Arterial hypertension as an uninvited player in hepatic stiffness?

Vlad Ratziu,1 Dominique Valla,2,3 and Pierre-Emmanuel Rautou2,3

1Service d’hépatogastroentérologie, Institute for Cardiometabolism and Nutrition, Hospital Pitié Salpêtrière, INSERM UMR S_938, Université Pierre et Marie Curie, Paris, France; 2INSERM, UMR-970, Paris Cardiovascular Research Center-PARCC, Université Paris Descartes, Sorbonne Paris Cité, Paris, France; and 3Service d’hépatologie, DHU Unity Hôpital Beaujon, APHP, Université Denis Diderot-Paris 7, Sorbonne Paris Cité, Clichy, France

CIRRHOSIS IS THE MAIN CAUSE of death in patients with liver diseases. Cirrhosis occurs after many years of fibrosis progression, a slow process that is highly variable among individual patients. It is therefore critical to stage liver fibrosis to gain insight into prognosis and to make therapeutic decisions, most of which are based on the risk of fibrosis progression. Like all invasive procedures, liver biopsy has substantial limitations: impossible to use in the large number of patients at risk, impractical for repeated use for monitoring, but also intrinsically limited due to sampling variability.

Transient elastography is an imaging-based method introduced a decade ago as a cheap, innocuous, and noninvasive replacement of liver biopsy. It measures the velocity of shear waves propagating through the liver, a physical variable that gives an indirect indication of the liver “stiffness”: the higher the stiffness, the faster the velocity of returning shear waves. The velocity is thus converted into a liver stiffness measurement (LSM) (ranging from 2.5 to a capped 75-kPa upper limit). Many studies, most of them in chronic hepatitis C, have shown a good correlation between liver fibrosis histological stages and LSM values, with a good diagnostic performance for advanced fibrosis and an excellent one for cirrhosis (20). The prognostic value of LSM for cirrhosis complications and for liver-related mortality has also been amply demonstrated (11, 22). Thus transient elastography became a very popular and trusted method for the assessment of the fibrosis stage in clinical practice. To a certain extent it replaced biopsy in therapeutic trials and clinical practice guidelines (6) and is now accepted for use by the Food and Drug Administration. Historically, the vibration-controlled transient elastography delivered by the Fibroscan device (Echosens, France) was the first implemented and most validated method (5). Other methods followed, all of them based on the principle of elastography (4, 18).

The trouble with the concept of hepatic stiffness is that it is not entirely clear what it represents. Stiffness is commonly defined as the resistance of the liver tissue to deformation and it was therefore assumed that liver fibrosis is largely the main determinant of liver stiffness. However, there are clinical situations where the liver is nonfibrotic, yet LSM values are very high. Hepatic vascular congestion can increase LSM values in the cirrhotic range, yet when blockade of the venous outflow is relieved, values go down dramatically (10, 12). The same is true for hepatic biliary congestion, as shown in animal studies with bile duct obstruction (13). Hepatic inflammation also, whether acute or chronic (1, 19), substantially disrupts liver stiffness and even moderate elevations of aminotransferases, insofar as they reflect a necroinflammatory process, should alert to increased LSM values. In fact, any process that modifies hepatic viscoelastic properties can affect LSM: food intake through increased postprandial splanchnic blood flow, liver fat (16) or steatohepatitis (9). Antiviral therapy results in a sharp decline in LSM in the short term, a time frame compatible with the control of viral replication and improvement in necroinflammation but not with meaningful fibrosis reversal (8). Even alcohol withdrawal can result in a significant reduction in liver elastometry, when measurements are made 1 wk apart (21). Clearly, not all livers that are stiff are fibrotic, and understanding the limitations of liver stiffness as a fibrosis surrogate is important in clinical practice.

Under physiological conditions the liver receives two-thirds of the blood flow through the portal vein and one-third through the hepatic artery. However, in advanced fibrosis and cirrhosis, the fraction of liver perfusion contributed by the hepatic artery increases. Some studies have documented a direct relation between the increase in hepatic arterial blood flow and increased elastometry in patients with cirrhosis subjected to a meal ingestion (3). However, it is not known whether increased systemic arterial pressure results in increases in liver stiffness.

To address this issue, Piecha et al. (17) set up a series of elegant experiments in rodents to find out whether an increase in arterial pressure contributes to liver stiffness. They used a miniaturized Fibroscan probe that was placed directly on the surface of the liver and was calibrated for the higher breathing and heart rate of rodents. To increase arterial pressure they perfused epinephrine and norepinephrine in normal rats and proceeded to serial monitoring of hemodynamic parameters and of liver stiffness. Upon perfusion of epinephrine, the mean arterial pressure (MAP) nearly doubled and this was closely followed by a doubling in liver stiffness. In contrast, a late and only minimal increase in portal pressure was evidenced with an unchanged caval pressure; this argued against hepatic congestion as an explanation for the increased liver stiffness in this rat model. Changes were qualitatively similar with norepinephrine. Dobutamine, which increased heart rate but reduced MAP, had no effect on liver stiffness. Volume expansion by portal or caval infusion of saline that left MAP unchanged did not modify liver stiffness either.

The authors went on to study whether these changes in liver stiffness induced by arterial pressure would still be noticeable in the fibrotic liver, where baseline stiffness is already increased. They used the thioacetamide toxic model of liver fibrosis, which after 8 wk increased liver stiffness from 3.8 to 9.7 kPa, an increase within the range of advanced, bridging fibrosis in humans. Strikingly, the increase in liver stiffness upon epinephrine infusion in the fibrotic liver was even higher than that obtained in the normal liver: a 2.7-fold increase from 9.5 to 26 kPa vs. a 1.9-fold increase, from

Address for reprint requests and other correspondence: V. Ratziu, 47 Bd. de l’Hôpital, Paris, France 75013 (e-mail: vlad.ratziu@inserm.fr).
4.1 to 7.8 kPa, respectively. Hence, liver fibrosis exacerbated the increase in liver stiffness induced by vasoconstrictive agents. In animals with liver fibrosis, a reduction in MAP (obtained via a nitric oxide vasodilator agent) resulted in a reduction in liver stiffness, thus further strengthening the demonstration that the increase in arterial pressure per se is sufficient for increasing liver stiffness.

Interestingly, the translational aspect of this study suggested the relevance of these findings in humans. Healthy volunteers engaged in an acute and intense physical exercise that increased the MAP. There was a small but significant, and, remarkably, dose-related and reversible increase in liver stiffness, together with the increase in arterial pressure. At the highest level of exercise, a third of healthy volunteers had increased liver stiffness values compatible with bridging fibrosis.

Altogether, these animal and human data suggest that an increase in arterial blood pressure augments liver stiffness, resulting in an overestimation of the fibrosis stage when using elastometry-based methods. This striking sensitivity of hepatic elastometry to changes in arterial pressure is exacerbated in the fibrotic liver, which is important to know in clinical practice. Nonalcoholic steatohepatitis, currently the most common cause of chronic liver disease and a major cause of liver fibrosis, often occurs in patients with arterial hypertension that is not always well controlled by antihypertensive medications. The clinical impact in patients with cirrhosis is, on the other hand, more difficult to evaluate and probably more variable on an individual basis. Indeed, in cirrhosis there is an increase in the fraction of arterial blood supply into the hepatic circulation and therefore, potentially, a higher impact of changes in arterial pressure than in the normal or slightly fibrotic liver; however, cirrhotic patients also develop systemic hypotension. Other complex hemodynamic alterations, such as a hyperkinetic circulation and a substantial shunting of hepatic flow bypassing the liver, occur at the cirrhotic stage with a variable overall impact on sinusoidal pressure. Unfortunately, the current study by Piecha et al. (17) could not measure changes in cardiac output or regional blood flow and their relationship to liver stiffness.

Some caution in interpreting the results of this study is required. It would be important to understand whether there is a tonic relationship between liver stiffness and arterial pressure, or if there is a threshold effect or a plateau effect. Moreover, there is still a missing link between arterial pressure and liver stiffness, particularly since the authors did not measure wedged hepatic venous pressure, a surrogate of sinusoidal pressure, or hepatic interstitial pressure. Importantly, in the current experiments, arterial hypertension was induced by epinephrine and norepinephrine, that can both induce intrahepatic vasoconstriction (2). The observed increase in liver stiffness might thus be due to a direct effect of epinephrine and norepinephrine on liver vasculature rather than to arterial hypertension itself. It would have been informative to confirm these findings by using other hypertensive agents such as renin, angiotensin, or vasopressin. Moreover, in an untrained healthy individual, acute exercise increases central venous pressure, a condition known to augment liver stiffness (7, 12, 14). The observed elevation of liver stiffness in humans during physical exercise might thus result from an elevation of the central venous pressure rather than of the arterial pressure.

While it is tempting to speculate that acute or transient increases in arterial pressure, some possibly caused by stressful situations or external conditions, can induce higher LSM values and therefore account for part of the variability documented in serial LSM measurements (15), the effect of chronic arterial hypertension remains to be determined. Clearly, this study should now provide the rationale for measuring the confounding effect of chronic arterial hypertension on hepatic elastometry values. The work by Piecha et al. (17) raises challenging questions but also helps us better understand the complexity of hepatic stiffness as a physiological concept.

REFERENCES


