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CLINICAL UP-DATE

Pulmonary hypertension and hepatic cirrhosis☆

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Abstract Pulmonary hypertension is a relatively common phenomenon in patients with hepatic cirrhosis and can appear through various mechanisms. The most characteristic scenario that binds portal and pulmonary hypertension is portopulmonary syndrome. However, hyperdynamic circulation, TIPS placement and heart failure can raise the mean pulmonary artery pressure without increasing the resistances. These conditions are not candidates for treatment with pulmonary vasodilators and require a specific therapy. A correct assessment of hemodynamic, ultrasound and clinical variables enables the differential diagnosis of each situation that produces pulmonary hypertension in patients with cirrhosis.

PALABRAS CLAVE
Hipertensión portal;
Hipertensión pulmonar;
Disfunción diastólica;
Síndrome portopulmonar;
Cirrosis;
Circulación hiperdinámica

Hipertensión pulmonar y cirrosis hepática

Resumen La hipertensión pulmonar es un fenómeno relativamente frecuente en los enfermos con cirrosis hepática y puede aparecer por diversos mecanimos. El escenario más característico que une la hipertensión portal y la hipertensión pulmonar es el síndrome portopulmonar. Sin embargo, la circulación hiperdinámica, la colocación de un TIPS o la insuficiencia cardíaca pueden elevar la presión media de la arteria pulmonar sin incremento de las resistencias. Estas situaciones no serán candidatas a tratamiento con vasodilatadores pulmonares y requieren una terapéutica específica. Una correcta valoración de variables hemodinámicas, ecográficas y clínicas permite el diagnóstico diferencial entre cada situación que produce hipertensión pulmonar en los pacientes cirróticos.

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Background

A 56-year-old woman, drinker of 40 g of alcohol daily, smoker of 40 packs/year and a history of breast carcinoma, was treated with lumpectomy and hormone therapy a year ago. Following a first episode of ascites, the woman was diagnosed with hepatic cirrhosis and started taking diuretics, which were discontinued due to acute renal failure. The patient required 6 evacuative paracentesis of considerable volume to control the ascites. The decision was therefore made to place a coated transjugular intrahepatic portosystemic shunt (TIPS), with a satisfactory clinical response. Three years later, the patient visited for the reappearance of ascites, leg edema and moderate effort dyspnea. Laboratory tests revealed preserved hepatic function with BNP level of 1032 pg/mL (<500 pg/mL) and severe respiratory failure with PaO_2 level of 57 mmHg (85–100 mmHg). Based on the suspicion of TIPS dysfunction, abdominal Doppler ultrasonography was performed, which showed preserved flow through the TIPS. A hemodynamic study was also performed of the porto-caval circulation in which the pressures in the inferior vena cava, atrium and porta were similar and high (25, 25 and 28 mmHg, respectively). The echocardiogram revealed considerable dilation of the right cavities, severe tricuspid regurgitation and moderate pericardial effusion. There was no observable passage of microbubbles from the right cavities to the left of the heart after the injection of agitated saline. The left ventricular ejection fraction was normal, and the systolic pressures of the right ventricle were high (59 mmHg). Cardiopulmonary catheterization showed pulmonary hypertension (PH), with a mean pulmonary arterial pressure (mPAP) of 46 mmHg, pulmonary vascular resistances (PVR) of 582 dyn s/cm^5, cardiac output (CO) of 8.1 bpm and a negative vasodilator test. Other causes of PH were ruled out through spirometry and chest CT angiography.

Are these symptoms of portopulmonary hypertension (PPH)?
What role has the TIPS played in this patient?
Would an echocardiogram prior to the placement of the TIPS have changed anything?

The clinical problem

PH is present in up to 0.5–5% of patients with portal hypertension, with or without hepatic cirrhosis.[1] Liver transplantation was initially considered contraindicated due to the high risk of respiratory distress in the anesthesia induction and right heart failure after the hepatic reperfusion phase.[2] However, the increased pulmonary pressures in patients with cirrhosis can be the result of several conditions, some of which should be interpreted as the body's physiological response to the advanced stages of cirrhosis. It is therefore essential to establish a proper differential diagnosis given that the therapeutic implications differ in each scenario. Undoubtedly, the clinical picture that has traditionally related hepatic diseases to PH is PPH.

Clinical guidelines and areas of uncertainty

Although we currently have clear diagnostic criteria, such as those proposed by Cartin-Ceba,[3] the limited experience in treating these patients means that we have no clear therapeutic guidelines that enable physicians to guide the management of these conditions based on a good level of evidence. It is tempting to take for granted the association between cirrhosis and PH under the epigraph ''portopulmonary hypertension''. Experienced physicians should, however, know how to direct their diagnosis so that it can establish, practically and simply, a proper differential diagnosis that results in the patient undergoing the correct treatment. Nevertheless, there are numerous difficulties, questions and areas of uncertainty that open up when studying and treating patients with cirrhosis and PH: should we suspect PPH in all patients with cirrhosis and PH? Is an echocardiogram sufficient to reach a diagnosis? On what data and tests should we focus to establish a proper differential diagnosis? Are all patients with PH and cirrhosis treated equally? Are patients with PPH treated the same as those with primary PH?

Pulmonary hypertension and cirrhosis

PH is a relatively common phenomenon in patients with cirrhosis and portal hypertension and generally occurs in the advanced stages of the disease. PH is present in up to 6–9% of patients who are evaluated as candidates for liver transplantation.[2] In general, the definition of PH includes patients who have an mPAP level >25 mmHg, measured through right cardiac catheterization.[4] In order to facilitate diagnosis and establish prognostic and therapeutic groups, the World Health Organization (WHO) recently proposed a new classification based on 5 groups: group 1: arterial PH, which includes PPH; group 2: PH secondary to left heart failure; group 3: PH secondary to lung disease or hypoxemia; group 4: PH due to chronic thromboembolic disease; and group 5: PH by multifactorial mechanisms.[5]

In cirrhosis, PH can be due to several conditions, which can be encompassed by the various PH groups. The characteristic syndrome that relates PH to portal hypertension is PPH, which fits within group 1 of the classification proposed by the WHO, due to its similar behavior and histological findings to primary or idiopathic PH. However, the increase in mPAP is a common occurrence in patients with advanced hepatic disease and is not always related to PPH; there are other conditions that can cause it. Thus, for patients with cirrhosis, we need other hemodynamic parameters, such as PVR, CO and pulmonary capillary pressure (PCP) (Fig. 1) and echocardiographic data, to help us establish a proper differential diagnosis.

To understand the pathophysiology of the various scenarios with cirrhosis, we should understand that pulmonary circulation is a closed circuit in which the blood circulates under low pressure. Thus, if we apply the formula that relates pressure and flow, we see that the change in pressure ($\triangle P$) is directly proportional to flow (Q) and resistance (R), i.e., $\triangle P = Q \times R$. Therefore an increase in