Systemic and pulmonary hemodynamics in patients with non-cirrhotic portal fibrosis (NCPF) is similar to compensated cirrhosis

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Abstract

Background Non-cirrhotic portal fibrosis (NCPF) is an important cause of portal hypertension (PHT) and variceal bleeding, especially in the developing countries. While the hepatic parenchyma and liver functions are normal, the patho-anatomic defect in these patients is pre- and peri-sinusoidal in nature.

Aim To study the systemic and pulmonary hemodynamic alterations in patients with NCPF and compare them with compensated cirrhotic patients.

Patients and Methods Patients with NCPF ($n = 20$, mean age 29.3 ± 9.8 year) and matched Child's A cirrhotic patients ($n = 17$, age 34.1 ± 9.8 year) who had bled in the past, underwent hemodynamic measurements using a balloon tipped catheter.

Results In NCPF patients, the hepatic venous pressure gradient (HVPG) was significantly lower than in the cirrhotic patients (4.9 ± 1.5 mmHg vs. 15.7 ± 4.5 mmHg; $P < 0.01$). NCPF patients had hyperdynamic circulation and peripheral vasodilatation comparable to cirrhotic patients; cardiac output (8.0 ± 1.2 l/min vs. 8.4 ± 1.9 l/min; $P = 0.4$), cardiac index (5.4 ± 0.8 l/min/m² vs. 5.5 ± 1.9 l/min/m²; $P = 0.86$), mean arterial pressure (88.2 ± 14.1 mmHg vs. 89.9 ± 17.3 mmHg; $P = 0.73$), systemic vascular resistance (852.8 ± 204.3 dynes · s/

cm⁵ vs. 854.1 ± 189.9 dynes · s/cm⁵; $P = 0.98$) and pulmonary vascular resistance (41.6 ± 18.1 dynes · s/cm⁵ vs. 41.3 ± 17.9 dynes · s/cm⁵; $P = 0.95$) were comparable in the two groups.

Conclusions NCPF associated portal hypertension leads to a hyperdynamic state with high cardiac index and low systemic and pulmonary vascular resistance comparable to compensated cirrhosis. These novel observations suggest a primary role of portal hypertension in the development of hyperdynamic state.

Introduction

Non-cirrhotic portal fibrosis (NCPF) is a vascular disease of the liver causing fibrosis of the medium and small branches of the portal vein which results in the development of portal hypertension with near normal liver function tests and patent spleno-portal axis. NCPF has been reported from all parts of the world, more so from the developing countries. It is believed to account for nearly one-sixth to one-quarter of all cases of variceal bleeding [1]. The condition has been commonly seen in people who are socio-economically disadvantaged. Improved hygiene and standards of living could explain the relative rarity of the disease in the West and its declining incidence in the East especially Japan [1–4]. Patients with NCPF are generally young, present with repeated attacks of well tolerated variceal bleeding and normal growth. Hepatic functions are well preserved [1].

Amongst the commonly encountered conditions which very closely mimic NCPF include compensated cirrhosis. The tests of liver function, viral serology and

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liver histology (lobular disarray, pseudolobule formation) can distinguish the two conditions. Moreover, a disproportionately large spleen with a dilated and thickened portal vein favors the diagnosis of NCPF [1].

Patients with cirrhosis and portal hypertension exhibit a hyperdynamic circulation: increased cardiac output, heart rate and plasma volume and decreased arterial blood pressure and systemic vascular resistance. These changes may be brought about by a peripheral and splanchnic arterial vasodilatation, leading to reduced systemic vascular resistance and abnormal distribution of blood with a reduced central or effective blood volume [5–7]. It is believed that these changes are related to both hepatocellular dysfunction and portal hypertension per se. The severity of hemodynamic abnormalities does correlate with the Child-Pugh status. Hepatic parenchymal dysfunction is considered to play a major role in the progressive hemodynamic anomalies.

There is scanty literature on the systemic and pulmonary hemodynamics in patients with NCPF [8, 9]. We had earlier shown that the wedged hepatic venous pressure and the hepatic venous pressure gradient HVPG are nearly normal in NCPF patients. In fact, these are used as diagnostic features, since the predominant sites of obstruction in NCPF are pre-sinusoidal and peri-sinusoidal [8]. It is not known whether the NCPF patients have same systemic and pulmonary vascular anomalies as seen in patients with cirrhosis of the liver. This knowledge is important as it will not only increase the basic understanding of the consequences of portal hypertension in NCPF; it would also add to the understanding of contribution of portal hypertension in the pathogenesis of vascular disturbances in cirrhosis.

We undertook a prospective study to measure the systemic and pulmonary hemodynamics in patients with NCPF and compared them with patients of Child's A cirrhosis. Since nearly 85% of patients with NCPF present with variceal bleeding [1], so, for homogeneity, we included only those patients with NCPF and Child's A cirrhosis who had history of variceal bleed.

Patients and methods

Study population

The study included consecutive patients of NCPF who attended our department between June 2005 and May 2006. The diagnosis of NCPF was based on criteria previously described [8]. In brief, the diagnosis of NCPF was made in a patient presenting with: (i) moderate to massive splenomegaly, (ii) history of variceal bleed, (iii)

well preserved hepatic functions, (iv) a dilated, patent, thickened portal vein on ultrasonography, (v) absence of fibrosis or cirrhosis on needle liver biopsy, (vi) normal HVPG (vii) negative for serology for viral etiology, and (viii) no evidence of any known etiologies of chronic liver disease such as autoimmune liver disease, Wilson's disease. Only those NCPF patients were included who had history of variceal bleed. For comparison, consecutive patients with Child-Pugh A cirrhosis and history of variceal bleed, attending our department during the same period, were included. Patients taking beta-blockers were excluded from the study. The history of variceal bleed in both the groups was more than one month old and any patient who had bled in last one month was excluded from the study.

Informed consent was taken from all the patients to participate in the study after giving complete and detailed information of the hemodynamic and laboratory investigations. Approval from institutional review board was also taken.

Hemodynamic studies

Hepatic venous pressure gradient (HVPG)

HVPG study was done to confirm the diagnosis of NCPF. After an overnight fast, hemodynamic investigations were carried out using standard procedure. Briefly, under local anesthesia and in supine position, a venous introducer was placed in the right femoral vein by the Seldinger technique. Under fluoroscopic guidance, a 7F balloon-tipped Swan Ganz catheter (Boston Scientific, Massachusetts, USA) was introduced in to the main right hepatic vein. Free hepatic venous pressure (FHVP) and wedged (occluded) hepatic venous pressure (WHVP) were measured using Nihon Kohden (Tokyo, Japan) hemodynamic monitor with pressure transducers. Measurements were made in triplicate, and the mean of three readings was taken in each case. If there was a difference of more than 1 mmHg between the readings, all the readings were repeated [10]. HVPG was obtained as the difference between WHVP and FHVP.

Cardiac output, systemic and pulmonary vascular resistance

After hepatic venography and pressure studies, the Swan-Ganz catheter was advanced into the right atrium and pulmonary artery under fluoroscopic control for measurement of cardiopulmonary pressures and cardiac output (CO) by Fick's principle. Arterial pressure was measured simultaneously via right femo-

ral artery and the mean arterial pressure was calculated. Heart rate was derived from continuous electrocardiogram monitoring. Blood samples were taken from the inferior and superior vena cava, right atrium, pulmonary artery, and right femoral artery at the time of pressure measurement for blood gas analysis.

The systemic vascular resistance ($\text{dynes} \cdot \text{s}/\text{cm}^5$) was calculated as $[\text{mean arterial pressure (mm Hg)} - \text{right atrial pressure (mm Hg)}] \times 80 / \text{cardiac output (l/min)}$. Pulmonary vascular resistance ($\text{dynes} \cdot \text{s}/\text{cm}^5$) was calculated as $(\text{pulmonary artery pressure} - \text{pulmonary capillary wedge pressure}) \times 80 / \text{cardiac output (l/min)}$. Cardiac index was calculated by cardiac output/body surface area and expressed in $\text{l min}^{-1} \text{m}^{-2}$ (Figs. 1, 2, 3).

Statistical analyses

Statistical analysis was performed using the SPSS version 11.0 statistical package (SPSS Inc., Chicago, IL). All results were expressed as the mean $\pm$ SD or as frequencies (%). Comparisons within each group were performed using the Student's *t*-test. Significance was established at a *p* level less than 0.05.

Results

Twenty patients (mean age 29.3 ± 10 year, male:female 9:11) of NCPF and 17 patients (mean age

Fig. 2 Scatter plot showing systemic vascular resistance in patients with compensated cirrhosis and non-cirrhotic portal fibrosis (Triangles: systemic vascular resistance values in patients; error bars: mean value $\pm$ standard deviation)

34.1 ± 9.8 year, male:female 14:3) with Child-Pugh A cirrhosis were included in the study. Of 17 patients with cirrhosis, 9 were due to hepatitis B, 4 due to hepatitis C and 4 due to alcohol. Patients in both the groups were comparable in terms of mean age, body surface area, ALT, AST and serum bilirubin (Table 1).

All patients had history of variceal bleed and the median grade of esophageal varices in both the groups

Fig. 1 Scatter plot showing cardiac output in patients with compensated cirrhosis and non-cirrhotic portal fibrosis (Triangles: Cardiac output values in patients; error bars: mean value $\pm$ standard deviation)

Fig. 3 Scatter plot showing pulmonary vascular resistance in patients with compensated cirrhosis and non-cirrhotic portal fibrosis (Triangles: pulmonary vascular resistance values in patients; error bars: mean value $\pm$ standard deviation)

was comparable (grade 3, range grade 2–4). The HVPG in the NCPF group was 4.9 ± 1.5 mmHg compared to 15.7 ± 4.5 mmHg in the Child's A cirrhotics ($P < 0.001$).

The results of pulmonary and systemic hemodynamics are presented in Table 2. The mean arterial pressure, cardiac output, cardiac index, systemic vascular resistance and pulmonary vascular resistance were comparable between the NCPF and Child-Pugh A cirrhotic patients (Figs. 1, 2, 3).

Discussion

NCPF reflects a group of patients who have normal liver functions and hepatic parenchyma and have raised portal pressures quite comparable to that seen in cirrhotic portal hypertension. Thus, these patients allow a unique opportunity to study the development of portal hypertension in the absence of hepatic parenchymal disease. The results of this first study on systemic and pulmonary hemodynamics of NCPF patients clearly shows that, these patients have hemodynamic alterations comparable to cirrhotic portal hypertension. It is important to consider that the patients with NCPF have preserved hepatic functions and a very good prognosis. The systemic vascular resistance indices were lower in both cirrhotic and NCPF patients as compared to the reported values in normal adults [11].

Non-cirrhotic portal hypertension encompasses a group of diseases of varied etiology. The characteristic features of this group are increase in portal pressure due to prehepatic or intrahepatic causes, with absence of liver cirrhosis as well as of hepatic venous outflow obstruction. The wedged hepatic venous pressure is normal or only mildly elevated. The most commonly encountered diseases in this group are NCPF {alternatively called as Idiopathic Portal Hypertension (IPH)[4]} and extrahepatic portal vein obstruction (EHPVO). Together, these two entities constitute 20–30% of total cases of portal hypertension in developing countries like India. Boyer et al. [12] initially used the term “Idiopathic portal hypertension” for this condition. In 1969, a workshop organized by the Indian Council of Medical Research reviewed all available information on this condition and renamed this distinct entity as “non-cirrhotic portal fibrosis” [13]. Patients with NCPF generally present with repeated well tolerated episodes of variceal bleeding and have preserved hepatic functions. They have nearly normal life span and good prognosis, once the variceal bleeding has been successfully controlled and rebleeding prevented [14].

Patients with cirrhosis and portal hypertension exhibit a hyperdynamic circulation with increased cardiac output, heart rate and plasma volume and decreased arterial blood pressure and systemic vascular

Table 1 Demographic profile and liver functions of NCPF and cirrhosis patients

Parameters	NCPF(n = 20)	Cirrhosis(n = 17)	P value
Age (years)	29.3 $\pm$ 9.8	34.1 $\pm$ 9.8	NS
Body surface area (m ²)	1.4 $\pm$ 0.1	1.5 $\pm$ 0.2	NS
Bilirubin (mg/dl)	1.4 $\pm$ 0.2	1.4 $\pm$ 0.2	NS
Albumin (gm/dl)	3.6 $\pm$ 0.2	3.7 $\pm$ 0.2	NS
ALT (IU/l)	33.7 $\pm$ 7.6	37.7 $\pm$ 6.8	NS
AST (IU/l)	31.6 $\pm$ 7.5	35.2 $\pm$ 7.7	NS
Median grade of varices (range)	3 (2–4)	3 (2–4)	NS

Table 2 Hepatic venous pressure gradients, Systemic and pulmonary hemodynamics in NCPF patients (MAP: mean arterial pressure; SVR: systemic vascular resistance; SVRI: systemic

vascular resistance index; RAP: right atrial pressure; PAP: pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance)

Parameter	NCPF(n = 20)	Cirrhosis(n = 17)	P value
HVPG (mmHg)	4.9 $\pm$ 1.5	15.7 $\pm$ 4.5	0.001
MAP (mmHg)	88.2 $\pm$ 14.1	89.9 $\pm$ 17.3	0.73
Cardiac output (l/min)	8.0 $\pm$ 1.2	8.4 $\pm$ 1.9	0.40
Cardiac index (l/min/m ²)	5.4 $\pm$ 0.8	5.5 $\pm$ 1.9	0.86
SVR (dynes $\cdot$ s/cm ⁵)	852.8 $\pm$ 204.3	854.1 $\pm$ 189.9	0.98
RAP (mmHg)	4.3 $\pm$ 2.3	3.9 $\pm$ 2.2	0.63
PAP (mmHg)	13.6 $\pm$ 5.6	11.7 $\pm$ 3.6	0.24
PCWP (mmHg)	9.0 $\pm$ 4.5	8.0 $\pm$ 3.1	0.45
PVR (dynes $\cdot$ s/cm ⁵)	41.6 $\pm$ 18.1	41.3 $\pm$ 17.9	0.95

resistance. The changes are primarily brought about due to increased plasma volume, peripheral arteriovenous shunting, increased vasodilators such as nitric oxide, calcitonin gene related peptide, glucagons, prostacyclins, adenosine and enhanced sympathetic nervous activity and activation of renin angiotensin system leading to peripheral and splanchnic arterial vasodilatation. Patients with NCPF have preserved liver functions compared to cirrhotic patients and thus there may be considerably less abnormal humoral factors causing these systemic abnormalities. Lieberman et al. [15] had shown that portal hypertension leads to increased plasma volume and it decreased after portocaval anastomosis though not to normal levels, in both cirrhotics and non-cirrhotic portal hypertension patients. Maddrey et al. [16] also reported plasma volume expansion in portal hypertension in cirrhotics and non-cirrhotics. Splenic and portal vein blood flow are known to be markedly increased in IPH patients from Japan, suggestive of a hyperdynamic circulatory state [17].

The intrasplenic and portal vein pressures are markedly elevated in patients with NCPF [8, 12]. The WHVP may be normal or slightly elevated in a small proportion of these patients. Variceal pressure has also been studied in NCPF patients and found comparable to that in cirrhotic PHT [8, 17, 18]. In the present study, the cardiac index and systemic vascular resistance were found to be comparable to that observed in cirrhotic portal hypertension. Since patients with NCPF have nearly always preserved hepatic functions, these hemodynamic alterations in NCPF patients are probably directly related to the increased vascular resistance to blood flow. In fact, NCPF is a pure form of portal hypertension without any hepatic parenchymal dysfunction. Our results demonstrate that the increased cardiac output and reduced systemic vascular resistance are secondary to the increased resistance and consequent hyperdynamic vascular state. The site of resistance in patients with NCPF has been shown to be pre- and perisinusoidal [8].

There are no previous reports on the systemic and pulmonary vascular resistances in patients with NCPF. Harada et al. [9] studied hemodynamics in patients with non cirrhotic portal hypertension consisting of 8 patients with EHPVO (extra hepatic portal vein obstruction) and 11 patients with idiopathic portal hypertension and concluded that systemic hemodynamics in NCPH are significantly abnormal and comparable to cirrhotic portal hypertension. They suggested that the expanded plasma volume secondary to enlargement of portal bed might be closely related

to the mechanism of hyperdynamic circulation. However, there are some differences in the patients with IPH and NCPF [1, 4, 17]. Patients with IPH are known to be of middle age, often females with the presence of auto antibodies in nearly 50% of the patients. In a fair proportion of IPH patients, the HVPg has been shown to be moderately elevated. Hence, while the terms NCPF and IPH are often used interchangeably, there could be a group of heterogeneous disorders comprising each of them.

The pulmonary capillary wedged pressure and the pulmonary artery pressures were also comparable in the NCPF and the cirrhotic patients. These results reconfirm some of our previous observations in which we had evaluated during sclerotherapy the effect of absolute alcohol on pulmonary hemodynamics in NCPF and cirrhotics patients [19, 20]. We took 8 patients of NCPF and 6 patients of cirrhosis and found mean PAP 12.6 ± 2.6 mmHg (NCPF 12.8 ± 3.0 and cirrhotics 12.4 ± 2.1 p = ns) [20]. Pulmonary hemodynamics in patients with NCPF has also been reported by De et al in his study where 2 of 22 patients had features of primary pulmonary hypertension (PPH) [21]. However, we found pulmonary vascular resistance to be lower in NCPF patients and comparable to cirrhotics.

The current pre-sinusoidal animal models of portal hypertension primarily deploy portal vein ligation for the development of portal hypertension. However, this model differs substantially from the NCPF seen in the human beings. Recently, a rabbit model of NCPF has been developed by repeated injection of *E. coli* through an indwelling cannula into the gastrosplenic vein. These animals show marked portal hypertension with peripheral vasodilation and obtunded response to vasoactive agents [22]. This information further substantiates that in NCPF, a state of hyperdynamic circulation exists and all major circulatory beds, the splanchnic, cardiac, pulmonary and systemic are affected.

In summary, the results of present study show that NCPF associated portal hypertension leads to a hyperdynamic state with high cardiac index and low systemic and pulmonary vascular resistance. These changes are significant and comparable to patients with Child's A cirrhosis. This suggests a predominant role of increased portal resistance per se rather than hepatocellular injury in the genesis of these hemodynamic alterations. We concluded that NCPF associated portal hypertension leads to a hyperdynamic state with high cardiac index and low systemic and pulmonary vascular resistance comparable to compensated cirrhosis.

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