DOI: 10.4149/BLL_2018_018

Bratisl Med J 2018; 119 (2)
98 – 102

CLINICAL ANALYSIS

Heart failure affects liver morphology and function. What are the clinical implications?

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ABSTRACT
Liver dysfunction in heart failure is common and usually clinically significant, especially in patients with advanced or severe acute heart failure. Lesions are caused by an impaired hepatic circulation due to congestion and hypoperfusion. Congestive lesions are more common and typically manifested by painful hepatomegaly and increased direct bilirubin and alkaline phosphatase.
The inferior vena cava and hepatic veins are usually dilated. Congestive lesions are characterized by dilatation of the central vein with fibrotic changes in the surrounding areas on histological examination. Isolated ischaemic lesions are rare and occur due to severe and prolonged ineffective perfusion, often accompanied by hypoxemia. Ineffective perfusion is reflected by an increase in total bilirubin and significantly increased transaminase levels. The prognosis of ischaemic lesions without an adequate treatment of the cause of hypoperfusion is poor. Increased levels of bilirubin and liver function tests, as well as signs of impaired liver proteosynthetic function, are associated with a poor prognosis. Knowledge of the phenotypes of hepatic lesions in heart failure is important to select the appropriate treatment for an acute decompensation. Changes in biochemical markers, hepatic perfusion or stiffness of the liver can be used to evaluate the effectiveness of diuretic treatment and achieve euvolemic status in the patients with heart failure *(Tab. 1, Fig. 3, Ref. 28)*. Text in PDF *www.elis.sk.*
KEY WORDS: liver dysfunction, heart failure, congestion.

Introduction

Heart failure (HF) is a complex syndrome, when a heart is unable to supply the organs with an adequate volume of oxygen- rich blood and is associated with blood congestion. For these reasons, HF exhibits multiple organ manifestations in its more advanced stages. The liver is damaged very often. This is the result of high metabolic activity associated with a high oxygen demand and anatomical location near the heart associated with a high central venous pressure.

Liver dysfunction in HF was discussed in literature in the first half of the 20th century. In 1930, N. Jolliffe reported that 80 % of patients with congestive HF had elevated levels of bilirubin, and more than 90 % had an impaired hepatic function (1). The awareness of liver dysfunction and the clinical presentation of liver lesions in acute or chronic HF do not correlate with its frequency. For better understanding of the clinical scenario, we added two case reports at the end of this review article.

According to the latest data, total bilirubin levels are increased in 20–26 % of patients admitted to the hospital for acute HF. Increased levels of cholestatic enzymes, especially gamma-glutamyltransferase (GGT) was detected in 62 % of patients (2, 3), and isolated elevation of aspartate aminotransferase and alanine aminotransferase (AST, ALT) was found in 26 % of the patients (4). Among patients with chronic HF, total bilirubin was increased in 13 % and transaminases were increased in 3.1 % of the patients. A decreased level of albumin was detected in 18.3 % of the patients (5).

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Hepatic portal circulation

The liver has a high metabolic activity that is dependent on sufficient perfusion (approximately 1 ml/g/min). Approximately 20–25 % of cardiac output flows through the liver at rest. The liver receives a dual blood supply. The hepatic artery supplies fully oxygenated blood to the liver under systemic pressure and delivers approximately 35 % of the liver's blood supply and 50 % of the liver's oxygen demand. The portal vein carries blood drained from the splanchnic area and provides not only the metabolic substrates, but also the remaining quantity of the liver's oxygen demand. Arterial and portal blood are mixed in liver sinusoids (second capillary bed). Liver sinusoids are porous channels connecting the portal areas with the central vein of the hepatic acinus. Central veins drain into gradually expanding hepatic veins. Major hepatic veins flow into the inferior vena cava near the right atrium. The right ventricle filling pressure is thus immediately transferred to the hepatic circulation. The pressure in the portal vein can be measured indirectly by inserting a catheter via the

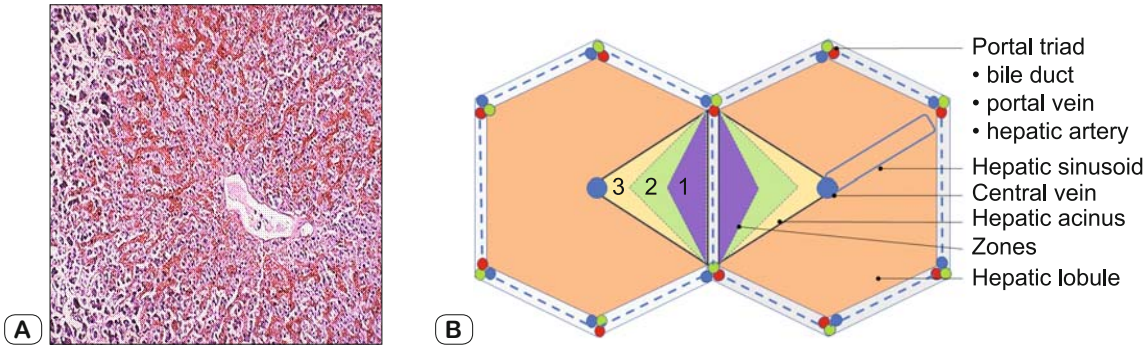

Fig. 1. A) Histology of a congested liver, the central vein and sinusoids are overloaded with blood. B) The anatomy of the hepatic functional unit.

femoral or jugular vein into the hepatic vein. The pressure at the end of the catheter reflects the hepatic sinusoidal pressure. Portal venous pressure is normally between 5 and 6 mmHg. An increase in the portal venous pressure greater than 10 mmHg is considered a definitive manifestation of portal hypertension (6).

Pathology and pathophysiology of hepatic lesions in HF

The basic structural unit of the liver is the hepatic lobule, which is composed of a central efferent vein surrounded by lined sinusoids and the portal tracts, which can be found running along each corner of the lobule. Portal tracts, also known as portal triads, consist of terminal branches of the hepatic artery, portal vein and the bile ducts. The functional unit of the liver is the acinus. It is a small part of liver parenchyma, which contains terminal branches of the portal triad as its central axis. Depending on the distance from the portal triad, three zones can be recognized in the acinus. The furthest zone, zone 3, is located around the central vein, receives blood with a low level of oxygen and is sensitive to hypoxia (7). Increased pressure in the right atrium is transmitted to the hepatic veins and results in dilatation of the sinusoids in zone 3 and the compression of hepatocytes in combination with hypoxia leads to atrophy, necrosis and fibrosis (1) (Figs 1A, B).

Functional changes in the local circulation are present in acute decompensated or advanced HF. α-adrenergic receptors are mostly located in the portal vein and ß2 receptors are located in the hepatic veins. Sympathetic activation causes portal vasoconstriction, splanchnic congestion and the worsening of liver ischaemia.

Centrilobular necrosis is a regular finding in hepatic lesions due to HF. If HF worsen, the necrosis spreads peripherally. Successful treatment leads to the healing of necrosis. Initially, fibrotic changes are localized around the central vein. When severe and longstanding hepatic congestion leads to bridging fibrosis between the central veins, it is called cardiac cirrhosis.

The pathological appearance of a liver affected by chronic congestion is “speckled” similar to a grated nutmeg kernel. Nutmeg liver develops typically in cases of a prolonged congestion due to right HF caused by pulmonary arterial hypertension, pulmonary hypertension due to mitral stenosis, primary failure of the right ventricle with tricuspid regurgitation, restrictive cardiomyopathy or constrictive pericarditis.

An important characteristic of cardiac cirrhosis is the absence of the intrahepatic obstruction of the portal vein resulting in the absence of hepatic portal hypertension (9).

Transient elastography is a non-invasive test to quantify liver stiffness, which is increased in patients with acute as well as chronic HF (10). In some studies, stiffness values were correlated with the level of N-terminal pro-brain natriuretic peptide (NT-proBNP). The elimination of congestion leads to the reduction, but not the normalization of the stiffness (11). Impairment of hepatic function may have far-reaching consequences, including a negative effect on myocardial function, but these relationships have not been extensively explored. The liver plays a key role in proteosynthetic and metabolic functions and in the elimination of circulating endotoxins. An impaired microcirculation causes a decrease in endotoxin clearance and an increase in the secretion of proinflammatory cytokines. Immune activation negatively affects nutrition and the metabolism of iron and participates in cardiac cachexia and anaemia (12).

Clinical presentation

We distinguished two phenotypes of manifestations of hepatic lesions. The congestive (venostasis) phenotype dominates in most patients and is caused by an acute worsening of HF. Perfusion disorder is associated with the ischaemic phenotype. Isolated ischaemic impairment is rare. Ischaemic lesions of the liver, sometimes inappropriately called ischaemic hepatitis, develop due to rapid and significant decrease in the perfusion of the liver resulting from a prolonged hypotension. Hypoxemia can also contribute to ischaemic lesions. The mixed forms of liver impairment are the most common in acute decompensated HF.

Congestive (venostasis) liver dysfunction is clinically manifested by pain in the right hypochondrium and epigastrium and heaviness after eating. Gastrointestinal signs may be significant and are caused by splanchnic congestion and increased intra-abdominal pressure (8). Significant gastrointestinal symptomatology is typical, especially in adolescents and young adults. According to one analysis, abdominal pain was the only symptom in 23 % of the cases in adolescents with the first manifestation of HF (13). Hepa-

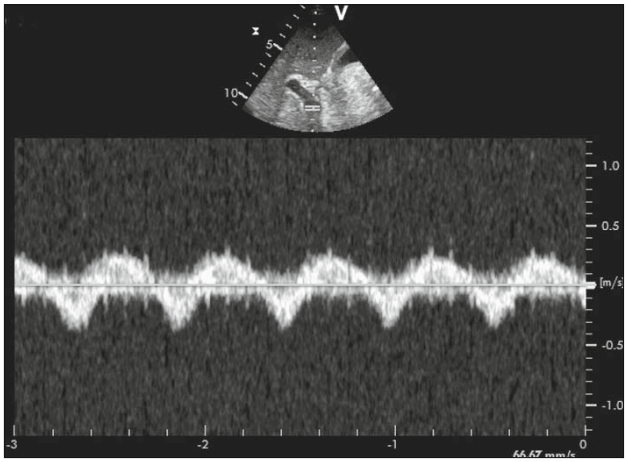

Fig. 2. Pulse Doppler measurement. Biphasic flow in the portal vein in a patient with severe right ventricular failure and liver congestion. The sampling volume is placed before bifurcation of the portal vein. Positive velocity signal is hepatopetal, negative is hepatofugal.

tomegaly with a positive hepatojugular reflux is a typical finding during physical examinations. Ascites is present approximately in 25 % of patients with right HF, especially splenomegaly.

When an enlarged hypoechoic liver is found on ultrasound, echogenicity may increase with advanced fibrotic changes. The surface of the liver is smooth. The inferior vena cava and hepatic veins are dilated and the portal vein is not enlarged. An ultrasound examination can detect even a small quantity of ascites and thickening of the gallbladder and the intestinal walls due to splanchnic congestion.

Pain in the right hypochondrium with gallbladder wall thickening and hyperbilirubinemia is sometimes misinterpreted as acalculous cholecystitis (14), which was the case in one patient in our case report.

The direction of blood flow in the hepatic veins is forward only during diastole of the chamber, while the flow during systole, with concomitant tricuspid regurgitation, is usually reversed. Under normal conditions, the flow in the portal vein is continuous or a slightly waving hepatopetal flow, which changes to a pulsatile pattern, sometimes with a visible hepatofugal phase during systole in advanced HF and congestion (Fig. 2) (15).

Chronic hepatic congestion changes the physical quality of the liver. In patients with chronic HF, liver stiffness is related to venous pressure and fibrosis. Some studies suggested that measurement using acoustic elastography could be an indicator of treatment´s success in HF (16). Liver stiffness may predict the outcome in patients after left ventricular assist device (LVAD) implantation (17).

In laboratory tests, a congestive hepatic lesion is manifested by hyperbilirubinemia with a predominant increase of conjugated bilirubin (direct bilirubin) and slightly elevated alkaline phosphatase and GGT levels. The concentration of transaminases (AST, ALT) is usually normal or only slightly increased. The proteosynthetic liver function is normal or slightly worsened, as reflected by an increased prothrombin time (PT), which does not respond to the administration of vitamin K. Hypoalbuminaemia is usually present in advanced HF in patients with cardiac cachexia or other disorders, such as enteropathy associated with the loss of protein (18–20).

Ischaemic damage, also called hypoxic hepatopathy, shock liver or ischaemic hepatitis, is a disorder that occurs as the result of a significant decrease in liver perfusion and leads to centrilobular hepatocyte necrosis. Hypoperfusion itself is usually not sufficient to produce centrilobular necrosis. In many patients, hypoxemia caused by pulmonary comorbidities can be identified as an additive cause. The ischaemic lesion is manifested by the sudden increase (often more than 100 times) in serum transaminases, along with an increase in lactate dehydrogenase (LDH), PT and bilirubin, but jaundice develops only rarely. If the treatment is successful, laboratory values quickly return to the normal level. Ischaemic aetiology is the cause of liver failure in approximately 5 % of inpatients admitted to departments specializing in acute liver failure and liver transplant and is associated with hospital mortality rates higher than 50 %. The strongest predictor of mortality is the cardiac index (CI) and its changes during treatment. At the time of admission, the average CI has been reported to be 1.6 l/min/m^2 in patients, who died and 2.1 l/min/m^2 in patients, who survived (21).

Congestion and hypoperfusion, two basic mechanisms leading to liver damage, are often combined. Van Dreusena et al (22) documented the link between a hepatic dysfunction and the haemodynamic profile in patients with HF. Increased central venous pressure (CVP) was associated with an increase in all indicators of liver dysfunction, especially direct bilirubin and GGT. Increases in AST, ALT and total bilirubin levels were related to a low CI. Table 1 provides a review of the typical laboratory changes in border phenotypes of liver dysfunction in HF.

Renal hypoperfusion, congestion and increased abdominal pressure are also major determinants of renal function impairment in decompensated HF. Several research groups have pointed out that the dominant problem is an increased renal venous pressure rather than low cardiac output as was previously proposed (23, 24).

Prognostic and therapeutic implications of liver disorder in HF

The recognition and understanding of liver lesions in HF is essential for the treatment and prognosis.

Tab. 1. Basic biochemical abnormalities of liver dysfunction in heart failure.

Laboratory Parameter	Congestion (Increased CVP)	Hypoperfusion (Low Cardiac Output)
AST	0/↑	↑↑↑
ALT	0/↑	↑↑
TB	↑	↑/↑↑
DB	↑/↑↑	↑
GGT	↑↑	0/↑
ALP	↑/↑↑	0/↑
LDH	↑	↑↑

ALP – alkaline phosphatase, ALT – alanine aminotransferase, AST – aspartate aminotransferase, CVP – central venous pressure, DB – direct bilirubin, GGT – gamma-glutamyltransferase, LDH – lactate dehydrogenase, TB – total bilirubin

Increased total bilirubin and decreased albumin in patients without a history of primary liver disease, who were admitted to the hospital for acute HF, were associated with a higher risk of rehospitalization and death in the following months (2, 4). Hypoalbuminemia appears to be a significant indicator of poor short-term prognosis in functional New York Heart Association (NYHA) class III / IV patients and patients with HF undergoing surgery (25).

In the study that analysed 330 patients with HF, Poelzl et al. (3) demonstrated the prognostic significance of GGT on other clinical and biological prognostic markers. The predictive value of increased GGT is higher in patients with milder (NYHA I/II) rather than severe (NYHA III / IV) symptoms.

Liver dysfunction is also an important prognostic factor after the implantation of an LVAD. Data analysis confirmed that liver dysfunction, quantified by the Model for End-Stage Liver Disease (MELD) score, was a simple and significant predictor of bleeding risk and death after LVAD implantation. The MELD score is calculated from serum creatinine, total bilirubin, sodium and international normalized ratio (INR) values. Patients with a MELD score ≥ 17 had 2.5 times higher risk of death within 6 months after LVAD implantation (26, 27). Histological changes and the extent of fibrosis in liver samples obtained by trans-jugular biopsy could be the determining factors for risk assessment of LVAD implantation and the contraindications of this procedure (28).

The recognition of liver dysfunction also affects the patient management. The congestive phenotype should be treated with diuretics or elimination therapy. Hepatic and splanchnic congestion indicates a right ventricle failure, and treatment should focus on the volume and pressure unloading of the right ventricle. However, if the ischaemic/hypoxic phenotype is dominant, it is appropriate to initiate or intensify the therapy aimed to increase the perfusion and oxygenation.

In patients with HF and impaired hepatic function, drug hepatotoxicity and the role of the liver in the drug effects and degradation should be considered. Liver dysfunction may reduce the effect of medications, such as prodrugs (e.g., clopidogrel). However, drugs degraded and excreted by the hepatic route can accumulate. Cardiovascular pharmacotherapy, amiodarone, statins, certain ACE inhibitors, diltiazem and verapamil have a higher risk of accumulation and increased toxicity. Special attention should be given to anticoagulant therapy with vitamin K antagonists, which have a high risk of accumulation.

Ilustrative cases reports

Congestive HF with systemic congestion imitating acute cholecystitis

A 59-year-old patient with a history of ST elevation myocardial infarction 7 years previously, arterial hypertension and bronchial asthma was presented to the emergency department due to a severe pain in the right hypochondrium and nausea. He did not have a chest pain. Recently, he had experienced an increased fatigue, shortness of breath during physical activity and swelling in the ankles in the evening. The patient was obese.

A physical examination revealed an irregular heart beat with two heart sounds, a faint systolic murmur at the apex and breathing with wheezing during prolonged expiration. His blood pressure was 155/85 mmHg. ECG confirmed atrial fibrillation. His heart rate was 68/min, a QS configuration was present in V1–V3 leads, and the ST segment did not exhibit elevation or depression. A chest X-ray showed an increased transverse diameter of the heart, without other pathology. Laboratory tests detected a mild leucocytosis, increased direct bilirubin and GGT and slightly increased C-reactive protein, cardiospecific enzymes were normal. Ultrasonography of the gallbladder and liver showed an enlargement of the liver, gallbladder wall thickening, no gallstones and a small quantity of free fluid in the abdominal cavity located mainly perihepatically (Fig. 3). Worsening dyspnoea was predicated to be associated with bronchial asthma and swelling in the ankles after the use of amlodipine for arterial hypertension. Surgeons suspected acalculous cholecystitis. Spasmolytic and antibiotic infusions did not improve the clinical status. A cholecystectomy was indicated. During the internal preoperative examination, the cardiologist reviewed the diagnosis and suspected a congestive HF with systemic congestion. The NT-proBNP level was significantly increased (3460 pg/ml). Diuretic therapy and intensification of antihypertensive medication quickly led to the improvement of clinical status, including relief of pain in the right hypochondrium. Echocardiography showed a mildly dilated dysfunctional left ventricle with a reduced ejection fraction (36 %), moderate mitral regurgitation and a mildly dilated right ventricle with a moderate tricuspid regurgitation. The systolic pulmonary artery pressure was estimated to be 70 mmHg.

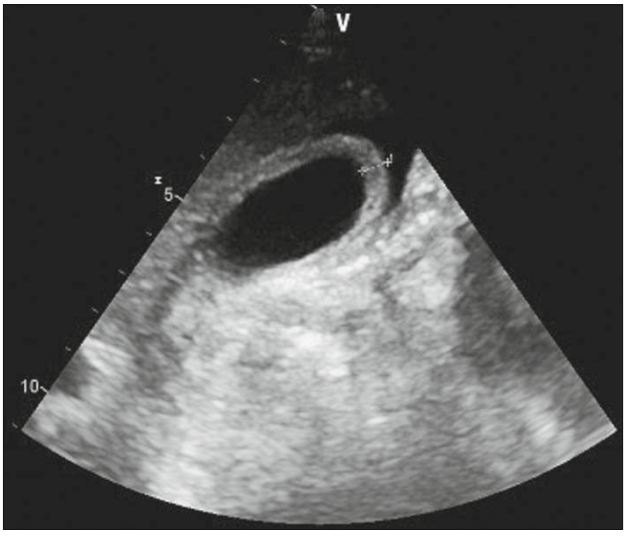

Fig. 3. Thickening of the gallbladder wall as a sign of splanchnic venostasis.

Acute liver dysfunction as the dominant symptom of acute HF

An 18-year-old healthy patient presented to a general practitioner complaining of low-grade fever, fatigue during ordinary physical activity, abdominal pain and subicterus. Laboratory tests detected significantly increased levels of ALT and AST (ALT 14.8 μmol/l, AST 15.4 μmol/l). The patient was admitted to the

infectious disease department with s suspected infectious hepatitis. Serological tests did not confirm a viral aetiology of the liver impairment. Abdominal ultrasonography revealed hepatosplenomegaly and ascites. A chest X-ray did not show any pathological changes. The patient was transferred to the Department of Internal Medicine with a suspected autoimmune hepatitis and treated with the hepatoprotective drugs and glucocorticoids. Gradually decreasing diuresis was observed and pleural effusions and swelling developed. This condition was diagnosed as hepatorenal syndrome. The patient became short of breath at rest, and an orthopneic position was observed. After consultation with a cardiologist, a diagnosis of acute HF was established. Echocardiography showed a severe dysfunction of a mildly dilated left ventricle. Coronarography results were normal. Magnetic resonance imaging (MRI) confirmed a reduced ejection fraction of the left ventricle (17 %) and intramyocardial "late enhancement". In accordance with the MRI results, an endomyocardial biopsy revealed chronic myocarditis and myocardial fibrosis, and the viral genomes of the eight most common viruses were not found. Conservative treatment for HF and immunosuppression therapy was initiated, and the patient was stabilized over the next year. After this period, HF resistant to treatment developed, and the patient underwent a heart transplant.

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Received October 6, 2017.
Accepted November 9, 2017.