HVPG as a Gold Standard: Accuracy Is Essential

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The progression of portal hypertension in patients with chronic liver disease (CLD) is directly related to the risk of complications such as ascites and variceal hemorrhage. Equally, the reduction of portal pressure (PP) reduces the risk of these events. PP measurements provide both diagnostic and prognostic information. The only validated method for assessing liver hemodynamics is the wedged hepatic venous pressure (WHVP), which indirectly reflects the actual portal vein pressure. Temporary catheter occlusion of a hepatic vein allows measurement of the pressure head of hepatic sinusoidal blood, which reflects the direct pressure of the portal venous system. The correlation between WHVP and portal vein pressure is high as long as presinusoidal portal vein occlusion is absent. The hepatic venous pressure gradient (HVPG) is calculated by subtracting the free hepatic vein pressure (FHVP) from the WHVP. This gradient is the gold standard for the diagnosis of clinically significant PH. It is also used to determine prognosis and response to treatments.

Accurate calculation of hepatic hemodynamics requires carefully standardized techniques. However, the U.S. and European surveys have suggested significant variability in the way these pressures are measured, potentially leading to variabilities and inaccuracies that could affect the validity of the results. The main objective of this section is to emphasize the importance of a standardized and reproducible technique to calculate liver venous pressures [1].

Procedure Technique

HVPG procedures should be performed in a state-of-the-art catheterization laboratory with standard pressure measurement equipment that can record digital or printed paper tracings. This facilitates assessment of venous waveforms, decreases inter- and intra-observer measurement variability, and allows external centralized review of data. Without waveform and pressure recordings, recording numerical measures directly from a monitor screen makes stable assessments of WHVP more difficult, prevents waveform inspection, reduces accuracy, and makes data inaccessible to other investigators, which is particularly important in research trials. For these reasons, isolated numerical recording of transient "on-screen" pressure values data should be avoided.

Measurement procedures are often performed under conscious (moderate) sedation to assure patient comfort using standard sedatives such as midazolam and fentanyl (or meperidine and propofol). Increased doses of these medications result in more profound depression of consciousness and may affect hemodynamic parameters. Two studies evaluated the effect of intravenous sedation, confirming that doses exceeding 0.02 mg/kg of midazolam reduced the accuracy of pressure data. Waveform changes also result from larger doses of sedatives as respiration becomes irregular and more profound [2, 3]. Importantly, low dose midazolam (0.02 mg/kg) did not modify the HVPG and currently is the only acceptable sedation for HVPG measurement [2].

Real-time ultrasound guidance should be used to assure safe jugular or femoral venous access. Using fluoroscopic guidance, the right or middle hepatic veins (HV)

are typically catheterized, followed by measurements of free and wedged hepatic vein pressures. These pressure measurements can be obtained using an end-hole angiographic catheter that is manipulated as distally as possible into the hepatic vein to achieve a "wedged" position. Preferably, an end-hole, compliant balloon occlusion catheter can be positioned within a more central portion of the HV. The occlusion balloon catheter allows a larger area of liver parenchyma peripheral to the point of temporary venous occlusion to be evaluated. Studies comparing angiographic catheters with compliant occlusion balloons demonstrate the superiority of the balloon approach, yielding more accurate and precise measurements of WHVP and, thus a better reflection of the direct PP. Based on these studies, compliant balloon occlusion catheters are recommended [4, 5] Of note, European and U.S. surveys performed for the Baveno VII conference revealed that approximately 40% of responding operators still use an end-hole angiographic catheter to measure the WHVP; this indicates areas for improvement and standardization.

Finally, with the occlusion balloon inflated within the HV, a small amount of contrast (5–10 mL) should be injected to confirm the complete occlusion of hepatic outflow [4–9] and exclude hepatic venovenous communications which can artifactually lead to underestimation of the actual PP [9, 10, 11]. If hepatic vein to hepatic vein connections are venographically demonstrated during balloon occlusion, they should be reported, and other sites of measurement should be sought.

Pressure Measurements and Data Recording

The pressure transducer should be placed at the level of the right atrium, i.e., at the midaxillary line. The transducer should record "zero" when open to air [9]. Monitor scales should be set at "central venous" pressure settings rather than "arterial" as their lower pressure ranges (up to 50–60 mmHg) are more suitable for detecting small changes in pressures (0.5 mmHg). In contrast, arterial pressure settings (up to 200 mmHg) are difficult to interpret [9]. Slow speed (up to 7.5 mm/s) permanent recording of pressure tracings is recommended [12].

Technical Aspects

The WHVP is recorded once the occlusion balloon is in its optimal occluded position. Recording should last at least 90 s to allow the pressure to plateau to its maximum level. WHVP should be measured in triplicate to reduce inconsistencies [9]. Once the wedge pressures have been measured, the balloon is deflated, and the catheter is withdrawn to a position within 2–3 cm from the junction of the HV to the inferior vena cava (IVC) to measure the free hepatic venous pressure (FHVP) [1]; this may also be measured prior to balloon inflation. IVC pressure should be measured as an internal control. The ideal site for the calculation of the pressure gradient has been a matter of debate. Some operators have advocated the use of pressures from the IVC or right atrium as an alternative to the FVHP. Results from a

comparative study by La Mura show that the HVPG has a significantly superior clinical prognostic value than the wedge-hepatic to atrial pressure gradient. Therefore, WHVP and FHVP must be used to calculate HVPG [6]. If a pressure gradient greater than 2 mmHg is found between FHV and IVC, contrast should be injected to rule out HV stenosis [13]; still, FHVP must be used for gradient calculation. Right atrial pressure is measured to rule out a post-sinusoidal component.

Diagnosis of Clinically Significant Portal Hypertension (CSPH) and Prediction of Main Outcomes in Patients with Different Etiologies of Cirrhosis

The Timolol study [14], a RCT comparing non-selective beta-blockers (NSBBs) to placebo for preventing the development of varices in patients with viral and alcoholic cirrhosis, identified an HVPG ≥10 mmHg as a high-risk marker for development of esophageal varices. A nested analysis of this study by Ripoll et al. found that an HVPG ≥10 mmHg identified patients at higher risk of decompensation, defined by the development of ascites, variceal hemorrhage (VH), or hepatic encephalopathy (HE) [15]. Robic et al. reported a 2-year prospective study of 100 patients with alcohol or viral CLD (65 with cirrhosis), wherein an HVPG ≥10 mmHg predicted the first event of decompensation (ascites, HE, or VH) [16]. These studies showed that an HVPG ≥10 mmHg identified compensated patients at risk for decompensation. Therefore, such patients must be considered as having CSPH [17].

In patients with CPSH, it is likely that the risk of decompensation increases in parallel with the severity of PH. A retrospective, single-center study of 86 patients with compensated cirrhosis not treated with NSBBs (54 viral, 11 alcohol, and 21 multifactorial/others) reported the incidence of the first decompensation to be significantly higher in patients with a baseline HVPG ≥16 mmHg compared with those with pressures <16 mmHg (35.1% vs. 11.5%, $p = 0.02$) [18]. A retrospective study of 741 patients with compensated cirrhosis of both viral and non-viral etiologies stratified them by HVPG: 6 to <12 mmHg; 12 to <20 mmHg; and ≥20 mmHg. All patients with an HVPG ≥12 mmHg were treated with carvedilol. An HVPG ≥12 mmHg was independently predictive of decompensation. Moreover, an HVPG ≥20 mmHg yielded a twofold higher risk of decompensation compared with an HVPG between 12 and <20 mmHg, and a 4.5-fold higher risk compared with an HVPG between 6 and <12 mmHg [19].

Non-alcoholic steatohepatitis (NASH) is an increasing cause of CLD. In a study of 258 patients with compensated NASH (95% Child-Pugh A), 19% experienced liver-related complications that were mainly associated with baseline HVPGs of ≧10 mmHg. Indeed, only 8% of those patients with an HVPG <10 mmHg developed decompensation, which led the authors to hypothesize that PH in NASH patients may partly depend upon a presinusoidal component unassessed by HVPG [20]. Furthermore, a recent study comparing direct PP measurement with WHVP showed that WHVP underestimated PP in NASH patients compared with other etiologies [21]. Finally, a large retrospective cross-sectional multicenter study, assessing the

association between HVPG values and clinical signs of PH in patients with advanced NAFLD (aNAFLD) showed that aNAFLD patients had a higher prevalence of portal hypertension-related decompensation at any value of HVPG as compared to aHCV patients; 9% of those patients with an HVPG <10 mmHg had decompensation, mainly with ascites [22].

Two independent cohort studies comparing patients with primary biliary cholangitis (PBC), alcohol and viral etiologies, showed a poor correlation between directly measured PP and WHVP in PBC [23, 24]. In a study by Navasa et al., five patients had esophageal varices despite HVPG <6 mmHg; this indirectly indicated the presence of a presinusoidal component of PH in PBC [25]. Porto-sinusoidal vascular liver disorder (PSVD) is another condition with a clear presinusoidal component wherein WHVP underestimates PP. In these patients, an HVPG <10 mmHg is frequently found despite the presence of severe complications of PH [26].

In conclusion, an HVPG ≥10 mmHg defines the presence of CPSH in patients with alcohol, viral, and NASH-related compensated cirrhosis. In patients with PBC and PSVD, HVPG is unreliable in defining the presence and severity of PH.

Variceal Hemorrhage

Variceal hemorrhage requires values of HVPG ≥12 mmHg. Conversely, patients whose HVPG is reduced to <12 mmHg are protected from PH-related bleeding [27–31] (Table 5.1). There is a consensus that higher values of HVPG are correlated with worse outcomes. One early study, performed when modern endoscopic treatments of VH were unavailable, demonstrated that an HVPG ≥16 mmHg measured within 48 h of hospitalization was strongly correlated with continued bleeding or

Table 5.1 Diagnostic and prognostic values of HVPG in patients with cirrhosis

Single HVPG measurement
≥10 mmHg: Defines "clinically significant portal hypertension" for the increased risk of developing varices, clinical decompensation (variceal hemorrhage, ascites, and hepatic encephalopathy) and HCC
≥10 mmHg: Increased risk of decompensation after hepatic resection for HCC
≥12 mmHg: Increased risk of rupture of varices
≥16 mmHg: Increased risk of death
≥20 mmHg: Treatment failure, early rebleeding, and mortality in variceal hemorrhage
≥16 mmHg and ≥ 20 mmHg: High and very high risk of death after non-hepatic surgery
Repeat HVPG measurement
Reduction to <12 mmHg: Abolition of risk of first variceal hemorrhage and recurrent hemorrhage
Reduction of ≥10% from baseline: Reduced risk first episode of variceal hemorrhage or other decompensating events
Reduction of ≥20% from baseline: Reduced risk of recurrent variceal hemorrhage, ascites, and mortality
Reduction of ≥10% from baseline after acute intravenous propranolol
Administration: Reduced risk of first variceal bleeding, rebleeding, and mortality

HCC hepatocellular carcinoma, *HVPG* hepatic vein pressure gradient

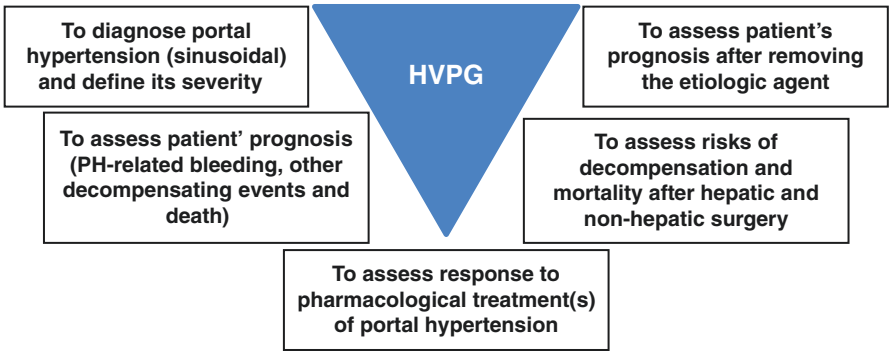

Fig. 5.1 Potential applications of HVPG in clinical practice

early rebleeding [32]. Multiple prospective cohorts, including a seminal randomized controlled trial, confirmed the association between increasing HVPG and a lower probability of hemorrhage control, and consistently found that an HVPG ≥20 mmHg strongly predicted failure, early rebleeding [33–38], and higher mortality [37, 38]. In these studies, a majority of patients were alcoholics or had viral-related cirrhosis. The correlation between HVPG and late rebleeding is less clear [36, 39]. Thus, the assessment of HVPG provides useful information to assess the risk of variceal bleeding or rebleeding in patients with viral and/or alcoholic cirrhosis (Fig. 5.1).

Hepatocellular Carcinoma (HCC)

Three studies evaluated the correlation between HVPG and risk of developing HCC [40–42], the largest by Ripoll et al. (n = 213) [41]. The authors found that HVPG was an independent predictor of HCC development, and that patients with CSPH had a sixfold higher risk of HCC compared with those with less severe PH [41]. Two other smaller studies confirmed that HVPG is an independent predictor of HCC in cirrhosis [40, 42].

Survival

The correlation between HVPG and survival in cirrhosis has been extensively studied. Most studies converge upon a strong and independent association between increased HVPG and the risk of death, especially in compensated patients (Table 5.1). In a 42-month prospective study of 81 patients with biopsy-proven alcoholic cirrhosis, Tage-Jansen et al. confirmed that death increased in parallel with the severity of baseline HVPG (<12 vs. 12–20 vs. ≥20 mmHg) [43]. Another study confirmed the association of CSPH with increased risk of mortality, independent of Model for End-Stage Liver Disease (MELD) scores [44]. However, the risk

thresholds were inconsistent among studies: ≥10 mmHg in 1 retrospective study [45]; ≥15 mmHg in 1 prospective [46]; ≥16 mmHg in 5 studies (3 retrospective and 2 prospective) [13, 18, 30, 39, 47]; ≥18 mmHg in 1 retrospective [48]; and ≥20 mmHg in 2 studies (1 retrospective and 1 prospective) [35, 42]. On the other hand, two studies with a relatively smaller sample size did not find that HVPG per se provided prognostic significant information for survival [31, 49]. These results likely reflect the marked heterogeneity of patient demographics, ranges of HVPG values, use of NSBBs, management of cirrhosis, and durations of follow-up. In conclusion, HVPG is an independent predictor of mortality in patients with cirrhosis, particularly in compensated ones. Despite marked heterogeneity among studies, a value of HVPG ≥16 mmHg appears to be the best threshold for identifying patients at higher risk for death.

Assessment of HVPG in Patients Receiving NSBBs for Prevention of Variceal Hemorrhage and Decompensation

There is strong evidence that lowering PH by NSBBs reduces the risk of the first episode of VH [29, 50–52]. The first RCT, by Groszmann et al., randomized 51 patients with esophageal varices to propranolol vs. 51 patients treated with placebo [29]. All patients who bled during follow-up had an HVPG >12 mmHg compared with none among patients with an HVPG <12 mmHg (Table 5.1). Merkel et al. reported similar findings in a prospective study of 49 cirrhotic patients (alcohol and HCV-related) with varices at risk who were started on NSBBs +/− isosorbide mononitrate (ISMN) [50]. Response to NSBBs was defined as a decrease of >20% from the baseline value. The cumulative probability of VH was higher in poor vs. good responders. Remarkably, no patient who achieved an HVPG <12 mmHg experienced VH during a 5-year follow-up. These findings were confirmed in a second 71 patient cohort treated with NSBBs + ISMN [52]. Merkel's target thresholds were modified by a larger study by Villanueva et al., in which reduction of HVPG by ≥10% from baseline showed a significantly higher prognostic value compared with the previously proposed ≥20% [53]. The same study also demonstrated that acute response to NSBBs, as assessed by an HVPG measurement before vs. after intravenous infusion of propranolol, provided useful information for the long-term management of cirrhotic patients at risk of VH. Chronic response to NSBBs was also associated with a significantly lower risk of ascites. This further emphasizes that the assessment of hemodynamic response after starting NSBBs is useful for distinguishing among groups at different risks of decompensation during follow-up [53]. This was corroborated by a prospective cohort study of patients with compensated, mostly HCV-related, cirrhosis with HVPGs >12 mmHg; NSBBs were correlated with reduced risk of ascites and increased survival during 5-year follow-up [54].

HVPG has value in secondary prophylaxis of VH. This was first evaluated in a prospective cohort of 69 bleeding cirrhotic patients in whom HVPG was reassessed 3 months after the start of NSBBs [55]. Rebleeding was significantly less in patients with a HVPG reduction of ≥20%. Similarly, another multicenter cohort with 8-year

follow-up showed that the cumulative probability of freedom from rebleeding was significantly higher in responders vs. non-responders. The cumulative probability of freedom from ascites, spontaneous bacterial peritonitis, HE, and overall patient survival was also higher in the responders [56]. A third study confirmed these results [57].

La Mura et al. investigated the utility of HVPG to improve prognostic stratification in 424 patients receiving secondary prophylaxis [58]. By combining clinical data such as ascites and/or HE plus severity of PH (HVPG ≥16 mmHg), they identified two groups of patients at significantly different risks of recurrent VH and mortality. The "Low" risk group included patients without ascites or HE, and patients with VH plus ascites or HE but an HVPG <16 mmHg. The "High" risk group included patients with ascites and/or HE and an HVPG ≥16 mmHg unresponsive to NSBBs. If confirmed by future prospective studies, this schema would further reinforce the utility of HVPG to identify patients at risk despite first-line secondary prophylaxis with ligation plus NSBBs, i.e., ones in whom TIPS may be considered. Further studies are also needed to explore whether an HVPG-guided strategy for secondary prophylaxis of VH may reduce the risk of rebleeding and improve survival as was indicated by a proof-of-concept seminal RCT, one in which, however, the standard of care treatment for PH was not applied [59].

A recent multicenter RCT of compensated patients with a high risk of decompensation (HVPG ≥10 mmHg) demonstrated that NSBBs patients had significantly better survival free of decompensation, particularly ascites, compared with the placebo group [60]. A post-hoc analysis showed that an HVPG reduction ≥10% correlated with a higher chance survival without decompensation.

In summary, in patients with viral and alcohol-related cirrhosis, a NSBB-driven decrease in HVPG significantly reduced the risks of variceal bleeding and other decompensating events. For primary prophylaxis of VH, an HVPG <12 mmHg or a decrease by 10% from the baseline value is clinically significant. For secondary prophylaxis, achieving an HVPG <12 mmHg or decreasing it by 20% from baseline protects patients from recurrent VH. For prevention of ascites, a decrease in HVPG of at least 10% from baseline is clinically relevant and reduces decompensation and liver-related death.

HVPG Predicts Risk of Decompensation and Mortality after Hepatic and Non-hepatic Surgery

Patients with Cirrhosis and HCC: Candidates for Hepatic Resection

Patients with cirrhosis, CSPH, and HCC who undergo hepatic surgery are at increased risk of postoperative decompensation and mortality [61–70]. A prospective series of 46 consecutive Child-Pugh A patients without clinical signs of PH and potentially resectable HCC reported a postoperative 1-year rate of ascites in 0% of patients without CSPH, compared with 30% in patients with HVPG from 10.5 to 12.5 mmHg [67]. There remains a need for defining a good-risk subset of CSPH

patients for hepatic resection. While HVPG can stratify risks of postoperative decompensation, approximately 25% of patients with CSPH may nonetheless experience a normal postoperative course [65]. In addition, in these patients, a laparoscopic approach may mitigate the risks due to CSPH [62, 66, 69, 70]. In a retrospective report of 79 patients with CSPH, laparoscopic resection was the only independent predictor of a "best" outcome [61]. A prospective study comparing 10 laparoscopic resection patients with HVPG ≥10 mmHg with six patients who underwent open surgery found that rates of postoperative ascites and death were significantly higher in the open surgery group [70]. Reduction in postoperative risk in laparoscopic patients with CSPH has been observed in two other studies [64, 66].

In summary, the presence of CSPH, evaluated by HVPG measurement, is independently associated with increased risks of post-surgical decompensation and death. However, further longitudinal studies, which should consider the amount of resected liver and the application of minimally invasive approaches, are needed.

Patients with Cirrhosis Who Undergo Extrahepatic Surgery

In a prospective multicenter study, Reverter et al. described the utility of HVPG to predict outcomes of non-hepatic elective surgery in 140 patients with cirrhosis; 116 (83%) had CPSH [71]. The variables independently associated with outcome were ASA class, high-risk surgery, and HVPG. An HVPG >16 mmHg (HR >2.5) was associated with significant increase in mortality. Death was particularly high (44%) in patients with HVPG values ≥20 mmHg [71]. Further studies on whether the use of TIPS *prior* to surgery may help to improve survival in this setting are awaited.

PPG in the Setting of Tips

PPG Measurement

Abundant evidence supports the critical relationship between HVPG/PPG and the development of PH complications, and their recurrence after TIPS [27–31, 72–74]. PPG should always be measured before and after TIPS creation. When measuring PPG, the impact of sedation and measurement timing on hepatic hemodynamics should be considered. In 2014, Reverter et al. reported a prospective study examining the impact of sedation on hepatic hemodynamics in 44 patients undergoing HVPG and PPG measurement during TIPS under deep sedation [3]. The investigators reported that deep sedation added substantial variability and uncertainty to HVPG and PPG measurements. In 2017, Silva-Junior et al. retrospectively investigated the effect of timing on PPG measurement [75] in 155 TIPS patients. PPG was measured immediately post-TIPS, at least 24 h post-TIPS in stable, non-sedated patients (early PPG), and 1-month post-TIPS (late PPG). The immediate PPG differed from early PPG during general anesthesia (8.5 vs. 10 mmHg, $P = 0.015$), and deep sedation (12 vs. 10.5 mmHg, $P < 0.001$). There was no difference between

early PPG and late PPG values (8.5 vs. 8 mmHg, $P > 0.05$). Thus, the immediate post-TIPS PPG may be influenced by various procedural factors and may not represent long-term PPG. PPG measurements in non-sedated hemodynamically stable patients without vasoactive agents or recent volume expansion may better reflect durable post-TIPS PPG values. Therefore, studies seeking correlations between post-TIPS PPG values and clinical outcomes should measure PPG accordingly.

Anatomic Location for PPG Measurement

La Mura et al. demonstrated, in 99 TIPS patients, that the post-TIPS porto-atrial gradient was a mean of 2.5 mmHg higher than the porto-caval gradient [6]. In considering a target gradient of 12 mmHg, 20% of the porto-caval gradients were <12 mmHg but had a porto-atrial gradient >12 mmHg; without needed perspective this could have prompted further TIPS dilation. Moreover, in the 1998 study by Casado et al., post-TIPS clinical outcomes were correlated with portal to caval gradients [72]. Notably, an unpublished survey of North American Interventional Radiologists (SIR Connect, September 2021) demonstrated the predominant use of right atrial pressure for post-TIPS PPG measurement (67% of 61 respondents), indicating a broad use of right atrial pressure to calculate the PP gradient. This could explain why a significant number of published studies have used the right atrial pressure for PPG calculation. Although these studies have supported the clinical effectiveness of TIPS while employing right atrial pressure, this does not mean that right atrial pressure is equivalent to IVC [76, 77]. In consideration of these data, anatomic locations for post-TIPS PPG measurement also should include the main portal vein and the IVC at the shunt outflow.

Optimal PPG Threshold for Portal Hypertensive Bleeding/Ascites

In a study of 122 TIPS patients, Casado et al. correlated clinical events to hemodynamic findings, reporting that all patients with rebleeding had a PPG (portal to caval) >12 mmHg [72]. In 2001, Rössle et al. reported a longitudinal study of 225 TIPS patients with variceal bleeding, wherein 80% of rebleeding occurred with PPGs similar to or greater than the baseline PPG, while only one (0.4%) and three (1.3%) patients rebled with a PPG <12 mmHg or PPG reduction by >50% [73]. In a 2007 retrospective observational cohort study of 118 TIPS patients, Biecker et al. found that patients with an initial PPG reduction >60% rarely suffered from rebleeding [74]. On these bases, it is recommended that in patients with variceal bleeding undergoing TIPS, reduction of absolute PPG to <12 mmHg is associated with near complete protection from portal hypertensive bleeding and is the preferred target for TIPS hemodynamic success. Relative reduction of PPG by at least 50% from the pre-TIPS baseline may be also useful but further studies are needed.

The optimal PPG threshold for ascites has been studied in several investigations. The 1998 study by Casado et al. found that all patients ($n = 26$) who developed

ascites after TIPS had a PPG >12 mmHg [72]. In 2003, Sanyal et al. published a multicenter, prospective clinical trial of 109 ascites patients randomized to medical therapy or medical therapy + TIPS and found no relationship between PP reduction (mean final PPG = 8.3 mmHg) and ascites recurrence [78]. In 2004, Nair et al. reported a retrospective observational cohort study of 28 patients who underwent TIPS for ascites (mean final PSG = 8.6 mmHg) and did not identify post-TIPS PPG as an independent predictor of response [79]. In 2007, Salerno et al. presented a meta-analysis of four RCTs of TIPS versus paracentesis for ascites, reporting recurrent ascites in 42% of TIPS patients with a mean final PPG of 11.4 mmHg versus 89% of paracentesis patients ($P < 0.0001$) [80]. In 2014, Parvinian et al. published a retrospective single center study of 80 ascites patients treated with TIPS (mean final PPG = 6.8 mmHg) and reported an ascites response rate of ~80%, but uncovered no optimal PPG threshold associated with clinical response (response rate for 8, 10, and 12 mmHg thresholds = 79%, 79%, 78%, $P = 0.965$) [81]. In conclusion, the optimal PPG decrease to control medically refractory ascites remains unclear. Further investigation correlating TIPS hemodynamic outcomes and ascites clinical response is necessary.

PPG Thresholds in Overshunting Adverse Events

Excessive reduction of PPG by TIPS is associated with a higher risk of overshunting-related adverse events, such as HE [82–84]. Although interventions to address overshunting-related adverse events (e.g., TIPS reduction) have been studied, the approaches, PPG modifications, and clinical outcomes still vary [85–95]. As such, the optimal PPG target or degree of PPG elevation for interventions to address overshunting-related adverse events (e.g., TIPS reduction) is unknown. Further investigation to define the relationship between PPG and the resolution of overshunting adverse events is necessary.

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