Changes in Hepatic Venous Pressure Gradient Predict Hepatic Decompensation in Patients Who Achieved Sustained Virologic Response to Interferon-Free Therapy

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BACKGROUND AND AIMS: Sustained virologic response (SVR) to interferon (IFN)-free therapies ameliorates portal hypertension (PH); however, it remains unclear whether a decrease in hepatic venous pressure gradient (HVPG) after cure of hepatitis C translates into a clinical benefit. We assessed the impact of pretreatment HVPG, changes in HVPG, and posttreatment HVPG on the development of hepatic decompensation in patients with PH who achieved SVR to IFN-free therapy. Moreover, we evaluated transient elastography (TE) and von Willebrand factor to platelet count ratio (VITRO) as noninvasive methods for monitoring the evolution of PH.

APPROACH AND RESULTS: The study comprised 90 patients with HVPG ≥ 6 mm Hg who underwent paired HVPG, TE, and VITRO assessments before (baseline [BL]) and after (follow-up [FU]) IFN-free therapy. FU HVPG but not BL HVPG predicted hepatic decompensation (per mm Hg, hazard ratio, 1.18; 95% confidence interval, 1.08-1.28; P < 0.001). Patients with BL HVPG ≤ 9 mm Hg or patients who resolved clinically significant PH (CSPH) were protected from hepatic decompensation. In patients with CSPH, an HVPG decrease ≥ 10% was similarly protective (36 months, 2.5% vs. 40.5%; P < 0.001) but was observed in a substantially higher proportion of patients (60% vs. 24%; P < 0.001). Importantly, the performance of noninvasive methods such as TE/VITRO for diagnosing an HVPG reduction ≥ 10% was inadequate for clinical use (area under the receiver operating characteristic curve [AUROC], < 0.8), emphasizing the need for HVPG measurements. However, TE/VITRO were able to rule in or rule out FU CSPH (AUROC, 0.86-0.92) in most patients, especially if assessed in a sequential manner.

CONCLUSIONS: Reassessment of HVPG after SVR improved prognostication in patients with pretreatment CSPH. An “immediate” HVPG decrease ≥ 10% was observed in the majority of these patients and was associated with a clinical benefit, as it prevented hepatic decompensation. These results support the use of HVPG as a surrogate endpoint for interventions that lower portal pressure by decreasing intrahepatic resistance. (HEPATOLOGY 2019;0:1-14).

Interferon (IFN)-free therapies have revolutionized the treatment of patients with chronic hepatitis C (CHC). Even in previous difficult-to-cure patient populations, such as patients with human
immunodeficiency virus coinfection\(^1,2\) or compensated advanced chronic liver disease (cACLD) and PH\(^3,4\) rates of sustained virologic response (SVR) increased to nearly 100%. Accordingly, the focus of attention has shifted to the regression of liver disease and risk stratification concepts for personalized follow-up (FU) of patients who had advanced chronic liver disease (ACLD) before treatment and achieved SVR.\(^5-7\)

Four studies have investigated the impact of viral suppression by SVR to IFN-free treatments on the evolution of PH,\(^8-11\) as assessed by hepatic venous pressure gradient (HVPG). Although patients with pretreatment subclinical PH (i.e., HVPG 6–9 mm Hg) did not progress to clinically significant portal hypertension (CSPH; HVPG ≥ 10 mm Hg\(^12-14\)), less than one fourth of patients who had CSPH before treatment resolved CSPH.\(^8,10,11\) Accordingly, the vast majority of patients remained at risk for hepatic decompensation despite the cure of hepatitis C virus (HCV) infection. However, nearly two thirds of patients with CSPH before antiviral therapy had an HVPG decrease ≥ 10% after achieving SVR to IFN-free regimens,\(^8,10\) which denotes a clinically meaningful decrease according to the Baveno VI chapter on the impact of etiological therapy.\(^13\) This recommendation is primarily based on studies evaluating the HVPG response to nonselective beta-blockers (NSBB).\(^15\) However, there is also limited evidence from patients with HVPG ≥ 12 mm Hg due to alcoholic liver disease (ALD) who were advised to abstain...
from alcohol (HVPG decrease cutoff ≥ 15%), (16) or patients with compensated cirrhosis due to nonalcoholic steatohepatitis (NASH) treated with simtuzumab or placebo (HVPG decrease cutoff ≥ 20%). (17) Besides variceal (re-)bleeding, HVPG response to conventional NSBB ± vasoactive drugs has been shown to decrease the risks of occurrence/worsening of ascites and its complications. (15) In addition, some studies even reported (trends toward) a decrease in hepatic encephalopathy (HE), a decompensating event that is less closely linked to PH. (15) However, conventional NSBB have completely different modes of action, as compared with etiological therapies or other treatments that primarily act by decreasing intrahepatic resistance. (18,19) HVPG is currently not accepted as a surrogate endpoint for the accelerated approval of medical therapies for PH by regulatory authorities, because there is limited evidence supporting its use as a surrogate endpoint for other treatments than NSBB. (20) This is particularly problematic in patients with cACLD, in whom the incidence of hepatic decompensation is comparatively low, resulting in tremendously larger trials and longer study periods, if clinical endpoints (e.g., hepatic decompensation) are assessed. Because resources are limited, only a minority of the emerging treatment approaches are tested in phase 3 clinical trials assessing direct endpoints, which greatly inhibits scientific progress in the field of PH. (21)

Thus, we aimed to assess the impact of pretreatment HVPG, changes in HVPG, and posttreatment values on the development of hepatic decompensation in patients with PH who achieved SVR to IFN-free therapy. Moreover, we investigated the use of transient elastography (TE) and von Willebrand factor (VWF) for monitoring the evolution of PH and the impact of HCV cure on markers of bacterial translocation and inflammation. (22)

Patients and Methods

STUDY DESIGN AND POPULATION

Ninety patients with PH (HVPG ≥ 6 mm Hg(12-14)) who underwent HVPG and TE before (baseline [BL], October 2013 to April 2018) and after IFN-free therapy at the Medical University of Vienna were prospectively characterized and followed for the development of clinical events after the end of treatment. An explorative analysis on changes in markers of bacterial translocation and inflammation (lipopolysaccharide-binding protein [LBP] and interleukin 6 [IL-6]) was performed in a subgroup of 73 patients.

Of note, a considerable proportion of our study cohort has been included in a previous study investigating the impact of SVR to IFN-free therapies on HVPG (and TE)(8); however, this previous study did not evaluate the association between hemodynamic changes and clinical outcomes (i.e., the primary objective of the present study) or the impact of HCV cure on markers of bacterial translocation and inflammation.

CLINICAL AND LABORATORY PARAMETERS

VWF/platelet count (PLT) ratio (VITRO) was calculated by dividing VWF antigen levels (%) over PLT (G × L−1), as previously described. (23,24)

See Supporting Information for further information.

HCV THERAPY

All patients were treated with IFN-free therapies. The choice of the regimen was at the physicians’ discretion and depended on the availability of early-access programs, reimbursement policies, and national and international clinical practice guidelines at the time of treatment initiation. Treatment durations ranged from 8 to 24 weeks.

HVPG AND LIVER STIFFNESS MEASUREMENT

HVPG measurements were performed by the Vienna Hepatic Hemodynamic Lab at the Medical University of Vienna in accordance with a standardized operating procedure (30) and in the absence of NSBB and nitrates. In patients on NSBB, treatment was paused 5 days before HVPG measurements. Liver stiffness was measured using TE (FibroScan; Echosens, Paris, France).

In patients with CSPH (HVPG ≥ 10 mm Hg(12-14)), a clinically meaningful change in HVPG was defined by a decrease of ≥10%, as recommended by the Baveno VI consensus for etiologic therapies. (13) Subclinical
and pronounced PH were defined by an HVPG of 6–9 mm Hg and ≥ 16 mm Hg, respectively. (12–14)

CLINICAL EVENTS

In patients with cACLD, hepatic decompensation was defined by variceal bleeding, incident ascites, or incident HE, whereas in patients with decompensated ACLD, further hepatic decompensation was defined by variceal (re-)bleeding, requirement of paracentesis, admission for grade 3/4 HE, or development of grade 3/4 HE during admission.

Although new onset of jaundice is commonly referred to as a decompensating event in natural history studies, (31) we did not incorporate jaundice in the definition of hepatic decompensation, because this term is poorly defined. (32) This is in line with previous studies investigating risk factors for hepatic decompensation. (32–34)

STATISTICAL ANALYSIS

See Supporting Information.

ETHICS

This study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee of the Medical University of Vienna. Patients were consented for HVPG measurements.

Results

BASELINE CHARACTERISTICS

The majority of patients were male (73%), with a mean age of 54.5 ± 1 years (Supporting Table S1). Overall, 22% of patients had a history of hepatic decompensation and 28% were Child-Turcotte-Pugh (CTP) score stage B, whereas no CTP score stage C patients were included. The median BL Model for End-Stage Liver Disease (MELD) score was 9 (3) points. All patients with varices and/or previous variceal bleeding (n = 34) were on NSBB treatment, except for 4 patients in primary prophylaxis who were intolerant to NSBB. Moreover, 8 additional patients received carvedilol for arterial hypertension. Accordingly, 38 (42%) patients were receiving NSBB treatment. Median BL HVPG, which was assessed 1.71 (10.3) months before treatment initiation, was 14 (8) mm Hg. Twenty-three (26%) patients had subclinical PH (i.e., HVPG 5–9 mm Hg; median HVPG, 8 [3] mm Hg) at BL, whereas HVPG values of 10–15 mm Hg (median HVPG, 12 [4] mm Hg) and ≥ 16 mm Hg (median HVPG, 19 [4] mm Hg) were observed in 29 (32%) and 38 (42%) patients, respectively. Accordingly, the prevalence of CSPH at BL was 74% (67/90).

Baseline characteristics of the subgroup of patients with pretreatment CSPH are shown in Table 1.

BASELINE CHARACTERISTICS ACCORDING TO THE SEVERITY OF PH

See Supporting Information.

CHANGE IN HEPATIC VENOUS PRESSURE GRADIENT AFTER TREATMENT

The FU HVPG measurement was performed 8.79 (6.67) months after the treatment initiation, which was 4.15 (6.58) months after the end of IFN-free therapy.

Absolute and relative changes in HVPG in this series of 90 patients are depicted in Supporting Fig. S1 and were consistent with our previous report on 60 patients, who were also included in this study. (8) No patient with subclinical PH at BL progressed to CSPH (i.e., FU HVPG ≥ 10 mm Hg); however, 57% (13/23) of these patients 38/90 resolved PH (i.e., FU HVPG ≤ 5 mm Hg). Among patients with CSPH at BL, 6% (4/67) of patients had an FU HVPG of ≤ 5 mm Hg, 18% (12/67) of patients regressed to subclinical PH (i.e., HVPG ≥ 5–9 mm Hg), and CSPH persisted in 76% (51/67). Of note, the proportion of patients with profound PH (i.e., HVPG ≥ 16 mm Hg) decreased from 57% (38/67) at BL to 33% (22/67) at FU.

Importantly, in patients with CSPH at BL, an HVPG decrease ≥ 10% was substantially more common (60% [40/67]) than a regression to HVPG values ≤ 9 mm Hg after antiviral therapy (24% [16/67]; P < 0.001).

SEVERITY OF PH AND CLINICAL EVENTS

During a median follow-up of 35.3 (21.8) months, 11 patients developed hepatic decompensation (n = 7 first hepatic decompensation; n = 4 further hepatic
<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>All, n = 67</th>
<th>HVPG Decrease ≥ 10%, n = 40</th>
<th>No HVPG Decrease ≥ 10%, n = 27</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>54.5 ± 1.18</td>
<td>56.1 ± 1.4</td>
<td>52.2 ± 2</td>
<td>0.101</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45 (67%)</td>
<td>25 (63%)</td>
<td>20 (74%)</td>
<td>0.428</td>
</tr>
<tr>
<td>Female</td>
<td>22 (33%)</td>
<td>15 (38%)</td>
<td>7 (26%)</td>
<td></td>
</tr>
<tr>
<td>BL BMI kg/m²</td>
<td>25.8 ± 0.6</td>
<td>25.8 ± 0.7</td>
<td>25.8 ± 1</td>
<td>0.966</td>
</tr>
<tr>
<td>≥ 25 kg/m²</td>
<td>35 (52%)</td>
<td>20 (50%)</td>
<td>15 (56%)</td>
<td>0.655</td>
</tr>
<tr>
<td>≥ 30 kg/m²</td>
<td>12 (18%)</td>
<td>7 (18%)</td>
<td>5 (19%)</td>
<td>1</td>
</tr>
<tr>
<td>Δ BMI kg/m²</td>
<td>0.211 (2.366)</td>
<td>0.106 (2.236)</td>
<td>0.316 (2.564)</td>
<td>0.691</td>
</tr>
<tr>
<td>FU BMI kg/m²</td>
<td>26 ± 0.6</td>
<td>26 ± 0.75</td>
<td>26 ± 0.91</td>
<td>0.976</td>
</tr>
<tr>
<td>≥ 25 kg/m²</td>
<td>38 (57%)</td>
<td>23 (58%)</td>
<td>15 (56%)</td>
<td>0.875</td>
</tr>
<tr>
<td>≥ 30 kg/m²</td>
<td>11 (16%)</td>
<td>6 (15%)</td>
<td>5 (19%)</td>
<td>0.745</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstinent</td>
<td>57 (85%)</td>
<td>34 (85%)</td>
<td>23 (85%)</td>
<td>0.517</td>
</tr>
<tr>
<td>Nonabstinent but below threshold*</td>
<td>5 (7%)</td>
<td>4 (10%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Above threshold*</td>
<td>5 (7%)</td>
<td>2 (5%)</td>
<td>3 (11%)</td>
<td></td>
</tr>
<tr>
<td>HCV genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>45 (67%)</td>
<td>25 (63%)</td>
<td>20 (74%)</td>
<td>0.545</td>
</tr>
<tr>
<td>3</td>
<td>15 (22%)</td>
<td>11 (28%)</td>
<td>4 (27%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>7 (10%)</td>
<td>4 (10%)</td>
<td>3 (11%)</td>
<td></td>
</tr>
<tr>
<td>History of hepatic decompensation</td>
<td>13 (19%)</td>
<td>7 (18%)</td>
<td>6 (22%)</td>
<td>0.632</td>
</tr>
<tr>
<td>BL CTP score, points</td>
<td>6 (2)</td>
<td>6 (2)</td>
<td>7 (2)</td>
<td>0.075</td>
</tr>
<tr>
<td>Stage A</td>
<td>43 (64%)</td>
<td>30 (75%)</td>
<td>13 (48%)</td>
<td>0.037</td>
</tr>
<tr>
<td>Stage B</td>
<td>24 (36%)</td>
<td>10 (25%)</td>
<td>14 (52%)</td>
<td></td>
</tr>
<tr>
<td>Δ CTP score, points</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.577</td>
</tr>
<tr>
<td>FU CTP score, points</td>
<td>6 (2)</td>
<td>6 (1)</td>
<td>6 (3)</td>
<td>0.066</td>
</tr>
<tr>
<td>BL MELD score, points</td>
<td>9 (3)</td>
<td>9 (3)</td>
<td>10 (4)</td>
<td>0.009</td>
</tr>
<tr>
<td>Δ MELD score, points</td>
<td>0 (2)</td>
<td>0 (1)</td>
<td>−1 (2)</td>
<td>0.521</td>
</tr>
<tr>
<td>FU MELD score, points</td>
<td>9 (2)</td>
<td>8 (3)</td>
<td>10 (4)</td>
<td>0.027</td>
</tr>
<tr>
<td>Varices</td>
<td>33 (49%)</td>
<td>17 (43%)</td>
<td>16 (59%)</td>
<td>0.178</td>
</tr>
<tr>
<td>Small</td>
<td>17 (25%)</td>
<td>10 (59%)</td>
<td>7 (44%)</td>
<td>0.387</td>
</tr>
<tr>
<td>Large</td>
<td>16 (48%)</td>
<td>7 (41%)</td>
<td>9 (56%)</td>
<td></td>
</tr>
<tr>
<td>NSBB treatment</td>
<td>35 (52%)</td>
<td>19 (48%)</td>
<td>16 (59%)</td>
<td>0.345</td>
</tr>
<tr>
<td>BL HVPG, mm Hg</td>
<td>16.2 ±0.5</td>
<td>15.8 ±0.6</td>
<td>16.7 ±0.9</td>
<td>0.395</td>
</tr>
<tr>
<td>≥ 16 mm Hg</td>
<td>38 (57%)</td>
<td>21 (53%)</td>
<td>17 (63%)</td>
<td>0.397</td>
</tr>
<tr>
<td>Absolute Δ HVPG, mm Hg</td>
<td>−2.64 ±0.46</td>
<td>−5.1 ±0.34</td>
<td>0.93 ± 0.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relative Δ HVPG, %</td>
<td>−17.8 ±2.9</td>
<td>−33 ±2.3</td>
<td>4.56 ± 2.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FU HVPG, mm Hg</td>
<td>12 (7)</td>
<td>10.5 (5)</td>
<td>17 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≤ 5 mm Hg</td>
<td>4 (6%)</td>
<td>4 (10%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6-9 mm Hg</td>
<td>12 (18%)</td>
<td>12 (30%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>10-15 mm Hg</td>
<td>29 (43%)</td>
<td>19 (48%)</td>
<td>10 (37%)</td>
<td></td>
</tr>
<tr>
<td>≥ 16 mm Hg</td>
<td>22 (33%)</td>
<td>5 (13%)</td>
<td>17 (63%)</td>
<td></td>
</tr>
<tr>
<td>BL liver stiffness, kPa†</td>
<td>27.7 (25.4)</td>
<td>27 (19.7)</td>
<td>29.1 (24.1)</td>
<td>0.269</td>
</tr>
<tr>
<td>Absolute Δ liver stiffness, kPa†</td>
<td>−4.6 (11.9)</td>
<td>−6.8 (11)</td>
<td>−3.6 (19.7)</td>
<td>0.004</td>
</tr>
<tr>
<td>Relative Δ liver stiffness, %†</td>
<td>−18.1 (43.1)</td>
<td>−31.9 (35.9)</td>
<td>−8.22 (52.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FU liver stiffness, kPa†</td>
<td>23 (26)</td>
<td>19.1 (13.5)</td>
<td>32.4 (27)</td>
<td>0.002</td>
</tr>
<tr>
<td>BL PLT, G × L⁻¹</td>
<td>83 (49)</td>
<td>100.5 (43)</td>
<td>68 (49)</td>
<td>0.004</td>
</tr>
<tr>
<td>Absolute Δ PLT, G × L⁻¹</td>
<td>7.16 ±2.95</td>
<td>8.73 ±3.99</td>
<td>4.85 ± 4.36</td>
<td>0.523</td>
</tr>
<tr>
<td>Relative Δ PLT, G × L⁻¹</td>
<td>8.11 (27.89)</td>
<td>8.6 (24.79)</td>
<td>3.03 (26.28)</td>
<td>0.51</td>
</tr>
<tr>
<td>FU PLT, G × L⁻¹</td>
<td>89 (64)</td>
<td>101 (62)</td>
<td>77 (59)</td>
<td>0.015</td>
</tr>
</tbody>
</table>
decompensation): n = 5 ascites, n = 5 HE, and n = 1 variceal bleeding. Three patients underwent liver transplantation. The death of 1 patient with further hepatic decompensation was considered liver related, whereas 1 compensated patient died of a non-liver-related (cardiac) cause.

Although there was only a trend toward an increased risk of posttreatment hepatic decompensation with increasing BL HVPG (per mm Hg, hazard ratio [HR], 1.13; 95% confidence interval [CI], 0.94-1.28; P = 0.069), FU HVPG showed a strong association with hepatic decompensation (per mm Hg; HR, 1.18; 95% CI, 1.08-1.28; P < 0.001). Accordingly, although BL HVPG stratified patients into subgroups with different risks of hepatic decompensation after treatment (log-rank: P = 0.04; Fig. 1), its discriminatory ability seemed to improve if HVPG was assessed during FU: Whereas none of the patients with FU HVPG ≤ 9 mm Hg (0/39) had hepatic decompensation, the Kaplan-Meier estimates for hepatic decompensation at 36 months in patients with FU HVPG values of 10-15 mm Hg and ≥16 mm Hg were 11.1% and 40.1%, respectively.

**CORRELATION BETWEEN THE CHANGE IN HEPATIC VENOUS PRESSURE GRADIENT AFTER TREATMENT AND CLINICAL EVENTS**

In the population at risk for hepatic decompensation (i.e., patients with CSPH at BL), FU HVPG (area under the receiver operating characteristic curve [AUROC], 0.819; 95% CI, 0.687-0.951; P = 0.001) as well as the absolute (AUROC, 0.872; 95% CI, 0.74-1; P < 0.001) and relative (AUROC, 0.877; 95% CI, 0.749-1; P < 0.001) changes in HVPG were associated with hepatic decompensation. In contrast, BL HVPG was not predictive (AUROC, 0.657; 95% CI, 0.468-0.951; P = 0.101).

Although the highest Youden’s index was observed at a relative HVPG decrease of 5% (sensitivity, 90.9%/specificity, 80.4%), we used the similarly sensitive but slightly less specific 10% cutoff (sensitivity, 90.9%/specificity, 69.6%) for further analyses, as recommended by the Baveno VI chapter on the impact of etiological treatment.(13)

Patients with CSPH at BL who achieved an HVPG decrease ≥ 10% had a substantially lower risk of hepatic decompensation after treatment (2.5% vs. 40.5% at 36 months; P < 0.001; Fig. 2). The results remained basically unchanged, if only events occurring after the FU HVPG-measurement were considered (2.6% vs. 30.7% at 36 months; P = 0.003). When stratifying patients according to the presence or absence of previous hepatic decompensation, patients with compensated CSPH at BL (n = 54) were completely protected from hepatic decompensation, if HVPG decrease ≥ 10% (0% vs. 36.4% at 36 months; P < 0.001). In the limited number of patients with decompensated CSPH included in our study (n = 13), the difference in the risk of further hepatic decompensation (14.3% vs. 55.6% at 36 months; P = 0.22) did not attain statistical significance.

Importantly, achieving an HVPG decrease ≥ 10% was associated with a substantially decreased risk of hepatic decompensation (adjusted HR, 0.102; 95% CI, 0.012-0.863; P = 0.036), even when accounting

### Table 1. Continued

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>All, n = 67</th>
<th>HVPG Decrease ≥ 10%, n = 40</th>
<th>No HVPG Decrease ≥ 10%, n = 27</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL VWF, % ‡</td>
<td>293 (151)</td>
<td>283 ± 15.7</td>
<td>311 ± 18</td>
<td>0.267</td>
</tr>
<tr>
<td>Absolute Δ VWF, % ‡</td>
<td>−58 (90)</td>
<td>−83.3 ± 10</td>
<td>−26.6 ± 8.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relative Δ VWF, % ‡</td>
<td>−19.1 (26.4)</td>
<td>−30.1 (23.5)</td>
<td>−9.7 (19.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FU VWF, % ‡</td>
<td>202 (141)</td>
<td>179 (88)</td>
<td>275 (198)</td>
<td>0.003</td>
</tr>
<tr>
<td>BL VITRO, % ‡</td>
<td>3.38 (3.42)</td>
<td>2.98 (2.41)</td>
<td>4.64 (3.56)</td>
<td>0.014</td>
</tr>
<tr>
<td>Absolute Δ VITRO ‡</td>
<td>−0.791 (1.176)</td>
<td>−0.979 (1.442)</td>
<td>−0.382 (1.532)</td>
<td>0.002</td>
</tr>
<tr>
<td>Relative Δ VITRO ‡</td>
<td>−25.5 (38.6)</td>
<td>−34.1 (28.9)</td>
<td>−11.2 (43.7)</td>
<td>0.013</td>
</tr>
<tr>
<td>FU VITRO, % ‡</td>
<td>2.4 (2.64)</td>
<td>1.96 (1.96)</td>
<td>3.31 (4.56)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

* >30 g/day and >20 g/day for males and females, respectively. (48)
† Information available in 64 patients.
‡ Information available in 65 patients.
Abbreviation: BMI, body mass index.
for history of hepatic decompensation as well as treat-
tment-induced changes in CTP and MELD score, or
their posttreatment values (Table 2).

COMPARISON WITH OTHER
POTENTIAL DEFINITIONS OF
HVPG RESPONSE

Using more restrictive definitions of HVPG
response, such as an HVPG decrease ≥ 20%, HVPG
decrease ≥ 20% or to ≤ 9 mm Hg, or an
HVPG decrease ≥ 20% or to ≤ 12 mm Hg (in the sub-
group of patients with BL HVPG > 12 mm Hg), did
not increase the sensitivity for hepatic decompensation
during FU, because 1 decompensated patient with
HVPG response developed further hepatic decompen-
sation, regardless of the definition used (Supporting
Table S2). However, a lower proportion of patients
(49%-51%) achieved HVPG response according to
these definitions, and thus, additional patients without
hepatic decompensation were assigned to the HVPG
nonresponse group. Accordingly, the probability of
hepatic decompensation in patients with HVPG non-
response tended to decrease, suggesting an inferior dis-
criminatory ability of these more restrictive definitions
of HVPG response.

PH AND DE NOVO
HEPATOCELLULAR CARCINOMA

Six patients were diagnosed with de novo hepato-
cellular carcinoma (HCC), who all had CSPH at BL.
However, HCC seemed to develop independently of
the evolution of PH during treatment: Two patients
who developed FU HCC showed an HVPG decrease
to ≤ 9 mm Hg at FU. Moreover, 83% (5/6) had an
HVPG decrease ≥ 10%.

FACTORS ASSOCIATED WITH
AN HVPG DECREASE ≥ 10% IN
PATIENTS WITH PRETREATMENT
CSPH

Please see Table 1 and the Supporting Information.

NONINVASIVE DIAGNOSIS
OF CSPH AT FU AND HVPG
DECREASE ≥ 10%

In the overall study population, liver stiffness
(AUROC, 0.92; 95% CI, 0.863-0.978; P < 0.001), platelet count (AUROC, 0.816; i.e., 1 minus 0.184,
due to indirect association; 95% CI, 0.724-0.908;
P < 0.001), VWF (AUROC, 0.807; 95% CI, 0.714-
0.9; P < 0.001), and VITRO (AUROC, 0.877; 95%
CI, 0.802-0.952; P < 0.001) showed a high diagnos-
tic accuracy for CSPH at FU (Supporting Table S3;
Fig. 3).
The diagnostic indices of the previously defined
FU liver stiffness cutoffs for ruling out (12.4 kPa;
sensitivity, 97.9%) and ruling in FU CSPH (25.3 kPa;
specificity, 94.4%) remained unchanged despite add-
itional patients, with 39.3% (33/84) of patients
being unclassifiable. The false-negative patient had
an FU liver stiffness of 11.8 kPa and an FU HVPG
value of 17 mm Hg and did not achieve an HVPG
response ≥ 10%; however, this patient did not develop
hepatic decompensation.
The newly defined FU VITRO cutoffs for ruling out and ruling in FU CSPH were 0.95 (sensitivity, 95.8%) and 3.3 (specificity, 94.4%), with 53.6% (45/84) of patients in the diagnostic gray zone. The false-negative patient had an FU VITRO 0.92, an FU liver stiffness of 17.1 kPa, and an FU HVPG value of 17 mm Hg and did not achieve an HVPG response ≥ 10%; however, this patient did not develop hepatic decompensation.

Using these tests sequentially (i.e., assessing FU VITRO in patients who were unclassifiable based on FU liver stiffness and vice versa) statistically significantly decreased the proportion of patients in the diagnostic gray zone to 25% (21/84; \(P = 0.047\)).
and $P < 0.001$ compared with FU liver stiffness and VITRO alone, respectively), while maintaining a high sensitivity (liver stiffness first, 93.8%; VITRO first, 93.8%) and specificity (liver stiffness first, 87.1%; VITRO first, 90.3%) for ruling out and ruling in FU CSPH, respectively.

Interestingly, the diagnostic performance of liver stiffness tended to worsen if the regression of CSPH was assessed, i.e., when the analysis was restricted to patients with CSPH at BL (AUROC, 0.86; 95% CI, 0.751–0.969; $P < 0.001$). In contrast, the AUROC of PLT and VWF numerically increased in this subgroup of patients, with VITRO showing the highest diagnostic accuracy (AUROC, 0.876; 95% CI, 0.749–1; $P < 0.001$) of all assessed parameters.

Although liver stiffness, platelet count, VWF, and VITRO, as well as their relative/absolute changes during treatment, showed statistically significant associations with HVPG decrease ≥ 10%, all AUROC values were below 0.8.

**FIG. 3.** Performance of noninvasive markers for diagnosing CSPH at FU. Bold lines indicate parameters statistically significantly associated with the condition. (A) All patients (AUROC: *0.92; **0.816, i.e., 1 minus 0.184, due to indirect association; ***0.807; ****0.877). (B) Subgroup of patients with CSPH at BL (AUROC: *0.86; **0.836, i.e., 1 minus 0.164, due to indirect association; ***0.822; ****0.876).
EVOLUTION OF HVPG AND HEPATIC DECOMPENSATION DURING LONG-TERM FU

Thirteen (19%) out of 67 patients with CSPH at BL underwent an additional HVPG measurement (“last”) after the first assessment of FU HVPG. These HVPG measurements were performed 31.2 ± 3.4 months after treatment initiation, which was 26.8 ± 3.36 months after the end of IFN-free therapy and 20.1 ± 2.8 months after the first post-treatment HVPG measurement.

In these selected patients, HVPG decreased from 15.2 ± 1.7 to 11.8 ± 1.8 mm Hg, which corresponds to an absolute change of −3.38 ± 0.68 mm Hg (P < 0.001) and a relative change of −24.4 ± 4.1% (Supporting Fig. S2). The proportion of patients who resolved CSPH increased from 15% (2/13) at the second (“FU”) assessment to 46% (6/13) at the last HVPG measurement. Seven (54%) out of 13 patients had achieved an HVPG decrease ≥ 10% at the second (“FU”) HVPG assessment, which was maintained in all patients. Moreover, 4 additional patients achieved an HVPG decrease ≥ 10% at the last measurement, resulting in an overall rate of long-term HVPG decrease ≥ 10% of 85% (11/13) in this series of patients.

Interestingly, we observed a close correlation between hemodynamic changes and the patients’ clinical course: Whereas all (11/11) patients who maintained/achieved an HVPG decrease ≥ 10% at last HVPG measurement had an uneventful post-treatment FU period (including 5 patients with a history of hepatic decompensation), both patients without a decrease ≥ 10% at last HVPG had hepatic decompensation (Fig. 4).

EXPLORATORY ANALYSIS ON CHANGES IN MARKERS OF BACTERIAL TRANSLLOCATION AND INFLAMMATION

See Supporting Information.

Discussion

The approval of highly effective IFN-free therapies has ushered in a new era in the treatment of CHC. Because even in patients with PH, SVR is almost universal, CHC is seen as an excellent model for the study of liver disease regression after the cure of the primary etiologic factor.

Although viral suppression in chronic hepatitis B may have comparable effects, its effect on HVPG has only been studied in a small series of patients and was not correlated with direct endpoints. Moreover, despite the high prevalence of ALD, information on the impact of alcohol abstinence on HVPG and its predictive value for clinical events is limited. Finally, the prognostic impact of HVPG decreases due to pharmacological therapies for NASH is currently being investigated. The results of a recent randomized controlled trial on simtuzumab, a monoclonal antibody against lysyl oxidase-like 2, in patients with compensated cirrhosis suggest that an HVPG decrease ≥ 20% is associated with a lower risk of hepatic decompensation. However, simtuzumab has been found to be ineffective in this setting, and one third of patients included in this analysis have been assigned to the placebo group. Thus, this study confirms the prognostic value of HVPG and its changes over time in compensated NASH cirrhosis rather than providing strong evidence for the use of HVPG response as a surrogate outcome for the clinical effectiveness of an etiological treatment. Accordingly, insights from patients with CHC are of great importance for advancing the understanding of the association between changes in HVPG due to therapies targeting intrahepatic resistance (i.e., etiological treatments) and clinical outcomes. Evidence from such studies is essential for promoting HVPG as a surrogate endpoint accepted by regulatory authorities.
In a previous study investigating hemodynamic changes during antiviral therapy with pegylated interferon and ribavirin, pretreatment HVPG/CSPH was predictive of hepatic decompensation during follow-up. However, because of the low efficacy of this regimen in patients with cirrhosis, only a minority achieved SVR, and thus, the prognostic impact of changes in HVPG and posttreatment values was not assessed. Although pretreatment HVPG strata were predictive of clinical events in our study, the discriminatory ability of these HVPG strata improved substantially when posttreatment HVPG values were considered. This may be explained by patients with pretreatment CSPH being reclassified as having no or only subclinical PH (i.e., HVPG ≤ 9 mm Hg) after treatment, which was fully protective of hepatic decompensation. In addition, the proportion of patients with profound PH (HVPG ≥ 16 mm Hg, i.e., patients at high risk for hepatic decompensation) decreased after treatment, which may have enriched this subgroup with patients who have already passed a potential point of no return in the natural history of liver disease, resulting in a particularly bad prognosis. Accordingly, posttreatment but not pretreatment HVPG was predictive of hepatic decompensation in AUROC analysis if only patients at risk (i.e., patients with pretreatment CSPH) were considered. This is in line with the recent observation that a dynamic model based on serial HVPG measurements is closely linked with the risk of hepatic decompensation and/or death.

However, the concept of using HVPG cutoffs for risk stratification has an important limitation, which has also been observed in studies assessing the HVPG response to NSBB. Although a decrease below a certain cutoff (i.e., HVPG ≤ 12 mm Hg) was protective and thus highly sensitive for (recurrent) variceal bleeding, such a decrease was only achieved by a small proportion of patients. Therefore, this cutoff was combined with the more commonly obtained HVPG reduction by ≥ 20% to increase the specificity of HVPG response. In order to further increase the positive predictive value (PPV) of this definition in patients at a lower risk of variceal bleeding, the Baveno VI faculty recently adopted the more specific 10% cutoff for primary prophylaxis. Interestingly, the Youden’s index-derived optimal cutoff would have been ≥5% in our study; however, considering the imprecision of the measurement, using this cutoff may have substantially limited the reproducibility of HVPG response assessment in patients with HVPG < 20 mm Hg. Accordingly, we used the slightly less specific 10% cutoff, which is also recommended by the Baveno VI chapter on the impact of etiological treatment. On the one hand, it cannot be ruled out that treatments targeting intrahepatic resistance (e.g., statins) have beneficial effects despite achieving less pronounced but consistent reductions in HVPG. Especially in patients undergoing etiological therapy, even small changes may denote a trend in the “right” direction (i.e., disease regression). However, on the other hand, the required HVPG reduction could also be higher, because of the absence of the nonhemodynamic effects of NSBB. In our study, more restrictive definitions of HVPG response (e.g., HVPG decrease ≥ 20%) seemed to worsen its discriminatory ability, which argues against the latter hypothesis.

In patients with pretreatment CSPH, an HVPG reduction ≥ 10% translated into a clinical benefit, especially in patients with cACLD who were completely protected from hepatic decompensation. In contrast, the trend toward a lower risk of further hepatic decompensation in patients with an HVPG decrease ≥ 10% did not attain statistical significance, which may be explained by the low number (n = 13) of patients with decompensated CSPH included in our study. Data obtained in a series of 13 patients with posttreatment CSPH undergoing a third HVPG measurement further strengthened the link between relative changes in HVPG and hepatic decompensation. Importantly, the use of relative changes in HVPG, rather than posttreatment HVPG, substantially increased the proportion of patients correctly identified as being at low risk (i.e., specificity/PPV of HVPG response). This is in line with the findings of the abovementioned studies, which defined HVPG response to NSBB treatment.

In line with previous reports, patients with more advanced liver disease were less likely to achieve HVPG response, possibly because of the perpetuation of mechanisms promoting PH in some of these patients. Although pretreatment values of HVPG and most noninvasive markers of PH were comparable between patients with an HVPG reduction ≥ 10%, or without, we observed profound differences in the absolute and relative changes, as well as posttreatment values of liver stiffness, VWF, and VITRO score, indicating that these markers of PH may have
utility for the noninvasive monitoring of the evolution of PH after SVR.

Although HVPG measurement is generally safe and well tolerated,\(^{(40)}\) its clinical use is limited by its invasiveness, and its availability is mostly restricted to academic centers. Accordingly, the development/ validation of noninvasive methods is essential for promoting personalized medicine in patients with ACLD who achieved SVR. Posttreatment liver stiffness and VITRO showed an excellent diagnostic performance for FU CSPH. Nevertheless, when restricting the analysis to patients with pretreatment CSPH in order to evaluate the regression of CSPH, the AUROC of TE numerically decreased, whereas the AUROC of VITRO increased. This might be a consequence of liver stiffness being less strongly correlated with HVPG at values ≥ 10–12 mm Hg in patients without NSBB treatment,\(^{(41)}\) and VWF may show a better correlation with HVPG in this patient population.\(^{(22,42)}\)

We confirmed the diagnostic value of our previously defined liver stiffness cutoffs (sensitivity/specificity of about 95%) for ruling in (25.3 kPa) and ruling out (12.4 kPa) posttreatment CSPH; however, a high proportion of patients were unclassifiable. Applying VITRO cutoffs chosen to obtain similar sensitivity and specificity (ruling out, 0.95/ruling in, 3.3), the proportion of patients within the diagnostic gray zone was even higher. However, performing these tests in a sequential manner substantially reduced the proportion of unclassifiable patients and thus increased their potential value for clinical practice. In addition, Thabut and colleagues\(^{(43)}\) recently validated the Baveno VI criteria for screening for high-risk varices in patients with SVR/viral suppression. Accordingly, there is an increasing number of noninvasive tools that may guide clinical decision making in this setting. Still, these noninvasive methods do not confer the same information as HVPG response, as they are incapable of monitoring the dynamics of PH with adequate accuracy. It would have been interesting to assess the diagnostic performance of spleen stiffness in this setting, because changes in spleen stiffness have recently shown some promise as a noninvasive marker of HVPG response to carvedilol.\(^{(44)}\) Future studies assessing clinical endpoints in larger cohorts should aim to refine the use of combinations and/or serial assessments of noninvasive tests for risk stratification.

SVR to IFN-free therapy was associated with a decrease in LBP and tended to lower IL-6 levels. However, changes were highly heterogenous and independent of the evolution of PH. Interestingly, a similar pattern has been observed in a study investigating the impact of NSBB treatment on measures of gastrointestinal permeability and LBP/IL-6 levels.\(^{(45)}\) Although NSBB treatment lowered HVPG and decreased all of these parameters, the changes were not interrelated. This may suggest that PH and bacterial translocation as well as inflammation are not as closely linked as assumed by some authors. Moreover, a recent study demonstrated substantial interindividual variability in measures of inflammation (i.e., peaks of IL-6 that resolved spontaneously),\(^{(46)}\) which may have interfered with the analysis of repeated assessments.

Of note, de novo HCC occurred only in patients with pretreatment CSPH, which is in line with the previous observations that patients with CSPH bear a 6-fold increased risk of HCC\(^{(47)}\) as compared with patients with cirrhosis but without CSPH. However, incident HCC was not linked to the changes in PH, as it commonly occurred in patients who showed clear evidence of liver disease regression. This suggests that despite the amelioration of hepatic inflammation,\(^{(9)}\) previously acquired genetic alterations and residual morphological changes/changes in the hepatic microenvironment in patients with pretreatment CSPH may play a central role in hepatocarcinogenesis after SVR. Because death due to complications of PH was rare, we would like to highlight the importance of screening programs for the timely diagnosis of HCC in these patients, who otherwise mostly have a favorable prognosis.\(^{(5,7)}\)

We must acknowledge several limitations of our study. Because of limited sample size, we combined patients with cACLD and decompensated ACLD for the main analyses. However, we were able to confirm the prognostic value of an HVPG decrease ≥ 10% in an analysis restricted to the important subgroup of patients with cACLD. Finally, we abstained from performing competing risk analyses,\(^{(31)}\) as the incidence of competing risks (i.e., liver transplantation/death without previous hepatic decompensation) was very low. Furthermore, it cannot be assumed that the observations on long-term changes in HVPG are generalizable, as only a minority of patients underwent an additional (“last”) HVPG measurement, which
may have led to selection bias. However, the profound long-term changes in HVPG raise questions about the optimal time point for the assessment of posttreatment HVPG. In our study, the time intervals between the end of treatment and posttreatment HVPG measurements were not standardized, although they were within a reasonable range in all patients. The median time span was close to the time to SVR assessment (i.e., 12 weeks). A later assessment may have resulted in more pronounced decreases in HVPG, which may have increased the rate of an HVPG reduction ≥ 10% and thus may have restratified more patients to lower-risk HVPG strata. However, it would have also led to a higher number of episodes of hepatic decompensation occurring before the posttreatment HVPG measurement.

In conclusion, reassessment of HVPG after the cure of hepatitis C improved prognostication. Patients with subclinical PH before/after IFN-free treatment are at negligible risk for hepatic decompensation, as we did not observe progression to CSPH. The cure of the primary etiologic factors induced an “immediate” HVPG decrease ≥ 10% in 60% of patients with pretreatment CSPH, which translated into a clinically meaningful benefit, as it prevented hepatic decompensation. This finding provides important evidence for the use of HVPG as a surrogate endpoint for interventions that lower portal pressure by decreasing intrahepatic resistance. Noninvasive methods such as TE and VITRO score cannot substitute HVPG measurement, as they are incapable of monitoring the dynamics of PH with adequate accuracy; however, they may be used for ruling in or ruling out posttreatment CSPH.

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