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Original Article

Blood test assessment of liver ultrasound findings in patients with Fontan surgery

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Abstract: Hepatic complications are common in patients with Fontan surgery. The objective of this observational study is to compare demographic, clinical and blood test data in patients older than 14 years old with a Fontan procedure (cases) and asymptomatic patients with single non-operated restrictive ventricular septal defect (VSD) (controls) and to determine whether there are differences in blood collection and liver disease scores according to the liver ultrasound findings in the group of Fontan patients. The liver findings were classified as mild (normal or heterogeneous echogenicity) and significant (nodular surface, small hyperechoic nodules or hepatocarcinoma). 74 patients (14 patients with a Fontan procedure and 60 patients with a restrictive VSD) were included in the study. Median age was 18 (14-45) years old and 41 patients were males. Fontan patients had significantly lower platelet count, lower mean platelet volume (MPV) and lower glucose levels than patients with single non-operated restrictive VSD. On the contrary, Fontan patients showed higher liver enzymes [aspartate aminotransferase (AST) and alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT)], N-terminal pro-brain natriuretic peptide (NT-pro-BNP) and thyroid-stimulating hormone (TSH) concentrations than patients with restrictive VSD. 4 out of 14 (29%) patients with Fontan operation and significant liver ultrasound findings showed greater number of cardiac surgeries, lower MPV values and higher GGT and TSH levels than Fontan patients with mild findings. In conclusion, Fontan patients showed higher liver enzymes (AST, ALT and GGT) than controls and Fontan patients with significant liver ultrasound findings had higher GGT and TSH concentrations than Fontan patients with mild findings.

Keywords: Fontan, adult, liver, blood test, ultrasound, congenital heart disease

Introduction

Hepatic complications in congenital heart disease (CHD) patients are common and may occur secondary to persistent chronic passive venous congestion, as seen in patients with Fontan circulation who are not amenable to a two-ventricle repair, palliative cardiac surgery with associated cyanosis, transfusions, or drug-related hepatitis [1, 2].

The Fontan operation is a staged palliation for CHD patients with a univentricular physiology in which the inferior vena cava is connected to the pulmonary arteries with a direct anastomosis of the right atrium to the main pulmonary artery (auricular) or using a cavo-pulmonary connection with an intraatrial tunnel or an extracardiac conduit that bypasses the heart (bicave). Prior to the Fontan procedure, typically the venous blood from the upper body is directly connected to the pulmonary arteries by surgery (bidirectional Glenn or hemi-Fontan).

The Fontan circulation is designed to reroute systemic venous blood, in patients with only one functioning ventricle, from the superior and inferior vena cava directly to the pulmonary arteries resulting in normalization of systemic oxygen saturation and ventricular volume load [3]. Despite the significant improvement in the survival, altered hemodynamics introduced after the Fontan procedure result in elevated central venous pressure, which is believed to trigger the cascade of sinusoidal dilation, sinusoidal fibrosis, cardiac cirrhosis, and liver neo-

plasms, which has been recognized to be highly prevalent in post-Fontan patients [4, 5] and known as Fontan-associated liver disease.

There is no consensus on timing or type of liver evaluation in patients with Fontan circulation [6]. Nonetheless, initial evaluation may include lab work, calculation of liver disease scores and liver imaging (ultrasound, computed tomography scan or magnetic resonance imaging) [7, 8]. Despite of this, routine imaging and serum biomarkers have shown to be unable to assess severity of liver fibrosis in Fontan patients [9].

The objective of this observational study is a) to compare Fontan patients and a control population of asymptomatic CHD patients with single non-operated restrictive ventricular septal defect (VSD) and b) to find out if there are significant differences in blood collection and liver disease scores according to the ultrasound liver findings in Fontan patients.

Material and methods

Subjects

Inclusion criteria included clinically stable CHD patients, older than 14 years with a Fontan procedure (cases) or a single non-operated restrictive VSD (controls) verified with imaging tests and recruited consecutively from a single adolescent and adult CHD outpatient unit between January 2017 and January 2020. CHD patients with a Fontan procedure were categorized in auricular or bicave depending on the type of surgical correction. Patients with a single non-operated restrictive VSD were included as a comparison group as they were representative of the CHD population, were asymptomatic and had little or no hemodynamic changes despite the patent septal defect. A restrictive VSD defect was classified as such if the echocardiographic inter-ventricular peak pressure gradient was higher than 60 mmHg [10]. Patients excluded from the study were those who did not meet the inclusion criteria or who did not give written inform consent to participate. The study was approved by the Hospital's Ethics Committee and the approval number of the manuscript was 2017-890.

Clinical data and blood test

Arterial hypertension was defined when systolic blood pressure was > 130 mmHg, diastolic blood pressure was > 80 mmHg or the patient was receiving medication for hypertension; diabetes mellitus when fasting blood glucose levels was > 126 mg/dL or the patient was treated with oral anti-diabetic agents or insulin. Dyslipidemia if the patient was under any lipid lowering treatment [11]. Body mass index (BMI) was defined as the body mass divided by the square of the body height (kg/m^2). The existence of previous hepatitis or the abusive consumption of alcohol was determined by reviewing the medical history. Age at which the Fontan surgery was performed, and the time elapsed from the Fontan surgery to the control abdominal ultrasound were also collected. Atrial fibrillation and flutter were determined by electrocardiogram. Medical treatment included antiplatelet therapy, oral anti-coagulation, beta-blockers, angiotensin-converting-enzyme inhibitor (ACE inhibitor), angiotensin II receptor blockers (ARBs), loop diuretics, spironolactone, and amiodarone. In the month following the abdominal ultrasound and after an overnight fast of at least 10 hours, a blood test was carried out. Blood sample was analysed as previously reported [12] and routine test carried out are shown in **Tables 1** and **2**. Hemoglobin oxygen saturation was assessed by pulse oximeter (Pulsox 300i, Konica Minolta Sensing Inc. Osaka, Japan). Also, MELD-XI score, a model for end-stage liver disease, was calculated as follows: 11.76 × Ln (creatinine) + 5.11 × Ln (total bilirubin) + 9.44 [13].

Abdominal and cardiac ultrasound

The liver findings of the first ultrasound imaging of the abdomen performed in our Fontan patients at the CHD unit were classified as normal, heterogeneous echogenicity, nodular surface, small hyperechoic nodules or hepatocarcinoma. It was cataloged as heterogeneous when the liver appeared to have different masses or structures inside it, a nodular aspect of the liver surface resulted from the effects of fibrosis and the regenerative nodules on the capsule, hyperechoic nodules if the structures appeared black with no internal echoes and hepatocarcinoma based on the imaging features alone. Spleen length was determined as a spleen measure up to 12 centimeters in craniocaudal length. Abdominal ultrasound measurements were performed using a Philips iU22 ultrasound system and the ventricular function was performed with a Philips iE33

Table 1. Demographic, clinical and blood test in Fontan and non-operated restrictive VSD patients

	Restrictive VSD	Fontan	p
CHD patients, n	60	14	
Age, years	18 (14-49)	21 (15-37)	0.516
Sex (male), n	35 (58)	6 (43)	0.294
Arterial hypertension, n	4 (7)	0 (0)	0.338
Dyslipidemia, n	9 (15)	1 (7)	0.487
Smoking, n	3 (5)	0 (0)	0.632
Body mass index, kg/m^2	22 (18-35)	22 (16-34)	0.956
Laboratory results			
Hemoglobin, mg/dL	14.5 ± 1.4	15.2 ± 1.9	0.161
Platelets, 10^3/μL	244 (149-376)	157 (76-273)	0.001
MPV, fL		9.3 (8.1-10.6)	0.005
Glucose, mg/dL	94 (80-110)	87 (74-99)	0.017
Creatinine, mg/dL	0.9 ± 0.2	0.8 ± 0.1	0.183
Albumin, g/dL	4.5 (3.9-5.0)	4.3 (4-4.9)	0.123
Total proteins, g/dL	7.4 (6.7-8.2)	7.5 (4.7-8.1)	0.847
Cholesterol, mg/dL	153 (105-219)	134 (119-205)	0.534
Total bilirubin, mg/dL	0.7 (0.3-2.5)	1.3 (0.6-2.1)	0.944
ALT, IU/L	17 (9-147)	25 (11-38)	0.002
AST, IU/L	22 (13-74)	27 (15-50)	0.032
AP, UL	71 (38-227)	77 (4-159)	0.209
LDH, UL	177 (129-402)	177 (131-376)	0.912
GGT, UL	17 (9-159)	65 (42-117)	<0.001
CRP, mg/dL	0.2 (0.0-1.0)	0.3 (0.1-3.4)	0.101
NT-pro-BNP, pg/mL	13 (0-161)	236 (40-1585)	<0.001
TSH, mUI/L	2.1 (0.8-3.7)	3.2 (1.6-8.3)	0.014
Medical treatment			
Antiplatelet, n	0 (0)	8 (57)	<0.001
Oral anticoagulation, n	1 (1)	6 (43)	<0.001
Beta-blockers, n	1 (2)	3 (21)	0.002
ACE inhibitors/ARBs, n	2 (3)	4 (29)	0.001
Loop diuretics, n	2 (3)	7 (50)	<0.001
Spironolactone, n	0 (0)	7 (50)	<0.001

CHD: congenital heart disease, n: number of patients, MPV: mean platelet volume, ALT: alanine aminotransferase, AST: aspartate aminotransferase, AP: Alkaline phosphatase, LDH: lactate dehydrogenase, GGT: Gamma-glutamyl transferase, CRP: C reactive protein, NT-pro-BNP: N-terminal pro-brain natriuretic peptide, TSH: thyroid-stimulating hormone, ACE: angiotensin converting enzyme, ARBs: angiotensin receptor blockers. No patient was under amiodarone treatment or had diabetes mellitus.

ultrasound machine (Philips Healthcare, Bothell, WA, USA). The ventricular systolic ejection fraction was calculated by echocardiography using the Simpson's biplane method [14]. The echocardiogram in patients with a Fontan procedure was performed within a month following the abdominal ultrasound.

Statistical analysis

Numerical data were evaluated for a normal distribution using the Kolmogorov-Smirnov test; parametric data are presented as mean and standard deviation (±) and non-parametric data are presented as median and 10-90 percentiles. Categorical values were compared by using the chi-square test. Statistical comparisons of parametric data were made with Student's t-test for two-group comparisons and non-parametric data were compared with the use of the Mann-Whitney rank-sum test. For statistical analysis liver ultrasound findings were dichotomized as mild (normal or heterogeneous echogenicity) and significant (nodular surface, small hyperechoic nodules or hepatocarcinoma). A p-value ≤ 0.05 was statistically significant. Statistical Package for the Social Sciences (SPSS 24, Chicago, IL) was used for data analysis.

Results

Demographic, clinical and blood test data

74 consecutive stable CHD patients out of 845 patients met the inclusion criteria. Median age in CHD patients was 18 (14-45) years and 41 patients were males. 14 patients (cases) had a previous Fontan procedure, and 60 patients (controls) had a single non-operated restrictive VSD. No patient had had previous viral hepatitis or alcohol abuse.

Table 1 compares demographic, clinical and blood test data in patients with Fontan surgery and patients with single non-operated restrictive VSD. No significant differences were seen in age, sex or cardiovascular risk factors between cases and controls. Fontan patients significantly showed a decreased platelet count, a lower mean platelet volume (MPV) and lower serum glucose con-

Table 2. Demographic, clinical and blood data in Fontan patients according to their liver ultrasound findings

	Liver ultrasound findings*		p
	Mild	Significant	
CHD patients, n	10	4	
Sex, male	3 (30)	3 (75)	0.294
Fontan type (bicave), n	6 (60)	4 (100)	0.251
Fontan stenosis, n	2 (20)	1 (25)	1.000
Age at which the Fontan procedure was performed, years	8.6 ± 2.9	11.5 ± 6.0	0.539
Time from Fontan to abdominal echo, years	18.3 ± 5.6	11.9 ± 6.7	0.142
Splenomegaly, n	2 (20)	3 (75)	0.095
Ascitis, n	1 (10)	2 (50)	0.176
Functional class, NYHA	1.7 ± 0.8	2.5 ± 0.6	0.142
Oxygen saturation, %	93 ± 2	88 ± 6	0.260
Systemic ventricular function, %	54 ± 8	51 ± 8	0.539
Number of cardiac surgeries	2 (1-3)	3 (3-4)	0.024
Atrial fibrillation/flutter, n	0 (0)	1 (25)	0.286
Laboratory results			
Hemoglobin, mg/dL	15.4 ± 1.6	15.6 ± 2.8	0.854
Platelets, 10^3/μL	157 (113-251)	183 (76-582)	1.000
MPV, fL	89 (72-92)	88 (80-91)	0.024
Glucose, mg/dL	87 (74-93)	91 (85-100)	0.240
Creatinine, mg/dL	0.8 ± 0.2	0.8 ± 0.5	0.635
Albumin, g/dL	4.5 (0.4-5.0)	2.9 (2.4-4.0)	0.076
Total proteins, g/dL	7.6 (5.6-8.3)	5.3 (4.7-5.3)	0.112
Total bilirubin, mg/dL	1.1 (1.6-4.0)	5.8 (5.6-6.0)	0.154
ALT, IU/L	27 (11-30)	20 (19-41)	0.945
AST, IU/L	25 (15-33)	38 (18-54)	0.142
AP, UL	73 (4-118)	126 (77-130)	0.364
LDH, UL	169 (131-274)	270 (134-290)	0.469
GGT, UL	62 (42-85)	95 (61-125)	0.036
CRP, mg/dL	0.1 (0.9-1.21)	1.5 (0.3-4)	0.065
NT-pro-BNP, pg/mL	244 (40-220)	228 (53-300)	1.000
TSH, mUI/L	2.5 (1.6-4)	5.8 (5.6-6)	0.036
MELD-XI, score	8 (0.8-11.9)	9 (2.8-10.7)	0.254
Medical treatment			
Antiplatelet, n	6 (60)	2 (50)	1.000
Oral anticoagulation, n	4 (40)	2 (50)	0.395
Betablockers, n	2 (20)	1 (25)	1.000
ACE inhibitors/ARBs, n	4 (40)	0 (0)	0.251
Loop diuretics, n	4 (40)	3 (75)	0.559
Spironolactone, n	4 (40)	3 (75)	0.559

CHD: congenital heart disease, n: number of patients, NYHA: New York Heart Association, MPV: mean platelet volume, ALT: alanine aminotransferase, AST: aspartate aminotransferase, AP: Alkaline phosphatase, LDH: lactate dehydrogenase, GGT: Gamma-glutamyl transferase, CRP: C reactive protein, NT-pro-BNP: N-terminal pro-brain natriuretic peptide, TSH: thyroid-stimulating hormone, MELD: Model for End-Stage Liver Disease, ACE: angiotensin converting enzyme, ARBs: angiotensin receptor blockers. *The liver findings were classified as mild (normal or heterogeneous echogenicity) and significant (nodular surface, small hyperechoic nodules or hepatocarcinoma).

centrations than patients with a single non-operated restrictive VSD. On the other hand, Fontan patients showed higher liver enzymes [aspartate aminotransferase (AST) and ala-

nine aminotransferase (ALT)], gamma-glutamyl transferase (GGT), N-terminal pro-brain natriuretic peptide (NT-pro-BNP) and thyroid-stimulating hormone (TSH) concentrations than patients with restrictive VSD.

Abdominal ultrasound

Abdominal ultrasound was carried out in all Fontan patients: 8 patients showed normal livers, 2 patients heterogeneous echogenicity, 1 patient nodular surface and 3 patients small hyperechoic nodules. No patient showed ultrasound hepatocarcinoma consistent finding. **Table 2** compares mild versus significant ultrasound liver findings in patients with a previous Fontan procedure (10 and 4 patients, respectively). As can be noted from the table Fontan patients with a more advanced liver ultrasound disease had significantly a greater number of cardiac surgeries, lower MPV values and higher GGT and TSH levels than Fontan patients with mild findings. On the contrary, no significant differences were seen according to the Fontan type (auricular or bicave), the time from birth to the Fontan procedure or the time from the Fontan operation to the abdominal ultrasound. Equally, there were no significant differences between both groups in the MELD-XI score or the existence of splenomegaly.

Discussion

The unique physiology of Fontan circulation is particularly prone to the development of hepatic complications arising from hemodynamic changes and systemic venous congestion and is, in part, related to the duration of the Fontan procedure. Laboratory abnormalities, specially related to liver disease, are common during routine follow-up of patients with Fontan palliation [15] as seen in our series were Fontan patients showed significantly higher AST, ALT and GGT concentrations than controls. Similarly, decreased blood platelet count, as seen in our Fontan patients, has been associated to hypersplenism secondary to advanced liver disease [2]. In relation to NT-pro-BNP levels Fontan patients showed significantly higher concentrations than patients with non-operated restrictive VSD. Although this can be explained by the coexistence of more severe heart disease in Fontan patients, we must take into account that Fontan patients palliated with an atriopulmonary connection, as occurred in almost 30% of our Fontan patients, involve more atrial tissue in the systemic venous pathway which may increase NT pro BNP levels independently of their cardiac status [16]. Similarly, venous congestion in Fontan patients may cause thyroid dysfunction, regardless of being under amiodarone treatment, due to decreased ventricular function and cardiac output. Thus, thyroid function should be routinely monitored after Fontan surgery [17].

Fontan-associated liver disease has been recognized as the disease process of liver structure and function resulting from the Fontan circulation, excluding other causes such as viral hepatitis or alcohol toxicity [18] leading to liver cirrhosis, nodular hyperplasia or hepatocarcinoma [19]. However, the natural history of Fontan-associated liver disease is not well established.

Liver disease can be easily overlooked in Fontan patients because abnormalities in routine liver tests tend to be mild. Despite of this, elevated serum levels of aminotransferases such as AST and ALT, markers of liver injury, are reported in about one-third of Fontan patients. This reflects the modest hepatocyte injury seen in most cases. Nonetheless, in decompensated patients with poor cardiac output aminotransferase levels may become markedly elevated because of hepatic ischemia [20]. Although liver enzymes, such as AST and ALT, and serum albumin are classic markers of liver dysfunction, we did not find significant differences between Fontan patients with mild or significant liver ultrasound findings. Similarly, no significant differences were seen in relation to the age at which the Fontan surgery was performed, or the time elapsed from the Fontan to the control abdominal ultrasound. On the contrary, Fontan patients with nodular surface or small hyper echoic nodules in the liver ultrasound showed significantly higher GGT [21] and TSH concentrations. GGT is a liver enzyme routinely used in clinical practice to help indicate liver injury and as a marker of excessive alcohol consumption [22]. However, increased GGT activity is also a marker of increased oxidative stress being linked to a remarkable array of chronic conditions and diseases, which also include cardiovascular disease. In fact, the most common abnormal finding seen in the blood test of Fontan patients is an elevation in

GGT, noted in 40-60% of patients in the outpatient setting [23, 24]. In fact, a 2018 report from the American College of Cardiology (ACC)/American Heart Association (AHA) [25] advises that "it is reasonable to perform biochemical and hematological testing on an annual basis for liver and renal function". On the other hand, Fontan circulation may have adverse effects on thyroid function due to congestion and low perfusion of the thyroid gland.

In relation to MELD score it has been found to be a prognostic tool in patients with cirrhosis. However, as many Fontan patients are under anticoagulation therapy, MELD is artificially increased. To overcome this limitation, a new score MELD-XI has been designed [26] using a modified MELD without INR to risk stratify patients with cirrhosis on anticoagulation. Despite it, no significant differences were seen between our Fontan patients with or without significant liver ultrasound findings despite this new score has shown good correlation with the extent of liver fibrosis in post-Fontan hepatic biopsy [13].

There are, however, limitations in our study that may impact our findings. Firstly, the low number of patients with Fontan procedure in our series. Secondly, although abdominal ultrasound remains inexpensive and is recommended as the first choice for the screening and surveillance of liver disease, Fontan patients have some peculiarities that may lead to false positive and false negative results. Finally, patients with Fontan surgery represent a heterogeneous population that includes complex congenital heart abnormalities such as tricuspid atresia, pulmonary atresia with intact ventricular septum, hypoplastic left heart syndrome or double-inlet ventricle, so it may be difficult to draw final conclusions.

In conclusion, Fontan patients showed higher liver enzymes (AST, ALT and GGT) than controls and Fontan patients with significant liver ultrasound findings had higher GGT and TSH concentrations than Fontan patients with mild findings. Therefore, liver and thyroid function blood tests may be helpful in the diagnosis of a more advanced Fontan-associated liver disease.

Disclosure of conflict of interest

None.

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