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## Clinical Significance of Chemosensitivity in Chronic Heart Failure: Influence on Neurohormonal Derangement, Cheyne-Stokes Respiration and Arrhythmias

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**ABSTRACT**

Increased chemosensitivity has been observed in heart failure (HF). To investigate its pathophysiological and clinical relevance, we evaluated its impact on neurohormonal balance, breathing pattern, response to exercise, and arrhythmic profile. Sixty patients with chronic HF (age  $66 \pm 1$  years, left ventricular ejection fraction, EF,  $31 \pm 1\%$ , mean  $\pm$  SEM) underwent assessment of hypoxic-normocapnic (HVR) and hypercapnic-normoxic ventilatory response (HCVR), neurohormonal evaluation, cardiopulmonary test, 24 h electrocardiographic monitoring assessment of Cheyne-Stokes respiration (CSR) by diurnal and nocturnal polygraphy. Sixty percent of patients had enhanced chemoceptive sensitivity. Those with enhanced chemosensitivity to both hypoxia and hypercapnia, as compared to those with normal chemosensitivity, showed significantly ( $P < 0.01$ ) higher norepinephrine and B-type natriuretic peptide level, higher prevalence of day-time and night-time CSR, worse NYHA class and ventilatory efficiency (higher VE/VCO<sub>2</sub> slope), and higher incidence of chronic atrial fibrillation and paroxysmal nonsustained ventricular tachycardia, but no difference in left ventricular volumes or EF. A direct correlation was found between HVR or HCVR and norepinephrine ( $R = 0.40$  and  $R = 0.37$ , respectively,  $P < 0.01$ ), BNP ( $R = 0.40$ ,  $P < 0.01$ ), NT-proBNP ( $R = 0.37$  and  $R = 0.41$ ,  $P < 0.01$ ), apnoea-hypopnoea index ( $R = 0.57$  and  $R = 0.59$ ,  $P < 0.001$ ) and VE/VCO<sub>2</sub> slope ( $R = 0.42$  and  $R = 0.50$ , respectively,  $P < 0.001$ ). Finally, at multivariate analysis, HCVR was an independent predictor of day-time and night-time CSR. In conclusion, increased chemosensitivity to hypoxia and hypercapnia, particularly when combined, is associated with neurohormonal impairment, worse ventilatory efficiency, CSR, and higher incidence of arrhythmias, and is likely to play a central pathophysiological role in HF patients.

## INTRODUCTION

Despite the advances in the treatment of chronic heart failure (HF), its epidemiological relevance is still increasing [1]. Ventricular remodelling, symptoms and final outcome are highly influenced by neurohormonal derangement [2], characterized by the activation of the sympathetic [3] and the renin-angiotensin-aldosterone system [4], and by the enhanced secretion of natriuretic peptides, whose plasma levels hold diagnostic and prognostic value [5]. Increased sympathetic activity, one of the major determinants of the evolution of the disease and of life-threatening events, is elicited by changes in autonomic afferent feed-back, *via* baroreceptor desensitisation [6], ergoreceptor [7], and chemoreceptor sensitisation [8].

In particular, increased chemosensitivity has been also associated with several markers of worse clinical status and prognosis in HF patients, such as ventilatory response to exercise [9] or night-time Cheyne-Stokes respiration (CSR) [10, 11]. Recently, increased peripheral chemosensitivity has been pointed out as independent prognostic factor in HF [12].

However, the importance of increased sensitivity to either hypoxia or hypercapnia and the possible role of their combination in the pathophysiology of heart failure have not been fully investigated. Moreover, there are few data on the impact of chemosensitivity on other neurohormonal axes than the adrenergic one, including renin-angiotensin-aldosterone and cardiac natriuretic peptide systems.

Our hypothesis is that chemosensitivity might play a central role in influencing neurohormonal activation and the overall clinical picture of HF patients, even on optimal pharmacological treatment.

The purpose of our study was to evaluate in a prospective cohort of patients with chronic HF (optimally treated by a complete neuro-hormonal antagonist drug approach) the actual prevalence of enhanced chemosensitivity to both hypoxia and hypercapnia and its significance with regard to neuro-hormonal activation, including cardiac endocrine function, occurrence of CSR, clinical status, and response to exercise.

## METHODS

### Subjects and study design

From 2005 to 2006 we screened 84 consecutive HF patients coming from our outpatient clinic, with echocardiographic evidence of impaired left ventricular systolic function (ejection fraction - EF- <45%). Exclusion criteria were New York Heart Association (NYHA) class IV, acute coronary syndrome within 6 months before examination, severe renal dysfunction (i.e creatinine clearance < 35 ml·min<sup>-1</sup>), pulmonary disease (vital capacity and total lung capacity < 50% of predicted value, FEV1 < 50% of predicted value, and FEV1/FVC < 70%), obstructive sleep apnoea syndrome (as determined by a preliminary polysomnography), and treatment with morphine or derivatives, theophylline, oxygen, benzodiazepines or acetazolamide. Sixty patients matched these criteria and were enrolled in the study (Table 1): all were on stable (i.e., > 1 month) optimal pharmacological treatment, with restriction of water-sodium intake. The study design included a standard clinical evaluation and: a) the detection of chemosensitivity to hypoxia and to hypercapnia, by assessment of the individual hypoxic-normocapnic (HVR) and normoxic-hypercapnic ventilatory response (HCVR); b) neuro-hormonal evaluation; c) echocardiography; d) arterial blood gas analysis; e) cardio-pulmonary exercise testing; g) 24-hour electrocardiographic recording; h) 20-minute day-time polygraphy and nocturnal polysomnography for CSR assessment. The entire protocol was completed for each patient within 3 days. The investigation was carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association, and has been approved by the Institutional Ethics Committee; informed consent was obtained from all subjects enrolled in the study.

### **Chemosensitivity evaluation**

Chemoceptive sensitivity was assessed using the rebreathing technique [13, 14] to assess. Subjects were examined in standardized conditions, in a quiet room at a comfortable temperature, while seated and connected to a rebreathing circuit through a mouthpiece. They were not allowed to smoke or to drink alcohol or caffeine-containing beverages in the 12 h preceding the study. Electrocardiogram, airway flow, and respiratory gases were recorded continuously through a breath-by-breath gas analyzer (Vmax, SensorMedics, Yorba Linda, CA, USA), and oxygen saturation (Masimo SET Radical, Pulse Oximeter). A 4-minute baseline recording was performed during spontaneous breathing. The mean SaO<sub>2</sub> and CO<sub>2</sub>-et during this recording were assumed as subject resting values. During the progressive isocapnic hypoxia trial (from resting SaO<sub>2</sub> values to 70-80%, according to individual tolerance), end-tidal CO<sub>2</sub> was kept at baseline

value, by passing a portion of the expired air into a scrubbing circuit before returning it to a 5 l rebreathing bag. Conversely, during the progressive normoxic hypercapnic trial (from resting end-tidal CO<sub>2</sub> values until 50 mmHg or an increase  $\geq 10$  mmHg from the basal values, according to individual tolerance), inspired partial pressure of O<sub>2</sub> was kept at baseline value by adding oxygen to the circuit. The two trials were performed in a random order. All signals were digitized on-line (National Instruments, USA, 500 sample·s<sup>-1</sup>) and analyzed to derive respiratory rate, breath-to-breath tidal volume (V<sub>t</sub>), and minute ventilation (VE), as well as SaO<sub>2</sub> and end-tidal pressure of CO<sub>2</sub>.

HVR was expressed by the linear regression slope between minute ventilation and SaO<sub>2</sub>, during a hypoxic-normocapnic trial. HCVR was expressed by the linear regression slope between minute ventilation and end-tidal pressure of CO<sub>2</sub>, during the hypercapnic-normoxic trial. The average HVR values obtained in a group of 12 age- and gender-matched healthy subjects (Table 1) were  $0.35 \pm 0.21$  l·min<sup>-1</sup>·%SaO<sub>2</sub><sup>-1</sup>, and HCVR values  $0.31 \pm 0.24$  l·min<sup>-1</sup>·mmHg<sup>-1</sup> (mean  $\pm$  S.D.). As cut-off value for defining increased chemosensitivity, we considered  $0.77$  l·min<sup>-1</sup>·%SaO<sub>2</sub><sup>-1</sup> as to HVR and  $0.79$  l·min<sup>-1</sup>·mmHg<sup>-1</sup> as to HCVR (i.e. two-fold the S.D. value of the control group).

#### **Neuro-hormonal assay, cardio-pulmonary exercise test, echocardiographic study and 24-hour electrocardiographic recording.**

Plasma BNP, catecholamines, aldosterone level and renin activity, and thyroid profile were assayed as described in detail elsewhere [15]; NT-proBNP was measured with an automated electrochemiluminescent immunoassay (Roche diagnostics, Germany). Patients underwent a symptom-limited cardio-pulmonary exercise test on a bicycle ergometer according to a ramp protocol with increments of 10 W·min<sup>-1</sup> (Vmax, Sensormedics, Yorba Linda, CA, USA). Peak oxygen uptake (VO<sub>2</sub>, the highest value at peak-exercise, over a 20-second average) and ventilatory efficiency (slope of the ventilation versus carbon dioxide production relation in its linear part, VE/VCO<sub>2</sub>) were determined. All CPTs and echocardiographic studies were performed by a same physician blinded to the blood sampling results. The echocardiographic studies were performed by the same physician. Twenty-four hour electrocardiographic recording was obtained by a three-lead (precordial, posterior, inferior leads) digital system (Elamedical,

France). In patients with sinus rhythm, from 24-hour electrocardiographic recordings we also computed 24-h average values of normal RR intervals (RR), standard deviation of all RR (SDNN), standard deviation of 5 min mean values of RR (SDANN), square root of the mean of the sum of the squares of differences between adjacent RR (RMSSD), and the number of adjacent RR differing by more than 50 ms, as percent of the total number of RR (pNN50).

### **Day-time cardio-respiratory recording and polysomnography**

All subjects underwent a 20-minute recording while awake and spontaneously breathing in a supine position, as previously described [16]. We recorded a two lead electrocardiogram, chest wall and abdominal movements by electrical inductance, oronasal airflow by nasal pressure transducers, beat-to-beat blood pressure (Colin® tonometry, San Antonio, TX, USA), SaO<sub>2</sub> (Pulse Oxymeter Pulsox-7, Minolta®) and end-tidal pressure of the CO<sub>2</sub> signal (Cosmoplus®, Novametrics). All patients also underwent nocturnal continuous polygraphic recording by conventional polysomnography (PSG, E-series 2, Compumedics) within the same day of the short-term recording. An episode of apnoea was defined as the cessation of inspiratory airflow for at least 10 seconds, whereas a hypopnoea was defined as a reduction in airflow (> 50% of tidal volume) lasting 10 seconds or more and associated with at least a 4 percent decrease in arterial oxyhemoglobin saturation [17]. Apnoea and hypopnoea were considered as central or obstructive by the absence or presence of rib-cage and abdominal excursions, respectively. As regards night-time polygraphy, the severity of apnoeas was quantified by means of the apnoea-hypopnoea index (AHI = the number of episodes of apnoea and hypopnoea per hour, cut-off for diagnosis of CSR = 10).

### **Statistical analysis**

Statistical analysis was performed by the SPSS 13.0 program (1989-2004, LEAD technologies Inc., USA). Norepinephrine, aldosterone, plasma renin activity, BNP and NT-proBNP were logarithmically transformed to correct for a skewed distribution. Mean differences among groups were evaluated through analysis of variance. Discrete variables were compared by chi-square test with Yate's correction, or Fisher's exact test when appropriate. Post hoc testing was performed using the Bonferroni correction. The Spearman rank correlation was used to determine the direct relationship between different numerical variables. The predictive power of



a variable was quantified in terms of the area under the receiver operating curve (ROC) and the statistical significance of AUC difference from that of the line of “no information” was evaluated by Mann-Whitney *U*-Statistics. Multiple logistic regression analysis was employed in order to evaluate the influence of different variables on CSR occurrence. Values are presented as mean  $\pm$  S.D.; *P* value < 0.05 was considered significant.

## RESULTS

On the whole, 60% of HF patients showed increased hypoxic and/or hypercapnic chemosensitivity, when compared to controls. Isolated increased HVR and HCVR were found in 13% in 20% of patients, respectively, whereas a combined increase in both HVR and HCVR was present in 27% of the patients (Table 2).

Patients with increased chemosensitivity to hypoxia and/or hypercapnia did not differ as concerns to age, gender, BMI, left ventricular dimensions and function, renal and pulmonary function and arterial gas analysis values, as compared to patients with normal chemosensitivity (Table 2). Enhanced HVR and/or HCVR were associated with worse clinical severity, as expressed by percentage of patients in NYHA class III (Table 2).

### Chemosensitivity and neurohormonal activation

Patients with combined enhancement of HVR and HCVR, as compared with patients with normal chemosensitivity, showed a significant increase of plasma norepinephrine concentration, and the highest plasma levels of BNP and NT-proBNP, despite a similar degree of left ventricular systolic dysfunction. No significant differences were found with regard to cortisol, PRA, aldosterone and thyroid profile (Table 3).

A significant relationship was found between HVR or HCVR, plasma norepinephrine level (*R* 0.40 and *R* 0.37 respectively, both *P* < 0.01) and B-type natriuretic peptide expression (BNP: both *R* 0.40, *P* < 0.01; NT-proBNP: *R* 0.37 and *R* 0.41 respectively, both *P* < 0.01) (Figure 1).

### Chemosensitivity and Cheyne-Stokes respiration

Day-time CSR was found in 17 patients (28%). All HF patients with preserved chemoceptive sensitivity had a normal breathing pattern, whereas day-time CSR occurrence increased



progressively when enhanced HVR or HCVR were present, and increased significantly ( $P < 0.001$ ) when combined (Figure 2). At multivariate analysis HCVR and plasma BNP level resulted the only independent predictors of diurnal CSR (HCVR:  $\beta = 9.2$ , BNP:  $\beta = 3.5$ ,  $P < 0.05$ ) among all univariate predictors (HVR, HCVR, VE/VCO<sub>2</sub> slope, norepinephrine, BNP and NT-proBNP). The strong ability of chemosensitivity to hypercapnia and BNP plasma level in predicting CSR occurrence was confirmed by ROC analysis (HCVR: AUC  $0.92 \pm 0.04$ , cut-off value  $0.88 \text{ l}\cdot\text{min}^{-1}\cdot\text{mmHg}^{-1}$ , sensitivity 88.2%, specificity 83.7%; BNP: AUC  $0.86 \pm 0.05$ , cut-off value  $169 \text{ ng}\cdot\text{l}^{-1}$ , sensitivity 94.1%, specificity 70.4%, both  $P < 0.001$ ; figure 3).

As regards nocturnal CSR, patients with combined enhancement of HVR and HCVR presented the highest AHI, at polysomnography (Figure 2). Moreover, a significant positive correlation between HVR/HCVR and AHI was found ( $R = 0.57$  and  $R = 0.58$ , respectively, both  $P < 0.001$ ). Finally, HCVR ( $\beta = 4.4$ ,  $p < 0.05$ ) was the only independent predictor of night-time CSR (defined by an AHI  $> 10$ ), among all univariate predictors (HVR, HCVR, VE/VCO<sub>2</sub> slope, norepinephrine, BNP and NT-proBNP), with significant findings at ROC analysis (AUC  $0.87 \pm 0.04$ , cut-off value  $0.76 \text{ l}\cdot\text{min}^{-1}\cdot\text{mmHg}^{-1}$ , sensitivity 81.1%, specificity 73.2%,  $P < 0.001$ ).

### **Chemosensitivity and response to exercise**

Patients with enhanced chemosensitivity both to hypoxia and hypercapnia showed lower ventilatory efficiency, as expressed by VE/VCO<sub>2</sub> slope at cardiopulmonary test, with a non significant trend towards lower peak VO<sub>2</sub>/kg and maximum exercise workload (Table 2). Moreover, the degree of ventilatory inefficiency was related to the level of chemosensitivity to both hypoxia ( $R = 0.42$ ,  $P < 0.01$ ) and hypercapnia ( $R = 0.50$ ,  $P < 0.001$ ) (Figure 4).

### **Chemosensitivity, arrhythmias and heart rate variability**

Fifteen patients (25%) were on chronic atrial fibrillation at 24 h electrocardiographic recording, while 25 (42%) presented at least one episode of nonsustained ventricular tachycardia (more than or equal to three consecutive ventricular complexes, at a rate of more than  $100 \text{ beats}\cdot\text{min}^{-1}$ , lasting for less than 30 s). Patients with a combined enhancement of chemosensitivity to hypoxia and hypercapnia showed a higher incidence of both atrial fibrillation ( $P < 0.01$ ) and nonsustained ventricular tachycardia ( $P < 0.001$ ), when compared to patients with normal chemosensitivity (Table 3), in spite of similar pharmacological treatment.

Furthermore, we also analysed heart rate variability in patients in sinus rhythm (n° 34): patients with combined enhancement of HVR and HCVR presented a significant reduction of SDANN, among time domain heart rate variability, with a non significant trend for SDRR, likely due to the small sample size (as shown in table 3). There were no differences among groups with regard to both RMSSD and pNN50 (data not shown).

## DISCUSSION

Our study shows that increased chemosensitivity is frequent in mild to moderate chronic HF, regardless of the optimized medical treatment (including beta-blockade, anti-aldosterone drugs, and ACE/Angiotensin II inhibition). Moreover, increased chemosensitivity (particularly when combined to both hypoxia and hypercapnia) enhances sympathetic activation and is associated with depressed heart rate variability and augmented plasma concentration of BNP and NT-proBNP. Finally, it is associated with the occurrence of respiratory abnormalities, such as altered ventilatory response to exercise, either day-time or night-time CSR, with increased incidence of atrial fibrillation and ventricular arrhythmias and worse clinical status, independently of the degree of left ventricular systolic dysfunction.

Isolated or combined enhancement of chemosensitivity to hypoxia and hypercapnia are present in 60% of our patients, in spite of optimal treatment. When considered separately, the overall prevalence of increased chemosensitivity to hypoxia (40%) is similar to that previously reported [12]. On the other hand, increased chemosensitivity to hypercapnia occurred less frequently in our series (47%), if compared with previous observations (76%) in patients with mild systolic heart failure [18]. This might be explained by a blunting effect of beta-blocker administration (more frequent in our series: 92% vs 17% of patients) on the sympathetic efferent arm, with a possible prevalent effect on central chemoreflex.

In regard to neuro-hormonal derangement, our findings support the hypothesis that chronic enhancement of chemosensitivity might play a central role in sustaining adrenergic activation, possibly by the direct stimulation of sympathetic centers from chemoreceptors [8,19], or by inducing CSR-related periodic hypoxemia [20, 21]. A role of chemoreflex in eliciting adrenergic activation in HF [22], is confirmed by its persistent action on the sympathetic axis in patients following cardiac transplant [23]. Furthermore, enhanced chemosensitivity seems also to be

associated with abnormal heart rate variability, indicating an autonomic imbalance at sinus node level.

To our knowledge, this is the first study which has evidenced the effect of chemoreflex on cardiac endocrine function in humans. We found that patients with combined enhancement of chemosensitivity were characterized by higher plasma levels of B-type natriuretic peptides, as compared to patients with normal chemosensitivity, despite a similar degree of left ventricular systolic dysfunction. In this subset, beyond haemodynamic stress, the production and secretion of natriuretic peptides could be elicited by a higher sympathetic drive and chronic periodical occurrence of hypoxia during CSR [24, 25], two recognized additional stimuli for the release of natriuretic peptides [26]. Plasma concentration of B-type natriuretic peptides, would be confirmed not merely as a marker of myocardial dysfunction, but rather as an index of overall neuro-hormonal activation, contributing to its diagnostic and prognostic value in HF.

The observation made by Cheyne and Stokes two centuries ago on periodic breathing at day-time in awake HF patients [27, 28], has been recently confirmed and associated with sleep-time respiratory abnormalities [29, 30]. Day-time [31, 32] and night-time CSR [33, 34] have been associated with poor prognosis in HF patients. Increased chemosensitivity, in particular to hypercapnia, has been suggested to play a central pathophysiological role in the onset CSR [10, 11, 35, 36], together with altered haemodynamics (or delayed circulatory time) [37]. Our results support this hypothesis, extending this concept to the day-time period. Indeed, all patients with normal chemosensitivity presented a normal breathing pattern, whereas there was a progressive increase in CSR occurrence from patients with isolated to those with combined chemosensitivity enhancement.

At multivariate analysis, increased chemosensitivity to hypercapnia was an independent predictor of both day-time and night-time CSR, suggesting that CO<sub>2</sub> changes could be more relevant than O<sub>2</sub> variations for the genesis of CSR, as previously proposed [38, 39]. This provides further support to the concept that the two entities share a common pathophysiological basis. BNP level resulted an independent predictor only for day-time CSR, suggesting a stronger influence of haemodynamic or neuro-hormonal factors during wakefulness.

Combined enhancement of hypoxic and hypercapnic ventilatory response was associated with an increased ventilatory response to exercise, as expressed by the VE/VCO<sub>2</sub> slope, a recognized

prognostic marker in HF [40, 41]. The level of chemosensitivity activation was inversely related to ventilatory efficiency, thus confirming the powerful influence of chemoreceptors on ventilation during exercise [9, 41, 42]. As a matter of fact, patients with altered chemoreflex presented a worse clinical status, as expressed by higher NYHA class, independently from the degree of left ventricular dysfunction. The lack of a significant association between chemoreflex and peak-VO<sub>2</sub> in this series suggests a secondary role of chemoreflex on functional capacity on effort, mainly dependent on altered haemodynamics [43] and loss of skeletal muscle mass and function [44].

Finally, the combined enhancement of HVR and HCVR was associated with a higher incidence of both chronic atrial fibrillation and nonsustained ventricular tachycardias at 24 h electrocardiographic recording, likely to be related to the increased sympathetic tone caused by the reflex alteration, supporting previous observations [45].

In conclusion, despite optimal pharmacological treatment, increased chemosensitivity to hypoxia and hypercapnia influences several pathophysiological pathways associated with disease progression in HF, such as neuro-hormonal activation, control of respiration at rest and during effort, and ventricular arrhythmias. Hence, we suggest that the assessment of chemoreflex sensitivity may contribute to the diagnostic definition of high risk HF patients [12] and that treating abnormal chemoreflex, either by optimization of conventional treatment or by specific intervention [42, 46], could be considered a novel therapeutic target in heart failure.

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## REFERENCES

1. The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure. (2005) *Eur Heart J.* 26, 1115-1140
2. Packer, M. (1992) The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. *J Am Coll Cardiol.* 20, 248-254
3. Floras, J.S. (1993) Clinical aspects of sympathetic activation and parasympathetic withdrawal in heart failure. *J Am Coll Cardiol.* 22 (Suppl), 72A-84A
4. Francis, G.S., Benedict, C., Johnstone, D.E., et al. (1990) Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). *Circulation.* 82, 1724-1729
5. Clerico, A., Emdin, M. (2004) Diagnostic accuracy and prognostic relevance of the measurement of the cardiac natriuretic peptides: a review. *Clin Chem* 50, 33–50
6. La Rovere, M.T., Pinna, G.D., Hohnloser, S.H., et al.; ATRAMI Investigators. (2001) Autonomic Tone and Reflexes After Myocardial Infarction. Baroreflex sensitivity and heart rate variability in the identification of patients at risk for life-threatening arrhythmias: implications for clinical trials. *Circulation.* 103, 2072-2077
7. Piepoli, M., Clark, A.L., Volterrani, M., Adamopoulos, S., Sleight, P., Coats, A.J. (1996) Contribution of muscle afferents to the hemodynamic, autonomic, and ventilatory responses to exercise in patients with chronic heart failure: effects of physical training. *Circulation.* 93, 940-952

8. Narkiewicz, K., Pesek, C.A., van de Borne, P.J., Kato, M., Somers, V.K. (1999) Enhanced sympathetic and ventilatory responses to central chemoreflex activation in heart failure. *Circulation*. 100, 262-267
9. Chua, T.P., Clark, A.L., Amadi, A.A., Coats, A.J. (1996) The relationship between chemosensitivity and the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol*. 27, 650-657
10. Javaheri, S. A mechanism of central sleep apnea in patients with heart failure. (1999) *N Engl J Med*. 341, 949-954
11. Solin, P., Roebuck, T., Johns, D.P, Walters, E.H., Naughton, M.T. (2000) Peripheral and central ventilatory responses in central sleep apnea with and without congestive heart failure. *Am J Respir Crit Care Med*. 162, 2194-2200
12. Ponikowski, P., Chua, T.P., Anker, S.D., et al. (2001) Peripheral chemoreceptor hypersensitivity: an ominous sign in patients with chronic heart failure. *Circulation*. 104, 544-549
13. Read, DJ. (1967) A clinical method for assessing the ventilatory response to carbon dioxide. *Australas Ann Med*. 16, 20-32
14. Rebeck, A.S., Campbell, E.J. (1974) A clinical method for assessing the ventilatory response to hypoxia. *Am Rev Respir Dis*. 109, 345-350
15. Emdin, M., Passino, C., Prontera, C., et al. (2004) Cardiac natriuretic hormones, neurohormones, thyroid hormones and cytokines in normal subjects and patients with heart failure. *Clin Chem Lab Med* 42, 627-636
16. Mortara, A., Sleight, P., Pinna, G.D., et al. (1997) Abnormal awake respiratory patterns are common in chronic heart failure and may prevent evaluation of autonomic tone by measures of heart rate variability. *Circulation*. 96, 246-252



17. Yamashiro, Y., Kryger, M.H. (1993) Sleep in heart failure. *Sleep*. 16, 513-523
18. Yamada, K., Asanoi, H., Ueno, H., et al. (2004) Role of central sympathoexcitation in enhanced hypercapnic chemosensitivity in patients with heart failure. *Am Heart J*. 148, 964-970
19. Morgan, B.J., Crabtree, D.C., Palta, M., Skatrud, J.B. (1995) Combined hypoxia and hypercapnia evokes long-lasting sympathetic activation in humans. *J Appl Physiol*. 79, 205-213
20. Naughton, M.T., Benard, D.C., Liu, P.P., Rutherford, R., Rankin, F., Bradley, T.D. (1995) Effects of nasal CPAP on sympathetic activity in patients with heart failure and central sleep apnea. *Am J Respir Crit Care Med*. 152, 473-479
21. Van de Borne, P., Oren, R., Abouassaly, C., Anderson, E., Somers, V.K. (1998) Effect of Cheyne-Stokes respiration on muscle sympathetic nerve activity in severe congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol*. 81, 432-436
22. Mansfield, D., Kaye, D.M., Brunner La Rocca, H., Solin, P., Esler, M.D., Naughton, M.T. (2003) Raised sympathetic nerve activity in heart failure and central sleep apnea is due to heart failure severity. *Circulation*. 107, 1396-1400
23. Ciarka, A., Cuyilits, N., Vachiery, J.L., et al. (2006) Increased peripheral chemoreceptors sensitivity and exercise ventilation in heart transplant recipients. *Circulation*. 113, 252-257
24. Carmona-Bernal, C., Quintana-Gallego, E., Villa-Gil, M., Sanchez-Armengol, A., Martinez-Martinez, A., Capote, F. (2005) Brain natriuretic peptide in patients with congestive heart failure and central sleep apnea. *Chest*. 127, 1667-1673
25. Pepperell JC, Maskell NA, Jones DR, et al. (2003) A randomized controlled trial of adaptive ventilation for Cheyne-Stokes breathing in heart failure. *Am J Respir Crit Care Med*. 168, 1109-1114

26. Clerico, A., Recchia, F.A., Passino, C., Emdin, M. (2006) Cardiac endocrine function is an essential component of the homeostatic regulation network: physiological and clinical implications. *Am J Physiol Heart Circ Physiol.* 290, 17-29
27. Cheyne, J. (1818) A case of Apoplexy, in Which the Fleasy Part of the Heart Was Converted into Fat. *Dublin Hospital Reports.* II, 216.
28. Stokes, W. (1846) Observations on some Cases of permanently slow Pulse. *Dublin Quart Jour Med Sc.* II, 83.
29. Sin, D.D., Fitzgerald, F., Parker, J.D., Newton, G., Floras, J.S., Bradley, T.D. (1999) Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. *Am J Respir Crit Care Med.* 160,1101-1106
30. Javaheri, S. (2006) Sleep disorders in systolic heart failure: a prospective study of 100 male patients. The final report. *Int J Cardiol.* 106, 21-28
31. Ponikowski, P., Anker, S.D., Chua, T.P., et al. (1999) Oscillatory breathing patterns during wakefulness in patients with chronic heart failure: clinical implications and role of augmented peripheral chemosensitivity. *Circulation.* 100, 2418-2424
32. La Rovere, M.T., Pinna, G.D., Maestri, R., et al. (2007) Clinical relevance of short-term daytime breathing disorders in chronic heart failure patients. *European Journal of Heart Failure*, in the press.
33. Lanfranchi, P.A., Braghiroli, A., Bosimini, E., et al. (1999) Prognostic value of nocturnal Cheyne-Stokes respiration in chronic heart failure. *Circulation.* 99, 1435-1440

34. Hanly, P.J., Zuberi-Khokhar, N.S. (1996) Increased mortality associated with Cheyne-Stokes respiration in patients with congestive heart failure. *Am J Respir Crit Care Med.* 153, 272-276
35. Cherniack, N.S. and Longobardo, G.S. (1986) Abnormalities in respiratory rhythm. In: *Handbook of Physiology. The Respiratory System. Control of Breathing.* (Bethesda, MD: Am. Physiol. Soc., sect. 3, vol. II, pt. 2, chapt. 22), p. 729-749
36. Francis, D.P., Willson, K., Davies, L.C., Coats, A.J., Piepoli, M. (2000) Quantitative general theory for periodic breathing in chronic heart failure and its clinical implications. *Circulation.* 102, 2214-2221
37. Hall, M.J., Xie, A., Rutherford, R., Ando, S., Floras, J.S., Bradley, T.D. (1996) Cycle length of periodic breathing in patients with and without heart failure. *Am J Respir Crit Care Med.* 154, 376-381
38. Duffin, J. (1990) The chemoreflex control of breathing and its measurement. *Can J Anaesth.* 37, 933-942
39. Mohan, R., Duffin, J. (1997) The effect of hypoxia on the ventilatory response to carbon dioxide in man. *Respir Physiol.* 108, 101-115
40. Francis, D.P., Shamim, W., Davies, L.C., et al. (2000) Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO<sub>2</sub> slope and peak VO<sub>2</sub>. *Eur Heart J.* 21, 154-161
41. Ponikowski, P., Francis, D.P., Piepoli, M.F., et al (2001) Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. *Circulation.* 103, 967-972

42. Chua, T.P., Harrington, D., Ponikowski, P., Webb-Peploe, K., Poole-Wilson, P.A., Coats, A.J. (1997) Effects of dihydrocodeine on chemosensitivity and exercise tolerance in patients with chronic heart failure. *J Am Coll Cardiol.* 29, 147-152
43. Wasserman, K. (1990) Measures of functional capacity in patients with heart failure. *Circulation.* 81 (Suppl II), 1-4
44. Piepoli, M.F., Kaczmarek, A., Francis, D.P., et al (2006) Reduced peripheral skeletal muscle mass and abnormal reflex physiology in chronic heart failure. *Circulation.* 114, 126-134
45. Chua T. P., Ponikowski, P., Webb-Peploe, K., et al. (1997) Clinical characteristics of chronic heart failure patients with an augmented peripheral chemoreflex. *European Heart Journal* 18, 480-486
46. Spicuzza, L., Gabutti, A., Porta, C., Montano, N., Bernardi, L. (2000) Yoga and chemoreflex response to hypoxia and hypercapnia. *Lancet.* 356, 1495-1496

## FIGURE LEGENDS

### Figure 1

Relationship between enhanced chemosensitivity to hypoxia (HVR) and to hypercapnia (HCVR) with norepinephrine (panel (a) and (b), respectively) and with B-type natriuretic peptide level (BNP, panel (c) and (d), respectively). The graph represents all 60 subjects studied.

### Figure 2

Prevalence of diurnal Cheyne-Stokes respiration at short-term polygraphy (CSR, left Y axis) and nocturnal apnoea-hypopnoea index at polysomnography (AHI, right Y axis) among patients with preserved chemoreflex, with isolated or combined enhanced chemosensitivity to hypoxia (HVR) and hypercapnia (HCVR). \* and † =  $p < 0.001$  vs normal chemoreflex

### Figure 3

Receiver operating characteristic curve of chemosensitivity to hypercapnia (HCVR, panel (a)) and B-type natriuretic peptide (BNP, panel (b)) for the prediction of day-time CSR.

### Figure 4

Relationship between enhanced chemosensitivity to hypoxia (HVR) and to hypercapnia (HCVR) with peak oxygen uptake ( $VO_2/kg$ , panel (a) and (b), respectively) and with  $VE/VCO_2$  slope (panel (c) and (d), respectively). The graph represents all 60 subjects studied.

**Table 1** Characteristics of control subjects and HF patients.

	Controls (n= 12)	HF patients (n= 60)
Age (years)	65 ± 1	66 ± 1
Male (%)	84	88
Body mass index (kg·m <sup>-2</sup> )	26.7 ± 0.4	27.4 ± 0.5
Creatine clearance (ml·min <sup>-1</sup> )	85.3 ± 6.8	79.2 ± 4.1
Ischaemic / idiopathic / secondary (%)	/	38 / 50 / 12
Atrial fibrillation (%)	/	25
NYHA class I / II / III (%)	/	10 / 50 / 40
Left ventricular ejection fraction (%)	60.2 ± 2.4	30.7 ± 0.9*
HVR (l·min <sup>-1</sup> ·%SaO <sub>2</sub> <sup>-1</sup> )	0.35 ± 0.21	0.74 ± 0.06†
HCVR (l·min <sup>-1</sup> ·mmHg <sup>-1</sup> )	0.31 ± 0.24	0.83 ± 0.07†
Furosemide (%)		90
Beta-blockers (%)		92
ACE inhibitors (%)		62
ARBs (%)		22
Spironolactone		62

Values are expressed by mean ± SEM, except for categorical data expressed by %.

\* = P < 0.05, † = P < 0.01 vs normal controls.

NYHA= New York Heart Association; HVR= hypoxic ventilatory response; HCVR= hypercapnic ventilatory response; ACE= angiotensin converting enzyme; ARBs= angiotensin receptor blockers.



**Table 2.** Clinical characteristics, cardiac, renal and pulmonary function according to chemosensitivity

	Normal HVR and HCVR	Increased HVR	Increased HCVR	Increased HVR and HCVR
N (%)	24 (40)	8 (13)	12 (20)	16 (27)
Age (yrs)	64 ± 2	64 ± 2	68 ± 5	69 ± 3
Male (n, %)	20 (83%)	7 (88%)	11 (92%)	15 (93%)
BMI (kg·m <sup>-2</sup> )	27.9 ± 0.9	28.8 ± 1.2	26.2 ± 0.9	27.7 ± 0.6
NYHA class III (%)	16	50*	50*	56*
LVEF (%)	31.4 ± 1.4	28.3 ± 2.9	29.8 ± 2.3	31.4 ± 2.0
LV-EDVi (ml·m <sup>-2</sup> )	135.1 ± 7.2	136.3 ± 16.4	146.9 ± 10.1	140.4 ± 9.2
LV-ESDi (ml·m <sup>-2</sup> )	86.4 ± 6.8	96.6 ± 13.1	94.1 ± 11.9	89.1 ± 6.9
Creatinine cl. (ml·min <sup>-1</sup> )	84.0 ± 6.6	84.8 ± 10.1	80.8 ± 7.7	74.1 ± 5.3
FEV 1 (L)	2.64 ± 0.24	2.61 ± 0.35	2.27 ± 0.23	2.56 ± 0.19
FEV1/VC	72.3 ± 1.9	78.7 ± 3.2	73.3 ± 4.9	68.5 ± 2.8
PH	7.44 ± 0.01	7.45 ± 0.01	7.44 ± 0.01	7.46 ± 0.01
paO <sub>2</sub> (mmHg)	80.2 ± 1.5	82.8 ± 1.9	78.0 ± 3.3	78.9 ± 2.1
paCO <sub>2</sub> (mmHg)	36.5 ± 1.0	35.1 ± 0.3	35.8 ± 0.9	33.3 ± 0.9
HVR (l·min <sup>-1</sup> ·%SaO <sub>2</sub> <sup>-1</sup> )	0.40 ± 0.04	1.12 ± 0.13*	0.55 ± 0.05	1.17 ± 0.07*
HCVR (l·min <sup>-1</sup> ·mmHg <sup>-1</sup> )	0.47 ± 0.04	0.66 ± 0.06	0.99 ± 0.04*	1.29 ± 0.09*†

Values are expressed by mean ± SEM, except for categorical data expressed by %.

\* = P < 0.001 vs normal HVR and HCVR; † = P < 0.05 vs increased HCVR alone.

BMI: body mass index; NYHA= New York Heart association; EF: left ventricular ejection fraction; HVR: chemosensitivity to hypoxia; HCVR: chemosensitivity to hypercapnia; LV-EDVi= left ventricular end diastolic volume index; LV-ESVi= left ventricular end systolic volume index; Creatinine cl.= creatinine clearance; FEV1= forced expiratory volume in 1 second; VC= vital capacity; PAO<sub>2</sub>= arterial partial pressure of oxygen; PACO<sub>2</sub>= arterial partial pressure of carbon dioxide.

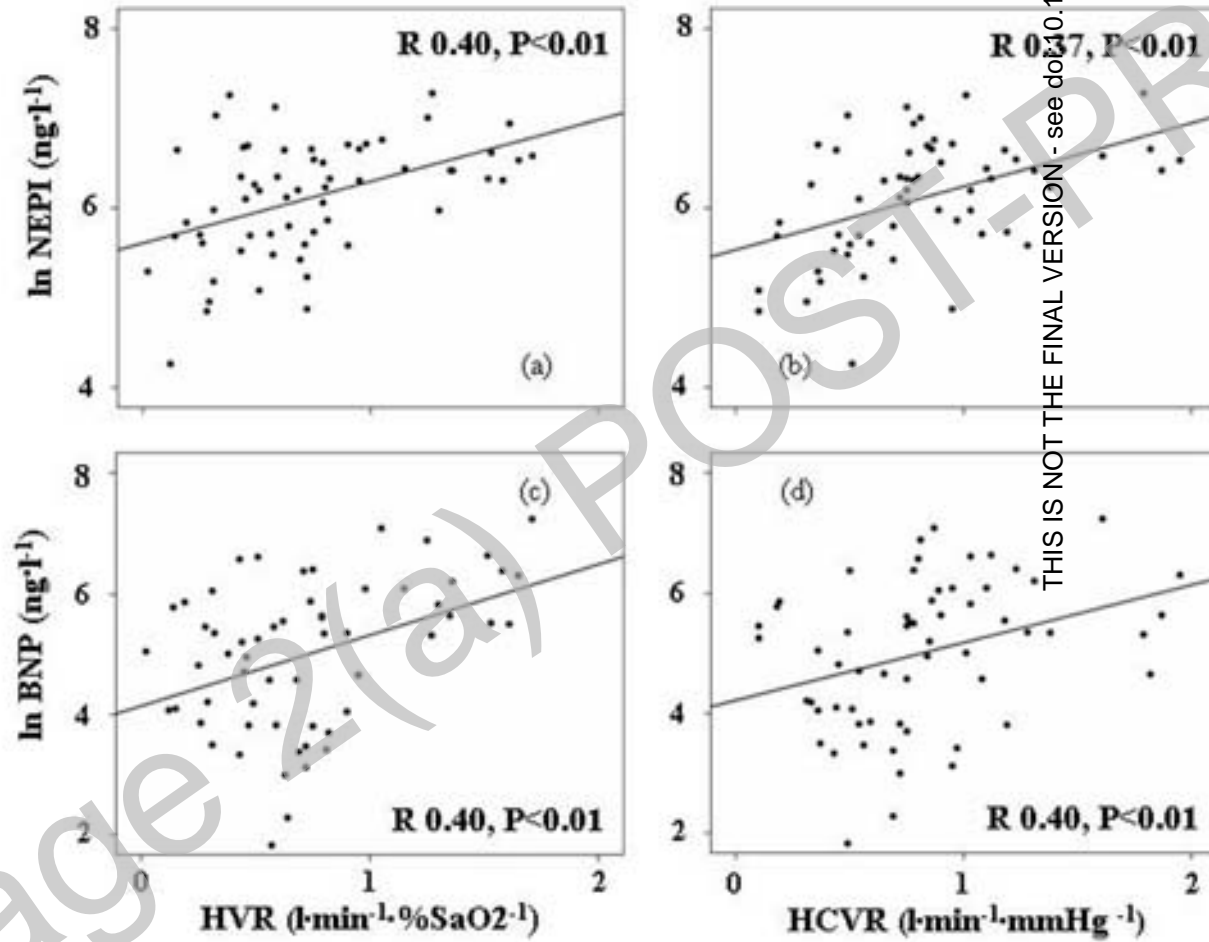
**Table 3:** Neurohormonal profile, functional capacity and ventilatory efficiency and arrhythmias according to chemosensitivity .

	Normal HVR and HCVR	Increased HVR	Increased HCVR	Increased HVR and HCVR
Norepinephrine (ng·l <sup>-1</sup> )	427.1 ± 69.9	619.1 ± 84.5	621.7 ± 97.9	689.0 ± 72.3†
BNP (ng·l <sup>-1</sup> )	102.4 ± 20.6	270.6 ± 77.6	314.2 ± 75.1*	413.2 ± 92.7‡
NT-proBNP (ng·l <sup>-1</sup> )	832.7 ± 195.5	1620.7 ± 381.9	2945.5 ± 713.6*	3035.0 ± 787.3†
Cortisol (ng·l <sup>-1</sup> )	155.4 ± 9.2	155.8 ± 24.8	196.1 ± 40.0	184.9 ± 15.7
PRA (ng·ml <sup>-1</sup> ·h <sup>-1</sup> )	3.3 ± 1.5	4.3 ± 1.6	2.7 ± 0.9	5.7 ± 2.4
Aldosterone (ng·l <sup>-1</sup> )	149.2 ± 24.3	152.8 ± 37.5	178.1 ± 36.8	272.7 ± 73.1
ft3 (ng·l <sup>-1</sup> )	2.5 ± 0.1	2.6 ± 0.1	2.3 ± 0.1	2.3 ± 0.1
ft4 (ng·l <sup>-1</sup> )	10.9 ± 0.5	11.2 ± 0.8	11.3 ± 0.7	12.8 ± 1.5
TSH (μUI·ml <sup>-1</sup> )	2.1 ± 0.2	2.2 ± 0.6	2.1 ± 0.4	2.2 ± 0.3
Peak VO <sub>2</sub> /kg (ml·min <sup>-1</sup> ·kg <sup>-1</sup> )	13.4 ± 1.1	12.0 ± 1.5	12.6 ± 2.3	10.5 ± 0.6
VE/VCO <sub>2</sub> slope	35.0 ± 1.3	42.8 ± 2.1	38.8 ± 2.8	46.3 ± 2.6‡
Workload (W)	97.1 ± 9.0	82.5 ± 8.4	89.4 ± 21.05	69.3 ± 5.4
SDANN (ms)	74.5 ± 4.3	87.7 ± 20.6	82.1 ± 8.1	33.5 ± 11.7*§
SDNN (ms)	95.4 ± 4.7	99.7 ± 18.7	90.6 ± 13.9	71.8 ± 28.4
Atrial fibrillation (%)	8	14	16	62‡§
NSVT (%)	20	38	58†	63†

Values are expressed by mean ± SEM, except for categorical data expressed by %.

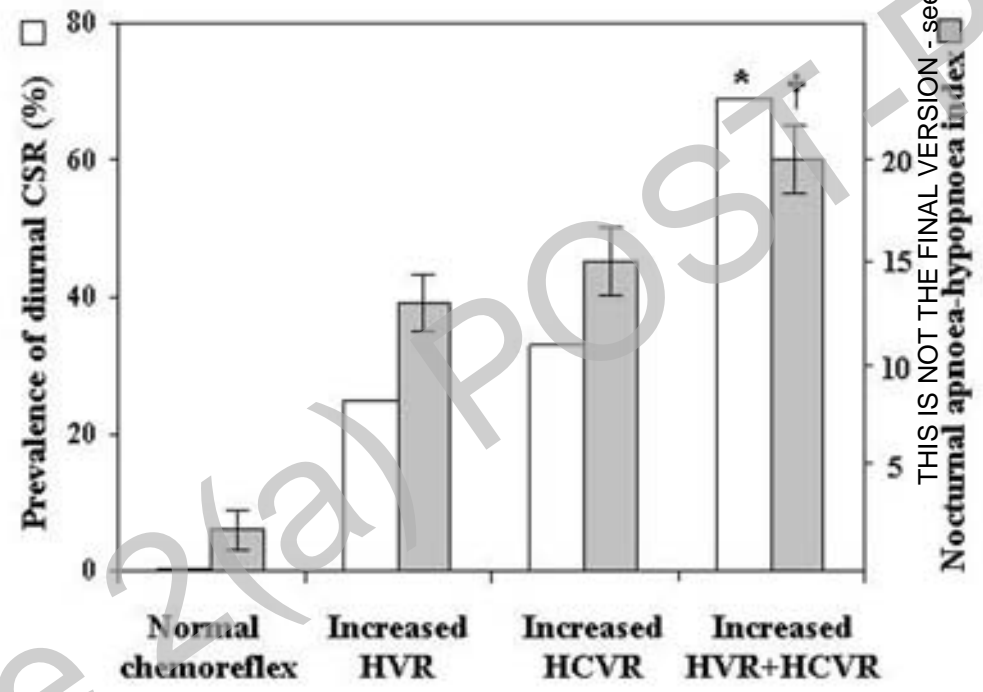
\*= P < 0.05, † = P < 0.01, ‡ = P < 0.001 vs normal HVR and HCVR; § = P < 0.05 vs increased HVR alone; || = P < 0.05 vs increased HCVR alone.

BNP= brain natriuretic peptide; NT-proBNP= amino-terminal pro-brain natriuretic peptide; PRA= plasma renin activity; ft3= free triiodothyronine; ft4= free tetraiodothyronine; VO<sub>2</sub>= oxygen uptake; VE/VCO<sub>2</sub> slope= regression slope relating minute ventilation to carbon dioxide output; SDNN= standard deviation of all RR; SDANN= standard deviation of 5 min mean values of RR; NSVT= non sustained ventricular tachycardia. SDNN and SDAN were computed only in patients in sinus rhythm (n° 34).



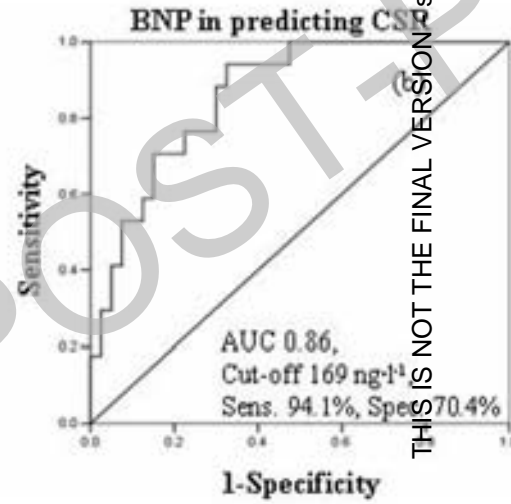
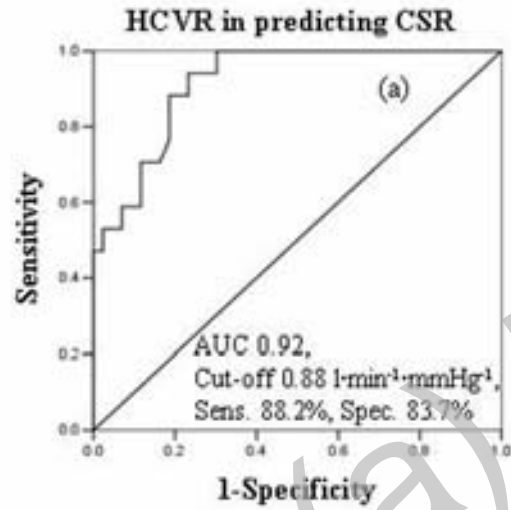
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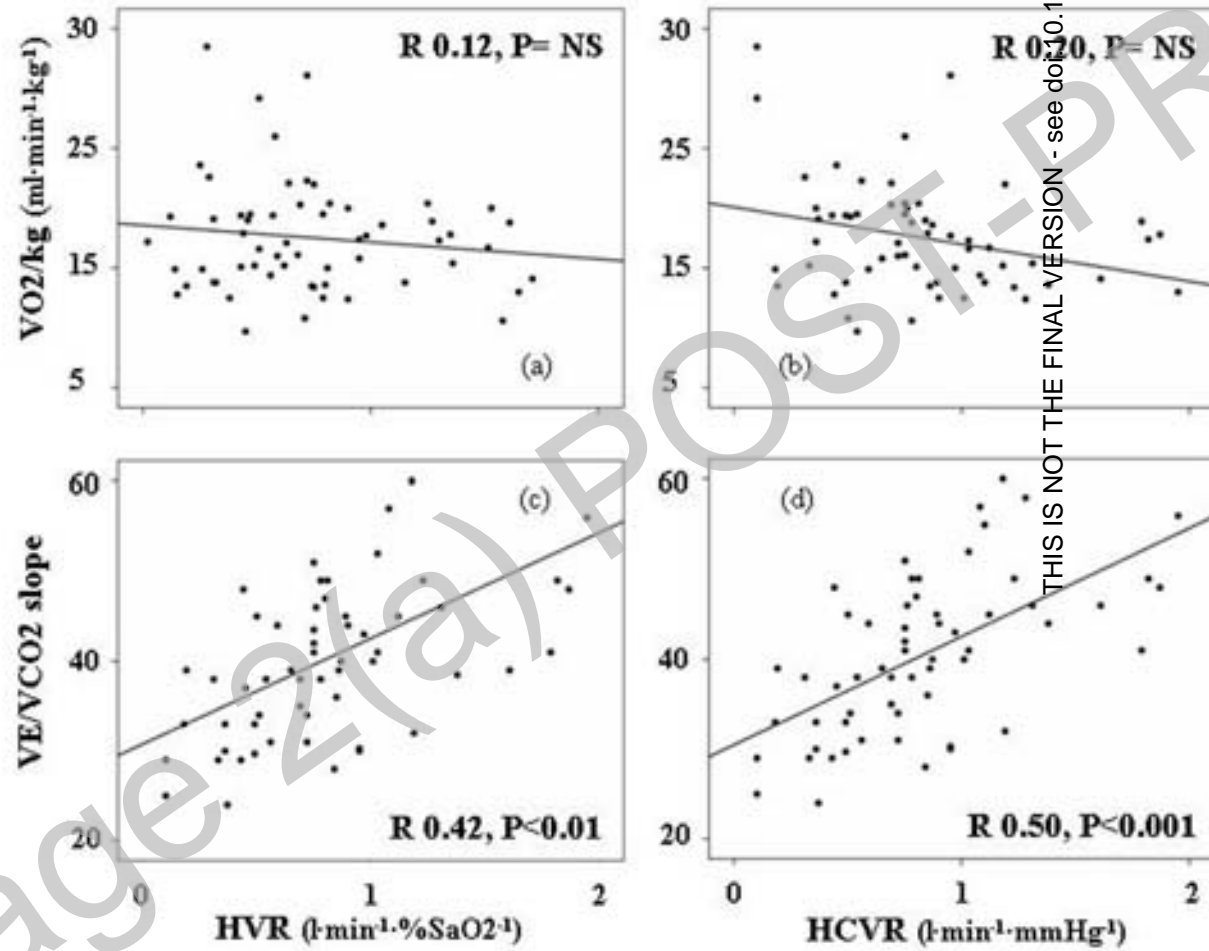
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