Hepatic pathology in patients after Fontan operation: A computed tomography imaging study

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Abstract

Background: Hepatic dysfunction is an important long-term complication in Fontan patients. The purpose of this study was to evaluate the hepatic computed tomography (CT) findings after Fontan surgery and identify their association with clinical parameters.

Methods: This study recruited 43 patients (23 male and 20 female patients aged 15.3 ± 6.8 years), who underwent Fontan surgery. Medical records were reviewed to collect their age, sex, congenital heart disease type, date of Fontan surgery, laboratory data, and hepatic CT findings. The relationship between hepatic findings and clinical parameters was analyzed.

Results: The follow-up duration was 6.8 ± 4.1 years. Abnormal hepatic parenchymal enhancement was observed in 77% of the patients, with mild degree in 18, moderate degree in 10, and severe degree in 5 patients. According to the univariate analysis, risk factors for hepatic parenchymal enhancement were follow-up duration (odds ratio [OR]: 1.354 [95% confidence interval (CI): 1.024-2.078]; $p = 0.042$), hypoplastic left heart syndrome (HLHS) (OR: 3.262 [95% CI: 1.145-5.628]; $p = 0.002$), mean pulmonary artery pressure (OR: 1.598 [95% CI: 1.089-2.132]; $p = 0.026$), pulmonary vascular resistance index (OR: 1.263 [95% CI: 1.068-1.245]; $p = 0.032$), and brain natriuretic peptide (OR: 1.956 [95% CI: 1.085-2.673]; $p = 0.045$). According to the multivariate analysis, only HLHS (OR: 3.856 [95% CI: 1.389-5.863]; $p = 0.001$), mean pulmonary artery pressure (OR: 1.846 [95% CI: 1.362-2.549]; $p = 0.015$), and pulmonary vascular resistance index (OR: 1.185 [95% CI: 1.042-1.736]; $p = 0.047$) were significant risk factors for abnormal parenchymal enhancement.

Conclusion: Abnormal hepatic parenchymal enhancement detected through CT is common in Fontan patients. Regular liver function test in conjunction with imaging studies may be considered when following up Fontan patients.

Keywords: Computed tomography (CT); Fontan surgery; Liver

1. INTRODUCTION

Since the past 40 or more years, Fontan surgery has extended the lifespan of patients with congenital single functional ventricle, such as those with tricuspid atresia.[1] Follow-up studies reported survival rates between 60% and 80% at 20 years after Fontan surgery.[2–5] The estimated event-free survival rates at 1, 5, and 10 years were 90.6%, 89.3%, and 77.2%, respectively, at our hospital.[6]

Although Fontan surgery has been greatly successful, failure of the Fontan procedure later due to ventricular dysfunction, elevated pulmonary vascular resistance (PVR), and increased central venous pressure (CVP) with protein-losing enteropathy is still a major concern.[3,7–9] Because of the absence of a pumping ventricle and the transmission of PVR to systemic circulation, the physiology of the Fontan circuit invariably leads to chronically elevated systemic venous pressure, resulting in potentially severe morbidities such as liver cirrhosis and hepatocellular carcinoma (HCC).[10–13]

Hepatic vascular congestion in Fontan patients can lead to parenchymal injury and flow change, which is presented as abnormal parenchymal contrast enhancement, hypervascular nodules, fibrosis and cirrhosis on sonography, computed tomography (CT), or magnetic resonance imaging (MRI).[10,14–16] Wallian et al reported that CT or MRI findings of 42 Fontan patients revealed abnormal parenchymal enhancement (n = 38), hypervascular nodules (n = 13), cirrhosis (n = 8), and HCC

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(n = 1).[14] In the study by Agnoletti et al, abdominal ultrasound showed that 23 (36%) patients had hepatomegaly, 10 (16%) coarse/lobulated liver contour, and 35 (50%) inhomogeneous parenchymal echogenicity.[10] Bae et al revealed that hepatic parenchymal changes (either heterogeneous echotexture or surface nodularity) were evident on ultrasound examination in 67% of 55 Fontan patients, and they further showed that these changes had a positive correlation with duration after Fontan surgery.[15] Furthermore, Pundi et al demonstrated that 10-, 20-, and 30-year rates of freedom from cirrhosis was 99%, 94%, and 57%, respectively, in 195 Fontan patients with liver biopsy or imaging (CT or MRI).[16] Thus, liver imaging survey in Fontan patients is crucial.

The purpose of this study was to evaluate the hepatic CT findings after Fontan surgery and their association with clinical parameters.

2. METHODS

2.1. Patients studied

In this institutional review board-approved study, we reviewed 124 patients who underwent Fontan surgery in our institution from 1995 to 2018. Medical records were reviewed for collecting their age, sex, congenital heart disease (CHD) type, date of Fontan surgery, laboratory data, and hepatic CT. Patients were excluded in case of the following: no available hepatic CT and associated laboratory data (n = 79), and hepatitis C infection (n = 2). The remaining 43 patients with complete liver data were enrolled into this study, and they had no liver disease before Fontan surgery or viral hepatitis.

Hepatic CT images were reviewed by two radiologists with expertise in hepatic imaging. The hepatic enhancement was graded on a scale of 0-3 with grade 0 being normal and grade 1-3 being abnormal. As illustrated in Fig. 1, the abnormal enhancement grades were classified as grade 1 (mild degree) = slight patchy enhancement visible in few of the sections, grade 2 (moderate degree) = coalescent or diffuse patchy enhancement in the majority of the sections, and grade 3 (severe degree) = diffuse patchy enhancement visible in all sections of the liver according to the definition in the previous studies.[14,17] The relationship between hepatic CT findings and clinical parameters was analyzed.

2.2. Statistical analysis

Continuous variables are expressed as means with standard deviation. Categorical variables are presented as absolute numbers and percentages. Risk analysis of abnormal parenchymal enhancement was performed using the Cox regression analysis to determine univariate and multivariate factors. In the multivariate analysis, we considered the significant univariate factors ($p < 0.05$) with model selection using the stepwise method. The odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using the Cox regression model. A p-value of <0.05 was considered statistically significant.

3. RESULTS

The demographic data of 43 patients with Fontan circulation are given in Table 1. The mean age at the time of Fontan surgery was 7.1 ± 6.3 years, and the mean follow-up duration (from date of Fontan surgery to CT imaging studies) was 6.8 ± 4.1 years. Oxygen saturation was 93% ± 2.5%. The type of Fontan operation included atriopulmonary connection (n = 2) and extracardiac conduit (n = 41). The most common type of CHD was tricuspid atresia (n = 15, 34%), followed by double-inlet single ventricle (n = 10, 23%). The NYHA class was class I (n = 21), class II (n = 15), and class III/IV (n = 7). During the follow-up period, six patients were diagnosed with protein-losing enteropathy, three with cirrhosis, and three dying of severe heart failure.

Hepatic CT images of 43 Fontan patients were studied. Ten patients had normal liver images, and the remaining 33 patients had abnormal hepatic enhancement with mild degree (n = 18), moderate degree (n = 10), and severe degree (n = 5). Hepatic nodules were found in nine patients. One 24-year-old female Fontan patient with single ventricle had multiple liver nodules and underwent liver biopsy. Her liver biopsy showed focal nodular hyperplasia, increased hepatocyte density, diffuse sinusoidal capillarization, and focal disarray of reticulin framework with focally thick hepatic plate (Fig. 2).

The hemodynamics, exercise test, and serum laboratory data are shown in Table 2. The mean pulmonary artery pressure was 16 ± 4.9 mmHg. The end-diastolic ventricular pressure was 3 ± 9 mmHg. The PVR index was 1.4 ± 2.9 WU × m^2. Peak oxygen consumption (VO_2) was 24.9 ± 5.6 mL/kg/min. The brain natriuretic peptide (BNP) level was 36.2 ± 47.2 pg/mL. The albumin level was 4.37 ± 0.38 g/dL. The aspartate aminotransferase level was 33.9 ± 9.8 U/L. The alanine transaminase level was 28.9 ± 16.6 U/L. The total bilirubin level was 0.93 ± 0.55 mg/dL. The γ-glutamyltransferase level was 51.2 ± 28.7 U/L. The platelet count was 222.1 ± 92.0 × 1000/mm^3.

The results of risk factor analysis of abnormal parenchymal enhancement are shown in Table 3. According to the univariate analysis, abnormal hepatic parenchymal enhancement was significantly associated in follow-up duration (OR 1.354 [95% CI 1.024-2.078]; $p = 0.042$), HLHS (OR 3.262 [95% CI 1.145-5.628]; $p = 0.002$), mean pulmonary artery pressure (OR 1.598 [95% CI 1.089-2.132]; $p = 0.026$), PVR index (OR 1.263 [95% CI 1.068-1.245]; $p = 0.032$), and BNP (OR 1.956 [95% CI 1.085-2.673]; $p = 0.045$). No significant association was observed between abnormal hepatic parenchymal enhancement and the following variables: age at operation, tricuspid atresia, pulmonary atresia with intact ventricular septum, double-inlet single ventricle, asplenia/heterotaxy, double-outlet right ventricle, end-diastolic ventricular pressure, peak VO_2, albumin, aspartate aminotransferase, alanine transaminase, total bilirubin, γ-glutamyl transferase, and platelet count. According to the multivariate analysis, only HLHS (OR 3.856 [95% CI 1.389-5.863]; $p = 0.001$), mean pulmonary artery pressure (OR 1.846

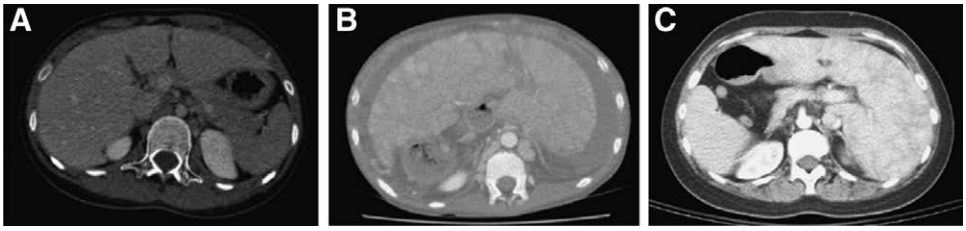

Fig. 1 CT image showing severity of liver enhancement. (a) Grade 1: Slight patchy enhancement visible in few of the sections in a Fontan patient with situs solitus. (b) Grade 2: coalescent or diffuse patchy enhancement in the majority of the sections in a Fontan patient with situs ambiguus. (c) Grade 3: diffuse patchy enhancement visible on all sections of the liver in a Fontan patient with situs inversus. CT, computed tomography

Table 1

Patient demographics

	Patients (n = 43)
Male/female	23/20
Age (y)	15.3 ± 6.8
Age at operation (y)	7.1 ± 6.3
Follow-up duration (from date of Fontan surgery to CT examination) (y)	6.8 ± 4.1
Oxygen saturation (%)	93 ± 2.5
Type of Fontan operation	
Atriopulmonary connection	2 (5%)
Extracardiac conduit	41 (95%)
Type of CHD	
Tricuspid atresia	15 (35%)
Pulmonary atresia with intact ventricular septum	4 (9%)
Double inlet single ventricle	10 (23%)
Asplenia/heterotaxy	3 (7%)
HLHS	5 (12%)
Double outlet right ventricle	6 (14%)
Average New York Heart Association functional class (1-4)	
Class I	21 (49%)
Class II	15 (35%)
Class III/IV	7 (16%)

Continuous variables are presented as mean (± SD).
Categorical variables are expressed as percentage.
CHD = congenital heart disease; CT = computed tomography; HLHS = hypoplastic left heart syndrome.

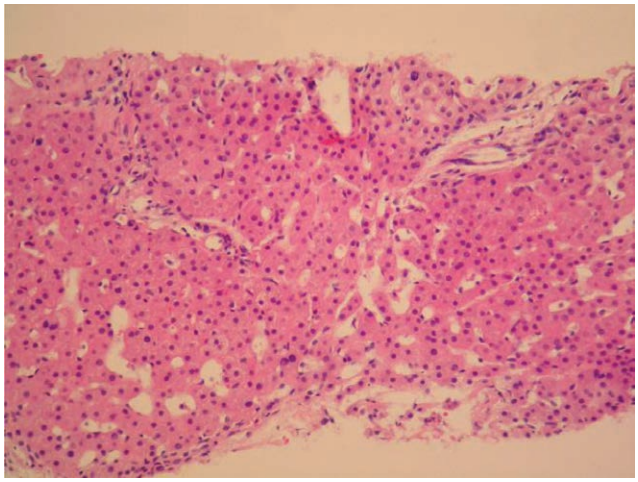

Fig. 2 Liver biopsy of a 24-year-old female Fontan patient with hepatic nodules: focal nodular hyperplasia with increased hepatocyte density with diffuse sinusoidal capillarization and focal disarray of reticulin framework with focally thick hepatic plate (hematoxylin and eosin staining, ×100).

[95% CI 1.362-2.549]; $p = 0.015$), and PVR index (OR 1.185 [95% CI 1.042-1.736]; $p = 0.047$) were significant risk factors of abnormal parenchymal enhancement.

4. DISCUSSION

CT findings in our study demonstrated that the percentage of patients with abnormal parenchymal enhancement of the liver was high (77%) at the mean follow-up duration of 6.8 years after Fontan surgery. Furthermore, Wallihan et al reported a higher rate of abnormal parenchymal enhancement of the liver (90%) and severe grade (40%) as per CT or MRI examination.[14] In this series, follow-up duration was a risk factor for abnormal

Table 2

Hemodynamics, exercise, and laboratory data in Fontan patients

Variable	Mean ± SD
Mean pulmonary artery pressure (mmHg)	16 ± 4.9
End-diastolic ventricular pressure (mmHg)	3 ± 9
Pulmonary vascular resistance index (WU × m^2)	1.4 ± 2.9
Peak VO_2 (mL/kg/min)	24.9 ± 5.6
BNP (pg/mL)	36.2 ± 47.2
Albumin (g/dL)	4.37 ± 0.38
Aspartate aminotransferase (U/L)	33.9 ± 9.8
Alanine transaminase (U/L)	28.9 ± 16.6
Total bilirubin (mg/dL)	0.93 ± 0.55
γ-Glutamyl transferase (U/L)	51.2 ± 28.7
Platelet (×1000/mm^3)	222.1 ± 92.0

BNP = brain natriuretic peptide; VO_2 = oxygen consumption.

parenchymal enhancement. The interval between Fontan surgery and image study in our study was shorter compared with Wallihan et al'[14] (mean 6.8 vs 15.1 years). This factor might partially account for the relatively low rate and severity of abnormal parenchymal enhancement in this series. Inhomogeneous hepatic parenchymal echogenicity was observed through sonography by Agnoletti et al and Bae et al in 50% and 67% of Fontan patients, respectively.[10,15] Both Agnoletti et al and Pundi et al emphasized cirrhosis risk associated with the long-term complications in Fontan patients.[10,16] The findings of these studies,[10,14–16] including ours, are in agreement with the previous findings of hepatic dysfunction in Fontan patients.[18–21]

Fontan-associated liver disease can be an asymptomatic disease, focal nodular hyperplasia-like nodules, liver cirrhosis, and even HCC.[10,16,21,22] The mechanisms of Fontan-associated liver disease may include chronic passive venous congestion due to elevated systemic venous pressure[19,21,22] and hypoxic damage related to low cardiac output.[21–23] Risk factors for the severity of hepatic disease include failing Fontan circulation, high hepatic venous pressure, old age, underlying hepatitis, alcohol abuse, and hepatotoxic drug use other than duration of Fontan circulation.[19,21,22,24] The quality of Fontan circulation can be adversely affected by the following factors: fenestration due to elevated PVR, protein-losing enteropathy, high CVP (>15 mm Hg), low oxygen saturation (<90%), substantial collateral flow (collateral vessels clearly visible in contrast-enhanced angiography), severely reduced exercise capacity (peak oxygen uptake <50% of normal), substantial atrioventricular valve insufficiency, ejection fraction (<50%), dilatation of the tunnel, diaphragm paralysis, cardiac index (≤2.5 L/min/m^2), and morphologically right systemic ventricle.[25] Burchill et al reported that elevated BNP is an independent predictor of Fontan failure and mortality in adulthood.[25] Pundi et al demonstrated a highly significant association of hypoplastic left heart syndrome with increased cirrhosis risk in Fontan patients.[16] Consistent with the previous studies,[16,19,21,24–26] in the univariate analysis in this series, risk factors for abnormal parenchymal enhancement included follow-up duration, HLHS, high pulmonary artery pressure, high PVR, and high BNP. However, only HLHS, high pulmonary artery pressure, and high PVR were significant risk factors in the multivariate analysis. Further prospective study of risk factors is needed, as this would allow for early screening of high-risk Fontan patients.

Liver biopsy is the gold standard for the diagnosis of liver fibrosis and cirrhosis in Fontan patients.[21] To minimize the need for an invasive procedure, a reliable noninvasive method for the early detection of hepatic dysfunction in Fontan patients is crucial. Some methods, including CT, MRI, ultrasound, and liver elastography, have been used as effective noninvasive techniques

Table 3

Risk factor analysis of hepatic parenchymal enhancement in Fontan patients

	Univariate OR (95% CI)	*p*	Multivariate OR (95% CI)	*p*
Age at operation	1.125 (0.860-1.389)	NS		
Follow-up duration	1.354 (1.024-2.078)	0.042	1.262 (0.934–1.867)	NS
Tricuspid atresia	1.026 (0.920-1.256)	NS		
Pulmonary atresia with intact ventricular septum	1.251 (0.619-1.874)	NS		
Double-inlet single ventricle	1.136 (0.825-1.973)	NS		
Asplenia/heterotaxy	1.326 (0.752-1.968)	NS		
HLHS	3.262 (1.145-5.628)	0.002	3.856 (1.389–5.863)	0.001
Double-outlet right ventricle	1.582 (0.862-2.183)	NS		
Mean pulmonary artery pressure	1.598 (1.089-2.132)	0.026	1.846 (1.362–2.549)	0.015
End-diastolic ventricular pressure	1.326 (0.95-1.875)	NS		
Pulmonary vascular resistance index	1.263 (1.068-1.945)	0.032	1.185 (1.042–1.736)	0.047
Peak VO_2	1.389 (0.762-1.684)	NS		
BNP	1.956 (1.085-2.673)	0.045	1.562 (0.875–2.163)	NS
Albumin	1.385 (0.912-1.854)	NS		
Aspartate aminotransferase	1.463 (0.873-1.924)	NS		
Alanine transaminase	1.225 (0.952-1.784)	NS		
Total bilirubin	1.036 (0.626-1.661)	NS		
γ-Glutamyl transferase	1.282 (0.874-1.673)	NS		
Platelet	0.728 (0.594-1.283)	NS		

BNP = brain natriuretic peptide; CI = confidence interval; HLHS = hypoplastic left heart syndrome; NS = not significant; OR = odds ratio; VO_2 = oxygen consumption.

for the assessment of liver diseases in Fontan patients.[21,27] In this series, the mean levels of hepatic biochemical parameters were normal. Most liver biomarkers, including aspartate aminotransferase and alanine transaminase, have been shown to be insensitive indicators of hepatic status in Fontan patients.[21,27,28] The need for the imaging study of liver cannot be overemphasized in Fontan patients. Considering the radiation exposure risk due to CT among the pediatric patients,[29] we recommend that ultrasound examination should be conducted first. MRI will be superior to CT for further evaluation of hepatic abnormalities in terms of radiation exposure risk. For patients with highly suspected HCC, α-fetoprotein can be measured to complement imaging finding.[21,27] More specialized serum tests and calculated scores of liver diseases should be established in Fontan patients.

In this series, hepatic nodules were found in 21% of Fontan patients. Approximately 20%-30% of Fontan patients had hepatic nodules in the previous reports.[14,19,30] Ibarrola et al classified these nodules as benign regenerative nodules and focal nodular hyperplasia in patients with hepatic venous outflow obstruction.[31] One of our patients underwent liver biopsy, revealing focal nodular hyperplasia. The mechanism of the formation of these nodules remains unclear, and previous studies suggested that increasing CVP may result in the reduction of portal flow complicated with arterilization.[14,30,32] Possible malignancy of these nodules is still controversial.[14,30,33,34] HCC should be suspected in Fontan patients with hepatic nodules in case of an increase in nodule size, washout in the portal venous phase, mosaic architecture, and elevated α-fetoprotein.[21,22,35] Routine evaluation of these nodules for possible HCC is recommended.

Owing to the high prevalence of liver complication after Fontan surgery, it is essential to develop a protocol and tailored strategy for screening Fontan patients.[10,21,22] Adequate medical control of PVR can improve Fontan-associated liver disease and exercise limitations, but its effectiveness in controlling pulmonary hypertension in Fontan patients is controversial.[36–41] Antifibrotic management using drugs that can inhibit aldosterone or change the renin-angiotensin system has been proposed to be useful.[28] Recent studies suggested that routine serologic liver tests and hepatic ultrasound should be performed every 1 to 2 years after Fontan surgery for early diagnosis and treatment of hepatic dysfunction.[21,27] Further liver examinations including CT/MRI, catheterization, and liver biopsy should be considered 10 years after the operation.[21,27]

Our study has several limitations. First, the follow-up duration in this series is short. This limitation may underestimate the prevalence and severity of liver disease after Fontan surgery. Second, no evidence is available to support the degree of abnormality of CT findings in predicting future outcomes independently in this retrospective cross-sectional study. The radiation exposure risk to pediatric patients undergoing hepatic CT study might outweigh the benefit of finding hepatic abnormalities. Third, our study is a single-center study with limited number of patients.

In conclusion, our study suggests that abnormal hepatic parenchymal enhancement detected through CT scan is common in patients after Fontan surgery. Regular liver function tests in conjunction with image studies may be considered when following up Fontan patients.

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