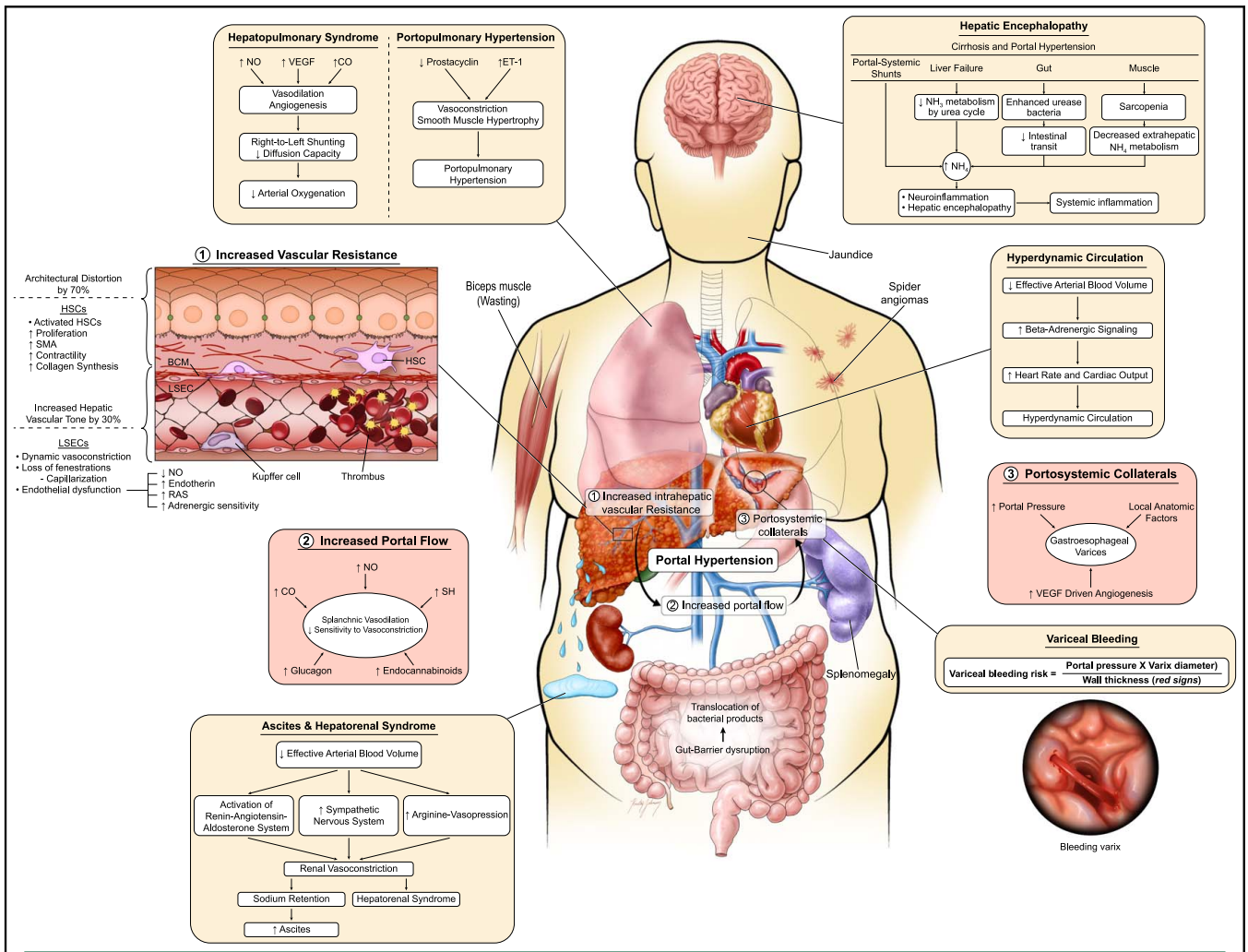

FIGURE 2 Pathophysiology of portal hypertension and related complications. Portal hypertension results from a series of maladaptive responses to chronic liver injury and cirrhosis. Initially, structural mechanisms because of accumulation of fibrous tissue, regenerative nodules, microthrombi, parenchymal extinction, and collapse lead to an increase in intrahepatic vascular resistance (1). In addition to architectural distortion, dynamic sinusoidal vasoconstriction contributes to 30% of the total increase in vascular tone. These structural changes lead to an increased portal pressure gradient; when this reaches values of about 10 mm Hg, it gives rise to formation of portal-systemic collaterals and compensatory splanchnic vasodilation, which, in turn, increases portal blood flow and, consequently, portal pressure (2). One of the first consequences of portal hypertension is the development of portosystemic collaterals, for which vascular endothelial growth factor (VEGF)-driven angiogenesis plays an important role (3). Gastroesophageal varices represent the most clinically relevant collaterals because of their increased risk of bleeding. Bleeding is directly dependent on increased wall tension at the varices, determined by portal pressure, variceal diameter, and thin wall thickness. Vasodilation occurs also in the systemic circulation resulting in a hyperdynamic circulatory state, driven by decreased effective arterial blood volume leading to activation of neurohumoral and vasoconstrictive systems, sodium and water retention, and increased cardiac output. This process eventually results in the development of ascites and, at late stages, hepatorenal syndrome because of compensatory renal vasoconstriction. Hepatic encephalopathy represents a multifactorial complication of portal hypertension, resulting from portosystemic shunting, impaired synthetic liver function, increased bacterial translocation, and muscle wasting (sarcopenia). Finally, imbalances on vasoconstrictors and vasodilators in the pulmonary circulation results in hepatopulmonary syndrome (increased vasodilation) and portopulmonary hypertension (increased vasoconstriction). CO, carbon monoxide; H_2S, hydrogen sulfide; HVR, hepatic vascular resistance; NO, nitric oxide; ET, endothelin.