Portal Hypertension

Patho-Physiology
&
Clinical correlation

Dr. Manish Madnani

Definition of PH

- Pathological increase of the portal pressure gradient (PPG)

  PPG = (Portal venous pressure – IVC pressure)

  PPG > upper normal value (5 mmHg)

- Formation of portal-systemic collaterals

  Shunting of portal blood flow to systemic circulation bypassing the liver

The history of PH

- 1543 - Andreas Vesalius

  First anatomical picture

  of the portal venous system

Figure 1. Vesalius's pictorial of the portal venous system

The history of PH

- 1650s - Francis Glisson
  - Established the function of the portal vein
- 1700s – Giovanni Batista Morgagni
  - Described varices in the splenic and short gastric veins
- 1832 – Jean Cruveilhier

  Described the clinical picture of splenomegaly, ascites and gastrointestinal haemorrhage
- 1841 - Philbert Constant Sappey

  Described porto-systemic collaterals

The history of PH

- 1902 - Augustin Nicolas Gilbert

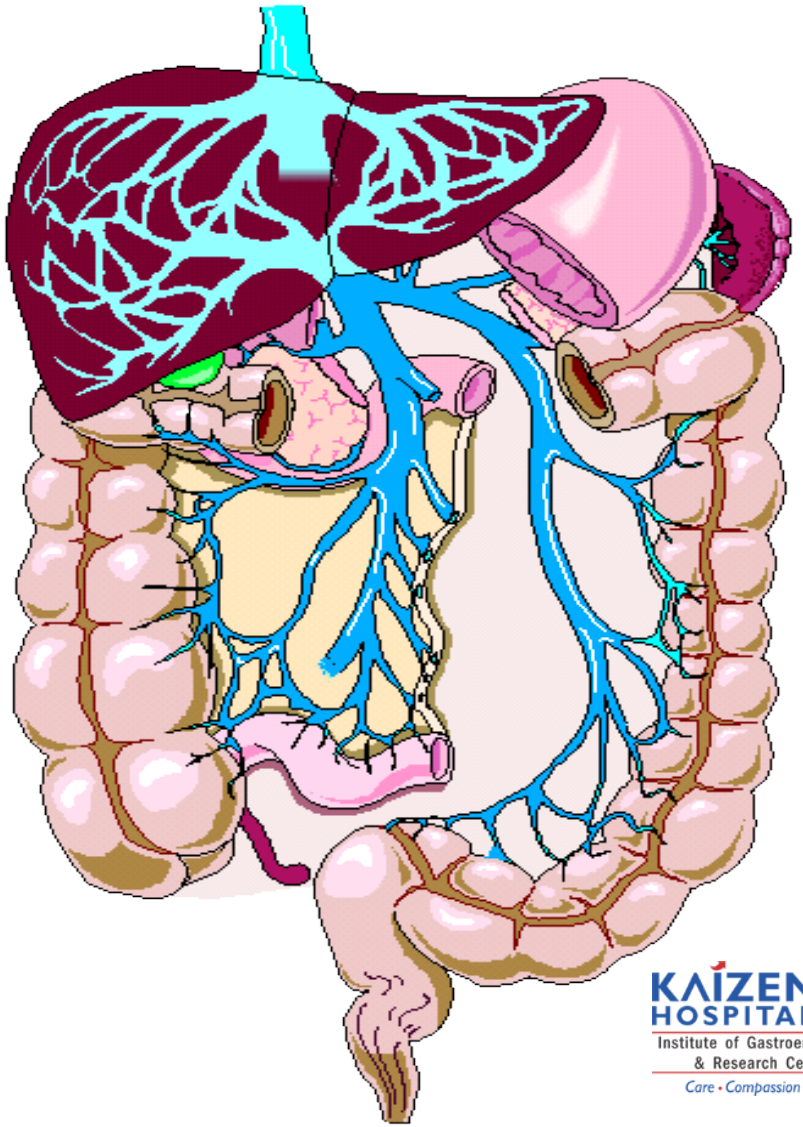
  Introduced the term “Portal hypertension”

Anatomy of portal hypertension

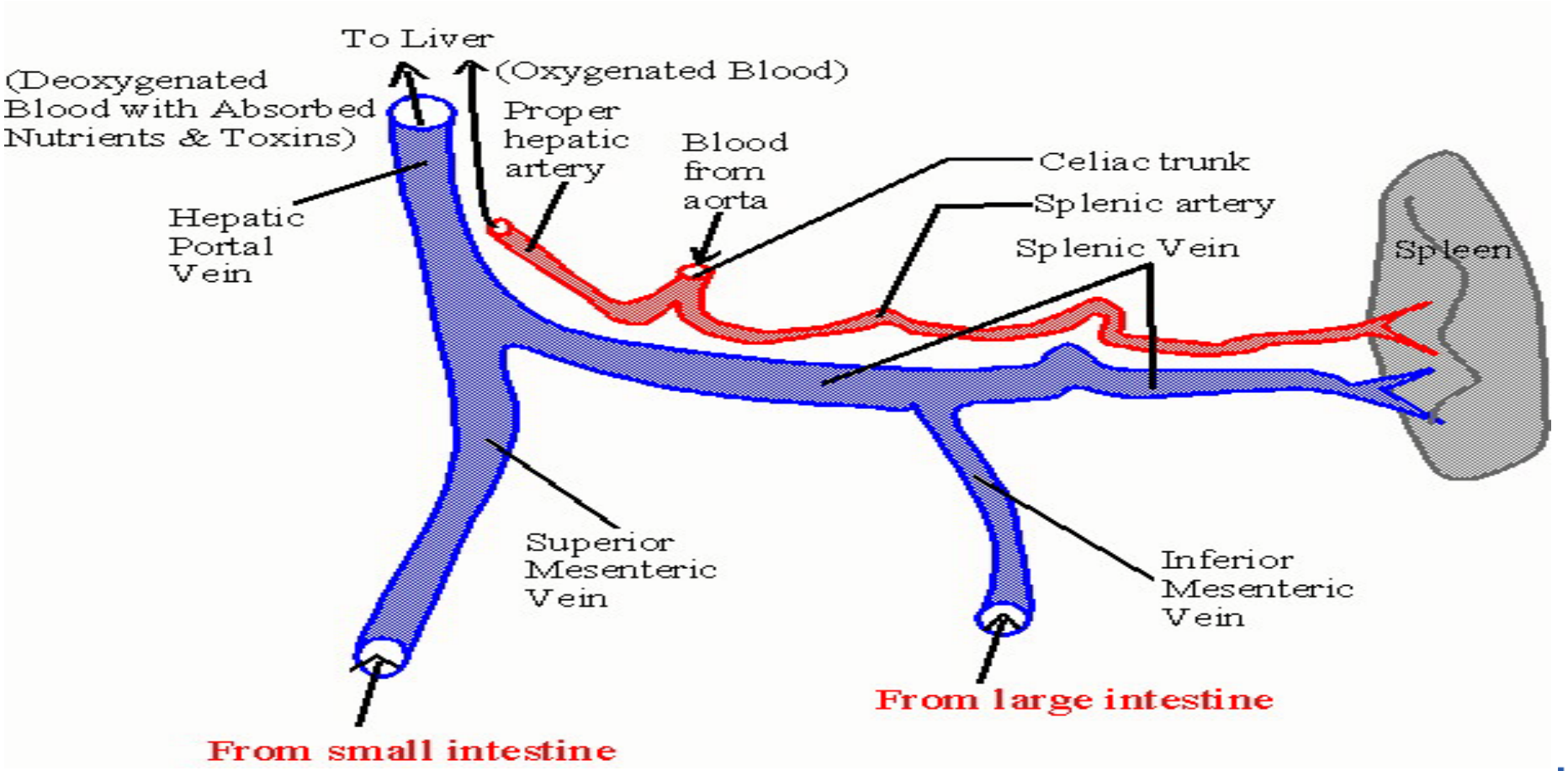
- The portal vein is formed from the confluence of the superior mesenteric ,

  inferior mesenteric and

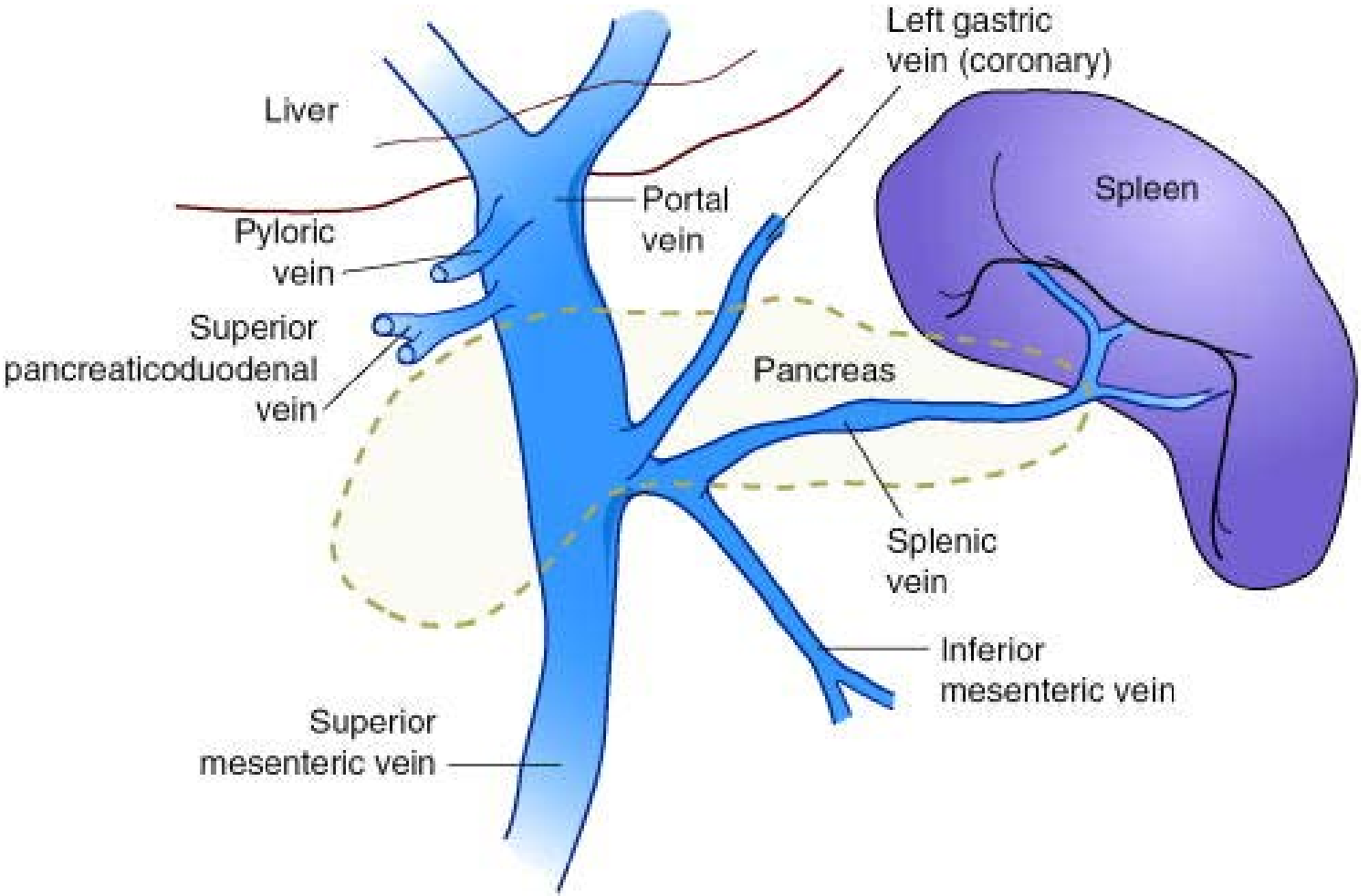
  splenic veins



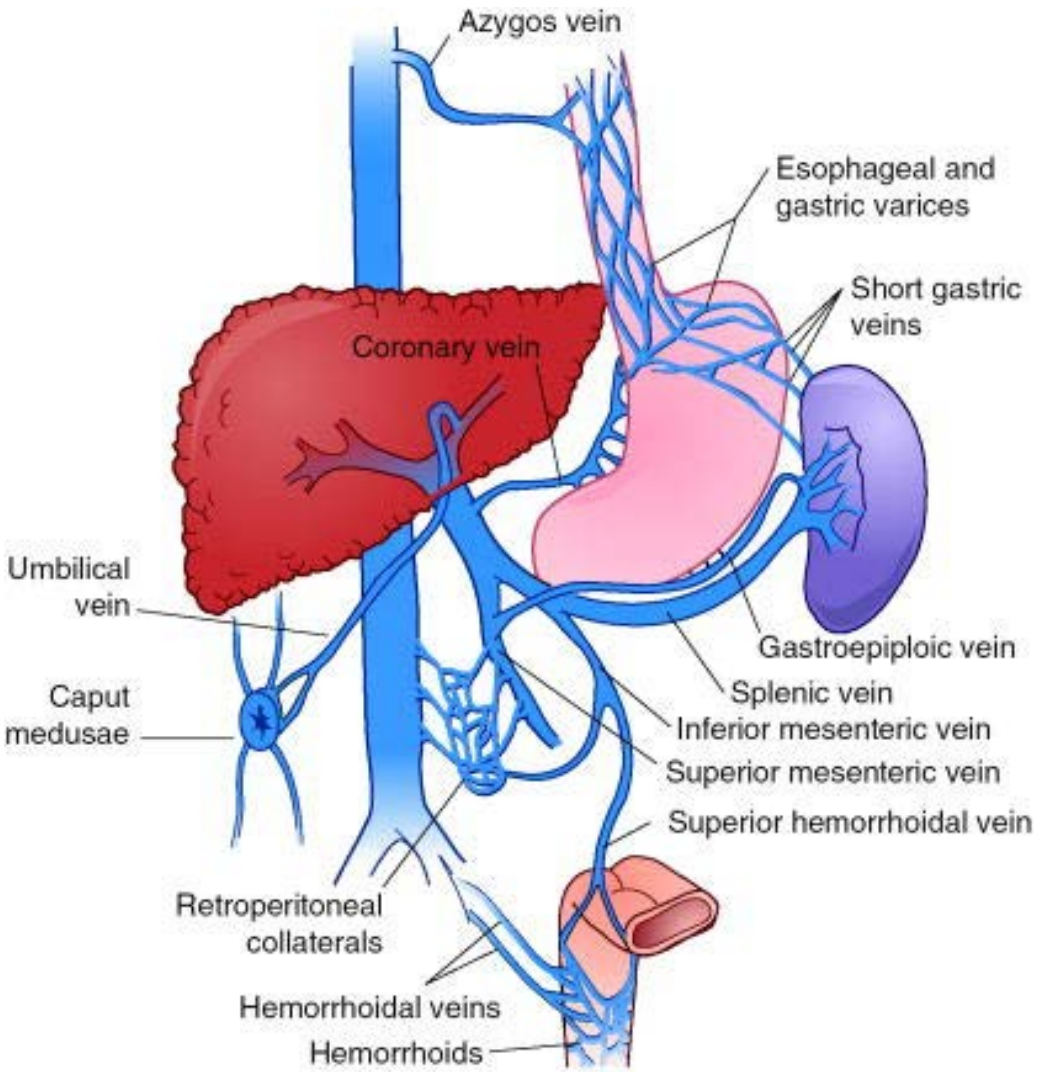
Portal anatomy



The extrahepatic portal venous circulation



Portosystemic collateral pathways



Pathophysiology of portal hypertension

- The portal vein contributes two thirds of the total hepatic blood flow
- Indirectly regulated by vasoconstriction and vasodilation of the splanchnic arterial bed.

Physiology blood supply

- 25% CO
- HA: 25% HBF, 45-50% O_2
- PV: 75% HBF, 50-55% O_2
  - Flow ∞ pre-portal arterioles
  - Flow + Resistance thru liver = portal pressure

- PV: Presinusoidal (pre-capillary) + post-sinusoidal → venous resistance via SNS stimulation

Portal hypertension

- ↑ blood flow into system
- Resistance portal system or portacaval collaterals

- → ↓ PV flow (partial compensation ↑ HA flow)
  - O_2 supply may be maintained
  - Total HBF ↓

- P=FR, where P is pressure gradient thru the portal system, F is the volumeof blood flowing thru the system, R is the resistance to flow.
- Changes in either F or R affect the pressure.
- In most types of portal hypertension, both flow and resistance are altered.

Increase in Resistance

- Liver disease is responsible for a decrease in portal vascular radius, producing an increase in portal vascular resistance.
- In cirrhosis, the increase occurs at the microcirculation (sinusoidal).
- The resistance is also due to active myofibroblasts, vascular smooth muscle cells in the intrahepatic veins.

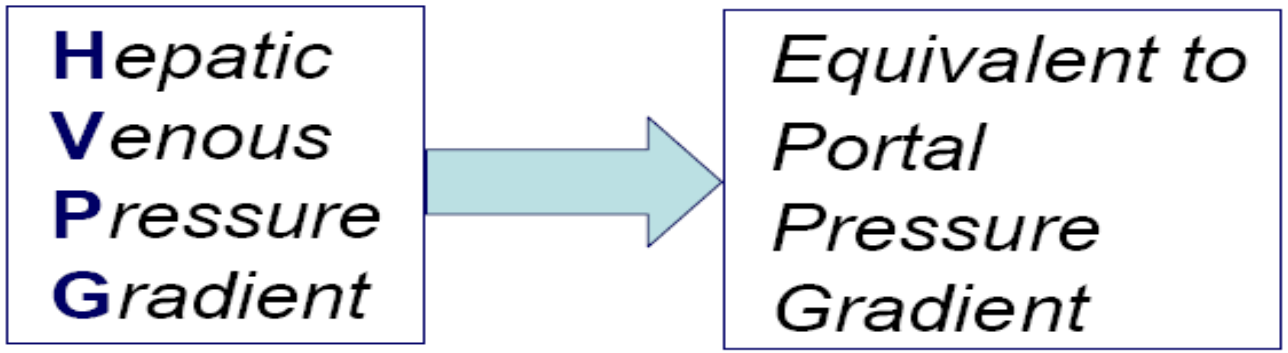
Increase in Flow

- The increase in blood flow is caused by splanchnic arteriolar vasodilitation caused by release of endogenous vasodilators.
- The increased flow aggravates the increase in portal pressure and contributes to why PT exists despite the formation of portosystemic collaterals that divert as much as 80% of portal flow.

Manifestations of Splanchnic Vasodilitation

- Increased cardiac output
- Arterial hypotension
- Hypovolemia
- The above explains rationale for treating patients with low sodium diet and diuretics to attenuate the hyperkinetic state

Assessment of PPG by HVPG

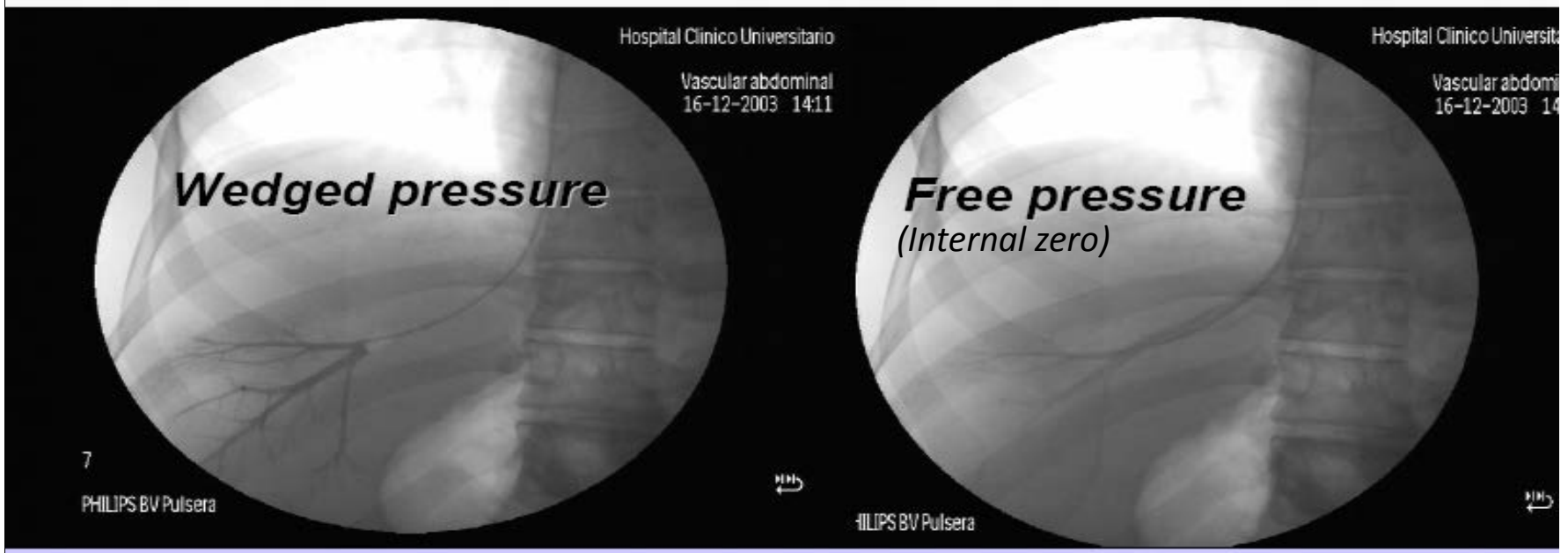


"Gold standard" in the assessment of portal hypertension*, the most common and lethal complication of cirrhosis

** defined by an HVPG > 5 mmHg*

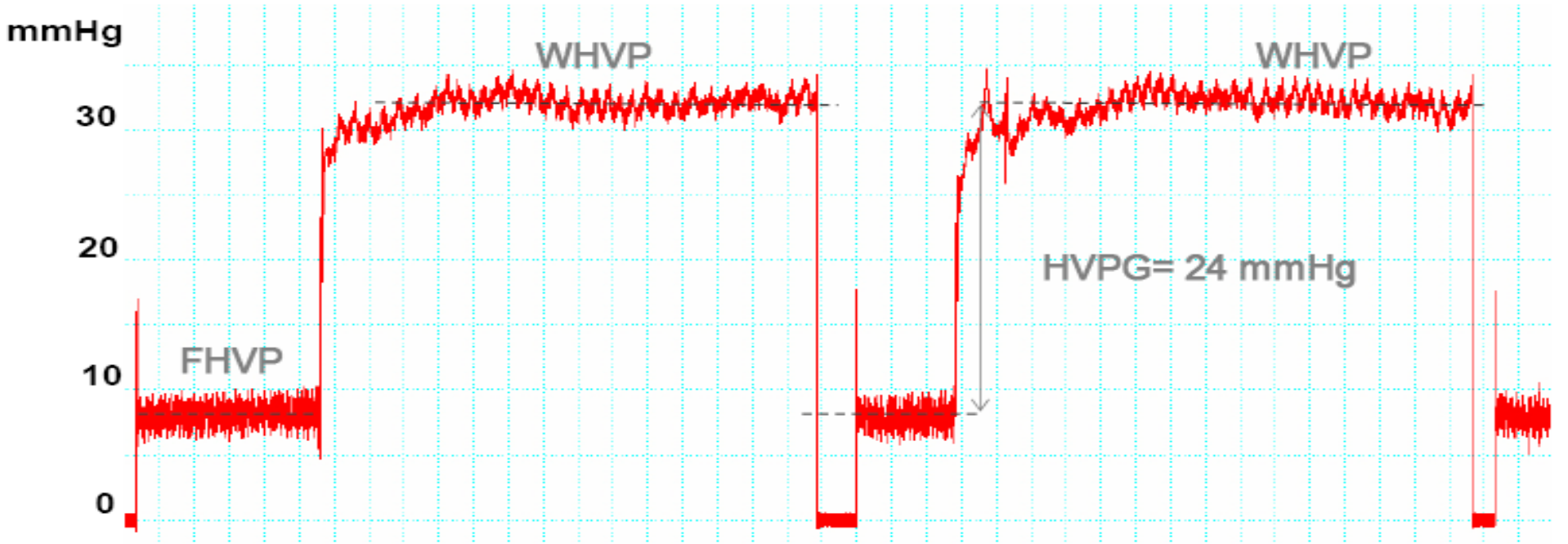
HVPG: *what is it?*

An indirect measurement of the portal pressure gradient based on hepatic vein catherisation

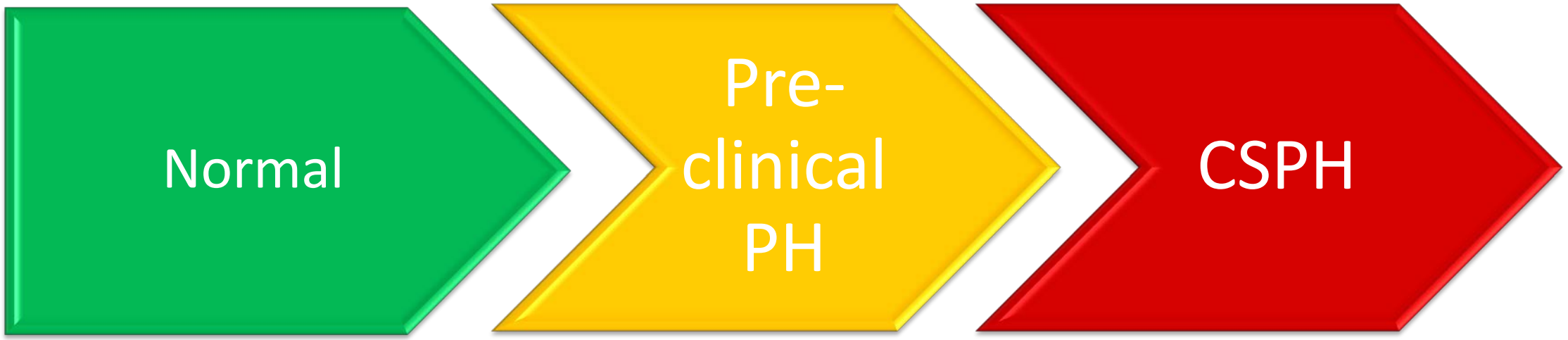


$$HVPG = WHVP - FHVP$$

Typical measurement of HVPG using balloon catheter



Spectrum of HVPG



Clinically significant PH (CSPH)

- In cirrhosis cases
  - Histologically proven
  - Well-compensated

- At the time of diagnosis
  - 60% will have CSPH

Causes of PH

- Prehepatic
  - Splenic vein thrombosis
  - Portal vein thrombosis
  - Congenital stenosis of the portal vein
  - Extrinsic compression of the portal vein
  - Arteriovenous fistulae
- Intrahepatic
  - Cirrhosis (viral, alcoholic, biliary, metabolic)
  - Partial nodular transformation
  - Nodular regenerative hyperplasia
  - Congenital hepatic fibrosis
  - Peliosis hepatic
  - Polycystic disease
  - Idiopathic portal hypertension
  - Hypervitaminosis A
  - Arsenic, copper sulfate, vinyl chloride monomer poisoning
  - Granulomatous diseases (sarcoidosis, tuberculosis, primary biliary cirrhosis, schistosomiasis)
  - Amyloidosis
  - Mastocytosis
  - Rendu-Osler-Weber syndrome
  - Liver infiltration in hematologic diseases
  - Acute fatty liver of pregnancy
  - Severe acute viral and alcoholic hepatitis
  - Chronic active hepatitis
  - Hepatocellular carcinoma
  - Cyanamide toxicity
  - Veno-occlusive disease
- Posthepatic
  - Hepatic veins thrombosis (Budd-Chiari syndrome)
  - Congenital malformation and thrombosis of the inferior vena cava
  - Constrictive pericarditis
  - Tricuspid valve diseases

Causes of PH

- Classified according to *site of obstruction to blood flow*
- Pre-hepatic
  - *Portal vein thrombosis*
- Intra-hepatic
  - *Cirrhosis* (90%)
    - Pre-sinusoidal
    - Sinusoidal
    - Post-sinusoidal
- Post-hepatic
  - *Hepatic vein thrombosis* (Budd-Chiari syndrome)

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Clinical manifestations

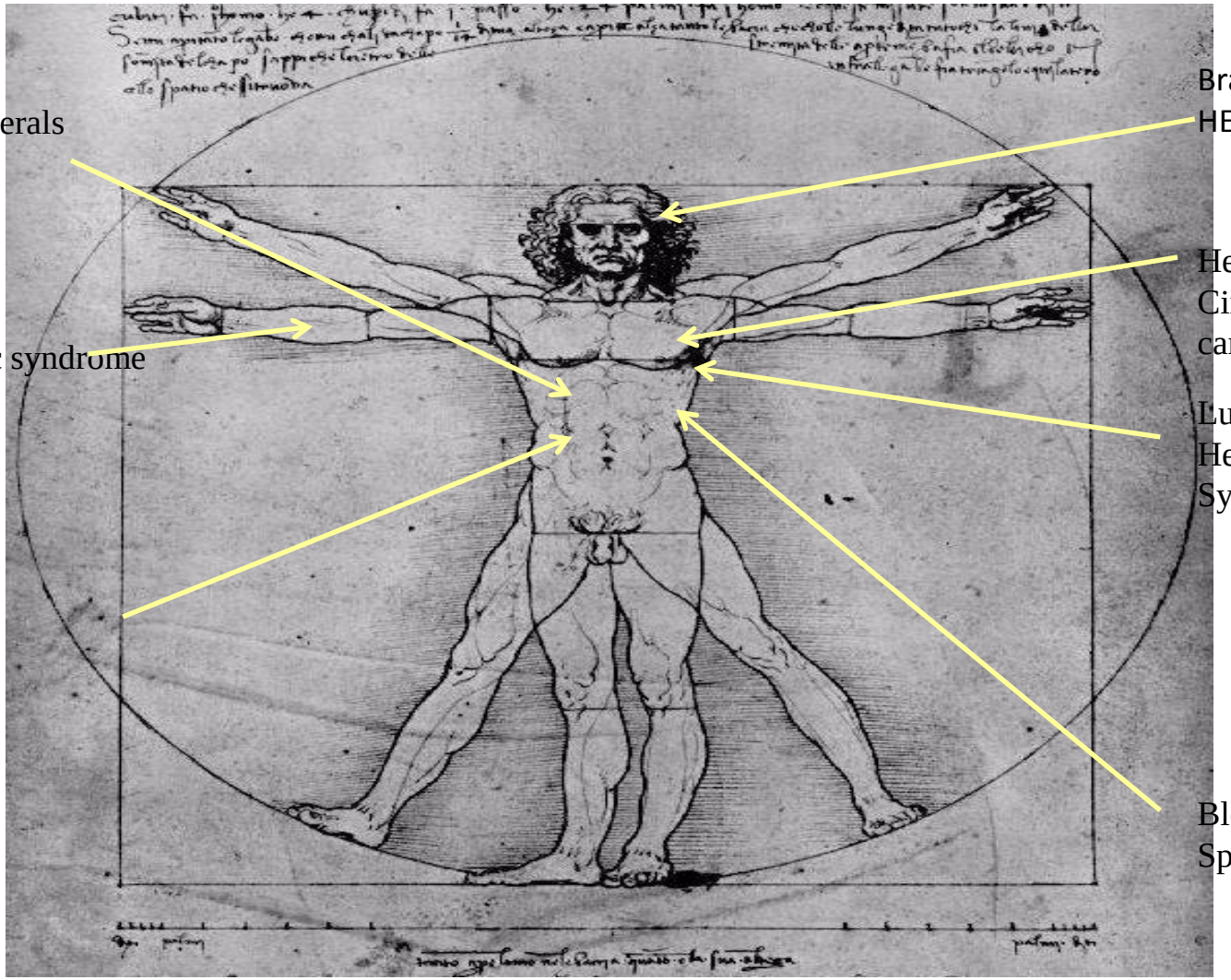
- Cirrhotic PH – “Vascular disease”
- Involves several systems and organs
- “A Multi-organ Disease”

Multi-organ involvement

Splanchnic vascular bed –
Formation of porto-systemic collaterals

Systemic circulation -Hyperkinetic syndrome

Kidneys -
Hepato-Renal Syndrome



Brain –
HE

Heart –
Cirrhotic
cardiomyopathy

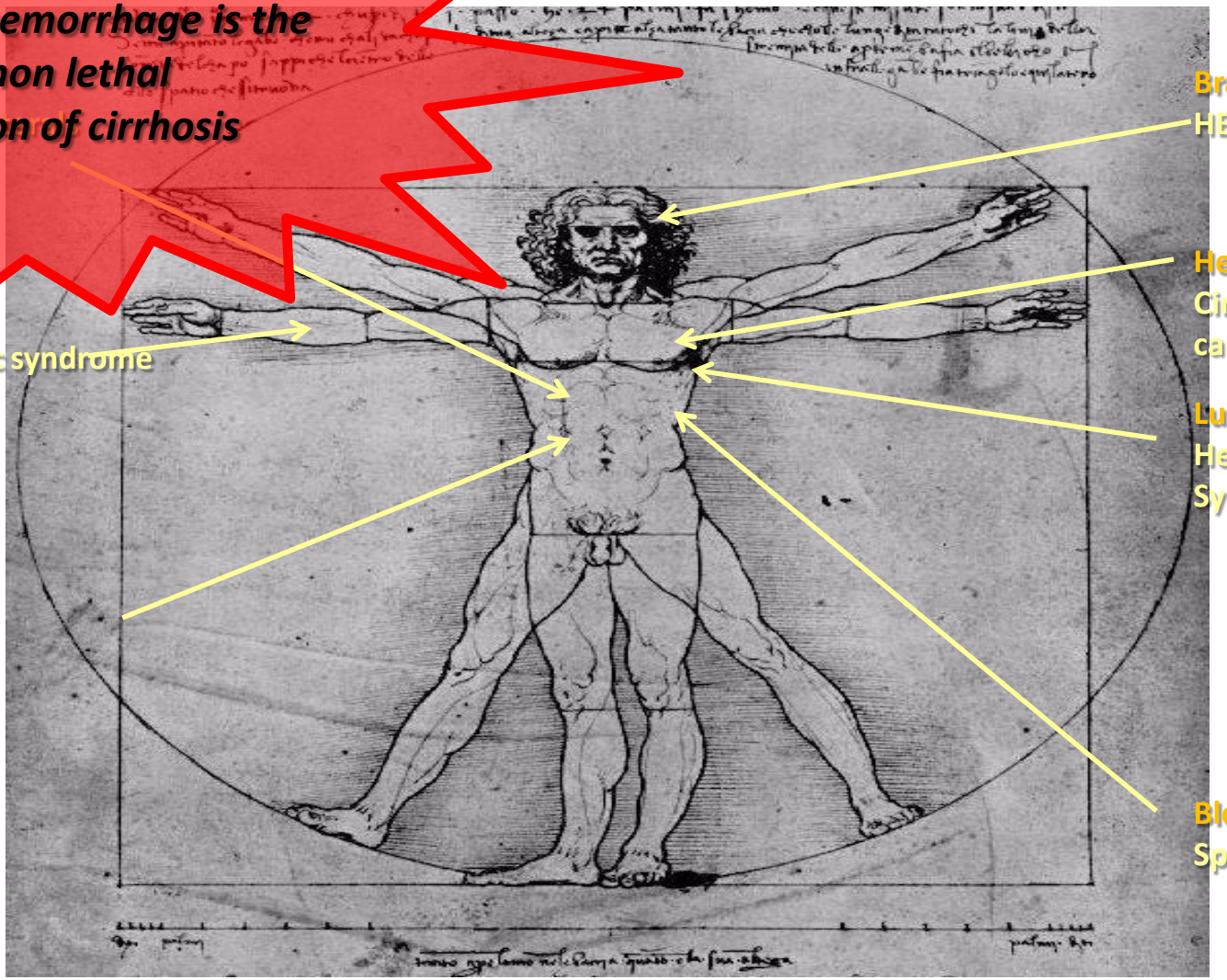
Lung –
Hepato-Pulmonary
Syndrome

Blood -
Splenomegaly and hypersplenism

Multi-organ involvement

Variceal haemorrhage is the most common lethal complication of cirrhosis

Splanchnic vascular bed -
Formation of porto



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Cirrhotic cardiomyopathy

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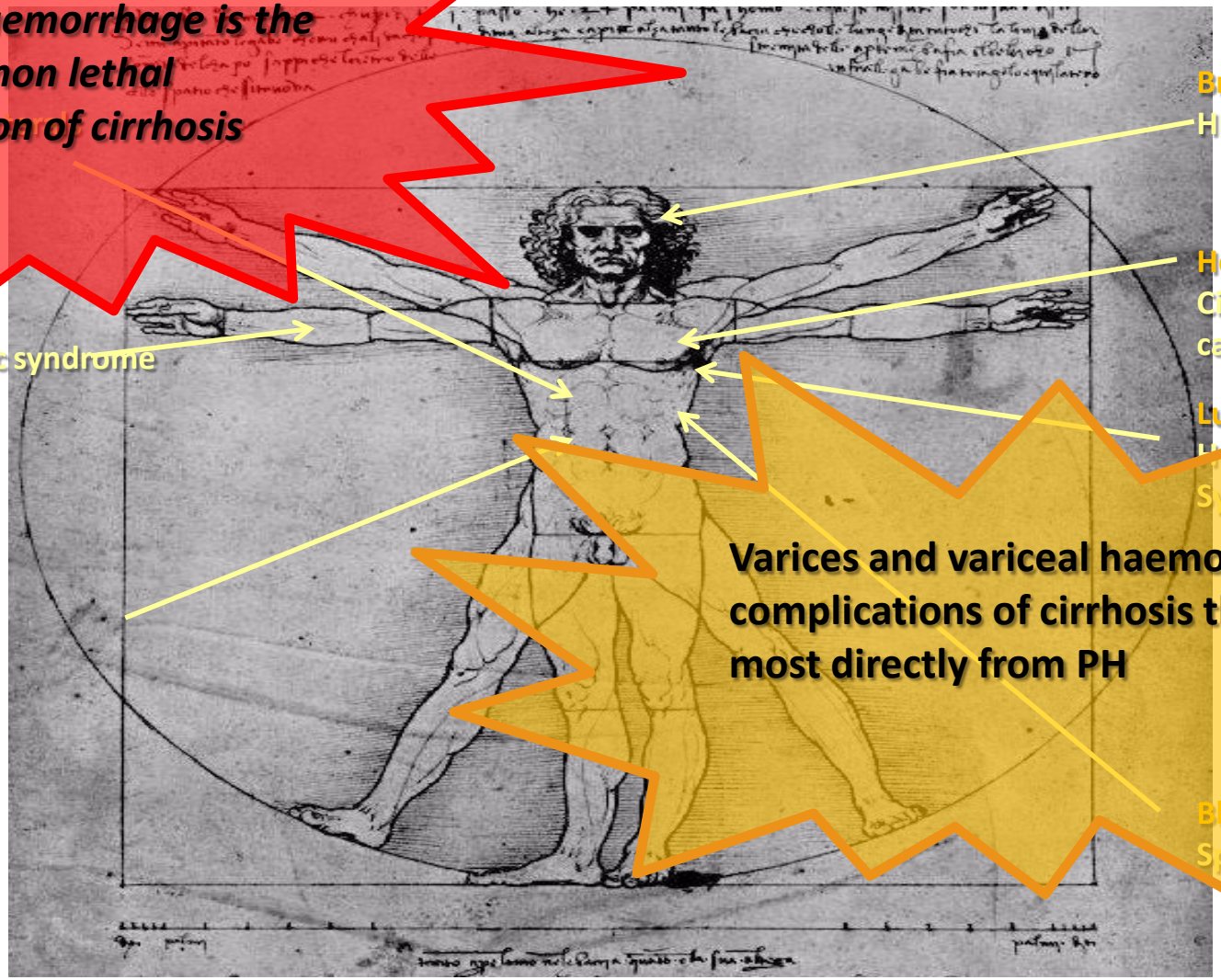


Brain –
HE

Heart –
Cirrhotic cardiomyopathy

Lung –
Hepato-Pulmonary Syndrome

Systemic circulation -Hyperkinetic syndrome

Kidneys -
Hepato-Renal Syndrome

Varices and variceal haemorrhage are the complications of cirrhosis that result most directly from PH

Blood -
Splenomegaly and hypersplenism

Porto-systemic collaterals

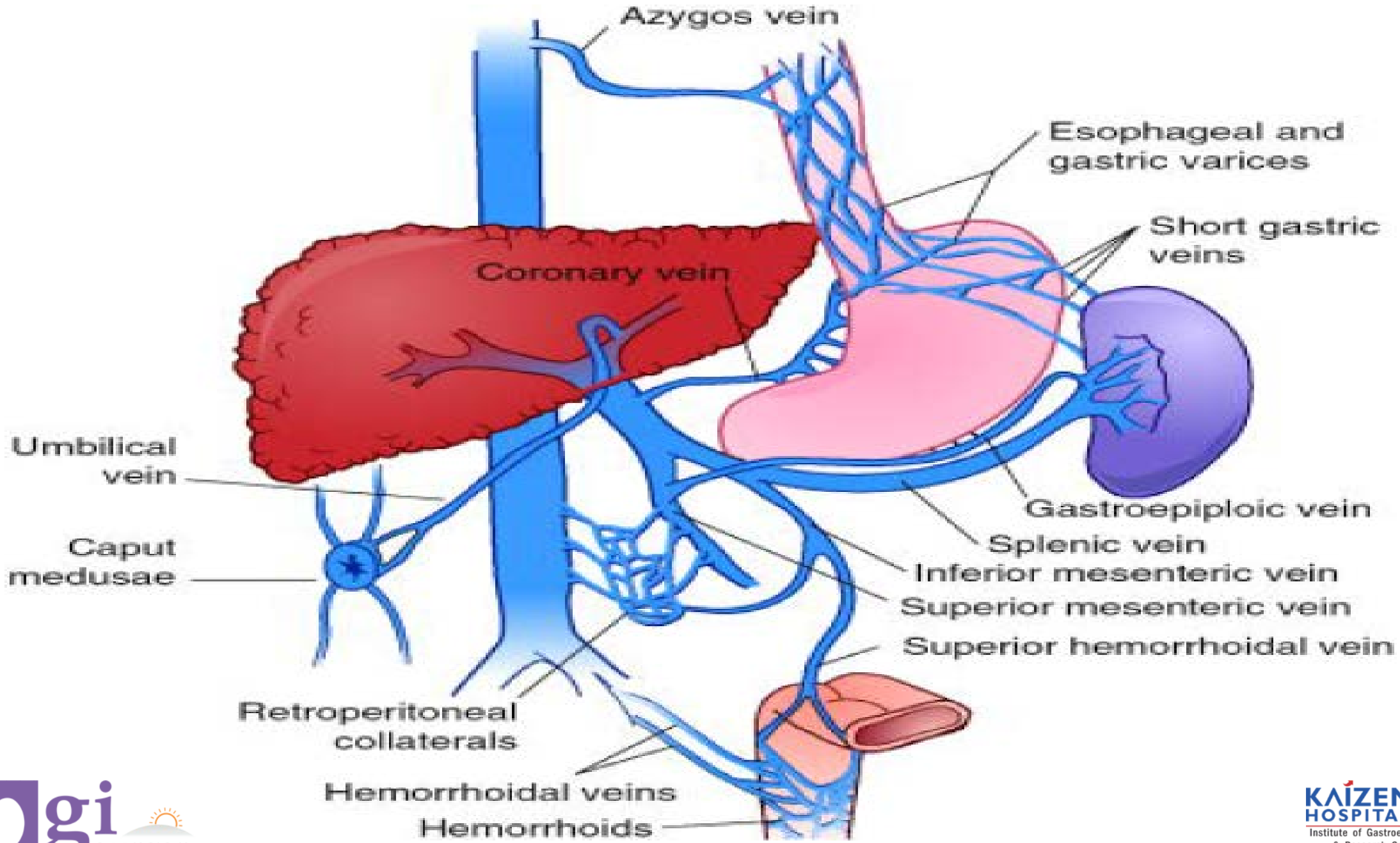
- Decompress the portal circulation
  - by shunting blood to systemic circulation
- Sites

  Distal oesophagus and proximal stomach
  - Gastroesophageal varices (GOV)
  - Major collaterals – largest flow via short and left gastric veins

  Rectum
  - Rectal varices

  Umbilicus
  - Caput medusa

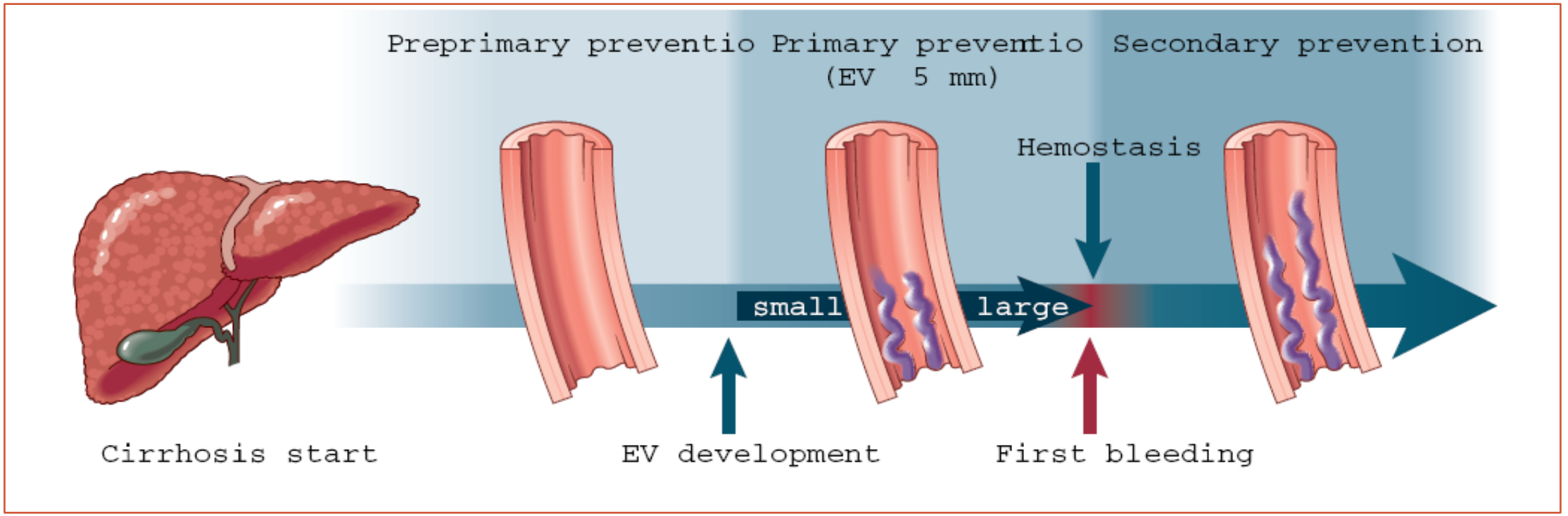
  Retroperitoneum



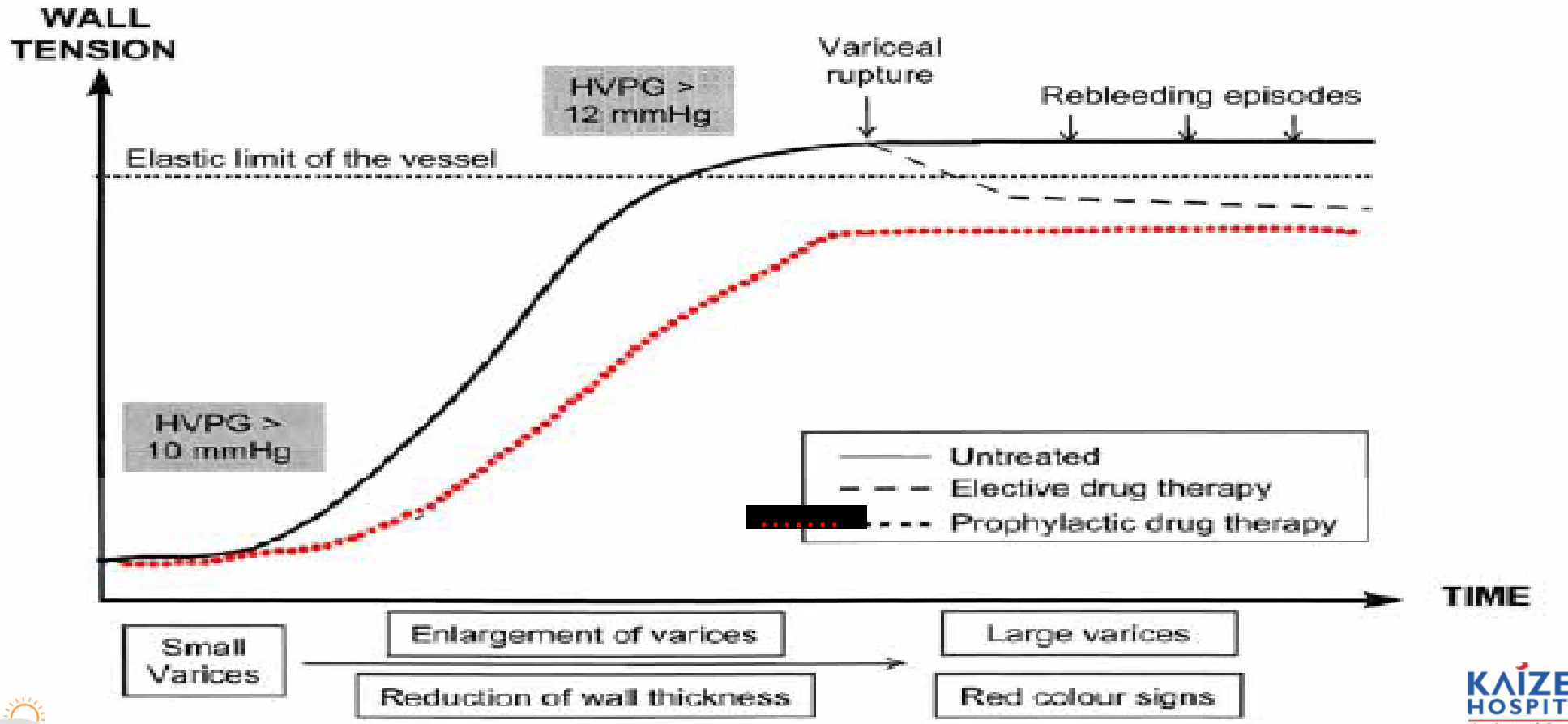
Natural History

- Progressive increase in HVPG

- Chain of events
  - Development of varices
  - Progressive dilatation of varices
  - Rupture and bleeding of varices



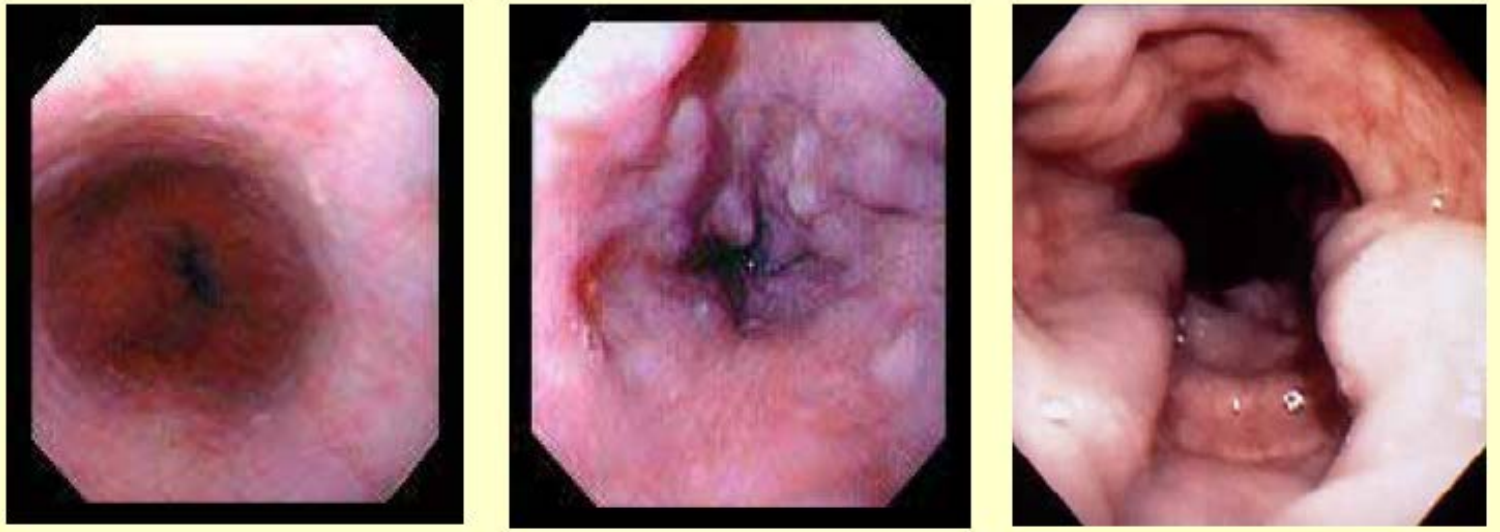
Pathogenesis of variceal bleeding



Prevalence and formation of varices

- At the time of diagnosis
  - Compensated cirrhosis
    - 30-40% have varices
  - Decompensated cirrhosis
    - 60% have varices
- Annual incidence of new varices (de novo)
  - 7% (5-10%) per annum
- Appearance
  - HVPG > 10 mmHg
  - Strong predictor for development of varices

Prevalence of varices in patients with cirrhosis without prior bleeding



18 %

58 %

24 %

(n = 548)

Lay et al., Hepatology 1997; 25: 1346

Progression of varices from small to large

- Rate or progression
  - 5 to 30% per year

- Predictors of progression
  - Child-Pugh class (most consistent)
  - Increase in HVPG
  - Alcoholic aetiology
  - Presence of red wale marks

Incidence of first bleeding

- Overall
  - Incidence 4% per year

- Large varices
  - Incidence 15% per year

Risk indicators of first bleeding

- Rupture and bleeding
  - Large varices
  - HVPG > 12 mmHg
  - Child-Pugh class C
  - Presence of red-signs
    - Red wale marks (longitudinal red streaks on varices)
    - Cherry-red spots (red discrete flat spots on varices)
    - Haematocystic spots (discrete, red raised spots)
    - Diffuse erythaema

Prognosis after a bleed

- 1/3 cirrhotic experience variceal bleeding
- Each episode
  - 15-20% mortality at 6 weeks
- Untreated
  - Rebleeding occurs in 60% within 1-2 years
  - 70% die < one year on the initial bleed

Diagnostic modalities

- Invasive
  - HVPG measurement
  - Endoscopy
  - Endoscopic video capsule
- Non-invasive
  - Clinical signs and lab findings
  - Imaging techniques
  - Liver stiffness (Fibroscan)

HVPG

- Invasive
  - Measured by hepatic vein catheterization
- Gold standard
  - Objective and quantitative equivalent of PPG in cirrhosis
- Add prognostic information
  - Compensated cirrhosis
  - Acute variceal bleeding
  - Liver transplantation

HVPG - limitations

- Lack of local expertise
- Poor adherence to guidelines
  - Cannot ensure reliable and reproducible measurements
- Invasive
- Cost

Endoscopy

- At time of diagnosis of cirrhosis
  - All patients
  - To document the presence of varices
  - To determine the risk for variceal haemorrhage

- To detect patients requiring prophylactic treatment

Endoscopy screening for GOV

- Without varices
- Small varices
  - Child class A
  - No Red signs

Rescreen every 2-3 years

At the time of hepatic decompensation

Endoscopy screening for GOV

- Small varices
  - Child class B or C
  - Red wale marks
- Evidence of hepatic decompensation

Repeat screening at 1-year intervals

Endoscopic video-capsule

- Repeated conventional endoscopies
  - Intolerant
- Capsule endoscopy
  - Improve patient tolerance
- Once swallowed records images at pre determined intervals

Endoscopic video-capsule

- Allows correct identification of varices in 80% cases
- Problems
  - Not good at assessing variceal size
  - Poor accuracy in identifying
    - Gastric varices
    - Portal hypertensive gastropathy
- Not recommended as the routine screening method for GOV

Non-invasive tests

- Ideal test to diagnose and follow-up PH
  - Reproducible
  - Inexpensive
  - Non-invasive
- No non-invasive procedure proved to be accurate enough to avoid endoscopy in patients with negative indicators

Fibro-scan (elastography)

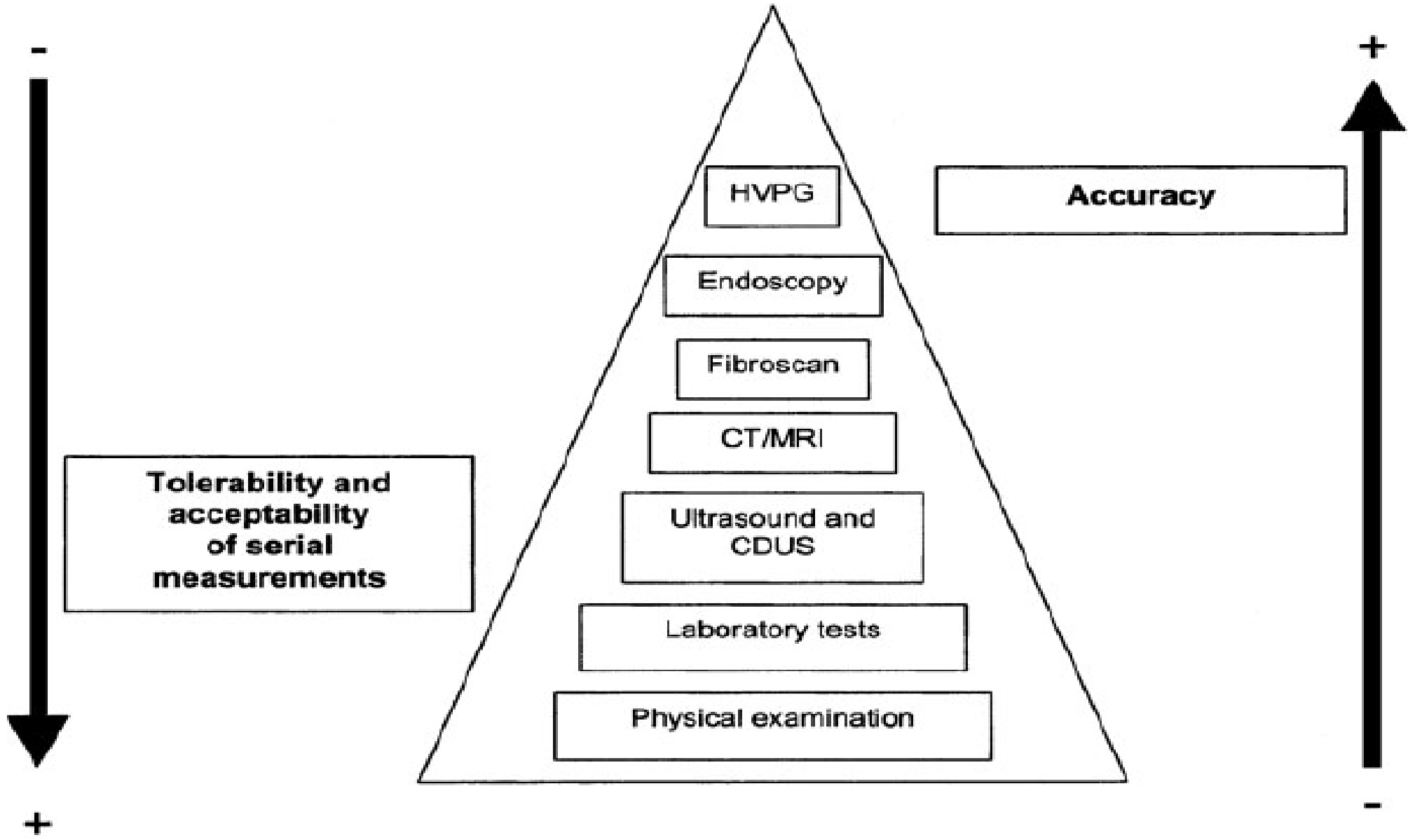
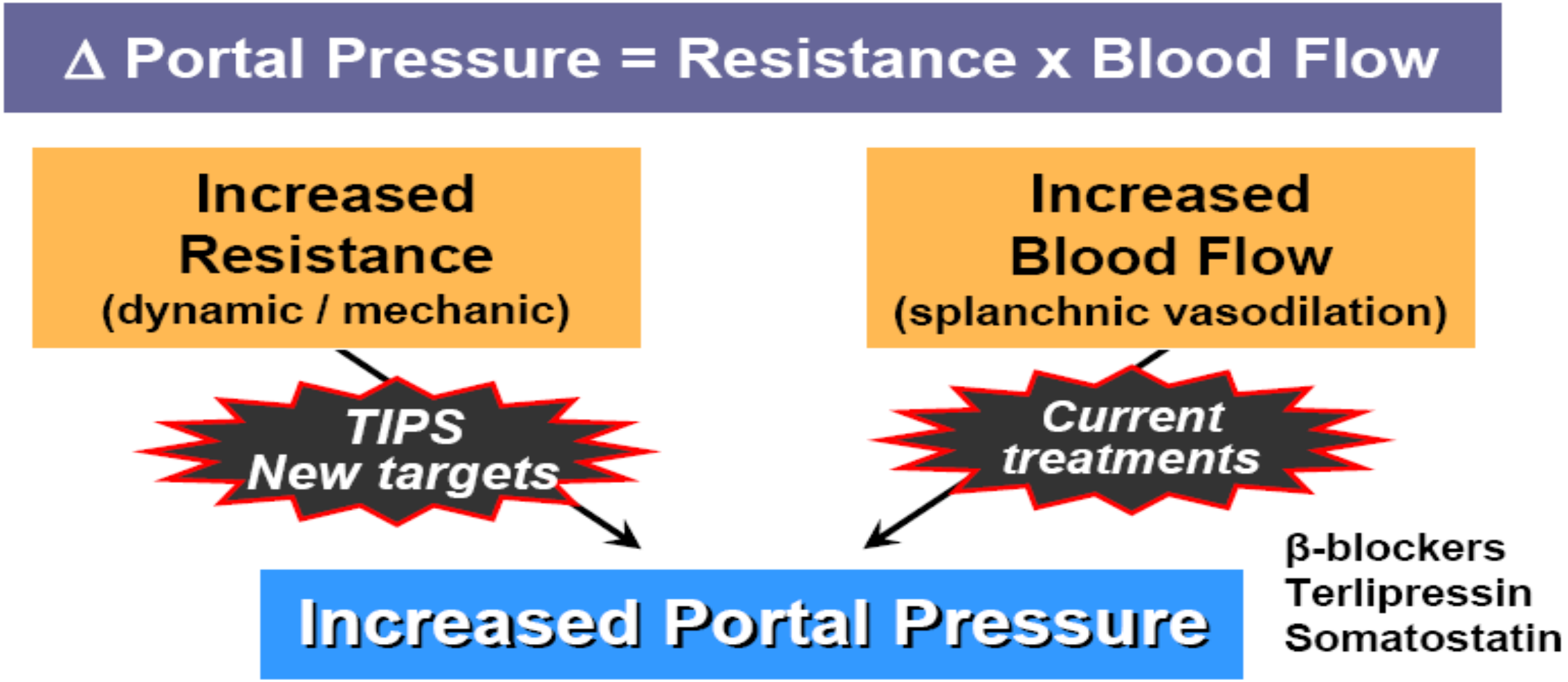


Figure 3 Existing diagnostic tools in the clinical assessment of portal hypertension. The ideal method to diagnose portal hypertension should be noninvasive, accurate, objective, and reproducible. HVPG, hepatic venous pressure gradient; CT, computed tomography; MRI, magnetic resonance imaging; CDUS, color-Doppler ultrasonography.

Pathophysiology of PH

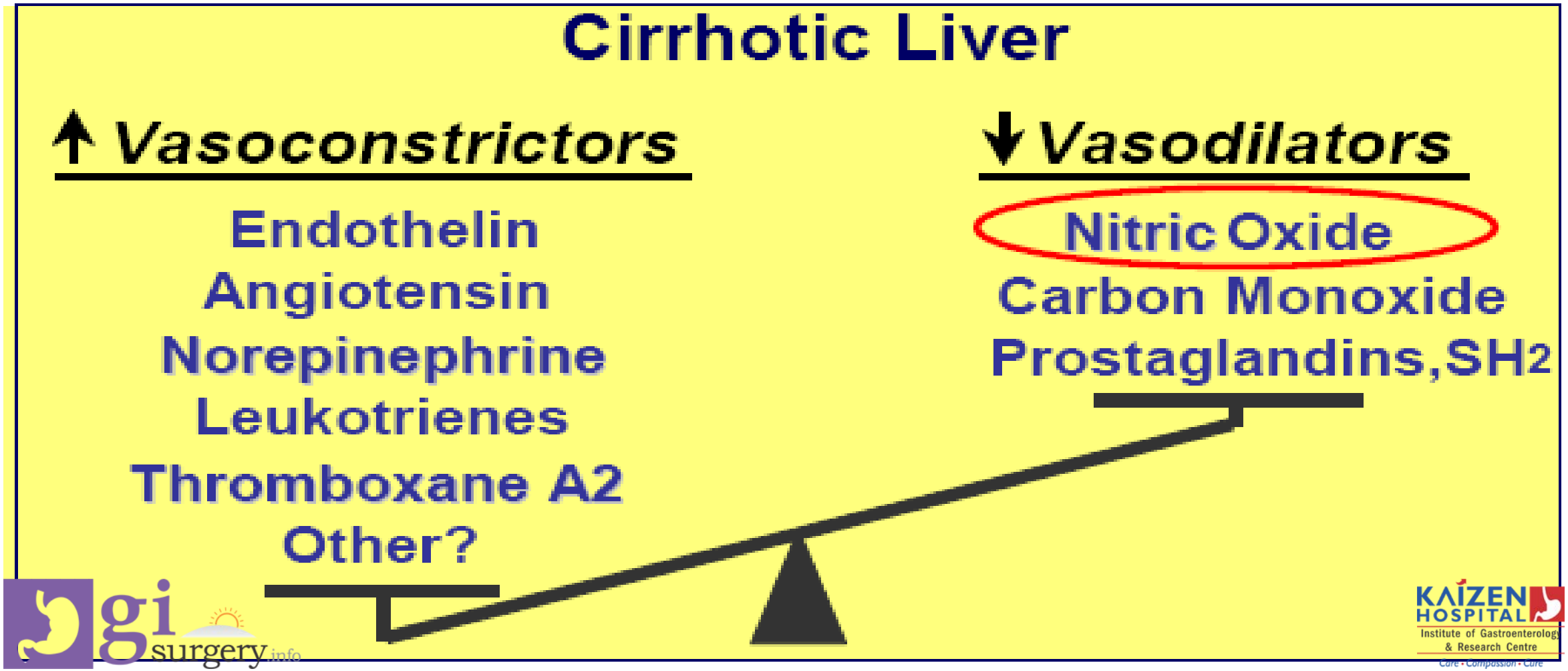


Increased hepatic resistance

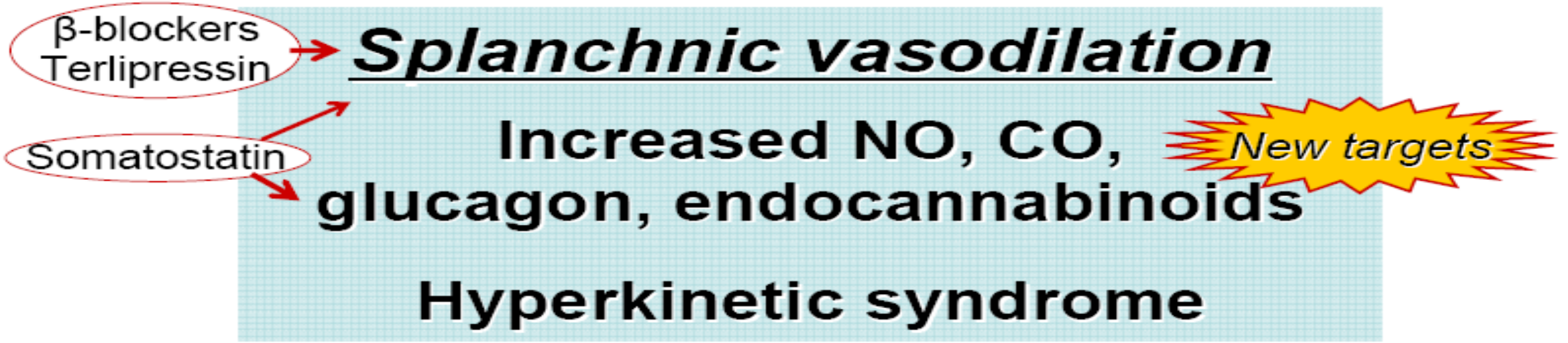
Two different components

Mechanical	***Dynamic***
Architectural changes Fibrosis Vascular occlusion	Endothelial dysfunction ↑ Vascular tone

Dynamic component



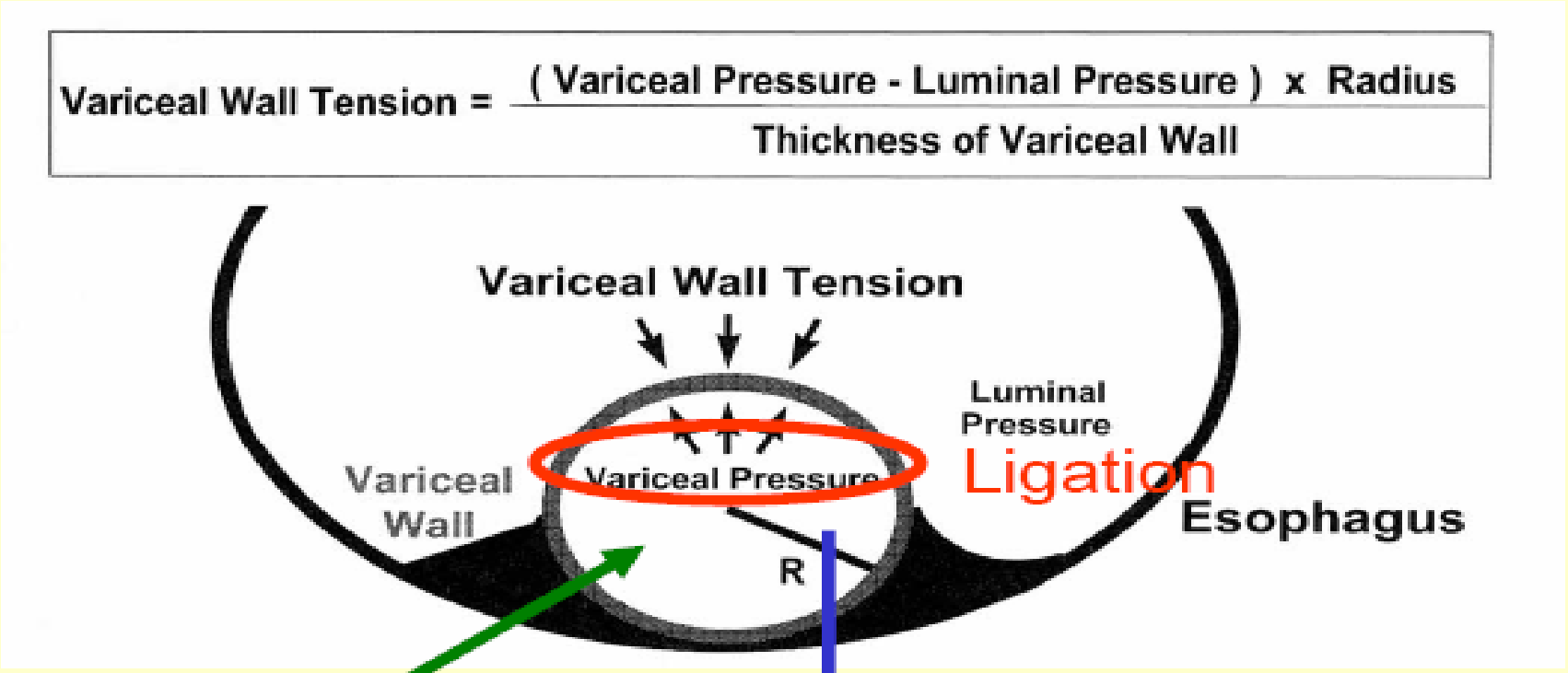
Increased portal inflow



Increased cardiac index
Decreased peripheral resistance
Hypotension & "Effective" hypovolemia
Activation of vasoactive factors
Na retention

Treatments for varices

$$\text{Variceal Wall Tension} = \frac{(\text{Variceal Pressure} - \text{Luminal Pressure}) \times \text{Radius}}{\text{Thickness of Variceal Wall}}$$



Escorsell and Bosch, Kluwer 2004

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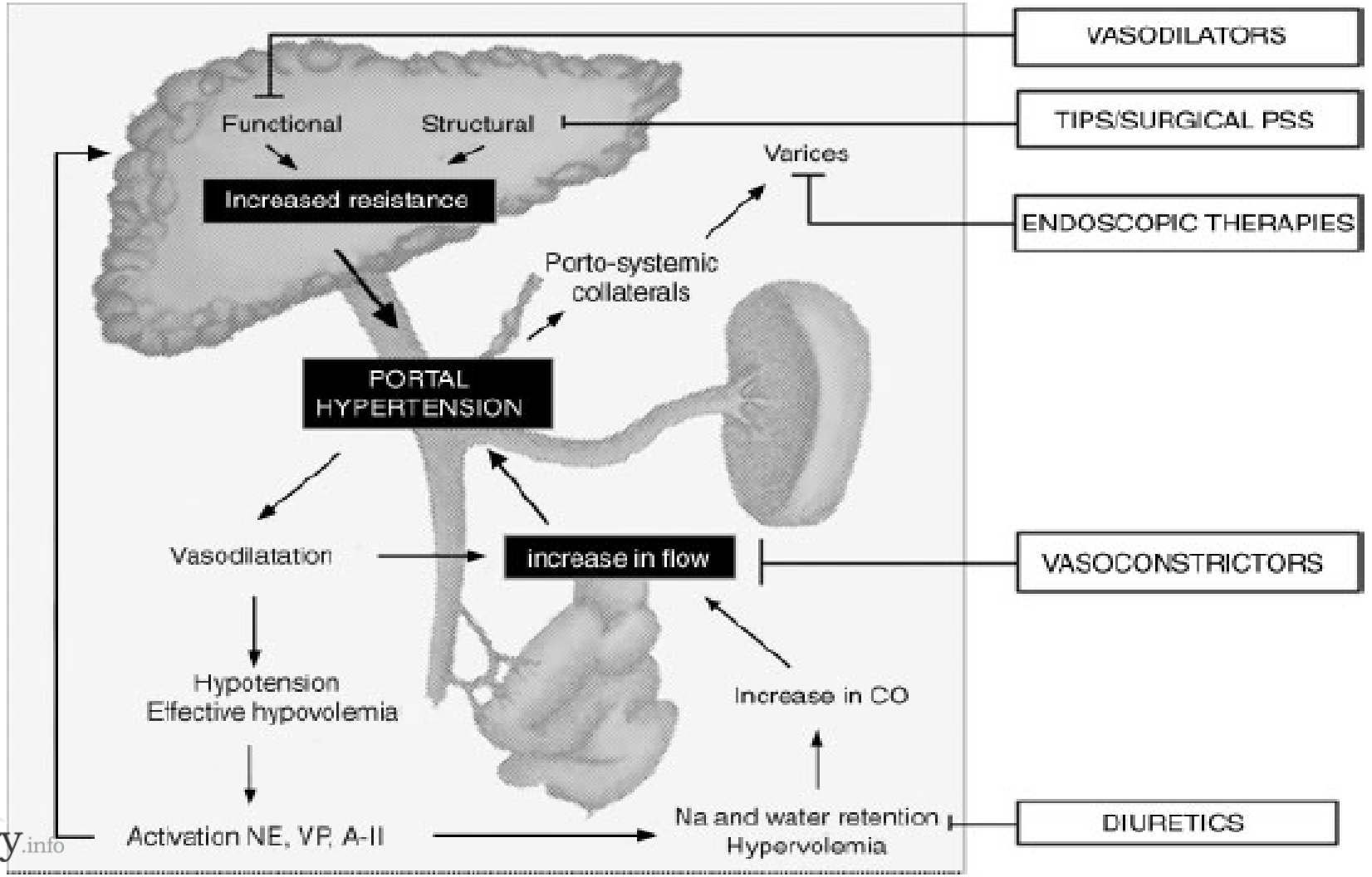
Care • Compassion • Cure

Rational basis for therapy



HVPG monitoring

- Sufficient HVPG decrease
  - ≤ 12 mmHg or
  - > 20% from baseline
- Effective protection from first variceal bleed

Turnes J, Garcia-Pagan JC, Abraldes JG, Hernandez-Guerra M, Dell'Era A, Bosch J. Pharmacological reduction of portal pressure and long-term risk of first variceal bleeding in patients with cirrhosis. Am J Gastroenterol 2006;101:506–512

HVPG monitoring

- Should HVPG be used to monitor PP response to drug treatment in clinical practice ?
- Two simulation analysis
  - Conflicting results
- Study of HVPG-guided therapy
  - Shift of non-responders from β-blockers to EBL
  - Does not improve outcome

Bureau C, Peron JM, Alric L, et al. ‘‘A la carte’’ treatment of portal hypertension: adapting medical therapy to hemodynamic response for the prevention of bleeding. Hepatology 2002;36:1361–1366

HVPG-guided therapy in the prevention of re-bleeding

- HVPG responders
  - Pharmacological (or spontaneous) reduction of HVPG to <12 mmHg or by ≥20 % of the baseline value
  - Markedly decreases the risk of re-bleeding and reduces mortality
  - Bleeding risk even lower than achieved using surgical shunts or TIPS

HVPG-guided therapy in the prevention of re-bleeding

- Drug therapy ‘ideal’ treatment in HVPG responders
- To add further treatment (i.e., ligation) is likely to not enhance efficacy but *increase the SEs*

HVPG-guided therapy in the prevention of re-bleeding

- HVPG non-responders
  - No data on how to improve outcome of this high risk population
  - Spanish multicentre RCT
    - HVPG non responders to nadalol with or without ISMN shifted to receive EBL
    - No significant difference in re-bleeding rates
  - EBL may not be best alternative to reduce re-bleeding in HVPG non-responders

Thank You