What does the liver tell us about the failing heart?

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Online publish-ahead-of-print 19 December 2012

This editorial refers to ‘Liver function abnormalities, clinical profile, and outcome in acute decompensated heart failure†, by M. Nikolaou et al., on page 742

The liver in heart failure

The high metabolic activity of the liver results in a high perfusion rate of ≈1 mL/g/min. Under resting conditions, this is about a quarter of the body’s total blood supply. The oxygen-rich blood of the hepatic artery contributes to about a quarter of the total liver perfusion that may rise substantially under conditions of excessive oxygen demand. The complex blood supply makes the liver extraordinarily vulnerable to acute circulatory disturbances. Both the severity and the pattern of hepatic injury depend on the relative contribution of passive congestion and diminished perfusion.1

Increased central venous pressure results in passive hepatic congestion and causes elevations of alkaline phosphatase (AP), γ-glutamyltransferase (GGT), and direct and indirect serum bilirubin. This ‘congestive hepatic injury’ is known as nutmeg liver on pathology. Decreased cardiac output with impaired organ perfusion is associated with acute centrilobular (zone 3 of the acinus) hepatocellular damage and necrosis. ‘Hepatic ischaemic injury’ results in elevations in serum aminotransferases (Figure 1).2,3

In contrast to acute perfusion abnormalities, prolonged and chronic haemodynamic disturbances may result in bridging fibrosis, ‘cardiac’ cirrhosis, and impaired hepatic function with decreased synthesis of coagulation factors and albumin.

Hepatic congestion occurs without particular symptoms in most cases. Some patients may suffer from jaundice, stretching of the liver capsule with right upper quadrant discomfort, and ascites. Rare cases of congestive heart failure (HF) associated with fulminant hepatic failure have been reported. However, most such cases occur in the setting of superimposed cardiogenic shock and consecutive hepatic ischaemic injury.4

Prevalence of abnormal liver biochemistry in chronic and acute decompensated heart failure and prognostic relevance beyond the heart: the ‘syndrome’ of heart failure and the role of ‘suffering’ organs

Most data about the interaction between HF and elevated liver biochemistry have been generated in patients with chronic HF.2,5 In contrast, data on acute decompensated heart failure (ADHF) patients are scarce. Nikolaou and colleagues6 now report data on liver biochemical tests from patients included in the SURVIVE trial, a large study involving patients with ADHF that investigated effects of inotropic therapy. Abnormal liver biochemical findings could be found in almost a half of the study population (isolated abnormal transaminases in 26%, isolated abnormal AP in 11%, and a combination of abnormal transaminases and AP in 9%).

A recently published post-hoc analysis of the placebo group of the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) trial, which enrolled patients hospitalized for ADHF with an ejection fraction ≤40% and no history of primary significant liver disease or acute hepatic failure, found baseline abnormalities in liver biochemical tests, with low albumin in 17%, and elevated levels of aspartate transaminase (AST) in 21%, alanine transaminase (ALT) in 21%, AP in 23%, GGT in 62%, and total bilirubin in 26%.7

The pattern of abnormal liver biochemistry was substantially different in patients with chronic HF (Figure 2). An analysis of data from 2679 patients with symptomatic chronic HF from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity program (CHARM) trial revealed ALT elevation in 3.1%, low albumin in 18.3%, and elevation of total bilirubin in 13.0% of patients.8 Data from a recently published series revealed...
a predominantly cholestatic pattern in patients with chronic HF, with elevated cholestatic enzymes and transaminases in 19.2% and 8.3%, respectively.\textsuperscript{9}

Elevation of the serum bilirubin concentration occurs in up to 70% of HF patients and is the most common abnormal biochemical liver test in patients with HF.\textsuperscript{10} Contributing factors for elevated bilirubin levels may include bile canalicular compression/obstruction due to distended hepatic veins and congested sinusoids, hepatocellular dysfunction, haemolysis, and concomitant medications. Previous studies found a linear correlation between serum bilirubin...
levels and right atrial pressures. No such correlation was demonstrated with cardiac output.\textsuperscript{11,12}

In summary, abnormal liver biochemical findings are common in both chronic and acute decompensated HF patients but show substantially variability between studies. Large differences in the total number and types of selected biochemical tests and differences in the population investigated (acute vs. chronic HF; use of contemporary medical therapy) across the studies may explain most of such variability. However, the reported prevalence of elevated levels of serum transaminases seems to be substantially higher in patients with ADHF, indicating a higher number of patients with decreased cardiac output and impaired organ perfusion resulting in hepatocellular damage compared with chronic HF patients.

**What is the prognostic relevance of abnormal liver biochemistry in heart failure?**

Abnormalities of biochemical liver tests including bilirubin, AST, GGT, and AP are associated with mortality. After multivariate adjustment, AST and bilirubin remained predictors of death in patients with chronic HF.\textsuperscript{13} Data from the CHARM trial in patients with chronic HF show that elevated total bilirubin is a strong and independent predictor of adverse outcome for both the composite outcome of cardiovascular death or HF hospitalization and all-cause mortality.\textsuperscript{8} Liver enzymes indicating cholestasis are more frequently elevated in chronic HF, and elevated AP and GGT are predictive of adverse outcome.\textsuperscript{9}

In a large analysis of ADHF patients, lower baseline albumin and elevated total bilirubin were associated with higher rates of all-cause mortality.\textsuperscript{7} In this post-hoc analysis of the SURVIVE trial, elevated serum transaminases predicted mortality at 1 month, and the presence of any elevation of biochemical liver tests predicted long-term mortality. The independent predictive value remains unknown. However, changes in liver tests parallel brain natriuretic peptide (BNP) changes. This may suggest that most of the predictive relevance of elevated serum transaminases could be lost if the severity of the underlying heart disease is accounted for. Thus, elevated liver enzymes may indicate that an organ ‘suffers from HF’, but it remains to be determined if the liver itself plays an important role in modulating the clinical course of ADHF patients.

**Which biochemical liver tests in patients with heart failure?**

In the post-hoc analysis of the SURVIVE trial, the authors measured ALT, AST, and AP. About half of the patients with abnormalities in liver biochemical tests had isolated abnormal transaminases. The other half had either isolated abnormal AP or a combination of elevated AP and transaminases.\textsuperscript{6} Elevations in transaminases usually result from ischaemic injury due to decreased cardiac output and correlate with hepatocellular damage and necrosis preferentially in zone 3 (Figure 2). Accordingly, clinical signs of hypoperfusion were associated with abnormal transaminases in the SURVIVE trial. In contrast, elevations of the serum AP correlated with signs of systemic congestion and with right-sided filling pressures.\textsuperscript{6}

Previous findings from chronic HF patients have demonstrated that bilirubin is independently associated with morbidity and mortality.\textsuperscript{8} Similar results have been shown in ADHF patients with low baseline albumin and elevated total bilirubin correlating with higher rates of all-cause mortality.

Unfortunately, the SURVIVE trial did not obtain information on serum bilirubin concentrations and missed the opportunity to confirm previous findings and to estimate a correlation between bilirubin and AP in ADHF patients.\textsuperscript{6} Additionally, we do not have any information from this report of the SURVIVE trial about serum albumin levels and coagulation factors.

**Abnormal liver biochemical tests: surrogate of haemodynamic disturbances or sustained impairment of hepatic function?**

In patients with ADHF, elevated liver enzymes decreased substantially from baseline to follow-up. The rate of improvement shows a large variability between markers. AP\textsuperscript{6} and bilirubin\textsuperscript{7} decrease progressively within a few days. In contrast, serum transaminases decreased progressively over weeks.\textsuperscript{6,7} A clear correlation between transaminases and markers reflecting cholestasis could not be demonstrated. In contrast to acute haemodynamic disturbance, only prolonged or chronic perfusion abnormalities may result in bridging fibrosis and cirrhosis that may then result in impaired
hepatic function with decreased synthesis of coagulation factors and albumin. The rate of decrements in biochemical liver parameters did not correlate with outcome.6 Thus, abnormalities in biochemical liver tests in patients with ADHF with no history of primary significant liver disease or acute hepatic failure primarily reflect acute haemodynamic disturbance and do not correlate with sustained hepatic dysfunction.

**Cardio-hepatic interaction or cardio-hepatic syndrome as a discrete, recognized state?**

Renal dysfunction commonly occurs in patients with chronic HF and in individuals suffering from ADHF.14 Pathophysiologically, there is a complex interaction between haemodynamic abnormalities, impaired renal perfusion, elevated venous pressure, and activation of neurohumoral systems. Acute or chronic renal dysfunction including azotaemia and oliguria may result in worsening cardiac function in HF patients. Currently, there is no evidence to suggest that there might be a similar interaction between the liver and the heart. Thus, elevated liver enzymes in individuals with HF are surrogates of haemodynamics15—at least in most cases. Further prospective studies have to elucidate the exact mechanisms of the liver—heart interaction.

In conclusion, elevated liver enzymes are common in patients with HF. The specific patterns of elevated liver tests differ between patients with chronic and acute decompensated HF and are surrogates of the type of haemodynamic alterations. Elevations of liver biochemical tests in HF patients are associated with poor outcome. However, the exact mechanisms of the liver—heart interaction and the role of abnormalities of biochemical liver tests in modulating the clinical course of ADHF patients remain to be determined.

**Conflict of interest:** none declared

### References