Intrinsic Renal Mechanisms of Hepatorenal Syndrome

Luis A. Juncos
Professor of Medicine
Central Arkansas Veterans Healthcare Systems
University of Arkansas for Medical Sciences
Case Presentation

52 year old male with alcoholic cirrhosis and ascites

- 3 week history of progressive weakness, malaise, lower back pain
- Increasing ascites and lower extremity edema
- Decreasing urine output - Creatinine 4.6 mg/dl (baseline is 0.9 mg/dl)
- Not seen 6 months - Has not been taking his medications regularly

- Diuretics held (furosemide + spironolactone)
- 2 liters of crystalloids + 200 gms of 25% albumin
- Albumin + octreotide + midodrine daily
Key Questions

1. Is this AKI or CKD?

2. What is the most appropriate therapy for this patient?

3. What is the etiology? → Pathophysiology
Causes of AKI in Cirrhosis

- **Pre-renal → 60-70%**
  - 2/3 are volume responsive
    - Overdiuresis
    - GI Losses
    - GI Bleeding
  - 1/3 are not volume responsive
    - AKI-HRS
    - Other

- **Intrarenal → 30-40%**
  - Inflammation (ACLF and ALF)
  - Sepsis
  - ATN → prolonged hypoperfusion
  - NSAID
  - Bile Acid Nephropathy
  - Intrabdominal Hypertension

- **Obstruction < 1%**
Causes of AKI in Cirrhosis

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Spectrum of renal diseases in cirrhosis

Cirrhosis

Structural

Dynamic

NO – CO - Prostanoids
Anandamide - CGRP
Adrenomedullin

Splanchnic Arterial Vasodilation
↓ Pressor Responses

Reduced EABV

Portal Sinusoidal Hypertension

Portosystemic Collaterals

Activation of Neurohumoral Systems

Increased Cardiac Output

Sodium & Water Retention
Activation of Neurohumoral Systems

- Sodium & Water Retention
  - Ascites/Edema
  - Hyponatremia

- Renal Vasoconstriction
  - Hepatorenal Syndrome

- Increased Cardiac Output
  - High Output CHF
Renal Blood Flow in Different Stages of Cirrhosis

Kidneys are Passive Victims

Holes in the Peripheral Vasodilation Theory

• Temporal inconsistencies:
  - Experimental cirrhosis: Na retention began before changes in hemodynamics

• RAAS activity is not ↑ in 1/3 of patients.

• Renal Na handling in Patients with compensated cirrhosis
  - Normal RAAS activity, but have ↑ Na retention when given a salt load.

• TIPS → ↑ sodium excretion and even function → ↓ SVR and ↑CO

• Hepatorenal Reflex (osmo, chemo, baroreceptors → Neural
Terlipressin in HRS?

A Randomized, Prospective, Double-Blind, Placebo-Controlled Trial of Terlipressin for Type 1 Hepatorenal Syndrome

- HRS Reversal 34% vs 13% (p=0.008)

Terlipressin Plus Albumin Is More Effective Than Albumin Alone in Improving Renal Function in Patients With Cirrhosis and Hepatorenal Syndrome Type 1

- HRS Reversal 24% vs 15% (p=0.13)

GASTROENTEROLOGY 2008;134:1360–1368

Gastroenterology 2016;150:1579–1589

37th Vicenza Course on AKI & CRRT – May 28-30, 2019
Experimental Models of Portal Hypertension

Models of Prehepatic Portal Hypertension
- Portal Vein Ligation

Models of Presinusoidal Portal Hypertension
- Schistosomiasis mansoni

Models of Sinusoidal Portal Hypertension
- Carbon Tetrachloride-induced cirrhosis
  - Chronic bile duct ligation (biliary cirrhosis)

Models of Postsinusoidal Portal Hypertension
- Dimethylnitrosamine-induced pericentral fibrosis

Models of Posthepatic Portal Hypertension
- Obstruction of the Hepatic vein or Inferior Vena Cava
CBDL: A Model of Cholestatic Liver Disease

- Secondary biliary cirrhosis → ~90% of Rats (4-5 weeks)
- Portal Hypertension
- Hyperdynamic Circulation:
  - \( \uparrow \) CO, Portal venous inflow
  - \( \downarrow \) Systemic and Splanchnic vascular resistance.
- Early \( \text{Na}^+ \) and \( \text{H}_2\text{O} \) Wasting → Late \( \text{Na}^+ \) and \( \text{H}_2\text{O} \) Retention.
- Progressive Renal Dysfunction
Effect of C-BDL in Rats

- Survival
- MAP (mmHg)
- RBF ml/min/g-bw
- GFR (ml/min/g-bw)
C-BDL-Induced Changes in Intrarenal Blood Flow Distribution

Intrarenal blood flow was measured by laser-Doppler.
Micro-CT Reconstructed Images of Kidneys in Control and Cirrhotic Rats
Micro-CT reconstructed image of kidneys from control, and cirrhotic rats.
Microperfused Afferent Arterioles: Schematic & Example

Af-Art: Afferent Arteriole
GL: Glomerulus
Hold-Pip: Holding pipette
Perf-Pip: Perfusion pipette
Exch-Pip: Exchange pipette
Pre-pip: Pressure pipette
Vascular Reactivity of Af-Art of C-BDL Rats

**Graphs:**

- **Left Graph:**
  - Y-axis: Luminal Diameter (% of Basal)
  - X-axis: Ang II (log M)
  - Data points represent control and C-BDL conditions.
  - Key:
    - *: Significant difference
    - #: Other significant difference

- **Right Graph:**
  - Y-axis: Luminal diameter (μm)
  - Data points represent Norepinephrine and ACh effects.
  - Key:
    - *: Significant difference
    - #: Other significant difference
Cerebral vascular Resistance Correlates with Renal Vascular Resistance in Cirrhotic Rats
Vitamin E Prevents CBDL-Induced Renal Dysfunction
Changes in Distribution of Intrarenal RBF in C-BDL Rats as Determined by Micro-CT: Effect of Vitamin E.

Vascular Volume Fraction (%)

- Control
- Control + VitE
- CBDL
- CBDL + VitE

* $p < 0.05$ vs. Control
# $p < 0.05$ vs. C-BDL
Intrarenal blood flow was measured by laser-Doppler.
Vascular Reactivity of Af-Art in C-BDL Rats

![Graph showing vascular reactivity](image-url)
Effects of Vit E on Diuresis and Natriuresis in C-BDL Rats.

* $p < 0.05$ vs. control

# $p < 0.05$ vs. CBDL
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NSAID Sensitivity in Liver Disease

Indomethacin was administered to patients with Cirrhosis and Ascites

Connecting Tubuloglomerular Feedback (cTGF)

Carretero et al.
Kidney International
Tubular Abnormalities

Thick Ascending Limb of Henle

- TALH → Hypertrophy during cirrhosis - CBDL
- NKCC2 is consistently overexpressed in experimental cirrhosis
  - Enhanced Loop responses to diuretics (during mild disease)
  - Human cirrhosis???

- Somatostatin receptors (SST1 & SST2) are abundant in the TALH
Intrarenal octreotide treatment prevents sodium retention in liver cirrhotic rats: evidence for direct effects within the thick ascending limb of Henle’s loop

Thomas E. N. Jonassen,¹ Sten Christensen,² Niels Marcussen,¹ and Jørgen Søberg Petersen¹
¹Department of Pharmacology, The Panum Institute, University of Copenhagen, Copenhagen; and
²University Institute of Pathology, Aarhus University Hospital, University of Aarhus, Aarhus, Denmark

• C-BDL for 5 weeks → No changes in systemic/renal hemodynamics.

• Intrarenal Octreotide (LAR) Normalized

  → TAL Hypertrophy / NKCC2 expression / Loop responses

  → Sodium and water handling in CBL rats.

• Systemic administration of this dose of octreotide had no effect.
Mechanisms of Cirrhosis-Induced Renal Microvascular Dysfunction

- Prolonged activation of RAAS
- Sustained ↑ increases in ROS → ↑ isoprostanes
- Inflammation
- Prolonged hypoperfusion
- Bile acid toxicity
Summary of Intrinsic Intrarenal Abnormalities that may be Present during Cirrhosis

- Direct Prolonged/ Sustained Vasoconstriction
- Enhanced Vascular Reactivity
- Abnormal Autoregulation
- Altered TGF and cTGF
- Mesangial contraction
- Abnormal Na handling by the TALH
Potential Therapeutic Implications of Intrinsic Renal Vasoconstriction

• Strict Avoidance of Additional Renal Vasoconstrictor Stimuli
  - NSAIDS
  - Intraabdominal Hypertension
  - Monitor Volume Status more Accurately - Methodology

• Treat Early, Before the Vasoconstriction Becomes Refractory?

• Blood pressure may need to be increased more.
  - Develop Methods of identifying responsiveness more accurately

• More specific therapies need to be developed and implemented
Progression to HRS: Stages of Sodium Retention

- Subtle Sodium Retention
- Obvious Sodium Retention
- Avid Sodium Retention
- Functional Renal Failure

- Pre-Ascites
- Responsive Ascites
- Refractory Ascites
- Hepatorenal Syndrome

- Hepatorenal Interaction

- Systemic arterial Vasodilation
- Renal Vasoconstriction

Clinical Medicine 2003; 3(2)
CIRRHOSIS

- Portal hypertension
  - Splanchnic arterial vasoconstriction
  - Increase in effective arterial blood volume
  - Suppressed vasoconstrictor systems

- Kidney vasodilation
  - Cerebral vasodilation??
  - Brachial/femoral vasodilation??

- Maintenance of effective arterial blood volume

IMPROVED KIDNEY FUNCTION
**Summary: The effects of Vitamin E on CBDL Rats**

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<th>Vitamin E did not help:</th>
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