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# Pulmonary blood transit time and impaired arterial oxygenation in patients with chronic liver disease

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***Background.*** Contrast-enhanced echocardiography (CEE) using agitated saline can detect intrapulmonary vasodilatation (IPVD) in patients with hepatopulmonary syndrome (HPS). We estimated the pulmonary transit time of erythrocytes (PTT) by CEE, using microbubbles, and studied its relationship to arterial oxygenation in chronic liver disease. ***Methods.*** Sixteen patients with chronic liver disease and seven healthy subjects were studied. PTT was defined as the time between opacification of the right atrium and left atrium on CEE, using human serum albumin-air microbubble complexes with a mean diameter of 4 μm (Albunex). IPVD was detected by CEE with agitated saline. Arterial blood gases were analyzed with patients in the supine position, and while they were seated. Cardiac output (CO) was determined by Doppler echocardiography. ***Results.*** The mean PTT value for all of the patients was 4.0 ± 1.4 s. One of the 3 patients who showed IPVD was normoxemic. Mild orthodeoxia was observed in the patients with abnormal alveolar-arterial oxygen difference ($A\text{-}aDO_2$) values (>15 mmHg), but not in those with normal $A\text{-}aDO_2$ values, or in the healthy subjects. PTT was correlated with $PaO_2$ ($r = 0.52$; $P < 0.05$; $n = 16$) and $A\text{-}aDO_2$ ($r = -0.54$; $P < 0.05$; $n = 16$) in the seated position. CO was significantly correlated with PTT ($r = -0.62$; $P < 0.05$; $n = 15$), but not with $PaO_2$ and $A\text{-}aDO_2$, in both positions. ***Conclusions.*** PTT may be a useful parameter for evaluating arterial oxygenation in patients with chronic liver disease with early HPS.

**Key words:** pulmonary transit time, hepatopulmonary syndrome, orthodeoxia, alveolocapillary oxygen disequilibrium, intrapulmonary vasodilatation

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## Introduction

Hypoxemia of varying severity is observed in about 45% of patients with advanced cirrhosis.[1–6] Profound hypoxemia with an arterial oxygen tension below 70 mmHg or an alveolar-arterial oxygen difference ($A\text{-}aDO_2$) greater than 20 mmHg strongly suggests the existence of hepatopulmonary syndrome (HPS) in these patients.[2,3,7] HPS is now a well-recognized clinical disorder, which is characterized by the triad of (1) chronic liver disease, (2) arterial hypoxemia, and (3) intrapulmonary vasodilatation (IPVD).[2,3] The presence of portal hypertension and the absence of intrinsic cardiopulmonary disease are prerequisites for a clinical diagnosis of HPS. The pathological basis of this condition encompasses a range of pulmonary vascular abnormalities, depending on the extent and magnitude of intrapulmonary vasodilatation. Aggravation of hypoxemia by standing up (orthodeoxia) is one of the pathophysiological traits of this disorder, indicating functional and/or anatomical derangement of the pulmonary vessels.[2,3,8–10]

IPVD is usually assessed by contrast-enhanced echocardiography (CEE) using manually agitated saline that contains air microbubbles,[4,5,9,11,12] or by intravenous injection of $^{99m}$Tc-macroaggregated albumin (MAA).[6,11,13] The latter method is employed for determination of the amount of blood shunted through the dilated intrapulmonary vessels, but a high sensitivity is not achievable. On the other hand, the diagnostic capability of CEE using agitated saline is limited to detecting the existence of intrapulmonary vasodilatation (vessels over 20 μm in diameter).[4,5] However, it has been recognized that air bubbles pass through the dilated pulmonary vessels and appear in the left atrium almost immediately (a few heartbeats) after opacification of the right atrium.[4] Although the flow velocity of the blood which passes through the lungs appears to be related to the extent of oxygenation (diffusion-

**Table 1.** clinical characteristics of patients with chronic liver disease

| | |
|---|---|
| Number of patients (male/female) | 16 (8/8) |
| Cirrhosis/chronic hepatitis | 12/4 |
| Etiology of liver disease | |
| Hepatitis C virus | 14 |
| Habitual alcohol intake | 2 |
| Child-Pugh score (range)[a,b] | 7.3 ± 0.5 (5–9) |
| A (no. of patients) | 6 |
| B (no. of patients) | 10 |
| Liver function tests | |
| AST (IU/l)[b] | 71 ± 35 |
| ALT (IU/l)[b] | 58 ± 32 |
| Total bilirubin (mg/dl)[b] | 1.2 ± 0.6 |
| Albumin (g/dl)[b] | 3.4 ± 0.5 |
| Prothrombin time (%)[b] | 76.7 ± 21.0 |
| Hemoglobin concentration (g/dl)[b] | 11.1 ± 3.3 |
| Platelet count ($\times 10^4$/mm$^3$)[b] | 12.0 ± 6.6 |

[a] Includes four patients with chronic hepatitis
[b] Mean ± SD

perfusion impairment),[1,2,14–18] no study of the pulmonary transit time of blood has been performed. Therefore, we explored the possibility that assessment of the pulmonary blood transit time would increase the usefulness of CEE. Accordingly, we estimated the pulmonary transit time of erythrocytes by CEE, using air microbubbles that were smaller than erythrocytes,[19] and we studied the relationship between the transit time and arterial oxygenation in patients with chronic liver disease.

## Patients and methods

### *Patients*

Sixteen consecutive patients with chronic liver disease were studied, including 12 with compensated cirrhosis (Child-Pugh class A or B) and 4 with chronic hepatitis (Table 1). None of the patients had ascites or pleural effusion. There were eight men and eight women, with a mean age of 63.0 ± 8.6 years, ranging from 40 to 77 years. The diagnosis of chronic liver disease was based on the results of physical examination, routine liver function tests, imaging using ultrasound or computed tomography, and the liver histology shown by biopsy. The etiology was hepatitis C virus infection in 14 patients and alcohol abuse in 2. Seven healthy volunteers (4 men and 3 women) were also studied, as a control group. The mean age of the control group was 47.3 ± 3.7 years, ranging from 47 to 54 years (significantly different from that of the patients; $P < 0.001$). The procedures were explained and informed consent was obtained before examinations were carried out. Physical examination and chest X-ray films showed no obvious lung disease, and echocardiography revealed no cardiac dysfunction, valvular heart disease, intracardiac shunting, or pulmonary hypertension.[20]

### *Methods*

#### *Measurement of pulmonary erythrocytes transit time*

The pulmonary erythrocytes transit time (PTT) was determined by CEE, using Albunex (human serum albumin-air microbubble complexes with a mean diameter of 4 μm; SHIONOGI & CO., LTD, Osaka, Japan).[20] In brief, 10 ml of Albunex was injected intravenously within 10 s while the subject was in the supine position. Opacification of the cardiac chambers was assessed in the four-chamber view by CEE (Hewlett-Packard SONOS 2500; Philips, Best, Holland) and was recorded on a video recorder (frame rate of 60 Hz) to determine the PTT, which was defined as the time between opacification of the right and left atria.

IPVD was also assessed by CEE. In brief, a four-chamber apical image was obtained via a transthoracic approach. Then 10 ml of saline that had been manually agitated with 0.5 ml of room air was injected through the intravenous line and a positive result was obtained if microbubbles were observed in the left atrium. $^{99m}$Tc-MAA lung perfusion scintigraphy was also carried out in 12 patients.

Cardiac output (CO) was calculated as the mean of triplicate measurements by Doppler echocardiography. The CO was determined with patients and control subjects in the supine position, and was measured when patients were stable.

#### *Arterial blood gas analysis*

After the supine and seated positions had been maintained for at least 15 min each, collection of blood samples for blood gas analysis was performed. We determined the partial pressure of oxygen ($PaO_2$) and carbon dioxide ($PaCO_2$), as well as the pH, of arterial blood, using an automatic blood gas analyzer (ABL505; Radiometer, Copenhagen, Denmark). A-a$DO_2$ was calculated using the modified alveolar gas equation: A-a$DO_2$ = $FiO_2 \times (PB-47) - (PACO_2/R) - PaO_2$, where $FiO_2$ is the fraction of inspired $O_2$($FiO_2 = 0.21$), PB is the barometric pressure (average, 760 mmHg), $PACO_2$ is alveolar $CO_2$ (which was assumed to be equal to arterial $PCO_2$ [$PaCO_2$], and R is the mean respiratory quotient (assumed to be 0.8 while a subject is breathing room air). The normal range of A-a$DO_2$ was less than 15 mmHg.

Values for results were expressed as means ± SD. Comparisons were performed using analysis of variance (ANOVA), Student's *t*-test for paired or unpaired data, and Fisher's exact test, as appropriate. Correlations between parameters were determined by linear regression analysis, and $P < 0.05$ was considered statistically significant.

**Table 2.** Comparisons of the hemodynamics and arterial blood gases between controls and patients, in the supine position

| | Controls | Patients | *P* |
|---|---|---|---|
| No. of subjects (male/female) | 7 (4/3) | 16 (8/8) | NS |
| Age (years) | 47.3 ± 3.7 | 63.0 ± 8.6 | $P = 0.000$ |
| Hemodynamics | | | |
| Heart rate (bpm) | 61.7 ± 7.2 | 68.2 ± 7.7 | $P = 0.07$ |
| Mean arterial pressure (mmHg) | 94.2 ± 22.5 | 97.0 ± 13.3 | NS |
| Cardiac output (l/min) | 3.66 ± 0.96 | 4.25 ± 0.94[a] | NS |
| Pulmonary transit time (s) | NT | 4.0 ± 1.4 | NA |
| Arterial blood gas analysis | | | |
| pH | 7.43 ± 0.02 | 7.44 ± 0.03 | NS |
| $PaO_2$ (mmHg) | 92.4 ± 3.9 | 87.7 ± 8.2 | NS |
| $PaCO_2$ (mmHg) | 39.3 ± 2.4 | 36.4 ± 3.8 | $P = 0.10$ |
| A-a$DO_2$ (mmHg) | 8.2 ± 4.6 | 16.4 ± 10.0 | $P = 0.07$ |
| No. of patients with IPVD | NT | 3 | NA |

Values are means ± SD
Comparisons were made by two-tailed unpaired *t*-test
NT, not tested; NA, not applicable; NS, not significant; IPVD, intrapulmonary vasodilatation
[a] $n = 15$

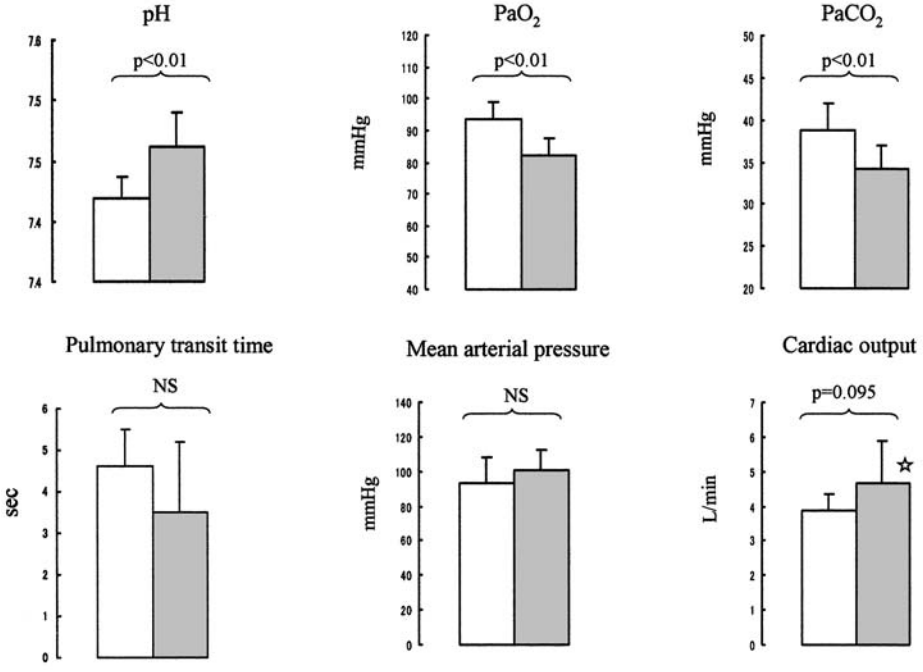


**Fig. 1.** Respiratory alkalosis and hypoxemia were observed in patients with an alveolar-arterial oxygen difference (A-a$DO_2$) of more than 15 mmHg (*gray bars*; $n = 8$) compared to those with a normal A-a$DO_2$ (≦15 mmHg; *white bars*; $n = 8$). However, there were no significant differences in hemodynamic parameters among these patient groups. $PaO_2$, arterial oxygen tension; $PaCO_2$, arterial carbon dioxide tension. Values are means ± SD; *P* values by two-tailed unpaired *t*-test. *NS*, not significant. *Star*, $n = 7$

## Results

### *Hemodynamics, PTT, and arterial blood gases in the stable state*

The hemodynamic and arterial blood gas values obtained with subjects in the supine position are shown in Table 2. The mean PTT value of all patients studied was 4.0 ± 1.4 s, ranging from 1.0 to 6.0 s. None of the patients showed profound hypoxemia, with a $PaO_2$ below 70 mmHg, and their values ranged from 73.3 to 103.3 mmHg. Hypocapnea, with a $PaCO_2$ below 35 mmHg, was seen in eight patients, and alkalosis with a pH above 7.45 was observed in seven patients. There were no patients who showed hypercapnia ($PaCO_2$ above 45 mmHg) or acidosis (pH below 7.35). There were seven patients with an A-a$DO_2$ greater than 20 mmHg among the eight patients who showed abnormal values (above 15 mmHg). These patients also showed respiratory alkalosis compared with those who had normal A-a$DO_2$ values (Fig. 1). The mean PTT value of the patients with an A-a$DO_2$ greater than 15 mmHg was smaller than the value in those with a normal A-a$DO_2$, but the difference was not significant (3.5 ± 1.7 vs 4.6 ± 0.9 s; $n = 8$ and $n = 8$, respectively;

$P = 0.145$). There was a weak, but significant, inverse correlation between CO and PTT in the whole patient group (Fig. 2).

*Intrapulmonary vasodilatation*

There were three patients with IPVD that was demonstrated by CEE using manually agitated saline. In these three patients, PTT (1 to 3.8 s) was lower than the mean value for all of the patients (4.0 s). These three patients also underwent $^{99m}$Tc-MAA lung perfusion scintigraphy, which showed that the shunt fraction was less than 15%. Although one of the three patients had IPVD, the $PaO_2$ and A-a$DO_2$ were within normal limits (90.0 mmHg and 10.3 mmHg, respectively), indicating that there was no impairment of arterial oxygenation.

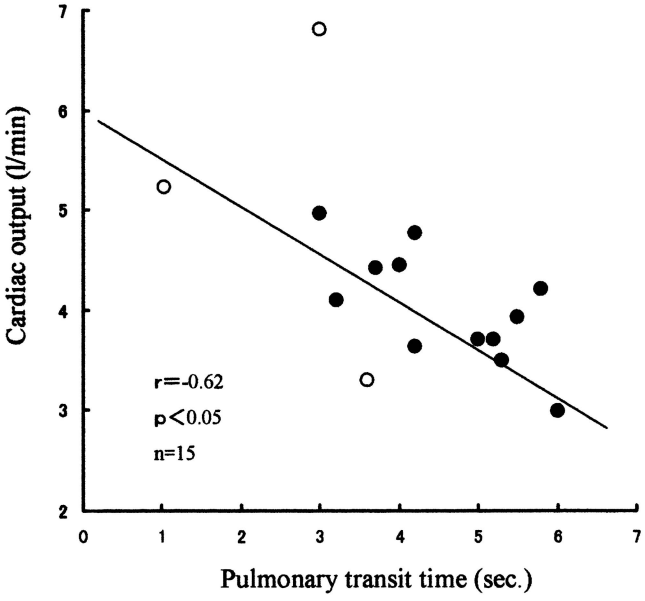


**Fig. 2.** There was a significant inverse correlation between cardiac output and the pulmonary erythrocyte transit time in patients with chronic liver disease. The *open circles* indicate patients with intrapulmonary vasodilatation

*Posture and arterial oxygenation*

In the whole patient group, $PaO_2$ decreased by 3.1% and A-a$DO_2$ increased significantly by 21.7% in the seated position (from 87.7 ± 8.2 to 84.7 ± 11.1 mmHg; $n = 16$; $P < 0.05$ and from 16.4 ± 10.0 to 19.8 ± 12.2 mmHg; $n = 16$; $P < 0.05$, respectively). As shown in Fig. 3, when limited to the patients with an A-a$DO_2$ Value of more than 15 mmHg, the decrease of $PaO_2$ (7.0%) and the increase of A-a$DO_2$ (20.4%) became more marked (from 81.9 ± 5.8 to 76.2 ± 7.1 mmHg; $n = 8$; $P < 0.05$ and from 25.2 ± 3.7 to 30.3 ± 6.0 mmHg; $n = 8$; $P < 0.05$, respectively). In the patients with a normal A-a$DO_2$, as well as in the healthy controls, the changes of these parameters were not significant. The net decrease of $PaO_2$ after sitting up in patients with a larger A-a$DO_2$ was significantly greater than the net decrease in those who had a normal A-a$DO_2$ (−5.7 ± 5.7 vs −0.4 ± 3.3 mmHg; $n = 8$ and $n = 8$; $P < 0.05$, respectively) or the healthy controls (5.8 ± 11.7; $n = 7$; $P < 0.05$). In the healthy subjects, the mean $PaO_2$ increased and the mean A-a$DO_2$ decreased when they sat up, but both changes were not significant (from 92.4 ± 3.9 to 98.2 ± 12.6 mmHg and from 8.2 ± 4.6 to 2.9 ± 10.4 mmHg, respectively; $n = 7$; both $P > 0.10$).

*Orthodeoxia, PTT, and liver function tests*

We could not find any significant correlation between PTT and the parameters of arterial oxygenation in the supine position. However, PTT was significantly correlated with $PaO_2$ and A-a$DO_2$ for the whole patient group in the seated position (Fig. 4). Furthermore, the net changes of $PaO_2$ and A-a$DO_2$ due to sitting up were significantly correlated with PTT ($r = 0.59$; and $r = -0.55$, respectively; $n = 16$; both $P < 0.05$). In contrast,

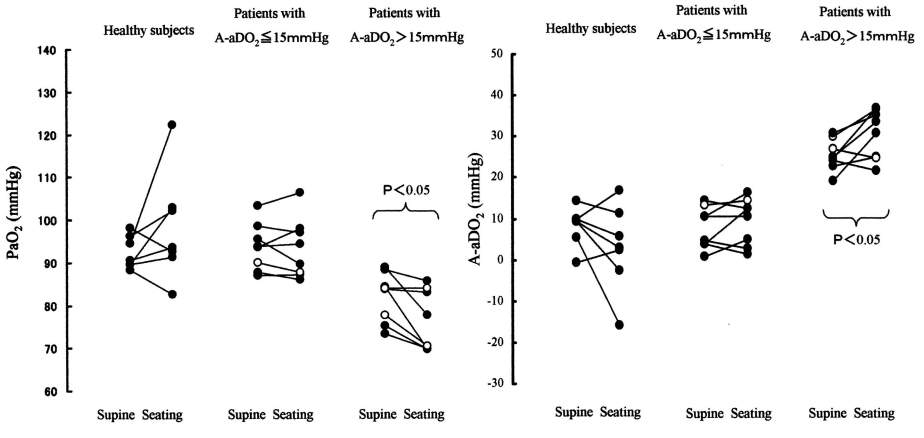


**Fig. 3.** Changes in the arterial oxygen tension ($PaO_2$) and alveolar-arterial oxygen difference ($A\text{-}aDO_2$) after sitting up from the supine position in patients with chronic liver disease and healthy controls. $PaO_2$ was significantly decreased and A-a$DO_2$ was significantly increased in patients with an A-a$DO_2$ of more than 15 mmHg in the supine position. The *open circles* indicate patients with intrapulmonary vasodilatation. *P* values by two-tailed paired *t*-test

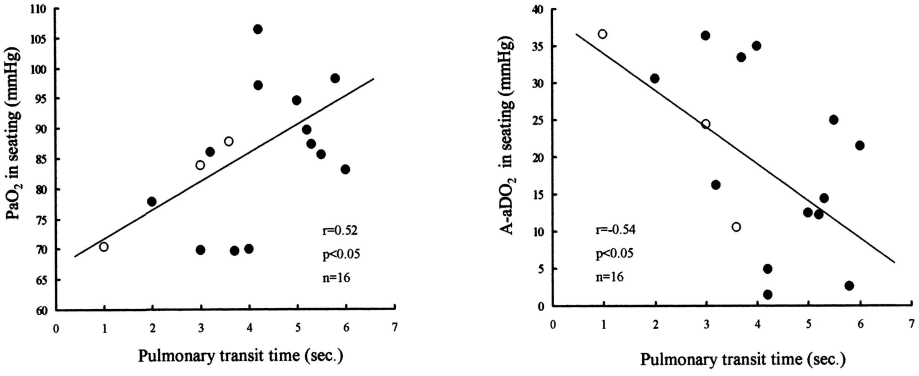


**Fig. 4.** The pulmonary erythrocyte transit time was significantly correlated with the arterial oxygen tension ($PaO_2$), as well as with the alveolar-arterial oxygen difference ($A\text{-}aDO_2$), when patients with chronic liver disease were in the seated position. The *open circles* indicate patients with intrapulmonary vasodilatation

**Table 3.** Comparison of liver function tests between patients with A-a$DO_2$ ≦ 15 mmHg and A-a$DO_2$ > 15 mmHg

| | Patients with A-a$DO_2$ ≦ 15 mmHg | Patients with A-a$DO_2$ > 15 mmHg | *P* |
|---|---|---|---|
| AST (IU/l) | 76 ± 45 | 66 ± 24 | NS |
| ALT (IU/l) | 70 ± 40 | 47 ± 18 | NS |
| Total protein (g/dl) | 6.8 ± 0.5 | 7.2 ± 0.5 | NS |
| Albumin (g/dl) | 3.6 ± 0.4 | 3.2 ± 0.5 | NS |
| Total bilirubin (mg/dl) | 1.0 ± 0.6 | 1.3 ± 0.6 | NS |
| Prothrombin time (%) | 87.2 ± 22.8 | 66.1 ± 13.1 | $P = 0.040$ |
| Child-Pugh score | 6.3 ± 1.4 | 7.4 ± 0.9 | $P = 0.076$ |
| Platelet count ($\times 10^4/mm^3$) | 9.9 ± 4.0 | 14.0 ± 8.2 | NS |

Values are means ± SD
Comparisons were made by two-tailed unpaired *t*-test
NS, not significant

cardiac output was not directly correlated with $PaO_2$ or A-a$DO_2$ in the seated position ($r = -0.17$; $P = 0.55$ and $r = 0.10$; $P = 0.72$; $n = 16$, respectively) or with the net changes on sitting up. We could not find any significant correlation between liver function tests and PTT in our patients with chronic liver disease. However, the mean prothrombin time of patients with an A-a$DO_2$ of 15 mmHg or less was significantly greater than the value in those with an A-a$DO_2$ of more than 15 mmHg (Table 3). The mean Child-Pugh score of the patients with widening of A-a$DO_2$ was also higher than the score in those with normal A-a$DO_2$ values, but the difference was not significant.

## Discussion

Half of the patients with chronic liver disease in the present study showed mild to moderate impairment of arterial oxygenation, but none of them had profound hypoxemia. Arterial hypoxemia is arbitrarily defined by a $PaO_2$ of less than 70 mmHg. However, the diagnostic criteria for HPS frequently state that an elevated A-a$DO_2$ (>20 mmHg) alone is sufficient to indicate the presence of impaired arterial oxygenation, and this maximizes the possibility of detecting "early" HPS.[3,5,7,11] One of our three patients who had IPVD was normoxemic and had a normal A-a$DO_2$. This is consistent with previous reports that some patients with IPVD do not show impaired arterial xoygenation.[7,11,12] Thus, it is considered that the detection of IPVD lacks specificity as a marker of impaired arterial oxygenation. In the present study, it seemed that an increase of CO contributed to a shorter PTT, but the CO was not correlated with any of the arterial blood gas parameters in either the supine or seated position. In contrast, $PaO_2$ fell as PTT decreased in the seated position. Therefore, it appears that the shorter PTT, rather than the increase of CO, contributed to the impairment of arterial oxygenation.

In the present study, patients who had an increased A-a$DO_2$ in the supine position showed mild, but significant, orthodeoxia. It has been demonstrated that there is impairment and/or a defective pressor response of the pulmonary vasculature (i.e., hypoxic vasoconstriction)[10,14] and that there is widespread pulmonary vasodilatation (particularly in the lung bases) in patients with advanced cirrhosis.[1,16,21–23] The pulmonary vascular bed

is a low-pressure system with a mean pressure below 25 mmHg, and it tends to be greatly influenced by gravity. In the bases of the upright lungs, physiological alveolar ventilation is minimal (i.e., the smallest ventilation-perfusion ratio), while blood flow is increased and the hydrostatic pressure rises due to the effect of gravity. In patients with chronic liver disease, therefore, sitting up should provoke and/or augment vasodilatation and increase blood flow in these regions because of the poor resistance to a rise in hydrostatic pressure, leading to a further reduction of the ventilation-perfusion ratio.[1,10,14,16–18,24] Thus, it is possible that the orthodeoxia observed in our patients indirectly indicates deterioration of the pressor response of the pulmonary vasculature and/or the existence of IPVD.

We found a weak, but significant, correlation between PTT and the parameters of arterial oxygenation when our patients were seated. This suggested that hyperperfused lung regions (probably the bases) allowed rapid transit of the albumin-air microbubble complexes in patients with an abnormal A-a$DO_2$ in the supine position, and that an increased CO was partially responsible.[16,18,22,23,25] In this situation (rapid transit of erythrocytes and pulmonary vasodilatation), even though capillary dilatation is not sufficient to impede the diffusion of oxygen, the time available for blood to take up oxygen molecules is reduced, and this leads to alveolocapillary oxygen disequilibrium (so-called "diffusion-perfusion" imbalance).[1,16,18] It has been reported that a considerable number of patients have mild IPVD, which can only be demonstrated by transesophageal echocardiography using agitated saline, and not by the transthoracic route that we employed.[12] Therefore, some patients (probably those with orthodeoxia) may have had mild IPVD that was missed by our method in the present study. If it is assumed that mild IPVD was overlooked, the above-mentioned hypothesis seems reasonable.

In the present data, we adopted 15 mmHg as the upper normal limit for A-a$DO_2$ in the supine position.[5,7] It is known that respiratory function declines with aging.[3,5] Because the control group was much younger than the patient group, we also analyzed the present findings by using predicted A-a$DO_2$ values corrected by age (based on the linear regression equation: A-a$DO_2$ = 10.06 + 0.026 × Age mmHg, and the 95% confidence interval)[26] and obtained results that were similar to those reported here. Unfortunately, we could not measure PTT in the control group, so we could not examine the correlation between PTT and arterial oxygenation in healthy subjects. However, there were no significant differences of arterial oxygenation in the supine or seated positions between healthy subjects and the patients with a normal A-a$DO_2$. Furthermore, the blood gas parameters of the patients with a normal A-a$DO_2$ responded to a change of posture similarly to those of the control group, indicating that the pulmonary vascular bed maintained a pressor response, at least in these patients.[10,14]

In the present study, it was difficult to define the PTT value that was associated with impairment of oxygenation. A previous study of the transit time from right atrium to left atrium in healthy subjects, using a radioactive tracer, showed that it was 5.1 ± 0.43 s, and the range was 4.24–5.96 s (mean ± 2 SD).[27] Using 4.2 s as the critical value, we analyzed the relationship between arterial oxygenation and PTT in our patients. As a result, the difference of arterial oxygenation between patients with a reduced PTT ($n$ = 8) and those with a normal PTT ($n$ = 8) became more prominent (supine $P$a$O_2$, 92.9 ± 6.4 vs 82.6 ± 6.4 mmHg; $P$ = 0.006; supine A-a$DO_2$, 10.9 ± 9.0 vs 21.9 ± 8.0 mmHg; $P$ = 0.021; and seated $P$a$O_2$, 92.6 ± 7.8 vs 76.8 ± 7.9 mmHg; $P$ = 0.001; seated A-a$DO_2$, 11.8 ± 8.5 vs 27.9 ± 10.0 mmHg, respectively; $P$ = 0.004), and the difference of CO ($n$ = 7) also became significant (3.81 ± 0.52 vs 4.75 ± 1.10 l/min respectively; $P$ = 0.048). Thus, 4.2 s may be the critical PTT value that is associated with impaired arterial oxygenation in patients with chronic liver disease.

In summary, the present study revealed that a considerable number of patients showed impaired arterial oxygenation independently of the presence of IPVD detected by CEE using agitated saline. Mild (but significant) orthodeoxia was observed in patients who showed an abnormal A-a$DO_2$. Furthermore, a reduced PTT was significantly correlated with the impairment of arterial oxygenation that was augmented by sitting up in these patients. Thus, it is concluded that PTT may be a useful clinical parameter to compensate for the defects of conventional CEE in patients with chronic liver disease with early HPS.

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