Author’s response to reviews

Title: Quantitative Modeling of the Physiology of Ascites in Portal Hypertension

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Author’s response to reviews: see over
We wish to thank the two reviewers for making the time and effort required to carefully read and comment on this rather long and involved manuscript. It is valuable to get their independent viewpoints and the manuscript has definitely been improved by these revisions. We have incorporated all of their comments and suggestions into this revised manuscript. Below, each of the individual reviewer comments (in italics) are listed along with our detailed response to them.

**Detailed responses to comments of referee #1:**

1. *One main pathomechanism is the activation of the RAAS in portal hypertension. Please discuss this mechanism more detailed.*

To address this, we have added the following sentences (p. 17) to the revision:

Also listed in Table 1 are the portal hemodynamic responses to nine other drugs. The activation of the renin-angiotensin-aldosterone (RAAS) system has a central role in the standard “forward theory” of ascites formation [6]. The RAAS antagonists in Table 1 (captopril, enalapril, losartan, saralasin) reduce $P_{HVPG}$ with little or no change in $P_{Free}$. A recent systematic meta-analysis of the RAAS antagonists concluded that the $P_{HVPG}$ response was a function of the Child Pugh class [73]. Despite this decrease in $P_{HVPG}$, ACE inhibitors do not seem to be of benefit in the treatment of ascites [74].

2) On page 14 (E), SAAG as differential diagnostic marker between different causes of ascites is discussed. “A SAAG of > 1.1 gm% is ... indicative of portal hypertension (either cirrhotic or cardiac ascites).” The authors should explain the pathophysiology of cardiac ascites in comparison to cirrhotic ascites. Portal hypertension is not the common cause for cardiac ascites.

To address this, we have added the following paragraph (p. 15) to the revision:

Although the above discussion is focused primarily on cirrhotic ascites, cardiac ascites is also associated with a SAAG of ≥1.1 gm%. In a series of patients with chronic hepatopathy (68% with ascites), the average value of the free hepatic vein pressure was 17 mm Hg, with a $P_{HVPG}$ of 2 mm Hg [70]. Thus, the liver sinusoidal pressure is about 18 mm Hg which, presumably, results in rupture of liver lymphatics and leakage of protein into the peritoneal space. The corresponding intestinal capillary pressure is about 22 mm Hg (3 mm Hg greater than portal vein pressure) which should wash down intestinal tissue albumin to a low value. Osmotic equilibration of the ascitic albumin with this intestinal tissue results in a large SAAG.
3) Please give references for a) “...administration of spironolactone or furosemid decreases P(HVPG) by about 20%” and b) decrease in cardiac output with corresponding fall in hepatic blood flow and P(HVPG) in the main text.
Changed as suggested. References have been added.

4) On page 17, the authors explain that clonidine produces a significant decrease in P (HVPG). Please explain the effect in more detail and add references. It is not common that clonidine is used for treatment of varices. The authors should comment on this and add references in the main text (not only in the attachment).

We have revised the clonidine section as recommended (p. 17):

Clonidine, an $\alpha_2$ receptor agonist, is unique among the 15 drugs in Table 1 in that its major action seems to be a decrease in hepatic resistance which produces a corresponding decrease in $P_{HVPG}$ with little change in hepatic blood flow [72-74]. In clinical trials of clonidine for the treatment of ascites, clonidine by itself was not effective but the combination of clonidine and spironolactone produced a greater weight loss and ascites decrease than spironolactone alone [75]. Because clonidine does not decrease portal blood flow, it is not regarded as an effective treatment for gastroesophageal varices [76, 77]

5) The authors should also discuss the effect of terlipressin and vasopressin-2 antagonists in the treatment of ascites in the main text.

We have revised as suggested, adding the following to the main manuscript (p. 18) and adding an entry in Table 1 for terlipressin:

Although vasopressin and terlipressin (vasopressin agonist) decreased $P_{HVPG}$, this decrease resulted primarily from an increase in $P_{RA}$ and $P_{Free}$ (Table 1) and, therefore, is unlikely to be beneficial in the treatment of ascites. The most recent candidate drug class for the treatment of ascites are the vasopressin V2 receptor antagonists (vaptans). These drugs increase plasma sodium by increasing solute free water excretion and it was hoped they would be useful in ascites. Although short term trials of satavaptan suggested a positive effect, a recent long term randomized trial concluded that it is not beneficial in the treatment of ascites [80].

Minor comments:
1) Page 8, line 22 (section II, A.): please change ascetic in ascitic (or contrariwise)
2) Typing error: Page 20, 2 mmHg instead of 2 mm

Corrections made.
Detailed responses to comments of referee #2:

1) Transfer some of the evidence from the literature for weeping from liver surface (Add. File 1D) to the main manuscript to support this concept without looking into the supplementary files.

As suggested, we have added the following paragraph to the revised version of the main manuscript (p. 9):

This protein leak from the liver surface is supported by a number of direct observations. Experimental inferior vena cava constriction leads to obvious “weeping” of fluid droplets from the liver surface [25-27] while the other visceral surfaces appear dry [27]. Clinical evidence that the weeping liver is the source of ascites protein is provided by the observation of Dumont and Mulholland [28] that “Lymph leaking from clusters of bulging lymphatics on the liver capsule and at the porta hepatis often is encountered at laparotomy in patients with Laennec’s cirrhosis”. Kuntz and Kuntz [29] provide a dramatic image of “Numerous, partially ruptured lymphocysts … on the liver surface with extravasation of protein-rich lymph in alcoholic cirrhosis” (fig. 16.5, p. 298). Tameda et. al. [30] observed “small lymphatic vesicles” on the liver surface in 65 out 372 cirrhotic subjects during peritoneoscopy. During laparoscopy, Heit et. al. [31] reported that 4 of 10 cirrhotic livers had surface “…lymphatic blebs indicating dilated lymphatic channels … and all 4 of these cases were complicated by ascites. Blebs were not seen in the absences of ascites. (see Additional file 1, Section ID for more details).

2) In their model, diuretics decrease ascites volume by lower central venous pressure. Please provide evidence that ascitic fluid reduces in patients with ascites that are refractory to diuretics or anuric (body weight would not be a sufficient measure, since AF should be redistributed to the venous compartment). How much ascites could be mobilized in an anuric patient with gross ascites without a change in HPVG?

We have added the following section to the revision to provide more details about the relative contributions of changes in $P_{RA}$ and $P_{HVPG}$ to the decrease in ascites (p. 23):

The reductions in $P_{HVPG}$ and $P_{RA}$ both contribute to the ascites reabsorption, but in different ways. At high initial $P_{HVPG}$ (> 18 mm Hg), when the hepatic vein pressure becomes decoupled
from $P_{RA}$ (eq. **Error! Reference source not found.**), lowering $P_{RA}$ (fig. 3, blue line) has a relatively small effect, while lowering $P_{HVPG}$ (green line) has a larger effect. In contrast, in the low pressure regime when the hepatic vein pressure is equal to $(P_{RA} + 2)$ (eq. **Error! Reference source not found.**) lowering $P_{RA}$ (blue line) has a dramatic effect. For example, if the initial $P_{HVPG}$ is less than 13 mm Hg, lowering $P_{RA}$ from 5 to 2 mm Hg is enough by itself to completely resolve the ascites.

3) The model and Figure 1 does not consider hepato-venous shunts in patients with decompensated cirrhosis. Please discuss how the presence of a certain shunt volume would change the critical pressure for protein weeping from the liver (PL-PA).

This is a good suggestion. In response we have now added another figure (fig. 5) and the following paragraph describing the influence of the percent shunt on the ascites volume (p. 23):

A standard treatment for cirrhotic ascites is surgically produced portal systemic shunting [88]. Assuming that this procedure reduces portal flow with no change in liver resistance or central venous pressure, then the percent reduction in $P_{HVPG}$ is equal to the percent reduction in liver blood flow. Figure 5 shows the reduction in ascites volume produced by a 20%, 35% and 50% reduction in $P_{HVPG}$ or, equivalently, liver flow as a function of the initial $P_{HVPG}$. It can be seen that in order to reduce ascites by shunting, large reductions (about 50%) in flow are required. This is consistent with the results of Rogriguez-Laiz et. al. [89] that showed that transjugular intrahepatic portasystemic shunts (TIPS) reduced liver blood flow by about 50%.

4) Figure 2 provides AF protein as a function of HPVG. Ascitic protein concentration is provided as colloid-osmotic pressure (COP) and varies between 7 and 11 mmHg. In clinical practice AF protein concentrations between 5 and 20 g/l are usually found. Please provide the corresponding concentrations (g/l) of AF protein COP (mmHg) in Figure 2 and discuss the narrow range observed by the quantitative model.

We have now added the following discussion of the narrow range of ascites protein that is observed in cirrhosis and listing the equivalent albumin concentrations (p. 22):
The ascites protein stays in a rather narrow range, falling from about 11 mm Hg when the ascites just starts to form to a minimum of about 7 mm Hg at \( P_{HVPG} \) of 18 mm Hg and then slowly rising to about 8 mm Hg. Assuming an albumin/total protein fraction of 0.65, these values correspond to albumin concentrations of about 2.5, 1.75 and 1.95 gm\% respectively [88]. For the assumed plasma colloid osmotic pressure of 25 mm Hg (albumin concentration of 4.45 gm\%), these values correspond to a SAAG of 1.95, 2.75 and 2.5 gm\%. The fall in ascites protein results from the wash down of intestinal tissue protein as the capillary blood pressure increases. At high \( P_{HVPG} \) the leak of high protein fluid from the liver makes a relatively greater contribution to the total ascitic fluid formation, producing the increase in the ascitic protein concentration.

**Discretionary Revisions**
1) Please insert a step in eq. 15 to allow easier understanding, i.e.
\[
PL-PA=(Phv+Ppv)/2-Phv=(P\wedge-\text{Pfree})/2
\]

Additional step added as suggested.