CORRESPONDENCE

Monitoring of HVPG During Pharmacological Therapy: Evidence in Favor of the Prognostic Value of a 20% Reduction

To the Editor:

We read with interest the articles on hepatic venous pressure gradient (HVPG) measurements.[1–3] We fully agree on the need to standardize HVPG measurements to get reliable, reproducible, and useful data.[1] We also agree that before recommending such measurements in clinical practice, it is necessary to demonstrate, in well-designed clinical trials, that HVPG may help to make clinical decisions.[2,3] However, we disagree with Thalheimer et al.[3] (and with their recent, very similar paper[4]) questioning the prognostic value of a reduction in HVPG >20% from baseline. Indeed, there is strong evidence suggesting that such a reduction in HVPG is associated with a marked reduction in bleeding risk during continued drug therapy. As shown in Table 1, patients decreasing HVPG >20% have a much lower bleeding risk on follow-up than nonresponders, even if not reaching <12 mmHg. Data are derived from original papers. When numbers were not provided, the worst hypothesis against a protective role of >20% HVPG reduction was taken. For example, the paper by Villanueva et al.[5] stated that 25 patients were responders, 7 of them reducing HVPG <12mmHg (therefore, 18 had >20% reduction, but not <12mmHg). Four responders rebled on follow-up. The worst hypothesis, used in the table, is that all had >20% HVPG reduction.

The message does not change when studies focused exclusively on prevention of rebleeding[6] are considered[5,7–9]: Rebleeding was 51% in nonresponders vs. 21% in patients reducing HVPG >20% (but not <12mmHg). Even after including the discrepant report by McCormick et al.[10](see Table) the figures are similar. The latter study also had an unusually high rate of responders: 64%, with 52% decreasing HVPG <12mmHg (the highest ever reported in secondary prophylaxis). Moreover, 7 patients had the second HVPG measurement after rebleeding. These peculiarities, and other inadvertent factors, might contribute to the discrepant findings of this study. A second look at the pressure tracings by independent observers may help clarify this issue.

Thalheimer et al.[3] further argue that observed changes in HVPG may be partly due to factors other than beta-blockers (*e.g.,* improved liver function, abstinence, diuretics). Nevertheless, independent of the reason for HVPG reduction, available evidence supports that reducing HVPG not only to <12 mmHg ("optimal response") but also by >20% from baseline is associated with a dramatic reduction of the bleeding risk. Thus, a 20% reduction in HVPG would be *per se* a valid therapeutic target.

Reliability of a 20% reduction in HVPG is an important issue. However, the low variability of correct HVPG measurements limits the degree of uncertainty of these assessments.[1] This is well illustrated, as several centers from different countries have confirmed the validity of the 12 mmHg threshold for bleeding and the prognostic significance of changes in HVPG (see Table).

It seems premature to challenge the concept that repeat measurements of HVPG provide prognostic information on the risk of (re-)bleeding in patients receiving beta-blockers based only on one discrepant study.[10] It also appears contradictory to challenge this concept while at the same time proposing to use the same technique to assess disease progression/regression in hepatitis C virus cirrhosis.[13]

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References

1. Groszmann RJ, Wongcharatrawee S. The hepatic venous pressure gradient: anything worth doing should be done right. HEPATOLOGY 2004;39: 280–282.
2. Boyer TD. Changing clinical practice with measurements of portal pressure. HEPATOLOGY 2004;39:283–285.
3. Thalheimer U, Mela M, Patch D, Burroughs AK. Targeting portal pressure measurements: a critical reappraisal. HEPATOLOGY 2004;39:286–290.
4. Thalheimer U, Mela M, Patch D, Burroughs AK. Monitoring target reduction in hepatic venous pressure gradient during pharmacological therapy of portal hypertension: a close look at the evidence. Gut 2004;53:143–148.
5. Villanueva C, Minana J, Ortiz J, Gallego A, Soriano G, Torras X, et al. Endoscopic ligation compared with combined treatment with nadolol and isosorbide mononitrate to prevent recurrent variceal bleeding. N Engl J Med 2001;345:647–655.
6. Feu F, Garcia-Pagan JC, Bosch J, Luca A, Teres J, Escorsell A, et al. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. Lancet 1995; 346:1056–1059.
7. Villanueva C, Balanzo J, Novella MT, Soriano G, Sainz S, Torras X, et al. Nadolol plus isosorbide mononitrate compared with sclerotherapy for the prevention of variceal rebleeding. N Engl J Med 1996;334:1624–1629.
8. Abraldes JG, Tarantino I, Turnes J, Garcia-Pagan J, Rodes J, Bosch J. Hemodynamic response to pharmacologic treatment of portal hypertension and long-term prognosis of cirrhosis. HEPATOLOGY 2003;37:902–908.
9. Escorsell A, Bordas JM, Castaneda B, Llach J, Garcia-Pagan JC, Rodes J, et al. Predictive value of the variceal pressure response to continued pharmacological therapy in patients with cirrhosis and portal hypertension. HEPATOLOGY 2000;31:1061–1067.

Table 1. Bleeding Risk According to Hemodynamic Response

Author (reference)	Bleeding/Nonresponders (reduction in HVPG <20% or >12 mmHg)	Bleeding/Responders (reduction in HVPG >20% or <12 mmHg)	Bleeding/Responders (final HVPG <12 mmHg)	Bleeding/Responders (reduction in HVPG >20% but not <12 mmHg)
Feu[6]	23/44 (52%)	2/25 (8%)	0/8	2/17 (11.7%)
Escorsell[9]	13/28 (46.4%)	1/19 (5%)	0/9	1/10 (10%)
Villanueva[7]	8/18 (44%)	1/13 (7.7%)	0/9	1/4 (25%)
Villanueva[5]	16/24 (66.6%)	4/25 (16%)	0/7	4/18 (22.2%)
Bureau[11]	9/14 (64%)	2/20 (10%)	0/8	2/12 (16.6%)
Merkel[12]	7/19 (36.8%)	2/30 (6.7%)	0/12	2/18 (11.1%)
Abraldes[8]	20/45 (44.4%)	6/28 (21.4%)	1/11	5/17 (29.4%)
Overall patients	96/192 (50%)	18/160 (11.2%)	1/64 (1.5%)	17/96 (17.7%)
McCormick[10]	4/16 (25%)	12/28 (43%)	7/23 (30 %)	5/5 (100%)
All	100/208 (48%)	30/188 (15.9%)	8/87 (9.2%)	22/101 (21.7%)

10. McCormick PA, Patch D, Greenslade L, Chin J, McIntyre N, Burroughs AK. Clinical vs haemodynamic response to drugs in portal hypertension. J Hepatol 1998;28:1015–1019.
11. Bureau C, Peron JM, Alric L, Morales J, Sanchez J, Barange K, et al. "A la carte" treatment of portal hypertension: adapting medical therapy to hemodynamic response for the prevention of bleeding. HEPATOLOGY 2002; 36:1361–1366.
12. Merkel C, Bolognesi M, Sacerdoti D, Bombonato G, Bellini B, Bighin R, et al. The hemodynamic response to medical treatment of portal hypertension as a predictor of clinical effectiveness in the primary prophylaxis of variceal bleeding in cirrhosis. HEPATOLOGY 2000;32:930–934.
13. Burroughs AK, Groszmann R, Bosch J, Grace N, Garcia-Tsao G, Patch D, et al. Assessment of therapeutic benefit of antiviral therapy in chronic hepatitis C: is hepatic venous pressure gradient a better end point? Gut 2002;50:425–427.

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Reply:

An objective of our commissioned paper was to stimulate debate on monitoring hepatic venous pressure gradient (HVPG) following variceal bleeding. We stress that our critique pertains to the clinical applicability of HVPG measurements based on current evidence, and not on the pathophysiological importance of a reduced portal pressure.

Whilst we do not disagree with the rebleeding rates in responders with a ≥20% reduction in HVPG but without a decrease to ≤12 mmHg, we have emphasized,[1] both in response to their review[2] and in our peer-reviewed article,[3] the need to separate primary and secondary prevention due to very different bleeding risks.[4] The secondary prevention studies[5–9] are a homogeneous cohort (risk of [re]bleeding is highest, these HVPG measurements should be most useful). However, many patients were excluded, not having baseline or repeat HVPG measurements; in some studies[5] rebleeding was worse in responders than in nonresponders, and some patients rebled early, before remeasurement,up to 22%.[9] These factors make it difficult to evaluate the utility of monitoring the reduction of HVPG in all the population at risk.

The heterogeneity extends to the proportion of Child-Turcotte-Pugh C patients (6%-47%)[5,9] defining in part the risk of early rebleeding. In some studies,[5,10] rebleeding is only 7% or 8% within 3 months. The clinical applicability of HVPG measurements is dependent on the measurement's timing, because if performed too late, many patients will have rebled, whereas if performed early on, it would capture most patients at risk. Our colleagues accept this view, proposing a second HVPG measurement at 2 weeks,[1] although there is no study that confirms this interval; they themselves have data based only on a median of 3 months.[5,10]

We agree our study[8] is "anomalous," having the longest interval to remeasurement (mean, 5.3 months) and having many alcoholics(70%); some patients abstained, which this may account for the many responders due to improvement of liver function. Seven patients[8] had HVPG measurements after having rebled, comparable to 5 patients in the study of Feu et al.,[5] and we noted this fact.[3]

We agree there is little variability with HVPG with correct measurements of HVPG; but at lower HVPG baseline values, measurement errors are greatest, in percentage terms. We found that baseline HVPG and rebleeding were correlated[9]; this fact was not commented on by others and would benefit from prospective evaluation. The ability to obtain a reduction of HVPG by 20% or more may reflect a lower baseline HVPG. Unfortunately, this effect cannot be deduced from published studies, but it is a plausible scenario. In simple terms, if HVPG is reduced by 20%, from 28 to 22.3 mmHg, does this confer the same protection against rebleeding as does a 20% reduction, from 19 to 15.2 mmHg? A suggestion that baseline HVPG is important is shown in the second Villanueva study[7] in which drugs were beneficial solely in Child-Turcotte-Pugh A patients, whilst in the first study,[6] in which mean baseline HVPG was lower (17.7 ± 3.4 vs. 19.9 + 3.5 mm Hg), rebleeding was reduced in all Child-Turcotte-Pugh classes.

The relationship between baseline and repeated HVPG, and severity of liver disease (potentially improving or worsening with time) should also be prospectively studied. The improvement in liver function or its absence was not commented on by Abraldes et al.[10] in relation to reduction of HVPG. Extending HVPG measurement to assess progression, or regression with therapy, of chronic hepatitis C is one of our proposals,[11] but it is separate from the clinical applicability of HVPG measurements for preventing variceal bleeding.

We hold the view that new prospective HVPG monitoring studies are needed for prevention of variceal bleeding. New studies could justify the extra resources and training required and prove the cost-effectiveness of implementing routine HVPG monitoring compared to empirical use of propranolol—a very cheap and simple management strategy.

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References

1. Bosch J, García-Pagán JC. Prevention of variceal rebleeding. Lancet 2003; 361:952–954.
2. Thalheimer U, Mela M, Patch D, Burroughs AK. Prevention of variceal rebleeding [letter]. Lancet 2003;361:2244–2245.
3. Thalheimer U, Mela M, Patch D, Burroughs AK. Monitoring target reduction in hepatic venous pressure gradient during pharmacological therapy of portal hypertension: a close look at the evidence. Gut 2004;53:143–148.
4. Bureau C, Péron JM, Alric L, Morales J, Sanchez J, Barange K, et al. "A la carte" treatment of portal hypertension: adapting medical therapy to hemodynamic response for the prevention of bleeding. HEPATOLOGY 2002; 36:1361–1366.
5. Feu F, Garcia-Pagan JC, Bosch J, Luca A, Teres J, Escorsell A, et al. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. Lancet 1995; 346:1056–1059.
6. Villanueva C, Balanzo J, Novella MT, Soriano G, Sainz S, Torras X, et al. Nadolol plus isosorbide mononitrate compared with sclerotherapy for the prevention of variceal rebleeding. N Engl J Med 1996;334:1624–1629.
7. Villanueva C, Minana J, Ortiz J, Gallego A, Soriano G, Torras X, et al. Endoscopic ligation compared with combined treatment with nadolol and isosorbide mononitrate to prevent recurrent variceal bleeding. N Engl J Med 2001;345:647–655.
8. McCormick PA, Patch D, Greenslade L, Chin J, McIntyre N, Burroughs AK. Clinical vs. hemodynamic response to drugs in portal hypertension. J Hepatol 1998;28:1015–1019.
9. Patch D, Sabin CA, Goulis J, Gerunda G, Greenslade L, Merkel C, et al. A randomized, controlled trial of medical therapy versus endoscopic ligation for the prevention of variceal rebleeding in patients with cirrhosis. Gastroenterology 2002;123:1013–1019.
10. Abraldes JG, Tarantino I, Turnes J, Garcia-Pagan JC, Rodés J, Bosch J. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. HEPATOLOGY 2003;37:902–908.
11. Burroughs AK, Groszmann R, Bosch J, Grace N, Garcia-Tsao G, Patch D, et al. Assessment of therapeutic benefit of antiviral therapy in chronic hepatitis C: is hepatic venous pressure gradient a better end point? Gut 2002;50:425–427.

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Relative Contribution of Iron Burden, HFE Mutations, and Insulin Resistance to Fibrosis in Nonalcoholic Fatty Liver

To the Editor:

We read with interest the paper by Bugianesi et al. recently published in HEPATOLOGY where fibrosis in nonalcoholic fatty liver disease (NAFLD) was thought to be associated with insulin resistance but not iron overload.[1] We would like to provide some preliminary data from the Polistena project that reached similar results.

The Polistena project, which started in 1998 in Modena, Italy, is a study specifically aimed at NAFLD in which 161 consecutive NAFLD cases have been enrolled so far. This series is unique because patients were referred by participating general practitioners on the basis of ultrasonographic evidence of "bright liver" and not on the basis of obesity, diabetes, hyperlipidemia, symptoms/signs of liver disease or altered liver function tests, or biochemical parameters of iron overload.[2,3]

Sixty-one biopsied NAFLD patients from the Polistena series were classified as types 1 to 4 according to Matteoni et al.[4] The following parameters were studied: age, body mass index, waist circumference, cholesterol, triglycerides, uric acid, alanine aminotransferase, ferritin, transferrin percent saturation, hemochromatosis gene (HFE) gene mutations, and indexes of insulin resistance. Median values (25th 75th percentile) of parameters significantly different (grades 1 and 2 vs. grades 3 and 4, $P < .05$) are shown in Table 1. This suggests that insulin resistance is closely associated to histologically advanced NAFLD in our series and probably has a key role in the pathogenesis of the fibrotic evolution of this disease.

In our overall series (HFE gene mutations data available in 122/161 cases), the prevalence of heterozygous C282Y and H63D HFE gene mutations is in the same order of magnitude as in the healthy Italian population.[5] Information about HFE gene mutations was available in 52 out of the 61 biopsied patients. Table 2 summarizes the distribution of early and advanced NAFLD cases according to HFE gene status. Although the majority of heterozygous patients tend to fall within the "advanced" NAFLD category while the majority of homozygous patients show an "early" NAFLD, this trend does not reach statistical significance ($P = .07$). Furthermore, HFE heterozygosity does not associate with any significant effect on biochemical phenotype and insulin resistance assessed through Homeostasis Model Assessment Insulin Resistance (data not shown).

In conclusion, data from the Polistena study support the hypothesis that insulin resistance appears not only to trigger the development of NAFLD but also to worsen the course of this disease. Such findings, along with the Bugianesi study, fully support the concept that one hit (namely, insulin resistance) is enough to account for a large part of the spectrum of primary NAFLD. The clinical implication of these findings is that insulin resistance (and not iron depletion *per se*) represents the primary therapeutic aim in NAFLD.[2] Interestingly, this lesson might also be applied to those cases where NAFLD exists with other hepatotoxic factors, such as chronic hepatitis C virus infection.[6] Whether insulin resistance in primary NAFLD is a peripheral (merely metabolic) or a central (endocrine due to growth hormone deficiency) phenomenon[7] remains a fascinating but as yet unsettled issue.

Table 1. Anthropometric and Metabolic Parameters in Early and Advanced NAFLD Types

NAFLD Types	Waist (cm)	Uric Acid (mg/dL)	HOMA-IR
1–2	95.0 (89.5–96.0)	4.95 (4.60–6.05)	2.85 (1.89–4.69)
3–4	100.5 (96.0–109.0)	6.10 (5.60–7.20)	4.11 (2.72–5.60)

Abbreviation: HOMA-IR, Homeostasis Model Assessment Insulin Resistance.

Table 2. HFE Gene Mutations in Early and Advanced NAFLD Types

	HFE Gene Status	
NAFLD Types	wt/wt n (%)	H63D/wt or C282Y/wt n (%)
1–2	18 (54.5)	7 (36.8)
3–4	15 (45.5)	12 (63.2)
Total	33 (100.0)	19 (100.0)

Abbreviation: wt, wild type.

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References

1. Bugianesi E, Manzini P, D'Antico S, Vanni E, Longo F, Leone N, et al. Relative contribution of iron burden, HFE mutations, and insulin resistance to fibrosis in nonalcoholic fatty liver. HEPATOLOGY 2004;39:179–187.
2. Lonardo A, Loria P, Leonardi F, Borsatti A, Neri P, Pulvirenti M, et al. Fasting insulin and uric acid levels but not indices of iron metabolism are independent predictors of NAFLD. Dig Liver Dis 2002;34:204–211.
3. Loria P, Lonardo A, Leonardi F, Fontana C, Carulli L, Verrone AM, et al. Non-organ-specific autoantibodies in nonalcoholic fatty liver disease: prevalence and correlates. Dig Dis Sci 2003;48:2173–2181.
4. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology. 1999;116:1413–1419.
5. Cassanelli S, Pignatti E, Montosi G, Garuti C, Mariano M, Campioli D, et al. Frequency and biochemical expression of C282Y/H63D hemochromatosis (HFE) gene mutations in the healthy adult population in Italy. HEPATOLOGY 2001;34:523–528.
6. Lonardo A, Adinolfi LE, Loria P, Carulli N, Ruggiero G, Day CP. Steatosis and hepatitis C virus: mechanisms and significance for hepatic and extrahepatic disease. Gastroenterology 2004;126:586–597.
7. Lonardo A, Loria P, Leonardi F, Ganazzi D, Carulli N. Growth hormone plasma levels in NAFLD [letter]. Am J Gastroenterol 2002;97:1071–1072.

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Reply:

We were pleased by the comments of Loria et al. on our recent paper published in HEPATOLOGY.[1] The finding that the Polistena study, recruiting a completely different population, reached the same conclusions, strengthen our results and points to insulin resistance as major factor in predicting fibrosis in nonalcoholic fatty liver disease (NAFLD).

Interestingly, uric acid was also significantly higher in Polistena patients with severe fibrosis, compared with mild fibrosis. Raised uric acid levels have been associated with insulin-resistance metabolic syndrome,[2] and NAFLD represents its hepatic feature.[3] Uric acid is a selective antioxidant that protects the ability of vascular endothelium to mediate vasodilatation in the presence of oxidative stress.[4] Elevation of uric acid occurs as a physiological response to increased oxidative stress and, as a consequence of its relatively high concentrations in blood, is the most abundant scavenger of free radicals in humans.[5] In prospective studies, uric acid was associated with increased total antioxidant capacity among individuals with atherosclerosis.[6] Accordingly, increased uric acid in NAFLD might simply represent a physiological response to advanced hepatic lipoperoxidation, the stimulus for progressive fibrosis.

To test this hypothesis, we extracted urate concentrations from the clinical records of our 263 NAFLD patients. Uric acid levels were available for 141 patients (89 patients submitted to liver biopsy). At histology, 31 cases had been classified as pure fatty liver, 41 had fibrosis grade 1 or 2, and 17 had severe fibrosis grade 3 or 4. Uric acid increased progressively with the presence and severity of fibrosis (Fig. 1; median, 5.6, 6.1, and 6.9 mg/dL, respectively; $P = .06$, Kruskal-Wallis test), but no significant differences among the groups were observed. In logistic regression analysis, uric acid was not associated with the presence and severity of fibrosis (mild fibrosis: OR, 1.21; 95% confidence interval, 0.82-1.79, $P = .335$; severe fibrosis: OR, 1.56; 95% confidence interval, 0.97-2.52, $P = .068$). These data do not support a specific role of hyperuricemia as an indirect marker of oxidative stress in NAFLD severity, but they need validation in prospective studies.

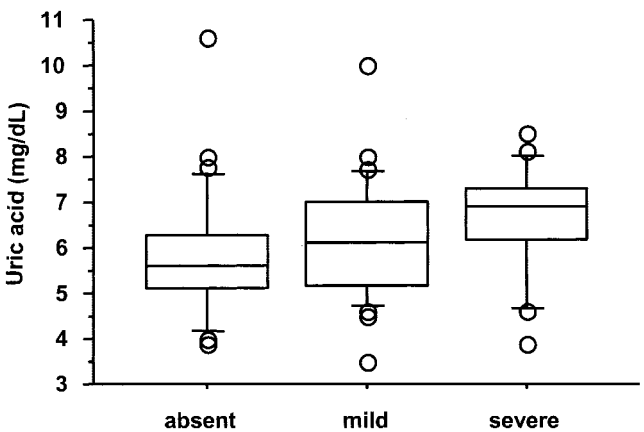

Fig. 1. Box-plot representation of uric acid levels in relation to the presence and severity of fibrosis. In this "box and whiskers" plots, the bar within each column represents the median value, the upper and lower border of the box are the quartiles, and the "whiskers" (error bars) at the extremities indicate the 10th and the 90th percentiles. Individual values exceeding this range are indicated as open circles.

A "second hit" was advocated to explain the passage from fatty liver to nonalcoholic steatohepatitis[7] and was tentatively related to oxidative stress. Oxidative stress is operative in NAFLD,[8] but our data suggest that it is more the effect than the cause of advanced disease. Insulin resistance remains the major culprit.

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References

1. Bugianesi E, Manzini P, D'Antico S, Vanni E, Longo F, Leone N, et al. Relative contribution of iron burden, HFE mutations, and insulin resistance to fibrosis in nonalcoholic fatty liver. HEPATOLOGY 2004;39:179–187.
2. Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Targher G, et al. Prevalence of insulin resistance in metabolic disorders: the Bruneck Study. Diabetes 1998;47:1643–1649.
3. Marchesini G, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. HEPATOLOGY 2003;37:917–923.
4. Becker BF. Towards the physiological function of uric acid. Free Radic Biol Med 1993;14:615–631.
5. Waring WS, Webb DJ, Maxwell SR. Systemic uric acid administration increases serum antioxidant capacity in healthy volunteers. J Cardiovasc Pharmacol 2001;38:365–371.
6. Nieto FJ, Iribarren C, Gross MD, Comstock GW, Cutler RG. Uric acid and serum antioxidant capacity: a reaction to atherosclerosis? Atherosclerosis 2000;148:131–139.
7. Day CP, James OFW. Steatohepatitis: a tale of two "hits". Gastroenterology 1998;114:842–845.
8. Videla LA, Rodrigo R, Orellana M, Fernandez V, Tapia G, Quinones L, et al. Oxidative stress-related parameters in the liver of non-alcoholic fatty liver disease patients. Clin Sci (Lond) 2004;106:261–268.

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