EDITORIAL

Pathogenesis of pulmonary arteriovenous malformations: role of hepatopulmonary interactions

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Pulmonary arteriovenous malformations—abnormal communications between pulmonary arteries and veins—can lead to serious haemodynamic consequences, predisposing to varying degrees of intrapulmonary shunting, resulting in cyanosis, clubbing, polycythemia, and impaired exercise tolerance.

The significance of organ interaction in the pathophysiology of tissue dysfunction is increasingly being recognised as a key determinant influencing resolution of tissue injury. The modulatory effects of such interactions, that incorporate the expanding number of markers of molecular and receptor level cell-to-cell communications, is complex. The liver is a unique organ as it is connected in series with the lung and portal system. It receives all the venous effluent from the portal system and directs its metabolites to the lungs before perfusing any other organ in the body.

Pulmonary arteriovenous malformations (PAVMs) are abnormal communications between pulmonary arteries and veins. They may be hereditary as in Osler-Weber-Rendu disease or acquired as in liver disorders, systemic diseases, venous anomalies, and after palliation of complex cyanotic congenital heart disease. They tend to be progressive and lead to serious haemodynamic consequences, predisposing to varying degrees of intrapulmonary shunting. This results in cyanosis, clubbing, polycythemia, and impaired exercise tolerance. Though hypoxemia and its clinical effects are the main consequences of this condition, serious complications like systemic embolisation, pulmonary haemorrhage, or cerebral abscesses are not uncommon. Evaluation of the underlying pathologic conditions, which predisposes to the development of PAVMs, supports a unifying hypothesis of liver–lung interaction.

HEPATOPULMONARY SYNDROME

The association of hepatic dysfunction with hypoxaemia in the absence of intrinsic cardiopulmonary disease is known as hepatopulmonary syndrome (HPS). These patients have intrapulmonary vascular dilations and some develop macroscopic PAVMs. Fluckinger first described it in 1884 and Kennedy and Knudson coined the term in 1977. Hepatic dysfunction includes fulminant hepatic failure, cirrhosis, portal hypertension, or rejection of allograft liver transplant. Several mechanisms have been postulated to explain intrapulmonary vascular dilatations in HPS. These include failure of the damaged liver to clear circulating pulmonary vasodilators, production of a circulating vasodilator or inhibition of a circulating vasoconstrictor by the damaged liver, blunted hypoxic pulmonary vasoconstriction, release of a substance from the diseased liver that promotes fistula formation, and inability of the diseased liver to metabolise various substances present in the portal venous blood.

However, conditions with completely normal liver function such as congenital hepatic fibrosis, portal vein thrombosis, non-cirrhotic portal hypertension, and congenital portovenous shunts also develop PAVMs. Some “unusual” cases of PAVMs reported in the literature in association with carcinoid syndrome also had associated portal vein obstruction. PAVMs are known to resolve after liver transplantation, further supporting the view that there is a mechanism of liver–lung interaction for the maintenance of normal pulmonary vasculature.

This concept is also supported by the occurrence of PAVMs in a subgroup of patients with palliated complex congenital heart defects.

PAVMS IN PALLIATED CONGENITAL HEART DEFECTS

Some patients with complex congenital heart defects and univentricular physiology, palliated by connecting the systemic veins directly to the pulmonary circulation, are known to develop PAVMs that are similar to those with hepatic dysfunction (cardiogenic hepatopulmonary syndrome, CHPS). The lungs of such patients are deprived of hepatic venous blood, as in superior cavopulmonary anastomosis or Kawashima operation. It is now well established that even in those patients who do not have macroscopic PAVMs, significant intrapulmonary shunting causing desaturation does occur. One of the logical explanations is the non-pulsatile nature of the systemic to pulmonary venous connections. However, patients who have undergone long term palliation with Fontan procedures, who share similar haemodynamics but have hepatic veins incorporated in the venous circuit, seldom develop PAVMs. Complete resolution of these malformations occurs after redirection of hepatic veins to the cavopulmonary connection.

Abbreviations: CHPS, cardiogenic hepatopulmonary syndrome; HF, hepatic factor(s); HPS, hepatopulmonary syndrome; PAVMs, pulmonary arteriovenous malformations; PVF, portal venous factor(s)
the direct role of hepatic venous effluent in the preservation of
the integrity of pulmonary vasculature.

If the pathogenic mechanisms of CHPS and HPS are
considered the same, then two possible aetiologic possibilities
emerge.

**Hepatic factor(s) (HF)**
The reversibility of HPS due to hepatocellular failure by liver
transplantation, and CHPS by connecting the hepatic veins
into the pulmonary circulation, points to the protective role of
metabolites normally present in the hepatic venous blood.
Such hepatic factor(s) (HF) have to be removed or signifi-
cantly reduced on first pass through the circulation to be un-
available in the systemic venous side. It is likely to be a physi-
ologically present constrictor influence. The occurrence of
pulmonary hypertension in a subgroup of patients with
advanced liver disease may represent excess production of HF.
The role of endothelins in this regard is worth further explo-
ration.

**Portal venous factor(s) (PVF)**
Other causes of hepatopulmonary syndrome, where hepatic
function is normal and diversion of portal venous flow from
the hepatic parenchyma is the dominant feature, suggest the
role of dilatory influences present in the portal venous blood
which on its own could lead to the development of PAVMs. The
portal vein is known to contain vasodilators such as substance
P which are metabolised almost completely by the liver and
are increased in other systemic conditions associated with
PAVMs.

**MECHANISM OF HEPATOPULMONARY
INTERACTIONS**
Severe hepatocellular dysfunction would decrease the produc-
tion of HF and its protective effects on the pulmonary vascula-
ture. This could lead to the development of HPS in fulminant
hepatitic failure. Obstruction to the portal veins, or portal
hypertension associated with porto-systemic shunts, would
prevent normal hepatic metabolism of the PVF and diversion
into the systemic veins, resulting in increased concentrations
of PVF perfusing the pulmonary vascular bed. Coexistence of
both hepatocellular injury (decreased production of HF) and
portal hypertension (decreased metabolism of PVF), as in the
rat bile duct ligation model of HPS or biliary cirrhosis, would
increase the propensity for the development of PAVMs. It is
possible that a mechanism of hepatic regulation of pulmonary
vascular tone is part of our normal physiology, such that the
HF is produced by the hepatic parenchyma under the stimula-
tion of the PVF. The common bile duct ligated rat model of
HPS by Luo and group provides further insight into the multi-
factorial influences in the pathophysiology of liver–lung
interaction.

**PATHOPHYSIOLOGICAL ASPECTS**
Pathologically, PAVMs are dilated capillary and precapillary
vessels associated with evidence of direct arteriovenous
communications. This finding in association with thinning of
the vessel wall suggests a process of persistent unopposed
vasodilatation rather than angiogenesis as the pathogenic
event. Presence of increased concentrations of nitric oxide and
constitutive endothelial nitric oxide synthase in the pulmo-
nary arteries of these patients further supports excessive
vasodilatory influence as the pathogenic mechanism. In
plexogenic arteriopathy of cirrhosis, vascular deformation
caused by medial hypertrophy and fibrosis is combined with
dilated thin walled distal channels, perhaps reflecting the end
stage of a long battle between constrictor and dilator
influences on the pulmonary vasculature. The vascular patho-
logy of pulmonary hypertension seen in 1–2% of patients with
cirrhosis is indistinguishable from other causes of pulmo-
nary hypertension. In this issue of the journal Ashrafian and
Swan are postulating some interesting views regarding the
pathogenesis of CHPS.

Careful delineation of the hepatic veins is important in the
assessment of all patients with PAVMs. On rare occasions, iso-
lated hepatic venous drainage into the left atrium or bilateral
drainage of hepatic veins into right and left atria have been
known to result in this condition. Assessing the proximity of
the hepatic veins to the azygos or hemiazygos continuation of
the inferior vena cava, with a view to incorporate it into the
venous circulation at the time of cavopulmonary anastomosis,
would prevent the onset of CHPS. In rare cases, diversion of
hepatic venous flow from the Fontan circulation into the left
atrium through collaterals or associated portal hypertension
and congenital or acquired porto-systemic shunts may need to
be excluded.

Currently the management of well established PAVMs is
limited. Though liver transplantation offers better outcome for
HPS patients, the slow regression of these anatomic defects
still pose a significant threat in the immediate postoperative
period. While redirection of hepatic venous flow in CHPS has
shown resolution of PAVMs, associated problems caused by
congestive hepatic dysfunction and persistence of malforma-
tions in the contralateral lung when preferential blood flow
from the hepatic veins is directed to one lung has been
observed. Experience with inhibition of nitric oxide
production using methylene blue is limited and risk of
increasing pulmonary vascular resistance in the setting of
Fontan circulation is prohibitive in its routine clinical use.

Further understanding of the pathophysiology of this com-
plex condition and identification of various factors involved
are crucial for the prevention and long term management of
these patients. The role of endothelins and the effect of its
receptor blockers may prove beneficial in future.
REFERENCES


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