Hepatorenal Syndrome 2018

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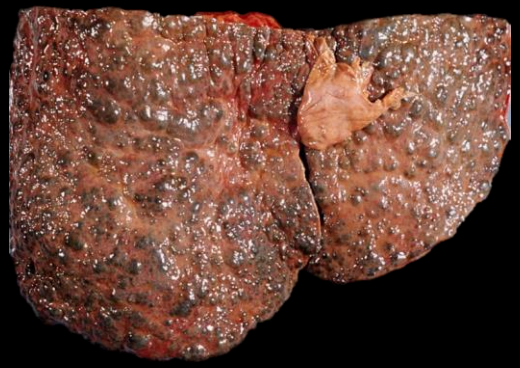
Case Presentation



60 year male with Diabetes
Cirrhosis : NASH
Stable : well compensated

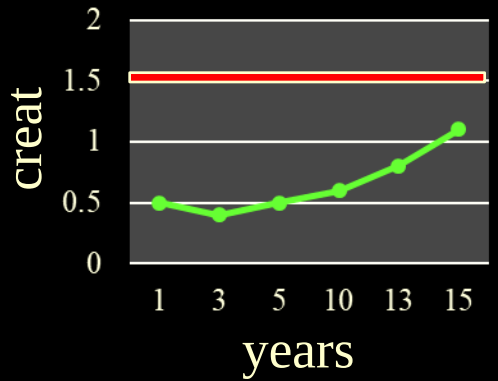
U.S. Prevalence
3.9 million with liver disease
633,000 cases of Cirrhosis
New cases of Cirrhosis / yr
30,000
Deaths / yr
20-40,000

10 yrs
(58% of all cases)

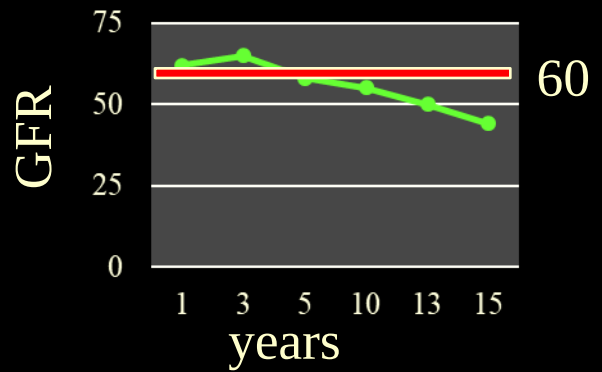
Portal HTN

Ascites
Stable : well compensated

1 -5 yrs
(20 – 40% of all cases)



Hepatorenal Syndrome



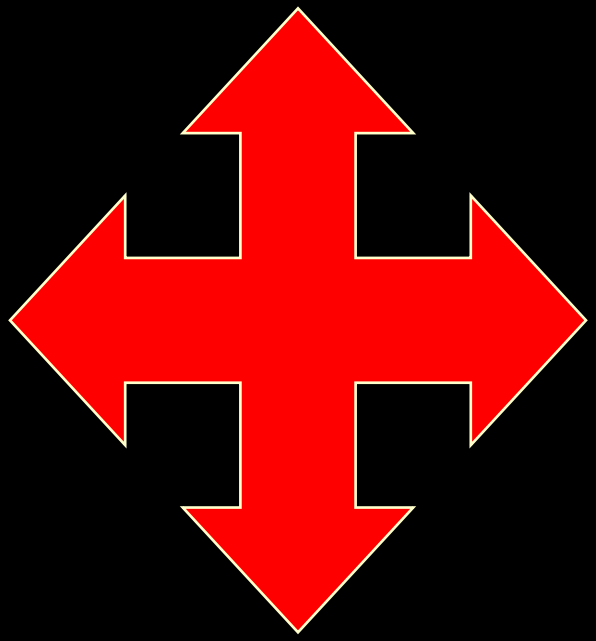
Outline of Discussion Topics

- **What are the diagnostic criteria for Hepatorenal Syndrome (HRS) ?**
- **Does a patient with HRS have Acute Kidney Injury or Chronic Kidney Disease or Both ?**
  - **Or is it Fake News and there is no "True" kidney disease ?**
- **What is the pathophysiology behind the development of HRS ?**
- **What therapeutic options are available for HRS ?**
- **Does a patient with Cirrhosis and HRS need a Liver Transplant only or a combined Liver and Kidney Transplant ?**
- **Will we finish this topic before noon ?**

Importance of Accurate Assessment of Renal Function in Liver Disease

Determine drug dosing

Calculate the MELD score



Determine the need for combined liver / kidney Transplantation

Diagnosis / Treatment response of HRS

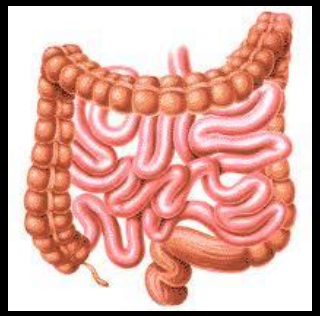
Serum Creatinine

- **Creatine**
  - **Synthesized in the liver and stored in muscle**
  - **Also ingested orally and localized to muscle**
- **Creatinine**
  - **Cyclic anhydride of creatine (nonenzymatic)**
  - **End product of muscle metabolism**
- **Renal excretion of creatinine**
  - **GFR - filtration**
  - **Tubular secretion**

Origin of Creatinine

Oral Ingestion-Meat

(creatine)



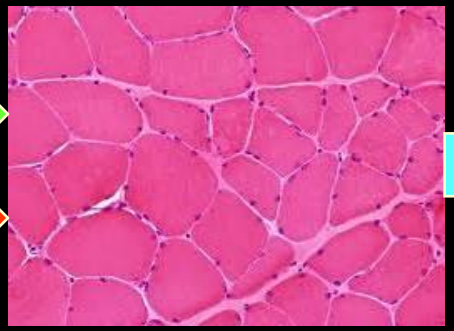
50%

50%

Muscle

(Energy source-

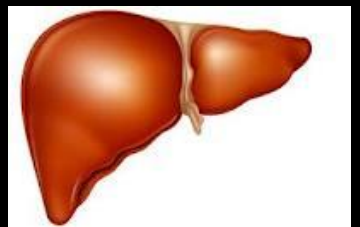
Metabolized)



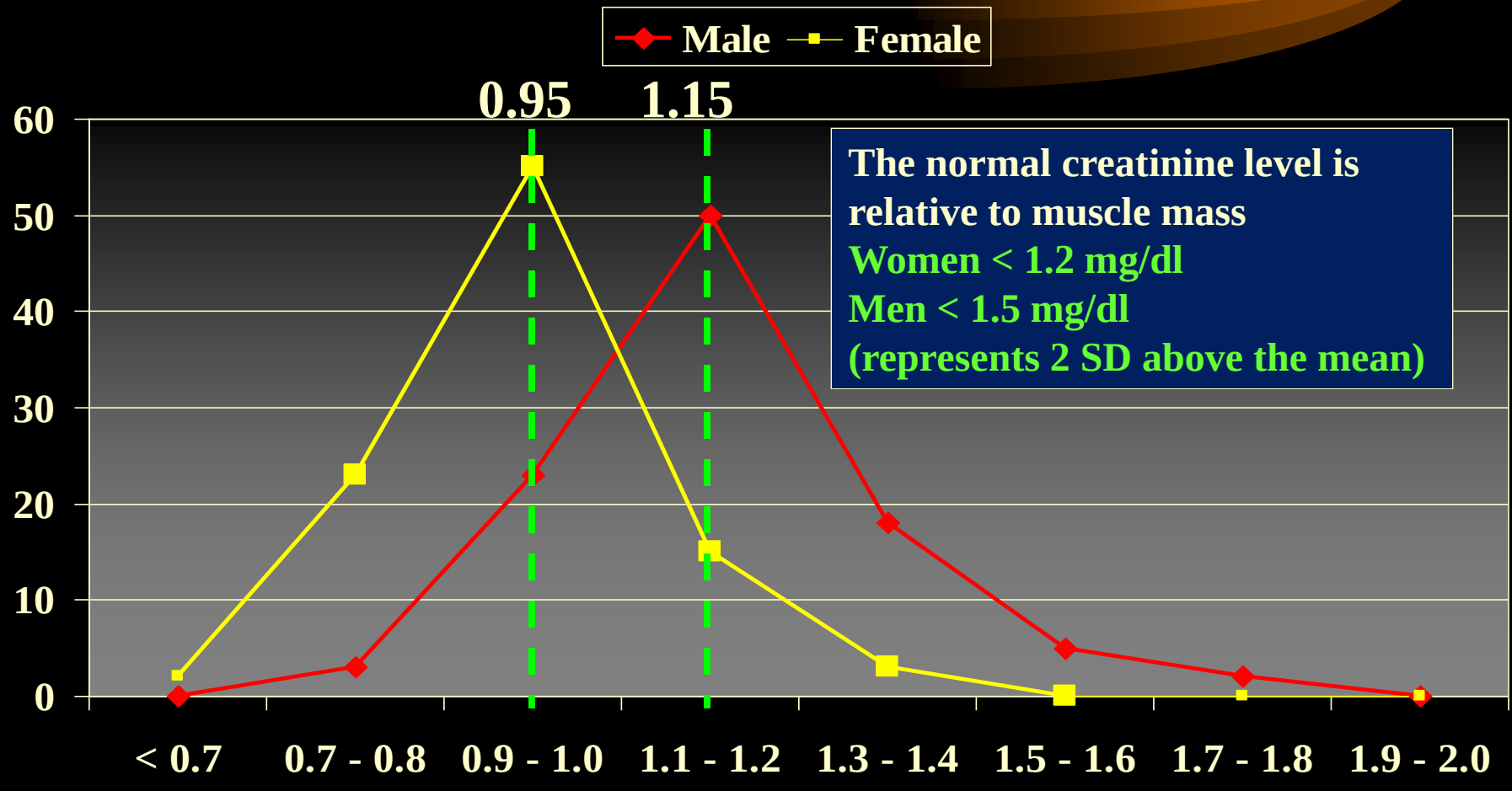
Creatinine

Hepatic Synthesis

(creatine)

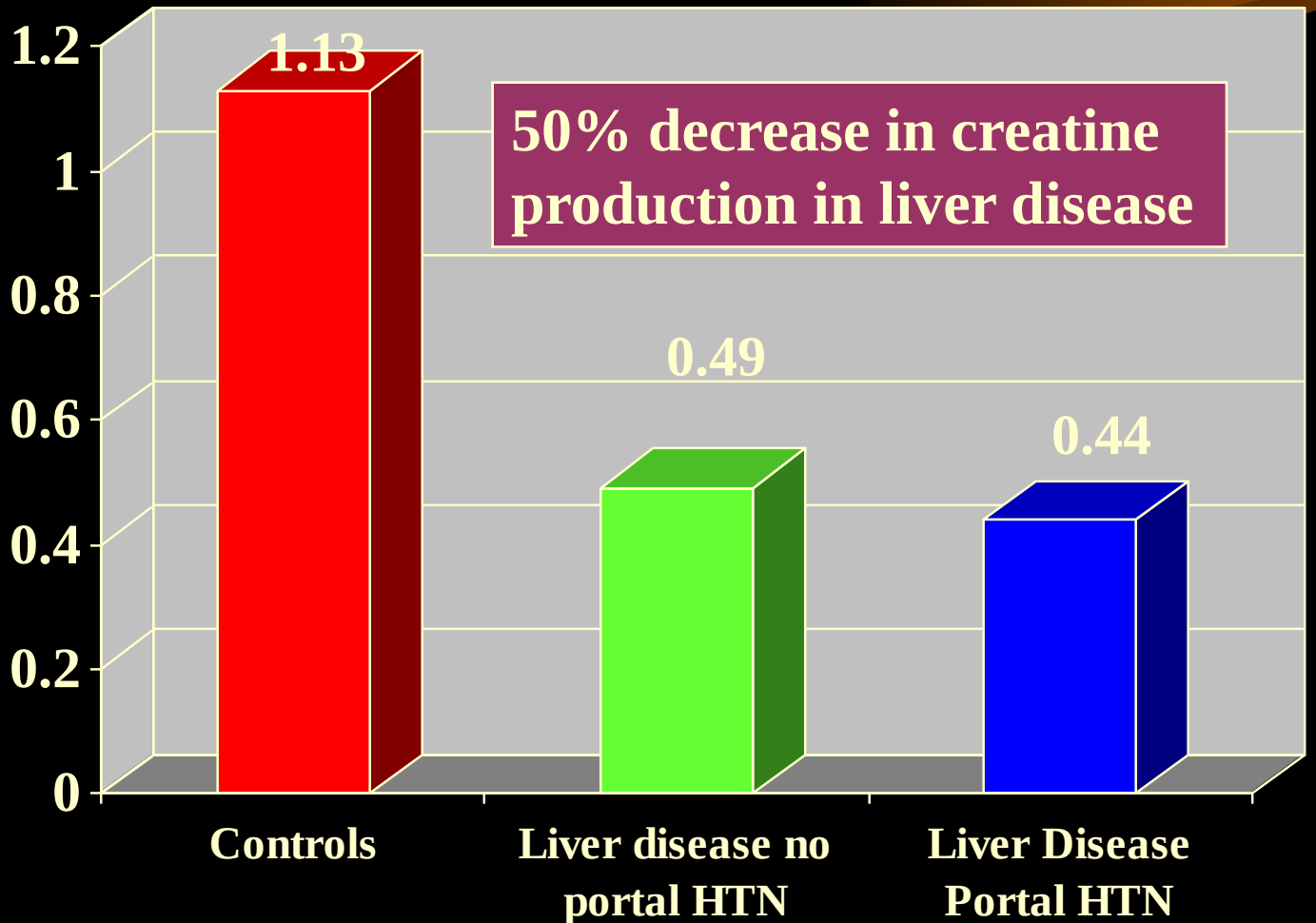


Range of Creatinine Values in the Population



Creatine Production in Patients with Cirrhosis

Gliedman et al. Ann Surg 174:892, 1971



Lower Baseline Creatinine Levels than the Normal Population

- **Cirrhosis**
  - **Minimal protein intake with severe malnutrition**
  - **Impaired liver synthesis of creatine**
- **Pregnancy**
  - **Volume expansion and an increase in GFR**
- **Extremes of age/nutrition – pediatric / elderly**

- **Baseline or "normal" creatinine in these conditions may be 0.4 - 0.6 mg/dl**
- **Patients can be in AKI or CKD in all these circumstances with <u>serum creatinines of 1.1 mg/dl</u>**

Bilirubin Interference and Creatinine Measurement

Jaffe Reaction

Creatinine + picric acid → Creatinine – picric acid complex

Reaction is read at a specific wavelength (570)

Bilirubin absorbs light at 570 which leads to a spuriously low serum creatinine

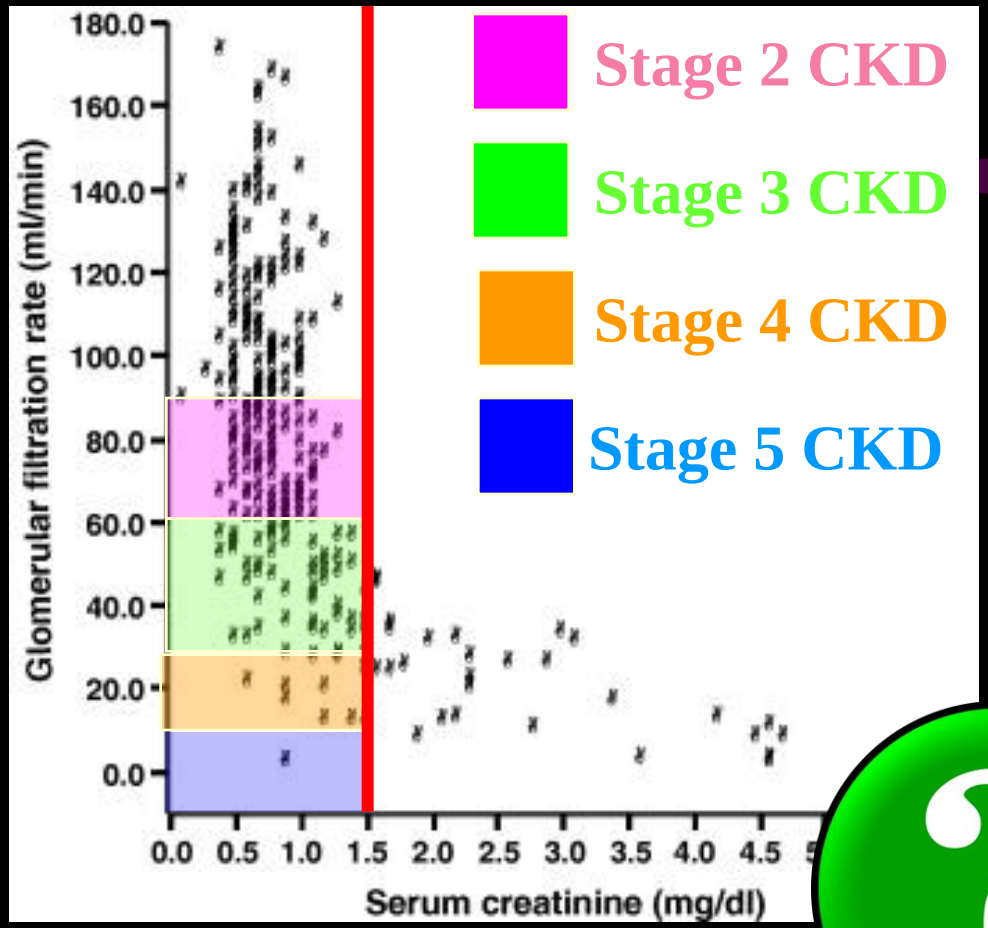
Usually noted with a bilirubin level > 25 mg/dl

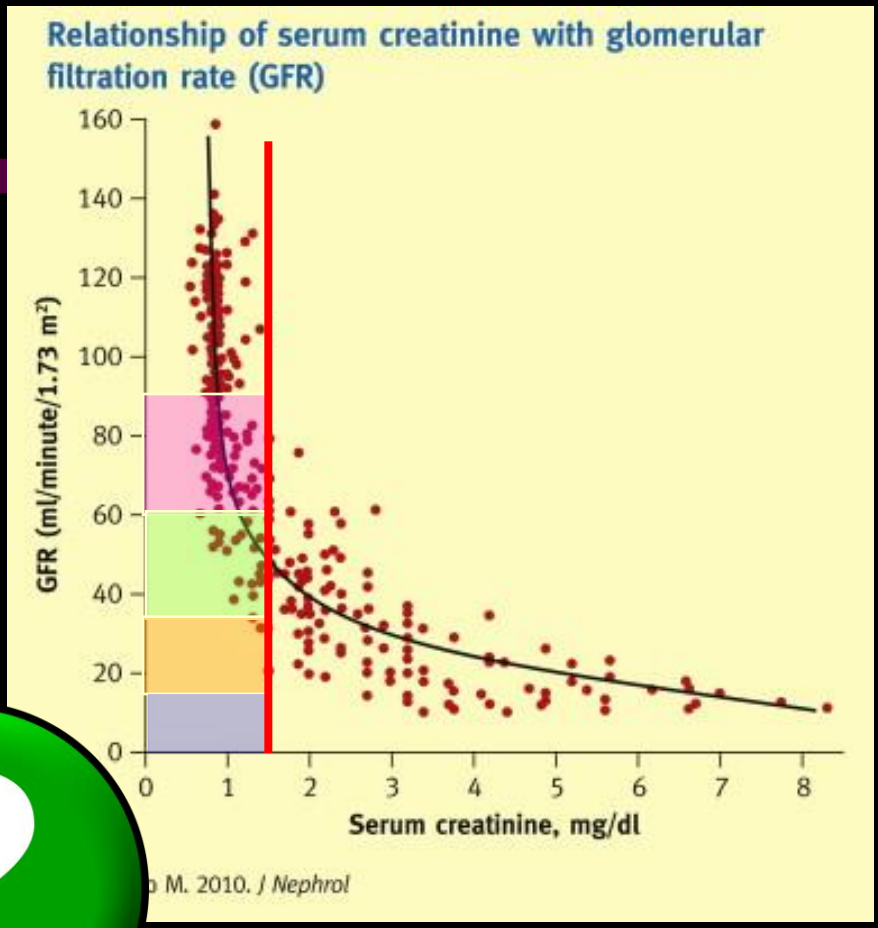
Assessment of Renal Function in Cirrhosis: Inaccuracy of the Serum Creatinine

- **Decreased Protein Intake**
- **Decreased Muscle Mass**
- **Decreased Hepatic Creatine Synthesis**
- **Spuriously Low Creatinine Measurement with Hyperbilirubinemia**

Arroyo V, J Hepatol 46:935, 2007

GFR and Cirrhosis





Cirrhosis

?

Normal

At serum Creatinine levels < 1.5 mg/dl : a significant proportion of patients with cirrhosis will have GFRs < 60 cc/min : much greater than the general population

Kidney Function in Cirrhosis

Creatinine

- **Real and Spurious decrease in serum concentration**
- **Renal Function "appears" better than it really is**

GFR

- **<u>True decline in GFR</u> compared to the general population**
- **Majority of these patients will have serum creatinine levels < 1.5 mg/dl**
- The CKD-EPI formula is not an accurate predictor of GFR and alternative formulas using cystatin C may be considered

Assessment of Renal Function in Cirrhosis: Inaccuracy of the BUN

- **Decreased Protein Intake**
- **Decreased hepatic synthesis**
- **Reduced efficacy of the BUN/Cr ratio to detect pre-renal azotemia**
- **Possible disproportionate increase in BUN in the setting of GI bleed**

Hepatorenal Syndrome : Diagnostic Criteria – International Ascites Club 2015

- **Cirrhosis or Acute Hepatic disease and Portal Hypertension**
- **Cr Increase of 0.3 mg/dl in 48 hrs or a 50% increase over 7 days**
- **Absence of nephrotoxic agents**
- **Absence of shock**
- **Absence of renal parenchymal disease**
  - **Proteinuria < 500 mg/d**
  - **No Hematuria**
  - **Normal renal ultrasound (size/echogenicity)**
- **No improvement after 48 hours following**
  - **Diuretic withdrawal**
  - **volume expansion with**
    - **Albumin 1 g/kg/day (maximum 100 g)**

Definition of AKI in the General Population

- **Increase of the serum creatinine by 0.3 mg/dl within 48 hours**

OR

- **Increase in serum creatinine by > 50% (over 7 days)**

OR

- **Urine output < 0.5 ml/kg/hr for more than 6 hours**

International Ascites Club 2015 Revised Definition of AKI in Patients with Cirrhosis

- **Increase of the serum creatinine by 0.3 mg/dl <u>within 48 hours</u>**

OR

- **Increase in serum creatinine by > 50% <u>(over 7 days)</u>**

OR

- **Urine output < 0.5 ml/kg/hr for more than 6 hours**

Conditions Causing Simultaneous Renal and Liver Failure

- **Hepatorenal syndrome**
- **Acute tubular necrosis**
- **Volume depletion**
- **Circulatory**
  - **CHF**
  - **Shock**
- **Genetic: ADPKD**
- **Collagen vascular disease**
- **Infections**
  - **Sepsis**
  - **Leptospirosis**
  - **Reye's syndrome**
  - **Hepatitis A**
  - **Hepatitis B**
  - **Hepatitis C**

Conditions Causing Simultaneous Renal and Liver Failure

- **Toxins and Medication**
  - Methoxyflourane
  - Carbon tetrachloride
  - Tetracycline
  - Acetaminophen
  - Elemental phosphorous
  - Toluene
  - Immunosuppressive drugs
- **Miscellaneous**
  - Amyloidosis
  - Sarcoidosis
  - Wilsons disease
  - Hemochromatosis
  - Venooclussive disease
  - Cryoglobulinemia

Key Point

- **Hepatorenal syndrome does not include every disease that affects the liver and kidney simultaneously**

- **Hepatorenal syndrome is a distinct syndrome that first requires the sequential initial development of liver dysfunction accompanied by portal hypertension and ascites culminating in the development of acute kidney injury**

Hepatorenal Syndrome : "Non Essential" Diagnostic Criteria

- **Additional supportive criteria but not required for diagnosis**
  - **Urine volume < 500 ml/day (65%)**
  - **Urine sodium < 10 mEq/l**
  - **Urine osm > plasma osm**
  - **Serum sodium < 130 mEq/l**

Clinical Types of Hepatorenal Syndrome

- **Type I HR**
  - **Rapid ...iora...n in renal fu...**
    - **< 2 week**
  - **Doubli... of i... Se... g/dl**

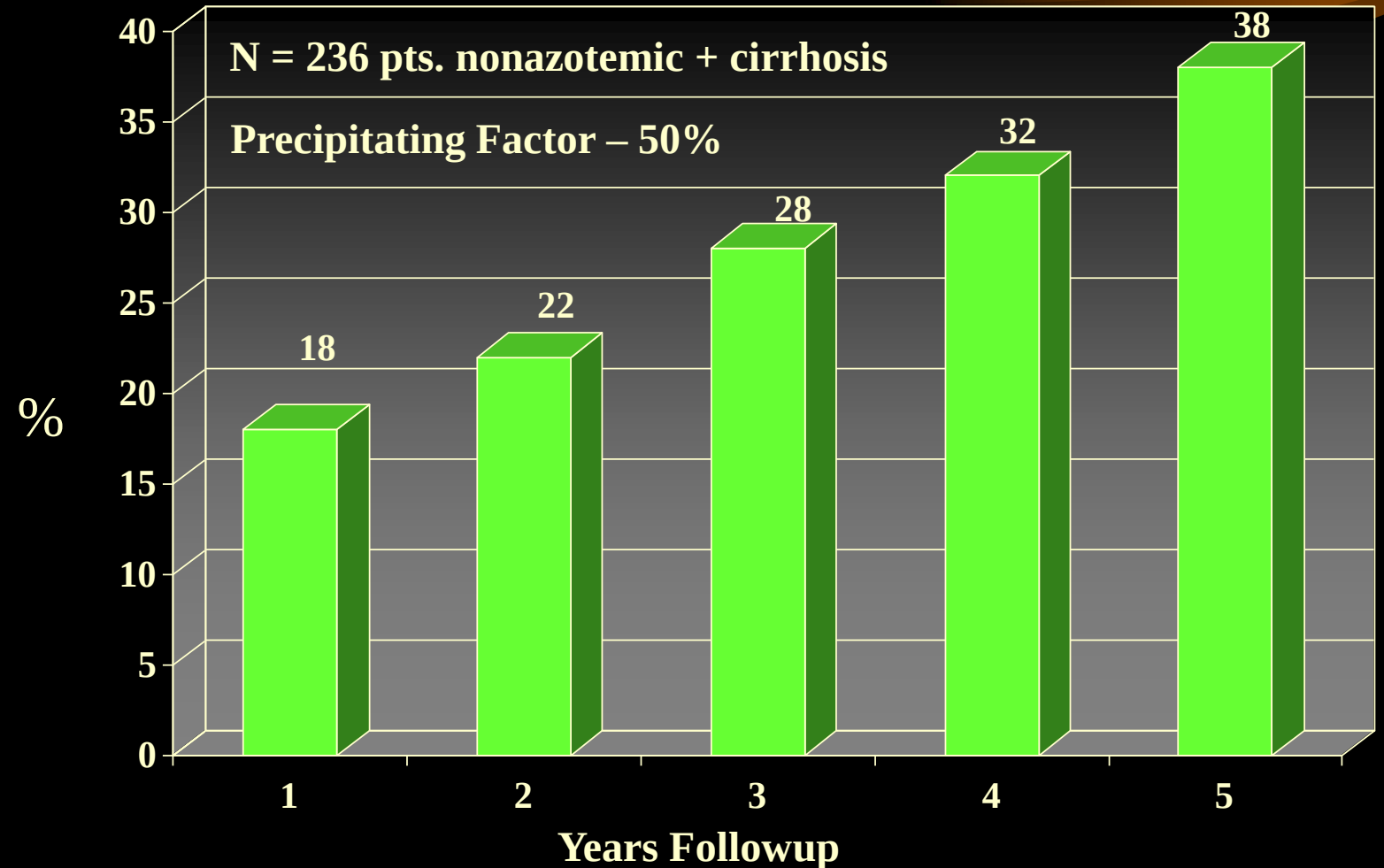
HRS - AKI

- **Type II HRS**
  - **Serum creatinine >**
  - **Slow progressive cou**

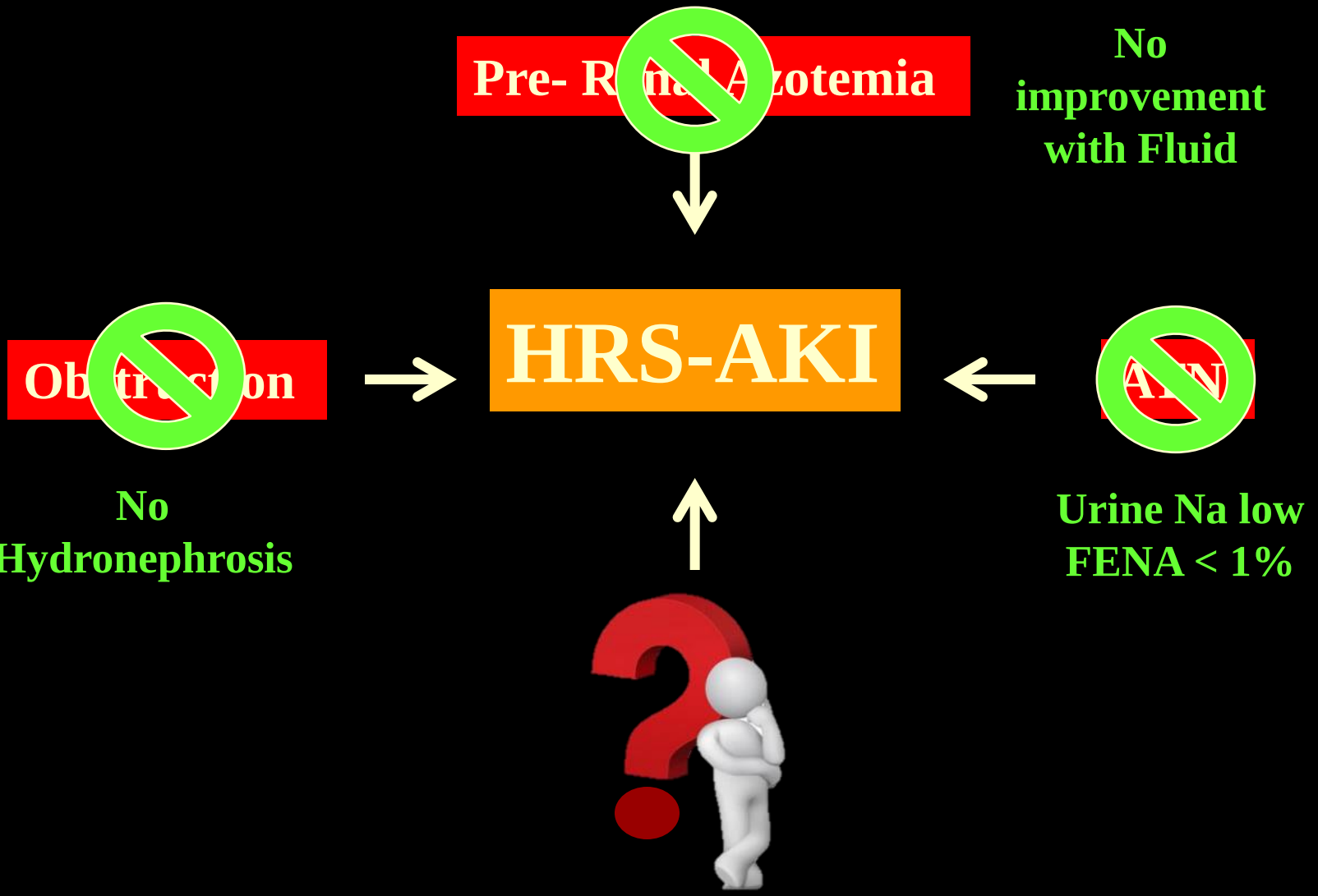
HRS - CKD

Probability of Hepatorenal Syndrome

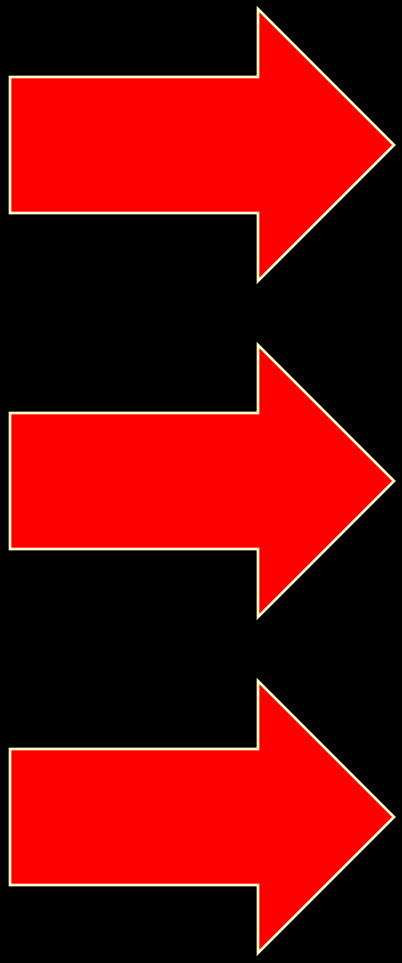
Gines A, et al. Gastroenterology 105:229-236,1993



AKI Classification of Hepatorenal Syndrome



Portal HTN



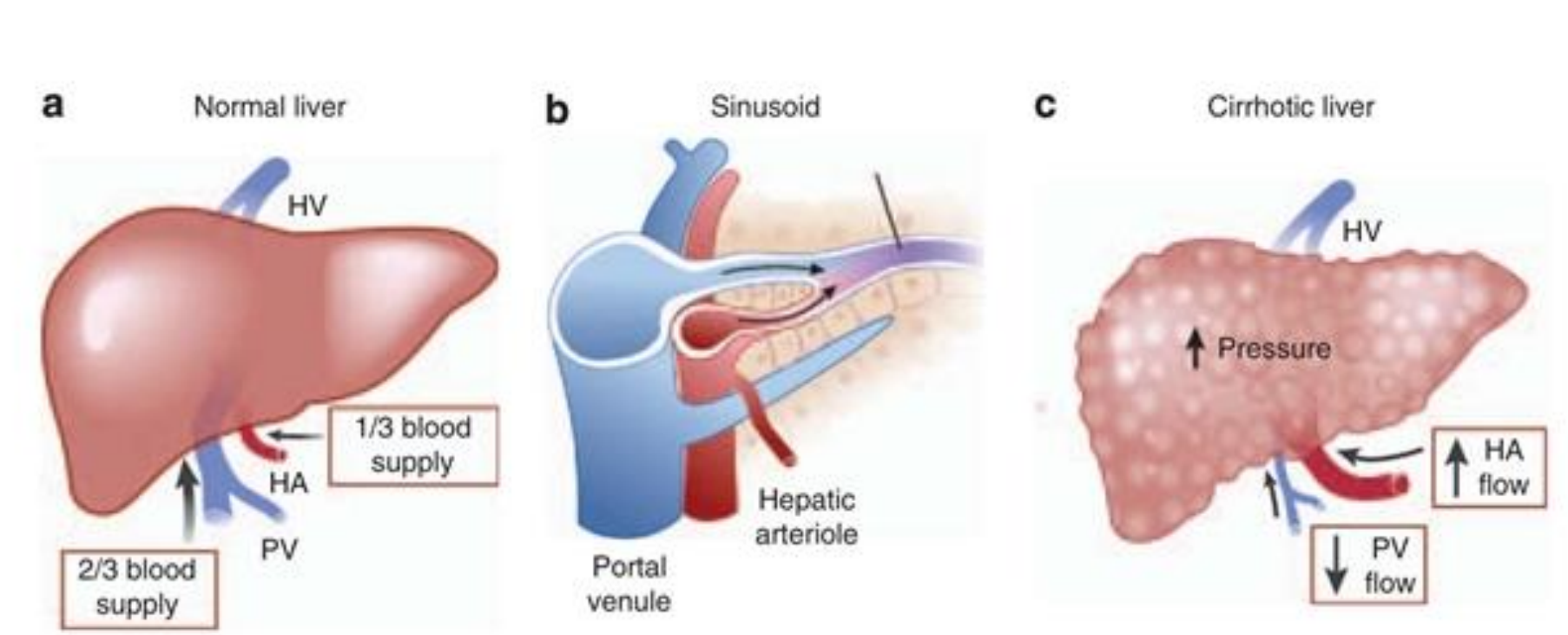
Compression, Distortion,
Obliteration of Hepatic Architecture

Decreased Hepatic production
of vasodilatory substances

Activated Hypercontractile
Intrahepatic stellate cells

Oliver J. Kidney Intern 77:669, 2010

Intrahepatic Pressure and Early Portal HTN



Hepatofugal

NFPF (Non Forward Portal Flow) Blood flow Away from the liver versus

Hepatopetal : normal flow into the liver

Backward Theory of Ascites Formation

Portal Hypertension / Hypoalbuminemia

↓

Reversal of Starling's Equilibrium in the Splanchnic Microcirculation

↓

Increased Splanchnic Lymph Formation

↓

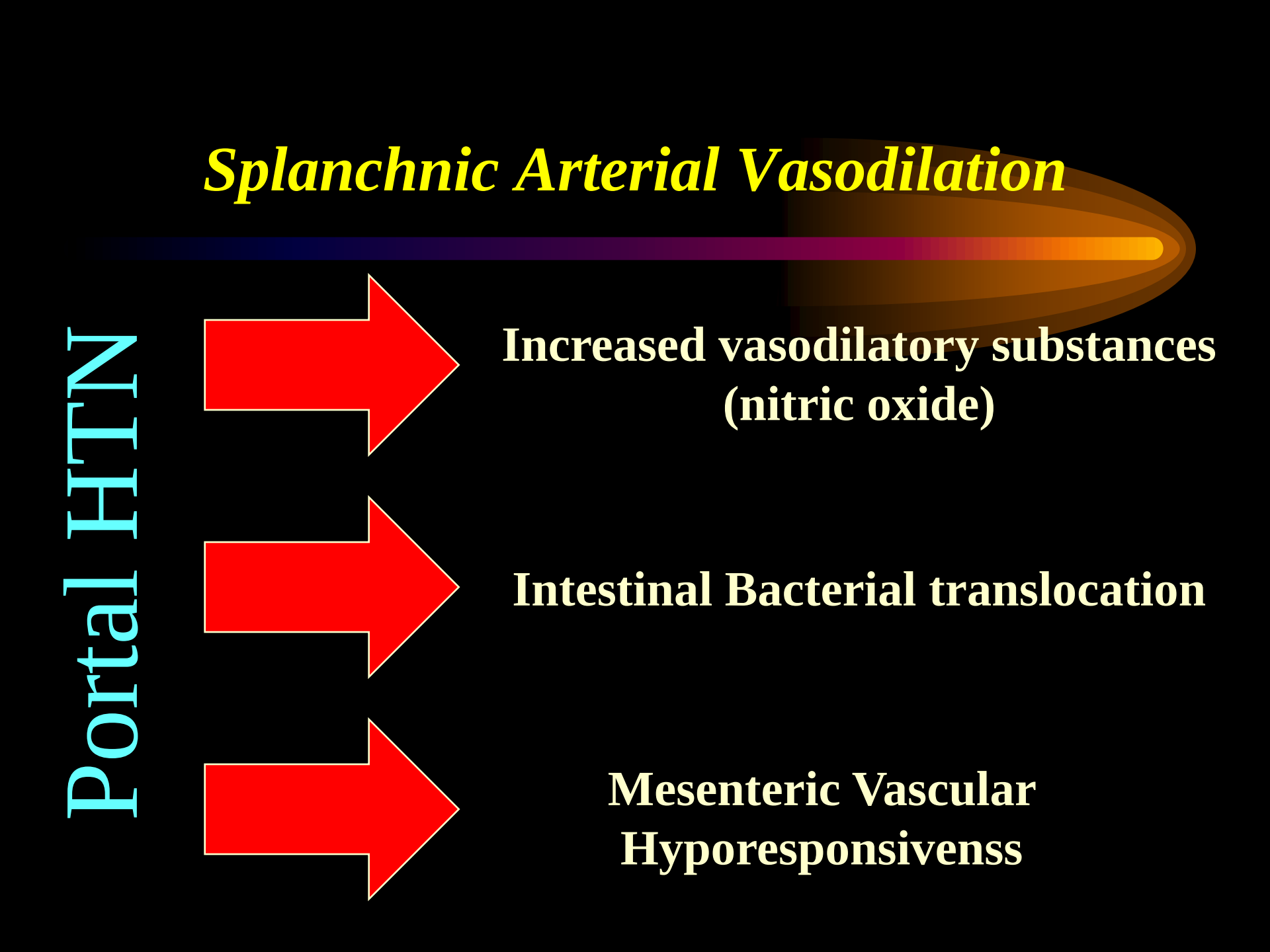
Ascites Formation

↓

Decreased Effective Circulatory Volume

Hepatorenal Syndrome

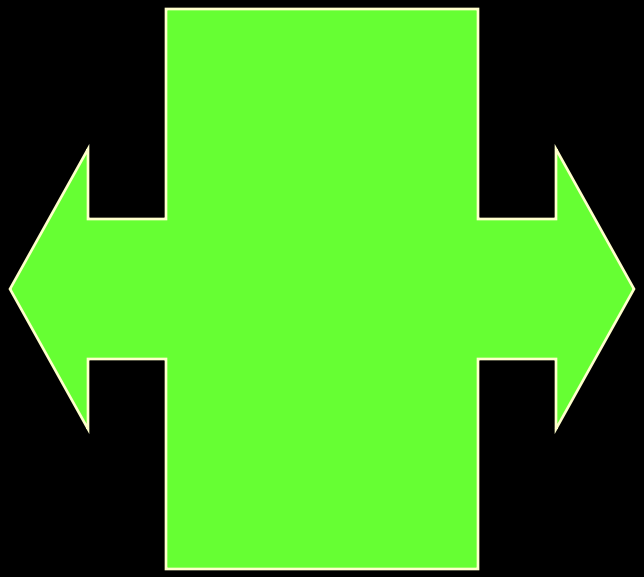
	Backward Theory	Hepatorenal Syndrome
Low urine sodium	Yes	Yes
Low blood pressure	Yes	Yes
Cardiac Output	Decreased	Increased
Systemic resistance	Increased	Decreased


Splanchnic Arterial Vasodilation
Portal HTN
Increased vasodilatory substances (nitric oxide)
Intestinal Bacterial translocation
Mesenteric Vascular Hyporesponsivenss

Nitric Oxide in Cirrhosis

Liver

Decreased



Splanchnic

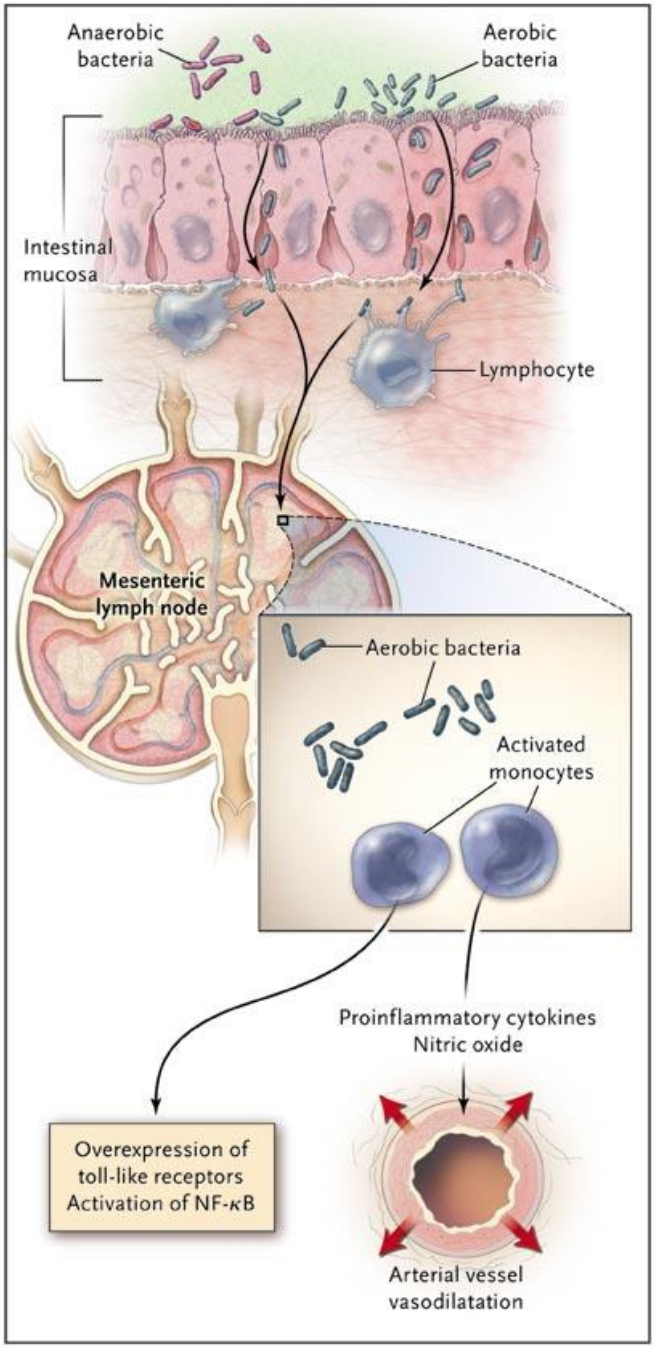
Increased

Role of bacterial translocation through permeable capillaries in the intestines

Migration to lymph nodes with increased cytokine release and local inflammatory response (PAMPs : pathogen-associated molecular patterns)

Vasodilation

Increase in ascites



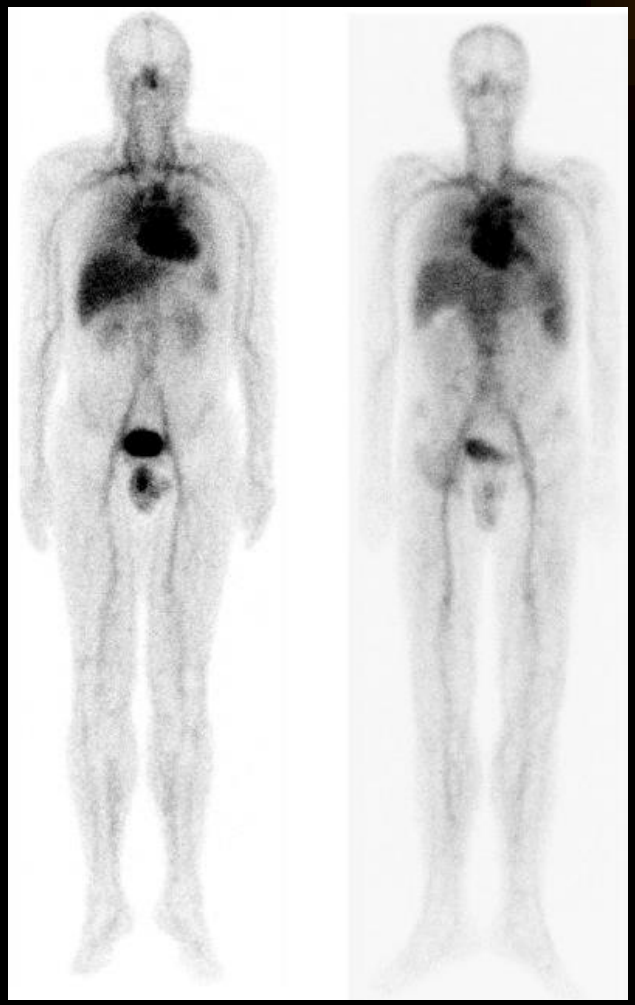
Gines P. N Engl J Med 361:1279, 2011

Hepatorenal Syndrome : Mediators of Vasodilation- Selective Splanchnic Vascular Hyporesponsiveness

- **Glucagon**
  - **Elevated levels in cirrhosis**
    - **Desensitizes mesenteric circulation to catecholamines and AII**
    - **Direct vasodilation**
    - **Increases cAMP leading to increased NO synthesis**

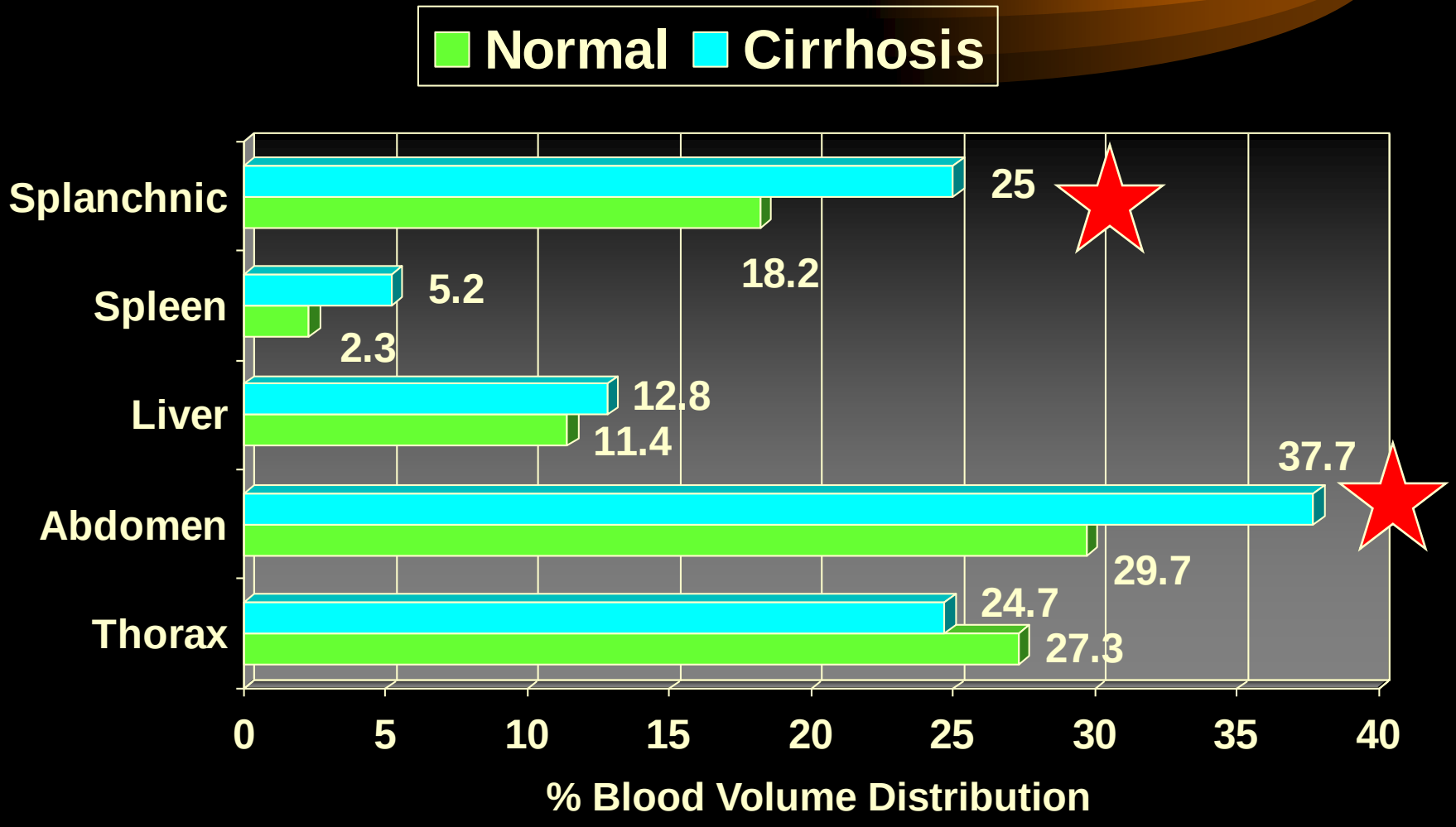
Blood Volume Distribution

Normal



Cirrhosis
(Splanchnic pooling)

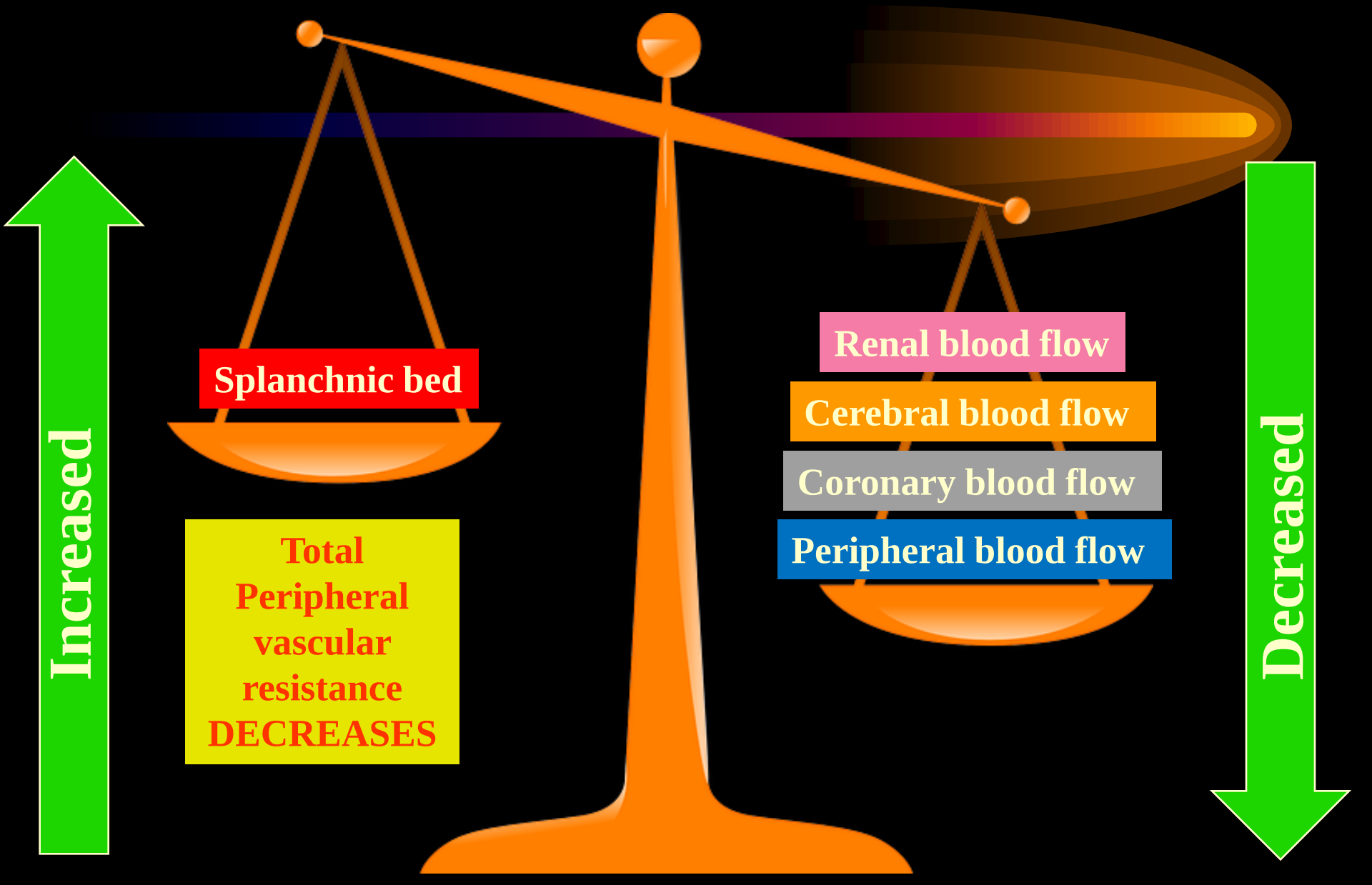
Blood Volume Distribution in Cirrhosis



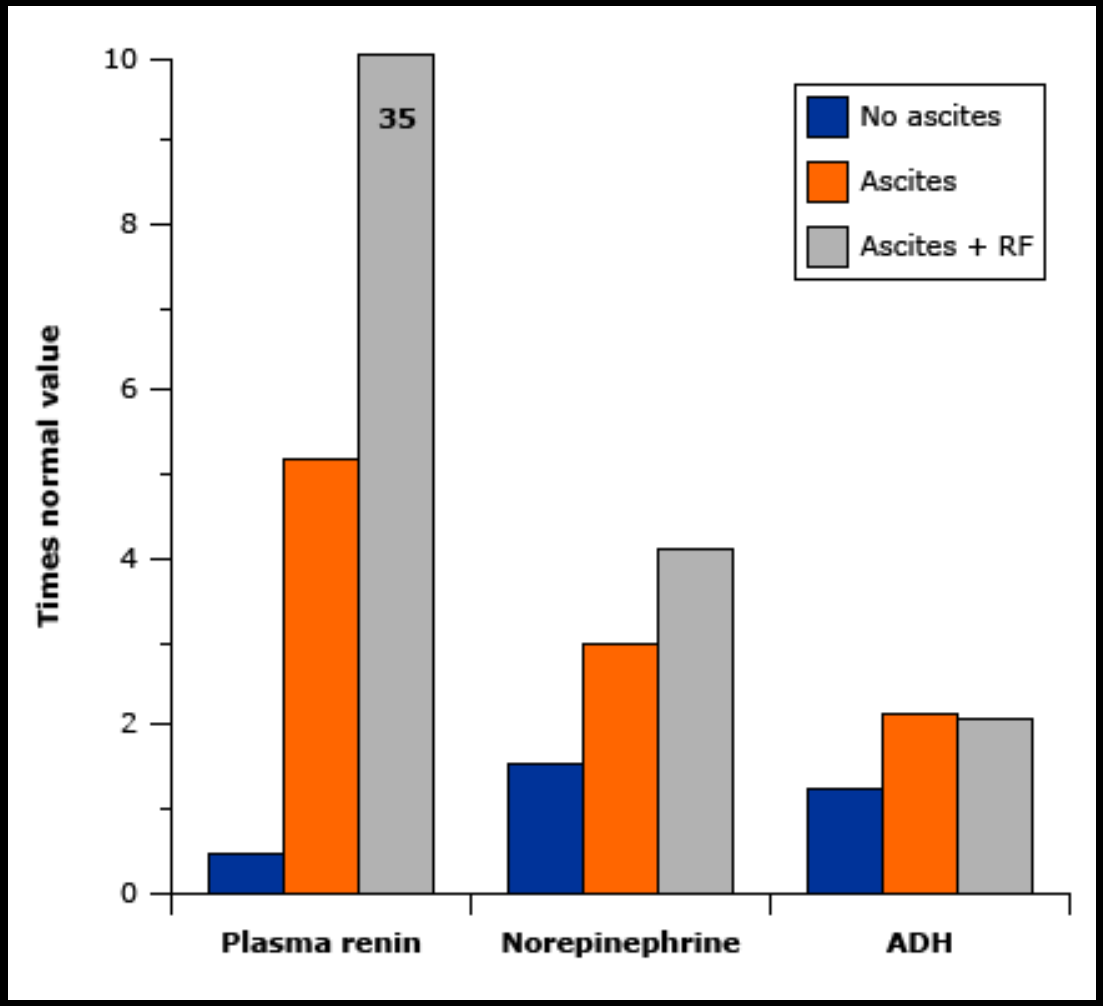
Systemic Blood Flow and HRS

- **Splanchnic arteriolar vasodilation IS NOT accompanied by peripheral vasodilation in all vascular beds**
  - **Cerebral / Femoral / Brachial / Hepatic beds all experience progressive vasoconstriction which is directly related to the GFR**

Organ Perfusion in Cirrhosis and HRS



RAAS Activation in Cirrhosis ± HRS



Progressive increase in RAAS activation with ascites formation indicating decreasing effective circulating volume

In HRS there is maximal RAAS activation

Hepatorenal Syndrome : Pathophysiology

Cirrhosis → **Splanchnic Arterial Vasodilation**

Nitric Oxide
Glucagon
Endocannabinoids
Cytokines
Carbon Monoxide

→ **Decreased Effective Circulating Volume**

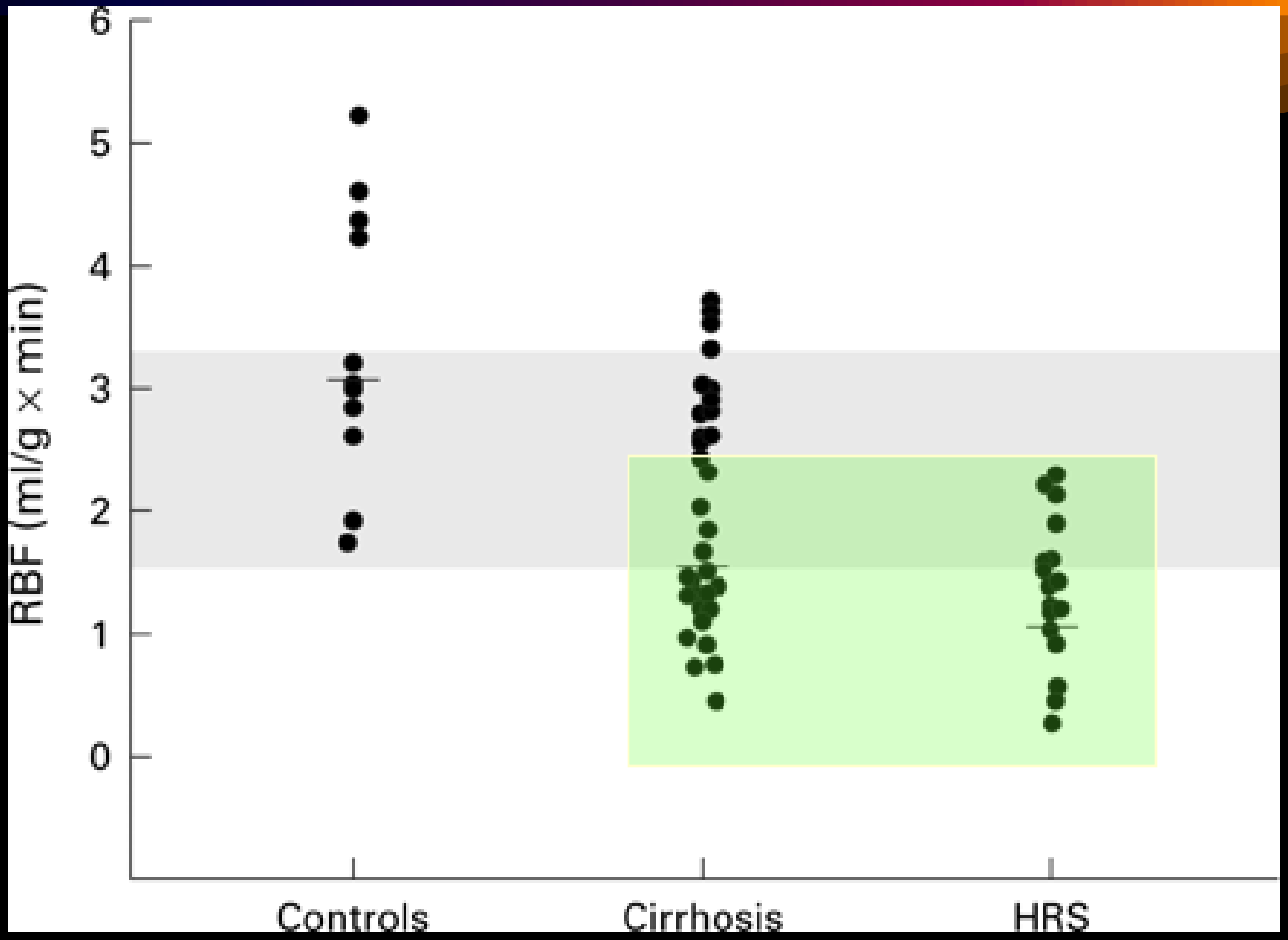
Adaptive Response :
Increased Renal Vascular Resistance
Sodium and water Retention

Renin-Angiotensin-Aldosterone
Sympathetic Nervous System
Vasopressin / Increase water channels
Leukotriene E2
Endothelin-1
F2-isoprostanes

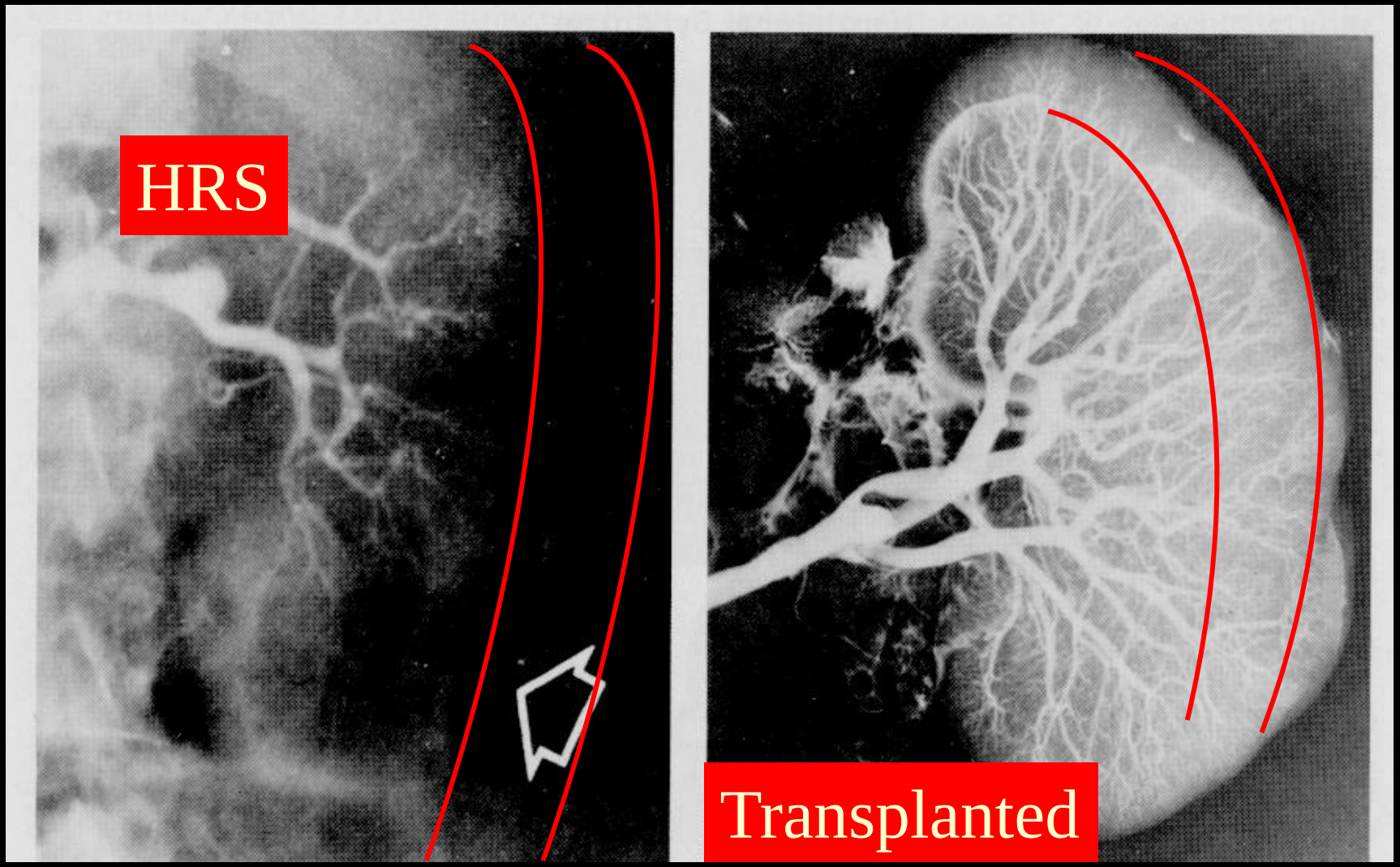
Counteradaptive Response :
Intrarenal vasodilation
Natriuresis

Prostaglandins
Kallikreins
ANP

Hepatorenal Syndrome



Ring-Larsen H, et al. Scand J Clin Lab Invest 37:635-42,1977

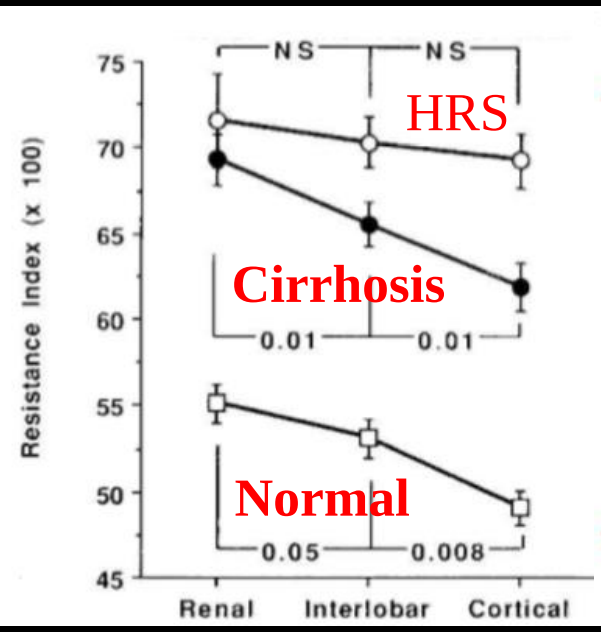


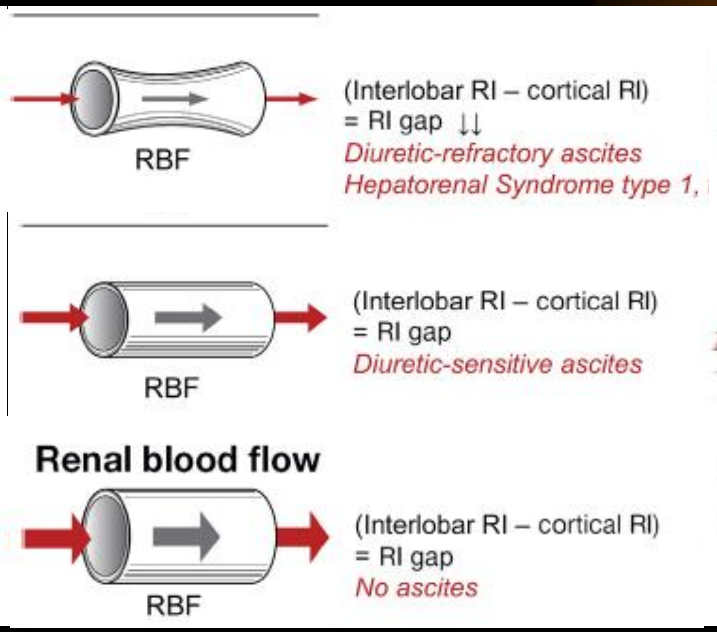
Severe vasoconstriction of the cortical vessels in the kidney in HRS which is completely reversible with therapy

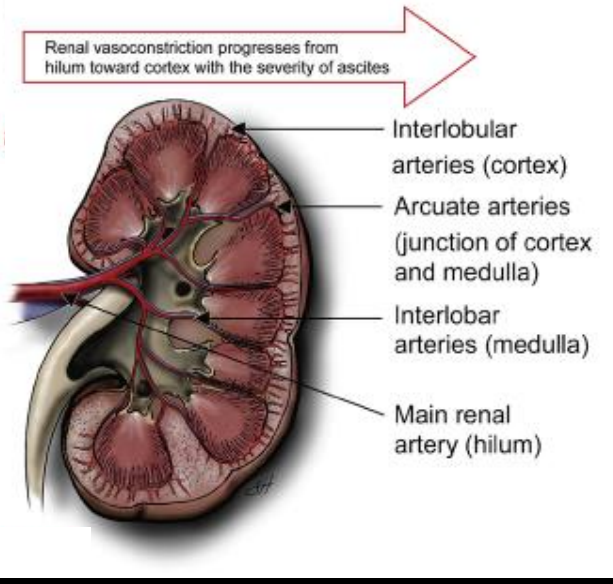
Confirms that the injury is one of vascular tone

Mindikoglu A. Clin Gastroenterology and Hepatology 2017

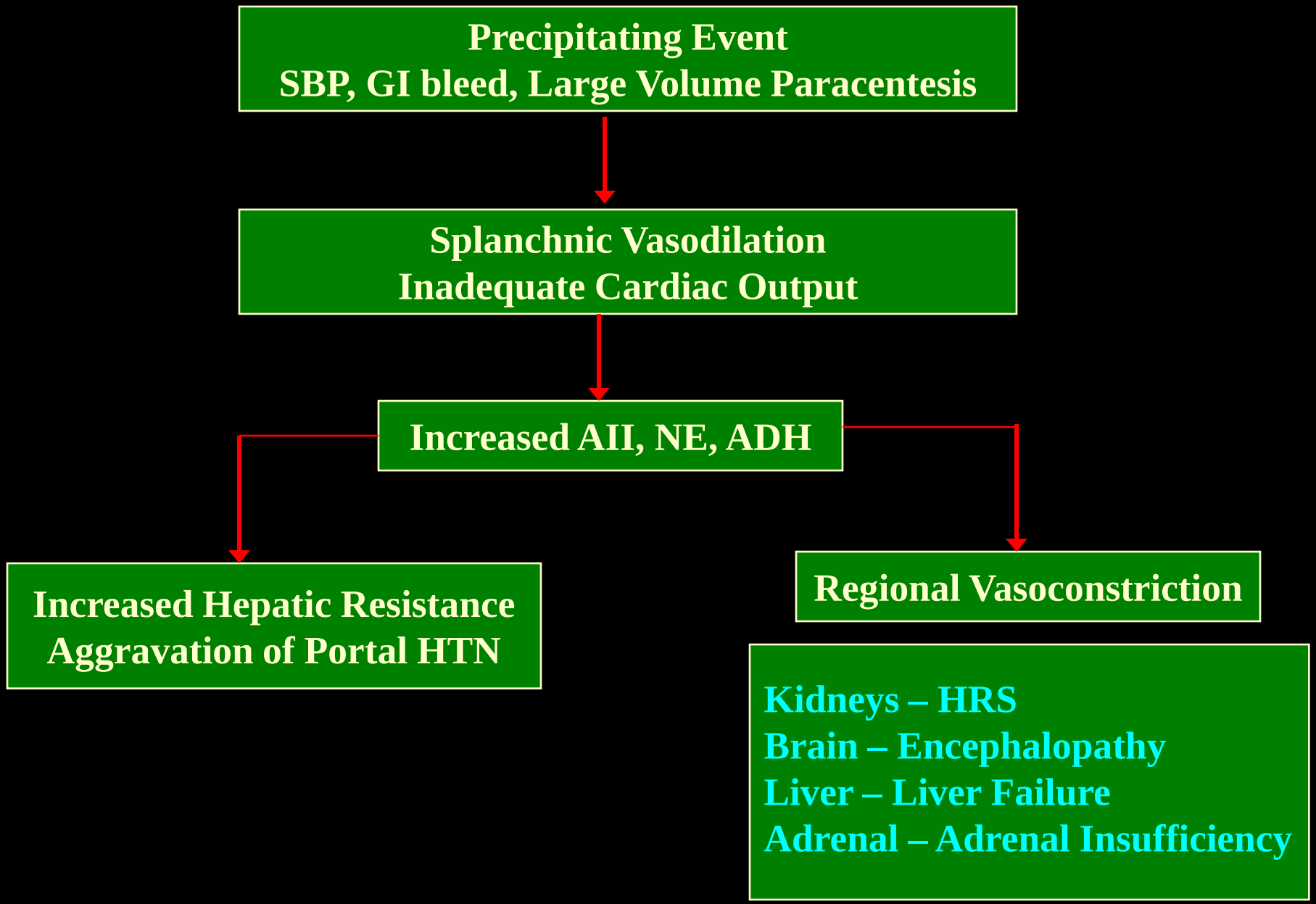
Doppler Ultrasound in HRS and Cirrhosis



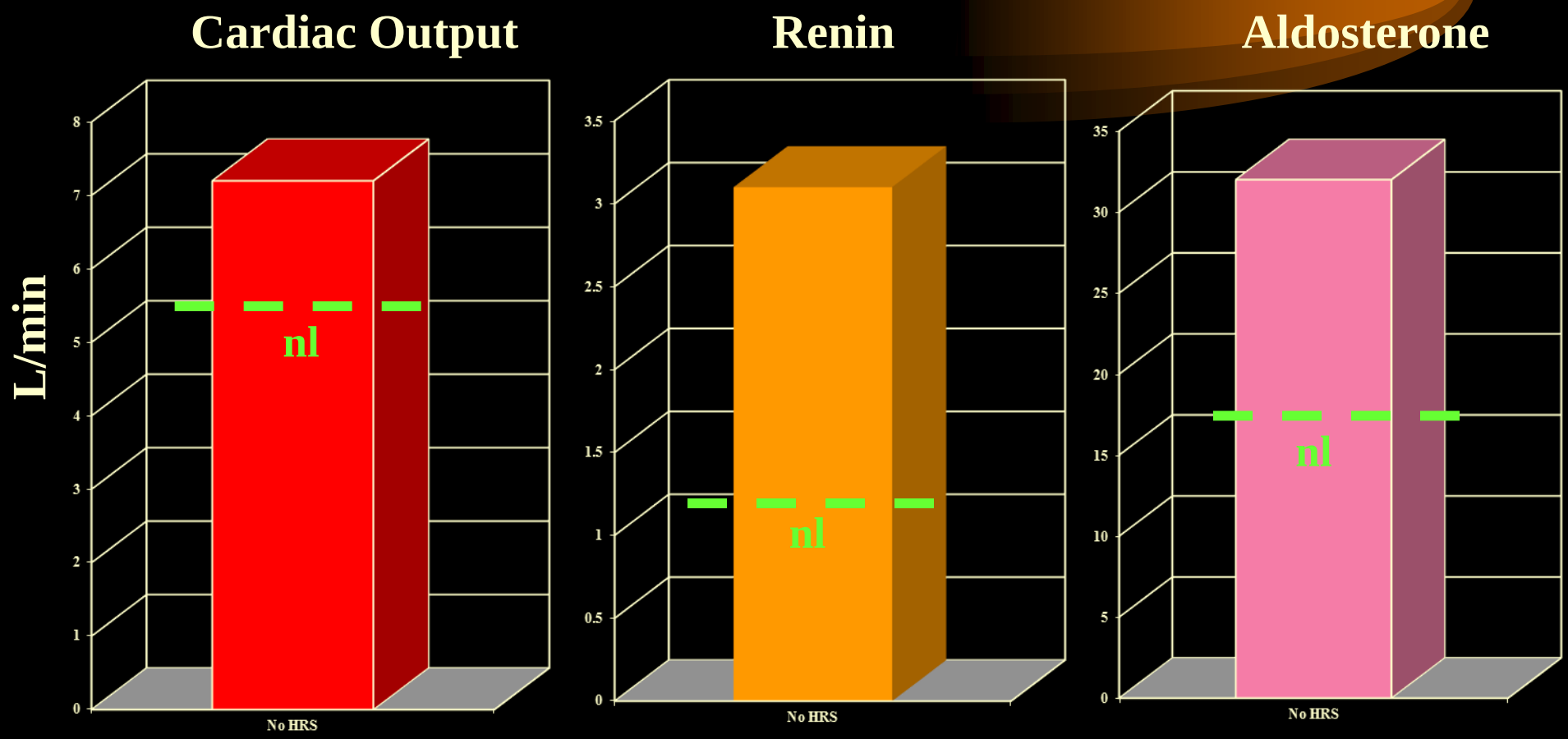




The resistive index is high throughout the renal vasculature in HRS to the same degree – (no RI gap !)
In Cirrhosis alone the resistance is high in the larger vessels and not as pronounced in the smaller vessels that have a lower resistive index (RI gap)


Precipitating Event
SBP, GI bleed, Large Volume Paracentesis
Splanchnic Vasodilation
Inadequate Cardiac Output
Increased AII, NE, ADH
Increased Hepatic Resistance
Aggravation of Portal HTN
Regional Vasoconstriction
Kidneys – HRS
Brain – Encephalopathy
Liver – Liver Failure
Adrenal – Adrenal Insufficiency

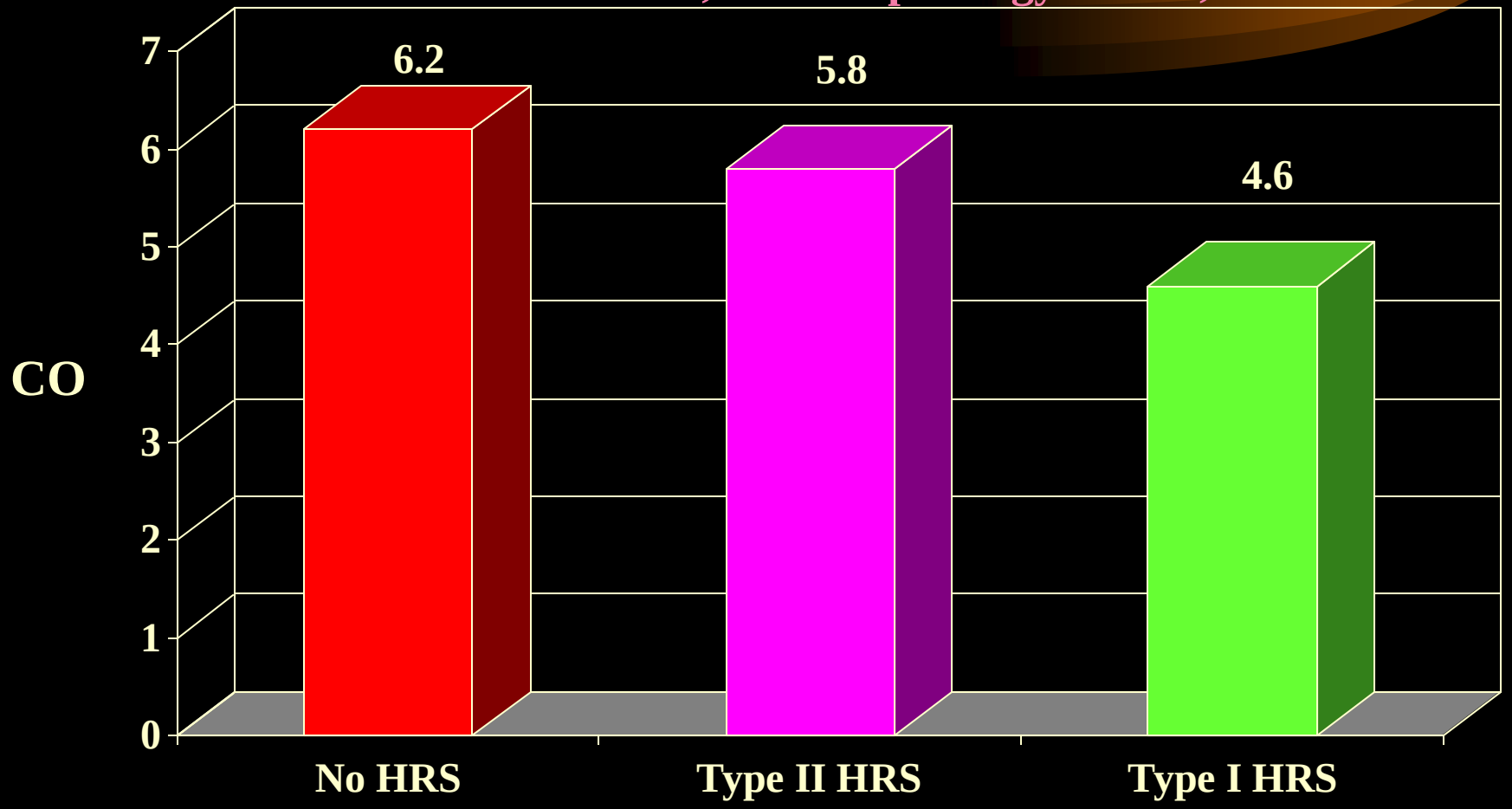
Circulatory Function and the Hepatorenal Syndrome



- Ruiz-del-Arbol L, et al. Hepatology 42:439,2005

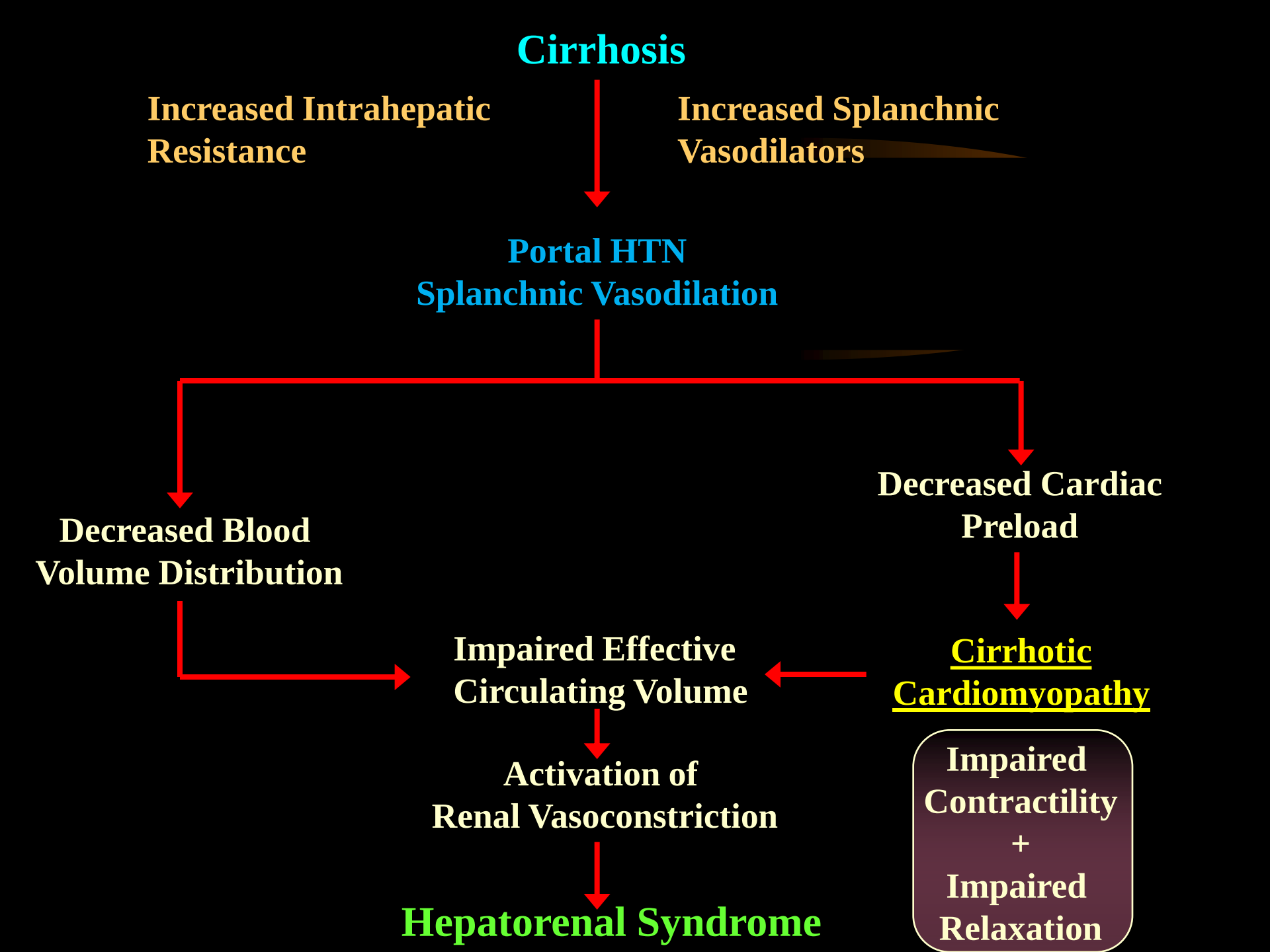
Circulatory Function and the Hepatorenal Syndrome
Differences Between Type I and Type II HRS

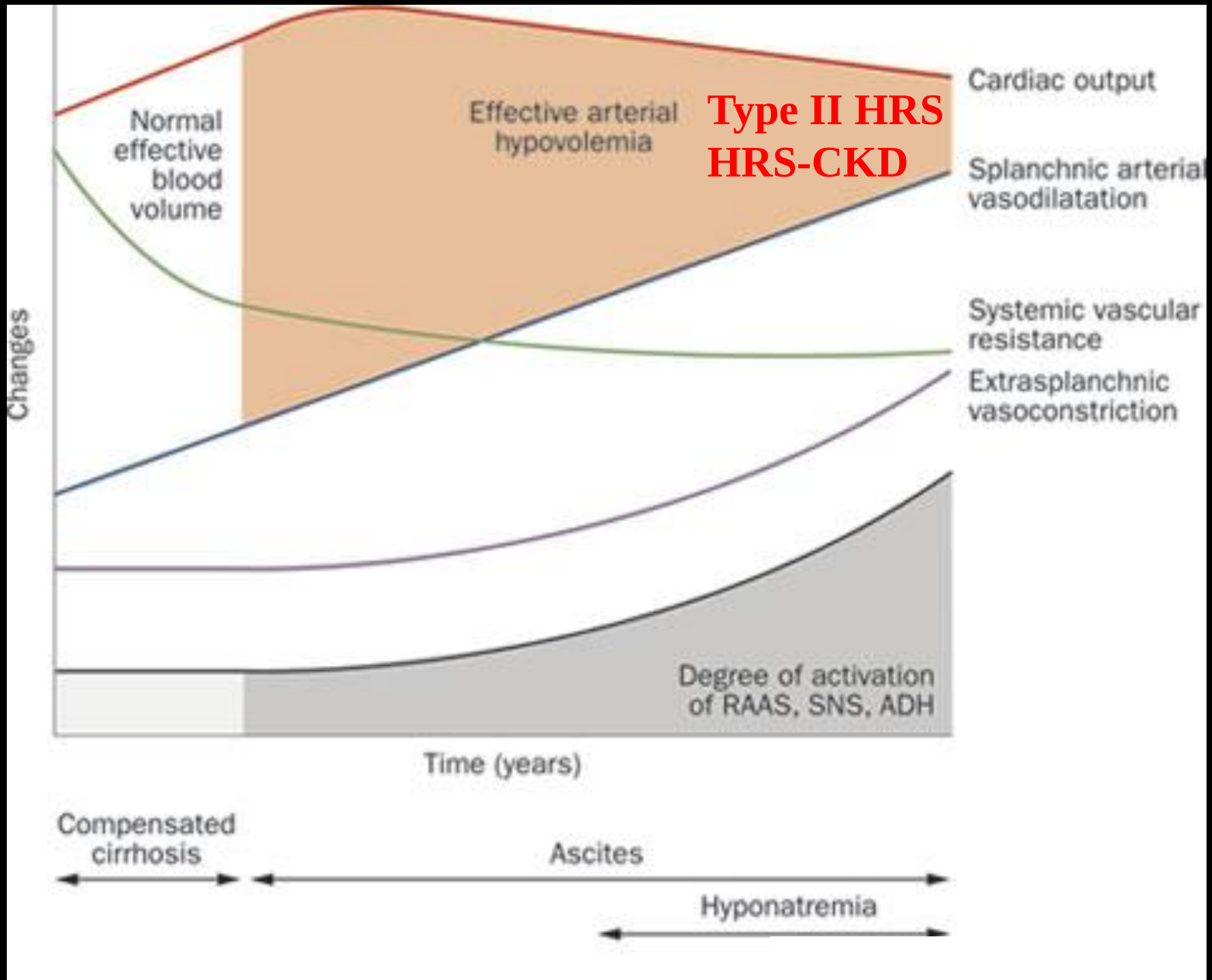
•Ruiz-del-Arbol L, et al. Hepatology 42:439,2005



Hepato-Cardio-Renal Syndrome

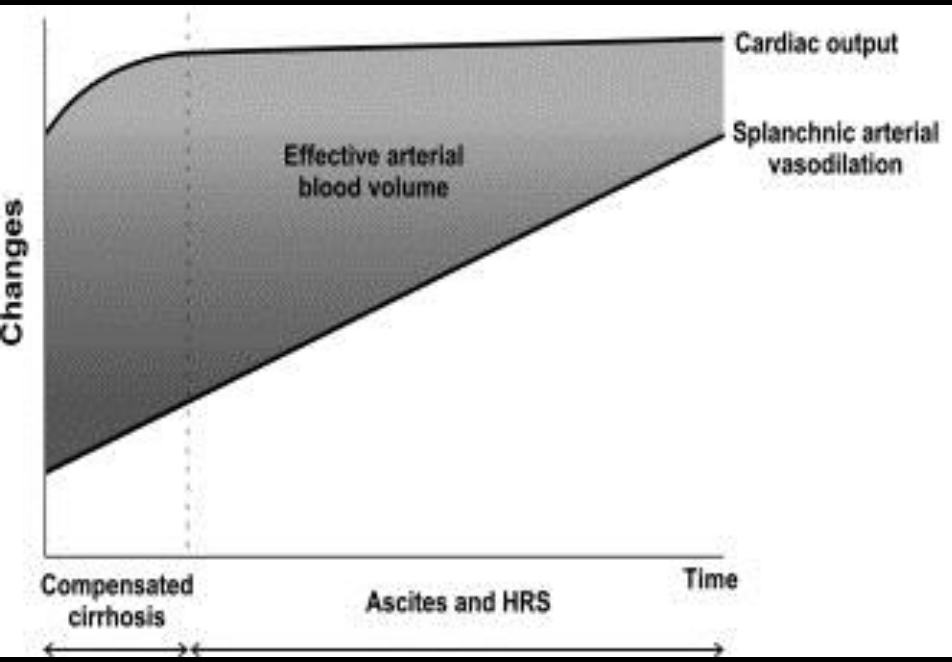
- **Cirrhotic Cardiomyopathy**
  - **Clinical Features**
    - **Blunted systolic and diastolic contractile response to stress**
    - **Ventricular hypertrophy / Dilation**
    - **Prolonged Q-T interval**

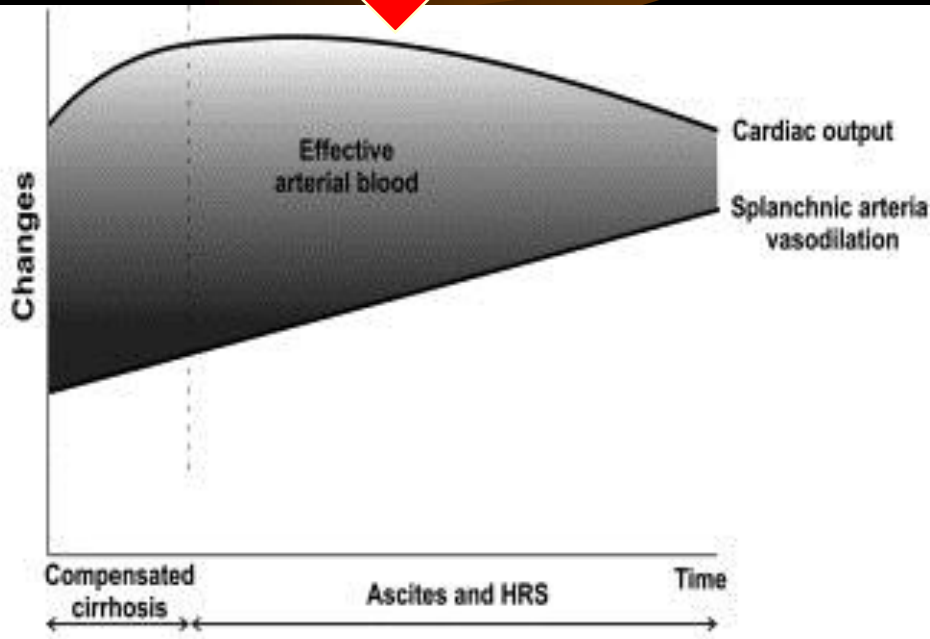

Cirrhosis
Increased Intrahepatic Resistance
Increased Splanchnic Vasodilators
Portal HTN
Splanchnic Vasodilation
Decreased Blood Volume Distribution
Decreased Cardiac Preload
Impaired Effective Circulating Volume
Cirrhotic Cardiomyopathy
Activation of Renal Vasoconstriction
Impaired Contractility + Impaired Relaxation
Hepatorenal Syndrome


Type II HRS
HRS-CKD
Normal effective blood volume
Effective arterial hypovolemia
Cardiac output
Splanchnic arterial vasodilatation
Systemic vascular resistance
Extrasplanchnic vasoconstriction
Degree of activation of RAAS, SNS, ADH
Changes
Time (years)
Compensated cirrhosis
Ascites
Hyponatremia

Pathogenesis of Type I HRS (HRS-AKI)
Hepato – Cardio – Renal Syndrome

Arroyo V, J Hepatol 46:935, 2007

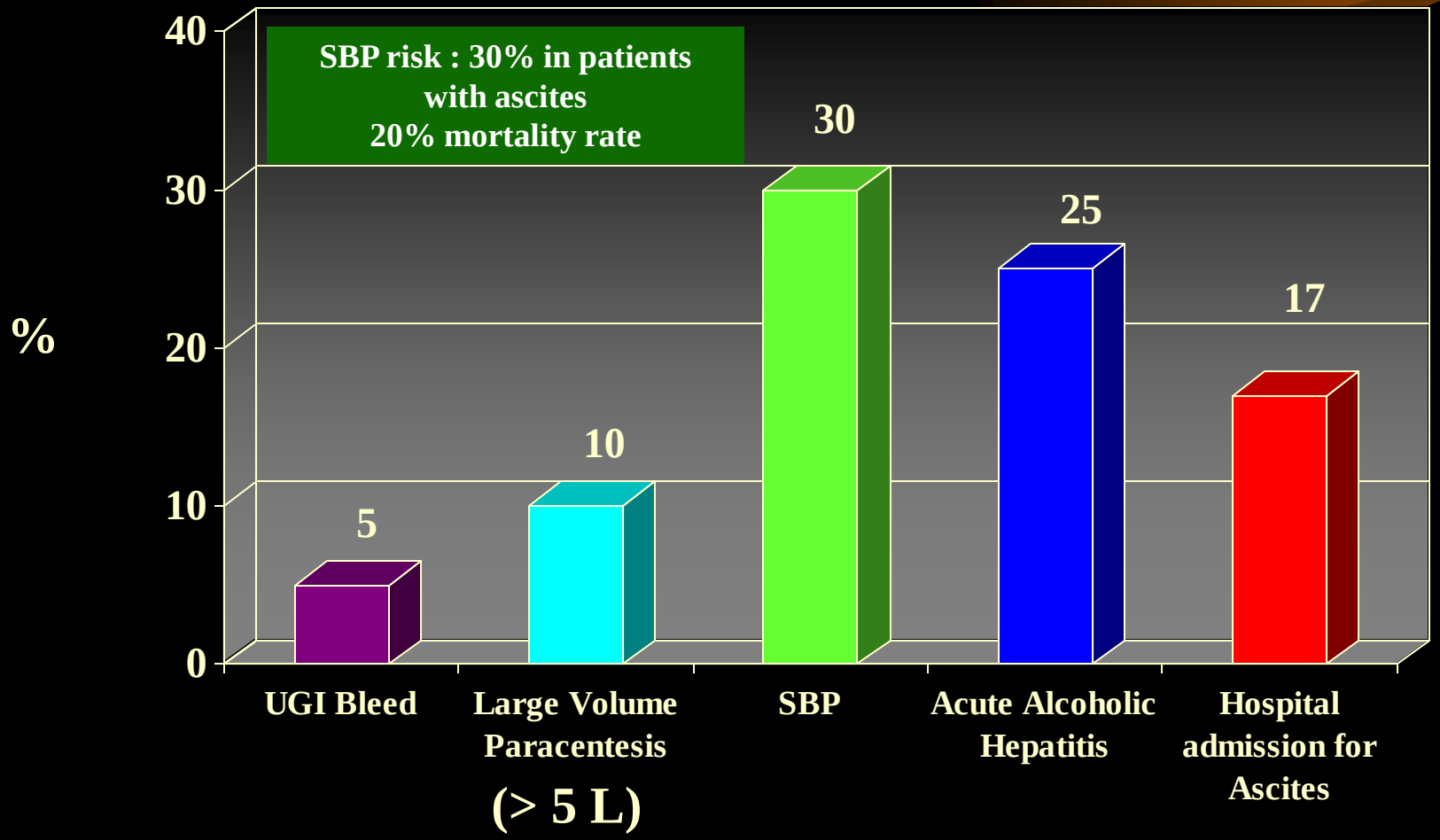




Peripheral Vasodilation Theory

Peripheral Vasodilation + Cardiomyopathy Theory + acute decrease in volume

Risk for Developing Type I HRS
The "Second Hit " Hypothesis

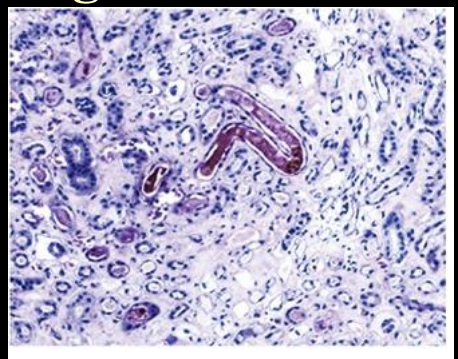


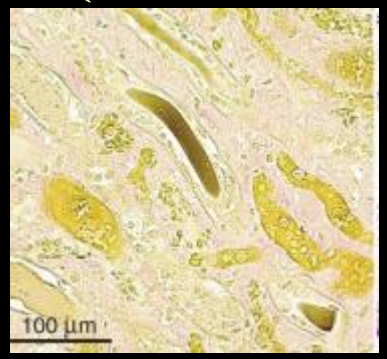
Circulatory Function and the Hepatorenal Syndrome

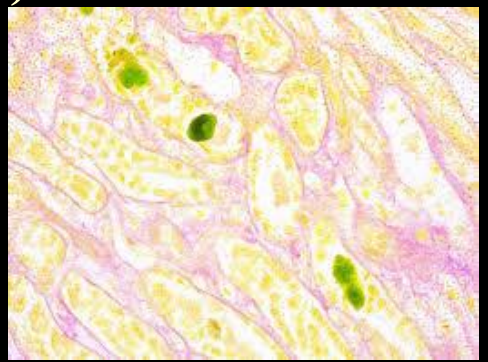
- **Conclusions**
  - **Patients who develop HRS have**
    - **Lower baseline CO**
    - **Higher baseline levels of renin / Aldosterone / Catecholamines**
  - **Cardiac output decreases dramatically in Type I HRS resulting in a greater severity of renal hypoperfusion**
- **Etiology of "Cirrhotic cardiomyopathy"**
  - **Chronic high catecholamine levels**
    - **Left ventricular remodeling / fibrosis**
    - **Diastolic dysfunction**

Bile Cast Nephropathy

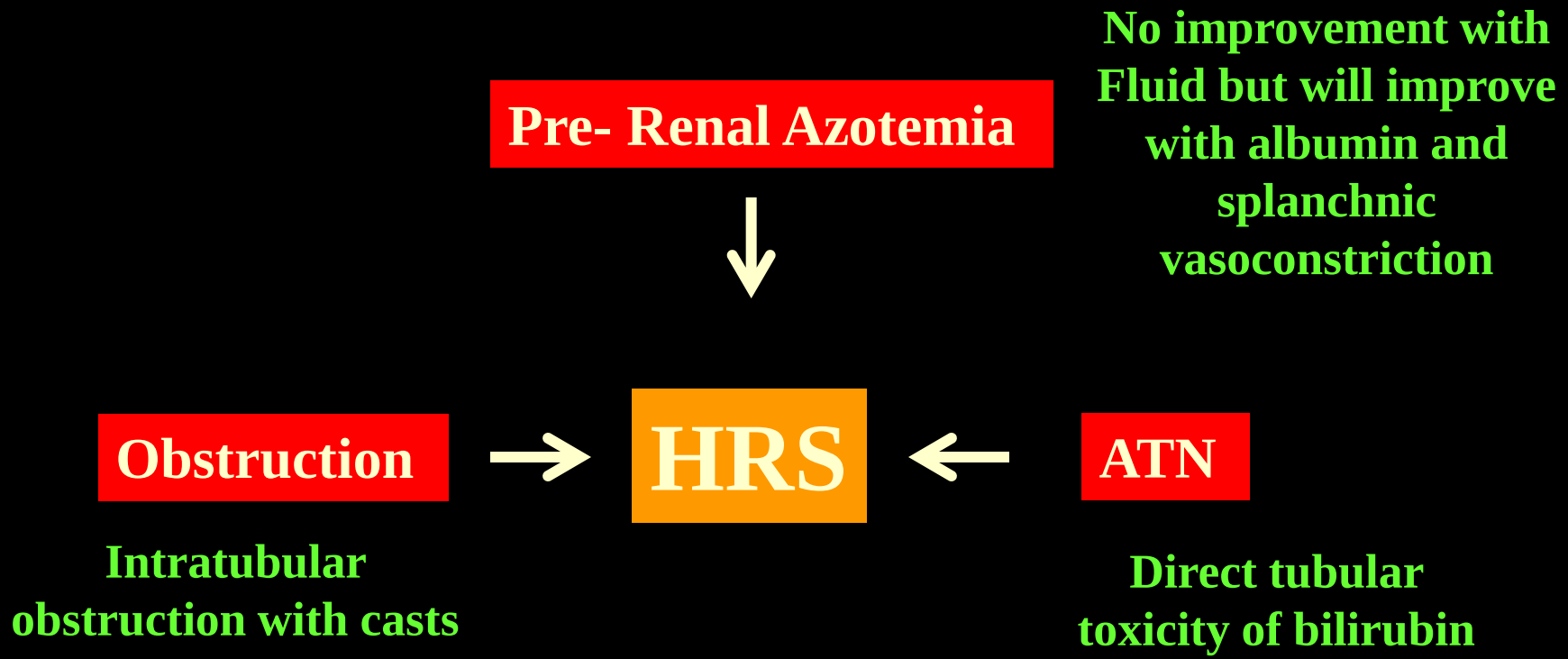
- **Reported in patients with Direct bilirubin levels > 6 mg/dl and Total bilirubin of 15 mg/dl**
- **Casts form primarily in the distal tubule but may be seen in the proximal tubule**
- **Direct tubular toxicity secondary to mitochondrial dysfunction from bile salts**
- **confirmed by two stains (Fouchet's stain and Perl's stain). Bile casts were considered positive according to green color on Fouchet's staining (Halls stain) and negative Perl's stain (Prussian blue)**







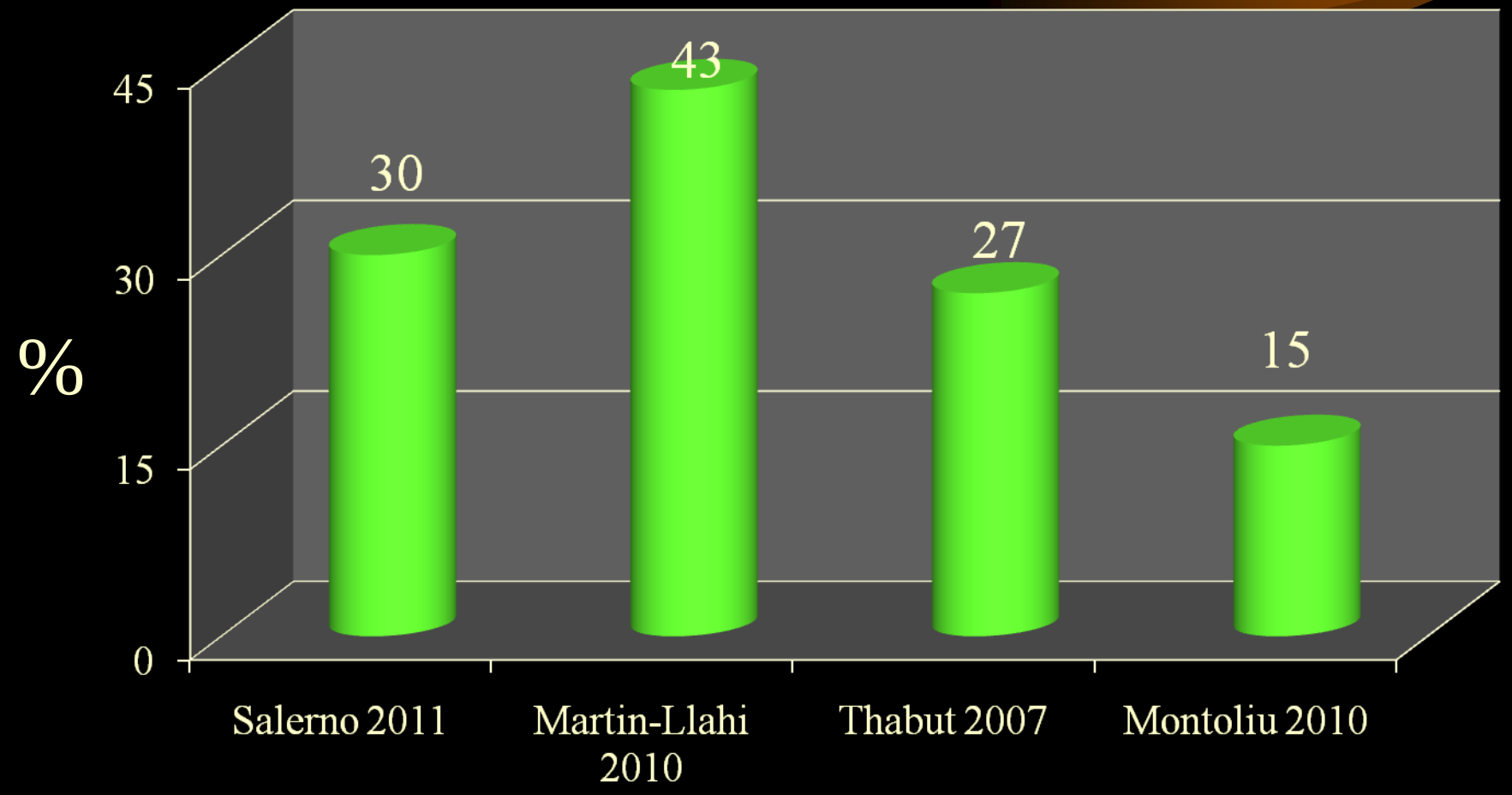
AKI Classification of Hepatorenal Syndrome



HRS is a combination of all 3 !

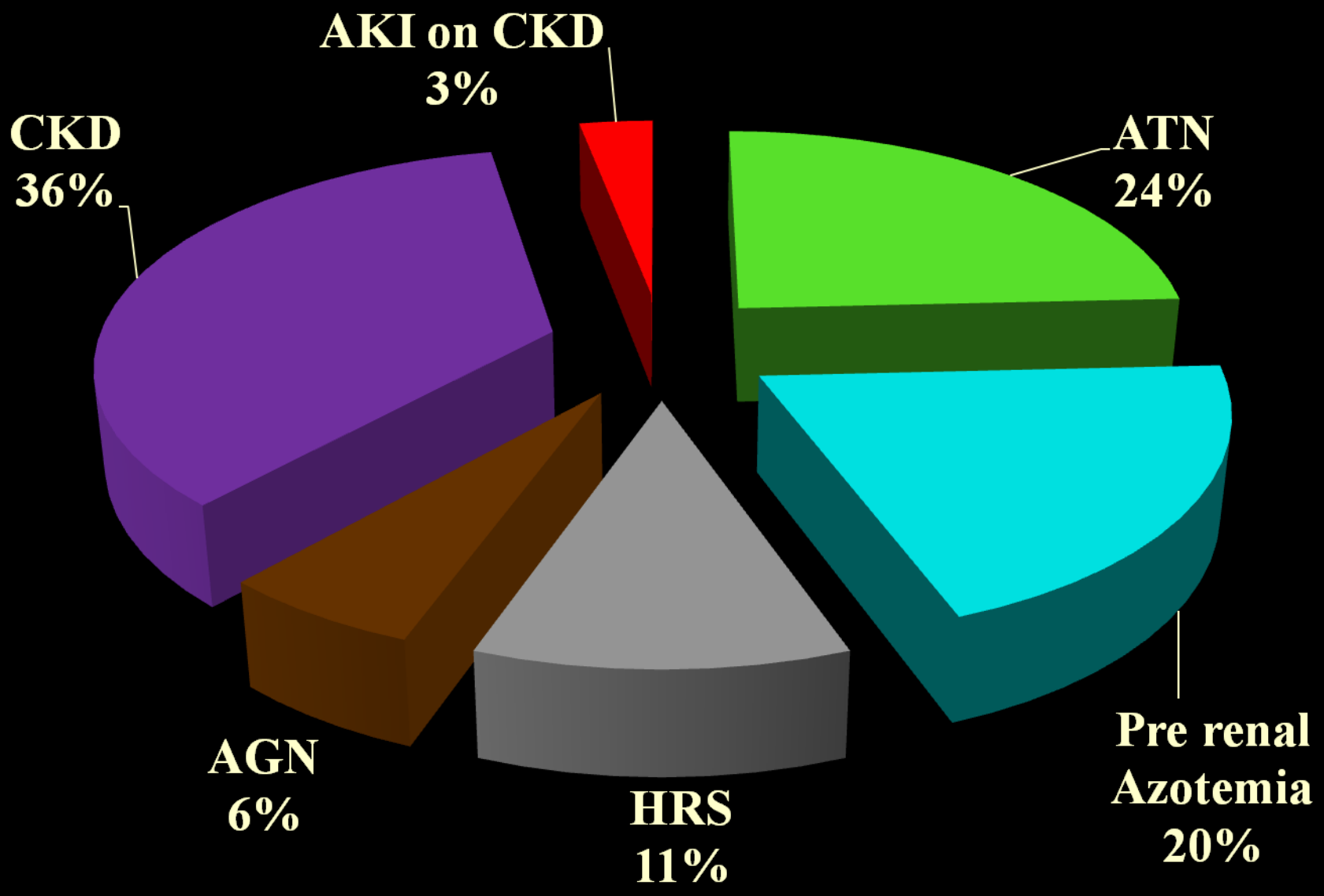
Pre Renal >>>>>>>>>>>>>> ATN >>>> Obstruction

Prevalence of HRS as a Cause of AKI in Cirrhosis



Prakash J. Renal Fail 33:40,2011

Types of Kidney Disease seen in Cirrhosis



Kidney Diseases other than HRS in Patients with Cirrhosis

- **Hepatitis C**
  - **Membranoproliferative glomerulonephritis**
  - **Membranous GN**
  - **Vasculitis**
- **Diabetes**
  - **Diabetic Nephropathy**
- **Hepatitis B**
  - **Membranous GN**
  - **IgA nephropathy**
  - **Vasculitis**

In patients with AKI and cirrhosis it is essential to know the cause of liver failure as it may contribute to the differential diagnosis

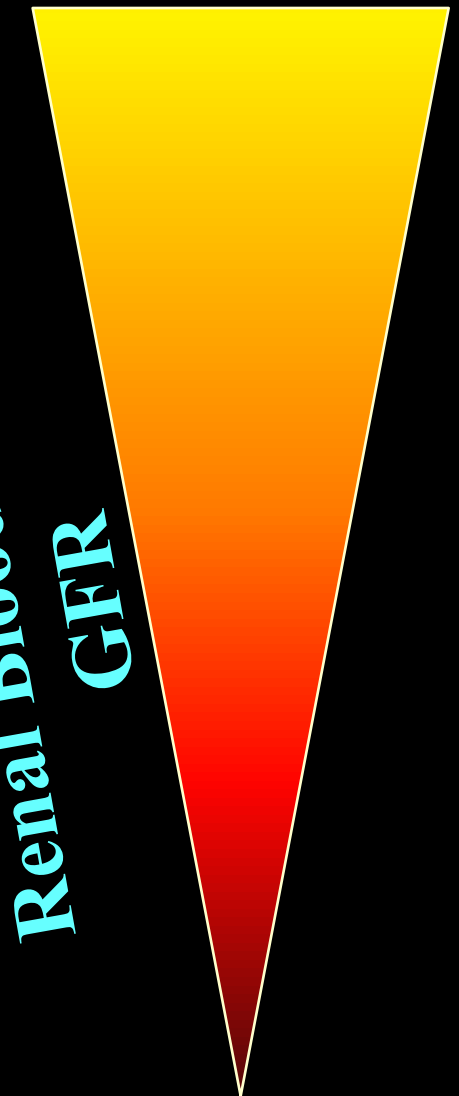
Do not forget !!!
Abdominal Compartment Syndrome and Cirrhosis : AKI

Normal
Intra-abdominal pressure (IAP)
4 – 7 mmHG

Intra-abdominal hypertension (IAH)
12 – 20 mmHG

Intra-abdominal Compartment Syndrome (ICS)
12 – 20 mmHG

Abdominal Compartment Syndrome and Cirrhosis : AKI



Increased Renal Venous HTN

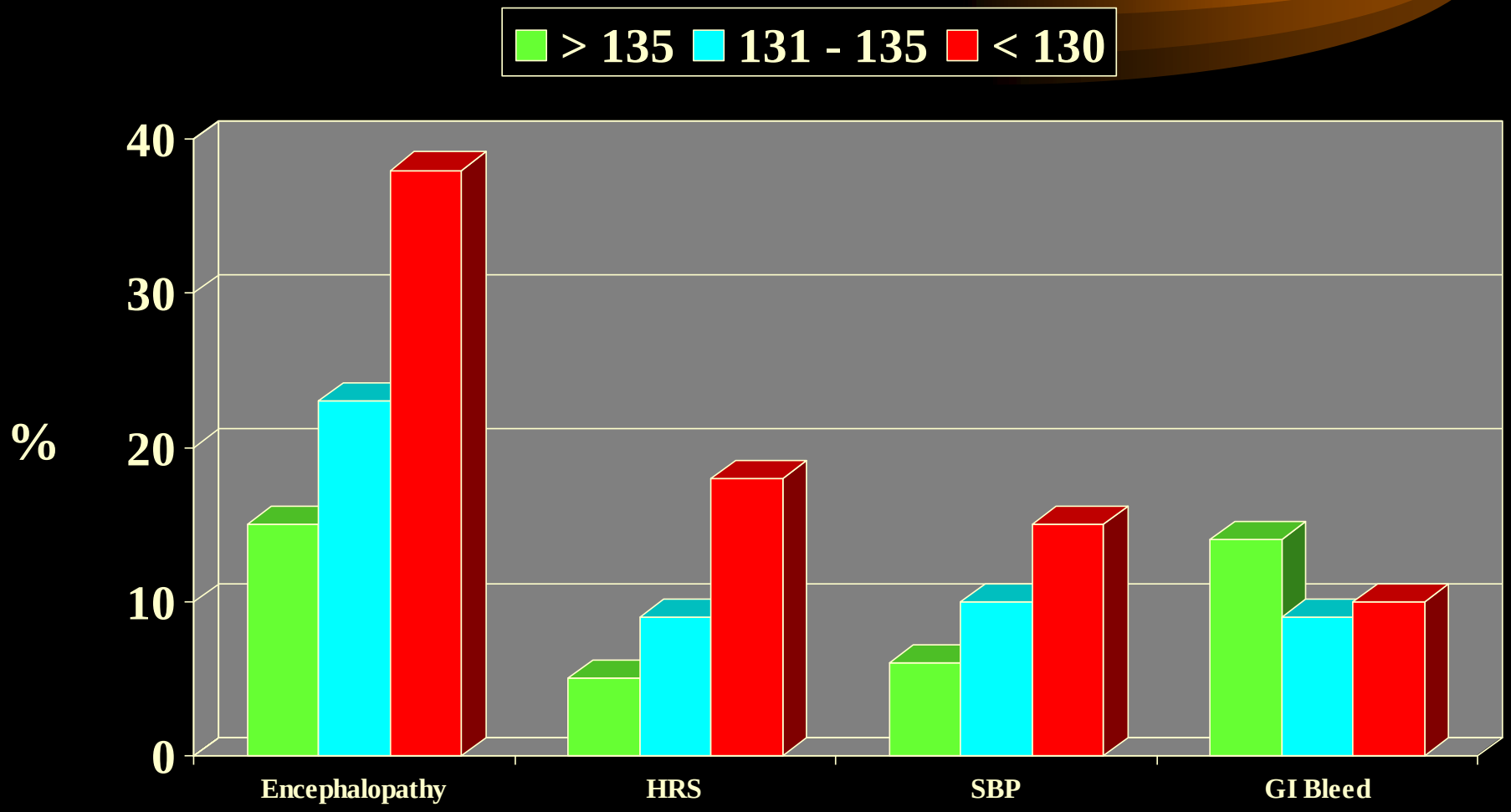
Increased sub-capsular pressure

Decreased Renal Blood Flow

Decreased GFR

Angeli P. Hepatology 44:1535, 2006

Hyponatremia in Cirrhosis and Ascites
Risk of Complications at 1 Month Followup

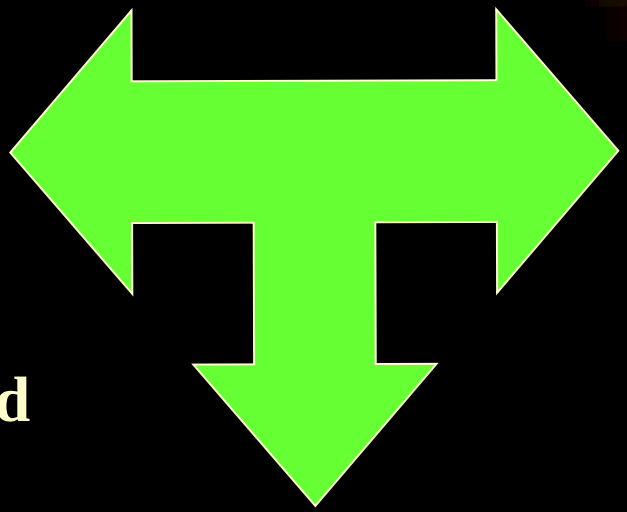


Hepatorenal Syndrome : Targets for Therapy

Antagonize Inflammation / Bile Acids

Albumin infusion

Ursodeoxycholic acid



Reduce Splanchnic Blood Flow

TIPS

Increase Splanchnic Vasoconstriction

α-1 agonists

- **Midodrine**
- **Noradrenaline**

Glucagon antagonism

- **Somatostatin**
- **Octreotide**

V-1 agonists

- **Vasopressin**
- **Terlipressin**

Albumin

- **Non-Oncotic Properties**
  - **Transport**
  - **Free radical scavenging**
    - **Sulfhydryl groups (thiols)**
      - **Bind reactive oxygen species**
        - **Superoxide hydroxyl**
        - **Peroxynitrite**
  - **Decreased Capillary permeability**
  - **Decrease neutrophil adhesion and activation**
  - **Anti-thrombotic and Anticoagulant effect**

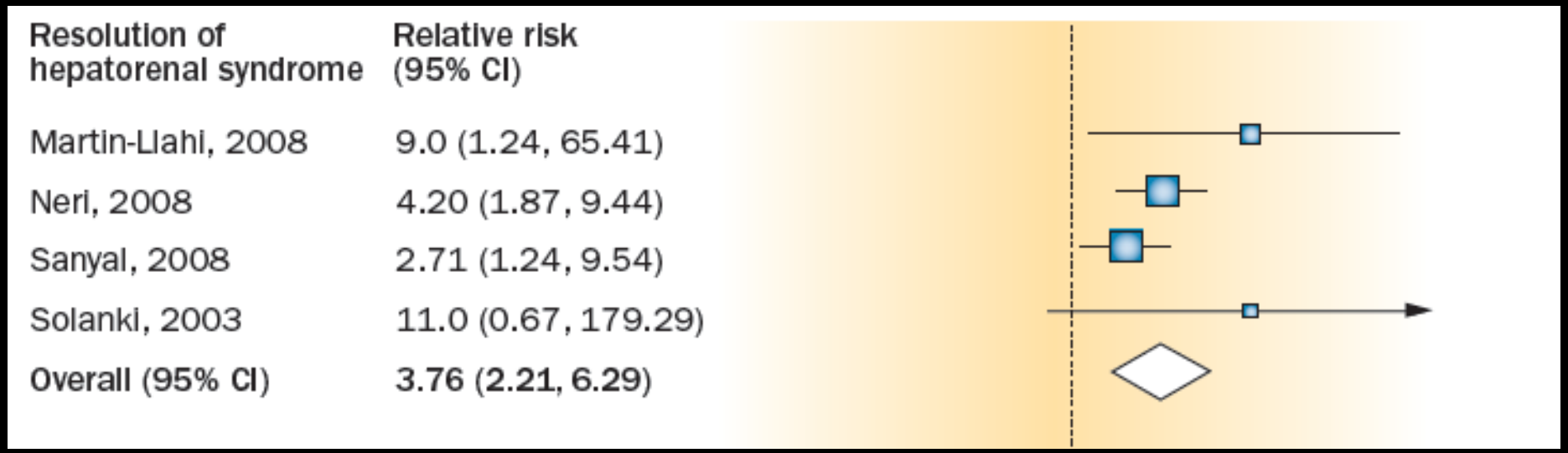
Hepatorenal Syndrome : Management

Increase Splanchnic Vasoconstriction

- **Terlipressin (non FDA approved)**
  - **Vasopressin analogue**
  - **Always combined with albumin infusion**
  - **Bolus infusion**
  - **Preferential vasoconstriction of the splanchnic vasculature (?)**
    - **Increases blood pressure and renal perfusion pressure**
    - **Decreases plasma renin, aldosterone, norepinephrine levels**
    - **Increases ANP levels**

Terlipressin in HRS : Meta Analysis of Randomized Trials

- **Sagi S. J of Gastroenterol Hepatol 25:880, 2010**



Reversal of Type I HRS – 46%

Terlipressin in HRS : Meta Analysis of Randomized Trials

- **Sagi S. J of Gastroenterol Hepatol 25:880, 2010**

Table 2 Side effects with Terlipressin requiring discontinuation of therapy

Side effect	Number of patients
Myocardial infarction	2
Chest pain	1
Intestinal ischemia	3
Livedo reticularis	1
Peripheral ischemia	1
Severe hypertension	1

One patient had both myocardial infarction and intestinal ischemia.

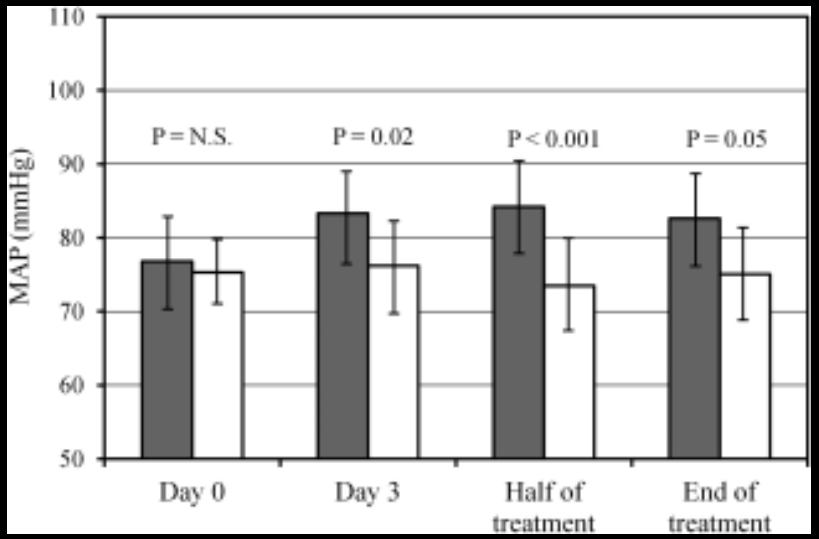
7% serious Ischemic complications

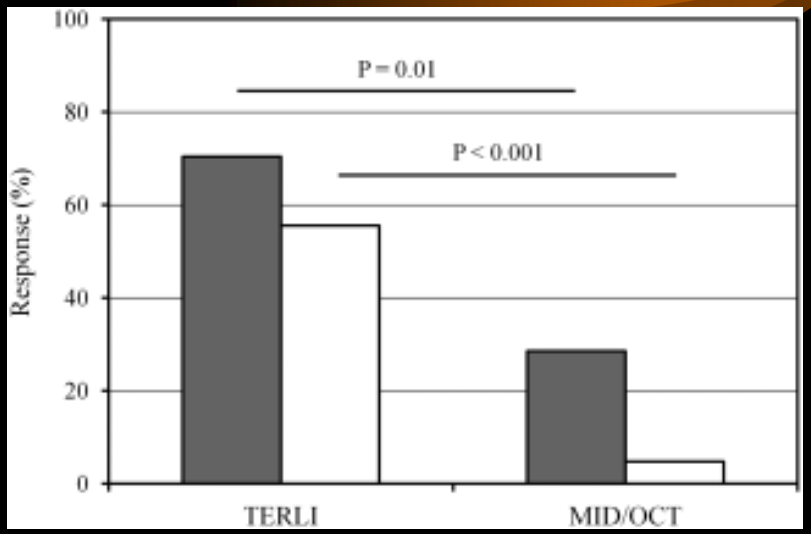
Hepatorenal Syndrome : Octreotide and Midodrine

- **Therapy**
  - **Target of treatment aimed at increasing mean arterial blood pressure by a minimum of 15 mmHg**
    - **Midodrine (α-1 agonist)**
      - **Oral administration**
      - **7.5 mg T.I.D. with maximum of 12.5 mg T.I.D.**
    - **Octreotide (antagonist of glucagon)**
      - **100 μg T.I.D. subcutaneously with maximum 200 μg T.I.D.**
  - **Albumin infused at 20 g/day and increased to a maximum of 40 g/day based on**
    - **achieving a CVP > 12**

Cavalin M.Hepatology Jan 16, 2015

Terlipressin vs Midodrine
Terlipressin Wins the Battle ! But ……..





Grey = Terlipressin
White = Midodrine + Octreotide

Grey = Partial response
White = Full response

Because Midodrine did not achieve a rise in BP the failure of therapy may be related not to the drug combination but the lack of titration to the proper blood pressure endpoint

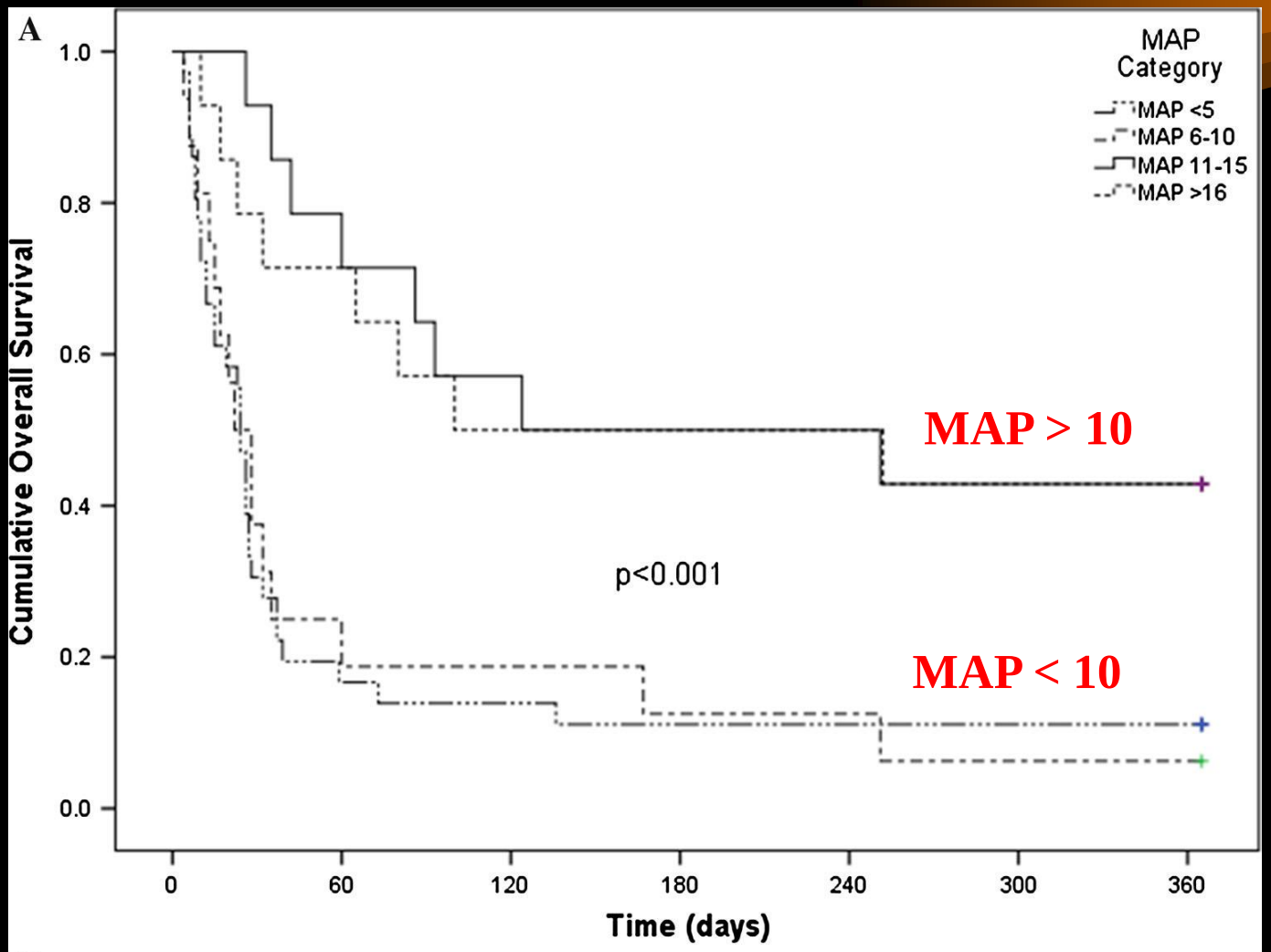
Vasocontrictor Therapy in HRS

Kiser T, et al. Neph Dial Transpl 20;1813, 2005

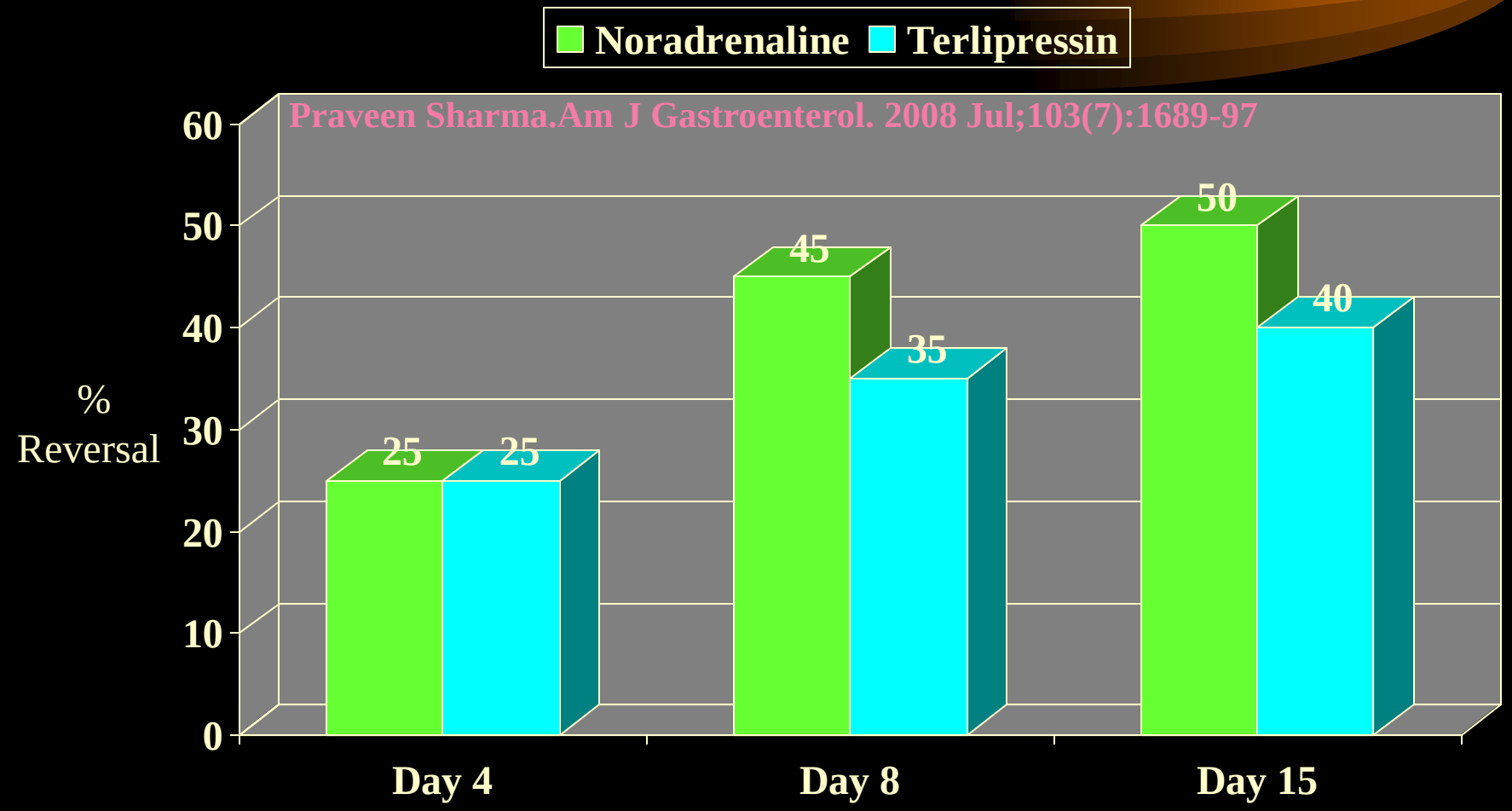
	Change MAP
Responders	10 mmHg
Non-Responders	6 mmHg

Cai CX. Dig Dis Sci 2014 Dec 23

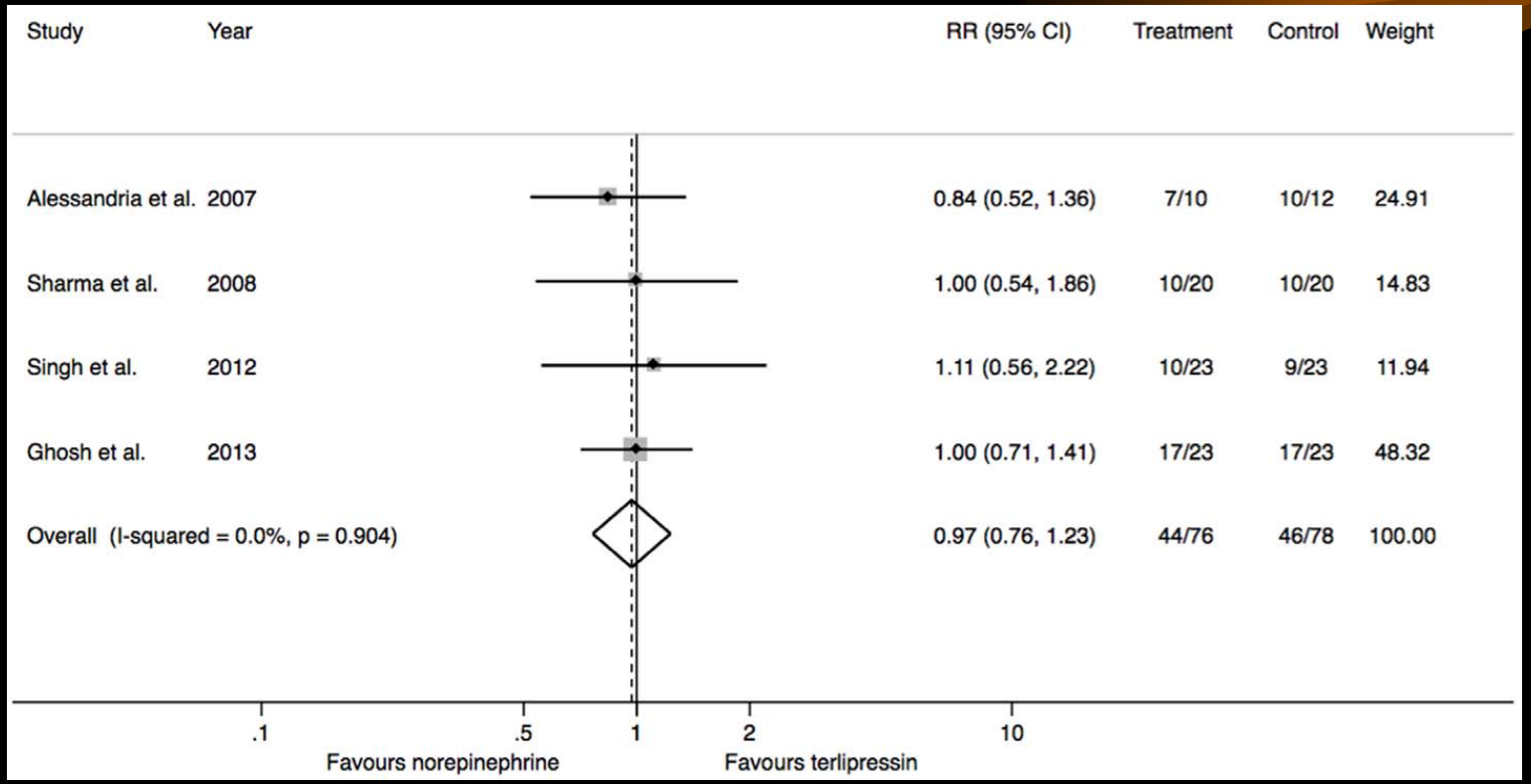
Increase in MAP > 10 Resulted in Improved Survival for HRS



Noradrenaline Versus Terlipressin in the Treatment of Type 1 Hepatorenal Syndrome



Terlipressin vs Norepinephrine
It's a Tie !!!



Nassar J.PLoS One. 2014 Sep 9;9(9):e107466

Cochrane Library

Cochrane Database of Systematic Reviews

Terlipressin versus other vasoactive drugs for hepatorenal syndrome (Review)

Israelsen M, Krag A, Allegretti AS, Jovani M, Goldin AH, Winter RW, Gluud LL

Terlipressin compared to other vasoactive drugs for hepatorenal syndrome

Patient or population: people with cirrhosis and hepatorenal syndrome
Setting: hospital
Intervention: terlipressin
Comparison: other vasoactive drugs

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Risk with other vasoactive drugs	Risk with terlipressin			
Mortality (All-cause)	Study population		**RR 0.96** (0.88 to 1.06)	474 (10 randomised clinical trials*)	⊕◯◯◯ **Very low**[a,b,c]
	601 per 1000	**577 per 1000** (529 to 637)			
Hepatorenal syndrome (Number of participants who did not achieve reversal of hepatorenal syndrome)	Study population		**RR 0.79** (0.63 to 0.99)	394 (9 randomised clinical trials)	⊕◯◯◯ **Very low**[b,c,d]
	560 per 1000	**442 per 1000** (353 to 554)			
Serious adverse events	Study population		**RR 0.96** (0.88 to 1.06)	474 (10 randomised clinical trials)	⊕◯◯◯ **Very low**[b,c,d]

No benefit of terlipressin compared to other vasoconstrictors

Israelsen M, Terlipressin versus other vasoactive drugs for hepatorenal syndrome.Cochrane Database of Systematic Reviews 2017, Issue 9.

Reversal of HRS Syndrome and Lack of Improvement of Mortality

Table 3. Meta-Analyses of Randomized Controlled Trials of Vasoactive Drugs for Reduction of Mortality

Meta-analysis studies	Studies, n	Drug combinations	OR or RR for all-cause mortality or survival (95% CI)	Heterogeneity, I^2	Test for overall effect, *P* value	Studies included in the meta-analysis
Fabrizi et al[96] (2009)	5	Terlipressin vs placebo	OR, 2.06 (0.94–4.54)[a]	55%	.07	Hadengue et al[106] (1998), Solanki et al[112] (2003), Sanyal et al[109] (2008), Martin-Llahi et al[107] (2008), Neri et al[108] (2008)
Gluud et al[99] (2010)	6	Vasoconstrictor drug alone or with albumin vs no intervention or albumin	RR, 0.82 (0.70–0.96)	0	Not reported	Yang et al[119] (2001), Solanki et al[112] (2003), Pornier-Layrargues et al[120] (2003), Sanyal et al[109] (2008), Martin-Llahi et al[107] (2008), Neri et al[108] (2008)
	Not reported	Terlipressin alone or with albumin vs no intervention or albumin	RR, 0.80 (0.66–0.97)	Not reported	Not reported	Not reported
	Not reported	Terlipressin + albumin vs albumin	RR, 0.81 (0.68–0.97)	Not reported	Not reported	Not reported
	Not reported	Terlipressin vs no intervention	RR, 0.13 (0.01–2.10)	Not reported	Not reported	Not reported
	Not reported	Octreotide + albumin vs albumin	RR, 0.86 (0.58–1.30)	Not reported	Not reported	Not reported
Sagi et al[102] (2010)	3	Terlipressin vs control/placebo	RR, 1.85 (1.00–3.41)[a]	0%	.05	Sanyal et al[109] (2008), Martin-Llahi et al[107] (2008), Neri et al[108] (2008)
Gluud et al[100] (2012)	5	Terlipressin alone or with albumin vs no intervention or albumin	RR, 0.75 (0.59–0.97)	39%	.028	Yang et al[119] (2001), Solanki et al[112] (2003), Sanyal et al[109] (2008), Martin-Llahi et al[107] (2008), Neri et al[108] (2008)
Mattos et al[101] (2016)	4	Terlipressin vs noradrenaline	RR, 1.04 (0.84–1.30)[a]	0%	.70	Alessandria et al[103] (2007), Sharma et al[110] (2008), Singh et al[111] (2012), Ghosh et al[105] (2013)
Gifford et al[98] (2017)	4	Terlipressin ± albumin vs no intervention/placebo ± albumin	RR, 0.79 (0.63–1.01)	53%	.06	Solanki et al[112] (2003), Sanyal et al[109] (2008), Neri et al[108] (2008), Boyer et al[117] (2016)
	1	Terlipressin infusion vs terlipressin bolus	RR, 1.58 (0.86–2.91)	Not applicable	.14	Cavallin et al[92] (2016)
	3	Terlipressin vs noradrenaline	RR, 1.04 (0.74–1.47)	0%	.81	Alessandria et al[103] (2007), Sharma et al[110] (2008), Singh et al[111] (2012)
	2	Terlipressin + albumin vs dopamine + standard care	RR, 0.98 (0.76–1.26)	0%	.87	Silawat et al[114] (2011), Srivastava et al[121] (2015)
	1	Noradrenaline + albumin vs octreotide + midodrine + albumin	RR, 1.50 (0.60–3.78)	Not applicable	.39	Tavakkoli et al[113] (2012)
Facciorusso et al[97] (2017)	6	Terlipressin vs placebo	OR, 0.65 (0.41–1.05)	20%	.08	Solanki et al[112] (2003), Sanyal et al[109] (2008), Martin-Llahi et al[107] (2008), Neri et al[108] (2008), Zafar et al[116] (2012), Boyer et al[117] (2016)
	4	Terlipressin vs noradrenaline	OR, 1.02 (0.46–2.28)	0%	.95	Alessandria et al[103] (2007), Sharma et al[110] (2008), Singh et al[111] (2012), Indrabi et al[115] (2013)
	1	Terlipressin vs dopamine + furosemide	OR, 1.00 (0.18–5.67)	Not applicable	1.00	Srivastava et al[121] (2015)
	1	Terlipressin vs octreotide + midodrine	OR, 0.90 (0.27–3.05)	Not applicable	.87	Cavallin et al[104] (2015)
	1	Noradrenaline vs octreotide + midodrine	OR, 2.50 (0.29–21.40)	Not applicable	.40	Tavakkoli et al[113] (2012)

No improvement in mortality compared to other vasoconstricting therapy

Terlipressin and the FDA

- **Approved in 40 countries for the treatment of HRS**
  - **Not approved in Canada or the U.S.**
- **U.S. Trials ongoing**
  - **Mallinckrodt : Type 1 HRS currently in Phase 3 trials**
  - **BioVie Inc : Ascites**
    - **No current drugs have been approved for the treatment of ascites**
    - **Phase 2 Trials : Orphan Drug Designation**
    - **Fast Track Application**

HRS : Current Treatment Recommendations

- **Administer one of the following vasoconsticting regimens**
  - **Norepinephrine (0.5 – 3.0 mg/hr IV)**
  - **Midodrine (7.5 – 12.5 mg p.o. T.I.D.) + Octreotide (100 – 200 μg SQ T.I.D.)**
  - **Terlipressin (0.5 – 2.0 mg IV q 4 – 12 hours)**
- **Concomitant administration of**
  - **Albumin (1 g/kg IV on day 1 followed by 20 – 40 g/day)**

- **Duration of therapy – maximum 2 weeks**
- **Target increase in MAP by 10 mmHg**
- **CVP > 10 cmH2O**
- **Endpoint = reduction of creatinine < 1.5 mg/dl**

Contraindications to Vasoconstrictor Use in HRS

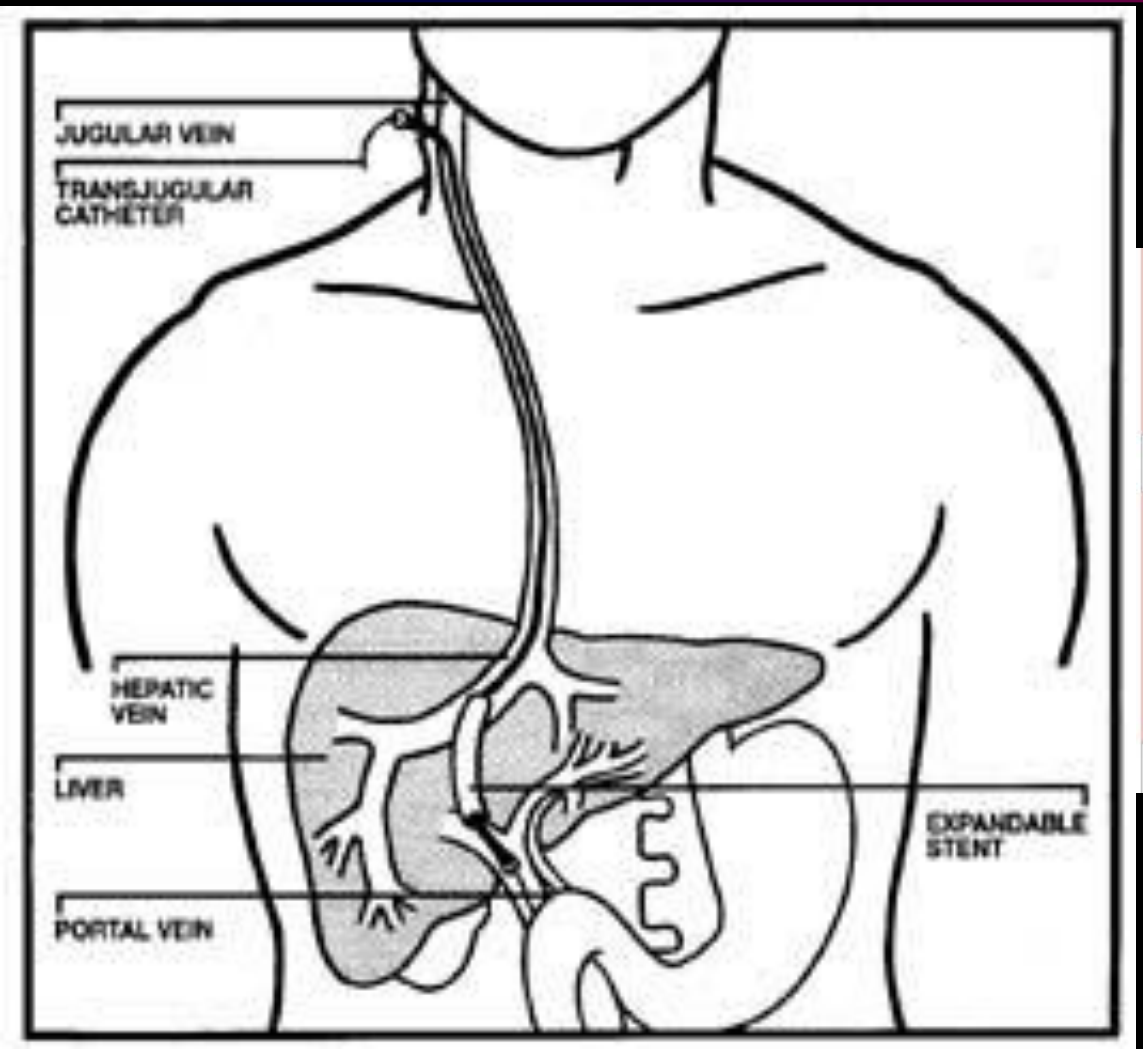
- **Active CAD**
- **Cardiomyopathy**
- **Cardiac Arrhythmias**
- **Cerebrovascular disease**
- **PVOD**
- **Severe HTN**

Treatment of Refractory Ascites

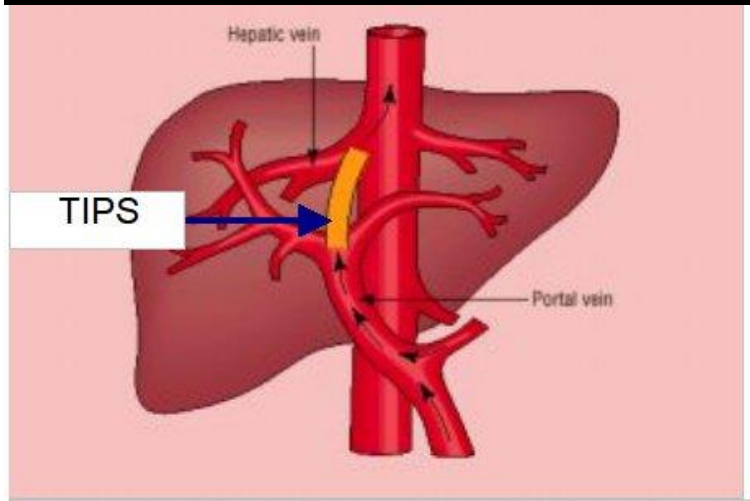
No response to 400 mg/day Spironolactone . 160 mg /day of Furosemide

- **Large Volume Paracentesis**
- **TIPS –Transjugular Portosystemic Shunt**
- **Alfa Pump**

Transjugular Intrahepatic Portosytemic Shunt TIPS Placement



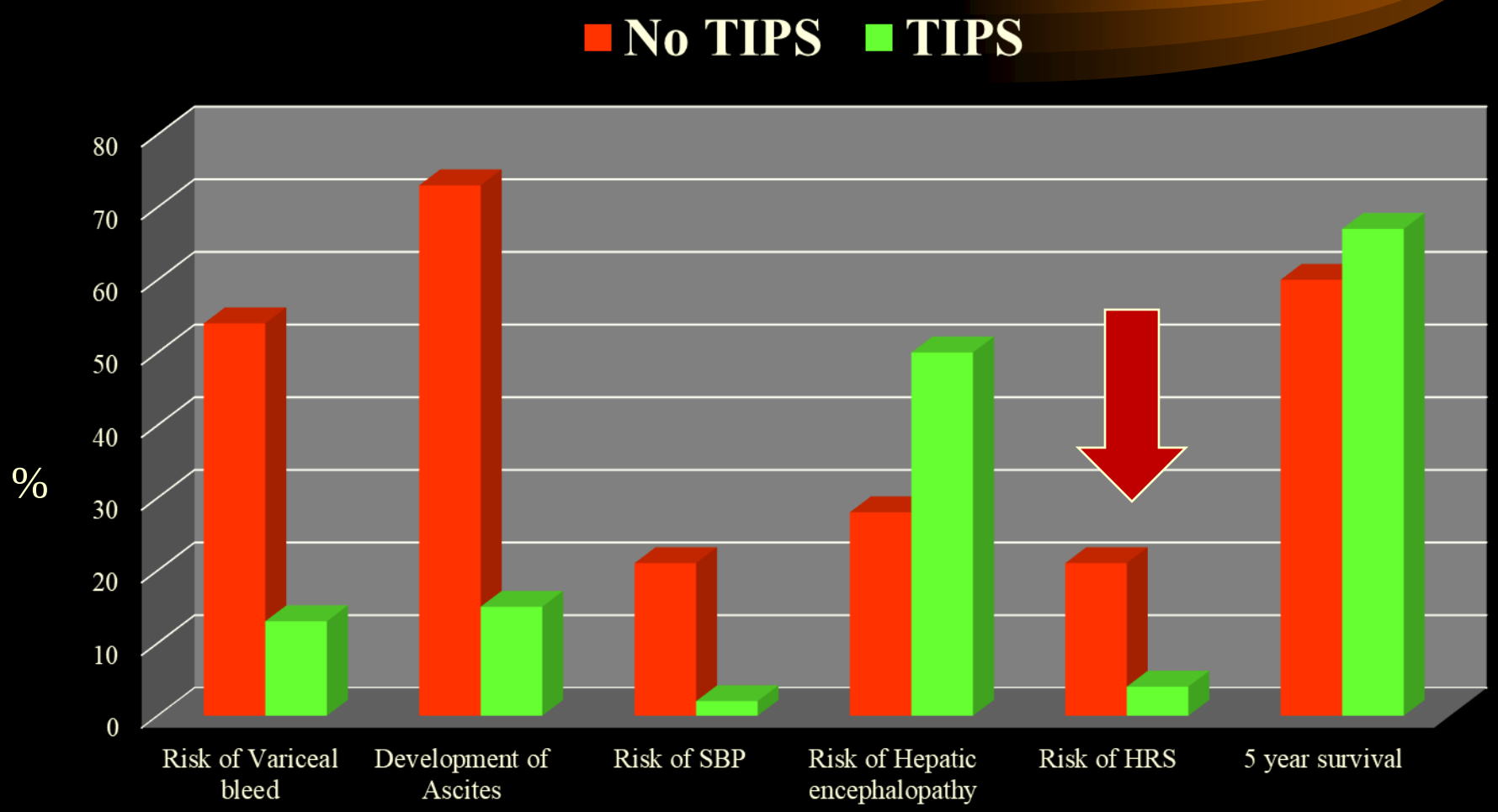
Reduces Portal Pressure



Transjugular intrahepatic portosystemic shunt

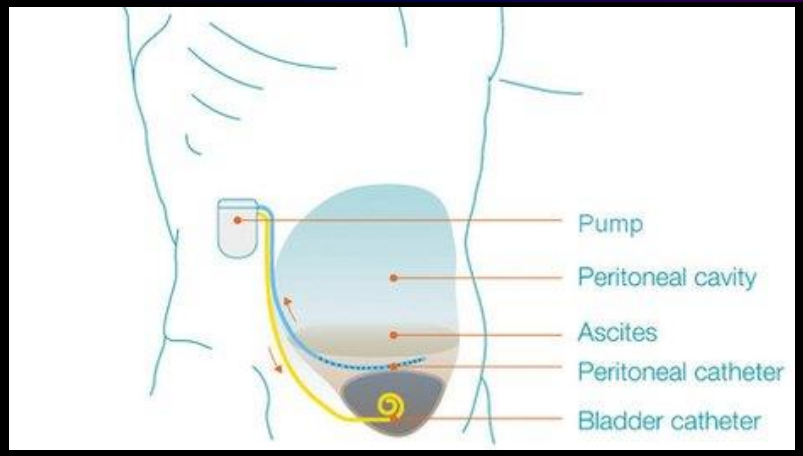
Castells A, Hepatology. 1994;20(3):584

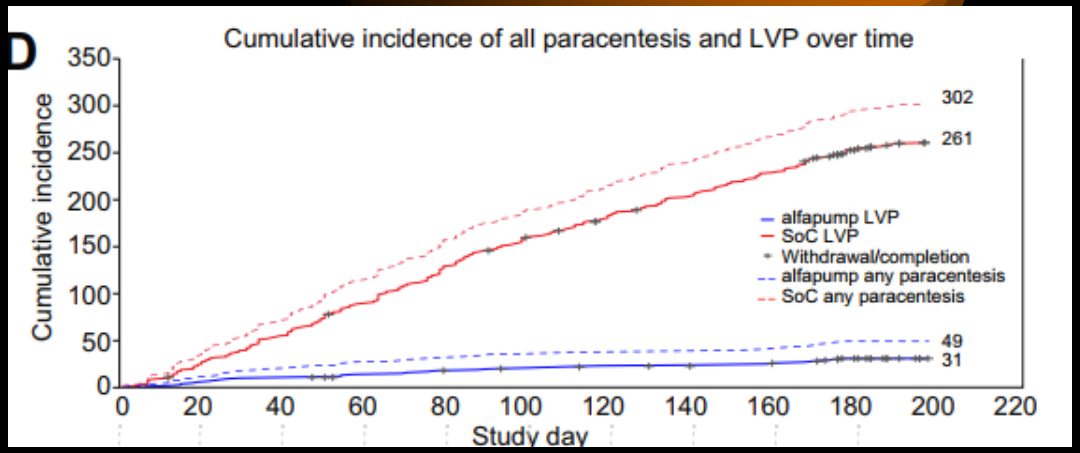
Prevention of HRS by Placement of TIPS



Bureau C. Journal of Hepatology 2017 vol. 67 j 940–949

Alfa Pump for Refractory Ascites (Automated Low-Flow Ascites Pump)



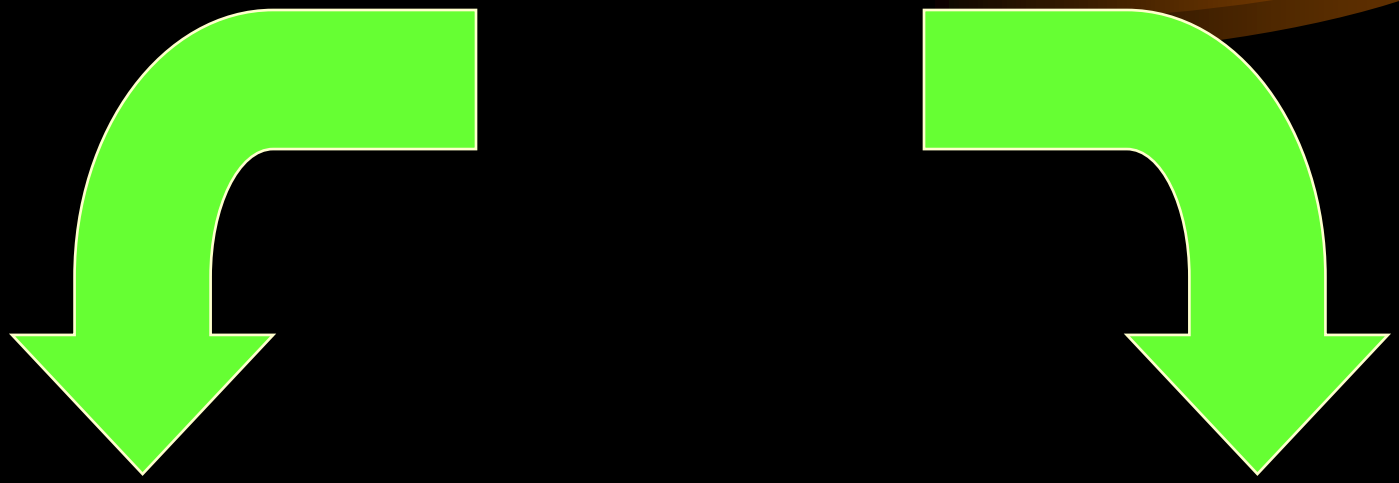


Efficacy currently limited by risk of infection

fully implantable, programmable, and rechargeable pump system that automatically diverts ascitic fluid from the peritoneal cavity to the urinary bladder, allowing fluid removal by micturition

Mean duration of implant procedure was 65.0 ± 20.6 min (min. 30, max. 130), all were performed under general anesthesia (12 laparoscopically [44.4%], 15 open [55.6%]).

Liver Transplantation in HRS



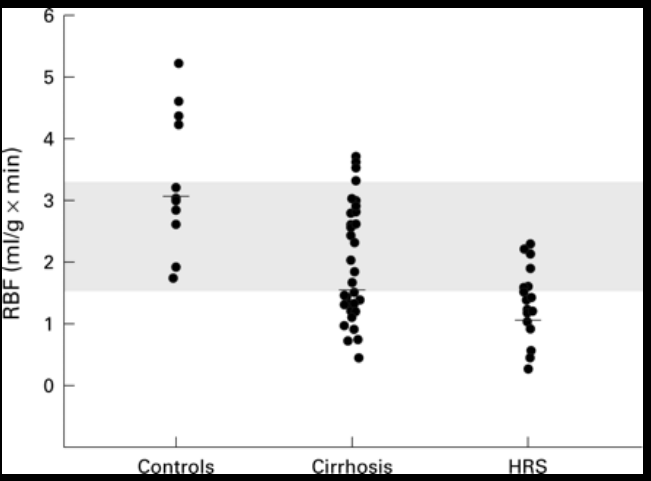
Liver TP Alone

?

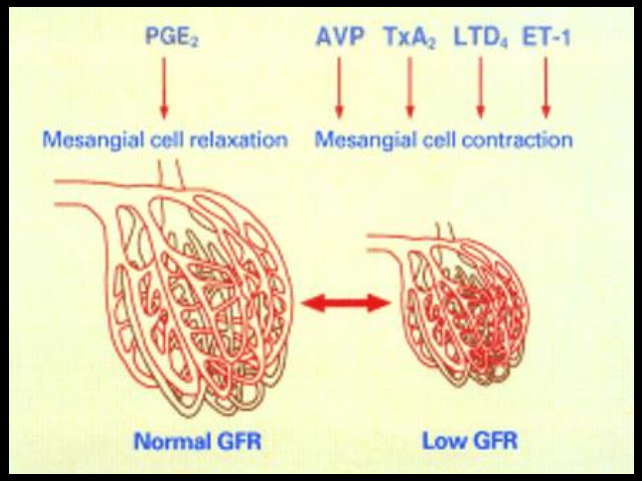
Liver / Kidney TP

HRS Diagnosis

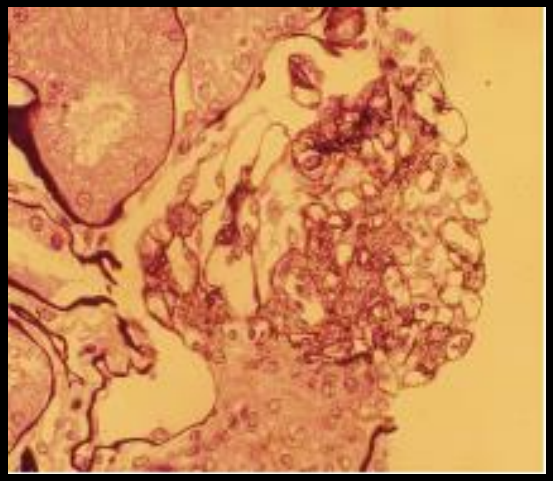
- **From a Nephrologic Perspective**
  - **Prolonged ischemic and vasoconstriction will lead to upregulation of cytokines that lead to progressive sclerosis**
  - **The duration of time required for these irreversible events is not measurable or defined**



Decreased renal blood flow



Mesangial contraction

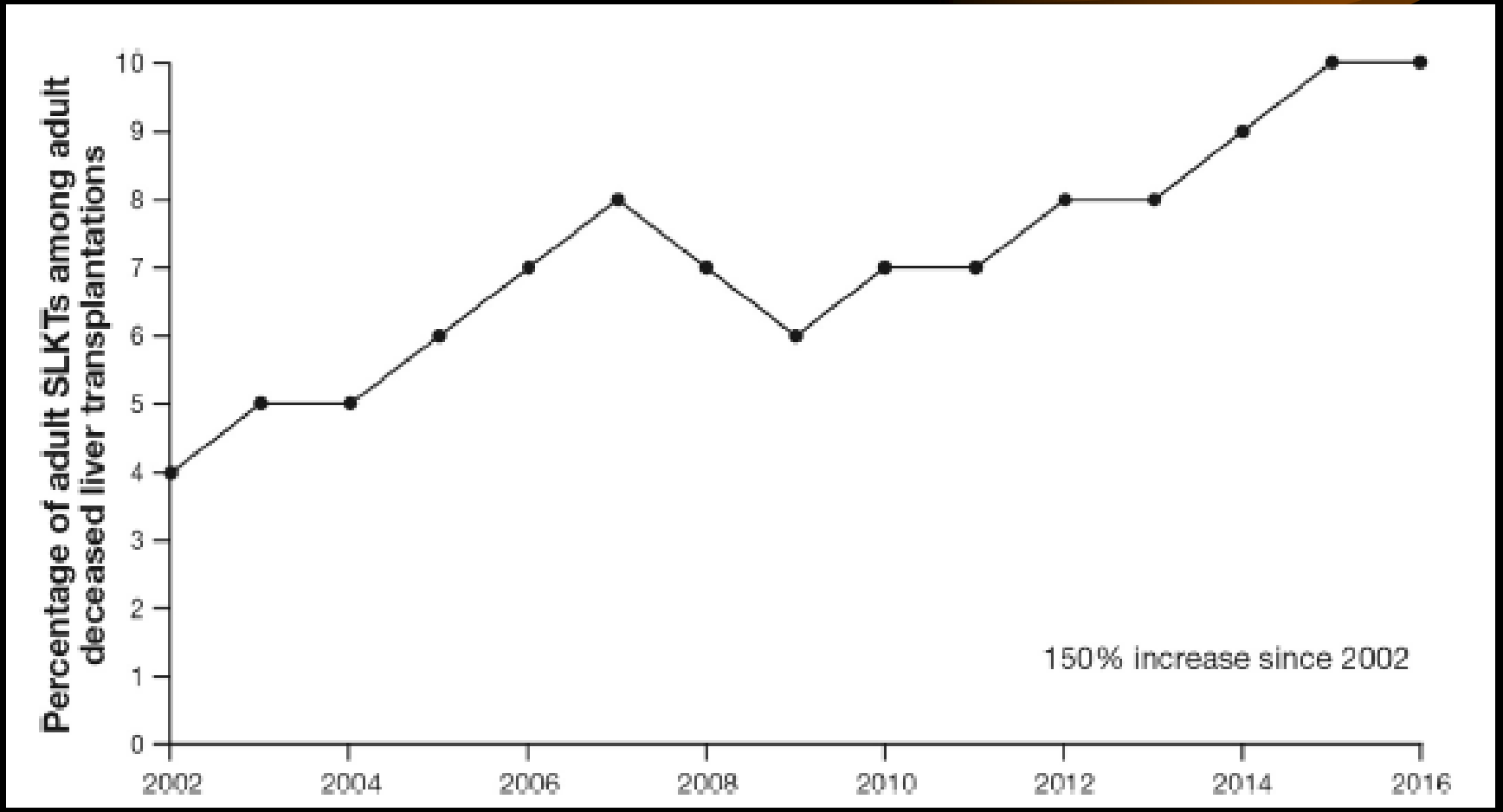


Hepatic Glomerulosclerosis

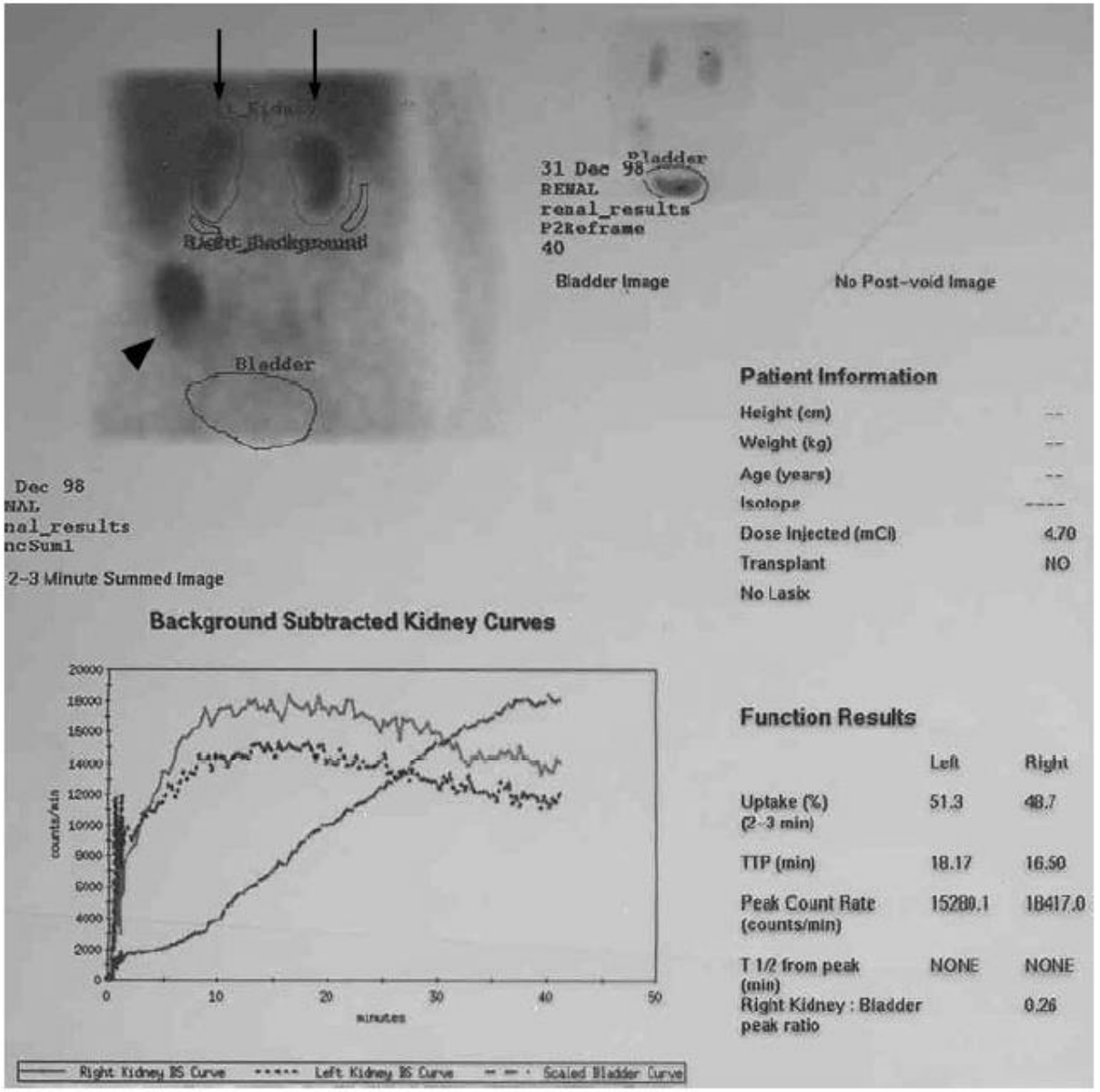
MELD Score

- **Point criteria for determining the allocation of liver TP**
- **MELD = Medical Evaluation of Liver Disease**
  - **Major factors**
    - **INR**
    - **Bilirubin**
    - **Creatinine**

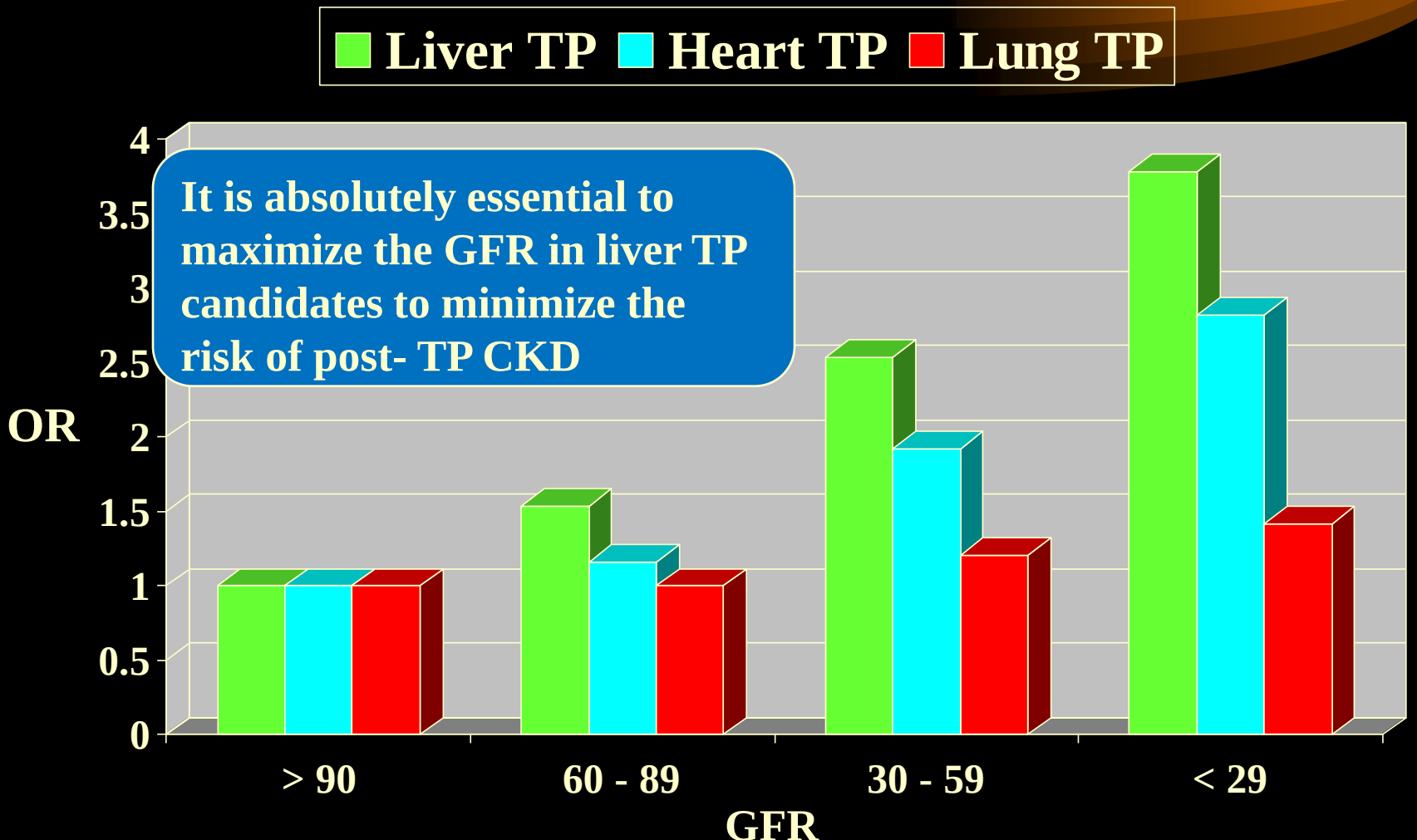
Marked Increase in the Number of Simultaneous Liver/Kidney Transplants since the Inception of the MELD Score



What We Want to Avoid !



Risk of CKD is Dependent on Pre-TP Renal Function in Non-Renal TP Patients



Transplantation in HRS : Liver or Combined Liver-Kidney

- **Key concepts**
  - **HRS is not an indication for combined liver –kidney transplant**
    - **HRS will recover in 80% of patients posttransplant**
  - **Kidney TP should be given only to patients with**
    - **ESRD : Dialysis > 3 months**
    - **CKD (3 months) with a GFR < 30 cc/min**
      - **These patients will likely require dialysis within 3 years after transplantation with CNI exposure**
    - **AKI**
      - **Dialysis > 6 weeks**
      - **GFR < 25 cc/min > 6 weeks**
  - **Pre-transplant renal function directly affects liver TP survival**
    - **All efforts to treat HRS and improve renal function before transplantation are important**

Hepatorenal Syndrome : Transplantation One or Two Organs ?

- **By definition –**
  - **Hepatorenal syndrome is a reversible phenomena of functional nature rather than structural damage**
  - **Patients meeting the strict criteria for this syndrome should be transplanted with a liver TP only**
  - **Kidney TP if Stage 4 CKD or dialysis dependent for > 6 weeks**
- **Management concern**
  - **Risk of calcineurin nephrotoxicity in a kidney that has been under prolonged ischemia**
  - **Difficulty of obtaining a renal biopsy due to the coagulopathy of liver failure**

Hepato(cardio)renal Syndrome

- **A unique constellation of hemodynamic events associated with advanced liver failure resulting in a form of vasomotor nephropathy**
  - **Must be distinguished from ATN, pre-renal azotemia and coincident involvement of the kidneys and the liver by specific disease states**
- **Primary splanchnic arteriolar vasodilation appears to be the main pathogenesis**

Hepatorenal Syndrome

- **HRS rarely develops spontaneously but often accompanies acute iatrogenic changes in intravascular volume**
- **Treatment with TIPS, Octreotide + Midodrine, Noradrenaline, Vasopressin analogues (with albumin-when approved!) and/or liver transplantation has been successfully employed in HRS**
- **HRS has a major adverse long term impact on patient survival and precautions must be initiated to avoid this syndrome**

Thank you !

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