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Liver stiffness measurements and short-term survival after left ventricular assist device implantation: A pilot study

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BACKGROUND: Hepatic dysfunction can contribute to the clinical outcome of patients with end-stage chronic heart failure (HF). This pilot study evaluated the importance of liver stiffness (LS) measurements by acoustic radiation force impulse (ARFI) imaging elastography in patients with end-stage chronic HF who underwent left ventricular assist device (LVAD) implantation.

METHODS: The study enrolled 28 patients (23 men), mean age of 54 ± 11 years, with end-stage chronic HF selected for LVAD implantation. At baseline, all patients received LS measurements using ARFI elastography. Hepatic venous pressure gradient measurements and transjugular liver biopsies were performed in 16 patients. Liver stiffness was measured 21 days (Follow-up 1, $n = 23$) and 485 ± 136 days (Follow-up 2, $n = 13$) after LVAD implantation. Patients were classified according to their baseline LS into Group I (low baseline LS [no significant fibrosis = Metavir F < 2]) or Group II (high baseline LS [significant fibrosis = Metavir F ≥ 2]).

RESULTS: LS at baseline was higher in Group II than in Group I ($p < 0.001$) and decreased significantly after LVAD implantation (Follow-up 1, $p = 0.002$; Follow-up 2, $p = 0.002$). Baseline LS correlated with liver fibrosis ($p = 0.049$) and central venous pressure ($p = 0.001$). Non-survivors showed higher LS ($p = 0.019$), bilirubin ($p = 0.018$), Model for End-Stage Liver Disease score ($p = 0.001$), and liver fibrosis ($p = 0.004$) compared with the survivors. In the univariate analysis, LS was a significant factor ($p = 0.017$) in predicting survival after LVAD implantation.

CONCLUSIONS: ARFI elastography shows that LS is influenced by central venous congestion and histologic changes of the liver in patients with end-stage chronic HF. LS may predict the outcome in patients after LVAD implantation.

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Patients with end-stage chronic heart failure (HF) who require mechanical circulatory support as a bridge or as destination therapy often present with hepatic dysfunction.[1–3] In addition, most patients develop some degree of hepatic dysfunction after LVAD implantation, which represents the

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surrogate factor affecting survival.[1–3] Despite LVAD implantation, 94% of patients develop progressive liver disease with higher morbidity and mortality.[1]

Mechanisms of heart-related hepatic dysfunction have, until now, been poorly understood. Several hypotheses illustrate the interrelated pathophysiology in pre-operative hypoxic centrilobular necrosis—represented in the form of hypoxic or ischemic hepatitis—or post-operative intrahepatic cholestasis or the doubled pathology.[1] Hepatic perfusion and the hepatosplanchnic axis are the weakest barriers through which inflammation-related cholestasis is induced. The centrilobular necrosis may progress in some patients to variable stages of liver fibrosis and up to cardiac cirrhosis.[4]

The liver biopsy specimen is the gold standard in diagnosing pathologic changes in patients with liver disease. However, in addition to the invasiveness and cost, it has other limitations.[5–7] Several non-invasive imaging methods —for example, transient elastography and acoustic radiation force impulse (ARFI) imaging—are able to evaluate the stage of liver fibrosis by measuring liver stiffness (LS), and may therefore replace the liver biopsy.[8] A higher LS is associated with higher stages of liver fibrosis. ARFI is a novel ultrasound-based elastography method that is integrated in a conventional ultrasound machine. ARFI can be performed using conventional ultrasound probes during the abdominal ultrasound examination.[9]

Several meta-analyses have shown that ARFI has high diagnostic accuracy in staging severe fibrosis and liver cirrhosis.[8–10] According to the Metavir scoring system, the optimal cutoff is 1.35 m/sec ($F \geq 2$) for the diagnosis of significant fibrosis, 1.61 m/sec ($F \geq 3$) for severe fibrosis, and 1.87 m/sec ($F = 4$) for liver cirrhosis.[10] The area under the summary receiver operating characteristic curve is 0.86 for $\geq$ F2, 0.89 for $F \geq 3$, and 0.93 for $F = 4$. The median velocity of a normal liver is 1.10 m/sec.[11]

Irrespective of liver fibrosis, several factors may influence the diagnostic performance of liver elastography in staging liver fibrosis, including necroinflammatory activity,[12–14] the fasting state,[15,16] the physical properties of the ultrasound array and positioning of the region of interest (ROI),[17] and biliary obstruction.[18–22] One study showed that LS by transient elastography is a direct function of the central venous pressure (CVP) in patients with congestive HF and decreases under diuretic therapy.[4] However, LS remained high in patients with associated fibrosis and corresponding cardiac cirrhosis; thus, LS is influenced by the coupled cardiac congestion and liver fibrosis.[4]

In this critically ill group, a non-invasive method for differentiating patients with chronic from acute (reversible) liver dysfunction due to passive congestion can be of value for predicting the risk process for LVAD candidates. Therefore, the aim of this prospective study was to evaluate, using ARFI elastography, changes in LS in patients with end-stage chronic HF who underwent LVAD implantation.

Methods

This prospective study was performed in compliance with the Declaration of Helsinki and with approval from the local Ethics Committee. Written informed consent was obtained from all patients. The study evaluated 61 patients indicated for LVAD implantation due to chronic HF. Of those patients, 33 did not fulfil the inclusion criteria because an ARFI measurement was not feasible due to their severe illness or death before LVAD implantation. Thus, 28 patients were enrolled upon referral to the Endoscopy Unit of the Gastroenterology, Hepatology and Endocrinology Department, Hannover Medical School, Germany, from July 2012 to December 2013. Data were obtained from patients' records at the Hannover Medical School.

Before LVAD implantation, all patients underwent a baseline ultrasound examination of the liver, including LS measurements using ARFI elastography. All patients in this study were candidates for heart transplantation; patients were selected for LVAD support with HeartMate 2 (Thoratec) or HVAD (HeartWare International) at a stage of the disease where death or permanent end-organ damage was likely to occur before a donor heart was available. The study excluded patients with known liver disease, hepatocellular carcinoma, obstructive cholestasis, or acute liver failure. Patients who did not satisfy the quality criteria of ARFI measurement at baseline were excluded.

At baseline, all patients underwent pulmonary arterial catheterization (Swan-Ganz catheter) to measure the pulmonary artery systolic pressure (PASP), pulmonary wedge pressure (PWP), right ventricular systolic pressure (RVSP), and CVP.

Follow-up period

Patients were prospectively followed up clinically and with ARFI elastography after LVAD implantation. The first follow-up was performed after 21 days ($n = 23$). A second follow-up to reveal primary liver regeneration[23] was performed at a mean of 485 $\pm$ 136 days ($n = 13$) for patients who had survived at least 1 year after LVAD implantation. Patients were grouped according to the results of LS measurements before LVAD implantation: Group I, $<$ F2 (mean LS $<$ 1.35 m/sec, $n = 4$); group II, $\geq$ F2 (mean LS $\geq$ 1.35 m/sec, $n = 24$).[10]

Laboratory parameters

Hemoglobin, platelet count, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), glutamate dehydrogenase (GLDH), alkaline phosphatase (ALP), γ-glutamyl transferase (γ-GT), cholinesterase, bilirubin, albumin, creatinine, brain natriuretic peptide (BNP), and hyaluronic acid (HA) were analyzed and recorded. The international normalized ratio was not considered because every patient was receiving anti-coagulation therapy.

Ultrasound examination

Ultrasonographic hepatic examinations were routinely performed in all patients at baseline and in Follow-up 1 and 2 by a Deutsche Gesellschaft für Ultraschall in der Medizin (DEGUM) II-III certified physician (www.degum.de) using the C4-1 array (Siemens Acuson S2000, Munich, Germany). The sonographer was blinded to all clinical data.

All patients were required to fast overnight before the procedure. Patients were examined while supine during quiet respiration. Sonographic signs of right-sided HF were evaluated by measuring the diameter of the inferior vena cava and its associated respiratory fluctuation. Hepatic congestion was evaluated by measuring diameter, flow direction, flow velocity, and flow volume in the hepatic and the portal veins. Measurements of the