Paris Portal Vein thrombosis meeting

Hôtel de de Ville de Paris
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VALDIG
VASCULAR LIVER DISEASE GROUP

Specificity of the portal vein wall in cirrhosis

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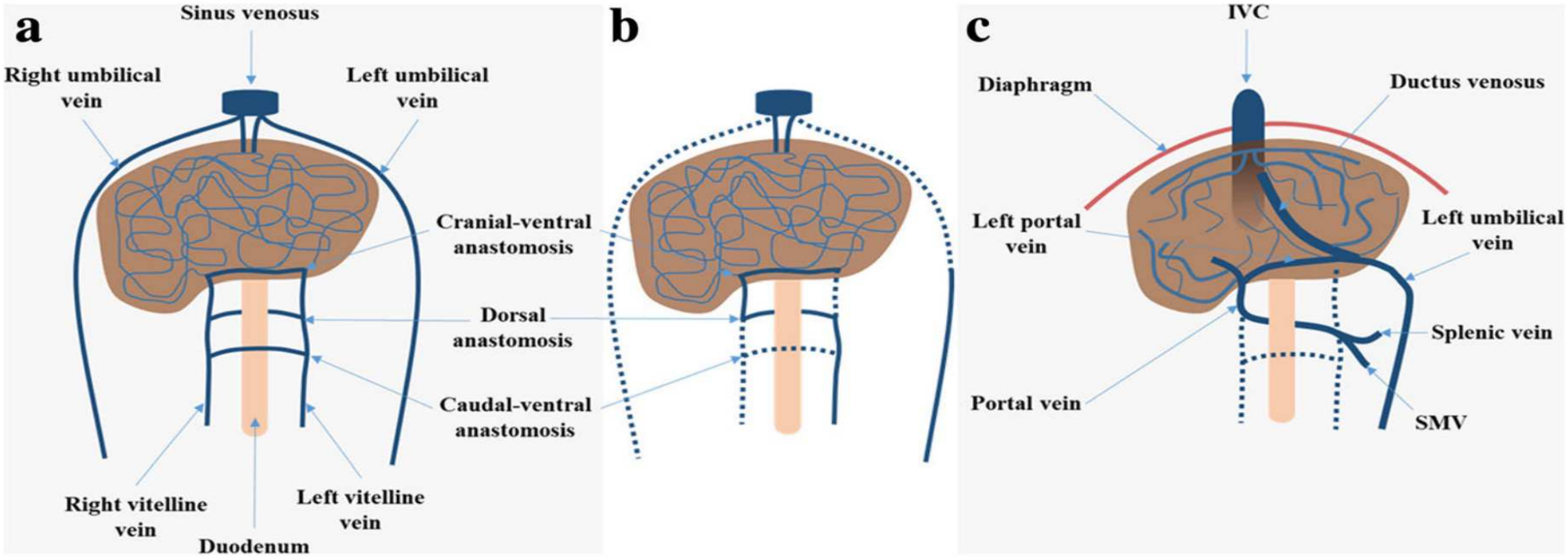
European Reference Network | Hepatological Diseases (ERN RARE-LIVER)

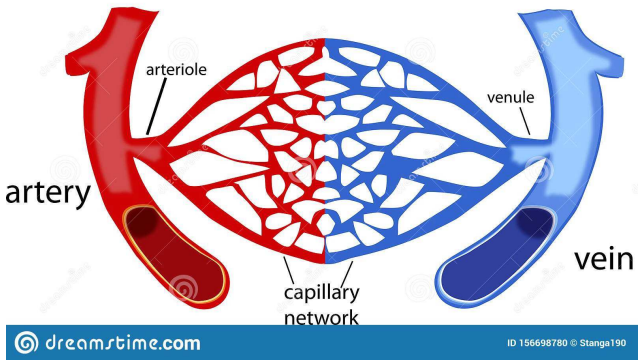
Embriological development of the Portal Vein System

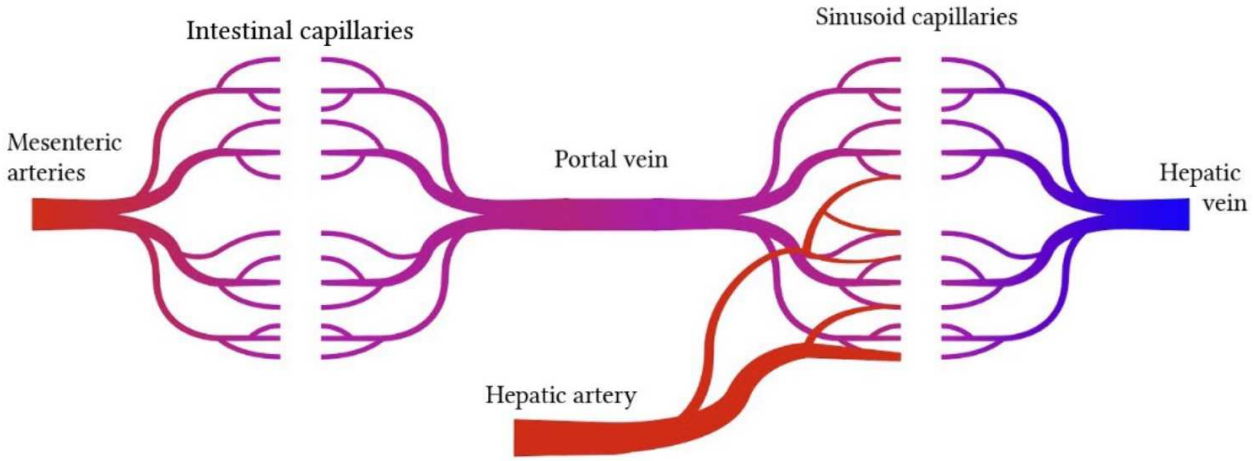


The portal vein system arises from the umbilical and the vitelline systems → From a developmental point of view all veins in the portal system are similar but different from the systemic venous system

Anatomical characteristics of the portal vein

General rule



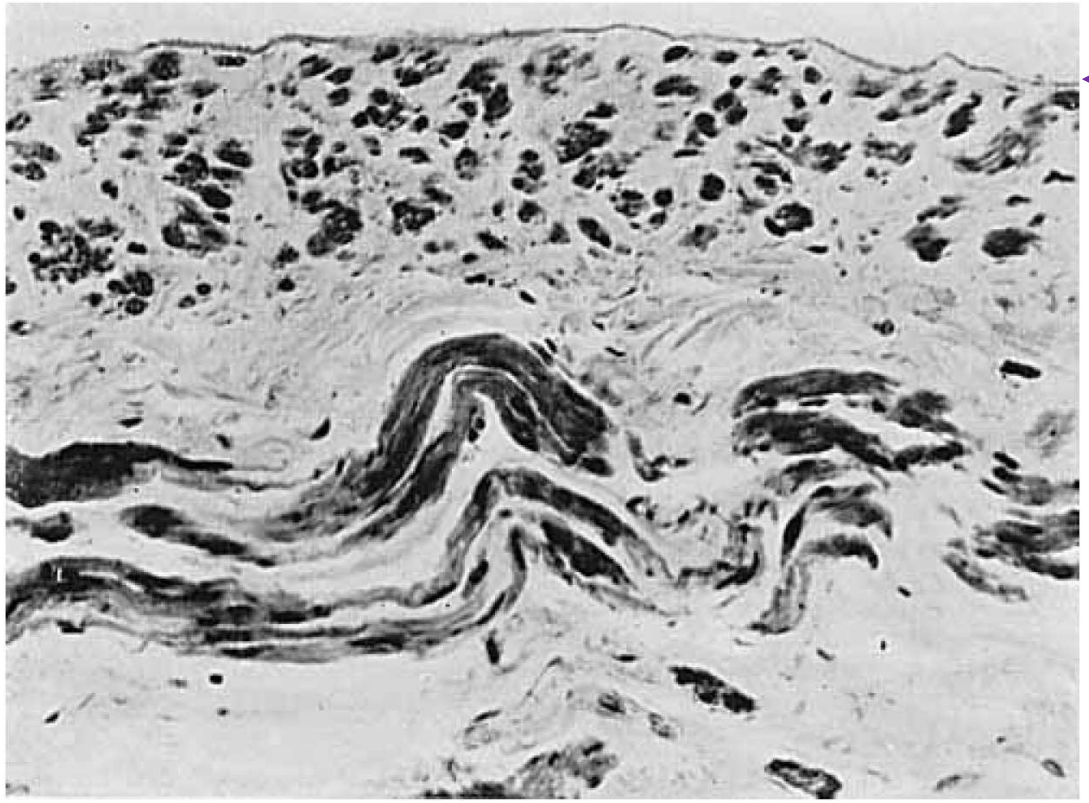


Capillary network of the abdominal organs drain into de PV that ramifies into an extensive network of sinusoids and converges into a system of vessels of increasing caliber to the hepatic vein (PV does not drain to the heart) and the PV does not have venous valves.

How is the “normal” portal vein wall?

Random samples of the extra-hepatic portion of the portal vein, the mesenteric and splenic veins and the inferior vena cava were collected from **54 cases post mortem**

PORTAL VEIN



Intima
Very thin **endothelial** lining
Some subendothelial connective tissue
A definite internal elastic membra

Media
Circular muscle fibres arranged singly / very thin strands of 2-4
Small amount of intervening connective tissue

Adventicia
Large number of closely packed **longitudinal** muscle bundles

Mesenteric & Splenic Veins: same general pattern, though its wall contains more circular and less longitudinal muscle the further away it is from the main portal trunk

Pei-Lin Li. Journal of Pathology 1940

How is the “normal” portal vein wall?

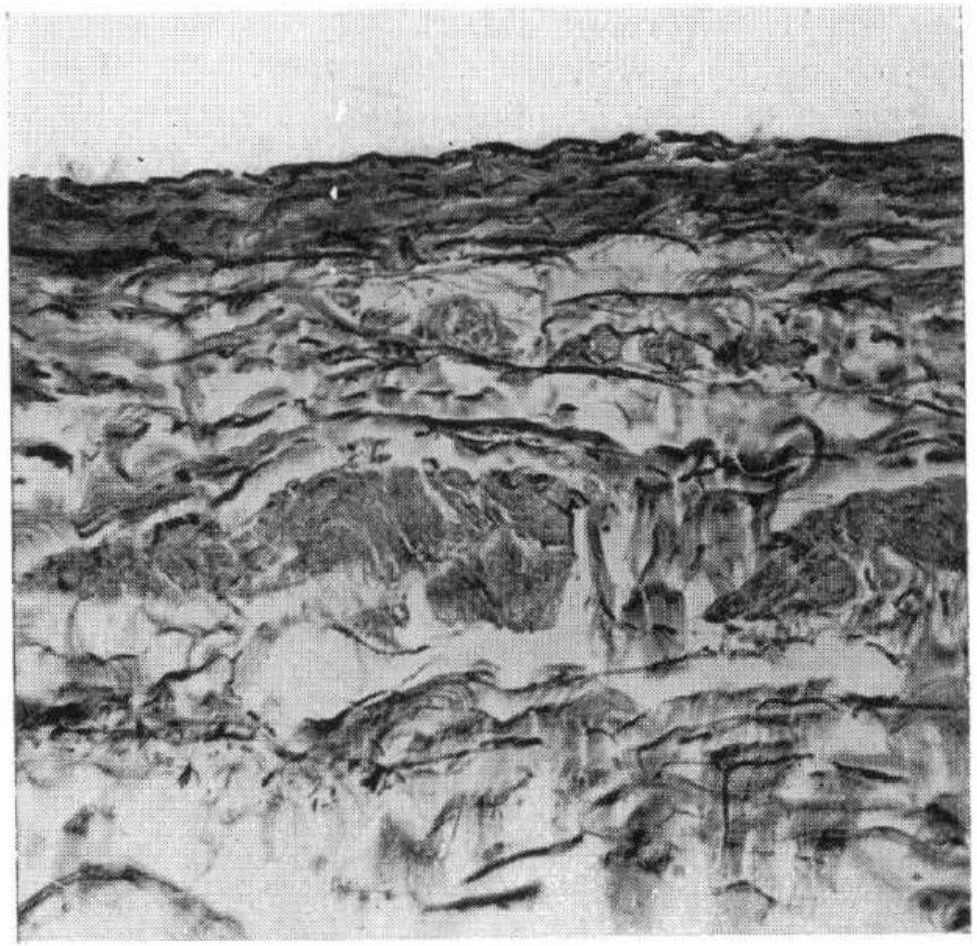


FIG. 1. *A normal portal vein. (Weigert and van Gieson. × 220.)*

The endothelium lining the vein was not always clearly seen
No subendothelial layer being visible.

The media is a compact layer of circular muscle fibres two to four bundles thick and separated from each other by a few loose strands of connective tissue.

The adventitia composed of two to three small bundles of longitudinally-arranged muscle cells.

Wilson JB. Gut 1961

Histological analysis “Normal” Extrahepatic Portal Vein

- Normal anatomy of portal vein seems to be variegated.
- Endothelial layer not always intact
- Vein wall remodeling occurs in normal conditions
- In our cohort of patients without known portal disease some amount of **intimal and medial fibrosis** was found in most of them as well as prominent presence of **smooth muscle in tunica intima and media**.

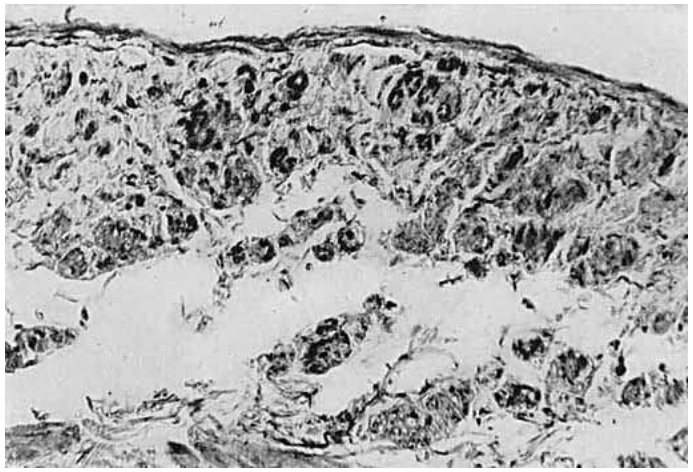
“La normalité n´existe pas”

Alexandre Lacassagne (1843 – 1924)
French physician and criminologist

How is the portal vein wall in cirrhosis?

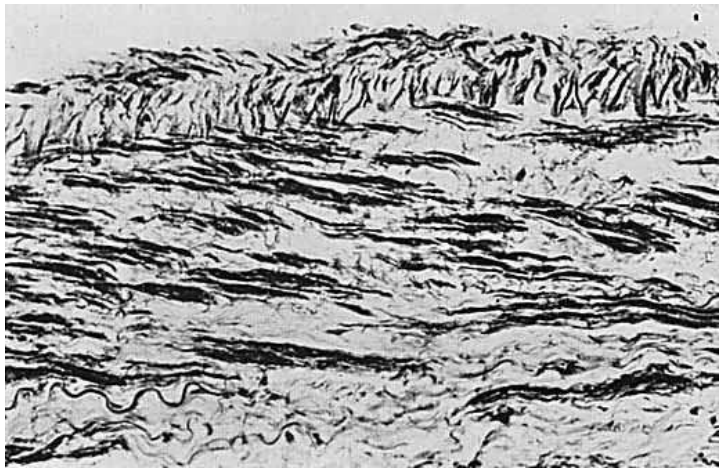
PORTAL VEIN

Intima: slight thickening
Media: marked muscular hypertrophy



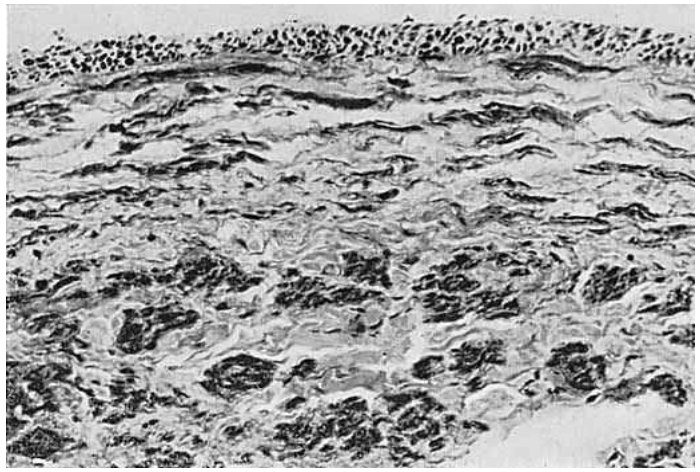
PORTAL VEIN

Thickened intima and longitudinal muscle fibres beneath the endothelium



SPLENIC VEIN

Thickened intima and longitudinal muscle fibres beneath the endothelium



"A frequent finding was **thickening of the intima** with the development of well defined longitudinal muscle fibres in the subendothelial connective tissue and muscular hypertrophy of the media. This was seen only in cases of cardiac failure, emphysema and cirrhosis of liver, i.e. **when the venous pressure was increased**. In the portal vein the intimal thickening is **generalised but not uniform**, being greater in some places than in others. This gives the impression that changes start as **multiple foci**".

Pei-Lin Li. Journal of Pathology 1940

How is the portal vein wall in cirrhosis?

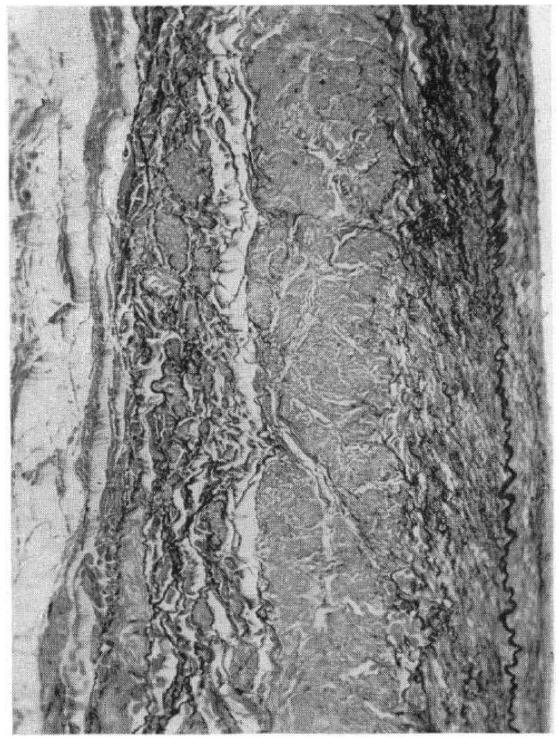
- Sections of the portal and splenic veins from
  - 30 cases of cirrhosis
  - 2 controls (necropsy)

Weight of Spleen (g.)	Changes in the Portal Vein			
	Group I	Group II	Group III	Group IV
0—199	2	3	1	—
200—399	—	6	7	1
400—599	—	1	7	—
600—799	—	—	—	1
800	—	1	—	1
Totals	2	11	15	3

Group II

Increase in the thickness of the vein due to slight hypertrophy of all its coats

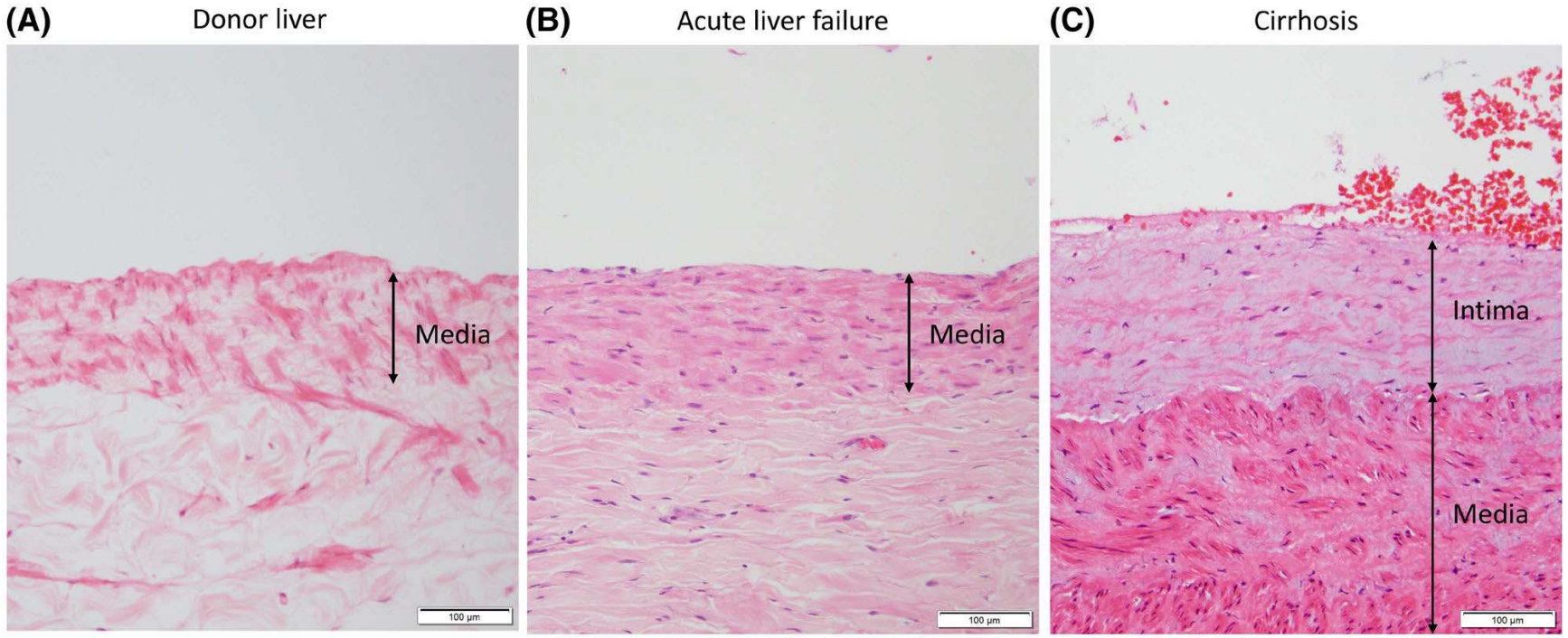
Group III



Definite thickening of the vein wall due to changes in all coats.

Wilson JB. Gut 1961

How is the portal vein wall in cirrhosis?



The tunica intima at the liver hilum in human donor liver and patients with acute liver failure consists of a flat lining of endothelial cells and is almost unrecognizable, and therefore not measurable

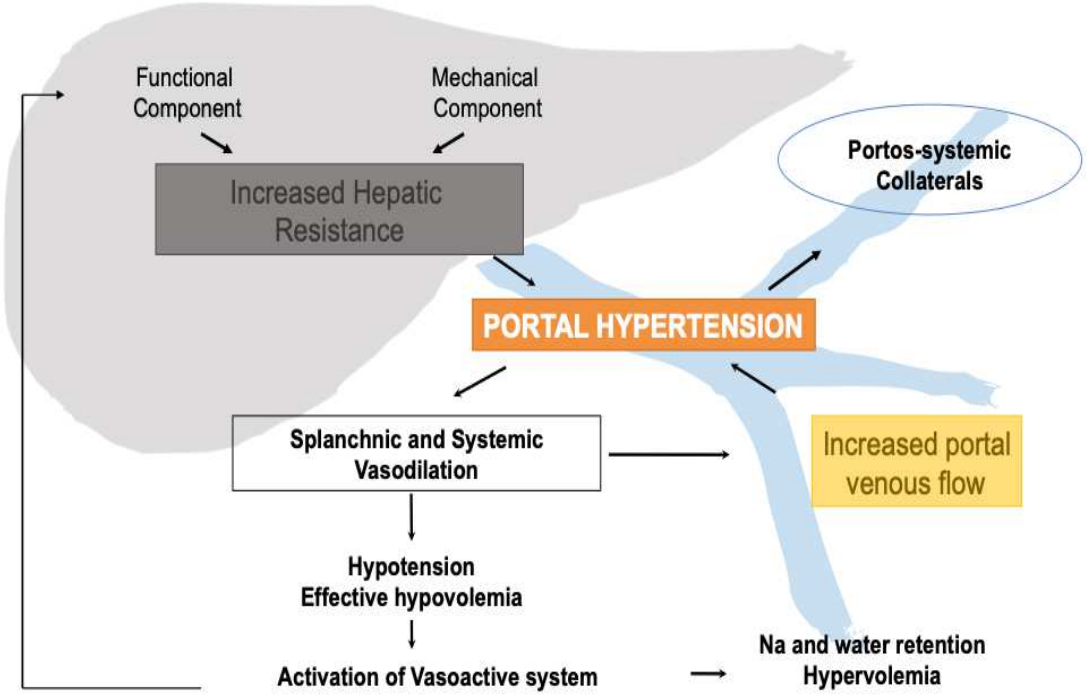
The portal vein vessel wall at the liver hilum in patients with cirrhosis without PVT shows a thickened tunica intima

Driever EG et al. Hepatology 2022

Portal Hypertension

Ohm's law : $\Delta P = Q \times R$

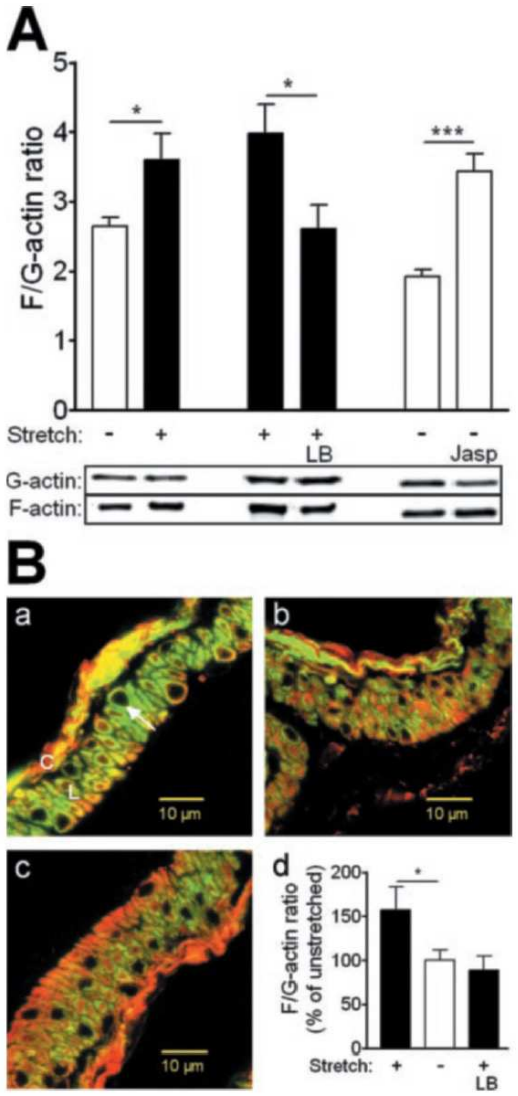
Portal Pressure = Portal Venous System Flow (including collaterals) × Vascular Resistance of the entire Portal Venous System



Increase vein caliber
Hyperdynamic and hypo-contractile mesenteric vascular phenotype
Increased portal venous flow
Intestinal permeability
Bacterial translocation
Increased levels of bacterial endotoxins
Shear stress
…

Adapted from Abraldes JG & Garcia-Pagan JC. Gastroenterol Hepatol 2006

Effect of Pressure-Induced Mechanical Stretch on Vascular Wall (*in vitro*)



- Intact mouse portal veins were cultured under longitudinal stretch for 72 h and compared with unstretched controls.
- The rat portal vein:
  - rapidly develops hypertrophy with preserved contractility in response to increased pressure
  - maintains the contractility phenotype of SMCx
- The signaling mechanisms of this response include Rho activation and actin polymerization, partly but probably not exclusively mediated via ROCK activity and cofilin phosphorylation.
- Vascular wall stretch by the intraluminal blood pressure stimulates protein synthesis and contributes to the maintenance of the smooth muscle contractile phenotype.

Albinsson S el al. J Biol Chem. 2004

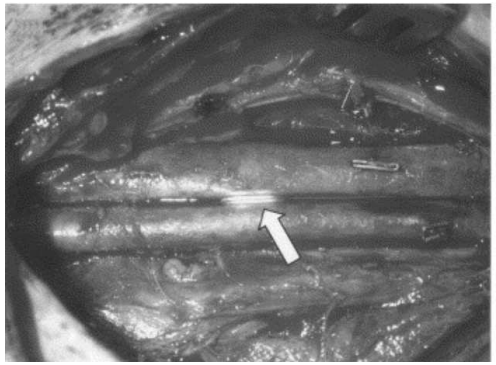
Effect of Pressure-Induced Mechanical Stretch on Vascular Wall (*in vivo*)

- Pressure-induced growth of the smooth muscle in the rat portal vein is associated with cellular hypertrophy and ultrastructural changes.
- The growth was initiated by an abrupt increase in the transmural pressure by PVL model. The portal vein responds with a growth of the vessel wall within days.
- 7 days is associated with a doubling of the thickness of the vessel wall and an increased smooth muscle cell mass.

Malmqvist & Amer. Circ Res 1990

Veins adapt to increased intravenous Pressure/ Flow (human data)

Arterio-venous anastomosis

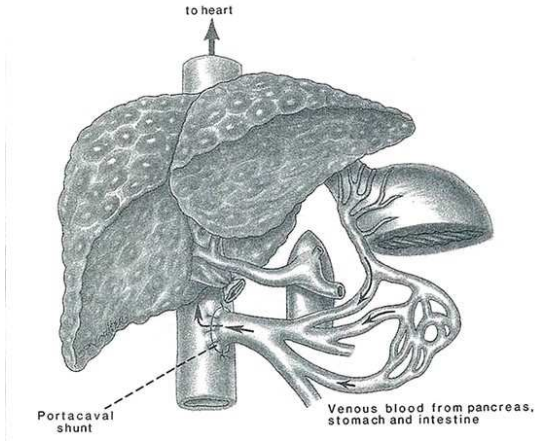


Veins adapt themselves very quickly to changes of **pressure**

- Uni-terminal anastomosis: the vein wall rapidly becomes thickened and its lumen dilates
- Bi-terminal anastomosis: thickening but no dilatation (arterial morphology)

Carrel A. Bull. Johns Hopkins Hosp. 1907

Venous-venous anastomosis



Eck fistula (anastomosing the inferior vena cava to the portal vein): increased **in-flow** → wall thickening

Wohlwill and Holm . Verh. path. Ges. 1927

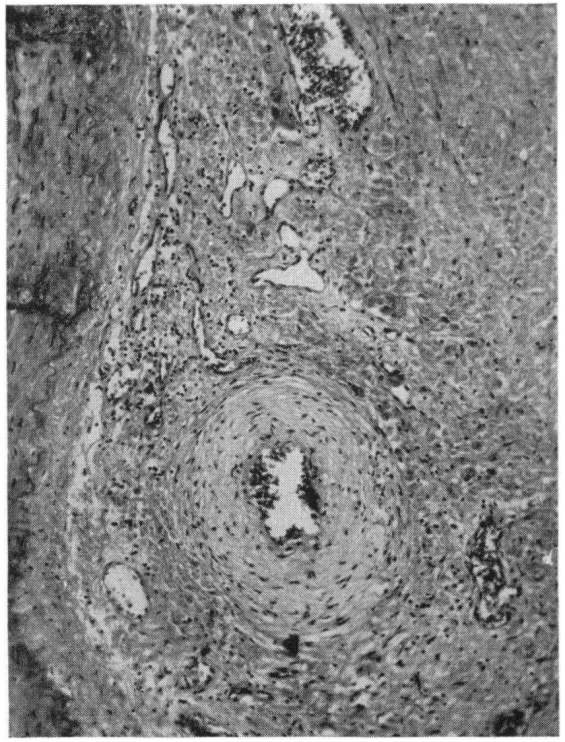
PV wall changes during cirrhois

- Liver cirrhosis is associated with changes in the portal venous system
  - Intimal thickening with development of longitudinal muscle beneath it
  - Muscular hypertrophy.
- The hypertrophic muscle gradually fails and undergoes degeneration and absorption, becoming replaced by fibrous tissue
- The thickened muscular coat becomes fibrosed to a varying degree.
- There is also replacement fibrosis of the longitudinal muscle in the thickened intima.

PV wall and PVT

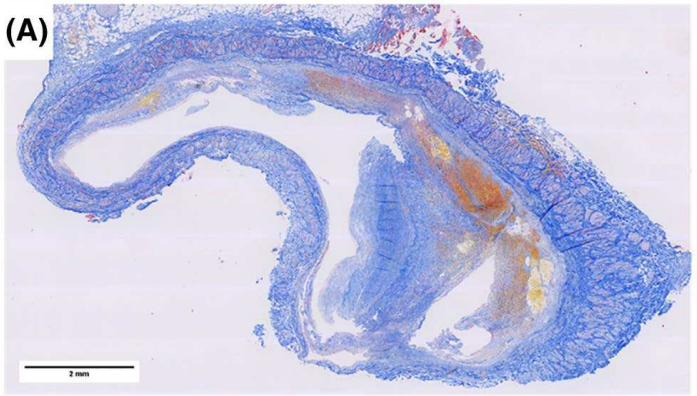
Group IV

Large, recently formed thrombus on an eccentrically thickened intima composed of dense collagenous tissues

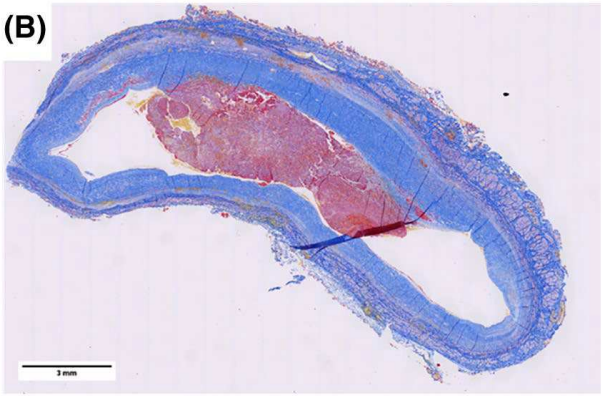


Vascularization of the deep portions of the **thrombus** adjacent to the internal elastic lamina.

Wilson JB. Gut 1961



A portal vein thrombus consisting of a **focally thickened intimal layer of the vessel** wall with some hemorrhage but without a fibrin-rich thrombus.



Portal vein thrombus consisting of a **circumferential thickened intima** with a fibrin-rich thrombus on top

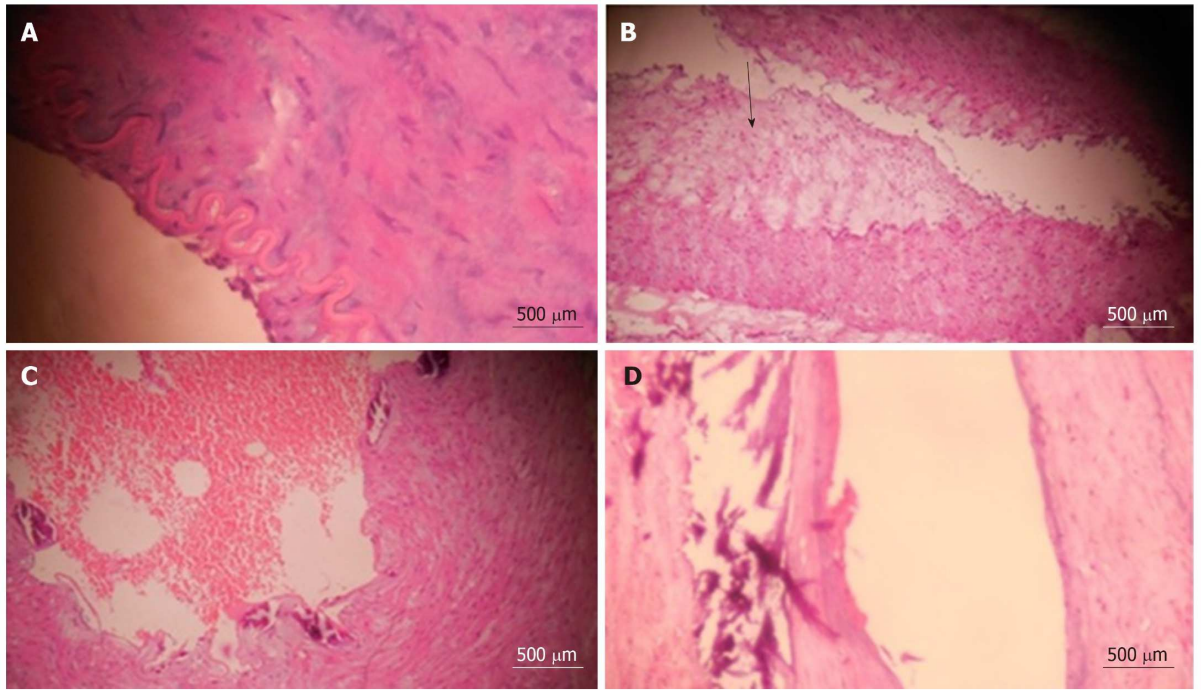
Driever EG et al. Hepatology 2022

Do changes in PV wall happen in the absence of cirrhosis?

116 consecutive patients with NCPH who underwent proximal splenorenal shunts, interposition shunts or splenectomy with devascularization

- EHPVO: 53 and
- non-cirrhotic portal fibrosis (NCPF): 63

splenic vein:
medial hypertrophy



splenic vein:
intimal fibrosis

splenic venous
thrombosis

splenic venous wall
calcification

Gupta S et al. World J Gastrointest Surg 2020

“Take home messages”

- The structure of veins presents regional differences during health and disease
- Vascular vein remodelling occurs during normal conditions
- The portal venous system (hilum, extrahepatic portal-, mesenteric- & splenic vein) but also inferior vena cava (hepatic veins) are affected during liver disease.
- Portal hypertension is associated with vein wall thickening (hypertrophy and fibrosis) in human and rodents regardless of the presence of PVT.
- Intimal thickening is generalised but not uniform, being greater in some places than in others (multiple foci)
- Thickening of the PVS increase progressively during disease (more PHT more thickening)

Thanks!!

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