Journal Club

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April 10th, 2008

Relationship Between Activation of the Sympathetic Nervous System and Renal Blood Flow Autoregulation in Cirrhosis

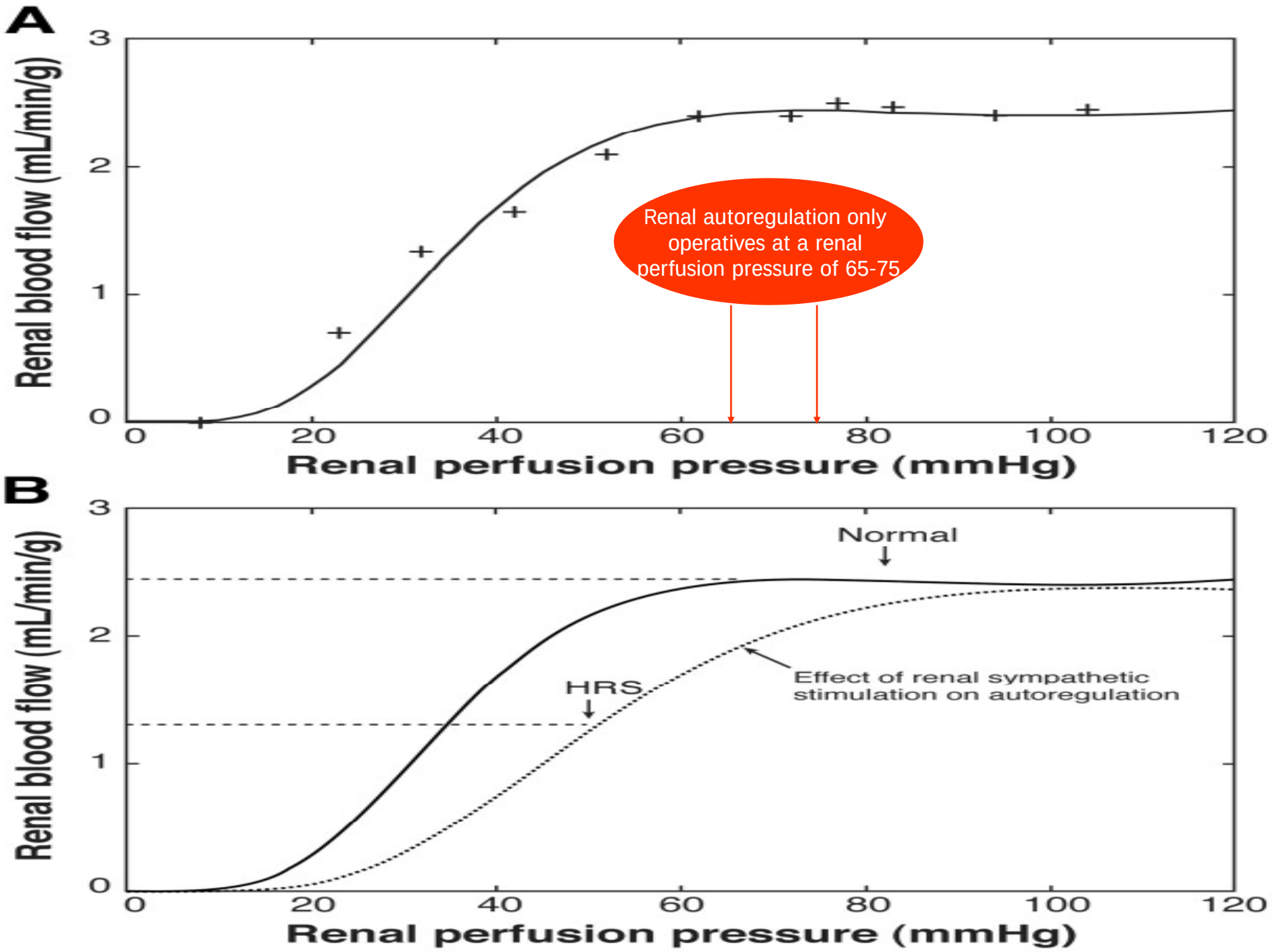
- Gastroenterology 2008
- Volume 134
- Pages 111-119
- Special Thanks to Dr. Marsano and Dr. Cave!!

Background

- Renal blood flow is critically dependent on blood pressure. Alteration of this relationship is seen during the activation of the sympathetic nervous system and this contributes to the development of hepatorenal syndrome.
- Examples: decompensated cirrhosis, infection, SIRS, cardiac failure.

Background

- Downward & rightward shift of the renal blood flow / renal perfusion curve is seen in cirrhotic patients with more severe renal dysfunction.
- Loss of the “sigmoid” shape of the curve indicates that at a given renal perfusion pressure the corresponding renal blood flow is lower in patients with decompensated liver disease compared with those with more compensated liver disease.


A
Renal blood flow (mL/min/g)
0
1
2
3
0
20
40
60
80
100
120
Renal perfusion pressure (mmHg)
Renal autoregulation only operatives at a renal perfusion pressure of 65-75
B
Renal blood flow (mL/min/g)
0
1
2
3
0
20
40
60
80
100
120
Renal perfusion pressure (mmHg)
Normal
HRS
Effect of renal sympathetic stimulation on autoregulation

Background

- Insertion of TIPS, reduced portal pressures through establishment of a shunt between portal and hepatic veins.
- Improved renal function and sodium excretion through decrease in the activity of the sympathetic nervous system (NE levels).

AIMS

- Determine the relationship of renal blood flow and renal perfusion pressure in patients with liver cirrhosis and determine whether this is related to the activation of the sympathetic nervous system and whether insertion of a transjugular intrahepatic portasystemic shunt (TIPS) alters this relationship.

Inclusion & Exclusion Criteria

- Inclusion:
  Clinical, biochemical, & histological evidence of cirrhosis
- Exclusion:
  GIB in last 4 weeks
  TIPS
  Hepatic Encephalopathy
  Active alcohol abuse
  Diabetes
  Cardiovascular disease
  Malignancy
  Pregnancy

Methods

56 patients recruited over 3 years

Study Group 1:

1. Never ascites: “Pre-ascites” (n=13)
2. Diuretic responsive ascites (n=12)
3. Refractory ascites (n=12)
4. Type II Hepatorenal syndrome (n=10)

Methods

- Study Group 2:
- Insertion of TIPS for refractory ascites (n=8).
- Baseline investigation were performed on the day of the TIPS procedure and repeated investigation performed 3 - 4 weeks afterward.

Study Design

1. Never ascites: allowed 150 mmol/day of sodium
2. Diuretic responsive & Refractory ascites: fixed diet with 100 mmol/day of sodium
3. Type II Hepatorenal syndrome: resuscitated with 1.5 L of IVF before inclusion in the study

Measurements

- Cardiac hemodynamics
  - HR,
  - Oxygen Sat,
  - EKG,
  - Mean arterial pressures (Swan-Ganz catheter),
  - Calculated Cardiac output
- Hepatic venous pressure gradient (balloon tipped catheter)
- Renal blood flow (calculated using continuous infusion of para-aminohippuric acid)
- Renal perfusion pressures (calculated)
- Portal pressure gradients (calculated)
- Norepinephrine levels measured by blood sample & liquid chromatography
- Renal autoregulatory model curves: heuristic methods

Statistical Analysis

- One-way analysis of variance
- Paired t test
- Pearson & Spearman correlation tests
- Multivariate linear regression analysis

Results

Characteristics:

- Refractory ascites and HRS II groups had higher Child-Pugh score, Bilirubin level, and prothrombin time. Lower Albumin concentration.
- HRS II group had higher creatinine levels compared to other groups (P = 0.0001)

Results – Cardiovascular

- HRS II and Refractory ascites group had lower mean arterial pressures ($P = 0.0001$) & associated with increased CO and lower SVR ($P < 0.05$).
- HRS II group had higher plasma levels of NE ($P < 0.0001$).
- Refractory ascites had higher levels of NE compared to non-ascitic and diuretic-responsive ascitic group ($P < 0.01$).

Results – Renal

- Renal blood flow was decreased in all groups.
- HRS II & Refractory ascites groups had lower renal blood flow ($P < 0.0001$) & renal perfusion pressure ($P < 0.05$) then non-ascites & diuretic responsive ascites.

Results – Renal

Renal blow flow correlated positively with:

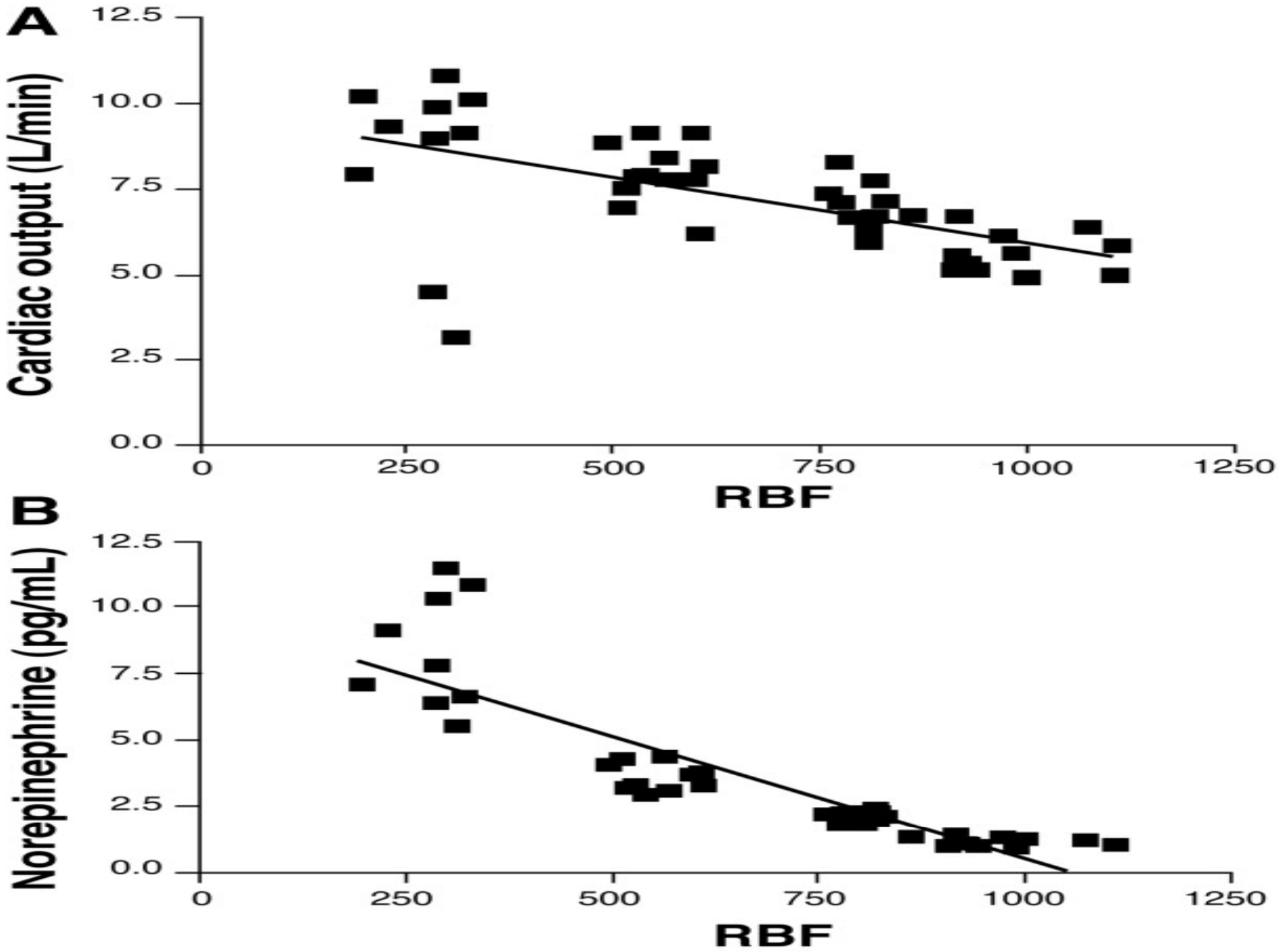
- Mean arterial pressure ($P < 0.0001$)
- Urinary sodium excretion ($P < 0.0001$)
- Creatinine Clearance ($P < 0.0001$)
- SVR ($P < 0.0001$)

Renal flow correlated inversely with

Cardiac output ($P < 0.0001$)

Hepatic venous pressure gradient ($P < 0.0001$)

NE levels ($P < 0.0001$)

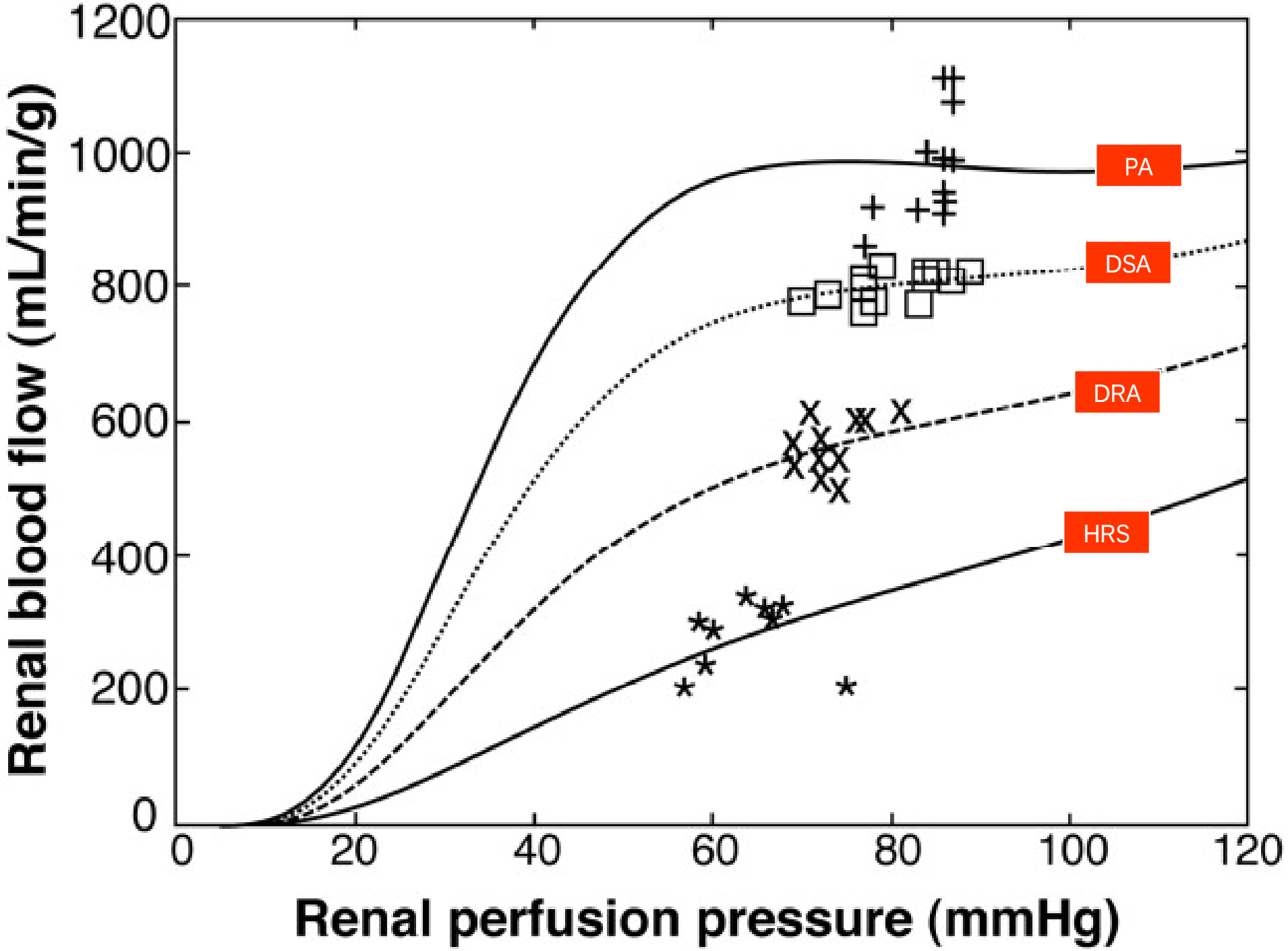

A
Cardiac output (L/min)
12.5
10.0
7.5
5.0
2.5
0.0
0
250
500
750
1000
1250
RBF
B
Norepinephrine (pg/mL)
12.5
10.0
7.5
5.0
2.5
0.0
0
250
500
750
1000
1250
RBF

Results – Hepatic Venous Pressure

- HRS II and Refractory ascites group has higher hepatic venous pressure gradients then the two other groups
- Hepatic venous pressure gradient correlated inversely with:
  - o renal blood flow ($P < 0.001$)
  - o renal perfusion pressure ($P<.001$)
- Positively with NE levels ($P<0.001$)

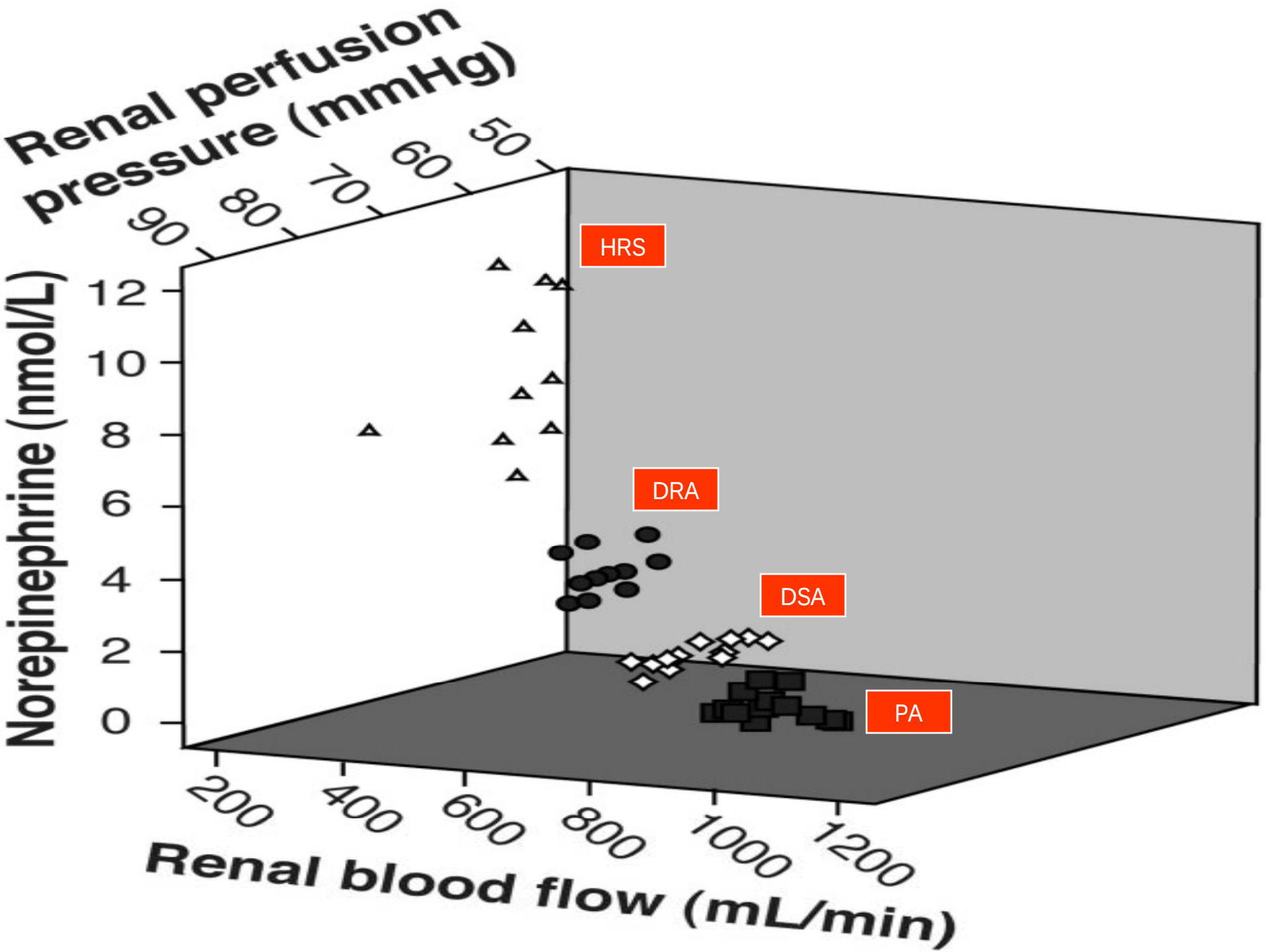
Results – RBF & RPP

- With increasing disease severity, there was loss of the renal blood flow / renal perfusion pressure curve.
- Mathematical model showed loss of the sigmoid shape of autoregulation curve with parallel increase in NE levels.
- Increasing vasoconstriction with increasing disease severity.


Renal blood flow (mL/min/g)
1200
1000
800
600
400
200
0
0
20
40
60
80
100
120
Renal perfusion pressure (mmHg)
PA
DSA
DRA
HRS

Results – RBF, RPP, NE

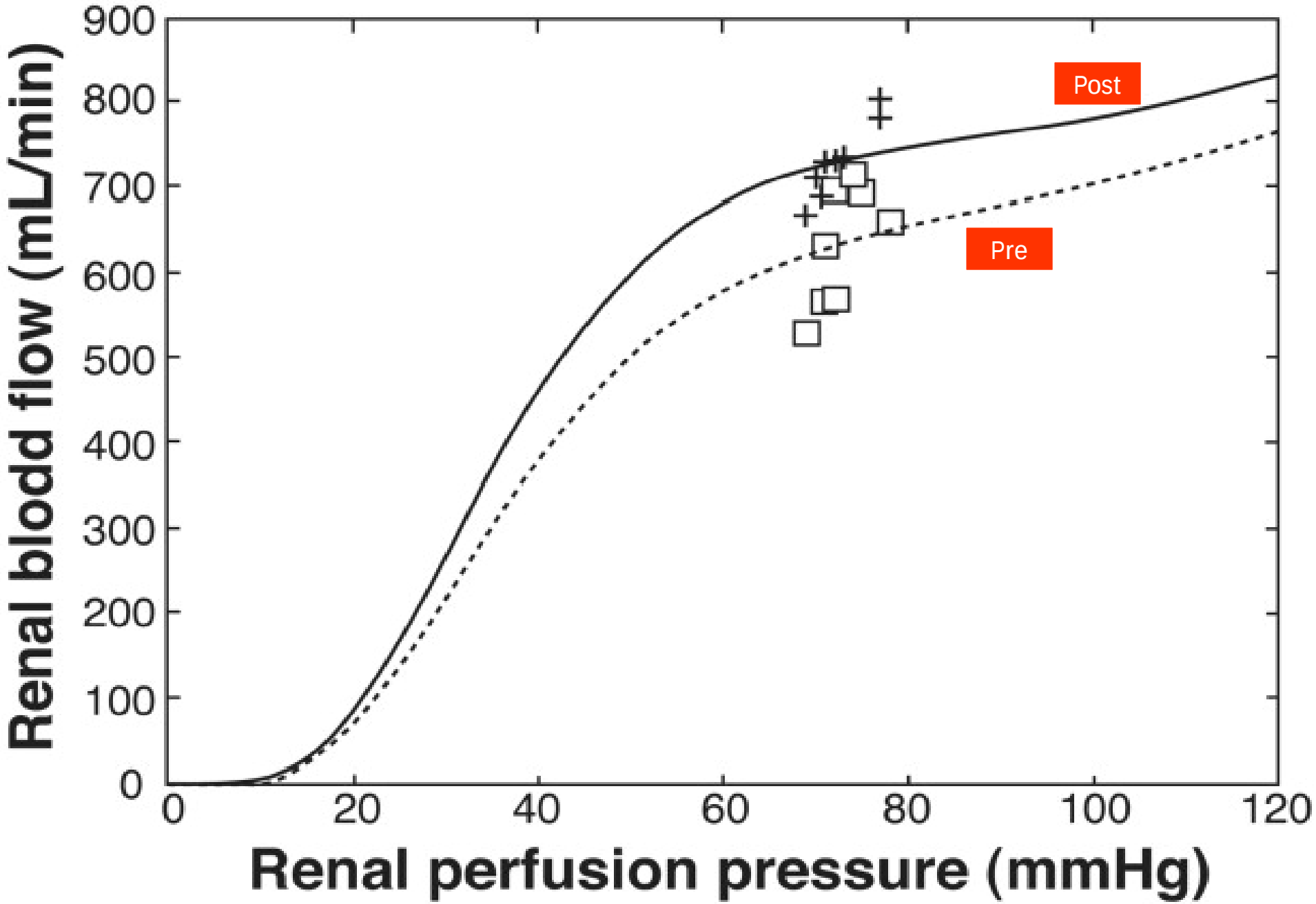
- The combination of the independent variable's renal perfusion pressure and NE levels were able to reliably predict renal blow flow.

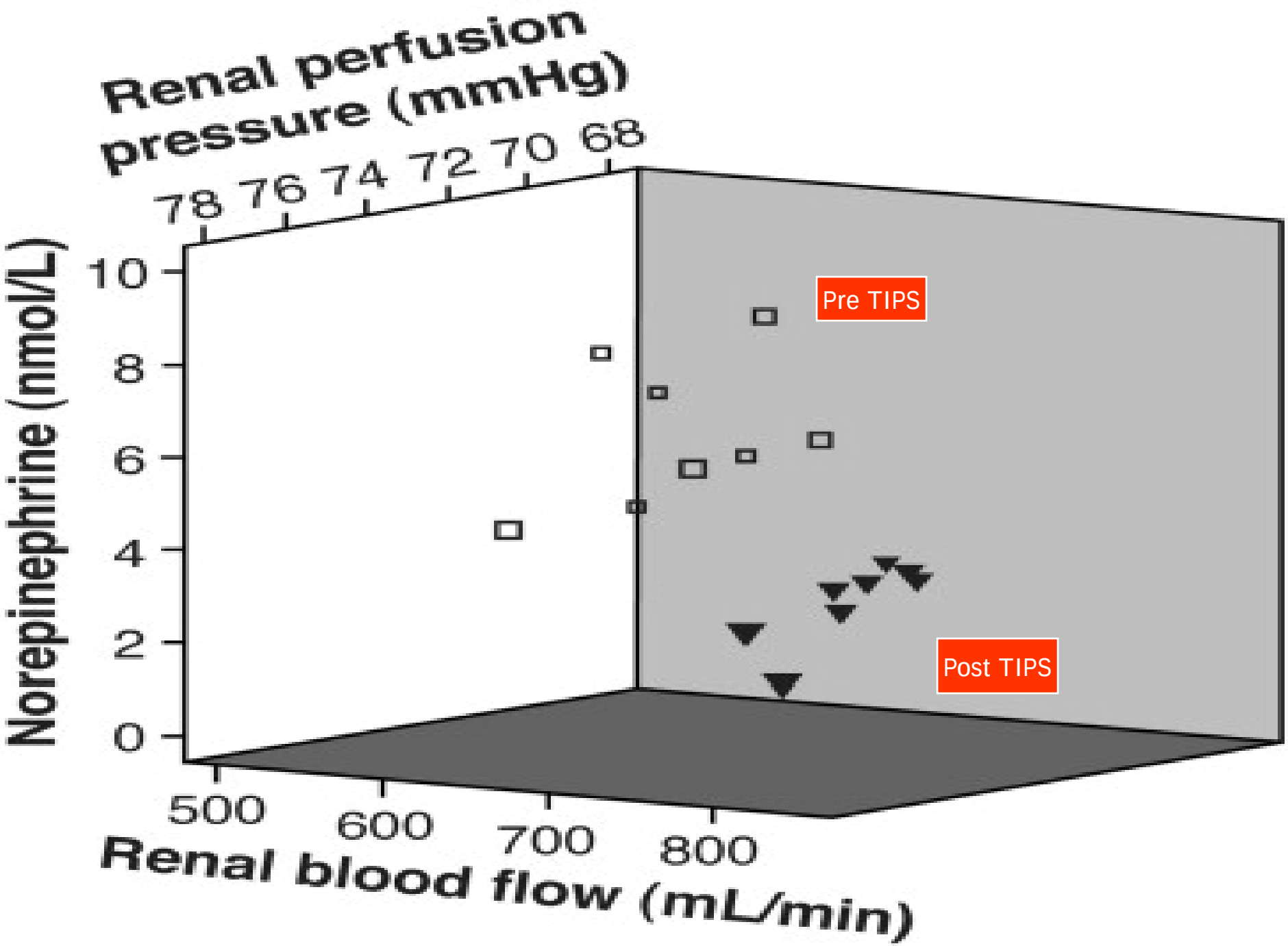

Renal perfusion pressure (mmHg)
90
80
70
60
50
Norepinephrine (nmol/L)
12
10
8
6
4
2
0
HRS
DRA
DSA
PA
200
400
600
800
1000
1200
Renal blood flow (mL/min)

Results – TIPS Effect

- Insertion of TIPS caused a significant decrease in hepatic venous pressure gradient and NE levels ($P < 0.001$) with significant increase in renal blood flow ($P < 0.01$)
- Upward shift of the curve after insertion of TIPS indicating a decrease in vasoconstrictory stimuli, higher renal blood flow due to decreasing levels of NE, partially reversing the symptoms of the disease.

Effect of TIPS in DRA




Renal perfusion pressure (mmHg)
78 76 74 72 70 68
Norepinephrine (nmol/L)
10
8
6
4
2
0
500 600 700 800
Renal blood flow (mL/min)
Pre TIPS
Post TIPS

Conclusion

- Cirrhotic patients with more severe renal dysfunction have a downward and rightward shift in the renal blood flow / renal perfusion pressure autoregulation curve.
- At a given renal perfusion pressure the corresponding renal blood flow is lower in patients with more severe liver dysfunction compared to those with more compensated disease

Conclusion

- TIPS insertion decreases sympathetic activation (decrease levels of NE) and improves renal function through positive effects of renal blood flow autoregulation, shifting the curve upwards.
- NE levels statistically & dynamically correlate with renal blood flow / renal perfusion pressure curve.

Noradrenalin vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study

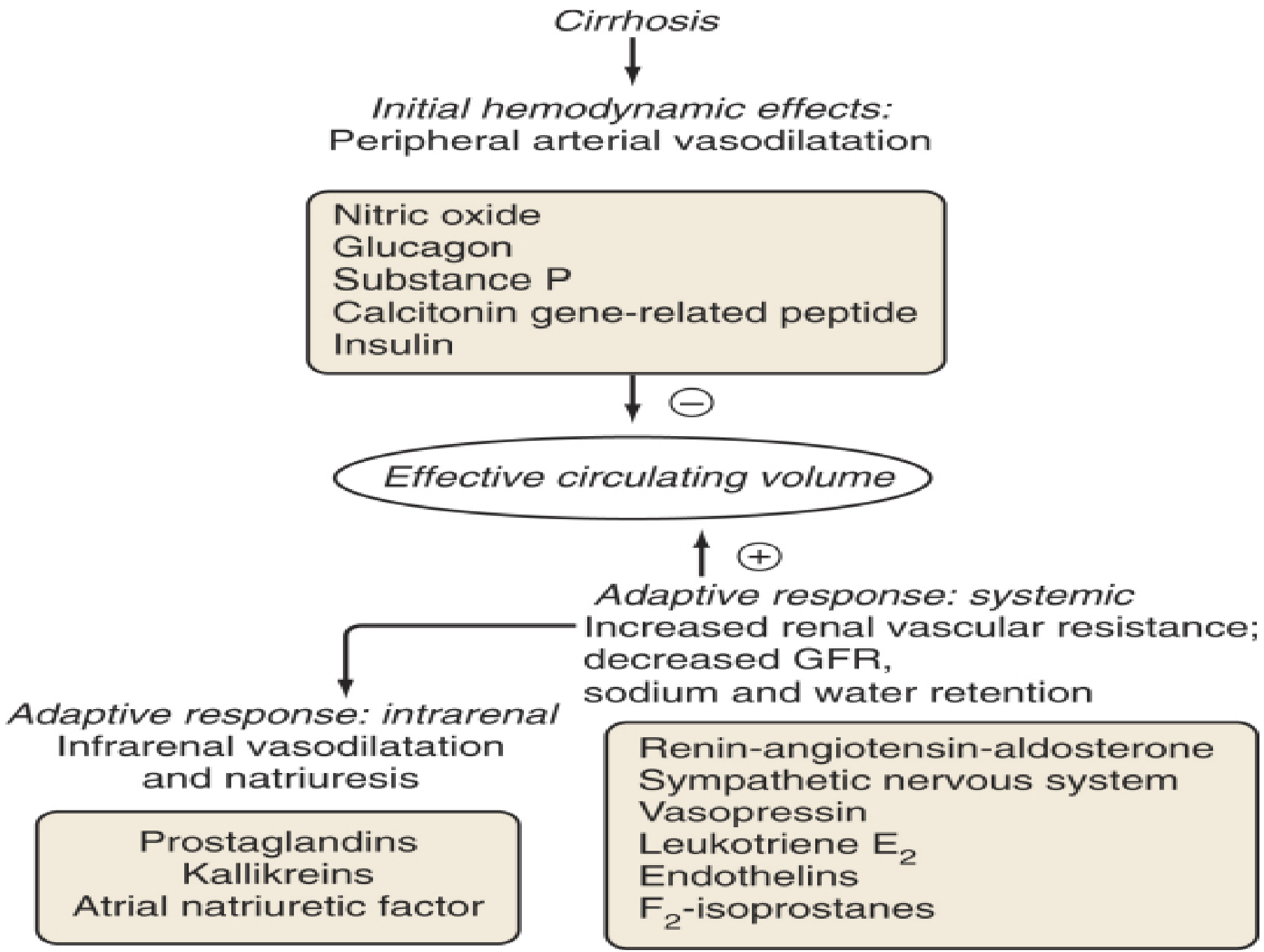
- Journal of Hepatology. 47(4):499-505, 2007 Oct.
- AIMS: assessing the efficacy and safety of noradrenalin vs terlipressin in patients with HRS.
- METHODS: 22 consecutive cirrhotic patients with HRS were included. Patients were randomly assigned to be treated with noradrenalin and albumin or with terlipressin and albumin. Treatment was administered until HRS reversal or for a maximum of two weeks.
- RESULTS: Reversal of HRS was observed in 7 of the 10 patients (70%) treated with noradrenalin and in 10 of the 12 patients (83%) treated with terlipressin.

Vasoconstrictor therapy for hepatorenal syndrome in liver cirrhosis. Journal Article. Review

- Journal Article. Review of 78 refs
- Current Pharmaceutical Design. 12(35):4637-47, 2006.
- Several vasoconstrictors including the alpha-adrenergic agonists, midodrine and noradrenalin, and the vasopressor analogues, ornipressin and terlipressin, have all been associated with a significant improvement in renal function in 57 to 100% of cases and even reversal of hepatorenal syndrome in 42 to 100% of cases.
- The majority of recent studies are on terlipressin. A randomized, controlled trial showed a significant effect of terlipressin on reversal of hepatorenal syndrome. The contribution of volume expansion to the beneficial effects of vasoconstrictors on hepatorenal syndrome remains to be determined. In general, reversal of hepatorenal syndrome was associated with an improved survival.
- However, it remains to be determined if vasoconstrictor therapy should be used in hepatorenal syndrome in general, or if it should be reserved for potential candidates for liver transplantation.
- Evidence for a beneficial effect of vasoconstrictor therapy for the treatment of hepatorenal syndrome is steadily accumulating. Confirmation of the preliminary data in larger randomized, controlled trials looking at long-term survival is required.

Discussion

- Limitations:
  - Focused Study
  - Clinical Implications


Cirrhosis
Initial hemodynamic effects:
Peripheral arterial vasodilatation
Nitric oxide
Glucagon
Substance P
Calcitonin gene-related peptide
Insulin
⊖
Effective circulating volume
⊕
Adaptive response: systemic
Increased renal vascular resistance;
decreased GFR,
sodium and water retention
Adaptive response: intrarenal
Infrarenal vasodilatation
and natriuresis
Prostaglandins
Kallikreins
Atrial natriuretic factor
Renin-angiotensin-aldosterone
Sympathetic nervous system
Vasopressin
Leukotriene E_2
Endothelins
F_2-isoprostanes