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Recumbent deoxygenation in mild/moderate liver cirrhosis: the "Clinodeoxia". The ortho-clino paradigm☆

Francesca Polverino [a,b,c,*], Carlo Santoriello [d], Filippo Andò [e], Giuseppe Girbino [e], Donato Cappetta [f], Bruno D'Agostino [f], Alessandro Vatrella [g], Mario Polverino [d,e], Joseph Milic-Emili [h]

[a] Department of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[b] The Lovelace Respiratory Research Institute, Albuquerque, NM, USA
[c] Pulmonary Department, University of Parma, Parma, Italy
[d] Department of Pulmonary Medicine, Cava de' Tirreni Hospital, Cava de' Tirreni, Italy
[e] Lung Diseases Institute, University of Messina Medical School, Messina, Italy
[f] Department of Experimental Medicine, Second University of Naples, Naples, Italy
[g] Lung Diseases Institute, University of Salerno, Italy
[h] Meakins-Christie Laboratories, McGill University, Montreal, PQ, Canada

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Summary
Background: While the effects of postural change on arterial oxygenation have been well documented in normal subjects, and attributed to the relationship of closing volume (CV) to the tidal volume, in liver cirrhosis such postural changes have been evaluated mainly in a rare, peculiar clinical end-stage condition which is characterized by increased dyspnea shifting from supine to upright position ("platypnea"). The latter is associated with worsening of PaO_2 ("orthodeoxia"). We evaluated the effects of postural changes on arterial oxygenation in patients affected by mild/moderate liver cirrhosis.
Methods: We performed pulmonary function tests and arterial blood gas evaluation in sitting and supine positions in 22 patients with mild/moderate liver cirrhosis, biopsy-proved, and 22 matched non-smokers control subjects.

Abbreviations: $AaDO_2$, alveolar-arterial oxygen difference; CV, closing volume; DLCO, diffusing lung capacity for carbon monoxide (CO); ERV, expiratory reserve volume; $FEV_{1.0}$, forced expiratory volume at 1 s; FVC, forced vital capacity; HPS, hepato-pulmonary syndrome; MELD, model for end-stage liver disease; RV, residual volume; SpO_2, oxyhemoglobin saturation; TV, tidal volume; VC, vital capacity.

☆ The work was performed at the Respiratory Pathophysiology Unit of Cava de' Tirreni Teaching Hospital, Italy.

* Corresponding author. Department of Medicine, Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston 02115 MA, USA.
E-mail address: fpolverino@partners.org (F. Polverino).

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Results: Recumbency elicited a decrease of PaO_2 (Δ(sup-sit)PaO_2) in 19 out of 22 controls and in all but one cirrhotics. The magnitude of this postural change was significantly ($p = 0.04$) greater in cirrhotics (9.6 $\pm$ 5.3%) compared to controls (6.7 $\pm$ 3.7%). In the subset of cirrhotics younger than 60 yrs and with PaO_2 greater than 80 mmHg in sitting position, the Δ(sup-sit)PaO_2 in recumbency further increased to 12 $\pm$ 5.8%, significantly ($p = 0.014$) greater than in same subgroup of controls (7.1 $\pm$ 3.8%).
Conclusions: In mild/moderate liver cirrhosis the postural variations in PaO_2 follow the normal trends, but are of greater magnitude probably as a consequence of hypoventilated units of lung for postural and disease-linked tidal airway closure, resulting in more pronounced recumbent hypoxemia ("*clinodeoxia*").

Introduction

The effects of postural changes on arterial oxygenation in normal subjects have been well documented [1—5] and, according to the findings of Craig et al. [6], are due to the phenomenon of closing volume (CV), that is the collapse of terminal bronchioles due to surface tension forces. In healthy young subjects, in the seated position, the CV is consistently below the tidal volume (TV), within expiratory reserve volume (ERV) range, so airways closure can occur exclusively with prolonged expiration until near the residual volume (RV). With advancing age, CV gradually approaches the end-expiratory TV, though in the sitting position the CV drops within TV even in normal subjects older than 75 years [7]. This has been attributed to age-related loss of lung recoil and decreased resistance to collapse of the aged airways [8]. In the lying position, ERV is smaller because of gravitational factors [9]; therefore, the CV drops within TV more easily and tidal airway closure appears at age lower than 50 years, approximately [10]. Tidal airway closure, both in sitting and supine position, results in cyclic opening and closure of peripheral airways with parallel inhomogeneity of distribution of ventilation and impaired gas exchange. Any condition that enhances peripheral airway closure can cause worsening of the gas exchange. In recumbency, enhanced air trapping caused by premature peripheral airway closure explains the decreased arterial oxygen in this position in comparison with standing or sitting.

In liver cirrhosis, the postural changes in PaO_2 have been described mainly in end stage patients, having dyspnea in the sitting position which was relieved in the lying position. Surprisingly, in these patients, unlike normal subjects, the supine position was accompanied by an improvement in PaO_2 [11—13]. Robin et al. [11] have depicted the clinical condition associated with platypnea and orthodeoxia, namely the hepatopulmonary syndrome (HPS), suggesting the term "*platypnea*" to describe the dyspnea produced by assumption of an erect position which was relieved when lying, while the term "*orthodeoxia*" was coined to describe the accentuated arterial oxygen desaturation in the sitting or standing position improved by the supine position. In their report Robin et al. [11] related this peculiar postural behavior to increased pulmonary right-to-left shunting of blood, which seemed to be due to a gravity-related increased basal flow through true vascular lung shunts (spider naevi) proved, by angiographic studies, to have a basal distribution.

Except for a study that evaluated only oxyhemoglobin saturation (SpO_2) [14], the effects of postural changes on arterial oxygenation have never been studied in patients affected by mild/moderate liver cirrhosis. With the current study, we aimed to fill this knowledge gap.

Material and methods

The protocol, in conformity with the Helsinki Declaration, was approved by the local Independent Ethics Committee "ASL Salerno" (n° 305/2009). Written informed consent for the study was obtained from each patient.

For our study, exclusively a non-smoker population (both cirrhotic and normal) was selected.

Cirrhosis was diagnosed by clinical history and examination, laboratory findings, and liver biopsy, which all patients underwent. Severity of liver disease was characterized according to Pugh's modification of Child's grading for hepatic functional reserve [15] and by MELD (Model for End-stage Liver Disease) [16] score according to the usual formula:

$$\text{MELD} = 3.8[\text{Ln serum bilirubin (mg/dL)}] + 11.2[\text{Ln INR}] + 9.6[\text{Ln serum creatinine (mg/dL)}] + 6.4.$$

Based on epidemiologic and serologic evidence (HBsAg, HBeAg, anti-HbC, HBV-DNA), we chose exclusively post-hepatic cases in mild/moderate stage according Child's grading. Presence of ascites was determined by abdominal ultrasounds technique. Patients were excluded if they had evidence of hepatic encephalopathy according usual diagnostic assessment [17] and pleural and parenchymal lung disease, which were excluded in all patients and controls by chest roentgengram. Furthermore, none of them had asthma, chronic bronchitis, or emphysema according to the American Thoracic Society Directions. Moreover, patients with cardiac disease (according to findings on electrocardiogram and echocardiogram), diabetes or severe comorbidity were excluded.

Accordingly to the study design and criteria, 22 patients with cyrrhosis were enrolled in the study (8 females and 14 males, age: 56 $\pm$ 12 yrs; height: 166 $\pm$ 7 cm; weight: 72 $\pm$ 3 kg), affected by cirrhosis due to type B (16 cases) and type C (6 cases) hepatitis virus (Table 1). No one

Table 1 Study population.

		Cirrhosis	Controls
n		22	22
Sex	M: males; F: females	14 M–8 F	14 M–8 F
Age (years)	Mean ± 1 SD	56 ± 12	55 ± 12
	Median (range)	58 (35–75)	58 (30–74)
Height (cm)	Mean ± 1 SD	166 ± 7	168 ± 6
Weight (kg)	Mean ± 1 SD	72 ± 3	70 ± 6

Values are means ± SD unless otherwise stated. Since the distribution of age was not Gaussian we also provide the median and range.

complained of platypnea defined as dyspnea induced by an upright position and relieved by recumbency (and comparing sitting and supine BORG dyspnea scales). Eighteen patients showed cutaneous spider naevi, and in 10 mild ascites was evident. To be sure that the study setting was limited exclusively to patients with milder degree of cirrhosis, we evaluated presence of portopulmonary hypertension, which was excluded by echocardiography and Doppler measurements [18].

The control group (14 males and 8 females), matching for anthropomorphic data (age: 55 ± 12 yrs; height: 168 ± 6 cm; weight: 70 ± 6 kg), according to the indications of Committee of Medical Ethics, was derived from subjects attending our Laboratory for preoperative evaluations: the patients were awaiting for minor and elective surgery (such as orthopedic disorders, inguinal hernia, eye and ear surgery, haemorrhoids) for which a sitting blood gas analysis and pulmonary function tests are routinely performed. The subjects matching our inclusion criteria were asked to participate in the present study for evaluation of a second recumbent arterial blood gas analysis.

Pulmonary function tests in sitting position, and arterial gas analysis (by ABL 520, Radiometer, Copenhagen) in sitting and lying position, each maintained at least for 10 min, were performed in all patients. The samples of radial arterial blood were collected in two consecutive days in random order. The pulmonary function tests, performed according to recommended standard methodology [19], included lung volumes and RV by body plethysmography (Jaeger, Wurzburg), and single-breath diffusing capacity for carbon monoxide (DLCO).

The alveolar-arterial oxygen gradient ($AaDO_2$) was calculated from the usual alveolar gas equation:

$$AaDO_2 = (FiO_2(PB - 47) - (PaCO_2/R) + FiO_2(1 - R)(PaCO_2/R) \times) - PO_2$$

Group data are expressed as mean ± SD. Differences between patients with cirrhosis and control group were compared with unpaired *t*-tests, and Pearson's coefficient was used to evaluate the correlations between variables. A stepwise regression analysis was then conducted to identify the variables that were independently correlated with postural changes of PaO_2. The analyses were carried out using a commercially available software package (SPSS 17.0). The level of significance was set at p less than 0.05.

Results

Patient and liver function data are shown in Table 2: all patients were in CHILD stages A or B and had a low MELD score (between 7 and 13).

Pulmonary function tests (in sitting position) and arterial gas tensions (in sitting and lying positions) are shown in Table 3: low DLCO was found in most of the patients affected by cirrhosis, with significant differences in comparison with control group; significant decrease of ERV was also found in cirrhotics in comparison with normal subjects. The mean values of forced expiratory volume in 1 s ($FEV_{1.0}$), forced vital capacity (FVC), vital capacity (VC) and of the $FEV_{1.0}$/VC ratio were not significantly different between the two groups.

In cirrhotics, PaO_2 and $AaDO_2$ were significantly lower (79 ± 10 vs. 84 ± 7 mmHg) and higher (20 ± 10 vs. 14 ± 9 mmHg), respectively, in comparison with controls; the same trend was recorded in supine position: PaO_2 and $AaDO_2$ were significantly lower (71 ± 9 vs. 79 ± 7 mmHg) and, respectively, higher (27 ± 9 vs. 17 ± 10 mmHg) in cirrhotics.

PaO_2 in sitting position was lower than 80 mmHg in 9 out 22 cirrhotics (41%) and in 7 of 22 controls (32%), and lower than 70 mmHg in 5 out 17 cirrhotics (29%) and in 1 of 22 controls (4.5%); in recumbency PaO_2 was lower than 80 mmHg in 20 out 22 cirrhotics (91%) and in 13 of 22 controls (59%), and lower than 70 mmHg in 10 out 22 cirrhotics (45%) and in 1 of 22 controls (4.5%).

Fig. 1 shows that the arterial PaO_2 decreased when shifting from the seated to the supine position in 19 out of 22 controls, in all but one patients: in the latter, the lying decrease was larger than controls, as shown by the greater distance from 0.9 isopleth of many patients.

The large intersubject variation of PaO_2 in both sitting and supine position is largely due to the age-related reduction in PaO_2 which has been previously described at least until 70 years [20] after which the regression by age is virtually flat [21]. Therefore, we age-correlated the PaO_2 values in each position: in control group a significant inverse relationship was found between age and PaO_2 in both positions, sitting (Fig. 2[A]) and supine (Fig. 2[B]). As shown in the same figure, a significant age-related decline in PaO_2 was also found in cirrhotics, both in sitting (Fig. 2[C]) and supine position (Fig. 2[D]). Since our patients and controls were matched for age, we postulate that the differences in PaO_2 between cirrhotics and controls in Table 3 reflect (in absence of any other comorbidity in patients group) the effect of mild/moderate post-hepatic cirrhosis.

Finally, the magnitude of the posture-related fall of PaO_2 (Δ(sup-sit)PaO_2) was significantly ($p = 0.04$) greater in cirrhotics (9.6 ± 5.3%) in comparison with control group (6.7 ± 3.7%): Fig. 3 (*left panel*). A stepwise regression analysis was then performed to identify the variables independently correlated to the Δ(sup-sit)PaO_2. Such an analysis identified 2 variables: a deeper Δ(sup-sit)PaO_2 was discriminated by an age younger than 60 yrs-old and a sitting PaO_2 higher than 80 mmHg. In this subgroup, the Δ(sup-sit)PaO_2 further increased to 12.0 ± 5.8% in comparison with 7.1 ± 3.8% of the same subgroup of control subjects ($p = 0.01$): Fig. 3 (*right panel*).

Table 2 Patient and liver function data.

Patient	Sex	Age	Spiders	Albumin	Bilirubin	[a]PRO	Ascites	[b]MELD	[c]CHILD
N°	M/F	yrs	YES/NO	g/dl	mg/dl	%	Mild/NO	Score	A/B/C
1	M	35	YES	2.0	2.0	68	NO	11	B
2	F	36	YES	2.3	1.1	80	NO	9	B
3	M	39	YES	4.0	1.1	85	NO	8	A
4	F	39	YES	3.0	1.0	88	NO	8	A
5	M	43	YES	2.5	1.1	74	Mild	10	B
6	M	47	YES	2.0	1.9	59	Mild	12	B
7	M	48	YES	3.1	1.1	86	NO	8	A
8	F	50	YES	3.0	1.0	82	NO	9	A
9	M	54	YES	3.0	2.0	71	Mild	11	B
10	F	56	YES	3.0	2.1	56	Mild	13	B
11	M	58	YES	3.0	2.1	63	Mild	12	B
12	F	58	YES	4.0	1.1	94	NO	7	A
13	F	58	YES	2.7	1.4	83	Mild	9	B
14	M	58	NO	2.4	1.5	79	Mild	9	B
15	M	60	YES	2.6	1.2	79	Mild	9	B
16	M	67	NO	2.1	1.0	92	NO	7	B
17	M	68	YES	3.0	1.1	90	NO	8	A
18	F	70	NO	2.1	1.0	88	NO	8	B
19	M	72	YES	3.1	2.0	68	Mild	11	B
20	M	74	YES	2.1	1.0	88	NO	8	B
21	F	74	NO	2.1	2.1	70	Mild	10	B
22	M	75	YES	2.1	1.1	86	NO	8	B

[a] PRO: Prothrombin time.
[b] MELD: Model for end-stage liver disease: for the calculation see text.
[c] CHILD: Pugh's modification of child's grading for hepatic functional reserve.

The Δ(sup-sit)PaO_2 was not age-related both in controls and in cirrhotics, but in the latter we observed that, as sitting PaO_2 declines, so the magnitude of the postural change (Δ(sup-sit)PaO_2) significantly ($p = 0.0237$) decreases; this behaviour was not observed in controls (Fig. 4).

Discussion

The main findings of this study are: (1) sitting hypoxemia is quite common also in a setting of mild/moderate liver

Table 3 Pulmonary function data and blood gas values in cirrhosis and in control group.

		Cirrhosis ($n = 22$)	Controls ($n = 22$)	Significance
		Mean $\pm$ 1 SD	Mean $\pm$ 1 SD	
FVC	% pred.	93 $\pm$ 11	94 $\pm$ 5	NS
FEV_1	% pred.	97 $\pm$ 11	97 $\pm$ 5	NS
FEV_1/VC	%	78 $\pm$ 5	81 $\pm$ 3	NS
IC	% pred.	100 $\pm$ 18	109 $\pm$ 9	0.037
RV	% pred.	156 $\pm$ 26	109 $\pm$ 9	<0.0001
ERV	% pred.	85 $\pm$ 10	96 $\pm$ 5	<0.0001
FRC	% pred.	126 $\pm$ 16	97 $\pm$ 4	<0.0001
TLC	% pred.	113 $\pm$ 11	108 $\pm$ 6	NS
DLCO	% pred.	74 $\pm$ 14	95 $\pm$ 4	<0.0001
Raw	kPa l^{-1} s	0.19 $\pm$ 0.05	0.19 $\pm$ 0.02	NS
PaO_2 sitting	mmHg	79 $\pm$ 10	84 $\pm$ 7	0.041
PaO_2 supine	mmHg	71 $\pm$ 9	79 $\pm$ 7	0.002
Δ supine PaO_2 (% sitt)	%	-9.6 ± 5.3	-6.7 ± 3.9	0.039
$PaCO_2$ sitting	mmHg	36 $\pm$ 3	37 $\pm$ 2	NS
$PaCO_2$ supine	mmHg	37 $\pm$ 3	39 $\pm$ 3	0.042
Δ supine $PaCO_2$ (% sitt)	%	3.3 $\pm$ 5.2	5.6 $\pm$ 4.7	NS
$AaDO_2$ sitting	mmHg	20 $\pm$ 10	14 $\pm$ 9	0.026
$AaDO_2$ supine	mmHg	27 $\pm$ 9	17 $\pm$ 10	0.001
Δ supine $AaDO_2$ (% sitt)	%	42.8 $\pm$ 46.4	35.2 $\pm$ 67.4	NS

Pulmonary function data are related to the sitting position; blood gas values are related to the sitting and supine positions.

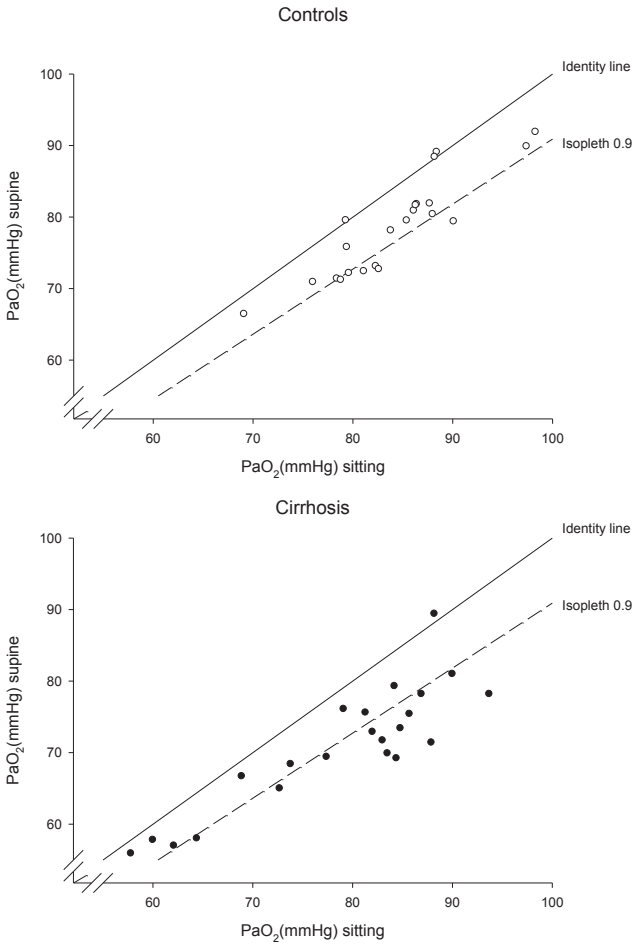

Figure 1 Postural behavior of PaO_2 in controls (upper panel) and in cirrhosis (lower panel). The continuous line shows identity line (that means relationship between *x* and *y* axis by $r = 1$); dashed line are the isopleths 0.9.

cirrhosis without portopulmonary hypertension; (2) in these milder stages of the disease, recumbency elicits supine hypoxemia: "*clinodeoxia*"; (3) milder is the disease, greater is the clinodeoxia.

Sitting hypoxemia

In order to better frame the results of our investigation, we emphasize that the study setting was limited to patients affected by milder stages of cirrhosis, in absence of any other comorbidity or confounding condition, including smoking history. For this purpose, we also assessed echocardiography and Doppler measurements to be sure that patients with portopulmonary hypertension were excluded.

A slight but significant sitting hypoxemia (79 ± 10 vs. 84 ± 7; $p = 0.041$) was found in most of our patients, even in an age-corrected evaluation, as evidenced by the regression line which sloped lower to the control regression line (Fig. 2). Arterial hypoxemia is common in the context of hepatic diseases [22]. In some reports, the prevalence of sitting hypoxemia ranges from about 30% to 70% [23—25]; Møller et al. [26] indicated that the prevalence of arterial hypoxemia in patients without encephalopathy is about 22%, ranging from 10 to 40% depending on the severity of the liver disease and upon what numerical threshold investigators chose for hypoxemia. Even with the above mentioned limitations due to the different assessment of hypoxemia, Nagata et al. [14] have demonstrated that low standing SpO_2 is present in one third of patients with mild cirrhosis and is associated with the severity of the liver disease. However, this study is not comparable with ours because it is known that, at pressures higher than 60 mmHg, the standard dissociation curve of oxygen is relatively flat, which means that the oxygen content of the blood does not change significantly even with large differences in the oxygen partial pressure. In our study population, with a mean sitting PaO_2 of 79 ± 10 mmHg, we could not appreciate any significant difference with recumbency on the basis of oxygen saturation.

At least six different threshold values have been recommended and have been used in previous publications to define arterial hypoxemia: a) $AaDO_2$ greater than 15 mmHg; b) $AaDO_2$ greater than 20 mmHg; c) PaO_2 less than 80 mmHg; d) PaO_2 less than 70 mmHg; e) Age corrected $AaDO_2$; f) Age corrected PaO_2. Whatever the criterion used, in the setting of our investigation sitting hypoxemia is quite common, even if slight, and severe arterial hypoxemia is rare (only 1 cirrhotic had PaO_2 less than 60 mmHg). In any case, to correctly frame the extent of the hypoxemia, we highlight that the study population was recruited in Bisaccia village, which is elevated 2820 feet above sea level.

As demonstrated by multiple inert gas elimination techniques [27—29], the three main mechanisms leading to hypoxemia in liver cirrhosis are ventilation-perfusion mismatch, alveolar capillary limitation of oxygen diffusion (so called "diffusion-perfusion defect") and, rarely, true intrapulmonary shunts.

At least two of this mechanisms are operating in our study population. Ruff et al. [30], using xenon-133, found a raised CV which was within the tidal volume in sitting position, indicating premature airway closure and consequent collapse of terminal bronchioles during normal breathing. The authors suggested that the gas trapping was mainly due to mechanical compression of small airways by interstitial pulmonary edema resulting from low albumin levels or by hormone-dependent water retention. This would produce perfused but unventilated units in the lung, creating microatelectasis. As a compensatory mechanism, as the albumin levels decrease, the patients increase the minute ventilation, leading to hypocapnia. Indeed in our study we found a significant relationship between albumin and $PaCO_2$ ($PaCO_2 = 27.1$ mmHg $+ 3.2$ albumin; $r^2 = 0.43$; $p = 0.0009$). The alveolar capillary limitation of oxygen diffusion was also present in our population, as demonstrated by a significant decrease of DLCO in comparison with control group. This is due to increased oxygen diffusion distance from alveoli to hemoglobin across the dilated vessels by impairment in hypoxic pulmonary vasoconstriction [31].

One of the limitation of this study could be the lack of demonstration, if any, of intrapulmonary vascular dilatations, which is the main cause of the HPS: in cirrhotics there are numerous reports of true shunts until 40% of the cardiac output [32]. The mechanism is not completely understood but is thought to be due to increased hepatic

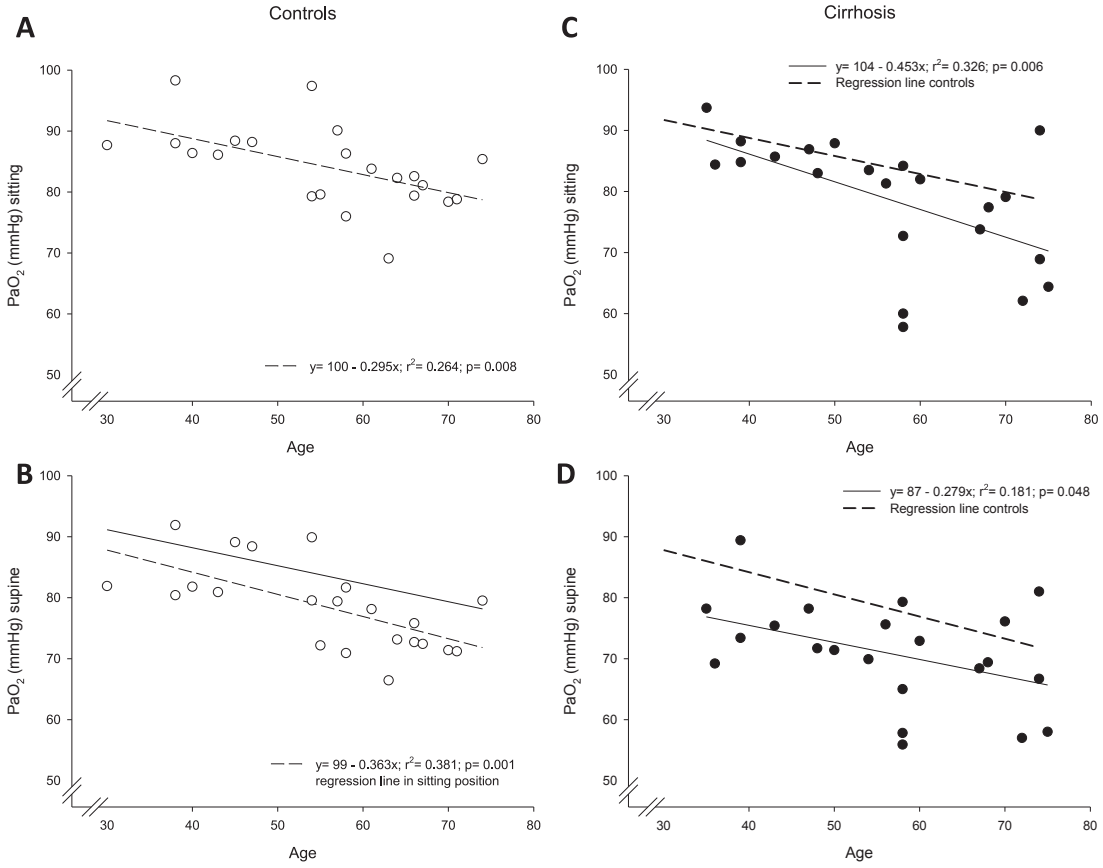

Figure 2 Relationship between age and PaO_2 with regression lines in controls (left), in sitting (panel A) and supine position (panel B) and in cirrhotics (right), in sitting (panel C) and supine position (panel D). In the group of cirrhotics, the regression line of controls (dashed line) is also shown for each position.

production or decreased hepatic clearance of vasodilators, possibly involving nitric oxide [22]: the vascular dilatations cause overperfusion relative to ventilation, leading to ventilation-perfusion mismatch and hypoxemia. The aim of our study was to evaluate the pattern of postural changes in cirrhosis and, in absence of any prediction of the results, we did not plan performing contrast echocardiography to demonstrate the presence of these dilatations. So, we

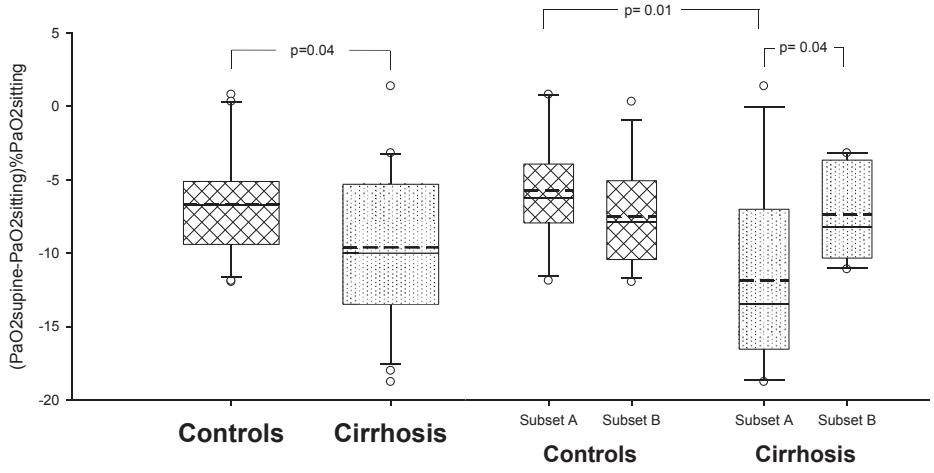

Figure 3 Box plots of (PaO_2supine—PaO_2sitting) % PaO_2sitting in controls and cirrhotics (left panel). The boundary of the box closest to negative values indicates the 25th percentile; the boundary of the box farthest from negative values indicates the 75th percentile; whiskers above and below the box indicate the 90th and 10th percentiles. Within the boxes, the continuous lines mark the median, and the dashed lines mark the mean. For each box, the outlying points are also shown. In the right part of the panel,the two subsets for each group are shown, according to the age and sitting PaO_2: Subset A: patients <60 yrs-old and with standing PaO_2 >80 mmHg; Subset B: patients >60 yrs-old and with standing PaO_2 <80 mmHg.

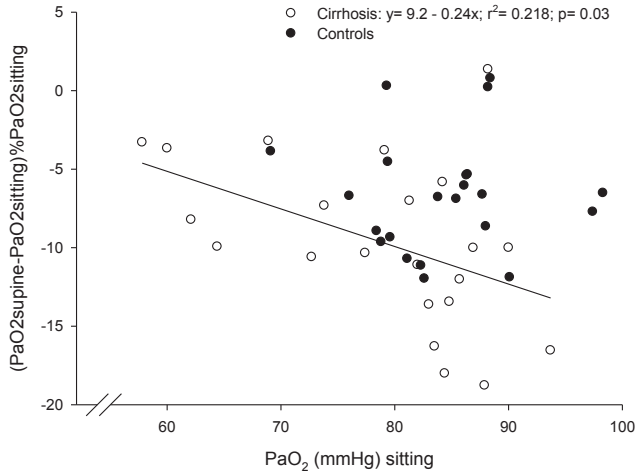

Figure 4 Δ [(PaO_2supine—PaO_2sitting) % PaO_2sitting] in relation with sitting value of PaO_2. A significant inverse relationship was found only in cirrhotics (straight line).

cannot rule out this mechanism in some of our patients. According with the postural behavior demonstrated by us, we can only speculate that, in our study setting, intrapulmonary vascular dilatations, if any, were not only basal in location, as demonstrated by Robin et al. [11] to explain orthopnea-platypnea syndrome, but distributed along the vertical axis.

Supine hypoxemia

As already stated, the main aim of our study was to evaluate the postural behaviour of PaO_2 and not the hypoxemia by itself. The supine position provoked, similarly to control subjects, a decrease in arterial oxygen tension in all but one patient, in whom a minimal increase in arterial oxygen tension of less than 2% (from 88.2 to 89.4 mmHg) was recorded. Gómez et al. [33], using a receiver operating characteristic analysis, determined that a 5% or 4 mmHg fall in upright PaO_2 was the cut-off threshold for the PaO_2 decrease, that can be defined as an upright-induced deoxygenation (orthodeoxia). According to this definition, we can state that not one of our patients showed orthodeoxia; therefore, our study confirms that if one does not have HPS, does not get platypnea or orthodeoxia. This finding was expected since the orthodeoxia in cirrhosis has been described only in end-stage disease, but we found that the supine fall was more pronounced than expected from predicted values by regression equation in normal people. The supine drop was significantly greater (9.6 $\pm$ 5.3%) in comparison with the control group (6.7 $\pm$ 3.7%); moreover, the number of cirrhotics showing a supine fall $\geq$10% (12 out of 22 = 55%) was three times higher than controls (4 out of 22 = 18%). This means that another pathophysiological mechanism contributes to a significant fall in oxygenation in response to a change of posture in these patients. We propose the term *"clinodeoxia"*, as reverse of orthodeoxia, to describe the deoxygenation in the lying position.

Under normal circumstances, there is a decrease in oxygenation when a patient is placed in the supine position. The reduced oxygenation is caused by a change in lung mechanics which promotes ventilation/perfusion (VA/Q) mismatching. The most common pulmonary function change is the reduction in the ERV and FRC since the abdominal content pushes the diaphragm upwards. In their early report, Craig et al. [6] demonstrated that the relationship between the FRC and CV differs according to body position. Because FRC falls in the supine position, whereas CV is unchanged, CV in recumbency falls in the TV, which results in tidal airway closure, air-trapping and worsening in oxygenation at a younger age in comparison with standing [10].

In some circumstances this phenomenon, when lying down, is more pronounced, as happens in people with high intra-abdominal pressure, like supine pregnant women and morbidly obese patients. In our population of mild/moderate cirrhosis, the recumbency accentuates the predicted drop in oxygenation. This happens because ascites, likewise other space occupying intra-abdominal processes, may exert, in supine position, an extrinsic compression on the diaphragm contributing to abolish the difference FRC-CV and, consequently, to increase airways collapse in the posterior dependent lung zones by tidal airway closure. Since the ascites was present in about half of patients, we can speculate that the hepatomegaly (especially present in the milder stages of the cirrhosis) may have exerted an extrinsic compression on the diaphragm, contributing to the tidal airway closure in recumbency as well.

Determinants of supine hypoxemia

In order to better understand the determinants of the supine hypoxemia, we performed a stepwise regression analysis to identify the variables independently correlated to the Δ(sup-sit)PaO_2. Such an analysis identified 2 variables: a deeper Δ(sup-sit)PaO_2 was discriminated by an age younger than 60 yrs-old and a sitting PaO_2 higher than 80 mmHg. In this subgroup, the Δ(sup-sit)PaO_2 further increased in comparison with the same subgroup of control subjects: Fig. 3 (*right panel*). Any difference disappeared by comparing the two subgroups of subjects older than 60-yrs old with a sitting PaO_2 lower than 80 mmHg. This outcome probably means that in this setting (older age and lower PaO_2) tidal airway closure is already working in sitting position, so that the change of posture doesn't act as an additional pathophysiological mechanism. An indirect proof of this mechanism is the observation that, as sitting PaO_2 declines, the magnitude of Δ(sup-sit)PaO_2 significantly decreases (Fig. 4). In any case, the age could be a confounding factor because, getting on the years, is feasible that the two time-related factors overlap: more severe is the liver cirrhosis and more is the probability that CV in recumbency falls in the range of tidal volume for the age-related loss of lung recoil [8]. As previously said, we did not perform contrast echocardiography to demonstrate presence of intrapulmonary vascular dilatations and their eventual role in the phenomenon of clinodeoxia. However, according with our results, we can only speculate that, if any, intrapulmonary vascular dilatations should be not only basal, whose location explains orthodeoxia, as in report of Robin et al. [11], but distributed along the vertical axis of the lungs.

In conclusion, in liver cirrhosis pulmonary gas exchange disorders are present, and seem to be highly dependent on

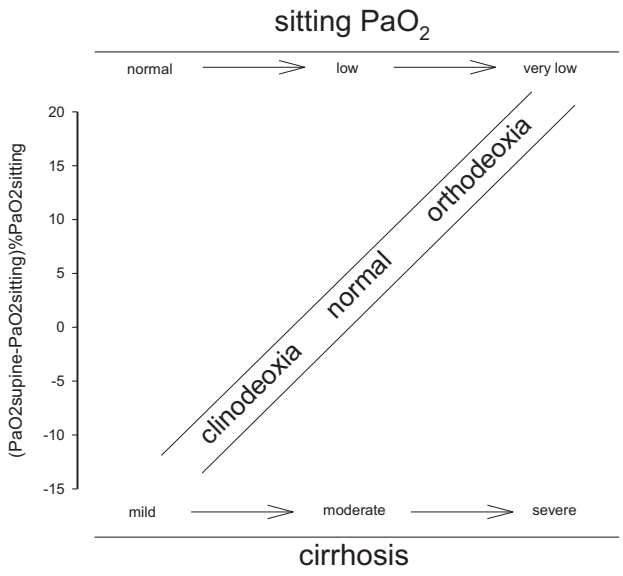

Figure 5 The *"Ortho-Clino Paradigm"* of the postural changes in liver cirrhosis: *"orthodeoxia"* in patients with end-stage disease and severe hypoxemia (right), and *"clinodeoxia"* in patients with milder degree of the disease and milder impairment (or normal) gas exchanges (left).

the severity of patient's disease and positioning: the *"ortho-clino paradigm"* (Fig. 5). More severe is the liver cirrhosis and lower is the initial PaO_2 in upright (or sitting) position, greater (positive) is the Δ(sup-sit)PaO_2 and the probability of HPS with its typical combination of platypnea-orthodeoxia. On the other hand, patients with mild cirrhosis exhibit higher (normal) PaO_2 in upright (or sitting) position, and postural fall of PaO_2 more pronounced than predicted: *clinodeoxia*. Whether this postural behavior can be an useful additional clinical information to monitor the liver cirrhosis, still remains an open question.

Conflict of interest

All the authors of the manuscript entitled "Recumbent deoxygenation in mild/moderate liver cirrhosis: the "Clinodeoxia". The "Ortho-Clino" paradigm." declare that:

- The manuscript has not been published elsewhere and, if accepted in Respiratory Medicine, will not be republished in any other journal in the same or similar form without the written consent of the Editor of Respiratory Medicine;
- Have no relationships that might lead to a conflict of interest;
- The manuscript has been read and approved by each author.

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