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REVIEW

LIVER ABNORMALITIES IN PATIENTS WITH HEART FAILURE

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Abstract

Cardiac hepatopathy is the term that describes liver damage due to cardiac diseases. The cardiac hepatopathy is divided into congestive hepatopathy, due to passive venohepatic congestion, and acute cardiogenic liver injury, due primarily to acute cardio-circulatory failure. Congestive hepatopathy can be determined by chronic heart failure, constrictive pericarditis, tricuspid regurgitation and right-sided heart failure. On the other hand, acute myocardial infarction, acute decompensated heart failure or myocarditis may cause acute cardiogenic liver injury. Monitoring of liver function tests, such as γ-glutamyltransferase, alkaline phosphatase and liver-derived metabolites, such as bilirubin, is an effective way to assess liver function. Also, the measurement of serum aminotransferases concentration is increasingly being studied, in order to identify the correlation between their values and the extent of the cardiac damage. Clinical examination, laboratory tests, and imaging tests are necessary for the diagnosis of cardiac cirrhosis in patients with heart failure. Patients with cardiac cirrhosis may be asymptomatic,

Résumé

Anomalies hépatiques chez les patients avec de l'insuffisance cardiaque

L'hépatopathie cardiaque est le terme qui décrit les lésions hépatiques dues à des maladies cardiaques. L'hépatopathie cardiaque est divisée en hépatopathie congestive, due à la congestion veino-hépatique passive, et la lésion hépatique cardiogénique aiguë, due principalement à une insuffisance circulatoire cardiaque aiguë. L'hépatopathie congestive peut être déterminée par l'insuffisance cardiaque chronique, la péricardite constrictive, la régurgitation tricuspide et l'insuffisance cardiaque droite. D'autre part, l'infarctus aigu du myocarde, l'insuffisance cardiaque décompensée aiguë ou la myocardite sont ceux qui causent la lésion hépatique cardiogénique aiguë. La surveillance des tests de la fonction hépatique, tels que la γ-glutamyltransférase, la phosphatase alcaline et les métabolites dérivés du foie, tels que la bilirubine, est un moyen efficace d'évaluer la fonction hépatique. De plus, la mesure de la concentration sérique

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but present abnormal liver biochemistry. Patients with congestive hepatopathy have elevated cholestasis markers, such as bilirubin, alkaline phosphatase, and γ-glutamyltransferase, while elevated levels of aminotransferases and lactate dehydrogenase are found in acute cardiogenic liver injury. There is no specific treatment for congestive hepatopathy, the treatment is that of the underlying cardiac disease. Restoration of the cardiac output and hemodynamics is the most important in the management of the acute cardiogenic liver injury.

Key words: aminotransferases, cholestasis, congestive hepatopathy, acute cardiogenic liver injury.

d'aminotransférases est de plus en plus étudiée afin d'identifier la corrélation entre leurs valeurs et l'étendue des lésions cardiaques. L'examen clinique, les tests de laboratoire et les tests d'imagerie sont nécessaires pour le diagnostic de la cirrhose cardiaque chez les patients atteints d'insuffisance cardiaque. Les patients atteints de cirrhose cardiaque peuvent être asymptomatiques, mais ils présentent une biochimie hépatique anormale. Les patients atteints d'hépatopathie congestive présentent une augmentation des marqueurs cholestatiques, tels que la bilirubine, la phosphatase alcaline et la γ-glutamyltransferase, tandis que des taux élevés d'aminotransférases et de lactate déshydrogénase sont retrouvés dans la lésion hépatique cardiogénique aiguë. Il n'y a pas de traitement spécifique pour l'hépatopathie congestive, le traitement est celui de la maladie cardiaque sous-jacente. La restauration du débit cardiaque et de l'hémodynamique est la plus importante dans la prise en charge de la lésion hépatique cardiogénique aiguë.

Mots-clés: aminotransférases, cholestase, hépatopathie congestive, lésion hépatique cardiogénique aiguë.

Introduction

The heart failure (HF) is the final stage of evolution of the majority of cardiovascular diseases. According to 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure, the prevalence of HF in Europe is approximately 1–2% of the adult population in developed countries, rising to ≥10% among people >70 years of age[1]. The lifetime risk of HF at age 55 years is 33% for men and 28% for women[1].

The heart failure is classified, according to the left ventricle ejection fraction (LVEF) values, in heart failure with preserved ejection fraction (HFpEF) (LVEF ≥ 50%) and heart failure with reduced ejection fraction (HFrEF) (LVEF< 40%). Patients with a LVEF in the range of 40–49% represent a 'grey area', which is nowadays defined as HFmrEF, according to the latest European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure[1].

Hypoxemia induced by heart failure causes damages to other systems and organs, such as kidney, liver, bone marrow etc. The complex pathophysiologic interrelationships between heart and liver in patients with heart failure lead to the development of true cardio-hepatic syndromes. Paraclinical, the cardio-hepatic syndrome manifests with anomalies of laboratory liver tests, which may be mild to severe, depending on the severity of cardiac dysfunction. The liver damage in heart failure patients may take the form of chronic congestive hepatopathy or ischemic hepatopathy – acute cardiogenic liver injury (ACLI).

On the other hand, patients with cirrhosis present cardiac abnormalities induced by the liver disease. It was documented that in cirrhosis, the cardiac contractile function is abnormal. Patients with altered hepatic function have hyperdynamic circulation, with increased cardiac output and heart rate and a reduced systemic vascular resistance. This phenomenon has been called „cirrhotic cardiomyopathy" and it is related to both portal hypertension and cirrhosis. Alcohol abuse might cause cirrhotic cardiomyopathy, but this form of cardiomyopathy can also occur in the absence of alcohol ingestion.

This is why the cardiovascular status must be carefully monitored in cirrhotic patients, especially if they are under stress, like liver transplantation or shunt implantation. Cardiac failure represents an important cause of morbidity and mortality in liver transplantation[2,3].

Pathophysiology and morphopathology of liver damage

The liver has a high metabolic activity and a perfusion rate of approximately 1 mL/g/min, which represents about a quarter of the total body's total amount of blood, making the liver an organ extraordinarily vulnerable to acute circulatory disturbances.

The sudden decrease of cardiac output, seen in patients with acute heart failure, causes the appearance of hypoxic or ischemic hepatitis, older terms, that have been replaced now with the term „acute cardiogenic liver injury". Acute decompensated heart failure or cardiogenic shock may lead to ACLI and persistent circulatory failure. This happens when the liver's compensatory mechanism of increasing oxygen extraction from the blood is insufficient. In acute cardiogenic liver injury, necrosis of pericentral zones 3 hepatocytes occurs, this area receiving a lower amount of oxygenated blood compared to hepatocytes from periportal zones 1 and 2. Elevated levels of aminotransferases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and lactate dehydrogenase are found in ACLI. Measurement of serum aminotransferases concentration is increasingly being studied in order to identify the correlation between these values and the predisposition to cardiac damage. Although clinical and laboratory diagnostic data are usually enough for the diagnosis, a liver biopsy may be useful in order to clarify the etiology of the acute elevation in aminotransferase levels[4].

The increased central venous pressure in patients with heart failure causes passive hepatic congestion, with cholestasis, manifested by alkaline phosphatase (AP), gamma-glutamyl-transferase (GGT), and direct and indirect serum bilirubin elevations.

The chronic liver stasis affects liver functions, with disorders in the synthesis of coagulation factors and albumin, bridging fibrosis and finally cardiac cirrhosis. In congestive hepatopathy (CH), the liver is increased in dimensions and consistency and it is histologically characterized by hemorrhage and necrosis of zone 3 of Rappaport acinus. Patients with congestive hepatopathy present steatosic alterations of the liver. In chronic heart failure patients, it has been demonstrated that hepatocytes are destroyed through apoptosis, while hepatocyte necrosis appears in acute liver injury.

High central venous pressure causes ascites formation, damage to the main biliary tract and thrombi formation in sinusoids, hepatic venules, and portal tracts. Its persistence will cause collagen deposits with formation of fibrous septa, ultimately all these changes leading to the occurrence of cardiac cirrhosis, a rather rare but significant pathology, especially in the case of patients with constrictive pericarditis or severe tricuspid insufficiency. The difference between cardiac cirrhosis and hepatic cirrhosis is mainly affecting zone 3 (vs. zone 1) as well as a distribution pattern of liver fibrosis and fibrous obstruction due to the development of thrombi in the hepatic and portal veins[5].

Clinical and paraclinical features

Signs and symptoms of congestive hepatopathy (CH): CH is usually asymptomatic for a long time. Some patients, however, could claim slight discomfort in the right upper quadrant caused by hepatic capsule stretching, early satiety, nausea, and marked weight loss. Physical examination also detects hepatomegaly, liver with high consistency, hepatojugular reflux, leg edema, ascites and pulsatile liver, most often caused by tricuspid regurgitation, tricuspid stenosis, constrictive pericarditis, restrictive cardiomyopathy or pulmonary hypertension. A small proportion of patients with chronic heart failure have splenomegaly (mainly those who develop cardiac cirrhosis). Esophageal varices are very rare.

Laboratory findings in CH: in CH, primary changes in laboratory tests are the increase in serum cholestasis markers, like bilirubin, alkaline phosphatase (AP) and γ-glutamyl-transferase (GGT). A study on patients with chronic heart failure demonstrated that both bilirubin and GGT values correlate with the severity of the cardiac disease[6,7]. Liver cytolysis enzymes (alanine aminotransferase – ALT and aspartate aminotransferase – AST) show very slightly elevated values, approximately 2-3 times higher than normal. Approximately 25% of patients experience a slight decrease in serum albumin and a slight increase in prothrombin time. As the changes in laboratory findings are more pronounced, cardiac function is more affected, with decreased cardiac index, increased filling pressures and severe tricuspid regurgitation[7].

One prospective study of 552 patients with HF has found that only total bilirubin and AST values are highly correlated with mortality risk. AP and GGT are independent predictors of death in patients with heart failure. Also, total bilirubin, AP, and GGT levels independently correlate with clinical findings in patients with HF, such as jugular venous distention, tricuspid regurgitation and peripheral edema[8].

Signs and symptoms of acute cardiogenic live injury (ACLI): ACLI is usually asymptomatic in most patients; some patients may present nausea, vomiting, weakness, right upper quadrant pain, and apathy[7]. In very rare cases, jaundice, mental confusion, flapping tremor, or hepatic coma may appear, which are more likely to be due to cerebral hypoxia rather than to hepatic encephalopathy. Fulminant hepatic failure has also been reported in patients with acute heart failure[9].

Laboratory findings in ACLI: the elevation of aminotransferases (10-20 times the normal values) and LDH is commonly found in ACLI, especially in 1-3 days after the acute decompensation of heart failure; the values return to normal in 7-10 days if

the hemodynamics improves[8,9]. The rapid increase in LDH and aminotransferases, with ALT decreasing in 72 hours, is useful in differentiating between viral, alcoholic or drug-induced hepatitis. A mild increase in serum bilirubin, AP and prothrombin time levels can also be found[10].

Which liver function tests are useful in patients with heart failure?

The patient with congestive hepatopathy presents a progressive deterioration in cholestasis tests, most of the time parallel to the altered cardiovascular status of the patient. It should be noted that cholestasis tests can reach very high values. Patients with ACLI have altered hepatic cytolysis tests: ALT, AST, and LDH. The hepatic injury of the patient with HF evolves over time to cardiac cirrhosis.

Diagnosis of cardiac cirrhosis in patients with chronic heart failure is established by clinical examination, laboratory tests and imaging. Patients with cardiac cirrhosis are in general asymptomatic, but present abnormal liver biochemistry. The symptoms may appear either progressively or suddenly (in acute right ventricular decompensation/ constrictive pericarditis/ decompensation of a valve disease). Right upper quadrant pain due to hepatic capsule dilation, nausea, vomiting, hepatomegaly, ascites and, very rarely, jaundice appear in symptomatic patients.

In all hospitalized patients with heart failure, hepatic tests are necessary in order to diagnose the hepatic injury. A careful history is necessary in order to find out if any drugs or infections are the cause of the liver injury. The most frequent change in laboratory tests, that appears in 70% of patients with cardiac cirrhosis, is the elevation of total bilirubin due to the increased level of indirect bilirubin. However, this increase in total bilirubin usually does not exceed 3 mg/dl. Alteration of the synthesis function of the liver is also encountered, with decreased serum albumin levels in 40% of patients and elevation of LDH and ALT/LDH ratio less than 1.5[11].

It is also very important to identify the causes of the heart failure exacerbation. The levels of cardiac enzymes and brain natriuretic peptide (BNP) might be elevated. The electrocardiogram could show arrhythmias, ischemic changes or right ventricular hypertrophy. Echocardiography might determine the presence of valvular diseases, wall motion abnormalities, can measure the pulmonary artery systolic pressure, together with the evaluation of pericardium or inferior vena cava. Computed tomography scan or magnetic resonance imaging could also be useful in determining the etiology of hepatic dysfunction. If ascites is present, paracentesis should be done; cardiac ascites usually has a high protein content (>2.5 g/dL) with high serum-ascites albumin gradient (>1.1 g/dL). For the differential diagnosis, a useful biomarker, with high sensitivity and specificity for the diagnosis of heart failure, is serum NT-proBNP level, which may predict HF as the cause of ascites.

Evolution – predictors of mortality in patients with HF and liver disease

In patients with heart failure and hepatic dysfunction, the risk of mortality can be predicted by using the biochemical liver tests, such as bilirubin, AST, GGT, and AP[12-17]. Data from CHARM trial showed that bilirubin and AST are predictors of death in patients with chronic HF, but especially elevated total bilirubin is a stronger predictor of cardiovascular death, HF hospitalization and all-cause mortality[10]. Another study also revealed that lower albumin and elevated total bilirubin are associated with higher risk of mortality in ADHF patients[14]. There is evidence suggesting that GGT may also have a potential role in predicting mortality and that a more than double value of GGT is associated with a 34% increase in the risk of cardiovascular events[18]. In the SURVIVE trial, mortality at one month was predicted by elevated aminotransferases and other modified liver tests predicted long-term mortality[11].

Complications

The presence of liver alterations in patients with heart failure may have consequences on cardiovascular drugs pharmacokinetics and pharmacodynamics. Liver disease usually induces moderate alterations in drug pharmacokinetics; cardiac cirrhosis leads to impaired hepatic function, impaired coagulation, decreased synthesis of albumin, and alterations in drug metabolism. Also, abnormal liver drug metabolism is associated with HF severity, so it may be improved when decompensated HF is adequately treated. There are not very clear recommendations regarding dose adjustments in patients with hepatic dysfunction. The Food and Drug Administration suggests using the Child-Pugh classification in order to estimate the extent of the hepatic damage[19]. For the drugs that have no specific information about the dose adjustment in patients with hepatic dysfunction, the pharmacokinetics features of the specific drugs will be taken into account.

The commonly used drugs, such as beta-blockers, statins, antiarrhythmic agents, anticoagulants, and antibiotics could potentially accumulate to toxic levels in these patients, leading to cardiac and non-cardiac adverse effects.

A very disputed subject is about the impact of hepatic dysfunction in patients being treated with anticoagulants. According to some studies, prothrombin level has been found to be decreased in 80% of patients with acute and chronic right HF and the administration of parenteral vitamin K had no positive result. This is a very important topic for patients who are in need of anticoagulation therapy, like atrial fibrillation, ventricular thrombi, and prior stroke. Hepatic congestion may also affect the intrinsic coagulation factors production, thus emphasizing the anticoagulant effect of vitamin K antagonists such as warfarin, resulting in a prolonged prothrombin time. The use of novel anticoagulants such as dabigatran, rivaroxaban or apixaban is even more disputable; that is why their use is limited when hepatic congestion occurs. Warfarin is still used in patients with HF, altered hepatic function and other comorbidities that have an indication of anticoagulation[20,21].

Treatment of hepatic dysfunction in patients with heart failure

There is no specific treatment for congestive hepatopathy. The treatment is that of the underlying cardiac disease. Studies show that by improving hemodynamics in patients with heart failure, the improvement of liver dysfunction will also be obtained.

Diuretics are recommended in symptomatic patients with HFrEF. The renal function might also be affected if the liver dysfunction is advanced, this is why liver congestion, ascites, and jaundice may also be improved by diuretic therapy. In more advanced cases, combined treatment is required: diuretics, paracentesis, ultrafiltration or peritoneal dialysis[21].

Angiotensin-converting enzyme (ACE) inhibitors or ARBs (angiotensin receptor blockers) and beta blockers are recommended for all symptomatic patients with HFrEF, in order to reduce mortality and morbidity, unless other contraindications exist. In symptomatic patients intolerant to ACE inhibitors and ARBs, hydralazine and nitrate combination can be administered. In HFpEF, no treatment was effective in decreasing mortality and morbidity. However, in order to improve symptomatology, diuretics, controlling systolic and diastolic blood pressure with ACE inhibitors and ARBs, and atrial fibrillation treatment are recommended.

Restoration of the cardiac output and hemodynamics is the first step in the management of ACLI. Also, inotropes/vasopressors, ventilator and mechanical circulatory support might also be useful in some patients[22].

Conclusions

The liver is an important and complex organ with a high metabolic activity that receives 25% of the cardiac output. Acute and chronic HF patients present alterations of liver functions. The characteristics of liver injury correspond to hepatic congestion and reduced perfusion. Hepatic zone 3 is more susceptible to hypoxia. In cirrhosis, the cardiac contractile function may also be abnormal, this phenomenon being called „cirrhotic cardiomyopathy". Patients may present dyspnea, fluid retention, and limited exercise capacity.

Cardiac hepatopathy is divided into congestive hepatopathy and acute cardiogenic liver injury. Patients with congestive hepatopathy present an increase of cholestasis markers, like bilirubin, alkaline phosphatase, and γ-glutamyl-transferase, while elevated levels of aminotransferases and lactate dehydrogenase are found in acute cardiogenic liver injury. Functional liver tests may be used as predictors of cardiovascular morbidity and mortality[23].

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article"

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law."

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