Imaging Assessment of Hepatic Changes after Fontan Surgery

Computed Tomography, Ultrasonography, and Transient Elastography

Jinyoung Song,^{1,*} MD, Kyunghye Kim,^{2,*} MD, June Huh,¹ MD, I-Seok Kang,¹ MD, Sung Hoon Kim,³ MD, Ji-Hyuk Yang,⁴ MD, Tae Gook Jun,⁴ MD and Ji Hye Kim,⁵ MD

Summary

The aim of this study was to evaluate hepatic dysfunction over 10 years following Fontan surgery. We assessed the clinical usefulness of diagnostic tools for the detection and follow-up of hepatic dysfunction in patients with Fontan circulation.

A total of 26 post-Fontan patients (median age 13 years, range 10-35 years; median duration from Fontan procedure 10.5 years, range 4-17 years) were enrolled in this study. Hepatic assessment was performed by ultrasonography, computed tomography (CT), and transient elastography (TE) with biochemical tests, echocardiography, and cardiac catheterization. Related parameters were compared on the basis of different findings in liver sonography, CT, and TE.

Liver CT and TE showed abnormal findings in all patients. Liver ultrasonography revealed abnormal results in 24 patients (92.3%). However, liver function test was normal and did not correlate with imaging studies. C-reactive protein was significantly correlated with severity of CT findings. White blood cell, platelet count, and N-terminal pro-brain natriuretic peptide were correlated with severity on TE. Post-Fontan high pulmonary vascular resistance ($P = 0.046$) and high mean pulmonary artery pressure ($P = 0.046$) correlated with hepatic changes on liver CT.

Changes in the liver post-Fontan surgery are common and occur even after 10 years the procedure. Liver imaging is more sensitive, and CT seems to be more useful for differentiation of severe hepatic changes.

(Int Heart J 2018; 59: 1008-1014)

Key words: Fontan procedure, Hepatic dysfunction

First described in 1971, the Fontan operation is now used widely for patients with single-ventricle physiology.¹⁾ Since the first description of hepatic fibrosis after the Fontan operation in 1981,²⁾ several studies have described high-grade hepatic fibrosis and hepatic cirrhosis in this population. The proposed mechanisms of hepatic injury and the resulting sinusoidal fibrosis include increased central and portal venous pressure, decreased cardiac output, and flow reversal in the hepatic veins. These changes can cause hepatic injury through hypoxia, chronic congestion, and stimulation of the fibrotic response.³⁾ A recent study reported that portal fibrosis can occur before the Fontan operation from pre-Fontan insults.⁴⁾ However, the pathophysiology of hepatic changes after Fontan operation and the risk factors remain to be investigated. Liver biopsy has been the standard method for the assessment of liver problems but is invasive and costly and has possible complications. Standard imaging

tools for hepatic dysfunction after Fontan operation have not been clearly established. Recent data indicate that ultrasonography can identify Fontan-associated liver disease before biochemical hepatic dysfunction.⁵⁾ Transient elastography (TE) is a newer tool that has been used for staging of hepatic fibrosis in adults.^{6,7)} Several studies have examined whether TE can be used to evaluate Fontan circulation.

This study aimed to investigate the hepatic dysfunction after Fontan operation and to evaluate the clinical usefulness of imaging tools of liver ultrasonography, liver computed tomography (CT), and TE.

Methods

This is a retrospective study based on the review of medical records. A total of 26 post-Fontan patients were enrolled in this study. The patients were hospitalized for

From the ¹Department of Pediatrics, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, ²Department of Pediatrics, Hongseong Medical Center, Hongseonggun Chungcheongnamdo, Republic of Korea, ³Department of Pediatrics, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwonsi Kyungsangnamdo, Republic of Korea, ⁴Department of Thoracic Surgery, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea and ⁵Department of Radiology and Center for Imaging Science, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea.

*These authors contributed equally to this study.

Address for correspondence: June Huh, MD, Department of Pediatrics, Division of Cardiology, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Irwon-ro 81, Gangnam-gu, Seoul, 06351, Republic of Korea. E-mail: herzhuh@skku.edu or herzhuh@gmail.com or herzhuh@samsung.com

Received for publication June 23, 2017. Revised and accepted August 9, 2017.

Released in advance online on J-STAGE August 29, 2018.

doi: 10.1536/ihj.17-349

All rights reserved by the International Heart Journal Association.

the investigation of hemodynamic status and hepatic function associated with Fontan physiology at about 10 years after Fontan operation. We confirmed negative for viral hepatitis and other hepatic congenital or metabolic problems prior to this investigation. All the investigations were performed over 2 or 3 days. Liver ultrasonography, liver CT, and TE were performed with physical examination, biochemical tests, and echocardiography (Vivid E9, GE Healthcare) 1 day prior to cardiac catheterization. Liver ultrasonography was performed by one specialized radiologist, and other radiological images were interpreted by specialized doctors. Regarding Fontan operation, extracardiac Fontan operation with fenestration was performed for all patients except for one patient, who underwent an adjustable fenestrated Fontan operation. Fenestrations were closed in 22 patients by device closure on catheterization (19 patients) or spontaneously (3 patients). Only four patients demonstrated patent fenestration flow.

This study was approved with waiver of consent by the Ethics Committee of the institute.

Imaging tools for hepatic changes:

Liver ultrasonography All patients underwent liver ultrasonography (Sequoia, Siemens Healthcare, Erlangen, Germany; LOGIQ E9, GE Healthcare, Waukesha, WI, USA). Chronic parenchymal liver disease (CPLD) was defined as a heterogeneous parenchymal echotexture. Fibrosis and liver cirrhosis (LC) were defined as contour nodularity, blunt margins, right hepatic atrophy, and caudate or left hepatic lobe hypertrophy on ultrasonography.^{5,8)} Signs of portal hypertension and extrahepatic manifestation of fibrosis or LC were determined by splenomegaly or ascites.^{9,10)}

Liver CT Liver CT was performed with multidetector CT (Light-Speed 16, GE Healthcare, Milwaukee, WI, USA). On the basis of CT findings, CPLD was defined as abnormal contrast enhancement (mosaic or reticular patterns) and nodules (benign focal nodular hyperplasia). LC was defined similarly as ultrasonography findings—contour nodularity, blunt margins, right hepatic lobe atrophy, caudate or left hepatic lobe hypertrophy, and extrahepatic manifestations of portal hypertension (enlarged spleen and enlarged portal vein).⁸⁾

Transient elastography Liver stiffness was measured by TE (Fibroscan[®], Echosens, France). All liver stiffness measurements (LSM) were obtained according to the instructions provided by the manufacturer. LSM was performed on the right lobe of the liver through the intercostal spaces on patients lying in the dorsal decubitus position with the right arm in maximal abduction. The results are expressed in kilopascals (kPa). The extent of liver fibrosis was classified according to the METAVIR scoring system (F0 = no fibrosis, F1 = portal fibrosis, F2 = bridging fibrosis with few septa, F3 = bridging fibrosis with many septa, F4 = cirrhosis). TE cutoff levels used for staging liver fibrosis $\geq$ F2, $\geq$ F3, and F4 were 8.8, 10.2, and 14.1 kPa, respectively.^{6,7)}

Statistical analysis: Statistical analysis was performed using Spearman's correlation coefficient to assess relationships between liver fibrosis and variable parameters. Kruskal-Wallis test was used for comparing related factors in ultrasonography and CT. Fisher's exact test was per-

formed to assess differences among imaging tools. Statistical Package for the Social Sciences (SPSS) 21.0 software program (Chicago, IL, USA) was used for data analysis. A *p* value of less than 0.05 was considered significant.

Results

Baseline characteristics: Baseline characteristics and biochemical and hemodynamic profiles are shown in Table I.

Demographic characteristics Of the 26 enrolled patients, 17 were male and 9 were female. Median age at investigation was 13.0 years (10.0–35.0 years). Mean duration from Fontan operation to investigation was 10.5 years (4.0–17.0 years). The morphology of single ventricle was right ventricle type in 7 patients, left ventricle type in 11 patients, and undetermined type in 8 patients. Eighteen patients underwent staged operation for single-ventricle morphology. The first stage operation was modified BT shunt in 13 patients, pulmonary artery banding in 5 patients, and subsequent bidirectional cavopulmonary shunt (BCPS) in all 18 patients. Six patients skipped over the first stage operation and underwent BCPS as the first operation. Two patients underwent one-stage Fontan operation. Mean age at Fontan operation was 3.6 years (1.0–29.0 years). Four patients required pacemaker implantation because of conduction problems.

Laboratory biochemical tests The levels of liver enzymes were within normal range in all patients, as were protein (6.0–8.2 g/dL) and albumin (3.5–5.2 g/dL). Total bilirubin was slightly elevated in 3 patients. γ -Glutamyltransferase (γ -GT) was elevated in 17 patients. White blood cell (WBC) counts were within normal range in all but 3 patients. Platelet count was within normal range in all but 1 patient with a value of 122,000 / μ L. C-reactive protein (CRP) was elevated in 2 patients. The coagulation profile was not included because several patients were taking an anticoagulant for arrhythmia or coagulopathy. N-terminal pro-brain natriuretic peptide (NT-proBNP) level was abnormal only in 3 patients.

Hemodynamic data Echocardiography showed preserved systemic ventricular function in all patients (ejection fraction, $56.7 \pm 8.5\%$). Systemic atrioventricular valve regurgitation was found to be minimal in 14 patients, mild in 6 patients, and moderate to severe in 6 patients. Based on the cardiac catheterization just before the Fontan operation, mean pulmonary artery pressure (mPAP) was 9.7 mmHg (range 6.0–16.0 mmHg), and mean pulmonary vascular resistance (PVR) was 2.1 indexed Wood units (range 1.1–4.6 indexed Wood units). At the time of this investigation, the mean arterial oxygen saturation was 94.7% (range 91.5–98.0%), mPAP was 12.8 ± 2.3 mmHg (range 8.0–18.0 mmHg), PVR was 1.5 ± 0.7 indexed Wood units (range 0.6–2.9 indexed Wood units), and ventricular end diastolic pressure was 10.6 ± 2.9 mmHg (range 4.0–17.0 mmHg).

Comparisons of imaging tools: Figure 1 presents various degrees of hepatic changes from CT and ultrasonography that were compared with LSM evaluated by TE in two patients who underwent Fontan operation around 10 years ago.

Table I. Laboratory and Hemodynamic Data

	Patients' values*	Normal values
Laboratory test		
WBC (/μL)	7727 ± 3846	3800-10580
Hemoglobin (g/dL)	15.4 ± 0.8	13.6-17.4 (M) /11.2-14.8 (F)
Platelet (10 ³ /mL)	214.5K ± 63.8K	138-347
Bilirubin (mg/dL)	0.9 ± 0.7	0.2-1.5
AST (IU/L)	25.9 ± 5.7	0-40
ALT (IU/L)	22.8 ± 6.7	0-40
NT-proBNP (pg/mL)	83.0 ± 105.2	0-153
CRP (mg/dL)	0.2 ± 0.3	0-0.3
γ-GT (U/L) (<i>n</i> = 18)	69.7 ± 33.9	21-31
AFP (ng/mL) (<i>n</i> = 20)	2.5 ± 1.3	0-8.1
Hemodynamics		
mPAP (mmHg)	12.8 ± 2.4	
mRA pre (mmHg)	9.6 ± 3.8	
TPG (mmHg)	4.2 ± 1.7	
PVRI (Wood units.m ²)	1.5 ± 0.7	
HVP (mmHg)	13.4 ± 2.4	
HWP (mmHg)	14.6 ± 2.7	
THPG (mmHg)	1.4 ± 0.7	
VEDP (mmHg)	10.6 ± 3.0	
SPO2 (%)	94.7 ± 1.7	

*Mean ± standard deviation. WBC indicates white blood cell; AST, aspartate transaminase; ALT, alanine transaminase; NT-proBNP, N-terminal pro-brain natriuretic peptide; CRP, C-reactive protein; γ-GT, γ-glutamyltransferase; AFP, alpha-fetoprotein; mPAP, mean pulmonary artery pressure; mRA pre, mean right atrium pressure before Fontan operation; TPG, transpulmonary pressure gradient; PVRI, indexed pulmonary vascular resistance; HVP, hepatic pressure; HWP, hepatic wedge pressure; THPG, transhepatic pressure gradient; and VEDP, ventricular end diastolic pressure.

Liver ultrasonography All patients underwent liver ultrasonography, and 24 patients (92%) had abnormal ultrasound findings that were classified as CPLD. No patient had cirrhotic change demonstrated by liver ultrasonography. There were no differences between patients with normal and abnormal ultrasonographic findings.

Liver CT Nineteen patients underwent liver CT. All patients had abnormal CT findings, compatible with CPLD in 13 patients and with LC in 6 patients. There were no cases of hepatocellular carcinoma. Table II shows the differences in related clinical factors between patients with CPLD and those with LC on liver CT. All biochemical tests for liver function showed normal findings and did not prove any correlate with CT findings. However, CRP in patients with LC was significantly higher than that in the other patients (0.04 ± 0.02 versus 0.49 ± 0.61 , $P = 0.046$).

For hemodynamic parameters, although transhepatic pressure (HP) gradient, ventricular EDP, and RA pressure before Fontan operation were not different between patients with CPLD and LC on liver CT, mean PA and PVR were significantly higher in the LC group (12.07 ± 1.75 versus 14.50 ± 2.73 and 1.35 ± 0.70 versus 2.08 ± 0.54 , $P = 0.046$).

Transient elastography All 26 patients showed abnormal results in TE (18.2 ± 3.3 kPa). Compared with the reference range of hepatitis B or hepatitis C, all patients were in hepatic fibrosis stage (stage 2 in 1 patient, stage 3 in 3 patients, and stage 4 in 22 patients). The extent of liver fi-

brosis had a significant correlation with WBC ($r = -0.48$, $P = 0.025$) and platelet count ($r = -0.47$, $P = 0.022$) and NT-proBNP ($r = 0.49$, $P = 0.019$) (Figure 2), whereas no significant correlations with age of investigation, time from Fontan operation, mean PAP, PVR, CRP, and albumin level were proved ($P > 0.05$).

Discussion

Our study revealed that all patients had abnormal results on liver imaging studies despite normal results from liver function tests. Although liver ultrasonography and TE showed hepatic changes after Fontan operation, liver CT seems to be more useful to differentiate liver parenchymal disease and cirrhosis in asymptomatic Fontan patients.

Many previous reports have focused on hepatic dysfunction after Fontan operation. Ghaferi, *et al.*¹¹⁾ reported that chronically increased hepatic venous pressure from Fontan surgery might lead to chronic passive congestion, cardiac cirrhosis, hepatic adenoma, and hepatocellular carcinoma, although our data showed no significant correlation with HP or fibrotic change. As chronic liver disease progresses, hepatic fibrosis is accompanied by the formation of septae and nodules that interfere with the portal blood flow, leading to portal hypertension and formation of the distinctive cirrhotic architecture.¹²⁾ The histologic changes identified on liver biopsy of adult Fontan patients are similar to those that occur with chronic passive liver

Figure 1. Comparisons of ultrasonography, computed tomography, and TE of two patients. **A, B:** A 13-year-old boy, 10 years after Fontan procedure: liver ultrasound showed normal size with scattered small echogenic nodules and coarse echogenicity that was compatible with chronic parenchymal changes (**A**). CT showed no focal lesions but chronic hepatic parenchymal changes. LSM (TE) of this patient was 17.3 kPa (**B**). **C, D:** An 11-year-old boy, 6 years after Fontan procedure: liver ultrasonography showed several hyperechoic nodular lesions and peri-portal echogenic thickening that suggested chronic liver disease (**C**). CT showed severe hepatic congestion and surface nodularity which was compatible with liver cirrhosis after Fontan operation. LSM (TE) of this patient was 18.0 kPa (**D**). CT, computed tomography; LSM, liver stiffness measurements; TE, transient elastography

congestion due to right-side heart failure.^{3,11} Several factors have been shown to be associated with hepatic complications in the Fontan group.^{3,11,13,14} Duration of Fontan circulation, Fontan type, decreased ventricular function, absence of initial fenestration, thrombus in Fontan tract, and arrhythmia were considered as risk factors, but duration after Fontan operation was the only significant factor in multivariate analysis.³ Hepatic dysfunction correlated with the duration of Fontan circulation in several other studies.^{15,16} Camposilvan, *et al.*¹⁴ reported that liver dysfunction over the long term is correlated with reduced cardiac index after Fontan operation. The reversibility of hepatic dysfunction has not been known even though Fontan hemodynamics might be getting better with several pulmonary vasodilators¹⁷ and cardiac synchronization.¹⁸ The findings of liver ultrasonography may be dependent on the skill of the operator, as they may not exactly reflect the whole liver parenchymal injury. Two cases in our study had normal liver ultrasonography findings but liver CT findings compatible with CPLD.

In our study, the group with CT findings of cirrhosis (or fibrosis) showed higher mPAP and PVR than the group with CPLD findings at the last follow-up after Fontan operation. CT findings were not related to HP or hepatic wedge pressure (HWP) at the last follow-up study.

Our results are similar to the findings of Fred, *et al.*¹⁹ which showed no significant positive correlation between fibrosis and HP. However, Kiesewetter, *et al.*³ reported that HP and HWP were related to hepatic fibrosis in liver biopsy. High RA pressure, high PVR, and high PAP before Fontan operation seemed to be unrelated to liver damage after the Fontan operation. It is already known that a certain time is required for hepatic changes. Our study was a cross-sectional study performed over 10 years in patients after Fontan operation. Even young patients showed hepatic changes just 10 years after Fontan operation. Hepatic changes seem to develop earlier than expected, necessitating aggressive follow-up.

The usefulness of TE for viral hepatitis in children and adults is accepted.²⁰ In our study, TE yielded abnormal results in Fontan patients, and the value of LSM was very high. Yoo, *et al.*²¹ reported that the LSM of TE in Fontan circulation is strikingly greater than the normal range (<5.5 kPa) and also higher than that of patients with right-side heart failure. Therefore, there is a limitation in applying the value of LSM from patients with viral hepatitis patients to the Fontan circulation because of the lack of sufficient data from a large-scale study in Fontan patients. Although TE could not accurately reflect the degree of liver dysfunction, it is still a useful tool for follow-up,

Table II. Comparisons the Laboratory Data and Hemodynamic Data between Chronic Parenchymal Liver Disease Group and Liver Cirrhosis Group Based on CT Findings

	CPLD (<i>n</i> = 13)	LC (<i>n</i> = 6)	<i>P</i>
Laboratory test			
WBC (/μL)	6851 ± 1366	10290 ± 4158	0.106
Hemoglobin (g/dL)	15.41 ± 0.81	15.38 ± 1.11	0.898
Platelets (10 ³ /mL)	220 ± 75	219 ± 46	0.579
AST (IU/L)	25.6 ± 5.6	24.8 ± 7.3	0.831
ALT (IU/L)	24.1 ± 7.1	21.6 ± 6.5	0.701
Bilirubin (mg/dL)	0.81 ± 0.91	0.78 ± 0.43	0.553
Protein (g/dL)	7.0 ± 0.4	7.1 ± 0.3	0.410
Albumin (g/dL)	4.7 ± 0.3	4.7 ± 0.2	0.890
NT-proBNP (pg/mL)	96.6 ± 143.8	50.2 ± 16.2	0.416
CRP (mg/dL)	0.04 ± 0.02	0.49 ± 0.61	0.046
AFP (mg/dL)	2.3 ± 0.8	2.0 ± 0.7	0.525
γ-GT (mg/dL)	71.5 ± 37.4	73.3 ± 27.1	0.660
Hemodynamics			
HVP (mmHg)	12.6 ± 1.8	14.5 ± 3.0	0.179
HWP (mmHg)	13.6 ± 1.9	16.0 ± 3.3	0.106
TPG (mmHg)	1.15 ± 0.55	1.50 ± 0.54	0.323
mPAP (mmHg)	12.07 ± 1.75	14.50 ± 2.73	0.046
mRA pre (mmHg)	8.46 ± 3.43	8.16 ± 2.13	0.966
PVRI (Wood units.m ²)	1.35 ± 0.70	2.08 ± 0.54	0.046
VEDP (mmHg)	10.0 ± 3.5	12.1 ± 1.7	0.152

WBC indicates white blood cell; AST, aspartate transaminase; ALT, alanine transaminase; NT-proBNP, N-terminal pro-brain natriuretic peptide; CRP, C-reactive protein; γ-GT, γ-glutamyltransferase; AFP, alpha-fetoprotein; HVP, hepatic pressure; HWP, hepatic wedge pressure; TPG, transpulmonary pressure gradient; PVRI, indexed pulmonary vascular resistance; mPAP, mean pulmonary artery pressure; mRA pre, mean right atrium pressure before Fontan operation; THPG, transhepatic pressure gradient; and VEDP, ventricular end diastolic pressure.

considering the simplicity of the test. Wu, *et al.*²²⁾ reported that TE was significantly correlated with Fontan pressure and cardiac index. High LSM on TE can be a guide for identifying Fontan patients requiring invasive study. In our study, WBC and platelet count and NT-proBNP level correlated with LSM severity. Inflammation may be related to liver dysfunction in Fontan circulation, and the high CRP level in the LC group in our study appears to support this. Similar to the data of Wu, *et al.*,²²⁾ LSM severity on TE was correlated with low platelet count in our study. Thrombocytopenia is known to be a characteristic feature of chronic liver disease and cirrhosis.²³⁾

In our study, laboratory findings associated with liver function (liver enzyme, platelet count, and bilirubin) were normal, but γ-GT was higher in all except one patient. Kaulitz, *et al.*²⁴⁾ reported similar findings of correlations between hepatic changes and ventricular EDP and mPAP. Hepatic transaminase often remains normal despite the presence of significant hepatic derangement.²⁵⁾ Liver function studies as a follow-up tool after Fontan operation have limitations, and data suggest that an imaging study is required.^{19,25,26)}

Because liver changes develop earlier in single-ventricle physiology, especially after Fontan operation, early detection of hepatic changes is important. Although TE and liver ultrasonography are noninvasive and feasible methods to detect hepatic changes, liver CT is more useful for evaluating objective hepatic changes and their pro-

gression.

Limitation: Our study has the limitations of a retrospective study and of small sample size. Consequently, we could not perform multivariable regression analysis, and it is difficult to ensure the accuracy of risk factors of liver dysfunction. Additional study with a larger study population is considered necessary. TE has been studied and validated in patients with hepatitis B and hepatitis C but has not been validated in the Fontan population. In spite of these limitations, analysis of the image is relatively important because liver biopsy is often not possible in a patient with liver disease associated with Fontan circulation.

Conclusions

Fontan circulation is known to be associated with high risk of hepatic dysfunction. Because biochemical liver function testing has limitations, various imaging tools should be considered for early detection of hepatic dysfunction even in early period after Fontan operation. Even though liver ultrasonography and TE may be recommendable for initial screening and follow-up, liver CT seems to be a better tool for differentiating serious hepatic dysfunction such as LC.

Figure 2. Significant correlations between the extent of liver fibrosis on TE and WBC count (A), platelet count (B), and NT-pro BNP level (C). TE, transient elastography; WBC, white blood cell

Disclosures

Conflicts of interest: None.

References

- Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax* 1971; 26: 240-8.
- Stanton RE, Lurie PR, Lindesmith GG, Meyer BW. The fontan procedure for tricuspid atresia. *Circulation* 1981; 64: II140-6.
- Kiesewetter CH, Sheron N, Vettukattil JJ, *et al.* Hepatic changes in the failing Fontan circulation. *Heart* 2007; 93: 579-84.
- Schwartz MC, Sullivan L, Cohen MS, *et al.* Hepatic pathology may develop before the Fontan operation in children with functional single ventricle: an autopsy study. *J Thorac Cardiovasc Surg* 2012; 143: 904-9.
- Bae JM, Jeon TY, Kim JS, *et al.* Fontan-associated liver disease: Spectrum of US findings. *Eur J Radiol* 2016; 85: 850-6.
- Sandrin L, Fourquet B, Hasquenoph JM, *et al.* Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol* 2003; 29: 1705-13.
- Kim BK, Kim SU, Kim HS, *et al.* Prospective validation of FibroTest in comparison with liver stiffness for predicting liver fibrosis in Asian subjects with chronic hepatitis B. *PLoS One* 2012; 7: e35825.
- Kudo M, Zheng RQ, Kim SR, *et al.* Diagnostic accuracy of imaging for liver cirrhosis compared to histologically proven liver cirrhosis. A multicenter collaborative study. *Intervirol* 2008; 51 Suppl 1: 17-26.
- Aube C, Oberti F, Korali N, *et al.* Ultrasonographic diagnosis of hepatic fibrosis or cirrhosis. *J Hepatol* 1999; 30: 472-8.
- Tchelepi H, Ralls PW, Radin R, Grant E. Sonography of diffuse liver disease. *J Ultrasound Med* 2002; 21: 1023-32; quiz 1033-4.
- Ghaferi AA, Hutchins GM. Progression of liver pathology in patients undergoing the Fontan procedure: Chronic passive congestion, cardiac cirrhosis, hepatic adenoma, and hepatocellular carcinoma. *J Thorac Cardiovasc Surg* 2005; 129: 1348-52.
- Baek JS, Bae EJ, Ko JS, *et al.* Late hepatic complications after Fontan operation; non-invasive markers of hepatic fibrosis and risk factors. *Heart* 2010; 96: 1750-5.
- Kendall TJ, Stedman B, Hacking N, *et al.* Hepatic fibrosis and cirrhosis in the Fontan circulation: a detailed morphological study. *J Clin Pathol* 2008; 61: 504-8.
- Camposilvan S, Milanese O, Stellin G, Pettenazzo A, Zancan L, D'Antiga L. Liver and cardiac function in the long term after Fontan operation. *Ann Thorac Surg* 2008; 86: 177-82.
- Baranova A, Lal P, Birendine A, Younossi ZM. Non-invasive markers for hepatic fibrosis. *BMC Gastroenterol* 2011; 11: 91.
- Wallihan DB, Podberesky DJ. Hepatic pathology after Fontan palliation: spectrum of imaging findings. *Pediatr Radiol* 2013; 43: 330-8.
- Ono Y, Mitsushita N. Case studies of patients successfully and unsuccessfully managed pre- and post-Fontan procedure. *Int Heart J* 2015; 56 Suppl: S31-4.
- Goto S, Nakamura M, Itatani K, *et al.* Synchronization of the flow and pressure waves obtained with non-simultaneous multipoint measurements. *Int Heart J* 2016; 57: 449-55.
- Wu FM, Jonas MM, Opatowsky AR, *et al.* Portal and centrilobular hepatic fibrosis in Fontan circulation and clinical outcomes. *J Heart Lung Transplant* 2015; 34: 883-91.
- Lee CK, Perez-Atayde AR, Mitchell PD, Raza R, Afdhal NH, Jonas MM. Serum biomarkers and transient elastography as predictors of advanced liver fibrosis in a United States cohort: the Boston children's hospital experience. *J Pediatr* 2013; 163:

- 1058-64 e2.
21. Yoo BW, Choi JY, Eun LY, Park HK, Park YH, Kim SU. Congestive hepatopathy after Fontan operation and related factors assessed by transient elastography. *J Thorac Cardiovasc Surg* 2014; 148: 1498-505.
 22. Wu FM, Opatowsky 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.
 23. Witters P, Freson K, Verslype C, *et al.* Review article: blood platelet number and function in chronic liver disease and cirrhosis. *Aliment Pharmacol Ther* 2008; 27: 1017-29.
 24. Kaulitz R, Haber P, Sturm E, Schafer J, Hofbeck M. Serial evaluation of hepatic function profile after Fontan operation. *Herz* 2014; 39: 98-104.
 25. 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.
 26. 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.