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Original Article

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,

RÉSUMÉ

Contexte : Le gradient de pression veineuse hépatique (GPVH) est une mesure de la pression portale et un paramètre permettant d'établir un pronostic chez les patients atteints de cirrhose virale ou alcoolique; on ne connaît toutefois pas son utilité en cas d'hépatopathie associée à une intervention de Fontan (FALD, pour *Fontan-associated liver disease*). Des données limitées semblent indiquer que les patients atteints d'une FALD ont un GPVH normal. En nous fondant sur les données disponibles, nous avons formulé l'hypothèse qu'il n'y a pas de lien entre le GPVH, la gravité de l'hépatopathie et la survie sans transplantation chez les patients atteints d'une FALD.

Méthodologie : Nous avons étudié rétrospectivement les dossiers de patients de la clinique Mayo ayant subi une intervention de Fontan ainsi qu'une biopsie hépatique et une évaluation du GPVH. Le GPVH a été obtenu en soustrayant la pression veineuse hépatique libre de la

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 or "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 $\leq$ 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

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Ethics Statement: The current research project adhered to ethical guidelines stipulated by the Mayo Clinic institutional review board.

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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.

Résultats : Chez les 56 patients de l'étude (âge moyen : 28 ± 7 ans), la pression dans le circuit de Fontan était de 16 ± 4 en moyenne et le GPVH, de 1,4 ± 0,3 mmHg (plage : 0 à 3) en moyenne. Une fibrose périsinusoïdale et une fibrose périportale étaient présentes chez 56 (100 %) et 54 (94 %) patients, respectivement; 18 (32 %) des patients répondaient aux critères diagnostiques d'une cirrhose. Il n'y avait pas de corrélation entre le GPVH et le degré de fibrose hépatique, ni entre le GPVH et aucun des scores de risque cliniques d'hépatopathie. Six (11 %) patients sont décédés et 2 (4 %) patients ont subi une transplantation cardiaque durant le suivi; aucun lien n'a été établi entre le GPVH et la survie sans transplantation.

Conclusions : Le GPVH n'est pas élevé chez les patients présentant une FALD même en cas de cirrhose, et il n'est pas corrélé avec la gravité de l'hépatopathie ni avec les résultats cliniques. Ces résultats semblent indiquer que l'utilité diagnostique et pronostique du GPVH dans la prise en charge de la FALD est limitée, et fait ressortir les écueils auxquels on pourrait se heurter en utilisant ce paramètre dans cette population de patients.

FALD.[4] This apparent dissociation between HVPG and FALD (ie, normal HVPG values in the setting of cirrhosis in Fontan patients) has not been systemically investigated. Of note, there are significant differences in the demographics, disease pathogenesis, and haemodynamics between FALD and other etiologies of cirrhosis.[1,3]

Because of the limited data showing normal HVPG values in patients with FALD, we hypothesized that there would be no association between HVPG and liver disease severity, haemodynamics, and clinical outcomes in patients with Fontan palliation.

Methods

Study population

We reviewed the Mayo Adult Congenital Heart Disease (MACHD) Registry and identified adult patients (aged $\geq$ 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 ($_{f}$HVP) and wedged hepatic venous pressure ($_{w}$HVP), 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.[13] 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 $_{f}$HVP and $_{w}$HVP. HVPG was calculated as $_{w}$HVP − $_{f}$HVP.

Assessment of liver disease severity and clinical outcomes

All liver biopsies were performed via the transvenous approach during cardiac catheterization as previously described.[14] 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.[2,4,14] Similar to previous studies,[4] 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 (F0-F3) vs those with cirrhosis (F4).

The following clinical liver disease risk scores were used for the assessment of liver disease severity:[8,10,14] (1) model for end-stage liver disease score; (2) model for end-stage liver

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 inlet left ventricle 15 (27%). The types of Fontan connection at the time of HVPG assessments were atriopulmonary Fontan 21 (38%), lateral tunnel/intra-atrial conduit 19 (34%), and extracardiac conduit 16 (29%). Of the 16 patients with extracardiac conduit, 11 initially had atriopulmonary Fontan but subsequently underwent conversion to extracardiac conduit Fontan before HVPG assessment. Two patients (4%) had hepatitis B, and no patient had hepatitis C.

The mean $_{f}$HVP was 16 ± 4 mm Hg (median, 17 [14-19] mm Hg) and the mean $_{w}$HVP was 17 ± 5 mm Hg (median, 18 [14-20] mm Hg). The mean HVPG was 1.4 ± 0.3 mm Hg (range, 0-3 mm Hg) (Table 2). Of the 56 patients, 56 (100%) had sinusoidal fibrosis, of whom 37 (66%) had severe sinusoidal fibrosis. Portal fibrosis was present in 54 (94%) patients, of whom 18 (32%) met the criteria for cirrhosis. There was no correlation between HVPG and sinusoidal fibrosis (OR, 1.17; 95% CI, 0.88-1.49; $P = 0.293$) and no correlation between HVPG and portal fibrosis (OR, 1.26; 95% CI, 0.75-1.66; $P = 0.328$). A prespecified analysis was performed assessing the correlation between HVPG and liver fibrosis, and in this analysis, the liver fibrosis stages were modelled as continuous variables. Based on this analysis, there was no correlation between HVPG and sinusoidal fibrosis ($r = 0.31$, $P = 0.155$) and between HVPG and portal fibrosis (0.36, $P = 0.102$) (Table 3).

The mean Fontan pressure was 16 ± 4 (median, 17 [13-19]) mm Hg, and the mean gradient between the hepatic vein and the Fontan conduit or right atrium ($_{f}$HVP minus Fontan pressure) was 0.8 ± 0.6 mm Hg. The clinical liver disease risk scores and liver function test data are shown in Table 2. There was no correlation between HVPG and Fontan pressure ($r = 0.01$, $P = 0.858$) and between HVPG and the clinical liver disease risk scores (Table 3).

The median duration of follow-up from the time of HVPG assessment was 6.3 (2.2-9.4) years. During this period, 6 (11%) patients died and 2 (4%) patients underwent heart transplant. The cause of death was postoperative (n = 2), heart failure (n = 3), and multifactorial (n = 1). HVPG was not associated with transplant-free survival (hazard ratio, 0.87; 95%, CI 0.39-1.44; $P = 3.56$) (Table 3).

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.[4,15] One of such studies is a cross-sectional study assessing the correlation between hepatic biomarkers and the severity of hepatic fibrosis in FALD.[4] In that study, the median HVPG was 1 (range, 0-3) mm Hg, even though 42% of that cohort had cirrhosis.[4] In another study, Hsia et al.[15] 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.[9-12] This practice is based on robust literature

Table 1. Baseline characteristics (n = 56)

Age (y)	28 ± 7
Age at Fontan operation (y)	6 (3-12)
Male	31(55%)
Body surface area (m^2)	1.8 ± 0.2
Left ventricle	38 (68%)
Oxygen saturation (%)	92 ± 2
Patent fenestration	4 (7%)
Fontan connection	
Atriopulmonary connection	21 (38%)
Lateral tunnel/intra-atrial conduit	19 (34%)
Extracardiac conduit	16 (29%)
Fontan-associated disease	
Atrial arrhythmia	29 (52%)
Prior heart failure hospitalization	5 (9%)
Thromboembolism	5 (9%)
Protein-losing enteropathy	2 (4%)
Chronic kidney disease*	6 (1%)
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 m^2)	2.1 ± 0.8
Cardiac index (L/min/m^2)	2.3 ± 0.4
SVR index (WU m^2)	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 (%).

AVV, atrioventricular valve; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; VEDP, ventricular end-diastolic pressure.

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

Table 2. Liver data (n = 56)

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 ($\times 10^9$/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.

†INR excluding patients receiving warfarin

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.[9-12] 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).[1,18]

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 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

Table 3. Correlation between HVPG and outcomes

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.

afterload).[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).[18,20,21] Another potential mechanism that may confound the assessment and interpretation of HVPG is the presence of intrahepatic venovenous collaterals that has been reported in FALD and the presence of massive sinusoidal dilatation (the so-called congestive) that is universal in FALD.[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 centre, and hence the population demographics may differ from that of patients at other centres. 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.

References

1. Rychik J, Veldtman G, Rand E, et al. The precarious state of the liver after a Fontan operation: summary of a multidisciplinary symposium. Pediatr Cardiol 2012;33:1001-12.
2. Johnson JA, Cetta F, Graham RP, et al. Identifying predictors of hepatic disease in patients after the Fontan operation: a postmortem analysis. J Thorac Cardiovasc Surg 2013;146:140-5.
3. Greenway SC, Crossland DS, Hudson M, et al. Fontan-associated liver disease: implications for heart transplantation. J Heart Lung Transplant 2016;35:26-33.
4. Wu FM, Earing MG, Aboulhosn JA, et al. Predictive value of biomarkers of hepatic fibrosis in adult Fontan patients. J Heart Lung Transplant 2017;36:211-9.
5. Wu FM, Opotowsky AR, Raza R, et al. Transient elastography may identify Fontan patients with unfavorable hemodynamics and advanced hepatic fibrosis. Congenit Heart Dis 2014;9:438-47.
6. Wu FM, Kogon B, Earing MG, et al. Liver health in adults with Fontan circulation: a multicenter cross-sectional study. J Thorac Cardiovasc Surg 2017;153:656-64.
7. Lindsay I, Johnson J, Everitt MD, Hoffman J, Yetman AT. Impact of liver disease after the Fontan operation. Am J Cardiol 2015;115:249-52.
8. Elder RW, McCabe NM, Hebson C, et al. Features of portal hypertension are associated with major adverse events in Fontan patients: the VAST study. Int J Cardiol 2013;168:3764-9.
9. D'Amico G, Garcia-Pagan JC, Luca A, Bosch J. Hepatic vein pressure gradient reduction and prevention of variceal bleeding in cirrhosis: a systematic review. Gastroenterology 2006;131:1611-24.
10. Kamath PS, Kim WR; Advanced Liver Disease Study Group. The model for end-stage liver disease (MELD). Hepatology 2007;45:797-805.
11. Ripoll C, Banares R, Rincon D, et al. Influence of hepatic venous pressure gradient on the prediction of survival of patients with cirrhosis in the MELD Era. Hepatology 2005;42:793-801.
12. Groszmann RJ, Wongcharatrawee S. The hepatic venous pressure gradient: anything worth doing should be done right. Hepatology 2004;39:280-2.
13. Egbe AC, Connolly HM, Miranda WR, et al. Hemodynamics of Fontan failure: the role of pulmonary vascular disease. Circ Heart Fail 2017;10:e004515.
14. Poterucha JT, Johnson JN, Qureshi MY, et al. Magnetic resonance elastography: a novel technique for the detection of hepatic fibrosis and hepatocellular carcinoma after the Fontan operation. Mayo Clin Proc 2015;90:882-94.
15. Hsia TY, Khambadkone S, Deanfield JE, et al. Subdiaphragmatic venous hemodynamics in the Fontan circulation. J Thorac Cardiovasc Surg 2001;121:436-47.
16. Assenza GE, Graham DA, Landzberg MJ, et al. MELD-XI score and cardiac mortality or transplantation in patients after Fontan surgery. Heart 2013;99:491-6.
17. Egbe A, Miranda WR, Connolly HM, et al. Temporal changes in liver stiffness after Fontan operation: results of serial magnetic resonance elastography. Int J Cardiol 2018;258:299-304.
18. Daniels CJ, Bradley EA, Landzberg MJ, et al. Fontan-associated liver disease: Proceedings from the American College of Cardiology Stakeholders Meeting, October 1 to 2, 2015, Washington DC. J Am Coll Cardiol 2017;70:3173-94.
19. Gewillig M, Brown SC. The Fontan circulation after 45 years: update in physiology. Heart 2016;102:1081-6.
20. Yoo SJ, Prsa M, Schantz D, et al. MR assessment of abdominal circulation in Fontan physiology. Int J Cardiovasc Imaging 2014;30:1065-72.
21. Bryant T, Ahmad Z, Millward-Sadler H, et al. Arterialised hepatic nodules in the Fontan circulation: hepatico-cardiac interactions. Int J Cardiol 2011;151:268-72.
22. Velpula M, Sheron N, Guha N, et al. Direct measurement of portosystemic gradient in a failing Fontan circulation. Congenit Heart Dis 2011;6:175-8.