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Structural and functional uncoupling of liver performance in the Fontan circulation

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ABSTRACT

Background: The liver is known to be structurally abnormal in long-standing Fontan circulation. The degree of liver dysfunction associated with such abnormalities is however largely unknown. We assessed structural changes (serum fibrosis markers) and function (indocyanine green clearance (ICG)) in Fontan patients.
Methods: 21 stable Fontan patients were prospectively assessed and compared with 8 histologically proven compensated viral cirrhotic patients. All subjects had standard liver profile, "Enhanced Liver Fibrosis" (ELF) score (including hyaluronic acid, aminoterminal type III procollagen peptide P3NP and tissue inhibitor of metalloproteinase TIMP-1 levels), and ICG using the LiMON Device. Plasma disappearance rate (PDR) and 15-minute retention (R15) were recorded after ICG infusion.
Results: Indocyanine clearance and retention (PDR and R15) were similar between Fontan and compensated cirrhotic patients (17 ± 5 vs 18 ± 6 ($p=0.75$) and 11 ± 10 vs 10 ± 10 ($p=0.75$)), as was degree of fibrosis (7.97 ± 1.16 vs 9.0 ± 1.43, $p=$NS). There was a positive correlation between PDR and ELF ($R=0.77$, $p=0.028$) as well as R15 and ELF ($R=0.905$, $p=0.002$) in the viral cirrhotics but not in the Fontan group. ($R=-0.243$, $p=0.302$; and $R=0.226$, $p=0.338$). PDR (17 ± 5) and R15 (11 ± 10) were not significantly different in Fontan as compared with the established cirrhotics.
Conclusions: Fontan patients have similar global hepatic function and fibrosis as compared with viral cirrhotic patients. However in Fontan patients, fibrosis was not closely correlated with global liver function, whereas viral cirrhotic patients exhibited a close correlation between function and fibrosis.

1. Introduction

The Fontan operation [1], introduced in 1968 for functionally single ventricles, creates a venous circulation that completely bypasses the heart, thereby reducing the single ventricle's volume load and separating oxygenated from deoxygenated blood, rendering the patient "pink". This is achieved by connecting the systemic venous return directly to the pulmonary circulation. The single ventricle is left as the systemic pump, driving blood through the arterial tree, venous circulation and then passively through the pulmonary capillary bed [2]. This results in persistently elevated systemic venous pressure, which we and other authors [3,4] have associated with the hepatic fibrosis seen during follow-up. Long-term survival with the Fontan circulation now is common, [5] therefore placing Fontan patients at increased risk of cirrhosis complications including hepatocellular carcinoma, variceal haemorrhage and hepatic failure. Serial liver biopsy in this setting is invasive and is limited by the localised nature of the biopsy sample. However it remains unclear what the degree of global hepatic function is in patients with a Fontan hepatopathy and obvious structural changes. Recent reports have verified good accuracy of non-invasive markers of liver fibrosis using serum markers [6,7]. Bedside techniques measuring hepatic clearance of indocyanine green (ICG, LiMON device, Pulsion Medical Systems, Munich) as a marker of global hepatic function are also well established. Not surprisingly the Limon monitor has rapidly acquired many uses in the field of hepatology due to its simplicity of design and current uses include assessing donor liver function prior to transplantation, assessing prognosis prior to liver resection and assessing prognosis in critically ill patients [8,9]. The aim of this study was to assess the structure of the liver using non-invasive serum markers of liver fibrosis (ELF test) and hepatic function using indocyanine green clearance (Limon Device) in a stable group of Fontan patients and to compare this with a compensated non-cardiac cirrhotic group.

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2. Methods

2.1. Subjects

This was a prospective study of consecutive Fontan patients >16 years of age, presenting to or being followed up at a supra-regional adult congenital heart centre. Exclusion criteria were: age <16, allergy to iodine, failure to obtain informed consent and known pre-existing intrinsic liver disease, active congestive heart failure, hepatotoxic drug exposure and associated other medical diseases. In addition, a separate cohort of patients with established cirrhosis secondary to chronic viral hepatitis (proven on liver biopsy) were recruited as a comparative group. These were consecutive patients presenting to the regional liver unit at Southampton University Hospital. Exclusion criteria for this cohort were: decompensated liver disease (ascites, jaundice and encephalopathy), history of alcoholic liver disease, history of biliary disease and any history of cardiac disease.

All subjects underwent a detailed history, physical examination and baseline blood tests (including full blood count, liver function test and renal function) at the study visit. Serum markers of fibrosis, indocyanine green analysis and abdominal ultrasonography was performed in all subjects. All subjects had detailed 2-D echocardiography performed on the IE 33, Phillips Inc.

2.2. Indocyanine green analysis

The LiMON_ (Pulsion Medical Systems, Munich, Germany) method of measuring indocyanine green (ICG) elimination by pulse spectrophotometry was used. ICG Plasma Disappearance Rate (PDR%/min) and ICG Retention Rate after 15 min (R15%/min) were measured in all patients instantaneously and non-invasively by pulse spectrophotometry after injection of an intravenous bolus of 0.25 mg/kg of ICG-PULSION_ dye dissolved in 5 ml of water, via the cubital vein and followed by a saline flush. The machine continuously measures optical absorption at wavelengths of 805 and 905 nm based on the principle of pulse spectrophotometry. The peak optical absorption of ICG occurs at 805 nm, whilst the absorption of ICG at 905 nm is negligible. In contrast, there is negligible absorption of oxyhemoglobin and at both 805 and 905 nm. One operator performed the ICG analysis on all the subjects in this study.

2.3. Serum markers of fibrosis

Serum samples were analysed for levels of TIMP-1, HA and PIINP at an independent reference laboratory (iQqur Limited, Southampton, UK). Results were entered into the established algorithm and expressed as Enhanced Liver Fibrosis (ELF) Discriminant Scores (DS). Tissue inhibitor of matrix metalloproteinases, PIIINP and HA (ELF test) were assayed on an automated IMMUNO 1 immunoanalyzer (Siemens Medical Solutions Diagnostics, Tarrytown, NY, USA). The assays are magnetic particle separation immunoassays and were identical to those used for the 2004 European Liver Fibrosis study [10]. The TIMP-1 and PIIINP assays each use two monoclonal antibodies (MAbs) that bind to independent binding sites on their respective antigens. The HA assay uses HA binding protein (HABP), which is isolated from cow nasal septum, in the place of MAbs. The ELF markers were analysed in singular, and the results continually refereed to a set of quality standards to ensure accurate analysis. The ELF assays require a total of 22.2 μL of serum for a single determination: 3.5 μL for HA, 15.0 μL for PIIINP and 3.7 μL for TIMP-1.

2.4. Statistics

Descriptive statistics including means ± SD and range, were used for delineating continuous variables. Proportions and median and ranges were used to describe non-continuous variables. Intergroup correlations and comparisons were carried out using non-parametric statistical tools including Spearman's rank correlation coefficient, Wilcoxon rank-sum test, Mann–Whitney *U* test and Fisher's exact test.

Ethics approval was obtained from the local Southampton and Isle of Wight ethics Committee.

3. Results

3.1. Fontan patients

Twenty one Fontan patients, 7 female, were recruited. The mean age was 26.2 (range 19 to 37) and the mean time following Fontan surgery was 18.9 years (range 12 to 28 years). The primary anatomic diagnosis was tricuspid atresia in 12 patients with 3 having associated transposition of the great vessels. Six patients has double inlet left ventricle whereas 3 had pulmonary atresia complexes. The Fontan was right atrium (RA) to pulmonary artery (PA) in 16; lateral tunnel in 2; RA to right ventricle (RV) in 2; and other variant in 1. None was in decompensated heart failure at the time of the study. Fontan patients had a mean systolic blood pressure of 99 ± 14 (range 80–130) mm Hg, and a mean diastolic blood pressure of 63 ± 10 (45–93) mm Hg. Ventricular function was assessed by means of ejection fraction obtained by echocardiography. Eleven had ejection fraction more than 55% (Normal systolic function). Five patients had ejection fraction between 45 and 55% (mild ventricular dysfunction) whilst 4 patients had ejection fraction less than 45% (moderate to severe ventricular dysfunction). All patients in non-cardiac cirrhotic group had normal ventricular function. Table 2 delineates the haemodynamic and echo differences between the Fontan and control group. 86% (n = 18) of patients in the group were anticoagulated with warfarin. Other medications included diuretics (8/21), amiodarone (7/21), beta-blocker (9/21) and ACE inhibitors (7/21).

3.2. Established viral cirrhosis group

Six patients had established cirrhosis secondary to chronic viral hepatitis C and 2 patients had established cirrhosis from chronic hepatitis B. All had a MELD score of <10 (mean score 5.2). The mean age of the cohort was 55.5 ± 10 (range 40 to 70). Baseline demographic details of the study subjects and cardiac parameters are shown in Tables 1 and 2.

3.3. Standard liver function tests and MELD score

Liver function parameters are displayed in Table 1. There was no significant difference in albumin, ALT and bilirubin levels between the Fontan and cirrhotic pts.

3.4. Liver fibrosis

The mean ELF score was 7.97 ± 1.16 (5.36 to 10.52) in the Fontan group vs. 9.0 ± 1.43 (6.64 to 11.37) in the established cirrhotic group p = 0.05.

3.5. Global liver function and indocyanine green clearance

PDR (17 ± 5) and R15 (11 ± 10) were not significantly different in Fontan pts as compared with the established cirrhotics (18 ± 6 and 10 ± 10 respectively) (Fig. 1). There was a positive correlation between PDR and ELF (R = 0.77, p = 0.028) as well as R15 and ELF (R = 0.905, p = 0.002) in the viral cirrhotics but not in the Fontan group. (R = −0.243, p = 0.302; and R = 0.226, p = 0.338) (Fig. 2).

3.6. Cardiac parameters and biomarkers in the Fontan group

PDR of ICG is negatively correlated with patients who have both impaired ventricular function and systolic blood pressure less than 100 (R = −0.492; p = 0.03).

Table 1
Baseline demographics.

	Fontan group (n = 21)	Established cirrhosis (n = 8)	p value
Age	26.2 (19 to 37)	55.5 (40 to 70)	p<0.001
NYHA functional class I	6 (29%)	5 (63%)	p = 0.038
NYHA functional class II	10 (48%)	3 (38%)	
NYHA functional class III	4 (19%)	0 (0%)	
NYHA functional class IV	1 (5%)	0 (0%)	
Albumin	39 (23 to 49)	38 (33 to 43)	p = 0.18
ALT	33.5 (14 to 87)	40.8 (16 to 84)	p = 0.52
Bilirubin	21.1 ± 11.5	17.3 ± 4.5	p = 0.27
Platelet count	196.4 (46 to 341)	169 (67 to 239)	p = 0.55
Sodium	136.6 (129 to 142)	138.6 (136 to 142)	p = 0.14
Creatinine	79.6 (43 to 119)	74 (46 to 97)	p = 0.58