Liver- Induced Pulmonary Vascular Disorders

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Introduction

Patients with chronic liver disease have an increased prevalence of pulmonary vascular disorders. Two forms of pulmonary vascular disorders can complicate chronic liver disease: the hepatopulmonary syndrome and portopulmonary hypertension. Both tend to occur in patients with chronic and late-stage liver disease ***(Badesch and Rubin 2005).***

Recognition of the importance of pulmonary vascular complications of hepatic disease states has increased due to the increasing practice of orthotopic liver transplantation. These liver-induced pulmonary vascular disorders namely, hepatopulmonary syndrome and portopulmonary hypertension influence survival and candidacy for orthotopic liver transplantation ***(Rodriguez-Roisin et al., 2004).***

In 1884 Fluckiger studied the interaction between lung and liver, when he first saw a woman with cirrhosis, and digital clubbing. "Hypoxemia of cirrhosis" was clarified by Sneel, who recognized a decreased arterial saturation in three patients with cirrhosis in 1935 and described what is currently called "hepatopulmonary

syndrome". In 1977 Kennedy firstly suggested this term ***(Lange and Stoller, 1995.)***

Hepatopulmonary syndrome, is a life-threatening condition defined as the triad of liver disease, pulmonary gas exchange abnormalities leading to arterial deoxygenation, and widespread pulmonary vascular dilatation. The prevalence of hepatopulmonary syndrome in cirrhotic patients varies from 4% to 19%, and this variation is due to varying cut offs for the abnormal alveolar-arterial gradient and partial pressure of oxygen that are used to define gas-exchange abnormalities, while the prevalence in series of patients awaiting orthotopic liver transplantation ranges from 5 to 32%. Clinical manifestations include dyspnea, which is the predominant presenting symptom, while digital clubbing, cyanosis, spider navi, and severe hypoxemia strongly suggest hepatopulmonary syndrome. Diagnosis of hepatopulmonary syndrome is practically confirmed by contrast-enhanced transthoracic echocardiography ***(Rodriguez-Roisin, and Krowka 2008).***

Many therapeutic agents have been tried in hepatopulmonary syndrome, but non has been clearly effective and orthotopic liver transplantation is the only effective treatment for improving outcome in patients with

hepatopulmonary syndrome ***(Rodriguez-Roisin et al., 2004).***

Both acute and chronic liver diseases have been associated with hepatopulmonary syndrome, but most commonly it presents in patients with cirrhosis. Portal hypertension seems to be the predominant factor related to this syndrome ***(Benjaminov et al.,2003).***

Portopulmonary hypertension, another dramatic pulmonary vascular condition, defined as an increased mean pulmonary artery pressure of > 25 mmHg, increased pulmonary vascular risistance of > 240 dyne/ s/ cm^{-5}, and pulmonary capillary wedged pressure of < 15 mmHg in the presence of portal hypertension, and has a prevalence of 0.25-4% of patient with cirrhosis, but in hepatic patients submitted to orthotopic liver transplantation the prevalence is 5%. In moderate to sever portopulmonary hypertension, orthotopic liver transplantation is not widely recommended, even being regarded as a contraindication due to its relative perioperative and postoperative impact ***(Rodriguez-Roisin et al.,2004).***

Management of portopulmonary hypertension varies according to severity. Generaly mild cases with good cardiac function are candidate for orthotopic liver

transplantation, while severe cases are treated with medical treatment as pulmonary vasodilator therapy, and moderate cases are treated firstly by pulmonary vasodilators prior to orthotopic liver transplantation ***(Ramsay et al., 1999)***.

Aim of the Work

The aim of this work is to review current knowledge regarding liver-induced pulmonary vascular disorders including pathophysiology, clinical features, methods for diagnosis, and management.

Physiological Considerations

Homeostasis in the pulmonary vasculature

In addition to gas exchange, pulmonary vasculature filters the entire circulating blood before the latter enters the systemic circulation, affecting both local and systemic vascular tones, inflammatory processes, and whole-body homeostasis. Pulmonary circulation possesses two major distinct features: in health it responds to hypoxia with Hypoxic pulmonary vasoconstriction (HPV) to maintain adequate ventilation/perfusion match; in critical illness pulmonary hypertension may develop, as opposed to the often occurring systemic hypotension. As these responses strongly depend on pulmonary endothelial functional and structural integrity, further understanding of the pulmonary endothelial properties will provide insights into lung disease pathophysiology and how the latter affects systemic cardiovascular homeostasis ***(Orfanos et al., 2000)***

Homeostasis in the pulmonary vasculature is maintained by the actions of vasoactive compounds, including nitric oxide (NO). NO is critical for normal development of the pulmonary vasculature and continues

to mediate normal vasoregulation in adulthood ***(Matthew et al.,2007).***

The low resting tone of the pulmonary circulation is established at birth. This tone is modulated by the balance of vasoconstrictors (endothelin-1, thromboxane A2, and serotonin) and vasodilators (prostacyclin and NO) produced by the pulmonary endothelium ***(Farber et al.,2004).***

1) Nitric Oxide effect on the Pulmonary Vasculature

NO is a secondary messenger molecule which participates in numerous biological processes, including vasodilatation, neurotransmission, and bronchodilatation. NO is synthesized by a group of enzymes referred to as NO synthases (NOSs), which are responsible of the conversion of L-arginine to L-citrulline and NO in presence of oxygen. NO is a free radical gas that diffuses from its site of production in the endothelial cell to its target, soluble guanylate cyclase, in the vascular smooth muscle cell. In this classical NO signaling pathway, activation of soluble guanylate cyclase enhances cyclic guanosine monophosphate production, which in turn mediates vasodilatation. ***(Kim-Shampiro et al., 2006).***

Alternative NO signaling pathways involve the oxidation of NO to nitrite, reactions of NO with protein thiols to form S-nitrosothiols, and NO derivatives that can function as vasodilators or as posttranslational modifiers of protein function ***(Hess et al.,2005).***

New theories are founded on the interaction of nitrite and S-nitrosothiols with hemoglobin (Hb) by exploiting the allosteric nature of Hb within red blood cells (RBCs), the NO signal is transported to the periphery, where its vasodilator potential enables selective delivery of oxygenated blood to hypoxic tissue ***(Matthew et al., 2007).***

Regulation of NO Production by NO synthase isoenzymes

The supply of NO is tightly regulated at the level of its synthesis through the oxidation of L-arginine by NOSs, a family of 3 isoenzymes with overlapping patterns of expression. The NOSs isoforms are distinguished not only by their sites of expression, but also by the regulation of their activities. Endothelial NOS (eNOS) is expressed in vascular endothelial cells throughout the body, while neuronal NOS (nNOS) is expressed in brain cells, and inducible NO (iNOS) is the isoenzyme present in a variety of body cells ***(Dudzinski et al., 2006).***

The eNOS is the predominant source of NO production in the pulmonary circulation.Characteristics of these izoenzymes are mentioned in table 1 ***(Shaul et al.,1995).***

Table (1): Characteristics of various forms of Nitric Oxide Synthase.

Enzyme	Gene	Cellular localization and expression	Regulation
nNOS	nNOS1	Brain	Ca^{2+}/CaM
iNOS	nNOS2	Variety of cells	Cytokine-inducible Ca^{2+}-independent
eNOS	nNOS3	Vascular endothelial cells and cardiomyocytes	Ca^{2+}/CaM

NOS1: neuronal NOS, NOS2: inducible NOS, and NOS3: endothelial NOS.

(Shaul et al.,1995).

neuronal NOS and inducible NOS are both expressed in airway epithelium and at low levels in the adult in vascular smooth muscle cell. The expression of inducible NOS is induced in virtually all pulmonary cells by exposure to endotoxin or inflammatory cytokines ***(Matthew et al., 2007).***

The action of nitric oxide

Reaction of NO with the soluble guanylate cyclase heme (in the ferrous state) induces a conformational change at the catalytic site leading to a several hundred–fold increase in production of cyclic guanosine monophosphate from guanosine triphosphate (GTP) ***(Ballou et al., 2002).***

In vascular smooth muscle cell, the effects of cyclic guanosine monophosphate are mediated through activation of its effector proteins— cyclic guanosine monophosphate- dependent protein kinase (PKG), cyclic guanosine monophosphate gated ion channels, and cyclic guanosine monophosphate regulated phosphor-diesterases ***(Munzel et al., 2003).***

Cyclic guanosine monophosphate relaxes vascular smooth muscle via several mechanisms including hyperpolarization of the cell membrane and inhibition of agonistinduced calcium influx. In addition, cyclic guanosine monophosphate decreases myofilament calcium sensitivity by activating myosin light chain phosphatase via PKG-mediated phosphorylation ***(Sauzeau et al.,2000).***

Because of its very short half-life in biological fluids, NO was not thought to be capable of affecting vascular tone remote from its site of production. One of the primary

scavengers of free NO is Hb: reaction with the heme iron to form nitrate or iron-nitrosyl adducts reduces circulating NO levels below those required to induce vascular smooth muscle cell relaxation. S-nitrosothiols, introduced above, were first described as stable NO derivatives that retain vasodilator properties. Rather than being degraded by Hb, S-nitrosothiols can undergo a transnitrosylation reaction using the heme iron to form systemic NO on a conserved cysteine residue of the beta subunit of Hb ***(Singel et al., 2005).***

In view of its pulmonary and systemic effects, NO has been proposed as a “third gas” that is transported by the respiratory system ***(Mahon et al.,2002).***

NO exploits the allosteric properties of hemoglobin to enhance O2 and CO2 exchange, directing micro-vascular distribution of flow into hypoxic tissue and away from oxygenated tissue. To a degree, particularly in the SNO-Hb model, the lung functions as the source of vasodilatory NO for the peripheral circulation ***(Matthew et al., 2007).***

2) Hypoxic pulmonary vasoconstriction

One of the main means by which the normal lung adjusts to low regional ventilation is to induce vasoconstriction of the associated pulmonary vasculature

to redirect perfusion away from nonventilated or under ventilated alveolar units. Thus Hypoxic pulmonary vasoconstriction (HPV) minimizes ventilation-perfusion inequality, limiting the decrease in PaO2 that would have occurred if such redistribution of blood flow had not occurred. Vasoconstriction of the pulmonary vasculature in response to acute hypoxia is the clearest divergence from the systemic vasculature, which is characterized by hypoxic vasodilation in the periphery. Disruption of the balance of pulmonary vasodilators and vasoconstrictors, for example by environmental stress (eg, prolonged hypoxia) or endothelial dysfunction, can lead to the pulmonary vasoconstriction, vascular smooth muscle cell proliferation, and in situ thrombosis that characterize pulmonary hypertension (PH) ***(Matthew et al., 2007)***

Some researches suggest an important role for pulmonary arteriolar smooth muscle cell oxygen-sensitive voltage-dependent potassium channels. Inhibition of these channels by decreased oxygen pressure inhibits outward potassium current, causing membrane depolarization, and calcium entry through voltage-dependent calcium channels. Endothelium-derived vasoconstricting and vasodilating mediators modulate this intrinsic smooth muscle cell reactivity to hypoxia. However, refined modeling of hypoxic pulmonary vasoconstriction operating as a feedback mechanism in

inhomogeneous lungs, using more realistic stimulus–response curves and confronted with direct measurements of regional blood flow distribution, shows a more effective than previously assessed ability of this remarkable intrapulmonary reflex to improve gas exchange and arterial oxygenation ***(Naeije and Brimioulle 2001)***.

The cellular mechanism of Hypoxic pulmonary vasoconstriction

Hypoxic pulmonary vasoconstriction continues to attract interest more than half a century because of persistent mystery about its biochemical mechanism and its exact physiological function ***(Naeije and Brimioulle, 2001).***

It has been shown that pulmonary vascular smooth muscle cells and type I cells of the carotid body share the ability to sense changes in oxygen pressure. Hypoxia has been demonstrated in both cells to inhibit outward potassium current, causing membrane depolarization and calcium entry through the voltage-dependent calcium channels. There is evidence in both cells to suggest that changes in the redox status of the oxygen-sensitive potassium channels may control the current flow, so that

the channel is open when oxidized and closed when reduced ***(Weir et al., 1995).***

In systemic arteries, hypoxia causes an inward current through ATP-dependent potassium channels and vasodilatation. Profound hypoxia also dilates pulmonary arteries by the same mechanism. Hypoxic pulmonary vasoconstriction occurs within seconds of the onset of alveolar hypoxia. Hypoxic pulmonary vasoconstriction is inhibited by a variety of mediators present in the blood or released from lung parenchyma, such as substance P, calcitonine gene-related peptide, atrial natriuretic peptides, and by endothelium-derived vasodilators such as prostacyclin and nitric oxide NO ***(Naeije and Brimioulle 2001).***