

# Pathogenesis of portal hypertension

By

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*Prehepatic*

- Splenic AV fistula
- Splenic or portal vein thrombosis
- Massive splenomegaly

*Intrahepatic*

- Sarcoidosis
- Schistosomiasis
- Nodular regenerative hyperplasia
- Congenital hepatic fibrosis
- Idiopathic portal fibrosis
- Early primary biliary cirrhosis
- Chronic active hepatitis
- Myeloproliferative disorders
- Graft-vs-host disease

Presinusoidal

- Established cirrhosis
- Alcoholic hepatitis

Sinusoidal

- Alcoholic terminal hyaline sclerosis
- Veno-occlusive disease

*Posthepatic*

- Budd-Chiari syndrome
- Membranous IVC web
- Right heart failure
- Constrictive pericarditis

Postsinusoidal

# HVPG

## Hepatic venous pressure gradient (HVPG)

The hepatic venous pressure gradient (HVPG)  
Is the difference between the wedged (WHVP)  
and the free (FHVP).

# Portal Hypertension

**HVPG (WHVP-FHVP) >12mmHg**

- **Pre-hepatic** → Normal HVPG
  - Portal or splenic vein thrombosis
  - AV fistulas in the splanchnic bed or spleen
- **Intra-hepatic**
  - Pre-sinusoidal → Normal HVPG
    - Sarcoid, Schistosomiasis
  - Sinusoidal → High HVPG (WHVP>FHVP)
    - Cirrhosis – any cause
  - Post-sinusoidal → Budd Chiari – can't get into hepatic veins (clot in veins)
- **Post-hepatic** → Normal HVPG (High WHVP and FHVP)
  - Webs in IVC
  - Cardiac disease → constrictive pericarditis, right heart failure

# Pathophysiology

- Ohm law is  $V = IR$
- This can be applied to vascular flow, ie,  
 $P = FR$
- Changes in either  $F$  or  $R$  affect the pressure.
- In most types of portal hypertension, both the blood flow and the resistance to blood flow are altered.

## Increase in vascular resistance

- Poiseuille law, which can be applied to portal vascular resistance states.
- $R = 8hL/\pi r^4$ , where  $h$  is the viscosity of blood,  $L$  is the length of the blood vessel, and  $r$  is the radius of the blood vessel.
- The viscosity of the blood is related to the hematocrit (HCT).

# Increase in vascular resistance

- The lengths of the blood vessels in the portal vasculature are relatively constant.
- changes in portal vascular resistance are determined primarily by blood vessel radius.
- Because portal vascular resistance is indirectly proportional to the fourth power of the vessel radius, small decreases in the vessel radius cause large increases in portal vascular resistance.

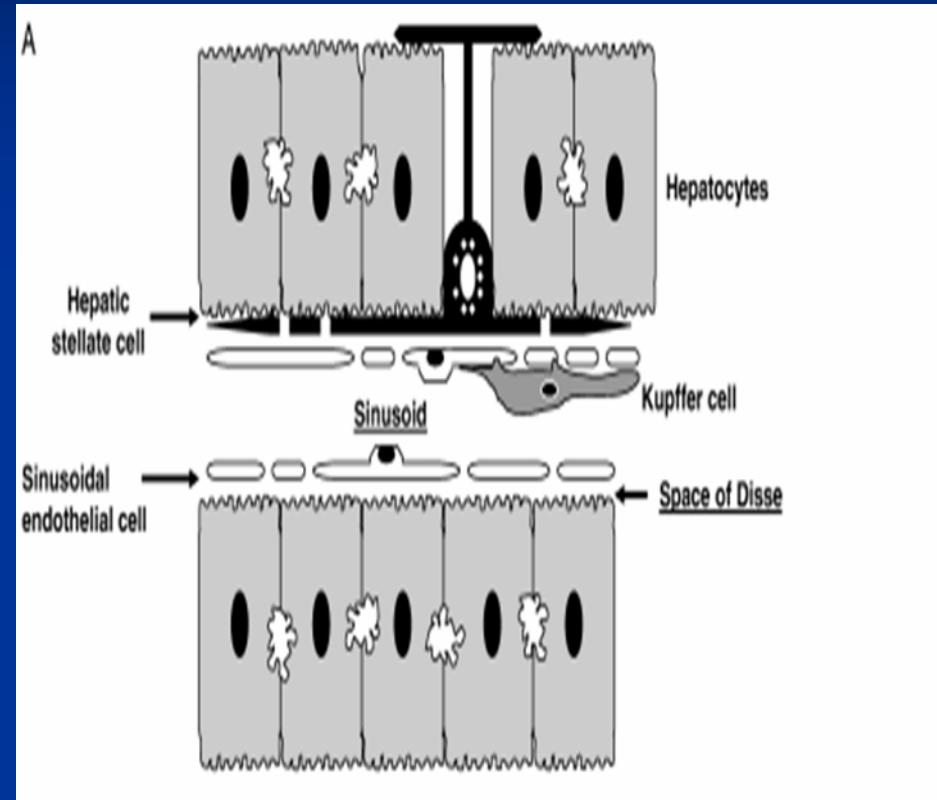
# Increase in vascular resistance

- Liver disease is responsible for a decrease in portal vascular radius, producing a dramatic increase in portal vascular resistance.

How ?

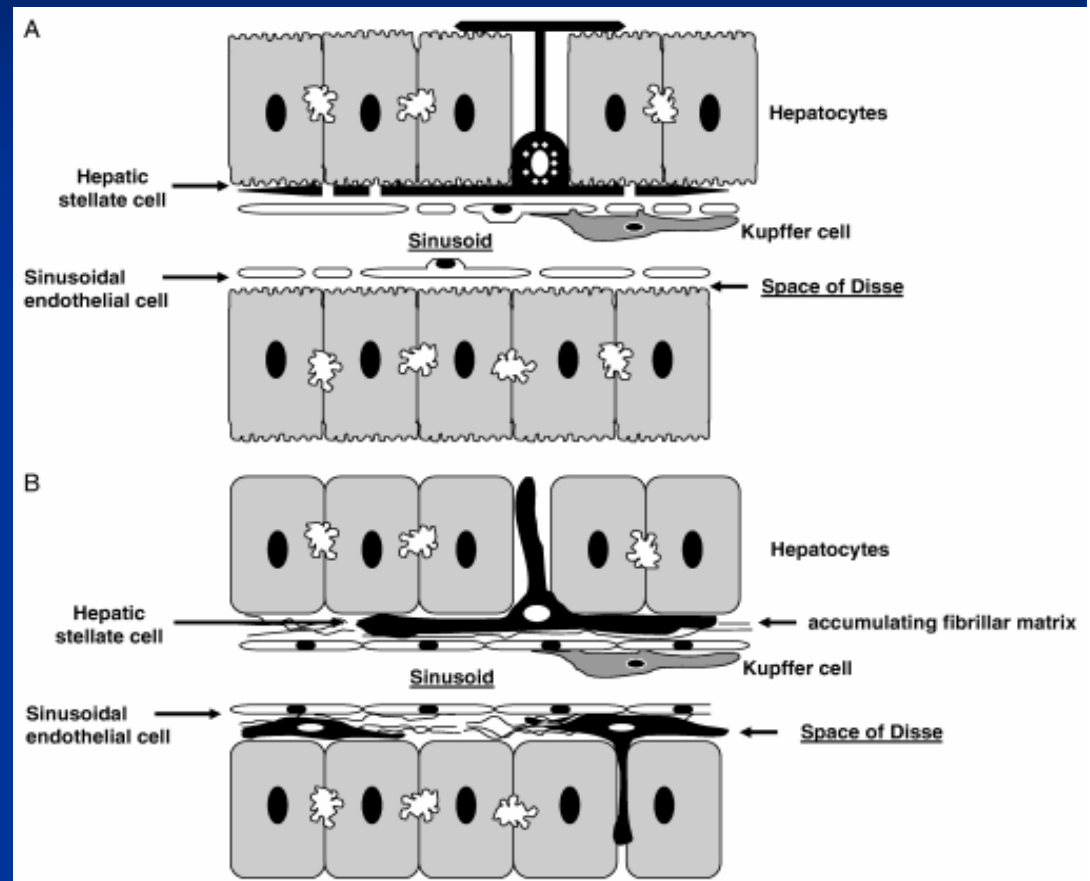
# Increase in vascular resistance

In cirrhosis, the increase occurs at the hepatic microcirculation (sinusoidal portal hypertension).



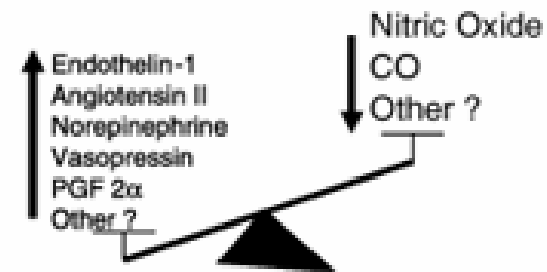
# Increase in vascular resistance

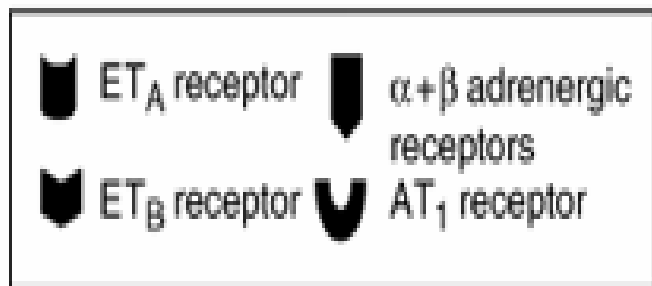
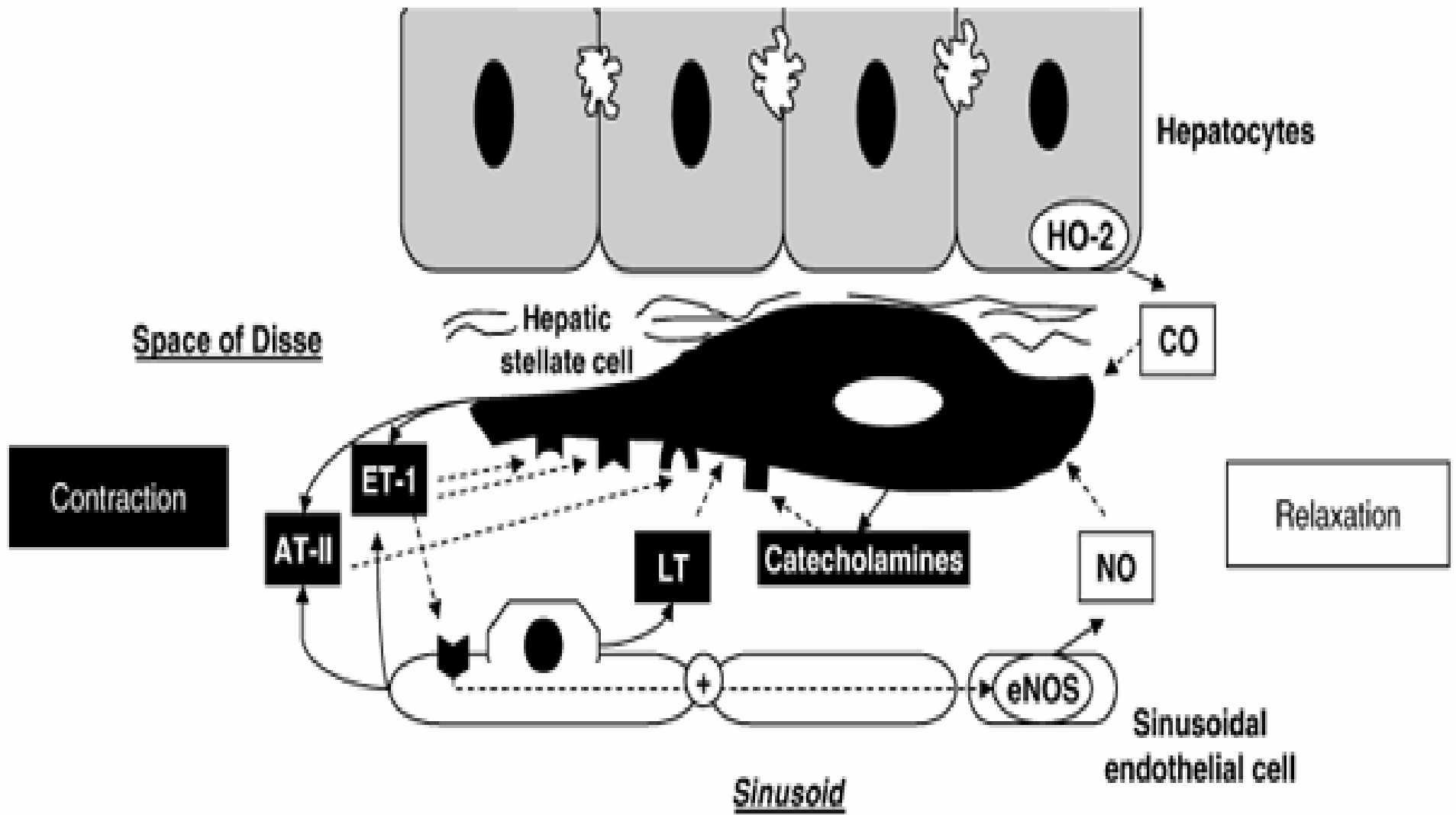
- Increased hepatic vascular resistance in cirrhosis is not only a mechanical consequence of the hepatic architectural disorder.
- A dynamic component also exists due to: contraction of myofibroblasts, activated stellate cells, and vascular smooth-muscle cells of the intrahepatic veins.



- An additional feature in the active IHVR is the imbalance in vasoactive substances

1. Passive, mechanical component : 60-70%  
(fibrosis, regenerative nodules, microthrombosis)
2. Active, dynamic component : 30-40%  
(activated HSC)





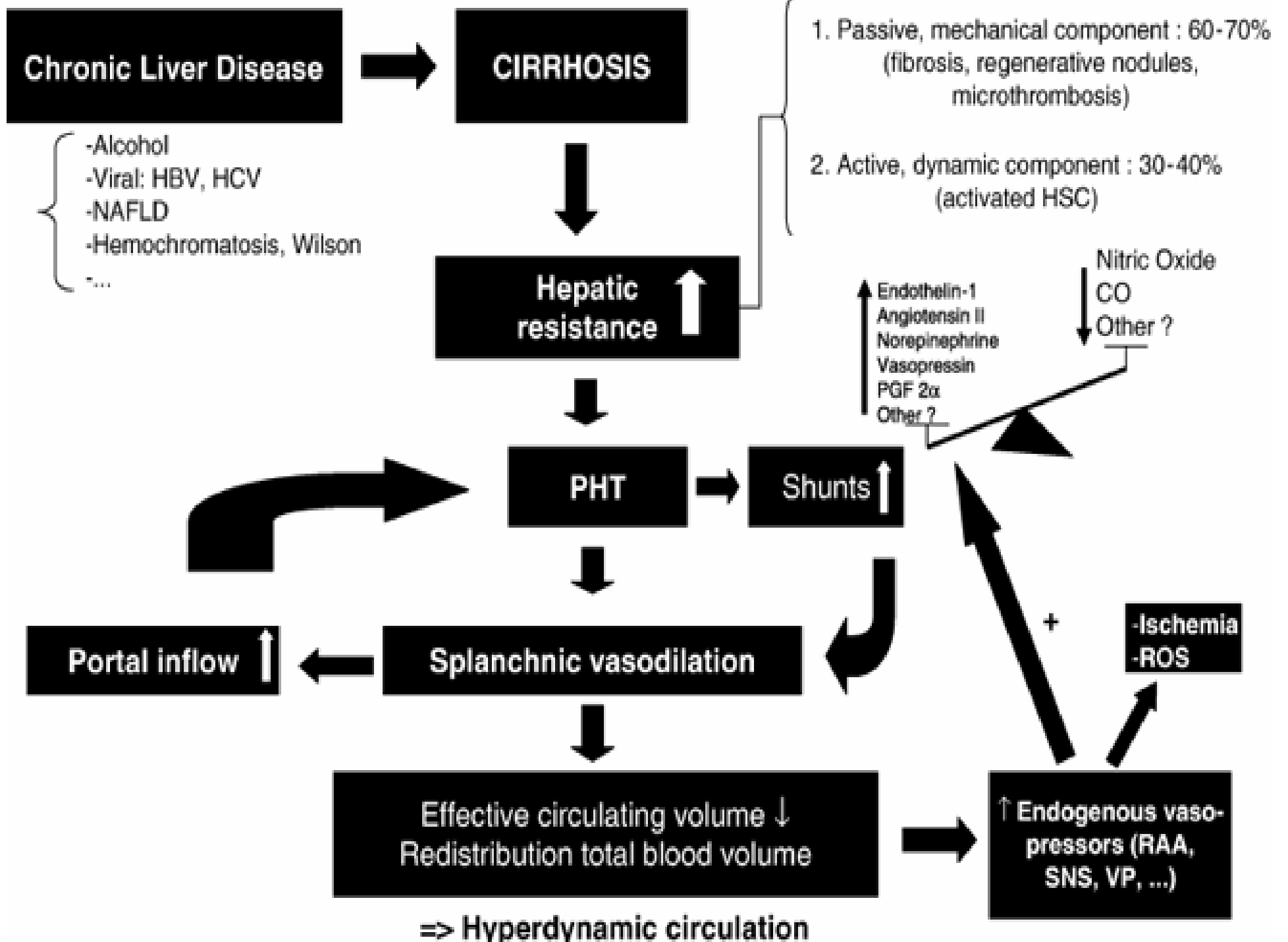
# Increase in portal blood flow

## Splanchnic Hyperaemia and Arterial Vasodilation

- **Increase in Blood Flow in the portal veins, for the splanchnic arteriolar vasodilatation caused by release of endogenous vasodilators (eg, endothelial, neural, humoral).**
- **The increase in Portal Blood Flow aggravates the increase in portal pressure and contributes to the formation of an extensive network of portosystemic collaterals that may divert as much as 80% of portal blood flow.**

# Increase in portal blood flow

- Manifestations of splanchnic vasodilatation:
  - Increased cardiac output
  - Arterial hypotension
  - Hypervolemia
- 
- This explains the rationale for treating portal hypertension with a low-sodium diet and diuretics to attenuate the hyperkinetic state.



## 1. Aiming to decrease increased intrahepatic resistance:

Active, dynamic resistance

### 1. Increase intrahepatic NO bioavailability

- a) Currently used: isosorbide-5-mononitrate and dinitrate, nitroglycerin
- b) Future potential strategies:
  - Gene transfer with eNOS or co-factor Akt
  - Statins
  - Selective hepatic NO delivery: V-Pyrro-NO, NO-ursodeoxycholic acid, etc.
  - Decrease intrahepatic NO-degradation to ONOO by increasing anti-oxidans capacity

### 2. Increase intrahepatic CO (?)

### 3. Antagonize effect of excess of intrahepatic vasoconstrictive substances

- a) Endothelin-1 antagonism
  - Bosentan
  - Newly developed ET-blockers: Tezosentan ?
- b) Angiotensin-II
  - Selective AT-II-blockers: Losartan, etc.
- c) Adrenergic antagonists
  - Prazosin ( $\alpha$ -1-blocker)
  - Carvedilol (combined  $\alpha$ -1- and non-selective  $\beta$ -blocker)
- d) Somatostatin-receptor-1 analogues

Passive resistance modulation: anti-fibrotic drugs (?)

## 2. Aiming to decrease splanchnic hyperaemia

- a) Non-selective  $\beta$ -blockers
- b) Vasopressin and its analogues
- c) Somatostatin and somatostatin analogues
  - Sustained-release preparations for chronic use?

# Conclusion

- Expansion in the knowledge of the pathophysiology of PHT is urgently needed as this might provide new and useful strategies for the future.
- Currently, some of these new pharmacostategies have already reached the clinic, and are being currently tested for efficacy and tolerance. The main drawback at present, however, is the lack of (hepato)selectivity, which is needed because of the paradoxal haemodynamic intra- and extrahepatic characteristics.