Hepatic Venous Pressure Gradient in Fontan Physiology Has Limited Diagnostic and Prognostic Significance

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ABSTRACT

Background: Hepatic venous pressure gradient (HVPG) is measure of portal pressure and a prognostic tool in patients with viral and alcoholic cirrhosis; its utility is unknown in patients with Fontan-associated liver disease (FALD). Limited data suggest that patients with FALD have normal HVPG. On the basis of the available data, we hypothesized that there would be no association between HVPG, liver disease severity, and transplant-free survival in FALD.

Methods: A retrospective study of Fontan patients who had liver biopsy and HVPG assessment at Mayo Clinic was performed. HVPG was calculated as wedged HVP minus free HVP; liver disease severity was measured by histologic assessment of fibrosis and standard clinical liver disease risk scores.

Results: Of 56 patients (aged 28 ± 7 years), the mean Fontan pressure was 16 ± 4 and the mean HVPG was 1.4 ± 0.3 mm Hg (range, 0.3 mm Hg [range,

Fontan-associated liver disease (FALD) represents a spectrum of liver disorders ranging from chronic fibrosis to advanced cirrhosis and has been reported in up to 80% of patients with Fontan palliation.1–7 It is associated with increased risk of mortality; hence assessment of the degree of hepatic injury in FALD is important for prognostication.2,8 FALD was first recognized as a post-Fontan complication less than 3 decades ago, and as a result, there are limited mechanistic and clinical outcome data about this disease entity.1–4,8 Because of the current knowledge gap about FALD, data derived from patients with other etiologies of cirrhosis have been extrapolated to patients with FALD.9–12

Some of the extrapolated data currently used in the management of FALD include histologic classification tools, risk stratification models, and haemodynamic indices such as the hepatic venous pressure gradient (HVPG).9–12

HVPG is the difference between portal venous pressure and hepatic venous pressure, and it is a measure of the hepatic sinusoidal “driving pressure” required to perfuse the liver.12 HVPG is typically elevated in patients with cirrhosis because structural changes in the hepatic sinusoids that occur in cirrhosis result in a high impedance to portal venous flow through the liver.12 HVPG strongly correlates with the risk of variceal bleeding, ascites, and mortality, and it is therefore used to monitor disease progression and response to therapy.9–12 The normal values of HVPG is ≤5 mm Hg. Portal hypertension is diagnosed when HVPG is >5 mm Hg, and HVPG >12 mm Hg is a prognostic marker for adverse outcomes in patients with viral and alcoholic cirrhosis.9,11,12 In contrast to data from this patient population, studies conducted in patients with Fontan palliation have reported HVPG values within the normal range even in patients with
0-3). Perisinusoidal fibrosis and periportal fibrosis were present in 56 (100%) and 54 (94%) patients, respectively; 18 (32%) met criteria for cirrhosis. There was no correlation between HVPG and degree of hepatic fibrosis. Similarly, there was no correlation between HVPG and any clinical liver disease risk score. Six (11%) patients died and 2 (4%) underwent heart transplantation during follow-up; HVPG was not associated with transplant-free survival.

Conclusions: HVPG is not elevated in FALD even in the setting of cirrhosis and does not correlate with liver disease severity or clinical outcomes. These results suggest the limited diagnostic and prognostic role of HVPG in the management of FALD and highlight the potential pitfalls of using HVPG in this population.

Methods

Study population

We reviewed the Mayo Adult Congenital Heart Disease (MACHD) Registry and identified adult patients (aged ≥ 18 years) with a history of Fontan palliation who underwent cardiac catheterization. The MACHD Registry contains data of all adults with congenital heart disease that received care at the Mayo Clinic Enterprise, from January 1, 1985. From this cohort, we selected consecutive patients who had assessment of free hepatic venous pressure (fHVP) and wedged hepatic venous pressure (wHVP), and liver biopsy at the time cardiac catheterization. The Mayo Clinic Institutional Review Board approved this study and waived informed consent for patients who provided research authorization.

Study objectives

The primary objective was to assess the correlation between HVPG and degree of hepatic fibrosis (portal and sinusoidal fibrosis). The secondary objectives were to assess the correlation between HVPG and clinical liver disease severity scores, Fontan pressure (as a measure of systemic congestion), and transplant-free survival.

Assessment of HVPG

Cardiac catheterization was performed on chronic medications in the fasted state and mild sedation using 7 Fr fluid-filled catheters as previously described. Catheter position was confirmed by appearance on fluoroscopy, characteristic pressure waveforms, and oximetry. Pressure measurements were recorded at end expiration and represent an average of 3 beats for patients in sinus rhythm and 5 beats for patients in atrial fibrillation. Haemodynamic pressure tracings were recorded, digitized (240 Hz), and stored for offline analysis. Offline review of haemodynamic tracings, angiographic images, and cardiac catheterization reports was performed in all patients.

For the assessment of hepatic haemodynamics, the catheter position in the hepatic vein was confirmed by appearance on fluoroscopy and contrast angiography before the measurement of fHVP and wHVP. HVPG was calculated as wHVP – fHVP.

Assessment of liver disease severity and clinical outcomes

All liver biopsies were performed via the transvenous approach during cardiac catheterization as previously described. Liver histologic data were abstracted from the pathology reports. The liver specimens were stained with trichrome and reticulin stains. Portal fibrosis was assessed using the Batts-Ludwig (stages 0-4) staging system, and sinusoidal fibrosis was staged (0-4) as previously described.

Similar to previous studies, we dichotomized the patients into those with no or mild sinusoidal fibrosis (stages 0-2) vs those with severe sinusoidal fibrosis (stage >2). Similarly, we also dichotomized the patients into those without cirrhosis (FO-F3) vs those with cirrhosis (F4).

The following clinical liver disease risk scores were used for the assessment of liver disease severity: (1) model for end-stage liver disease score; (2) model for end-stage liver disease survival.
disease excluding international normalized ratio score; (3) Child-Pugh score; (4) varices, ascites, splenomegaly, and thrombocytopenia score; and (5) aspartate aminotransferase to platelet ratio index.

The occurrence of heart transplant was ascertained by review of medical records, and all-cause mortality was ascertained using the Accurint database in 100% of the patients as of December 31, 2018. Accurint is an institutionally approved death registry containing data of all deaths in the United States.

Statistical analysis

Data were presented as mean ± standard deviation, median (interquartile range), or count (%). Between-group differences were assessed with Fisher’s exact test, t test, and Wilcoxon rank sum test as appropriate. The correlation between HVPG and liver fibrosis was assessed using 2 different methods. First, linear regression analysis was used to assess the correlation between HVPG and sinusoidal fibrosis (modelled as a continuous variable: 0, 1, 2, 3, 4) and between HVPG and portal fibrosis (modelled as a continuous variable: 0, 1, 2, 3, 4). Next, logistic regression analysis was used to assess the correlation between HVPG and sinusoidal fibrosis (modelled as a binary variable: no or mild fibrosis vs severe fibrosis) and between HVPG and portal fibrosis (modelled as a binary variable: no cirrhosis vs cirrhosis). The strength of the correlation was expressed as unit odds ratio (OR) and 95% confidence interval (CI) for the logistics regression models.

Linear regression analyses were used to assess the correlation between HVPG and Fontan pressure, and liver disease risk scores. Cox regression analysis was used to assess the correlation between HVPG and transplant-free survival. The time of HVPG assessment was used as “time zero” for time-to-event analysis. A P value < 0.05 was considered statistically significant. All statistical analyses were performed with JMP software (version 14.1.0; SAS Institute Inc, Cary, NC).

Results

There were 56 patients who met the study inclusion criteria, and the age at the time of liver biopsy was 28 ± 7 years. Table 1 shows the baseline clinical and haemodynamic characteristics of the cohort. The most common congenital heart disease diagnoses were tricuspid atresia 19 (34%) and double-outlet right ventricle 15 (27%). The types of Fontan connection at disease diagnoses were tricuspid atresia 19 (34%) and double-outlet right ventricle 15 (27%). The types of Fontan connection at disease diagnoses were tricuspid atresia 19 (34%) and double-outlet right ventricle 15 (27%).

Table 1. There was no correlation between HVPG and sinusoidal fibrosis (modelled as a continuous variable: 0, 1, 2, 3, 4). Next, logistic regression analysis was used to assess the correlation between HVPG and sinusoidal fibrosis (modelled as a binary variable: no or mild fibrosis vs severe fibrosis) and between HVPG and portal fibrosis (modelled as a binary variable: no cirrhosis vs cirrhosis). The strength of the correlation was expressed as unit odds ratio (OR) and 95% confidence interval (CI) for the logistics regression models.

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Discussion

The diagnostic and prognostic significance of HVPG is unknown in patients with FALD. In this study of 56 patients with Fontan palliation, we reported that HVPG was normal even in patients with cirrhosis. There was no correlation between HVPG and liver fibrosis, clinical liver disease risk scores, and systemic venous congestion (Fontan pressure). Furthermore, HVPG was not associated with transplant-free survival, suggesting that HVPG may not have prognostic significance in the Fontan population.

The FALD literature is evolving, and as a result, only a few studies have reported HVPG data in this population. One of such studies is a cross-sectional study assessing the correlation between hepatic biomarkers and the severity of hepatic fibrosis in FALD. In that study, the median HVPG was 1 (range, 0-3) mm Hg, even though 42% of that cohort had cirrhosis. In another study, Hsia et al. compared subdiaphragmatic haemodynamic indices between 27 asymptomatic Fontan patients, 29 symptomatic Fontan patients, and 20 patients with biventricular circulation. The HVPG gradient was similar between the symptomatic and asymptomatic Fontan patients (mean HVPG, 1 mm Hg) but significantly lower in comparison with the control group of patients with biventricular circulation (mean HVPG, 3 mm Hg). These prior studies are consistent with our results showing that HVPG is typically not elevated in FALD regardless of the severity of fibrosis. In contrast to these prior studies, the current study provides novel data by demonstrating that HVPG had no diagnostic utility as shown by the lack of correlation with Fontan haemodynamics and liver disease severity and no prognostic utility as shown by the lack of correlation with transplant-free survival. These findings have important clinical implications that are addressed below.

HVPG is an important prognostic metric used in deciding on the timing of therapy, treatment response, and the need to intensify therapy in patients with viral or alcoholic cirrhosis. This practice is based on robust literature.
Table 1. Baseline characteristics (n = 56)

| Characteristic                        | Value     |
|---------------------------------------|-----------|
| Age (y)                               | 28 ± 7    |
| Age at Fontan operation (y)           | 6 (3-12)  |
| Male                                  | 31 (55%)  |
| Body surface area (m²)                | 1.8 ± 0.2 |
| Left ventricle                        | 38 (68%)  |
| Oxygen saturation (%)                 | 92 ± 2    |
| Patent fenestration (%)               | 4 (7%)    |
| Fontan connection                     |           |
| Arterio-pulmonary connection          | 21 (38%)  |
| Lateral tunnel/intra-atrial conduit   | 19 (34%)  |
| Extracardiac conduit                  | 16 (29%)  |
| Fontan-associated disease             |           |
| Atrial arrhythm                       | 29 (52%)  |
| Prior heart failure hospitalization   | 5 (9%)    |
| Thromboembolism                       | 5 (9%)    |
| Protein-losing enteropathy            | 2 (4%)    |
| Chronic kidney disease *              | 6 (11%)   |
| Echocardiography                      |           |
| Estimated ejection fraction (%)       | 50 ± 5    |
| Calculated ejection fraction * (%)    | 47 ± 6    |
| ≥ Moderate AVV regurgitation          | 6 (11%)   |
| Cardiac catheterization               |           |
| Fontan pressure (mm Hg)               | 16 ± 4    |
| PAWP (mm Hg)                          | 11 ± 4    |
| VEDP                                  | 12 ± 3    |
| PVR index (WU m²)                     | 2.1 ± 0.8 |
| Cardiac index (L/min/m²)              | 2.3 ± 0.4 |
| SVR index (WU m²)                     | 29 ± 6    |
| Systemic saturation (%)               | 92 ± 3    |
| Mixed venous saturation (%)           | 66 ± 7    |
| Mean arterial pressure (mm Hg)        | 81 ± 15   |

Data are presented as mean ± standard deviation, median (interquartile range), or number (%).

* Chronic kidney disease: creatinine clearance < 60 mL/min. Calculated ejection fraction: assessed using monoplane Simpson’s method.

Table 2. Liver data (n = 56)

| Characteristic                        | Value     |
|---------------------------------------|-----------|
| Liver haemodynamics                   |           |
| Free hepatic venous pressure (mm Hg) | 16 ± 4 (17 [14-19]) |
| Wedged hepatic venous pressure (mm Hg)| 17 ± 5 (18 [14-20]) |
| Hepatic venous pressure gradient (mm Hg) | 1.4 ± 0.3 (1 [0-2]) |
| Liver biopsy                          |           |
| Sinusoidal dilation                   | 56 (100%) |
| Sinusoidal fibrosis (categories 1-4)  | 56 (100%) |
| Portal fibrosis (categories 1-4)      | 54 (94%)  |
| Liver disease severity                |           |
| VAST (normal < 1) (n = 14)            | 2.3 ± 1.0 |
| APRI (normal < 0.3)                   | 0.5 ± 0.2 |
| Child-Pugh score (normal < 5)         | 6 ± 2     |
| MELD score (normal < 6)               | 13 ± 2    |
| MELD-XI score (normal < 11)           | 10 ± 2    |
| Liver function                        |           |
| AST (U/L) (normal 8-43)               | 39 (27-61) |
| ALT (U/L) (normal 7-45)               | 41 (29-76) |
| ALP (U/L) (normal 37-104)             | 92 (63-128)|
| Total bilirubin (mg/dL) (normal 0.1-1.2)| 1.3 (0.8-1.8) |
| Direct bilirubin (mg/dL) (normal 0-0.3)| 0.3 (0.1-0.6) |
| Albumin (g/dL) (normal 3.5-5.0)       | 3.9 (3.2-4.1) |
| Alpha-fetoprotein (ng/mL) (normal < 0.6)| 3 (1-7) |
| INR* (normal < 1.2)                   | 2.4 (1.8-2.9) |
| INR (normal < 1.2)                    | 1.3 (1.0-1.5) |
| Platelet (×10⁹/L) (normal 150-450)    | 153 (122-264) |

Data are presented as mean ± standard deviation and median (interquartile range).

ALP, alkaline phosphatase; ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; INR international normalized ratio; MELD, model for end-stage liver disease; MELD-XI, model of end-stage liver disease excluding INR; VAST, varices, ascites, splenomegaly, and thrombocytopenia.

* INR in all patients.

1 INR excluding patients receiving warfarin

the hepatic venous pressure (downstream pressure) is normal in these patients, there is an obligatory rise in portal venous pressure (upstream pressure) to maintain portal venous flow through the liver. HVPG is the pressure difference between “upstream pressure” and “downstream pressure,” and provides a measure of impedance to hepatic blood flow and an indirect measure of the severity of portal hypertension.1,12,18

In contrast, high central venous pressure is the hallmark of the Fontan physiology, and the central venous pressure is transmitted to the hepatic veins resulting in an increase in the “downstream pressure” (the so-called hepatic venous pressure gradient).1,12,18

Table 3. Correlation between HVPG and outcomes

| Characteristic                        | Value     |
|---------------------------------------|-----------|
| Liver fibrosis                        |           |
| Sinusoidal fibrosis                    | r = 0.31, P = 0.155 |
| Portal fibrosis                       | r = 0.36, P = 0.102 |
| Haemodynamics                         |           |
| Fontan pressure                       | r = 0.01, P = 0.858 |
| Disease severity score                |           |
| VAST                                  | r = 0.01, P = 0.644 |
| APRI                                  | r = 0.02, P = 0.287 |
| Child-Pugh score                      | r = 0.01, P = 0.516 |
| MELD score                            | r = 0.37, P = 0.083 |
| MELD-XI score                         | r = 0.24, P = 0.189 |
| Clinical outcomes                     |           |
| Transplant-free survival HR           | 0.87 (95% CI, 0.39-1.44), P = 3.56 |

APRI, aspartate aminotransferase to platelet ratio index; CI, confidence interval; HR, hazard ratio; HVPG, hepatic venous pressure; MELD, model for end-stage liver disease; MELD-XI, model of end-stage liver disease excluding international normalized ratio; r, correlation coefficient; VAST, varices, ascites, splenomegaly, and thrombocytopenia.

Demonstrating a strong correlation between HVPG and adverse outcomes, as well as a lower morbidity and mortality in patients showing a reduction in HVPG during therapy.1,12 Because there are no such studies conducted in the Fontan population, the management and risk stratification of patients with FALD are based on prognostic models derived from patients with other etiologies of cirrhosis. Although some of these prognostic models have been shown to predict clinical outcomes in the Fontan population,16,17 the current study calls attention to the potential limitations of using HVPG in clinical decision making in this population.

The poor diagnostic and prognostic performance of HVPG in patients with FALD observed in this study clearly contradicts the current literature endorsing its clinical utility in patients with other forms of cirrhosis. These observed differences in the role of HVPG may be related to fundamental differences in the haemodynamics and pathogenesis of FALD as compared with other forms of cirrhosis. Hepatic venous congestion and ischemic injury initiate and perpetuate chronic liver disease in Fontan patients (haemodynamics-based cirrhosis), whereas an inflammatory response is responsible for the pathogenesis in viral and alcoholic cirrhosis (inflammatory-based cirrhosis).1,12,18

In patients with inflammatory-based cirrhosis, there is hepatic structural remodelling in response to chronic inflammation, and this leads to high impedance to portal venous flow.1,12,18 Because
afterload).\textsuperscript{15,18,19} This unique physiology results in an adaptive change in the hepatic circulation that is characterized by less of the hepatic blood supply coming from the portal vein and more of the hepatic blood supply coming from the hepatic artery (the so-called arterIALIZation of hepatic blood supply or hepatic artery buffer response).\textsuperscript{18,20,21} Another potential mechanism that may confound the assessment and interpretation of HVPG is the presence of infranephric venous collaterals that has been reported in FALD and the presence of massive sinusoidal dilatation (the so-called congestive) that is universal in FALD.\textsuperscript{22} We postulated that normal HVPG values observed in FALD may be related to these adaptive changes in the setting of high “hepatic afterload.”

**Limitations**

The study was conducted in a selected cohort of adult Fontan patients undergoing cardiac catheterization at a referral center, and hence the population demographics may differ from that of patients at other centers. However, the hepatic venous haemodynamics reported in this study is consistent with the results of prior studies, suggesting that the current data can be generalized to other Fontan cohorts.

**Conclusions**

HVPG is not elevated in FALD even in the setting of cirrhosis, and it does not correlate with histologic and clinical liver disease risk scores. Furthermore, there was also no correlation between HVPG and transplant-free survival during follow-up. These results suggest the limited diagnostic and prognostic role of HVPG in the assessment and management of FALD. Because the prevalence of FALD continues to rise over time, there will be a complementary increase in the number of Fontan patients being referred for evaluation in the hepatology clinic. The current practice is to risk stratify these patients based on prognostic models derived from patients with other forms of cirrhosis; HVPG is one of them. This study highlights the potential pitfalls of using HVPG in this population.

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**Disclosures**

The authors have no conflicts of interest to disclose.

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