Carboxyhemoglobin Levels in Cirrhotic Patients With and Without Hepatopulmonary Syndrome

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Background & Aims: **Heme oxygenase (HO) catalyzes hemoglobin into bilirubin, iron, and carbon monoxide (CO), a known vasodilator. HO expression and CO production as measured by blood carboxyhemoglobin (COHb) levels increase in experimental hepatopulmonary syndrome (HPS) and contribute to vasodilatation. Whether CO contributes to HPS in humans is unknown. Our aim was to assess if arterial COHb levels are increased in cirrhotic patients with HPS relative to those without HPS.** ***Methods:*** **We collected data prospectively in stable nonsmoking outpatients with cirrhosis. Demographic and clinical data and room-air arterial blood gases were collected and analyzed. HPS was diagnosed using established criteria.** ***Results:*** **A total of 159 patients were studied. HPS was present in 27 (17%) patients. Mean age was 52 ± 9 years, 54% were men, and hepatitis C and/or alcohol were the most common causes (53%). Fourteen percent were Child–Pugh class A, 53% were Child–Pugh class B, and 33% were Child–Pugh class C. Demographic and clinical features were similar between HPS and non-HPS patients except for the Child–Pugh score, which was lower in patients with HPS. Arterial Pao_2 levels were lower and the alveolar-arterial oxygen gradient was higher in patients with HPS ($P < .001$). COHb levels were increased in HPS relative to non-HPS ($P < .001$) and correlated with Pao_2 ($P < .001$) and $AaPo_2$ ($P < .001$) levels.** ***Conclusions:*** **COHb levels are increased in cirrhotic patients with HPS and correlate with gas exchange abnormalities. These results are consistent with findings in experimental HPS and suggest that CO may contribute to human HPS.**

The hepatopulmonary syndrome (HPS) occurs when intrapulmonary vasodilatation results in hypoxemia.[1] This syndrome occurs most commonly in the setting of cirrhosis and portal hypertension and is found in 8%–15% of such patients, although the mechanisms remain incompletely characterized.[2] The syndrome frequently is progressive and associated with significant morbidity and mortality. Currently, no clearly effective medical therapies are available, and liver transplantation is the only treatment of proven benefit. However, posttransplantation mortality is increased in HPS patients with severe hypoxemia ($Pao_2 < 50$ mm Hg), underscoring the need to develop effective medical treatments.[3]

Improvements in the understanding of the pathogenesis of HPS may allow the development of effective medical therapy. A number of potential mechanisms for intrapulmonary vasodilatation have been identified recently in human and experimental HPS. In human studies, pulmonary nitric oxide overproduction appears to contribute to vasodilatation, although the source of nitric oxide production is unknown.[4–8] In experimental HPS, both increased pulmonary microvascular endothelial nitric oxide synthase levels and increased inducible nitric oxide synthase levels in pulmonary intravascular macrophages have been observed and may contribute to nitric oxide production.[9,10] Recently, a marked increase in expression of heme oxygenase-1 (HO-1) also has been found in intravascular macrophages in experimental HPS.[11,12] HO-1 is an inducible enzyme that catalyzes the metabolism of hemoglobin into bilirubin, iron, and carbon monoxide (CO).[13] CO may function as a vasodilator and circulates bound tightly to hemoglobin, resulting in the formation of carboxyhemoglobin (COHb).[14,15] The measurement of COHb levels in blood is used as a reflection of CO production, and venous COHb levels have been evaluated in a cohort of patients with cirrhosis.[15] In experimental HPS, arterial COHb levels are increased significantly relative to normals, and inhibition of pulmonary HO normalizes arterial COHb levels and improves vasodilatation, supporting the theory that HO-1–mediated CO production is involved.[12]

However, whether CO contributes to intrapulmonary vasodilatation and HPS in humans remains unknown. Therefore, the aim of the present study was to assess if arterial COHb levels, as a measure of CO production, are

Abbreviations used in this paper: $AaPO_2$, alveolar-arterial oxygen gradient; COHb, carboxyhemoglobin; HO, heme oxygenase; HPS, hepatopulmonary syndrome; Pao_2, arterial oxygen tension.

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increased in cirrhotic patients with HPS compared with cirrhotic patients without HPS.

Materials and Methods

Subjects and Data Collection

Subjects. We prospectively analyzed a cohort of 159 patients with cirrhosis who were referred for initial liver transplant evaluation to the University of Alabama at Birmingham Liver Center outpatient clinic. Data were collected from January 2000 through January 2002. The Institutional Review Board approved the present study.

All study participants were at least 18 years of age and were not selected on the basis of sex, race, socioeconomic status, or cause of liver disease. Cirrhosis was defined histologically or by a combination of characteristic clinical, laboratory, and radiologic findings. For inclusion into the study, patients had the following: (1) a negative history of smoking or had achieved and maintained cessation for at least 12 months before enrollment, (2) a negative history of chronic pulmonary disorders, and (3) an absence of intrinsic pulmonary disease (normal chest radiography and normal spirometry and lung volumes on pulmonary function testing).

Screening for HPS. All patients underwent screening for HPS, which was defined by: (1) a positive contrast echocardiogram consistent with intrapulmonary shunting and (2) an arterial oxygen tension (PaO_2) $<$ 70 mm Hg or an age-corrected alveolar-arterial oxygen gradient ($AaPO_2$) $>$ 20 mm Hg.

Arterial blood gases and COHb levels. Arterial specimens for blood gas analyses were obtained at room air in the sitting position immediately before pulmonary function test measurements. To define the presence of HPS, we used an age-corrected $AaPO_2$ value greater than 20 mm Hg in the setting of a positive contrast echocardiogram. For statistical analyses, we used the age-corrected $AaPO_2$ value—age-corrected $AaPO_2$: ([age $-$ 20] $\times$ [0.43] $-$ 10). COHb was measured by CO oximetry by using the ABL 700 Series Analyzer (Radiometer, Copenhagen, Denmark) and corrected for hemoglobin levels. The coefficient of variation in COHb levels derived from repeated testing on individual specimens is 0.1%.

Demographic, clinical, room-air arterial blood gas results, and corrected COHb values were collected and recorded into a computerized database.

Data Analysis

Descriptive data are expressed as proportions and quantitative data are summarized as mean $\pm$ SD. Comparisons between groups were performed with the Student *t* test or 1-way analysis of variance with Bonferroni correction, as appropriate. For qualitative data, χ^2 analysis or Fisher exact test was used. Relationships between variables were assessed by the Spearman coefficient. For all comparisons, statistical significance was defined as a *P* value less than .05.

Table 1. Demographic and Clinical Data

Variable	HPS (n = 27)	Non-HPS (n = 132)	*P* value
Age (*mean* $\pm$ *SD*)	50 $\pm$ 13	53 $\pm$ 8	NS
Men (%)	52	54.5	NS
Race (Caucasian %)	81	89	NS
Total (bilirubin, *mg/dL* (*mean* $\pm$ *SD*)	2.5 $\pm$ 1.1	3.4 $\pm$ 3.2	.02
Ascites (%)	42	82	.001
Child–Pugh score (*mean* $\pm$ *SD*)	7.1 $\pm$ 1.5	8.9 $\pm$ 1.7	.001
Child–Pugh class (%)			.001
A	44	8	
B	52	53	
C	4	39	
Cause (%)			NS
Hepatitis C	21	35	
Alcohol	26	19	
Cryptogenic	42	24	
Cholestatic liver disease	10	13	
Other	1	9	

NS, not significant.

Results

Baseline Characteristics

Data were collected and analyzed in a total of 159 patients. Twenty-seven patients (17%) fulfilled criteria for HPS. Demographic and clinical data are summarized in Table 1. The mean age of the entire cohort was 52 $\pm$ 9 years and 86 participants were men (54%). The most common causes of liver disease were hepatitis C virus infection and/or alcoholic liver disease (53%). Patients were distributed according to the severity of liver disease as follows: Child–Pugh class A (14%), Child–Pugh class B (53%), and Child–Pugh class C (33%). At the time of arterial blood gas measurements, no patients had clinical or routine laboratory evidence of infection (fever, leukocytosis, neutrophilia).

There was no significant difference in basic demographics (sex, race, age) or cause of cirrhosis between HPS and non-HPS patients (P = not significant). However, in patients with HPS, liver disease was significantly less severe as determined by Child–Pugh score ($P <$ .001) and Child–Pugh class ($P <$ .001). These patients also had a lower prevalence of ascites ($P <$ .001) and had lower mean total bilirubin levels (P = .02).

Arterial Blood Gases

The results of arterial blood gas measurements are summarized in Table 2. Arterial PaO_2 levels were significantly lower in HPS patients compared with non-HPS patients (56 $\pm$ 13 mm Hg vs. 87 $\pm$ 8 mm Hg, respectively) ($P <$ .001). The age-corrected $AaPO_2$ value was higher in patients with HPS compared with non-HPS