

Letters to the Editor

The relationship between liver function and portal pressure: what comes first, the chicken or the egg?

To the Editor:

The paper by Villanueva et al. [1] is a very important paper in clinical Hepatology, having implications for the management of cirrhotic patients. It documents a reduced probability in developing complications of cirrhosis (in addition to less variceal bleeding) in patients who achieve a target reduction in portal pressure with pharmacological therapy. However, their findings may not be generalisable as patients were very selected. The exclusion criteria removed cirrhotics who might be considered at most risk of developing complications: (1) those in whom medical therapy failed to control the index bleeding episode, (2) those with Child-Pugh score above 12 points, (3) those who had bled previously and received any therapy to prevent rebleeding and (4) those with hepatocellular carcinoma and (5) if death was expected within 6 months. All had to have at least two haemodynamic measurements between 1–4 months apart, so that 132 patients were selected (representing well compensated cirrhotics whose acute bleeding resolved with medical therapy).

The 64 haemodynamic responders (48%) were defined as previously: an absolute HVPG reduction <12 mmHg ($n=14$) or a 20% or more HVPG reduction from baseline ($n=60$) also seen in 10 with HVPG <12 mmHg. The Child-Pugh score at the second HVPG measurement had improved significantly more in the responders (mean 7.8–5.9 mmHg responders and 8.2–6.8 mmHg non-responders). This difference was also seen in the 28 responders and 40 non-responders who had repeat HVPG measurement between 11 and 29 months. The worse liver function in non-responders accounts for a significantly higher transplantation rate, although whether non-responders were transplanted for repeated variceal rebleeding is not stated.

Nevertheless, a multivariate Cox model evaluating mortality (one assumes the time of transplantation was censored and that the starting point for evaluation was the index bleeding episode) found non-responder status to be independently predictive of death, i.e. a separate effect from the degree of liver dysfunction at baseline. This relates to survival after the second HVPG measurement, but the Cox model was based on characteristics around the index

bleeding episode. It would be interesting to evaluate if the rate of deterioration of liver function overtime (e.g., change in Pugh score over 6-month intervals) influenced HVPG response.

Indeed the patient's individual HVPG response could be evaluated against the change in Child-Pugh score (or some of its components) at the time of the subsequent HVPG measurements. In addition, abstention in the intervals between measurements needs to be looked at, given that abstention was more frequent in responders (93% versus 74%) amongst the 84 in whom an alcohol history was available, and that alcohol consumption also had the strongest independent association with a haemodynamic responder status (OR 14.9, 95% 1.8–98), and 6 of the 7 late responders (i.e., at the third HVPG measurement) were abstainers. An improvement of liver function with abstention can be presumed and its relationship to HVPG is important [2].

Lastly, the potential clinical value of a haemodynamic non-response is masked by the fact that 12 patients in the non-responder group, but none in the responder group (is this pure chance?), took no drugs ($n=2$), or could not or did not take nadolol ($n=6$), or isosorbide mononitrate ($n=4$). Another 11 in the non-responder group stopped either nadolol ($n=5$) or ISMN ($n=6$) because of complications of therapy. If all of these did develop a complication of cirrhosis, the association between administration of drugs reducing HVPG, and the prevention of complications would be far stronger. The evaluation between responders and non-responders should be repeated excluding the 12 patients not taking pharmacological therapy to assess the strength of the association.

Thus, the key question which the authors could answer by further evaluating their data, is whether for a similar worsening (or improvement) of liver function, there is a difference in either the onset or severity of cirrhotic complications, with respect to taking pharmacological therapy and the reduced HVPG thresholds reached.

If non-selective beta-blockers with or without isosorbide mononitrate can modify the progression of cirrhosis, despite worsening of liver function, then these drugs would become the 'aspirin' of clinical

hepatology—cheap, few contraindications, relatively little intolerance and of universal application in cirrhotics irrespective of the presence of varices or history of bleeding.

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References

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Reply

To the Editor:

We appreciate the correspondence by Dr. Triantos and coworkers. To discuss whether the chicken or the egg comes first may take us a whole lifetime. However, several of their points deserve further comment. They suggest that deterioration of liver function overtime may influence hemodynamic response, and that the worse outcome of nonresponders regarding cirrhotic complications may reflect a more advanced liver disease instead of a lower effect on portal pressure. After a variceal hemorrhage, a marked improvement in hepatic function occurs in survivors. Our study shows that even nonresponders have a significant improvement in liver function. However, in responders such an improvement is greater. Hemodynamic response in addition to decrease the risk of developing complications related with portal hypertension by decreasing portal pressure, may also improve liver function by avoiding rebleeding given that bleeding episodes may further deteriorate liver function in cirrhosis. On the other hand, response to drug therapy may be affected by liver dysfunction [1].

As suggested by our colleagues, we have further evaluated our data to clarify the link between response and liver dysfunction. At the time of the second hemodynamic evaluation the Child-Pugh score had improved in 101 patients, while it had worsened or remained unchanged in 31. Hemodynamic response was observed in 53 (52%) vs 11 (35%) cases, respectively ($P=0.1$). Considering only patients without an improvement in Child-Pugh score, responders had as compared with nonresponders: a lower likelihood of rebleeding (9% vs 55%, $P=0.01$) and need for rescue therapy (0% vs 30%, $P=0.03$), as well as developing ascites (18% vs 60%, $P=0.04$), hepatorenal syndrome (9% vs 20%, $P=0.3$) and SBP (0% vs 25%, $P=0.04$). In this subgroup without improvement of Child-Pugh, responders also had a lower requirement of liver transplantation (0 vs 25%, $P=0.1$) and mortality (18% vs 35%, $P=0.4$), although these differences were not significant may be due to a small sample size. These additional results suggest that hemodynamic response may really have a true effect on complications related with portal hypertension. Moreover, both response and liver dysfunction were independent determinants of survival. These two

factors have also shown independent predictive value for rebleeding and development of ascites and SBP, in patients receiving drug therapy to prevent variceal rebleeding [1].

Other factors may influence hemodynamic response to drug therapy, such as abstinence from alcohol, the extent of collaterals or the dose of medication [2]. Abstinence from alcohol as well as continuing the intake of isosorbide mononitrate and achieving the 25% target decrease of resting heart rate were independent predictors of response in our study, while alcohol abstinence and changes in the dose of nadolol were in addition associated with a late change of hemodynamic response during follow-up. This is in keeping with previous studies which have shown that sustained alcohol abstinence improves both the clinical and hemodynamic condition of alcoholic cirrhotic patients [3], and that the dose of β -blockers is an independent predictor of hemodynamic response [1]. Three responders (5%) and 16 nonresponders (23%) did not receive complete combined therapy with nadolol and nitrates in our study due to contraindications, complications or non-compliance (shown in Table 4). Both nadolol and nitrates were discontinued more often in nonresponders. Nevertheless, a good adherence to a medication regimen is a relevant property of any chronic treatment, which rely on patient compliance but also in drug characteristics such as safety or contraindications. Excluding nonadherent patients from the analysis, as suggested by our colleagues, will introduce a source of bias and may lead to erroneous conclusions.

Our study supports available data showing that hemodynamic response provides a substantial reduction in variceal rebleeding risk [2,4], as well as in the development of other complications of portal hypertension [1]. Certainly, other factors may influence response besides medication. However, whatever the factors involved, evidence support that assessment of hemodynamic response provides strong prognostic information. Furthermore, our study also shows that in some instances there may be a change of chronic response mainly due to factors such as variations in the dosage of medications or to withdrawal from alcohol. These changes in response may help to explain some discrepant results [5]. Moreover, it should be noted that the prognostic value of hemodynamic response cannot be extrapolated to