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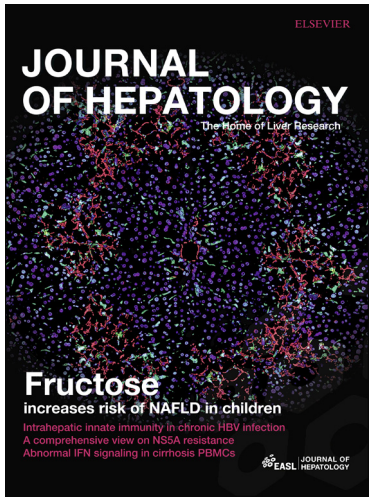

Reply to "The Relationship of Hyperdynamic Circulation and Cardiodynamic States in Cirrhosis"

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Title: Reply to "THE RELATIONSHIP OF HYPERDYNAMIC CIRCULATION AND CARDIODYNAMIC STATES IN CIRRHOSIS".

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To the Editor,

We appreciate Dr. Alvarado and colleagues' comments regarding our study published in Journal of Hepatology describing that different cardiodynamic states (as determined by cardiac index at rest in a supine position) and systemic inflammation (as assessed by an elevated serum C reactive protein, CRP) are independent predictors of disease outcomes in both compensated and decompensated patients with cirrhosis. [1]

Our initial goal was to describe hepatic and systemic hemodynamics at each of the recently described prognostic stages (PSs) of cirrhosis and to identify predictors of decompensation/death at each of the PSs. We classified the patients at the time of their first measurement of hepatic venous pressure gradient (HVPG)/hemodynamic study and, as per any prognostic study, looked at their clinical course thereafter. We cannot make any assumptions or comments regarding their previous state (hemodynamic or other).

As stated by Dr. Alvarado et al, when looking at the average value of cardiac index (CI) across the five PSs, the average results are in concordance with previous studies. However, when looking for more granularity, we were surprised to find that CI was lower than the PS1 (i.e., patients with HVPG < 10 mmHg) mean value (CI < 3.2 L/min/m^2, "relatively hypodynamic") in about one third of patients with clinically significant portal hypertension across all the remaining PSs. We were also surprised to observe that both this status and the truly hyperdynamic (CI >4.2L/min/m^2) were associated with a worse prognosis compared to the intermediate ("normodynamic").

The prognostic relevance of these two extreme cardiodynamic states is most probably due to a decrease in heart work as demonstrated in Figure S2 of our study where it can be observed that in relatively hypodynamic (panel A) and hyperdynamic (panel C) states there is a progressive decrease in left ventricular stroke work index (LVSWI) across prognostic stages that does not occur in the normodynamic status (panel B). LVSWI is a more reliable marker of left ventricle (LV) cardiac performance than stroke volume index (SVI) because it also takes into account the initial pressure of work of the left ventricle as it is being filled (mean arterial pressure – LV end-diastolic pressure or mean pulmonary artery wedged pressure) and SVI].[3] While Dr. Alvarado et al show us the tables of their published results, it would have been very valuable if they had explored the presence of these cardiodynamic states in their population (which, at least in the compensated stages, seems to be less sick and less hyperdynamic than ours given differences in MELD and average CI)[4] and, if present, to describe the proportion of patients with these states and to validate our LVSWI findings across stages.

We agree with Dr. Alvarado et al that patients with and without post capillary pulmonary hypertension (pcPH) are different. In fact, we demonstrated that, in decompensated cirrhosis, pcPH is another cardiac parameter that predicts death independent of MELD, CRP and cardiodynamic state.[1]

We have to disagree with Dr. Alvarado regarding the possible confounding effect of treatment with non-selective beta-blockers (NSBB) during follow up. Indeed, NSBB were evaluated as potential predictors of outcomes both in compensated and decompensated patients (see the Fine & Gray proportional hazards regression analysis presented in table 3 of our study), but they were not significant in the final multivariable model.

We also have to disagree with Dr. Alvarado et al regarding the possible bias introduced by large volume paracentesis (LVP) with albumin infusion the day before hemodynamic assessment in patients with refractory ascites. LVP was precisely performed to minimize the effect of increased abdominal volume (and pressure) on the intra-thoracic pressure due to cephalad displacement of the diaphragm. This may reduce venous return, resulting in reduced cardiac output, and may also compress the heart, reducing ventricular compliance and contractility. Moreover, due to abdomino-thoracic transmission, mean pulmonary artery wedged pressure (and consequently pcPH estimation) may be erroneously elevated during right heart catheterization in the presence of ascites. In fact, it has been demonstrated that within the first 12 hours after LVP, there is an improvement in circulatory function with an increase in cardiac output and stroke volume, a reduction in cardiopulmonary pressures, and a deactivation of vasoconstrictor and antinatriuretic systems.[5] Albumin maintains the initial improvement in circulatory function after paracentesis and prevents the subsequent activation of vasoconstrictor systems and impairment in cardiac and renal functions in particular if the volume of removed ascites is <8L (our average is <6L as reported in table 1 of our work).[6] Therefore, having performed LVP and given albumin prior to hemodynamic measures actually minimized the risk of overestimating the proportion of patients with relatively hypodynamic circulation and pcPH and also reduced the risk of underestimating the proportion of patients with preserved systolic function and/or underlying hyperdynamic features.

We finally agree with Dr. Alvarado et al that further characterization of the subgroup of patients with relatively hypodynamic state is very necessary. With the objective of determining whether extra-hepatic factors may have led to cardiac dysfunction, we looked at the effect of etiology, body mass index and co-morbidities in the three cardiodynamic states (Table) but could find no significant differences. Nevertheless, we cannot exclude that etiology, comorbidities (and the drugs to treat them) and systemic inflammation may have a different impact on hearts in different cardiodynamic states. For example, it would be of great interest to see if the relatively hypodynamic patients have a different pathogenesis of portal hypertension, which may be influenced, among other factors, by a different genetic background of alfa/beta adrenoreceptors.

In conclusion, we think that our paper rather than being misleading is trying to add granularity to a complex syndrome and is providing a “vertical” subclassification of each prognostic stage that requires validation. Our expectation is that both the recognition of patients in different cardiodynamic states and the identification of stress test aimed to explore their functional cardiac reserve may better help in the selection of subgroups, who would be candidates for different therapies (NSBB, transjugular intrahepatic portosystemic shunt, etc). In fact, Dr. Alvarado et al have recently shown, in patients with decompensated cirrhosis, that a NSBB-induced decrease in cardiac output to levels below 5/lmin (or CI <3L/min/m^2) were predictive of a poor survival. [7]

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Table: Etiology and main cardiovascular comorbidities in the three cardiodynamic states.[1]

	CI < 3.2 L/min/m^2 (n=83)	**CI ≥3.2 - ≤4.2 L/min/m^2** (n=102)	**CI > 4.2 L/min/m^2** (n=53)	***p* value**
Etiology (%)				
Viral	42 (50.60)	54 (52.94)	24 (45.28)	
Alcohol	14 (16.87)	18 (17.65)	9 (16.98)	
Alcohol + Viral	9 (10.84)	9 (8.82)	9 (16.98)	0.842°
NASH	10 (12.05)	12 (11.77)	6 (11.33)	
Miscellaneous	8 (9.64)	9 (8.82)	5 (9.43)	
BMI*	25.72 ± 0.47	26.02 ± 0.43	26.14 ± 0.55	0.828°°
Comorbidities (%)				
None/Non-cardiovascular	42 (50.60)	49 (48.04)	33 (62.26)	
Arterial Hypertension	19 (22.89)	20 (19.61)	7 (13.21)	0.615°
Diabetes	13 (15.67)	17 (16.67)	8 (15.09)	
Arterial Hypertension & Diabetes	9 (10.84)	16 (15.68)	5 (9.44)	

BMI, body mass index; CI, cardiac index (normal range 2.5-4.2 L/min/m^2); NASH, non-alcoholic steatohepatitis.
*Data are expressed as mean ± SE.
° Chi-square test was applied.
°° One-way ANOVA was applied.