Review

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Physiopathological, clinical and therapeutic aspects of hepatopulmonary syndrome

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Abstract

Patients with cirrhosis or portal hypertension may develop hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPHT). HPS occurs in 25% of the subjects with cronic hepatopathy waiting for a liver transplantation. HPS is characterized by cronic hepatopathy and/or portal hypertension, increased $P(A\text{-}a)O_2$ gradient (>20 mmHg) with hypoxemia and intrapulmonary vascular dilatations without a primary cardiovascular disease. Hypoxiemia is due to intrapulmonary arteriovenous shunts and to dilatation of microvessels in basal parts of the lung and of pleural vessels. In patients with cirrhosis an impaired cardiovascular function is frequent, often in a subclinical phase of the disease. Left ventricular systolic and diastolic dysfunction may develop a cronic hepatopathy and the relation between right ventricular and liver failure has been studied. During cirrhosis characteristic alterations of systemic hemodynamic can cause the hyperdynamic circulatory syndrome. Contrast enhanced 2D ECHO cardiography is the preferred screening test for intrapulmonary arteriovenous shunts. The aim of HPS therapy is to contrast intrapulmonary vasodilatation, increased portal flux and hyperdynamic syndrome. New therapeutical agents are fosfodiesterase inhibitors, ET-1 receptor antagonists and selective NOS inhibitors. However, medical treatment is not much effective in HPS and liver transplantation is considered the only therapeutical chance.
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Key words: *hypoxiemia, orthodeoxia, pulmonary arteriovenous shunts, platypnea*

Introduction

In the presence of chronic hepatopathy and/or portal hypertension, two different vascular pulmonary complications can be seen: Primary Pulmonary Hypertension (PPHT) and Hepato-Pulmonary Syndrome (HPS). The two conditions represent two different physiopathological entities as the former is characterized by a significant reduction of the pulmonary vascular resistances associated to the presence of intrapulmonary vascular dilatation and also to the formation of arterial-venous shunt that alters the gas exchange; the second, given by the association between the pulmonary hypertension (values of PAP >25 mmHg at rest or of 30 mmHg during exercise) and portal hypertension, is characterized by a hemodynamic damage with the increase of vasoconstrictor substances and the increase of pulmonary vascular resistance (1, 2). The progressive pulmonary vascular alteration results therefore strictly correlated to the proliferation and hypertrophy of the pulmonary endothelial cells and of the smooth muscular cells of the vessels associated to concentric fibrosis of the intimate parts (3). Therefore the imbalance between vasodilator agents (reduced pulmonary expression of e-NOS and of prostacyclin12) and vasoconstrictors agents (increased expression of ET-1 and angiotensin1) is responsible for the pulmonary hypertension (4). It should be remembered that the prevalence of the pulmonary hypertension in cirrhotics varies from 0.73 to 12.5% with a proportional increment to the degree of hepatic dysfunction (5, 6).

Hepato-Pulmonary Syndrome

The term Hepato-Pulmonary Syndrome (HPS) was coined by Kennedy and Knudson in order to describe the cyanosis that appeared years after the operation of the port-caval shunt in a cirrhotic patient (7). HPS is found in almost 25% of the subjects with the chronic hepatopathy (4) waiting for transplant. However, the cause of the hepatic disease t-hat leads to portal hypertension doesn't seem to concern the development of this syndrome; that is shown by the presence of such condition even in subjects with the pre-hepatic portal hypertension in absence of the chronic hepatopathy (3). Rarely, in fact, it has been noticed even in primitive biliary cirrhosis without portal hypertension or in acute hepatic pathologies like fulminating hepatitis and the Budd-Chiari Syndrome (8).

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Hepatopulmonary syndrome is a clinical entity, characterized by an advanced liver disease and/or portal hypertension (more commonly cirrhosis), increased alveolar-arterial gradient (AaPO2) (>20 mmHg), changed diffusion of the pulmonary gas leading to arterial hypoxemia (PaO2 <70 mmHg) and pulmonary vascular dilation in absence of primary cardio-pulmonary disease (9-12). However, as per some authors, such definition is unsatisfactory since the syndrome can be verified even in association with the portal hypertension without cirrhosis and because, in presence of pulmonary vasodilators, the AaPO2 results higher than 20 mmHg (12); this, therefore, can surpass 20 mmHg even in subjects with normal pulmonary functionality (13). Research has proved that the predictive values of HPS are 30% to be AaPO2 than 20 mmHg, but almost 100% for the values of PaO2 less that 65 mmHg (14). The phenomenon of the hypoxemia is related to the presence of intrapulmonary arterial-venous shunt, to the micro-vascular precapillary and capillary dilatations that take place especially in the lower areas of lungs and to the pleural vascular dilatations. The change in the ventilation perfusion relationship (V/P) is present from the moment when the vasodilators of the cirrhotic and, especially, the loss of reflex in hypoxic vasoconstriction in the process of alveolar hypoxia, determine an increase of the perfusion in the unventilated areas. The light hypoxemia is present in almost one third of the chronic hepatopathic subjects. The anastomosis and arterial-venous communications between the portal and arterial blood circulation, as it is between bronchial and pulmonary vessels are functional in cirrhotics and are responsible for hypoxemia (15). An asymmetrical relation also exists between the availability of oxygen (DO2) that is more than the normal, and the consumption of O2 (VO2). At high heart capacity, it is entrusted the maintenance of VO2 near to the norm, being reduced its fringe extraction. Different studies have evaluated the alterations of the main parameters in the arterial blood of ascitic cirrhotics and, especially, it is observed that the portopulmonary shunt, the intrapulmonary shunt and the discrepancy of ventilation/perfusion (V/P) can induce a reduction of PaO2 and SaO2 with the consequent alteration of the EAB (16). Recently (15) a group of 49 ascitic cirrhotics without any cardio-pulmonary disease and a group of 50 volunteers were examined. In the cirrhotic patients hypoxemia (PaO2 75.2 mmHg Vs 94.2 mmHg), a reduced saturation of O2 (SaO2 94.5 Vs 97.1%) and hypocapnea (PaCO2 33.9±1.5 mmHg) have been observed. The alterations of the EAB observed were: respiratory alkalosis in the 44.89%, metabolic alkalosis in the 14.28%, metabolic acidosis in the 6.12%, respiratory acidosis in the 6.12% and metabolic acidosis associated to respiratory alkalosis in 8.16%. The hypocapnea associated to the pulmonary vasodilators has been found in almost 73% of the cirrhotic patients; therefore, the hypocapnea associated to the vasodilatation action of the nitric oxide can contribute to the hypoxemia and pulmonary vasodilatation results more in subjects with advanced hepatopathy (15).

Pathogenesis

The physiopathological mechanism of the formation of shunt are not all noticed, but animal models suggest that the levels of endothelin-I, NO pulmonary and other vasodilator substances, altered in the course of cirrhosis, result related to the entity of the shunt. These play a key role in the pathogenesis of the hepatopulmonary syndrome; in fact the hepatic damage and/or portal hypertension trigger the release of Endothelin-1, TNF-α, Cytokines, NO and carbon monoxide, all suitable to determine the capillary pulmonary dilatation with a consequent increase of the arterial-alveolar ratio of O2 (4). Declaux and others (17) have shown that the high levels of exhaled NO observed in the cirrhosis are of alveolar origin and result, therefore correlated to the arterial-alveolar ratio of O2. Different studies considered in cirrhosis, the relation that exists between the production of NO and the anomalies of oxygenation. The operation of NO in the development of the intrapulmonary vasodilators has been verified both in animal models as well as in the human HPS (18). Others authors measured V'A,NO and compared V'A,NO with pulmonary haemodynamics and gas exchange parameters. In cirrhotic patients, NO was produced in excess by the alveolar compartment of the lungs. Alveolar NO production was associated with hyperdynamic circulatory syndrome but not with arterial oxygenation impairment (19).

In the hepatopulmonary syndrome, an increased synthesis of pulmonary NO is found and its hepatic reduction (20). Such mediator, as it is noted, is produced through two different enzimatic ways by two biosynthetic mediators: the inducible NO synthase and the constitutive one. The researches on humans and animals have demonstrated an increase of synthesis of NO through its determination and that of its metabolites in the systemic splanchnic circulation (21), in the leukocytes (22) or in the exhaled air (23). It has also been evaluated the activity of the NO-synthase in polymorphonucleats and monocytes isolated by cirrhotics and healthy volunteers. Comparing the results obtained with the plasmatic levels of endotoxins and with some hemodynamic parameters, a high activity of the NO-synthase of the cirrhotic leucocytes co-related to the levels of endotoxins and to the increase of the cardiac index is shown (22). One experimental research conducted on rats with HPS (20) has hypothesized that the correct regulation of NOS with the regulating protein, caveolin and HPS90, can explain the inverse production of NO at the hepatic and pulmonary level (20). Among other authors, in a case-control study, the distribution of genetic polymorphism MCP-1, e-NOS, t-PA and PAI-1 has been evaluated and a higher frequency of HPS in patients that used to present the gene MCP-1 2518G; has demonstrated it was found less frequent in patients with high frequency of e-NOS (24).

Signs and Symptoms

Clinically, the symptoms of the HPS are dyspnea, platypnea (or rather the facilitated ventilation in supine prone position and not in the sitting position) and orthodeoxia (reduction of the PaO2 when assumed the orthopnoeic position) (25-27). The spider nevi are present in one percentage more of subjects (3). However, a specific symptom doesn't exist considering that the anemia, ascites and right pleural effusion are the common causes of the dyspnea in the cirrhotics (18). The cyanosis and digital clubbing can be

present in more serious cases, instead in some patients the cyanosis is shown only in orthostatism (standing position). The presence of pulmonary vascular dilatation directly allows the passage of emboli or microorganisms towards the systematic circulation and that can favor, in these patients, the development of complications like stroke or the cerebral infections (29, 30).

Diagnosis

The negative link that exists between the chronic hepatopathy and cardiac function is well documented (31). Different research has shown that the cardiac arrest, the cirrhotic cardiomyopathy, left ventricular dysfunction both systolic and diastolic can develop in the course of chronic hepatopathies (32, 33). It is necessary to demonstrate that even pulmonary pathologies can coexist with HPS, especially the BPCO, bronchial asthma and Idiopathic Pulmonary Fibrosis (18). The impairment of the cardio-circulatory apparatus in the course of cirrhosis is, a frequent occurance that is often present in the form of sub-symptom in the initial phase (preascitic) of the disease and, at times, underestimated. The presence of hystological alterations due to the myocardial load of the cirrhotics is well noted, such as the association between the hepatic cirrhosis and "hyperdynamic circulation" that has already been described at the start of the 50s (34, 35). The histological examination of the cirrhotic heart shows a number of elements (characteristics) that can, in part, explain the impairment of the contractile function; there are frequent finds such as hypertrophy of the myocardio, the fibrosis, resin-bleeding, nuclear vacuolization and abnormal pigmentation. In an autopsy examination (36) of 180 cirrhotics the results were that 48% of the men and 24% women had a higher than normal heart weight (>400 g) and, further, it has been verified a dilatation of ventricles and a minor compaction of myocardio respect to the subjects with notable cardiopathy. Different research has contributed to show that the structural and functional modifications that may arise in the heart of a cirrhotic patient involves a diastolic dysfunction and a reduced myocardio reactivity in response to the physical exercise, ostensibly to be referred and anomalies of the beta-adrenergic function (37). It has been shown (38) that advanced state cirrhosis is associated with left ventricular diastolic dysfunction and with an increase of the pressure of the posterior myocardial wall and of the interventricular septum. Such alterations are confirmed by the echocardiographic tests that have proved the anomalies of the pattern of transmitralic filling (marked increase of the velocity of wave A, reduced relation E-A, significant increase in the time of deceleration of the wave E), significant increase of the diameters of the arterial and ventricular cavities and of the wall pressures (38). Other studies have shown that the left ventricular dysfunction, systolic and/or diastolic, can induce a chronic hepatopathy, although some recognized research aimed to test the right ventricular function in course of the hepatic pathology. For such an aim, in the presence of HPS, some authors (39) have even shown a diastolic dysfunction of the right ventricle. The diastolic dysfunction of the right ventricle can evolve towards the dilatation and hypertrophy of the right sections (39). Further, other investigations suggest that more than 50% of cirrhotics can be suffering from a preclinic or latent cardiomyopathy which is manifested, at least initially, only during physical stress and is externalized, both as dysfunction systo-diastolic and with the alterations of the electromechanic pairing of the contraction (40). However, the typical element in the course of cirrhosis is represented by the progressive development of the alterations of the sistemic hemodynamic that come under "hyperdynamic circulation syndrome". In fact, if in the initial phases of the cirrhosis such condition cannot be noted, with the progression of the disease it is evidenced an association between the seriousness of the cirrhosis and the entity of the hyperdynamic circulation.

Such syndrome can be found in a high percentage (up to 70%) of the cirrhotics in advanced stage and is expressed, on the clinical (symptomatic) level, with the arterial hypotension, increase of the differential pressure, peripheral vasodilatation, tachycardia, increase in the cardiac output and rest, and the appearance of the hot extremities and subcyanosis (41). The increase of the heart capacity is due to both the increase of the systolic volume as well as the increase of the cardiac frequency. The reduced peripheral resistances probably constitute the determining fundamental of the hemodynamic pattern of the cirrhotic and acknowledge as the principle causes an imposing peripheral vasodilatation and a reduced response to the catecholamine in presence of an increased orthosympathetic stimulation. It seems that the hyperdynamic circulation has early origin in the splanchnic venous bed as result of the portal hypertension developed in following to the rearrangement of the hepatic architecture and to the formation and opening of the arterial-venous or venous-venous shunt. In 1988 Schrier (42) proposed "the peripheral vasodilatation arterial hypothesis", according to which the primary splanchnic arterial vasodilatation leads to the reduction of the systematic vascular resistances, of the intravascular volume and of the arterial pressure. A reduced blood volume, above all in those sectors where are located the baroceptors, determines activation of the vasocontrictors and hydro-saline retention (42 - 44). However, the greater part of the hemodynamic variations present in the cirrhotics can be explained in accordance with this theory. That explains, especially, the verification of the arterial hypotension and the increase of the cardiac output in association to the high levels of vasocontrictors substances that are found in the ascitic cirrhotics (45). On the other hand, another confirmation comes from the proof that many cirrhotics in early stage and in absence of the signs and symptoms of hemodynamic alterations, develop the hyperdynamic circulation syndrome only when they assume the supine position (34), or when the venous return is developed by the transfer of a determinate quota of the blood volume by the splanchnic area, where it is found "*abducted*" because of the portal hypertension. The vasodilatation principally involves the splanchnic circulation (34) and in minor quantity those pulmonary (46), while the renal circulation is characterized by vasocontriction. In cirrhosis the circulation condition involves a significant increase of the heart work. That, in other circumstances, shall be responsible for the cardiac arrest, but the contemporary reduction of the systemic

vascular resistance and the increase of the arterial compliance make it difficult for the left ventricular dysfunction to appear (47, 48). The cardiac arrest can be discovered under force or under treatment with vasocontrictors. All that is defined as cirrhotic cardiomyopathy, characterized by the altered cardiac contractility with systolic and diastolic dysfunction and electromechanical anomalies with the extension of the QT period. In addition to the actesed function of the channels of the Ca++ (49), a reduction of the current of K+ in the cardiomyocytes of the cirrhotic rats that had extended QT period has been shown (45). This latter is usually present in chronic hepatopathy and can potentially lead to severe arrhythmia ventricles until cardiac arrest (47, 50, 51). It can be, therefore, maintained as an index of probable cirrhotic cardiomyopathy and used for identifying the patients at risk (45). When the after load is reduced, the cardiac pressures are almost normal and therefore, hide a left ventricular dysfunction. After stress, instead, an increase of the diastolic pressure of the left ventricle is determined, but if the fraction of the ejection results less than normal, a ventricular reserve is configured inadequate to the increase of pressure (45). In some research (52, 53) the base ejection fraction is found normal, or even increased, in consideration of the missing adjustment of the cardiac output to the increase of the requests (54); however, after exercise can reduce or increase less in the cirrhotics respect to the controls (55, 56). The expansion of the blood volume in cirrhotics contributes to a persistent increase in the volemic that can overload the heart, with consequent reduction of the cardiac contractility (57, 58). Therefore, in subjects with advanced cirrhosis and severe vasodilatation, the activation of the renin-angiotensin system, the altered renal function and the reduced systolic function seem to be the determining factors for the development of the HPS (59).

As a result, the appearance of the hyperdynamic circulation syndrome in course of cirrhosis assumes an unfavorable prognostic meaning, determining an increase of the morbidity and the mortality of the patients that develop it. Such negative prognostic meaning is related to the fact that the hyperdynamic circulation represents the pathogenic substrate of the more formidable complications of hepatic insufficiency, which are the hepatorenal syndrome (60), hepatopulmonary syndrome (61), and the hepatic encephalopathy (62).

Diagnostic

Contrast echocardiography is the diagnostic investigation widely used for showing the presence of the intrapulmonay shunts (18). The result of this examination, following peripheral injection of the stirred saline solution, is expressed as positive or negative, on the basis of the presence or absence of microbubbles in the left side of the heart. Research relative to this investigation (63) has shown the presence of the intrapulmonary shunt dx-sn when the microbubbles appeared late in the left atrium (three or more stirs after the initial appearance of the contrast in the right atrium). Instead, the appearance of the microbubbles in the left atrium during the first or second beat or only after the provocative maneuvers (cough or Valsalva maneuver) is indicative of the intracardiac shunt.

In a research (63) there were enlisted 41 subjects with HPS (medium age 47.1 ± 10.6 years) and 108 cirrhotics (average age 49.2 ± 9.3 years), with negative contrast echocardiography and normal AaDO2 (age-correlated), selected as a check group, with the aim of accessing the entity of the enlargement of the left atrial volume. It was shown that the subjects with HPS, apart from presenting a reduced PaO2, showed also a considerable left atrial volume in respect with the test group (55.1 ml Vs 37.1 ml, $P<0.05$). This data seems to suggest therefore that the left atrial volume can be considered a precursor of HPS in cirrhotic patients. The alteration of the pulmonary vascularization can be shown even with angiography and perfusory pulmonary scintigraphy (PLS/DPLS) with macroaggregates of strong albumin with 99Tc (Tc-MMA) (9). It is evident that in the study of the patients with the hepatopulmonary syndrome, even the hemogasanalytic examination has a fundamental role, as like the transcutaneous monitoring of the respiratory gases. It has further been examined that the role of radiography of the chest can assume the evaluation of the possible pulmonary involvement in the hepatic cirrhosis (64); the standardized reading of the radiography has been put in relation with the physiological parameters of the pulmonary function and with the degree of severity of the hepatic disease (64).

Therapy

The purpose of the medical therapy is contrasting the generalized vasodilatation, the hyperdynamic condition, the plasmatic volume expansion and the increment of the portal flow. Therefore special attention should be paid to nitrates and ACE-inhibitors for the potential capacity of positively influencing the hemodynamic systemic in course of hepatic cirrhosis (65). The nitrates are able to reduce the portal pressure through the reduction of the portal flow, reducing the direct flow towards the collaterals and promoting the splanchnic vasocontrictor reflex. The beneficial effects of the propanolol and of the spironolactone in association with the nitrates have proved a desirable approach on the basis of triple association (67). In addition, the greater part of the ascitic cirrhotics show an activation of the SRAA, for which the use of the ACE-inhibitors seems indicated in these subjects, to allow a reduction of the synthesis of the aldosterone and an increase of renal plasmatic flow.

Most of the knowledge on the regulation of the pulmonary vascular tone and the identification of the genes that increase the risk of development of the pulmonary vascular disease have been guided by new therapeutic prospects; for that purpose, the inhibitors of the phosphodiesterases and the antagonists of the receptors for endothelin deserve attention and above all those that block the receptors B (3). The same consideration is valid for the selective inhibitors of the isoforms of the nitric oxide synthase (3). Other research indicates how the chronic administration of the inhibitor of TNF-α (a potent activator of nitric oxide synthase) prevents the development of HPS and of the hyperdynamic syndrome in cirrhotic rats (68). However, the medical treatment has not shown high efficiency for the HPS and today the

real therapeutic possibilities seem to be represented by liver transplant (1). Garlic powder and iloprost inhalation demonstrate clinical improvements in the pre- and in the post-transplant period (69). Further, the best results after transplant have been shown prevalently for subjects with hepatopulmonary syndrome, where as the effect for the patients with portopulmonary hypertension is still uncertain For the patients with the hepatopulmonary syndrome, the preoperative mortality varies from 9% to 16%, with a mortality of 26% in 12 months (70-75). An improvement of the oxygenation is observed in the majority of transplants, even in those that presented a serious case (18).

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