Cardiohepatic Interactions – from Humoral Theory to Organ Transplantation

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Introduction

Heart and liver were already put into reciprocal interaction when attempting to explain the health-disease process from the humoral theory. This suggestion attributed to Empedocles (490 BC), and later applied to medicine by Hippocrates (460 BC) and Galen (AD 129), despite being devoid of any pathophysiological basis, suggested that such organs were protagonists of illness by participating in the production of blood and yellow bile, two of the four humors whose imbalance would be closely related to the emergence of diseases. With the progress of knowledge of physiology and pathophysiology, the close relationship between heart and liver has been defined more precisely.

In this article, we will discuss the cardiohepatic interactions subdividing them didactically in the following: (1) impact of heart diseases on the liver; (2) effects of liver failure and portal hypertension on the heart; and (3) concomitant diseases affecting both the liver and the heart.

Impact of heart disease on the liver (cardiac hepatopathy)

The liver is an organ sensitive to hemodynamic changes. Due to its high metabolic activity, it receives around 25% of the cardiac output, coming by two systems of blood vessels: the hepatic artery and the portal vein. The venous drainage occurs by hepatic veins and the inferior vena cava, which have no valves, resulting in direct transmission of the rise of right heart filling pressures to the liver. The systemic circulatory disorders transmitted to the liver determine two major forms of liver damage: the ischemic hepatitis and the congestive liver disease or congestive liver (formerly named cardiac cirrhosis).

The former, called "shock liver", today known as ischemic hepatitis, occurs in some cases of cardiogenic shock. There is a predominant change of the aminotransferases (ALT and AST), with elevation up to 10 to 20 times the upper limit of the normal value[1]. Such hepatitis should be differentiated from those caused by drugs (many of them used in cardiology), acute viral hepatitis and from chronic hepatitis exacerbation of different etiologies. To aid in the differential diagnosis, the pattern of the curve of aminotransferases should be taken into account, with aminotransferases increasing a few hours after the injury and improving with the resolution of the circulatory dysfunction. Serum levels start to reduce within 48 to 72 hours after the event, with normalization in 10 to 14 days. Another feature that assists in identifying the ischemic hepatitis is the marked increase in lactic dehydrogenase, which doesn't usually happen in hepatitis by other causes.

Congestive liver disease is more frequent than ischemic hepatitis. Studies on liver biopsy in candidates for implantable ventricular assistance devices show findings compatible with cirrhosis in 34% of patients[2]. Congestive liver disease can manifest itself with pain in the right hypochondrium, sensation of abdominal growth and early satiety. In laboratorial tests, changes suggestive of cholestasis are displayed, i.e. increased canaliculares enzymes, with varying degrees of elevated bilirubins. Around 19% of outpatients show elevation of these markers. The finding of increasing canaliculares enzymes in blood demonstrates greater severity of heart failure (HF)[3].

Recently, with the incorporation of new technologies for the treatment of refractory HF, the assessment of hepatic effects has gained importance. Liver markers denote the prognosis in candidates for implantable ventricular assistance devices. The MELD score (Model for End-Stage Liver Disease), numeric scale of severity in the short term for liver disease and extensively used in the management of liver transplantation lists, has emerged as a promising marker to identify the best candidates for treatment with such devices.

Effects of liver failure and portal hypertension in the heart

Circulatory changes associated with cirrhosis have been described for more than 60 years, when it was observed that patients with alcoholic cirrhosis showed increased cardiac output, decreased systemic vascular resistance and reduction of arteriovenous oxygen gradient. The decrease of systemic vascular resistance leads to a state of central hypovolemia, which, in turn, activates the sympathetic nervous system and the renin-angiotensin-aldosterone system. The activation of these neuro-humoral axes and the consequent hyperdynamic circulation in cirrhosis can lead to morphological and functional changes, especially cardiac dilatation of the left chambers[4]. The so called cirrhotic cardiomyopathy is characterized by the presence of the following parameters: cirrhosis, systolic dysfunction under stress conditions (decreased systolic reserve) with normal systolic function at rest, diastolic dysfunction and change of

Keywords

Heart failure; Hypertension, portal; Hepatic insufficiency; Liver diseases; Liver cirrhosis / complications.

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repolarization evidenced by QT interval prolongation, in the absence of any primary heart disease[5].

Some authors suggest that cirrhotic cardiomyopathy would be implicated in the emergence of complications of cirrhosis as ascites and hepatorenal syndrome. In cases of spontaneous bacterial peritonitis patients with lower cardiac output have worse prognosis[6]. In liver transplantation, the manifestation of cirrhotic cardiomyopathy can be associated to post-reperfusion syndrome. This is characterized by increased cardiac filling pressures with decrease in cardiac index after reperfusion of liver graft. An incidence of more than 20% of post-reperfusion syndrome is reported, but the prognostic implication of such a complication is not clearly defined. The real impact of cirrhotic cardiomyopathy in clinical evolution of cirrhosis is unknown, because there is no clear definition of either the entity or its diagnostic criteria and even fewer prospective studies with evaluation of their effect.

Portal hypertension, usually associated with cirrhosis, may cause pulmonary circulatory complications and therefore repercussions both on the right and on the left cardiac chambers. The portopulmonary hypertension is a form of precapillary pulmonary arterial hypertension whose prevalence is of 5% among patients with cirrhosis. It is a known factor of worse prognosis. In perioperative of liver transplantation, severe portopulmonary hypertension is associated with right ventricular failure and mortality rates of up to 100%, being one of the factors of contraindication to surgery. The hepatopulmonary syndrome is an important cause of hypoxemia among patients with cirrhosis, with a prevalence of 20% on the liver transplantation waiting list. It is characterized by: portal hypertension, hypoxemia and intrapulmonary fistulas. Recent data show that in patients with cirrhosis, the volume of the left atrium above 50 ml is associated with the presence of hepatopulmonary syndrome.

Diseases concomitantly affecting liver and heart

The modern lifestyle is associated with high prevalence of metabolic syndrome, a condition associated with the development of non-alcoholic steatohepatitis (NASH) and coronary heart disease. The presence of NASH is an independent risk factor for atherosclerotic disease, being that, among patients with cirrhosis by NASH, there is prevalence of 23% of severe coronary atherosclerotic disease. This data is relevant in cardiac evaluation prior to liver transplantation, where in the cases of cirrhosis by NASH, one must consider the increased risk of concomitant coronary heart disease and increased risk of perioperative cardiovascular events.

Other systemic diseases may compromise liver and heart by targeting both organs parenchyma. In a series of 32 patients with concomitant liver and heart dysfunction, hepatic and cardiac biopsy showed that nine (28%) patients presented the same etiology, the diagnosed diseases being: haemochromatosis, alcoholism and amyloidosis[7].

The definition of disease concomitance and severity of failure in each organ is an important step of treatment strategy. Advanced failures of both organs have been addressed by performing double transplantation (heart and liver) in some medical centers. However, often it is not possible to define which component is largely responsible for clinical manifestations. Depending on the clinical profile, it is possible to use biological markers in the definition of the involvement and the magnitude of the disease in one organ or the other. In cases where there is ascites in patients with cardiac and hepatic dysfunction, propaedeutics must be the instrument of differentiation, but the serum dosage of B-type natriuretic peptide can help to define the cause of ascites and, consequently, help to guide treatment.

Conclusion

The knowledge of the interactions between liver and heart guides the management of different organ dysfunctions, which on first impression, appear unrelated from the etiopathogenic point of view. Evaluation of liver function is particularly important for the treatment of refractory HF, for organ transplantation and device implantation recommendations. The detailed cardiac assessment, in turn, must not be forgotten in cases of metabolic syndrome, non-alcoholic steatohepatitis, not to mention its critical importance for liver transplantation, notably due to the effects of cirrhotic cardiomyopathy in surgical risk and prognosis. Still, one must take into account that same disease can cause both hepatic and cardiac dysfunction.

Knowing that the liver and the heart are attuned, Pablo Neruda, Nobel Prize for literature in 1971, was not mistaken in his "Ode to the liver" by asking these two noble organs to keep working in harmony:

> *"...While the heart resounds and attracts the music of the mandolin, there, inside, you filter and apportion, you separate and divide, you multiply and lubricate, you raise and gather the threads and the grams of life, the final distillate, ... giver of syrups and of poisons, regulator of salts, from you I hope for justice: I love life: Do not betray me! Work on!"*

Author contributions

Conception and design of the research: Silvestre OM, Bacal F, Carrilho FJ, D'Albuquerque LAC, Farias AQ; Writing of the manuscript: Silvestre OM, Ximenes RO, Farias AQ; Critical revision of the manuscript for intellectual content: Silvestre OM, Bacal F, Ximenes RO, Carrilho FJ, D'Albuquerque LAC, Farias AQ.

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Study Association

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