50 yo hispanic M, consulted for refractory edema

PMH: HIV on ART, hep C, B c/b liver cirrhosis, ho refractory peripheral edema, ascites, with multiple admissions requiring IV diuretics, paracentesis, ho SBP, AKI thought to be hemodynamic, chronic mild hyponatremia, reportedly impaired response to po diuretics, was maintained on IV bumatenenide throughout the hospital stay since re-opening after storm Sandy in Feb.
Allergy: ?lasix, bactrim
Meds: bumex 2 mg IV BID, spirinolactone 25 mg po.
On exam: vitals: P: 90  BP: 100s/60s, RR: 20
general: AOx3, NAD, sitting position with severe generalized anasarca
HEENT: icteric sclera, no LAD, mild JVD.
CV: regular, functional murmur, no rub
chest: diminished BS at bases, scattered rales
abd: severe distention, ascites, thick edematous skin
generalized edema up to mid chest.
<table>
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<th>Date</th>
<th>S Na</th>
<th>K</th>
<th>BUN</th>
<th>Cr</th>
<th>U Na</th>
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Although many aspects of the pathogenesis of edema in cirrhosis are understood, the stimulus that initiates and maintains sodium retention remains elusive.
There is no ‘set point’ for ECFV, and normal humans can be in salt balance at extremely high sodium intake for example 1500 mmol/day.

Hence, in the absence of renal failure, development of systemic edema requires pathological activation of the efferent mechanisms regulating sodium balance.
the severe renal sodium retention of cirrhosis, even with hepatorenal syndrome can be reversed by changing intra-hepatic circulatory hemodynamics or by organ transplantation.
Pathogenesis of Circulatory Abnormalities and Renal Failure in Cirrhosis.

How does cirrhosis provide the signal that triggers mechanisms for salt and water conservation, mechanisms that under normal conditions would only be activated during ECFV depletion?
PROPOSED INITIAL STIMULUS FOR EDEMA FORMATION IN CIRRHOSIS

1. Decreased plasma volume:
   “Lieberman et al 1967” found that patients with cirrhosis and edema had increased, not decreased plasma volume.
2. Decreased ‘effective’ plasma volume

“Levy et al 1977” found on dogs with cirrhosis that renal sodium retention and ECFV expansion preceded the appearance of ascites, he measured total plasma volume and its different ‘compartments’ and found that total plasma volume was increased, including both the splanchnic and non-splanchnic compartments.
3. Increased vascular capacitance: “Schrier et al 1988” postulated that the primary event in edema formation in cirrhosis was systemic vasodilation caused by the disease, perhaps mediated by nitric oxide.
Potential Role of Bacterial Translocation and Cytokine Overproduction on Splanchnic Arterial Vasodilatation.

AFFERENT SENSORS AND HOMEOSTATIC RESPONSES IN VOLUME REGULATION

- ECFV regulation
- Afferent sensors
- Complexities, difficulty in measuring the afferent sensors’ neuronal pathways.
- Determination of the efferent response is widely used as a surrogate for what is being ‘sensed’.
Adapted from Watkins et al
Several lines of evidence strongly suggest that rather than a primary event, the systemic vasodilation and increased CO in cirrhosis are secondary to the marked expansion in ECFV.

Increased ECFV by salt, or IV volume reduces vascular resistance, and increase cardiac output.  “Levy and Allotey”
ACTIVATION OF AN INTRA-HEPATIC VASCULAR SENSOR IN CIRRHOSIS INITIATES SALT RETENTION

- The liver has afferent sensors that regulate renal function: via neuronal pathways, afferent hepatic sensors modulate renal function.
- Morita et al found that an oral salt load increases urinary sodium excretion, and that these responses are decreased after hepatic denervation.
- Perimutt et al found that infusion of isotonic saline into the portal vein causes greater renal sodium excretion than when infused in the inferior vena cava.
The liver has afferent sensors that regulate thirst and salt appetite: Intra-portal infusions of hypertonic sodium chloride in experimental animals increases plasma vasopressin and reduces renal water excretion, and this response is abolished by transection of hepatic vagal fibers.
Cirrhosis alone is not sufficient to induce renal salt retention

- In elegant experiments from Levy: normalizing intrahepatic pressure by providing an outflow tract for the cirrhotic liver will abolish component of early renal tubular sodium retention, and they even escaped from DOCA.
partial reductions of intra-hepatic pressures with TIPS, or porto-systemic shunt increases renal sodium excretion and blunts volume retention in patients with cirrhosis
• hepatic artery shows significant autoregulatory capacity, maintaining a narrow hepatic arterial blood flow over a wide range of perfusion pressures.
• the two other organs with similarly brisk autoregulation, the kidney and the brain, both contain sensors critical for cardiovascular and volume control.
• This suggests that the search for a volume sensor in the hepatic circulation could first be focused on the hepatic artery.
Hepatic vascular hemodynamics and sodium balance
Intrahepatic adenosine-mediated activation of hepatorenal reflex is via $A_1$ receptors in rats

- Ming et al. found stimulation of intrahepatic adenosine receptors via $A_1$ receptors is involved in activation of a hepatorenal reflex to regulate renal sodium and water excretion in normal and cirrhotic rats.

- 8-phenyltheophylline blocks the hepatorenal reflex in healthy and cirrhotic rats.
The effect of intraportal vein (i.p.v.) and intravenous (i.v.) administration of a selective adenosine A1 receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine (DPCPX) or vehicle (control) on urine flow and urinary sodium excretion (UNaV) in rats. Intraportal DPCPX induced a significant increase in urine flow and UNaV. In contrast, intravenous DPCPX showed only a weak effect on urine production. \( n = 5-6 \) in each group. \( *p < 0.05, **p < 0.01 \) vs. correspondent time point in control group; \( #p < 0.01 \) vs. DPCPX, i.v.
The effects of intraportal vein (i.p.v.) administration of a selective adenosine A1 receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine (DPCPX) or vehicle (control) on urine flow and urinary sodium excretion (UNaV) in rats with liver denervation. The significant increase in urine production induced by DPCPX i.p.v. seen in normal rats (Fig. 1) was significantly blunted in rats with liver denervation. \( n = 7 \) pairs. *\( p < 0.05 \) vs. denervation control.
Concluding remarks:

- the hepatic circulation has an afferent sensor that modulates the efferent pathway of volume regulation (that is, a ‘volume’ sensor)
- cirrhosis or restriction of hepatic vein flow raises intra-hepatic vascular resistance, increases sinusoidal pressure, decreases portal vein blood flow, and increases hepatic artery flow.
Concluding remarks:

- cirrhosis alone is not sufficient to induce edema, side-to-side porto-caval shunt prevents or corrects renal Na retention. This could be due to decreases in sinusoidal pressure or maintenance of mixing of portal venous and hepatic arterial bloods irrigating the liver.
- In contrast, end-to-side porto-caval shunt only partially decreases the elevated sinusoidal pressure and prevents mixing of the venous and arterial hepatic blood supplies. Under these conditions and despite normalization of portal vein pressure, sodium retention continues unabated.