Supplemental Tables

Supplemental Table 1 Various etiologies of liver cirrhosis and their association with liver stiffness and AST/ALT ratio

Disease category	Cause	Example	LS	AST/ALT
Inflammatory liver diseases	Viral	HCV	increase	< 1
		HBV	increase	< 1
	Parasitic	Schistosomiasis	increase	< 1
	Genetic	Hemochromatosis	increase	< 1
		Mb. Wilson	increase	
	autoimmune	Autoimmune hepatitis (AIH)	increase	< 1
		Sarcoidosis	increase	
	metabolic	NASH	increase	< 1
	toxic	ALD	increase	> 1
		CCl_4	increase	> 1
		TAA	increase	> 1
Hemodynamic		Congestion	increase	> 1
		Portal vein thrombosis	?	
		Portal vein ligation/chronic	?	
		Budd Chiari Syndrome	increase	
		Sinusoidal obstruction syndrome	increase	
Cholestatic				
		Mechanic cholestasis	increase	
		Primary biliary cirrhosis (PBC)	increase	
		Primary sclerosing cholangitis (PSC)	increase	

End-stage cirrhosis (arterialization)	all	all	High	> 1

All liver pathologies cause LS elevation that precedes fibrosis. Endstage cirrhosis is characterized by low transaminase levels with an AST/ALT level > 1 which is, according to SPH, due to irreversible arterialization (see also Figures 6 and 7).

Supplemental Table 2 Established and preliminary observations (general or liver-related) in support of the SPH Part I and II

Observation in support of SPH/Part I: Pressure causes matrix deposition (Initiation)	**Ref.**
Irrespective of cirrhosis, LS can be drastically but reversibly elevated under various pressure-related conditions such as inflammation, cholestasis and congestion.	[3,25]
Pressure-related elevation of LS precedes the development of fibrosis.	[3,26,27]
An elevated LS is an increased risk factor for fibrosis progression such as LS elevation in response to alcohol or HCV infection. In contrast, patients do not develop fibrosis if no LS elevation has been observed during HCV infection or during alcohol consumption.	[22]
In short-term liver disease, LS improves after elimination of liver pathology e.g. after clearance of HCV, weight reduction or alcohol withdrawal.	[28,29]
A normal LS excludes chronic liver disease and liver pathology.	[22]
Comparable stiffness values are observed in patients with liver disease and in cellular studies inducing a pro-fibrogenic response.	See Figure 10
The liver is anatomically localized at the so-called indifferent pressure point (about 10 cm below the diaphragm). According to SPH, this would guarantee a minimum change of pressure-mediated LS elevation due to changes in body posture. It would also explain why lowest LS values are found in horizontal body position with normal	[54]

breathing frequency.	
Acute forms of hepatitis (e.g. acute hepatitis A or acute autoimmune hepatitis with short flair show an limited LS elevation of up to 30 kPa for a limited time of 3-5 weeks which apparently do not cause fibrosis progression.	[56]
Inflammation in the lobular zone (ALD) translates into higher LS elevation as compared to a portal-tract-pronounced inflammation (HCV infection) [45]. This can be explained by more efficient SP elevation in ALD.	[45,83,84]
Likewise, in patients with large esophageal varices, mean LS is higher in lobular-pronounced alcoholic cirrhosis (47.2 kPa) as compared to cirrhosis due to portal-tract-pronounced viral hepatitis (19.8 kPa).	[85]
It is well known that small animals do not develop fibrosis e.g. in response etiology-mimicking models such as high fa feeding or alcohol-exposure despite transaminase elevation and steatosis. This could be due to the lobularized livers in rats or the mere small size of mice livers not allowing to accumulate the stretch forces as compared to large human or pig livers. Indeed, first studies indicate that small liver show not the same LS elevation in response to alcohol and congestion.	[22,27,86]
The mechanistic effects of non-selective beta blockers (NSBB) on patients with liver fibrosis is still not completely settled. NSBB not only decrease the incidence of variceal bleeding and ascites but also improve survival of patients with cirrhosis. According to newer recommendations, NSBB should not be discontinued. According to SPH, NSBB could decrease SP via reduction of the arterial pressure	[76,77]

and hepatic flow both via the hepatic artery and the splanchnic arteries.	
Decrease in plasma noradrenaline by the alpha 2-agonist clonidine caused significant reductions of cardiac output (-17.4%), mean arterial pressure and hepatic venous pressure gradient.	[87]
Carriers of PNPLA3 GG genotype have an increased LS in response to alcohol. After detoxification, LS decreases much slower in GG carriers most likely due to delayed resolution of inflammation. Moreover, protected CC carriers show no change of LS in response to alcohol withdrawal despite changes in inflammation/AST levels.	[55]
Hypervitaminosis A causes non-inflammatory perisinusoidal fibrosis and massive accumulation of HSC mostly due to impairment of blood flow.	[88,89]
The venous wall of operative dialysis shunts (operative arterio-venous fistula built from an arm vein) rapidly transforms into a thick arterial wall (commonly termed 'arterialization' of the dialysis shunt).	[22]
servations in support of SPH/Part II: Fibrosis/elevated SP causes arterialization leading to continued SP elevation (Perpetuation)	**Ref.**
Hepatic arterial flow is already elevated in liver diseases before the onset of fibrosis.	[58]
Hepatic arterial flow becomes predominant in cirrhotic liver and further increases with cirrhosis Child-Pugh stage.	[44]

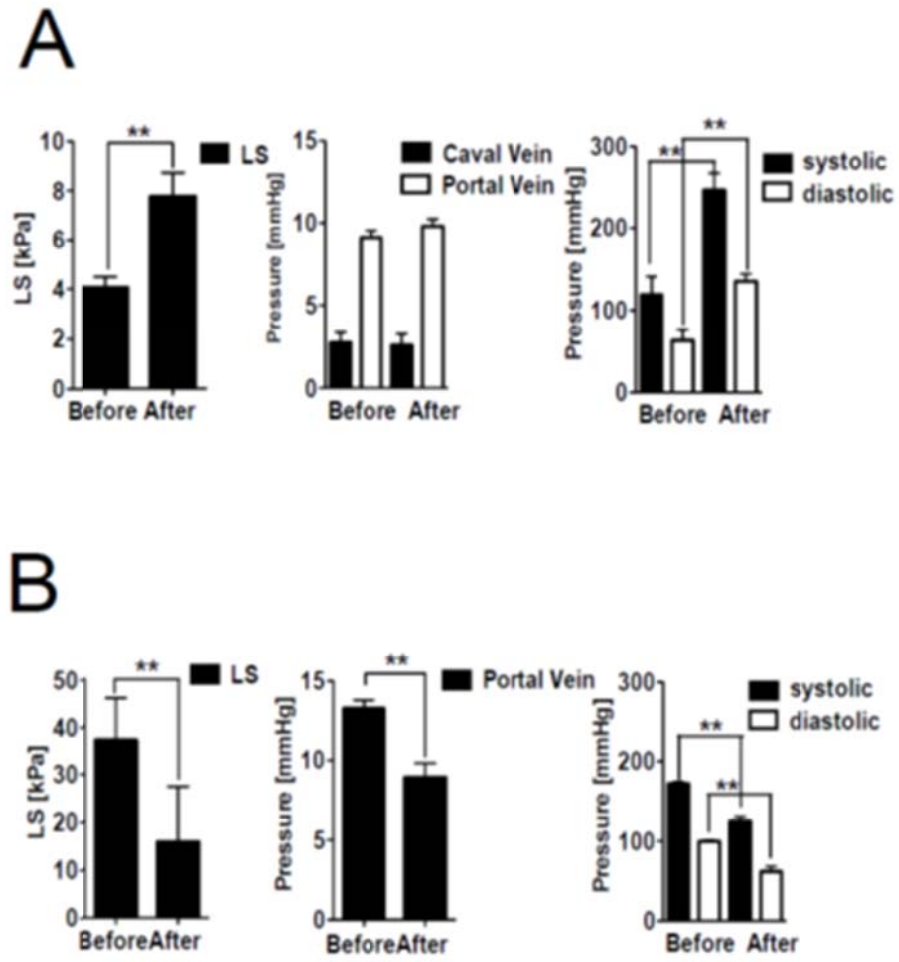
In patients with complete reversed portal flow, the wedged hepatic vein pressure is higher than the portal pressure. This clearly points to a predominant arterial origin for this reversed perfusion.	[39,40,42]
Arterio-portal spleen shunts cause portal hypertension without elevated LS and fibrosis. It suggests compensation of elevated portal inflow by the HABR with a reduced arterial inflow. Recent observations indicate that a drastic increase of portal flow (e.g. during ligation of esophageal varices) immediately leads to a increase of LS within minutes.	[22]
More drastic LS elevation is observed in patients with liver cirrhosis in response to food intake or alcohol consumption as compared to non-cirrhotics. This underscores the fact that in patients with manifest cirrhosis most of the hepatic perfusion is operated by the hepatic artery. In contrast, increased portal flow e.g. in response to food intake is compensated by a reduced arterial flow in normal livers (HABR).	[45,55,60]
Portal vein ligation also results in liver fibrosis. According to SPH, portal vein ligation causes via HABR a compensatory arterial flow that exposes the sinusoidal bed permanently to high pressure.	[55,77]
Elevation of arterial pressure (e.g. by catecholamines) causes a significant elevation of LS independent of the central venous pressure and portal pressure. These data underline the importance of arterial flow for LS and SP elevation especially in cirrhotic livers with predominant arterial perfusion.	[90]
Decrease of arterial pressure by NO significantly decreases LS in cirrhotic livers (TAA fibrosis model).	[22]

LS is significantly and immediately (within 2-5 min) increased in response to ligation of esophageal varices. These observations demonstrate that such an immediate elevation of portal pressure cannot be fully compensated e.g. by a decrease of arterial flow via the HABR.	[22]

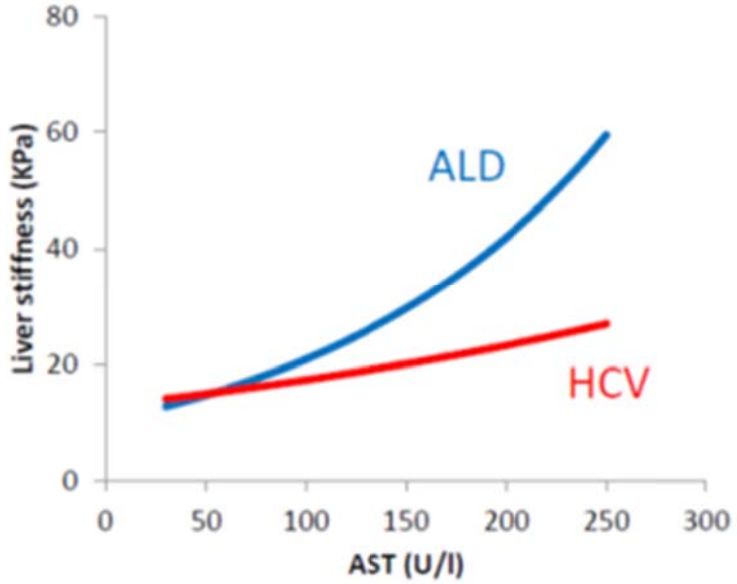
Supplemental Table 3 Start and end of fibrosis progression and relation to sinusoidal pressure hypothesis[91]

Parameters	**Localization of fibrosis at beginning and end for various etiologies**			
Start of fibrosis	Portal	Central	Portal	Central
Bridging at end of fibrosis	Central	Portal	Portal	Central
Example	HCV HBV AIH	ALD NAFLD	Cholestatic liver diseases	Budd Chiari syndrome Cardiac cirrhosis
SP at start of disease	Portal	Pentral	Portal	Central
SP at end stage disease	Portal and central due to arterializati on	Central and portal due to arterialization	Portal to portal	Central to central

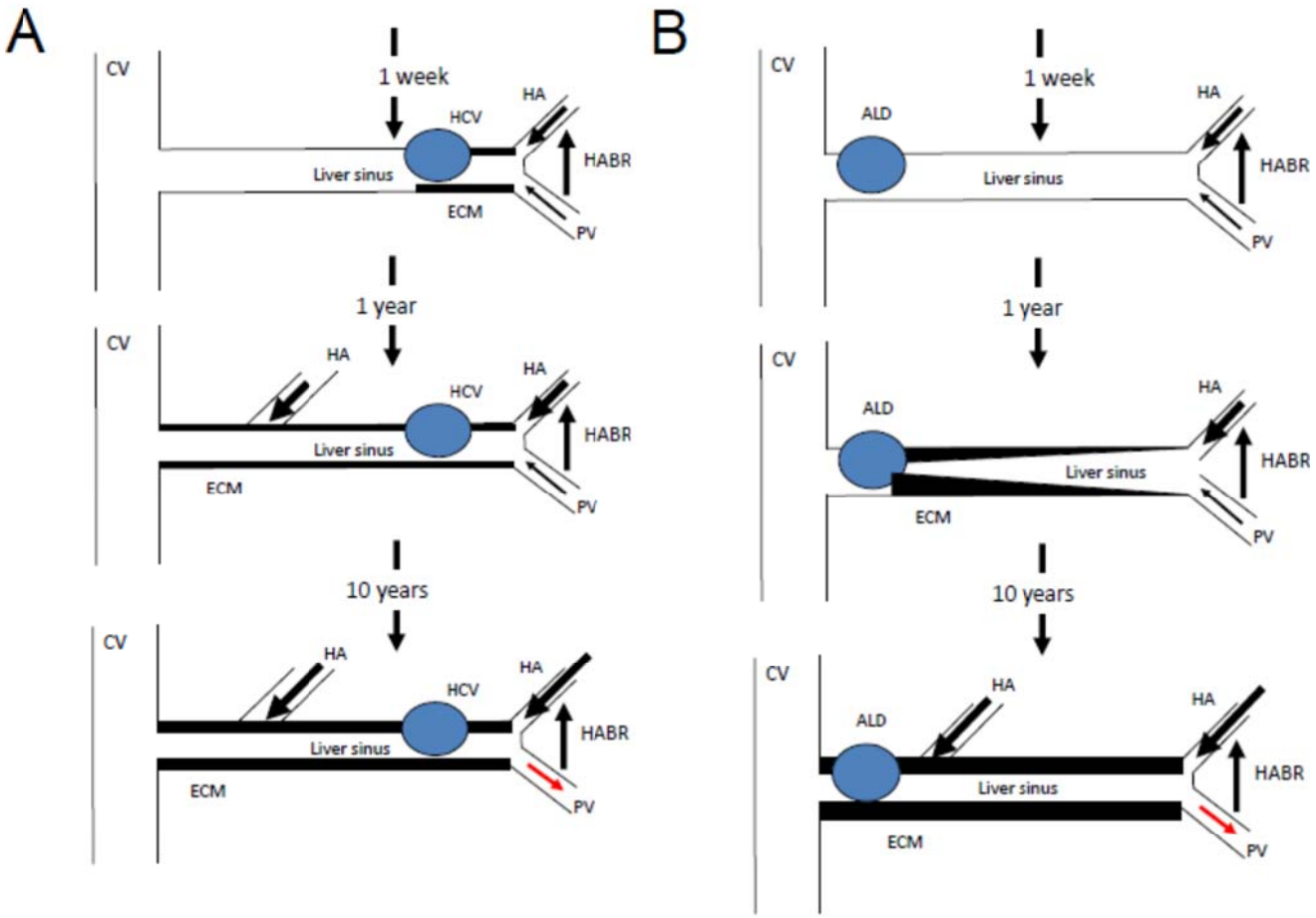
Supplemental Figures



Supplemental Figure 1 LS and pressure measurements in liver-relevant vessels in male Wistar rats using the µFibroscan and Powerlab device (A) in untreated control rats before and after single dose of epinephrine (0.05 mg) *i.v.* injection and **(B)** in six week TAA treated cirrhotic rats before and after NO (0.25 mg) *i.v.* injection. Modified from Ref.[55].



Supplemental Figure 2 Cut-off liver stiffness values for F4 vs F3 fibrosis are shown as a function of median AST levels for ALD and HCV. Cut-off LS values for F4 vs F3 fibrosis increase exponentially as a function of the median level of AST (inflammation). They increase more drastically in lobular-pronounced ALD (blue) as compared to portal-tract localized HCV (red). Data are from Ref.[45]. According to SPH, this could explain the faster progression of ALD starting from the pericentral zone 3.



Suppl. Fig. S3 A

Suppl. Fig. S3 B

Supplemental Figure 3 Potential sequence of pressure-mediated fibrosis formation according to SPH in A) a portal-tract (zone I) pronounced liver disease (chronic HCV infection) and B) a pericentral (zone III) liver disease (ALD). A: In HCV, portal-tract associated inflammation causes increased arterial blood flow with elevated SP in the portal-tract area and accompanied pressure-mediated fibrosis formation. In the presence of continued chronic HCV infection, deposition of extracellular matrix (ECM) increases the vascular resistance, causing further enhanced arterial blood flow *via* the hepatic arterial buffer response (HABR) and other mechanisms that ultimately causes a complete arterialization of the whole liver with permanent pressure elevation, further fibrosis (vicious cycle) and flow reversal in the portal vein. **B:** In contrast to HCV, an even mild inflammation in ALD causes a pressure gradient in the whole sinusoidal bed leading more rapidly to elevation of liver stiffness, arterialization and end-stage cirrhosis**.** Note that SPH also helps to explain hepatofugal portal blood flow (red arrows) as seen in (lower panels). In HCV, fibrosis starts first in the portal areas in contrast to ALD. At later stages, due to arterialization and continued pressure exposure, bridging fibrosis with large fibrous septa

will form in both diseases. Abbreviations: CV, central vein; ECM; extracellular matrix; HA, hepatic artery; HABR, hepatic arterial buffer response; PV, portal vein