European Review for Medical and Pharmacological Sciences 2014 18: 380-386

The role of hemodynamic and vasoactive substances on hepatopulmonary syndrome

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Abstract. – BACKGROUND: Hepatopulmonary syndrome (HPS) is a chronic hepatic complication characterized by defect in arterial oxygenation induced by pulmonary vascular dilatation and vasoactive substances in the setting of chronic liver disease (CLD). This study is to investigate the abnormality of hemodynamic and vasoactive substances in hepatopulmonary syndrome.

PATIENTS AND METHODS: From September 2007 to September 2012, 58 patients with HPS in the General Surgery Department and Transplantation Center of Renji Hospital were enrolled for the case-control study. HPS patients enrolled were referred to as group H, CLD without HPS to as group C and case controls to as group N. Hemodynamic parameters of the systemic and pulmonary circulations as well as vasoactive substances in the radial and pulmonary arteries were measured in all patients. Univariate and multiple regression analysis were performed afterwards.

RESULTS: The mean pulmonary arterial pressure, pulmonary artery wedge pressure, systemic vascular resistance and pulmonary vascular resistance (PVR) in HPS patients were significantly lower than those in CLD patients without HPS ($p < 0.05$). The nitrite-to-nitrate ratio (NO_2^-/NO_3^-), endothelin-1 (ET-1) and tumor necrosis factor-α (TNF-α) in the radial and pulmonary arteries differed significantly among group H, group C and case controls (group N) separately ($p < 0.05$). The vasoactive intestinal peptide and 6-keto-prostaglandin-F1α in the radial and pulmonary arteries of group H were significantly higher than those in group N ($p < 0.05$). The NO_2^-/NO_3^- levels correlated negatively with PVR ($r = –0.535$, $p < 0.05$) and Endothelin-1 ($r = –0.624$, $p < 0.05$). CO ($p < 0.05$), CI ($p < 0.05$), SI ($p < 0.05$) and TNF-α ($p < 0.05$) level are considered significantly when performed with multiple regression analysis.

CONCLUSIONS: The CO increases and PVR decreases in HPS patients. The abnormally elevated NO2-/NO3-level in the pulmonary circulation leads to pulmonary vasodilation. ET-1 may induce nitric oxide synthesis and correlated negatively with PVR in HPS. CO, CI, SI and TNF-α level are independent risk factors for HPS patients' survival.

Key Words:

Hepatopulmonary syndrome, Hemodynamic, Vasoactive substance, Chronic liver disease, Pathogenesis.

Introduction

Chronic liver diseases (CLD) associated intrapulmonary vascular dilatations was described for more than 100 years. As many as 70% patients with CLD suffer from respiratory problems[1]. Hepatopulmonary syndrome (HPS) is a chronic hepatic complication characterized by a defect in arterial oxygenation induced by pulmonary vascular dilatation in the setting of chronic liver disease[2]. Patients of all ages can be affected[3]. Lung abnormalities are always observed before the onset of clinical symptoms.

Although vasoactive substances, such as nitric oxide (NO), endothelin-1 (ET-1), tumor necrosis factor-α (TNF-α), vasoactive intestinal peptide (VIP) and prostaglandin (PG) may influence HPS[2,4-9], most of these results were based on animal cirrhosis models caused by bile duct ligation. Currently, the only effective medical treatment for HPS is liver transplantation, which may cause cardiopulmonary complications correlating with a higher mortality[10,11]. Therefore, it is clinically relevant to study the abnormality of hemodynamic and vasoactive substances in HPS. This research may offer clues to the pathogenesis of HPS and help to discover new therapies.

Patients and Methods

We completed a diagnostic examination for patients with portal hypertentsion due to CLD who underwent surgical treatment such as devascularization, splenorenal shunt, splenorenal shunt combined with devascularization or orthotopic

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liver transplantation from September 2009 to June 2011 in the General Surgery Department and Transplantation Center of Renji Hospital. After ruling out intrinsic cardiopulmonary diseases, HPS was diagnosed if the following criteria were met: positive findings on contrast-enhanced echocardiography (microbubble suspension of the left atrium within three to six cardiac cycles after right-atrial opacification indicates microbubble passage through an abnormally dilated vascular bed) and an arterial partial pressure of oxygen (PaO_2) < 80 mmHg and/or an alveolar-arterial oxygen gradient (A-aDO_2) ≥ 15 mmHg while breathing room air. In all 104 CLD patients with 73.1% caused by Hepatitis B Virus infection, eighteen patients (17.3%, 11 males and 7 females) with a mean age of 52.3±12.3 years were diagnosed with HPS, referred to as group H. 10 patients of them were caused by Hepatitis B Virus infection, 3 by biliary cirrhosis, 2 by autoimmune hepatitis, 1 by schistosomiasis and 1 by Hepatitis C Virus infection combined with schistosomiasis.

Eighteen CLD patients with neither primary cardiopulmonary disease nor HPS were selected as the CLD group, referred to as group C. These patients matched with the HPS patients from group H in regards to age (difference within ± 10 years), sex ratio and severity of liver disease according to Child-Pugh classification. During the same period, 18 patients who underwent surgery due to benign diseases (e.g., ulcer, adhesive ileus) were identified as case controls without primary cardiopulmonary and liver disease (age difference within ±10 years), referred to as group N.

All patients involved in this study were well prepared for selective operations without obvious infection or other severe complications. The regular administration of antibiotics and anti-oxidants was not included in the preoperative treatment.

Informed consent was obtained from each patient enrolled to our study, and all examinations were accepted of their own accord.

Pulmonary Circulation Hemodynamic Parameters

The hemodynamic parameters detected by right heart catheterization were determined before the operation while the patients were conscious. Patients abstained from eating for 12 hours before the surgery. After entering the operating room, the peripheral venous forearm was opened, and a right radial artery catheterization was performed to monitor the systolic arterial pressure (SAP) and diastolic arterial pressure (DAP) continuously. The pulmonary artery flotation catheter (Swan-Ganz CCOmbo V774 HF75; Edwards Lifesciences Co., Ltd., Irvine, CA, USA) of the right jugular vein was located before induction of anesthesia. A hemodynamic monitor (Vigilance CCO/SvO_2, Edwards Lifesciences Co., Ltd., Irvine, CA, USA) was used to continuously monitor hemodynamic parameters, including cardiac output (CO), systolic pulmonary arterial pressure (SPAP), diastolic pulmonary arterial pressure (DPAP), pulmonary artery wedge pressure (PAWP) and central venous pressure (CVP). Systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), cardiac index (CI) and stroke index (SI) were calculated using the following formulas

1. SVR = (MAP-MRAP) × 80/CO
[Mean right atrial pressure (MRAP), replace MRAP for CVP]
2. PVR = (MPAP – PAWP) × 80/CO
3. MAP = DAP + (SAP-DAP)/3
4. MPAP = DPAP + (SPAP-DPAP)/3
5. CI = CO/BSA (body surface area)
6. SI = (CO × 1000)/(HR × BSA).

The right atrium level, located at the junction of the right middle axillary line and the fourth rib, was set as the pressure baseline.

Blood Sample Collection

The right heart flotation catheter was verified to be in the correct position. After the measurement of hemodynamic parameters was completed, a 4 mL blood sample was drawn from each of the radial and pulmonary arteries before the operation with patients being in stable condition. Half (2 mL) of each blood sample was mixed with 0.2 mL 2% EDTA-Na. The remaining 2 mL of the blood sample was placed under room temperature. The samples were centrifuged at 3000 rpm for 5 minutes at 4°C and extracted separately as supernatant plasma and serum for detection. The serum levels of NO, ET-1, TNF-α, PGI and VIP were determined by enzyme-linked immunosorbent assay (ELISA) (ELISA kit: R&D Systems Company, Minneapolis, MN, USA). NO and PG were determined indirectly by the level of their stable metabolites NO_2^-/NO_3^- and 6-keto-prostaglandin-F1α (6-keto-$PGF_{1\alpha}$).

Statistical Analysis

The data were analyzed with SPSS 16.0 statistical software (SPSS Inc., Chicago, IL, USA) and presented as the mean ± SD or median. Enumeration data were presented as a rate or ratio and calculated using ^{2} testing. A Pearson's correlation coefficient was used when appropriate. p values < 0.05 were considered to be statistically significant.

Results

Hemodynamic Parameters in HPS Patients

First of all, compared with patients from group C and group N, those in group H displayed significant lower PaO_2, higher A-aDO2 and reduced pulmonary diffusion capacity for carbon monoxide, which were consistent with the diagnostic criteria for HPS.

No significant differences in MAP or CVP were found among patients from all three groups ($p > 0.05$). The levels of CO, CI and SI in patients with HPS were significantly higher than those in patients without HPS, even though these parameters manifested higher levels in CLD patients without HPS compared with those in case controls ($p < 0.05$). The MPAP ($p = 0.041$), PAWP ($p = 0.024$), SVR ($p = 0.005$) and PVR ($p = 0.001$) in HPS patients were significantly lower than those in CLD patients. Whereas, the MPAP ($p = 0.003$) and PVR ($p = 0.042$) from case controls were significantly lower than those from CLD patients ($p < 0.05$) (Table I).

Then the vasoactive substances in all patients were analyzed and the results showed that there was a significant difference in the NO_2^-/NO_3^-, ET-1 and TNF-α levels from the radial and pulmonary artery among these three groups, respectively ($p < 0.05$). The levels of VIP and 6-keto-PGF1α in the radial and pulmonary artery in HPS and CLD patients were significantly higher than those in case controls ($p < 0.05$). However, there was no significant difference in VIP and 6-keto-PGF1α between HPS and CLD patients ($p > 0.05$) (Table II). We did not examine catecholamines, but we ruled out the patients with intrinsic cardiopulmonary disease.

Moreover, to clarify the relationship between hemodynamic parameters and levels of vasoactive substances in HPS patients, we conducted a correlation analysis between the vasoactive substances with significant difference (i.e., NO_2^-/NO_3^-, ET-1, TNF-α, VIP and 6-keto-$PGF_{1\alpha}$) and PVR separately. The results showed that only NO_2^-/NO_3^- and ET-1 correlated negatively with PVR ($r = –0.535$, $p < 0.05$ and $r = –0.624$, $p < 0.05$, respectively), while other substances did not correlated with PVR ($p > 0.05$).

Risk Factors for Patient Survival

We identified 58 patients who were diagnosed as HPS and concluded the risk factors of patients' survival from the parameters above. The univariate analysis showed that hemodynamic parameters including CO ($p = 0.02$), CI ($p = 0.04$), SI ($p = 0.02$), SVR ($p = 0.03$) and PVR ($p = 0.02$) were considered as significant factors of patients' survival. For the vasoactive substances, patients with higher TNF-α level had a higher risk of death (Radial artery, $p = 0.04$; Pulmonary artery, $p = 0.03$). In a further multiple regression analysis, we found that HPS patients with higher levels of CO ($p = 0.02$), CI ($p = 0.04$), SI ($p = 0.03$) and TNF-α (Radial artery, $p = 0.04$; Pulmonary artery, $p = 0.02$) had higher risk of death while other parameters made no contributions to patients' survival.

Table I. Comparison of hemodynamic parameters.

Hemodynamic parameters	Normal reference values	Group H (n=18)	Group C (n=18)	Group N (n=18)
CO (L/min)	4-6	7.2 ± 1.8†,‡	5.4 ± 1.2§,‡	4.4 ± 0.7§,†
CI (L/min/m^2)	2.8-4.2	4.2 ± 1.0†,‡	3.3 ± 0.7§,‡	2.6 ± 0.4§,†
SI (ml/beat/m^2)	30-65	54.0 ± 11.0†,‡	46.3 ± 10.5§,‡	37.9 ± 7.3§,†
CVP (mmHg)	5-10	11.9 ± 3.0	12.4 ± 2.5	10.7 ± 3.7
MPAP (mmHg)	10-20	20.3 ± 4.0†	23.2 ± 4.8§,‡	18.9 ± 3.8†
PAWP (mmHg)	5-15	13.6 ± 2.4†	16.0 ± 3.2§	14.2 ± 3.5
SVR (dyn·s^{-1}·cm^{-5})	900-1400	812.0 ± 234.7†,‡	1112.6 ± 358.8§	1346.0 ± 306.4§
PVR (dyn·s^{-1}·cm^{-5})	150~250	73.6 ± 24.7†	116.9 ± 49.8§,‡	90.5 ± 35.5†

†: Significantly different from group C, $p < 0.05$: ‡: Significantly different from group N, $p < 0.05$; §: Significantly different from group H, $p < 0.05$.

Table II. Comparison of vasoactive substances.

		Group H	Group C	Group N
NO_2-/NO_3- (μmol/L)	Radial artery	122.4 ± 16.3†,‡	111.3 ± 10.0‡,§	102.4 ± 12.1§,†
	Pulmonary artery	140.7 ± 21.1†,‡	122.6 ± 20.6‡,§	106.8 ± 13.2§,†
ET-1 (pg/mL)	Radial artery	122.8 ± 25.6†,‡	102.8 ± 14.3‡,§	88.6 ± 16.2§,†
	Pulmonary artery	148.8 ± 15.5†,‡	116.1 ± 24.1‡,§	92.4 ± 21.7§,†
TNF-α (ng/L)	Radial artery	359.7 ± 42.9†,‡	317.2 ± 68.5‡,§	277.6 ± 37.9§,†
	Pulmonary artery	404.6 ± 39.1†,‡	363.3 ± 49.3‡,§	256.6 ± 49.0§,†
VIP (ng/L)	Radial artery	184.4 ± 33.8‡	169.1 ± 23.8‡	139.3 ± 13.2§,†
	Pulmonary artery	204.3 ± 26.0‡	181.4 ± 24.2‡	141.4 ± 13.5§,†
6-keto-PGF1α (ng/L)	Radial artery	119.8 ± 15.2‡	118.9 ± 11.0‡	99.6 ± 11.1§,†
	Pulmonary artery	123.6 ± 27.3‡	124.4 ± 24.4‡	105.4 ± 22.6§,†

†: Significantly different from group C, $p < 0.05$; ‡: Significantly different from group N, $p < 0.05$; §: Significantly different from group H, $p < 0.05$.

Discussion

Pulmonary Hemodynamics in HPS

The pulmonary capillary bed plays an important role in filtration by blocking and metabolizing various kinds of vasoactive substances and cytokines. When these substances are overproduced and "overflow" to the systemic circulation, a hyperdynamic circulation characterized by hemangiectasis begins. In our study, the CI increased and the SVR decreased in HPS and CLD patients with respect to case controls. A comparison of the three groups demonstrated that normal patients have the highest SVR and HPS patients have the lowest SVR, respectively. Due to the decrease of vasodilator decomposition in HPS patients, vasodilator factors abnormally increase and lead to a low resistance circulatory state.

The quantity, density and type of vasoactive substance receptors in the pulmonary vascular walls are different from those in the systemic vascular walls, leading to a different hemodynamic state in the systemic and pulmonary circulations. Type B (ET_B) has been reported as the dominant subtype of the ET-1 receptors in pulmonary vascular endothelial cells[12]. The activated ET_B receptor promotes the synthesis of NO, which leads to pulmonary vasodilation. Our study showed that the PVR in CLD patients were significantly higher than those in normal and HPS patients with no

Table III. Univariate analysis of patients' parameters.

		OR	95% CI	*p*-value
Hemodynamic parameters				
CO (L/min)		4.64	(1.45-13.54)	0.02
CI (L/min/m^2)		10.65	(2.04-32.05)	0.04
SI (ml/beat/m^2)		8.66	(1.83-18.47)	0.02
CVP (mmHg)		1.57	(0.32-2.65)	0.57
MPAP (mmHg)		2.54	(0.68-6.28)	0.12
PAWP (mmHg)		1.43	(0.57-7.36)	0.07
SVR (dyn·s^{-1}·cm^{-5})		0.68	(0.24-0.97)	0.03
PVR (dyn·s^{-1}·cm^{-5})		0.56	(0.16-0.98)	0.02
Vasoactive substances				
NO_2-/NO_3- (μmol/L)	Radial artery	0.83	(0.53-6.34)	0.18
	Pulmonary artery	0.88	(0.42-10.53)	0.11
ET-1 (pg/mL)	Radial artery	0.99	(0.68-2.07)	0.09
	Pulmonary artery	1.32	(0.35-8.65)	0.07
TNF-α (ng/L)	Radial artery	2.94	(1.48-5.85)	0.04
	Pulmonary artery	3.57	(1.08-8.54)	0.03
VIP (ng/L)	Radial artery	3.65	(0.83-4.59)	0.06
	Pulmonary artery	2.76	(0.59-8.35)	0.09
6-keto-$PGF_{1\alpha}$ (ng/L)	Radial artery	6.34	(0.89-13.54)	0.53
	Pulmonary artery	5.38	(0.74-12.94)	0.32

Table III. Univariate analysis of patients' parameters.

		OR	95% CI	*p*-value
Hemodynamic parameters				
CO (L/min)		4.64	(1.07-10.47)	0.02
CI (L/min/m^2)		10.65	(1.53-7.27)	0.04
SI (ml/beat/m^2)		8.66	(2.37-20.13)	0.03
PAWP (mmHg)		1.43	(0.33-8.26)	0.15
SVR (dyn·s^{-1}·cm^{-5})		0.68	(0.63-3.25)	0.14
PVR (dyn·s^{-1}·cm^{-5})		0.56	(0.34-1.48)	0.07
Vasoactive substances				
ET-1 (pg/mL)	Radial artery	0.99	(0.24-5.35)	0.15
	Pulmonary artery	1.32	(0.65-5.37)	0.22
TNF-α (ng/L)	Radial artery	2.94	(1.64-7.26)	0.04
	Pulmonary artery	3.57	(1.26-7.53)	0.02
VIP (ng/L)	Radial artery	3.65	(0.47-10.57)	0.14
	Pulmonary artery	2.76	(0.45-7.86)	0.29

significant difference between the latter two groups. The pulmonary vascular resistance was lower in HPS patients than in CLD patients without HPS because of the elevated vasodilative factor level in the pulmonary circulation.

Relevant animal experiments have confirmed HPS patients have a normal level of PAWP[13]. The elevation of PAWP reflects water-sodium retention, an increase in circulation capacity, left ventricular preload and pulmonary hydrostatic pressure[14]. In our study, PAWP was lower in HPS patients than that in CLD patients, which demonstrates that the left ventricular preload and pulmonary hydrostatic pressure is lower in HPS patients than in CLD patients.

The Vasoactive Substances in HPS

The striking pathological feature of HPS is pulmonary telangiectasia, which is also considered the reason for an abnormal ventilation/perfusion ratio with a functional or anatomic shunt occurrence, resulting in arterial hypoxemia. The level of NO is speculated to increase significantly in HPS patients, supported by the restoration of a normal level of NO in patients who underwent successful orthotopic liver transplantation in the 1990s[15,16]. As the strongest vasodilator discovered to date, NO plays a key role in the accommodation of human vascular tone and the vascular response. In our research, the level of NO metabolites, the NO_2^-/NO_3^- in the radial and pulmonary arteries increased significantly in HPS patients than in normal patients, indicating an abnormally increased NO synthesis in HPS patients. The level of NO_2^-/NO_3^- was obviously higher in the pulmonary artery than in the radial artery in HPS patients. This finding indicates a substantial amount of NO in the pulmonary circulation of HPS patients. The lung, as a major organ downstream of the liver, is the most important site for the metabolism of vasoactive substance. Endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS) are highly expressed in the pulmonary capillaries[17]. Up-regulation of these synthases leads to a substantially increased amount of NO in HPS patients.

The metabolism of ET-1 occurred mainly in the lung. The pulmonary vascular endothelial cells not only produce ET-1 but also contain a large number of ET-1 receptors that uptake 90% of the ET-1 in circulation. In normal conditions, the pulmonary vascular endothelial cells produce ET-1 to regulate the pulmonary vascular tonus. Upon binding to the receptors of the vascular smooth muscle tissue (ETA), ET-1 functions as vasoconstriction. However, when binding to receptors located in the pulmonary vascular endothelium (ETB), ET-1 causes vasodilatation due to the synthesis of NO by stimulating eNOS. Thus, ET-1 balances the vasoconstricting effect of NO and helps maintain the pulmonary ventilation/perfusion ratio within normal limits[18]. In our study the levels of ET-1 were significantly higher in HPS and CLD patients. As liver damage in CLD patient increases, the capability of hepatocytes to inactivate ET-1 is reduced, which results in an elevation of the ET-1 level in the pulmonary circulation. That explained why the level of ET-1 was significantly higher in HPS patients than in normal patients. Interestingly, the level of ET-1 was significantly higher in the pulmonary artery than in the radial artery of both HPS and normal patients. The varying levels of vasoactive substances in the radial and pulmonary arteries re-

flect metabolism of these substances in the lung. The elimination of ET-1 depends on its binding to the ET_B receptors of the pulmonary capillaries. The activated ET_B receptor complex mediates the production of NO, which leads to pulmonary telangiectasis, a decrease in pulmonary vascular resistance and a reduction of pulmonary diffusion and oxygenation. After filtration through the pulmonary capillary network, the level of ET-1 decreases noticeably, but is still higher than the normal level.

In our study TNF-α level was clearly higher in HPS patients. TNF-α, as an inflammatory mediator, plays an indirect role in the pulmonary vasodilatation of HPS. Most CLD patients suffer from portal hypertension and intestinal microcirculation disorder. A decline in the intestinal mucosal barrier function, ischemia or hypoxia of the intestinal mucosa and an alteration of intestinal flora cause endotoxemia and microorganism removal. Endotoxins stimulate the mononuclear phagocyte system to produce a large amount of TNF-α[19]. The level of TNF-α rises with the development of CLD, leading to macrophage accumulation in the lumens of the pulmonary vessels. These macrophages stimulate the expressions of iNOS and heme oxygenase-1 (HO-1), resulting NO and carbon monoxide synthase[20]. Carbon monoxide, as well as NO, has a vasodilatory effect. Similar to ET-1, the level of TNF-α in the pulmonary artery is significantly higher than that in the radial artery in our study, which indicates the chemotaxis of the lung. These findings suggest that patients with HPS deteriorate because of the pulmonary vasodilation due to NO and carbon monoxide simultaneously. It was reported that administration of antibiotics could relieve HPS patients from the dilation of the pulmonary vasculature at a certain degree and improve pulmonary arteriovenous exchange[21], which indicates the function of TNF-α in the setting of HPS.

Other reports have found elevated TNF-α level in prehepatic portal hypertension rat models, but HPS did not occur in those rats, which indicates that the catabolism of TNF-α is probably performed mainly in liver[22]. However, HPS develops from exogenous ET-1, whether portal hypertension exists or not[22]. The analysis of PVR showed that the correlation coefficient of ET-1 ($r = -0.624$) is greater than that of NO_2^-/NO_3^- ($r = -0.535$). Nevertheless, there was no significant relationship between TNF-α and PVR. It suggests that ET-1 plays a significant role in the development of HPS.

Our results also revealed that the levels of VIP and 6-keto-$PGF_{1\alpha}$ were higher in CLD patients with or without HPS and HPS patients manifested as similar levels of VIP and 6-keto-$PGF_{1\alpha}$ as CLD patients, which may be associated with the decreased metabolism of vasoactive substances caused by liver dysfunction and portosystemic shunt.

Conclusions

This study confirms that CO increases and PVR decreases in HPS patients with the hyperdynamic circulation stage. The abnormally elevated NO level in the pulmonary circulation leads to pulmonary vasodilation. The levels of ET-1 and TNF-α increase in HPS patients and may induce NO synthesis in different ways. The increased ET-1 correlated negatively with the decreased PVR, which indicates the particularly important role of ET-1 in HPS. At last, we find that CO, CI, SI and TNF-α level are independent risk factors for HPS patients' survival.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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