be

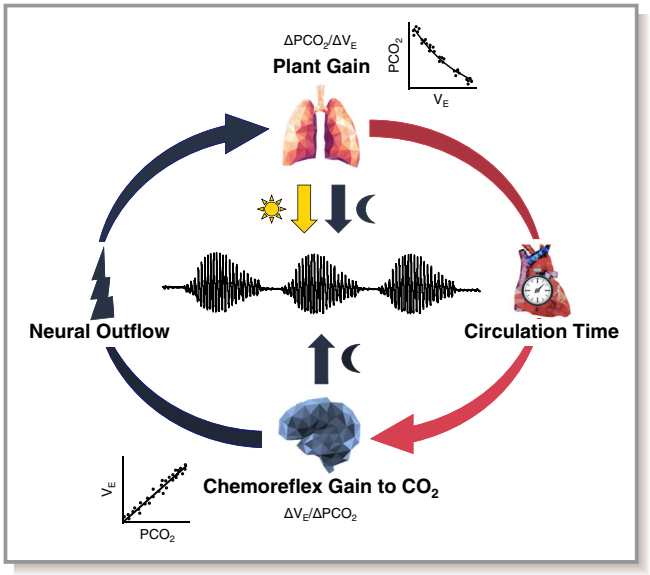

Figure 9. Testing the instability loop hypothesis in patients with heart failure: an overview. In patients with heart failure, plant gain determines Cheyne-Stokes respiration (CSR) severity at daytime and, together with chemoreflex gain to CO_2, CSR severity at nighttime. On the contrary, circulation time has no role in prediction of CSR severity, but it is associated with CSR cycle length. V_E, minute ventilation.

explained by the use of LFCt over the 24-hour period in place of the lung-to-ear Ct, evaluated only in phase 2 non–rapid eye movement sleep in the article by Hall et al,[20] or by the higher number of patients with HF recruited in the current study. Both methods (LFCt and lung-to-ear Ct) were inversely correlated with cardiac output.[20,28,29]

Study Limitations

The PG test requires patient cooperation, and so it is unsuitable when there is marked physical and/or cognitive impairment. Nonetheless, in our population, the feasibility was 100%, even in patients with unstable breathing. Although the LFCt is only an estimation of the true Ct, it has the advantage of being measurable directly from cardiorespiratory monitoring. However, being based on SaO_2, LFCt may also be influenced by the lungs and hemoglobin levels, so that direct measurements of Ct are needed to further improve the precision of the model.

The CG and the PG were only evaluated during the daytime, when the patient was awake, and this may decrease our capacity to predict the ventilatory behavior (stability/instability and CSR severity and length) throughout the 24 hours. Currently, there is no evidence in patients with HF about the potential changes in the CG and the PG from awake to sleep conditions. Although we can hypothesize that the CG would remain high at night in patients with unstable breathing, as observed in animals,[35] the potential changes of the PG at night are less predictable. We believe that, at night, the change in body position may reduce lung volumes, and further potential influences on the PG may be also related to the typical rostral fluid shift of patients with HF.

Finally, the relatively small sample size of the study seems to hardly support the development of multivariable models. However, having used only 3 variables (independent variables; namely, the CG, the PG, and the LFCt) with a strong pathophysiological relationship with CSR severity and length (dependent variables), together with the lack of any relationships between the independent variables, apart from that observed between CG_{CO_2} and LFCt, has actually increased the power of analysis (in each multivariable regression model, the calculated power was always >98%). Furthermore, the variance inflation factor observed makes the risk of multicollinearity rather low.

Conclusions and Perspectives

Ct does not predict CSR severity, but it influences the CSR cycle and hyperpnea and apnea length. The PG can be easily measured in patients with HF and is increased in patients with HF presenting with unstable ventilation, as previously hypothesized by mathematical models. Its estimation may help in predicting the severity of CSR at daytime and in refining the prediction of CSR severity at nighttime, when evaluated together with the CG. Future treatment strategies should consider those triggers to tailor a rational and thus effective approach in individual patients with HF and CSR.

Disclosures

None.

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