

Background and aims

In cirrhosis, liver microvascular dysfunction is the key factor increasing hepatic vascular resistance (HVR) to portal blood flow that leads to portal hypertension. De-regulated inflammatory and pro-apoptotic processes due to chronic injury play a key role in the dysfunction of liver sinusoidal endothelial and hepatic stellate cells (LSEC & HSC). The present project aimed at characterizing the effects of the pan-caspase inhibitor emricasan on the systemic and hepatic hemodynamic, and LSEC & HSC phenotype in a pre-clinical model of advanced chronic liver disease.

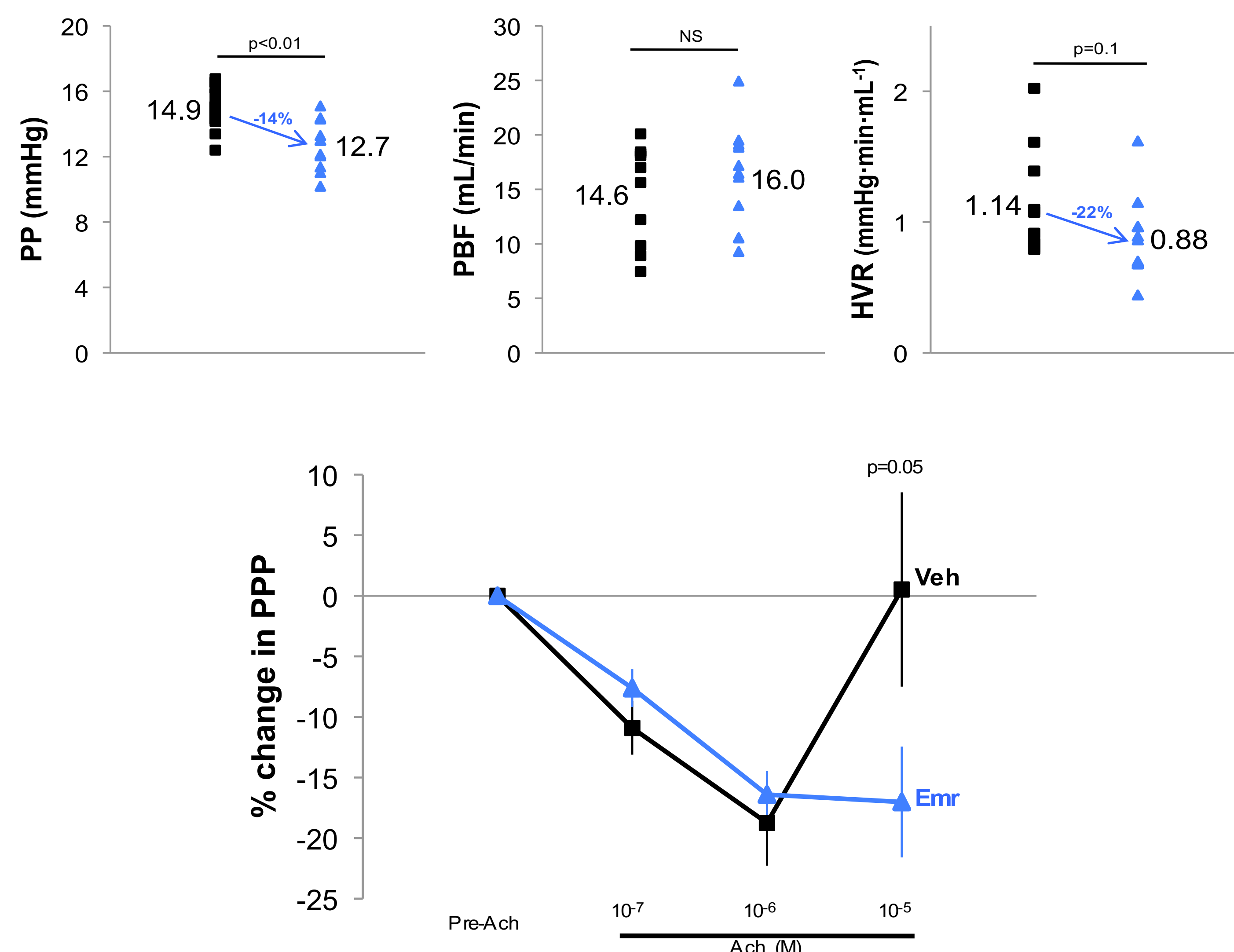
Methods

CCl₄-cirrhotic rats received emricasan (10mg/kg/day, p.o.) or vehicle (carboxymethylcellulose) for 7 days (n=12 per group). Measurements: *in vivo* systemic and hepatic hemodynamic (mean arterial pressure, MAP; portal pressure, PP; portal blood flow, PBF; and HVR), liver function & injury (bile production, AST, ALT, bilirubin), hepatic microcirculatory function (portal perfusion pressure [PPP] response to incremental doses of acetylcholine), inflammation (IL-1 β , IL-6 & TNF- α), phenotype of LSEC (eNOS, vWF, fenestrae porosity) & HSC (α -SMA, desmin and rho kinase [p-moesin/moesin]), and fibrosis (Sirius red & collagen).

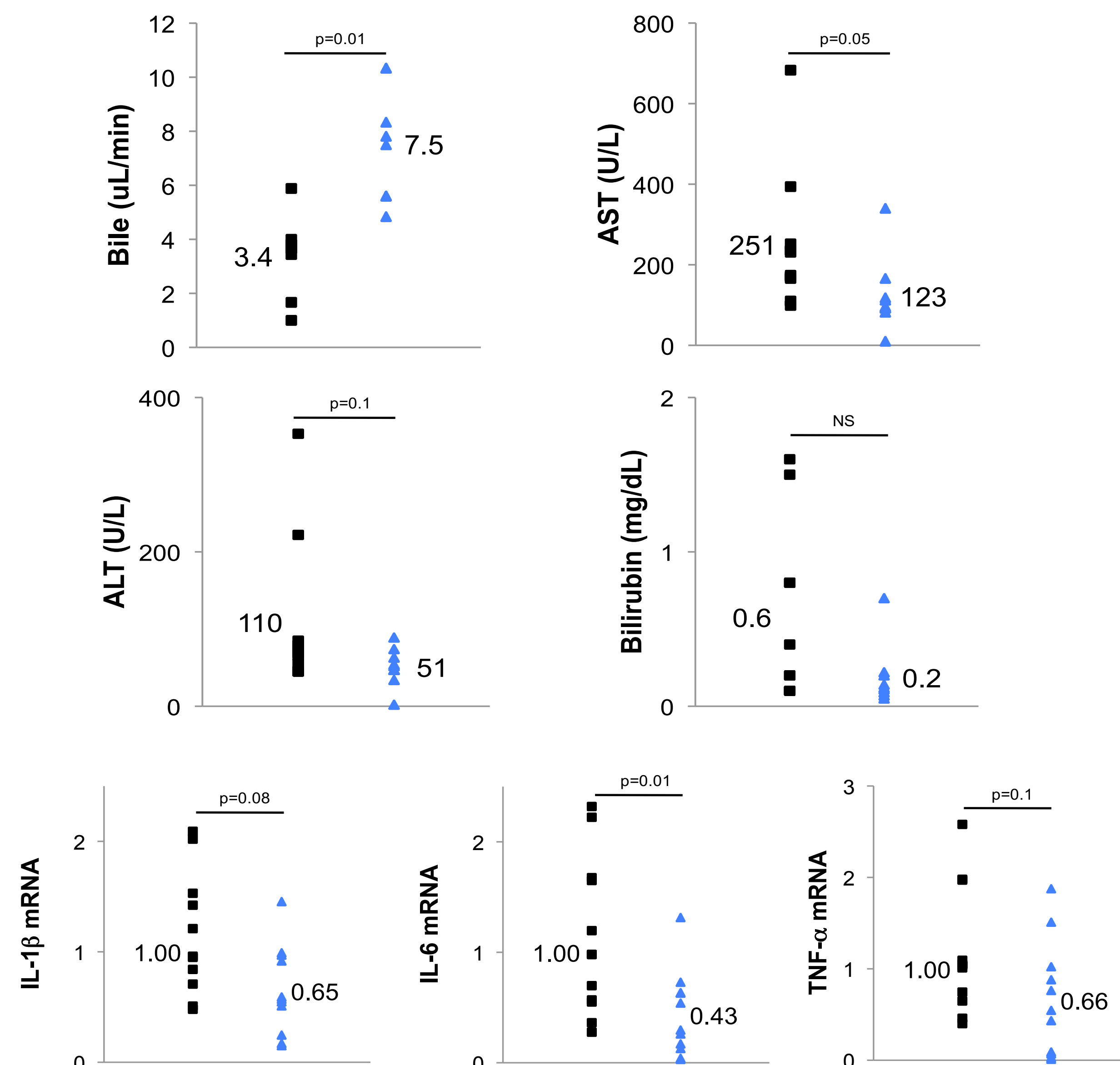
Results

■ Veh ▲ Emr

1- Hepatic and systemic hemodynamic



2- Liver function, injury and inflammation

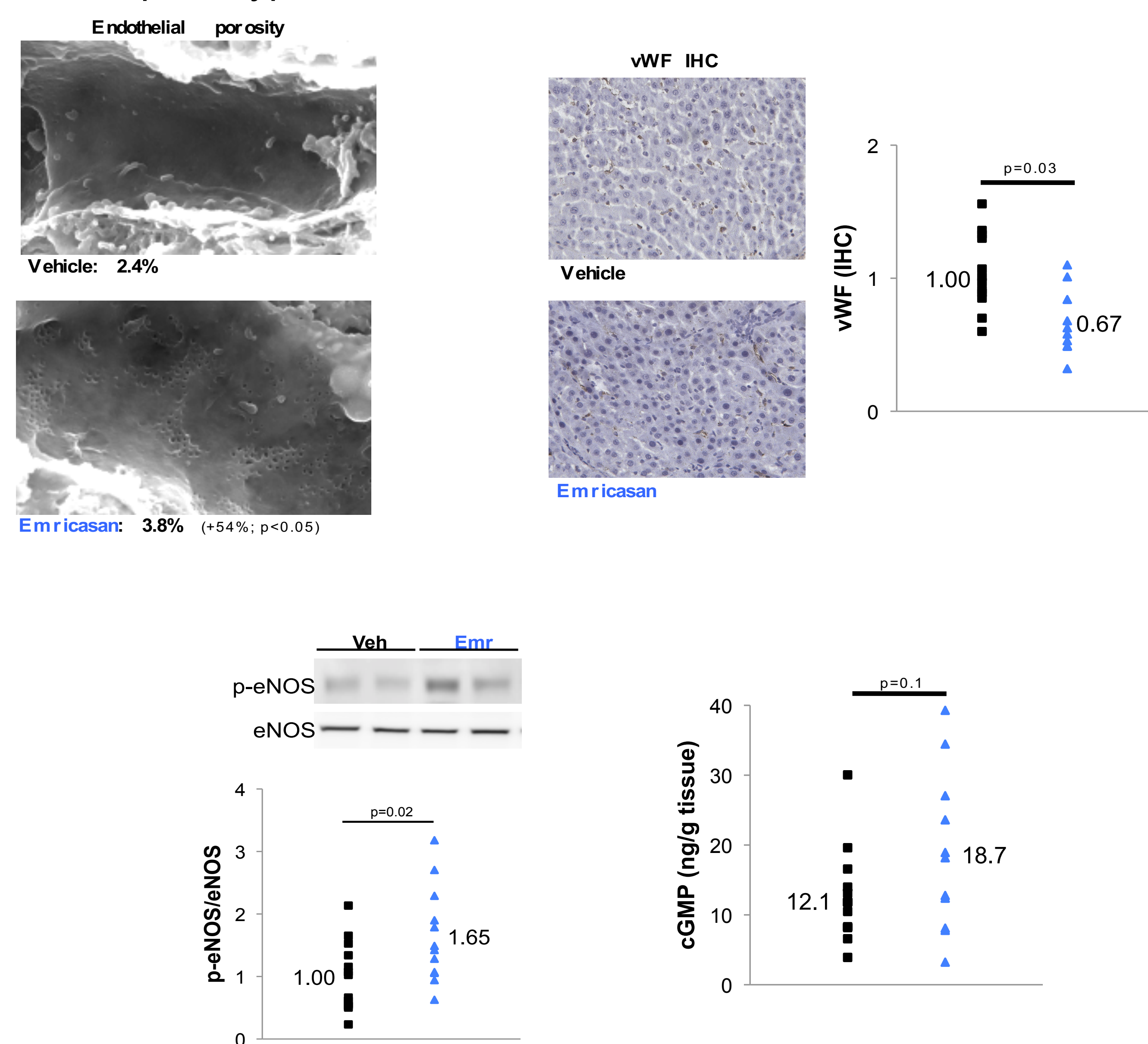


Top, cirrhotic rats receiving emricasan showed significantly lower PP due to a reduction in HVR. No systemic effects were observed.

Bottom, endothelial dysfunction improvement in animals receiving emricasan.

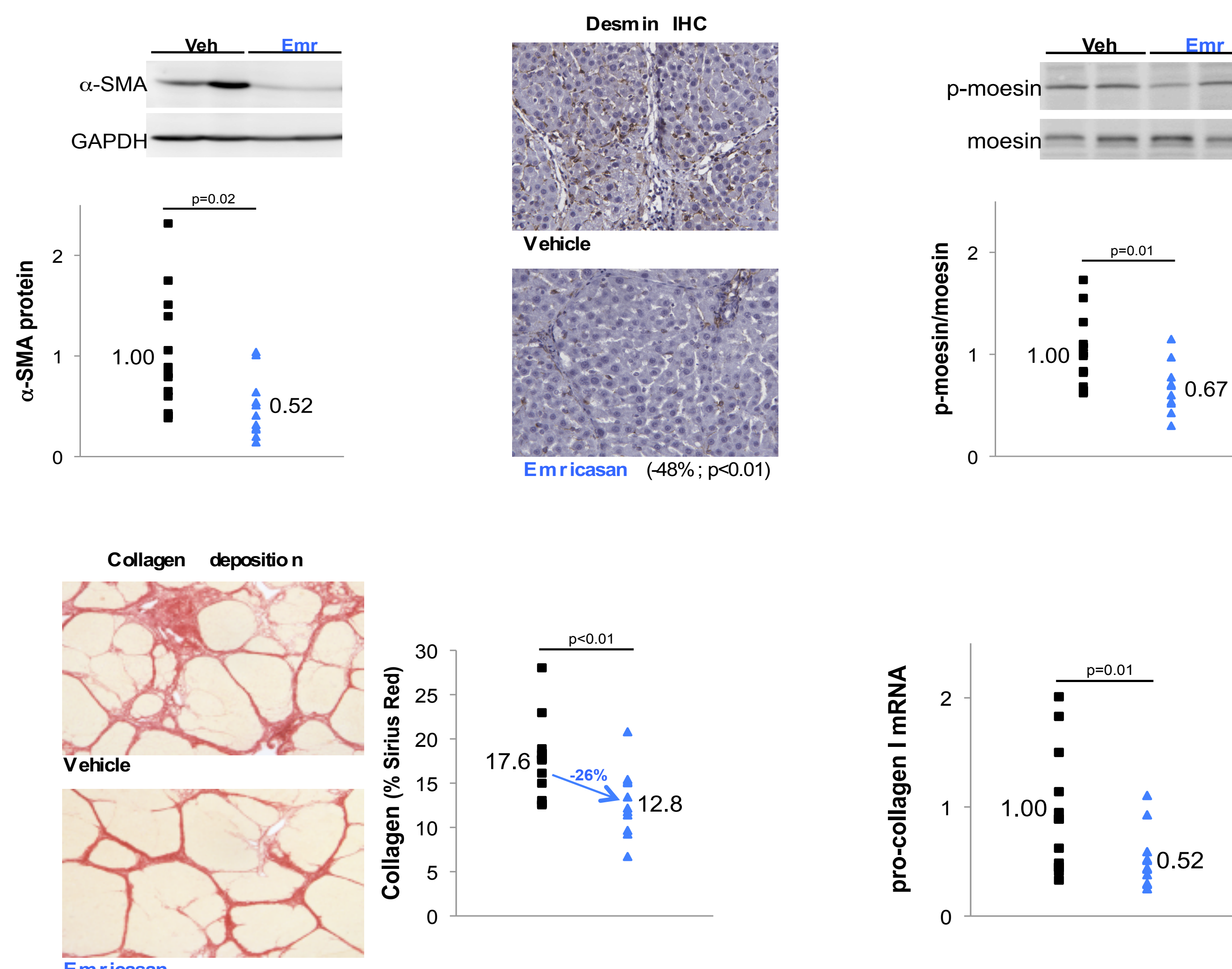
Emricasan-treated cirrhotic animals exhibited better liver function and less liver injury (bile production, transaminases release and bilirubin), which was accompanied by marked anti-inflammatory effects.

3- LSEC phenotype



Cirrhotic rats receiving emricasan exhibited improved LSEC phenotype (fenestrae porosity, sinusoidal vWF expression, p-eNOS and cGMP).

4- HSC phenotype & Fibrosis



Emricasan-treated cirrhotic animals exhibited improved HSC phenotype (α -SMA, desmin and Rho kinase). Global sinusoidal amelioration led to significant reduction on liver fibrosis (collagen expression by Sirius Red and qPCR).

Conclusions

- Emricasan improves liver sinusoidal microvascular dysfunction in a pre-clinical model of advanced cirrhosis, which leads to marked amelioration in fibrosis, portal hypertension and liver function.
- These results encourage its clinical evaluation in the treatment of advanced chronic liver disease.