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Abnormal hyperventilation in patients with hepatic cirrhosis: Role of enhanced chemosensitivity to carbon dioxide

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ABSTRACT

Background: Patients with hepatic cirrhosis frequently show idiopathic hyperventilation at rest, despite no concomitant cardiopulmonary disease. The aim of the study was to determine whether altered chemosensitivity either to hypoxia or hypercapnia could underlie inappropriate hyperventilation in cirrhotic patients.

Methods: We consecutively recruited 30 biopsy proven cirrhotic patients equally distributed in the three Child's classes A, B and C (age 54 ± 8 years, mean ± SD). All patients underwent evaluation of chemosensitivity to hypoxia and to hypercapnia and blood sampling for brain natriuretic peptide, norepinephrine and progesterone, besides full clinical characterization. We also recruited 10 age- and gender-matched healthy controls (age 55 ± 7 years).

Results: Overall, 18 patients (60%) showed an increased chemosensitivity to carbon dioxide (CO_2), while 8 patients (27%) showed enhanced chemosensitivity to hypoxia. Child's class C patients had lower arterial partial pressure of CO_2 ($PaCO_2$), higher rest ventilation, increased chemosensitivity to hypercapnia, plasma level of norepinephrine and serum progesterone levels when compared to class A patients and controls (all $p<0.05$). Rest ventilation was positively related to pH ($R=0.41$, $p=0.023$), chemosensitivity to hypercapnia ($R=0.54$, $p=0.002$), and progesterone ($R=0.53$, $p=0.016$) and negatively to $PaCO_2$ ($R=0.61$, $p<0.001$), but not to hemoglobin level and chemosensitivity to hypoxia. Chemosensitivity to hypercapnia was positively related to $PaCO_2$ ($R=0.74$, $p<0.001$), serum progesterone ($R=0.50$, $p=0.016$), and to plasma norepinephrine ($R=0.57$, $p=0.004$).

Conclusions: Enhanced chemosensitivity to hypercapnia was found in more decompensated cirrhotic patients and was associated with sympathetic overactivity and elevated serum progesterone, likely representing a key mechanism underlying the "unexplained" hyperventilation observed in such patients.

1. Introduction

A reduction in respiratory gas exchange efficiency is a rather common finding in patients with hepatic cirrhosis, resulting in a wide spectrum of arterial oxygenation abnormalities [1,2]. On the one hand, an association between vascular abnormalities and parenchymal pulmonary diseases is believed to be responsible for oxygen delivery failure [3]: in particular, a mismatch between pulmonary ventilation and perfusion has been described as a consequence of abnormalities involving vascular bed (intrapulmonary vasodilatation), hemodynamics (hyperdynamic circulation) and ventilation (early airway closure, alveolar restriction, organic parenchimal causes) [4]. On the other hand, some cirrhotic patients in a pre-transplant stage frequently show "idiopathic" hyperventilation at rest, associated with hypocapnia and alkalosis, in absence of detectable organic cardiopulmonary dysfunction [1,3]. Several mechanisms, including hypoxemia, increased serum ammonia and hypoproteinemia have been proposed and rebutted [5–7].

Under physiological conditions ventilation is controlled by both peripheral and central chemoreceptors [8]. A raised chemosensitivity either to hypoxia [9] or hypercapnia [10], due to hemodynamics and neurohormonal factors, has been described in chronic heart failure and linked to a respiratory pattern similar to the one observed in cirrhotic patients: rest hyperventilation, hypocapnia and alkalosis. Circulating sex hormones and in particular progesterone levels have been found to affect ventilation not only in healthy subjects [11] and pregnant women [12], but also in patients with impaired hepatic

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metabolism [13]. At present, the mechanism by which progesterone affects ventilation in cirrhotic patients is not known. Moreover, it is unclear whether this phenomenon is linked to changes in the function of peripheral and/or central chemoreceptors.

We hypothesized that an altered chemosensitivity to hypoxia and/or hypercapnia, possibly driven by hormonal changes, might be the pathophysiological mechanism underlying the "idiopathic" abnormal ventilatory pattern observed in cirrhotic patients. In order to test our hypothesis, we studied a population of cirrhotic patients in pre-transplant stage and no cardiopulmonary disease.

2. Methods

2.1. Patients and study design

We prospectively studied consecutive patients with hepatic cirrhosis and portal hypertension who were undergoing liver transplant evaluation, ten in each of the three categories of the Child–Pugh classification (A, B, C), with a total of 30 patients finally recruited (age, mean ± SD, 54 ± 8 years, 73% males). Patients were compared with a control population that consisted of 10 age and gender matched healthy subjects (age 55 ± 7 years, 70% males). For the patient population, the diagnosis was biopsy-verified and based on established clinical, biochemical, and ultrasonographic criteria. Exclusion criteria were: significant functional intra-pulmonary shunt (i.e. PaO_2 <500 mm Hg after a 20-minute period of 100% oxygen breathing), impaired left ventricular systolic function (i.e. ejection fraction ≤50%), chronic pulmonary disease, acute hepatic encephalopathy or reduced renal function (i.e glomerular filtration rate <50 ml/min). Patients taking morphine or derivates, theophylline, oxygen, benzodiazepines or acetazolamide and premenopausal women were also excluded. All patients were afebrile at time of evaluation. We screened 67 consecutive patients, in order to achieve the goal of ten patients in each of the three Child–Pugh classes and to comply the above mentioned inclusion/exclusion criteria.

The study protocol consisted of comprehensive clinical evaluation and same day assessment of: a) chemosensitivity to hypoxia and to hypercapnia by evaluation of the individual hypoxic–normocapnic (HVR) and normoxic–hypercapnic ventilatory response (HCVR); b) neuro-hormonal evaluation; c) echocardiography (HP Sonos 7500, Philips); d) 20-minute polygraphy during day-time for assessment of breathing pattern; e) arterial blood gas analysis (semiautomatic gas analyser Instrumentation Laboratory, IL 1302); f) pulmonary function tests by means of a spirometer (Comprehensive pulmo-lab, Morgan LTD); g) single-breath carbon monoxide diffusion capacity by a gas-analyser (PK Morgan LTD); and h) hyperoxia testing for evaluation of functional shunts. Due to the possible influence of smoking habit on several of the measured parameters, all subjects who were smoker (9 patients and 4 controls) were asked to avoid smoking at least 12-hours before examination. Written informed consent was obtained from each subject and the study protocol conformed to the Declaration of Helsinki and was approved by our institutional review committee.

2.2. Rest ventilation and chemosensitivity evaluation

After a 20-minute period of familiarization with the laboratory, breath-by-breath measurements of ventilation, tidal volume, and breathing frequency were collected using automated equipment (Sensormedics,Vmax 229, USA) during steady-state breathing at rest in all patients and controls. Simultaneously, arterial blood was drawn into a heparinized syringe through a 20-gauge catheter previously inserted into the right or left radial artery. The arterial blood samples were immediately processed for blood gas analysis.

We used the re-breathing technique to assess chemoceptive sensitivity, as described elsewhere in detail [14,15]: briefly, subjects were examined in standardized conditions, in a quiet room at a comfortable temperature, while seated and connected to a re-breathing circuit through a mouthpiece. They were not allowed to drink alcohol or caffeine-containing beverages in the 12 h preceding the study. During the progressive isocapnic hypoxia trial (from resting SaO_2 values to 70–80%, according to individual tolerance), end-tidal CO_2 was maintained at a baseline value by passing a portion of the expired air into a scrubbing circuit before returning it to a 5-litre rebreathing bag. Conversely, during the progressive normoxic hypercapnic trial (from resting end-tidal CO_2 values until 50 mm Hg or an increase >10 mm Hg from the basal values, according to individual tolerance), inspired PO_2 (partial pressure of oxygen) was kept at the baseline value by adding oxygen to the circuit. The hypoxic ventilatory response (HVR) was expressed by the linear regression slope between minute ventilation and SaO_2, during the hypoxic–normocapnic trial. The hypercapnic ventilatory response (HCVR) was expressed by the linear regression slope between minute ventilation and end-tidal pressure of carbon dioxide (CO_2), during the hypercapnic–normoxic trial. The mean value of the control group plus two standard deviations was used as cut-off values to define increased chemosensitivity ($0.76\ L\cdot min^{-1}\cdot\%SaO_2^{-1}$ for HVR and $0.75\ L\ min^{-1}\ mm\ Hg^{-1}$ for HCVR, respectively).

2.3. Daytime cardio-respiratory recording and neurohormonal assay

All subjects underwent a 20-minute polygraphic recording while awake and breathing spontaneously in a supine position, as previously described in chronic heart failure patients [16,17], to identify the presence of periodic breathing (i.e. occurrence of cyclical episodes of apnea/hypopnea followed by hyperpnea) [18].

Venous blood samples were withdrawn between 8 and 9 a.m. from an antecubital vein, after a 20-min period of supine rest according to a standardized experimental protocol [19]. Plasma B-type natriuretic peptide (BNP) was measured with two-site immunoradiometric assays (IRMA; Shionogi, Osaka, Japan). Plasma concentration of norepinephrine was determined by automatic HPLC 725 (Eurogenetics-Tosoh, Torino, Italy), as described elsewhere [19]. Serum progesterone concentration was measured by a competitive binding immunoenzymatic assay (Access Progesterone, Beckman Coulter, Inc.).

2.4. Statistical analysis

Statistical analysis was performed using SPSS version 13.0 (1989–2004, Inc., USA). Values are presented as mean ± standard deviation (SD), or median and interquartile range (for values with non-normal distribution); variables with a skewed distribution were logarithmically transformed, in order to perform parametric statistics. Mean differences among groups were evaluated through analysis of variance with Bonferroni *post hoc* correction, when appropriate. Discrete variables where compared by chi-square test with Yates' correction, or Fisher's exact test. The Pearson correlation coefficient was used to determine the direct relationship between different numerical variables. P value <0.05 was considered significant.

3. Results

Baseline characteristics of patients and controls are summarized in Table 1. All patients and controls had normal pulmonary function tests, as well as a preserved diffusion capacity for carbon monoxide (Table 1). None of the patients demonstrated periodic breathing at the 20-min daytime monitoring. Overall, 18 patients (60%) showed an increased chemosensitivity to CO_2, while 8 patients (27%) showed an enhanced chemosensitivity to hypoxia. When comparing all cirrhotic patients with the control group, the former showed a higher rest ventilation (11.3 ± 2.6 versus 8.7 ± 1.8 L/min, p = 0.006) and chemosensitivity to hypercapnia (0.94, IQR 0.56–1.29 versus 0.26, IQR 0.16–0.57 $L\ min^{-1}\ mm\ Hg^{-1}$, p = 0.005) and lower $PaCO_2$ (33.2 ± 3.8 versus 38.2 ± 3.0 mm Hg, p = 0.001), with only a non significant trend toward higher chemosensitivity to hypoxia (0.45, IQR 0.28–0.41 versus 0.38, IQR 0.1–0.52 $L\cdot min^{-1}\cdot\%SaO_2^{-1}$, p = 0.09).

When patients were stratified according to Child–Pugh class, as compared to patients in class A, those in class C demonstrated lower $PaCO_2$, higher ventilation, and enhanced chemosensitivity to CO_2 (Table 2, Fig. 1). Moreover, patients with more advanced liver disease had higher plasma norepinephrine and serum progesterone concentrations (Fig. 1). No difference among groups was found for plasma BNP concentration (Table 2). In general, patients in class B had an intermediate behavior (Table 2).

Taking the cirrhotic population as a whole, ventilation was positively related to pH (R = 0.41, p = 0.023, Fig. 2, panel a), to

Table 1
Characteristics of the control subject and patients with HC.

	Controls (n = 10)	HC patients (n = 30)
Age (years)	55 ± 7	54 ± 8
Sex (M/F)	7/3	22/8
Body mass index (kg/m^2)	25.0 ± 2.9	26.1 ± 3.6
Child–Pugh class (n)	–	A: 10; B:10; C:10
Left ventricular ejection fraction (%)	57.7 ± 6.1	54.3 ± 4.6
Smokers (%)/pack/year	30%/25 ± 19	40%/21 ± 20
Total lung capacity (% predicted)	105 ± 17	100 ± 11
Slow vital capacity (% predicted)	109 ± 14	112 ± 13
FEV_1 (% predicted)	112 ± 9	110 ± 10
D_LCO (% predicted)	90 ± 15	87 ± 16
Etiology (n):		
Hepatitis B	–	6
Hepatitis C	–	12
Alcoholic	–	5
Cryptogenic	–	3
Mixed	–	4

Values are expressed as mean ± standard deviation. FEV_1: forced expiratory volume in 1 s; D_LCO: lung diffusing capacity for carbon monoxide.

Table 2
Arterial blood gas analysis, ventilation, chemoreflex sensitivity and neurohormonal plasma levels of patients in Child–Pugh class A, B and C.

Class	A	B	C
MELD score	7.2 ± 3.5	10.5 ± 3.6*	14.8 ± 6.2†§
Creatinine (mg/dl)	0.82 ± 0.17	0.90 ± 0.24	0.88 ± 0.33
Bilirubine (mg/dl)	1.41 ± 0.90	2.08 ± 1.09*	4.05 ± 2.85†§
INR	1.25 ± 0.56	1.41 ± 0.19*	1.63 ± 0.47†
$PaCO_2$ (mm Hg)	34.9 ± 3.6	31.9 ± 3.7	30.4 ± 3.9†
PaO_2 (mm Hg)	91 ± 12	99 ± 11	99 ± 15
pH	7.42 ± 0.02	7.43 ± 0.02	7.44 ± 0.04
Hemoglobin (g/dL)	14.1 ± 1.5	11.7 ± 1.2	10.6 ± 2.2‡
Ventilation (L/min)	9.6 ± 1.5	11.1 ± 2.4	12.8 ± 2.6†
HVR ($L\,min^{-1}\cdot\%SaO_2^{-1}$)	0.63 (0.35–1.01)	0.45 (0.30–0.75)	0.31 (0.26–0.63)
HCVR ($L\,min^{-1}\,mm\,Hg^{-1}$)	0.59 (0.43–0.94)	0.88 (0.63–1.22)	1.14 (0.93–1.56)†
Norepinephrine (ng/L)	372 (297–539)	518 (352–602)	866 (566–1076)*§
BNP (ng/L)	11 (4.5–25.5)	30 (12–53)	22.5 (17–73)
Progesterone (ng/mL)	1.6 (1.3–1.9)	2.5 (1.6–3.2)	3.8 (2.9–4.8)†§
Diuretic use (%)	0	20	60
Transplanted within 1 year (%)	50	60	70

Values are expressed as mean ± standard deviation or as median (interquartile range), unless otherwise stated.
MELD: model for end-stage liver disease; INR: international normalized ratio; $PaCO_2$: arterial partial pressure of carbon dioxide; PaO_2: arterial partial pressure of oxygen; HVR: hypoxic ventilatory response; HCVR: hypercapnic ventilatory response; BNP: brain natriuretic peptide.
* $p<0.05$.
† $p<0.01$.
‡ $p<0.001$ versus class A.
§ $p<0.05$ versus class B.

HCVR ($R=0.54$, $p=0.002$, Fig. 2, panel b) and to progesterone ($R=0.53$, $p=0.016$, Fig. 2, panel c) and negatively to arterial partial pressure of carbon dioxide ($PaCO_2$, $R=0.61$, $p<0.001$, Fig. 2, panel d). Conversely, no significant relationship was observed between ventilation and HVR, hemoglobin and norepinephrine.

Chemoreflex sensitivity to CO_2 (but not to hypoxia) was positively related to basal $PaCO_2$ ($R=0.74$, $p<0.001$), progesterone serum level ($R=0.50$, $p=0.016$, Fig. 3, panel a) and to the degree of sympathetic activation, as expressed by the norepinephrine plasma concentration ($R=0.57$, $p=0.004$, Fig. 3, panel b).

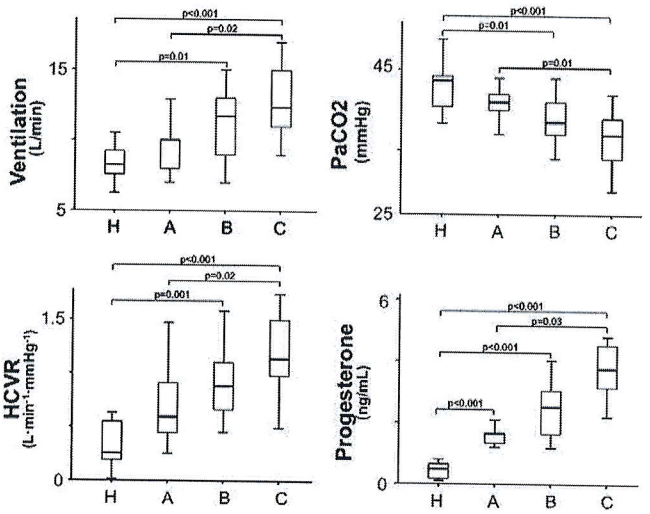

Fig. 1. Behaviour of ventilation, partial pressure of carbon dioxide, chemosensitivity to carbon dioxide and plasma progesterone in healthy subjects (H) and cirrhotic patients divided according to the three Child's class (A, B and C). The 10th, 25th, 50th (median), 75th, and 90th percentiles are indicated as boxes and lines.

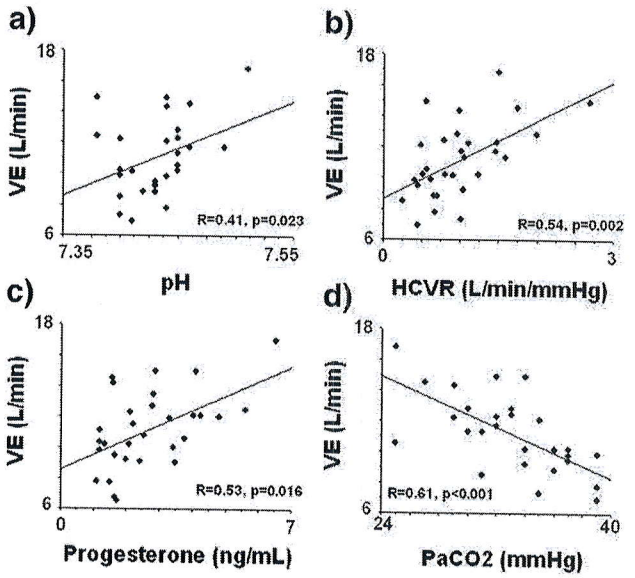

Fig. 2. Relationship between ventilation at rest and pH values (a), degree of chemosensitivity to carbon dioxide (b), plasma levels of progesterone (c), and partial pressure of carbon dioxide (d) in cirrhotic patients. $PaCO_2$: arterial partial pressure of carbon dioxide; HCVR: hypercapnic ventilatory response.

4. Discussion

Our study first reveals that increased chemosensitivity to hypercapnia, but not to hypoxia, is a frequent finding in patients with cirrhosis, and more marked the more advanced the disease. It is associated with increased sympathetic activity and serum progesterone concentrations and appears to contribute to the "unexplained" hyperventilatory, hypocapnic and alkalotic pattern typical of the advanced stages of the disease. Unlike heart failure patients, none of the patients demonstrated day-time periodic breathing despite rest hypocapnia.

Although a mismatch between pulmonary ventilation and perfusion is a well recognised causal factor for ventilatory inefficiency in cirrhotic patients [4,20–22], there are currently no consistent data on the mechanisms responsible of the "idiopathic" hyperventilation state observed in some cirrhotic patients whose cardiopulmonary function is otherwise normal [1,3]. Several mechanisms have been proposed, including increased serum ammonia [6], hypoxia [5], and, more recently, raised sex hormones (namely progesterone) [13]. Hyperammonemia is a common finding in cirrhotic patients: however, venous ammonia concentration has not been shown to correlate with minute ventilation [6]. Patients with cirrhosis often present with hypoxia from different causes including intrapulmonary shunts, mismatch between pulmonary ventilation and perfusion, the

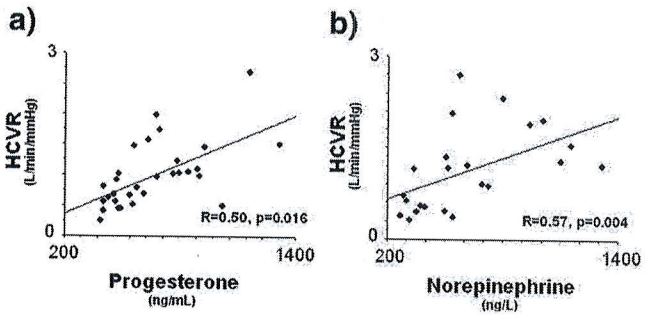

Fig. 3. Plots showing the direct relationship between chemosensitivity to hypercapnia and the level of plasma progesterone (a) and norepinephrine (b) in cirrhotic patients. HCVR: hypercapnic ventilatory response.

presence of ascites and/or pleural fluid [4,22]: however, the mild degree of hypoxemia present in cirrhotic patients has been shown not to cause hyperventilation [5,20]. In our series, in which patients with hypoxia were excluded, the arterial partial pressure of oxygen was normal in all patients. Moreover, no differences in the arterial partial pressure of oxygen was observed among the three Child–Pugh classes, nor was there any correlation with resting pulmonary ventilation.

On the contrary, and consistent with the results of the previous findings [1,5,6,13], we found that patients with Child–Pugh class C cirrhosis demonstrated both alveolar hyperventilation and reduced $PaCO_2$ at rest compared to patients with less decompensated disease. In addition, patients in class C showed increased chemosensitivity to CO_2 and elevated values of plasma norepinephrine and serum progesterone compared to patients in class A. Progesterone is able to affect ventilation in healthy subjects and a strong correlation between $PaCO_2$ and serum progesterone levels has been observed in pregnant women [12]. The mechanisms of progesterone-induced hyperventilation are not completely understood: however, progesterone significantly increases the sensitivity of the central ventilatory chemoreflex response to CO_2 in healthy subjects [23]. It is unclear whether progesterone acts directly on central chemoreceptors and/or on other central neural sites involved in the processing of chemoreceptor activity [11].

We hypothesise that in cirrhotic patients the elevation of serum progesterone may increase ventilatory drive, through its facilitating action on the central chemoreflex. This hypothesis is supported by the relationship between progesterone, chemosensitivity to CO_2 and ventilation observed in our population. In particular, the highest value of ventilation and the highest prevalence of enhanced central chemosensitivity were observed among those patients with a more severe impairment of liver function (i.e. class C patients): in these patients the highest progesterone level was also found, likely due to the less efficient hepatic metabolism of the hormone.

The observed increase in plasma norepinephrine among Child–Pugh class C patients, confirming previous findings [24], is likely to be related to the reflex activation of the sympathetic nervous system in response to central hypovolemia due to peripheral and splanchnic shift of central blood volume in patients with decompensated cirrhosis. However, there is growing evidence that the enhancement of chemosensitivity may be important in increasing the sympathetic drive both in healthy subjects [25] and in heart failure patients [26], *via* the efferent arm of the reflex arch. On the other hand, central afferent sympathoexcitation and catecholaminergic stimuli may modulate chemoreflex sensitivity and medullary autonomic centres [27].

Conversely, BNP concentrations did not demonstrated a significant increase in line with severity of liver disease, nor any relationship with ventilation, $PaCO_2$ or chemoreflex sensitivity: this was somewhat expected in a population with no evidence of structural myocardial abnormalities, but it also rules out that in the study population the hemodynamic impairment could act as a determinant of central chemoreflex enhancement, as happens in heart failure [15,28]. This observation may also help to explain the fact that, despite rest hypocapnia, no patient had day-time breathing pattern abnormalities, as already pointed out at night-time [29]. The lack of an association between low $PaCO_2$ and central apneas, differently from heart failure patients [30], could be the result of the presence of a normal or hyperdynamic circulatory time in cirrhotic patients, supporting the hypothesis that the coexistence of enhanced chemosensitivity and increased circulatory time is necessary for the occurrence of periodic breathing [10,31,32]. In fact, referring to our own laboratory, in a population of heart failure patients with isolated enhancement of chemosensitivity to hypercapnia, the HCVR mean values were comparable with Child's C ones (1.17 versus 1.14 L/min/mm Hg) but the prevalence of daytime periodic breathing was much higher (45% versus 0%) [15].

5. Limitations

The number of patients enrolled in the study is rather low: however, patients were highly selected and homogeneous within each group. For these reasons, we believe that the small sample size does not affect the results of the study, but suggests a descriptive rather than an inferential approach. Plasma norepinephrine level is only an approximate marker of sympathetic drive: however, Iga et al. [33] investigated autonomic nervous function by [123I]-metaiodobenzylquanidine myocardial scintigraphy and circulating catecholamines and found that the washout rate of [123I]-metaiodobenzylquanidine and, consistent with our findings, blood levels of norepinephrine increased with the progression of the severity of cirrhosis. We measured total serum progesterone levels, but the components active on the central chemoreceptors are likely the free levels in the cerebrospinal fluid. The inter-patient variability in brain–blood barrier permeability might alter the relationship between the levels of progesterone in serum and in cerebrospinal fluid, thus explaining the imperfect relationship between serum level on the one hand and ventilatory parameters on the other. Better correlation could be likely achieved by measuring the cerebrospinal fluid unbound progesterone; however, due to the high frequency of coagulation disturbances, this assay was not considered ethical in this setting.

6. Conclusions

Enhanced chemosensitivity to hypercapnia has been observed in cirrhotic patients at an advanced stage of the disease and is associated with sympathetic overactivity and elevated serum progesterone levels. An abnormally excited central chemoreflex is likely to play a role in the pathophysiology of the "unexplained" hyperventilation observed in patients with liver cirrhosis.

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The authors of this manuscript have certified that they comply with the principles of ethical publishing in the International Journal of Cardiology [34]. The authors have no conflicts of interest to disclose.

References

[1] Hourani JM, Bellamy PE, Tashkin DP, Batra P, Simmons M. Pulmonary dysfunction in advanced liver disease: frequent occurrence of an abnormal diffusing capacity. Am J Med 1991;90:693–700.
[2] Yigit IP, Hacievliyagil SS, Seckin Y, Oner RI, Karincaoglu M. The relationship between severity of liver cirrhosis and pulmonary function tests. Dig Dis Sci 2008;53:1951–6.
[3] Krowka MJ, Cortese DA. Pulmonary aspects of chronic liver disease and liver transplantation. Mayo Clin Proc 1985;60:407–18.
[4] Castro M, Krowka MJ. Hepato-pulmonary syndrome. A pulmonary vascular complication of liver disease. Clin Chest Med 1996;17:35–48.
[5] Heinmann HO, Emirgil C, Mijnssen JP. Hyperventilation and arterial hypoxemia in cirrhosis of the liver. Am J Med 1960;28:239–45.
[6] Heinmann HO. Respiration and circulation in patients with portal cirrhosis of the liver. Circulation 1960;22:154–9.
[7] Rossing TH, Boixeda D, Maffeo N, Fencl V. Hyperventilation with hypoproteinemia. J Lab Clin Med 1988;112:553–9.
[8] Cherniack NS, Longobardo GS. Abnormalities in respiratory rhythm. Handbook of Physiology. The Respiratory System. Control of BreathingAm. Physiol. Soc.; 1986. p. 729–49. Bethesda, MD.
[9] Ponikowski P, Anker SD, Chua TP, et al. Oscillatory breathing patterns during wakefulness in patients with chronic heart failure: clinical implications and role of augmented peripheral chemosensitivity. Circulation 1999;100:2418–24.
[10] Javaheri S. A mechanism of central sleep apnea in patients with heart failure. N Engl J Med 1999;341:949–54.
[11] Bayliss DA, Millhorn DE. Central neural mechanisms of progesterone action: application to the respiratory system. J Appl Physiol 1992;73:393–404.
[12] Jensen D, Wolfe LA, Slatkovska L, Webb KA, Davies GA, O'Donnell DE. Effects of human pregnancy on the ventilatory chemoreflex response to carbon dioxide. Am J Physiol Regul Integr Comp Physiol 2005;288:R1369–75.
[13] Lustik SJ, Chhibber AK, Kolano JW, et al. The hyperventilation of cirrhosis: progesterone and estradiol effects. Hepatology 1997;25:55–8.
[14] Giannoni A, Emdin M, Bramanti F, et al. Combined increased chemosensitivity to hypoxia and hypercapnia as prognosticator in heart failure. J Am Coll Cardiol 2009;53:1975–80.

[15] Giannoni A, Emdin M, Poletti R, et al. Clinical significance of chemosensitivity in chronic heart failure: influence on neurohormonal derangement, Cheyne–Stokes respiration and arrhythmias. Clin Sci (Lond) 2008;114:489–97.
[16] Mortara A, Sleight P, Pinna GD, et al. Abnormal awake respiratory patterns are common in chronic heart failure and may prevent evaluation of autonomic tone by measures of heart rate variability. Circulation 1997;96:246–52.
[17] Poletti R, Passino C, Giannoni A, et al. Risk factors and prognostic value of daytime Cheyne–Stokes respiration in chronic heart failure patients. Int J Cardiol 2009;137: 47–53.
[18] Yamashiro Y, Kryger MH. Sleep in heart failure. Sleep 1993;16:513–23.
[19] Emdin M, Passino C, Prontera C, et al. Cardiac natriuretic hormones, neurohormones, thyroid hormones and cytokines in normal subjects and patients with heart failure. Clin Chem Lab Med 2004;42:627–36.
[20] Augusti AG, Roca J, Rodriguez-Roisin R. Mechanisms of gas exchange impairment in patients with liver cirrhosis. Clin Chest Med 1996;17:49–66.
[21] Ruff F, Hughes JM, Stanley N, et al. Regional lung function in patient with hepatic cirrhosis. J Clin Invest 1971;50:2403–13.
[22] Vachiery F, Moreau R, Hadengue A, et al. Hypoxemia in patients with cirrhosis: relationship with liver failure and hemodynamic alterations. J Hepatol 1997;27:492–5.
[23] Zwillich CW, Natalino MR, Sutton FD, Weil JV. Effects of progesterone on chemosensitivity in normal men. J Lab Clin Med 1978;92:262–9.
[24] Møller S, Iversen JS, Henriksen JH, Bendtsen F. Reduced baroreflex sensitivity in alcoholic cirrhosis: relations to hemodynamics and humoral systems. Am J Physiol Heart Circ Physiol 2007;292:H2966–72.
[25] Morgan BJ, Crabtree DC, Palta M, Skatrud JB. Combined hypoxia and hypercapnia evokes long-lasting sympathetic activation in humans. J Appl Physiol 1995;79:205–13.
[26] Narkiewicz K, Pesek CA, van de Borne PJ, Kato M, Somers VK. Enhanced sympathetic and ventilatory responses to central chemoreflex activation in heart failure. Circulation 1999;100:262–7.
[27] Yamada K, Asanoi H, Ueno H, et al. Role of central sympathoexcitation in enhanced hypercapnic chemosensitivity in patients with heart failure. Am Heart J 2004;148: 964–70.
[28] Schultz HD, Sun SY. Chemoreflex function in heart failure. Heart Fail Rev 2000;5: 45–56.
[29] Javaheri S, Almoosa KF, Saleh K, Mendenhall CL. Hypocapnia is not a predictor of central sleep apnea in patients with cirrhosis. Am J Respir Crit Care Med 2005;171: 908–11.
[30] Javaheri S, Corbett WS. Association of low partial pressure of carbon dioxide with central sleep apnea and ventricular arrhythmias in ambulatory patients with stable heart failure. Ann Intern Med 1998;128:204–7.
[31] Francis DP, Willson K, Davies LC, Coats AJ, Piepoli M. Quantitative general theory for periodic breathing in chronic heart failure and its clinical implications. Circulation 2000;102:2214–21.
[32] Hall MJ, Xie A, Rutherford R, Ando S, Floras JS, Bradley TD. Cycle length of periodic breathing in patients with and without heart failure. Am J Respir Crit Care Med 1996;154:376–81.
[33] Iga A, Nomura M, Sawada Y, Ito S, Nakaya Y. Autonomic nervous dysfunction in patients with liver cirrhosis using 123I-metaiodobenzylguanidine myocardial scintigraphy and spectrum analysis of heart-rate variability. J Gastroenterol Hepatol 2003;18:651–9.
[34] Coats AJ. Ethical authorship and publishing. Int J Cardiol 2009;131:149–50.