には淡黄色 800ml の腹水貯留を認めた．腹部臓器は内臓逆位で肝臓は左上腹部に位置し，重量は 1,240g であった．肉眼的に肝辺縁は鈍で表面に粗大な凹凸を多数認めた．割面では大小の結節が肝両葉にわたって多数認められ，尾状葉は 3.5×5.0cm 大の腫瘤性病変で占められていた(Fig. 2A，2B)．ルーペ像において腫瘤性結節内には壊死や線維化および出血は認められなかったが腫瘤周囲の肝には著明な線維化と比較的新鮮な出血壊死像がみられた（Fig. 3A，3B)．組織学的に結節内の肝細胞は異型に乏しく，肝細胞索は良く保たれていた．また，結節内には中心静脈・Glisson 鞘の構造が認められた（Fig. 4A，4B)．類洞は全体的に開大し(Fig. 4C)，鍍銀染色では小葉中心性に軽度の線維化を認めた(Fig. 4D)．結節周囲の線維化は中心静脈～Glisson 鞘を架橋するように存在し，大小様々な偽小葉を形成しており，肝硬変の所見であった(Fig. 5A，5B)．免疫染色では腫瘤内において CD68 陽性細胞の減少は認めなかった(Fig. 6A，6B)．CD34 染色は腫瘤内の門脈域の血管や門脈域周囲の一部の類洞内皮で陽性を呈しており(Fig. 6C，6D)，Glypican 3 染色では Glypican 3 陽性肝細胞は観察されなかった（Fig. 6E，6F)．

以上より肝の多発結節はうっ血性肝硬変を背景にした再生結節と診断した．

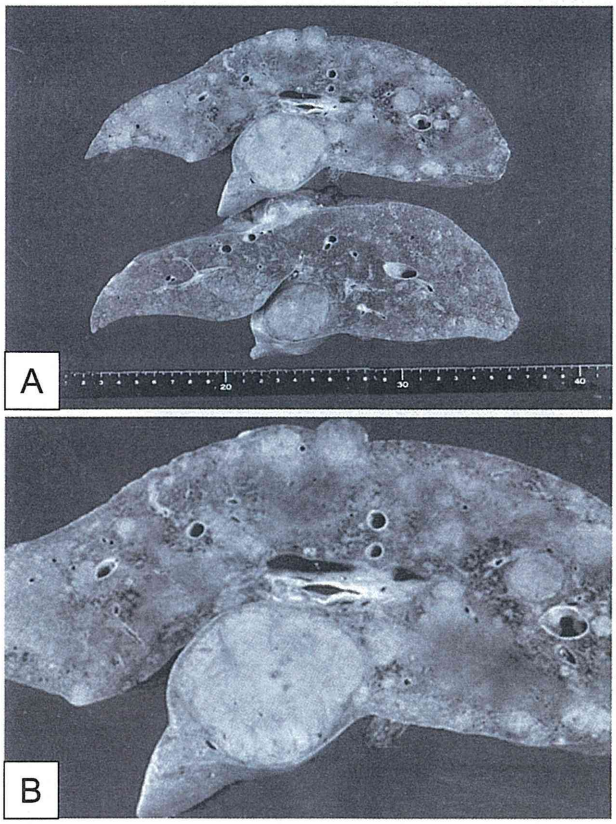

Fig. 2 Macroscopic appearance of the liver at autopsy
A: The liver specimen showed multiple nodules in both lobes.
B: A large mass, 3.5×5.0 cm, was observed in the caudate lobe.

考　察

Fontan 術後の肝病変の報告は 1981 年に Stanton らによる Fontan 術後 21 ヵ月で死亡した剖検例においてみられた肝硬変の症例が始めである[4]．以来，2000 年代以降 Fontan 術後の肝合併症の報告は増加し，肝線維症をはじめ肝硬変や HCC の発症の報告もみられている．Ghaferi らは Fontan 術後の 9 例の剖検例の肝病変を検討し，4 例にうっ血性肝硬変が

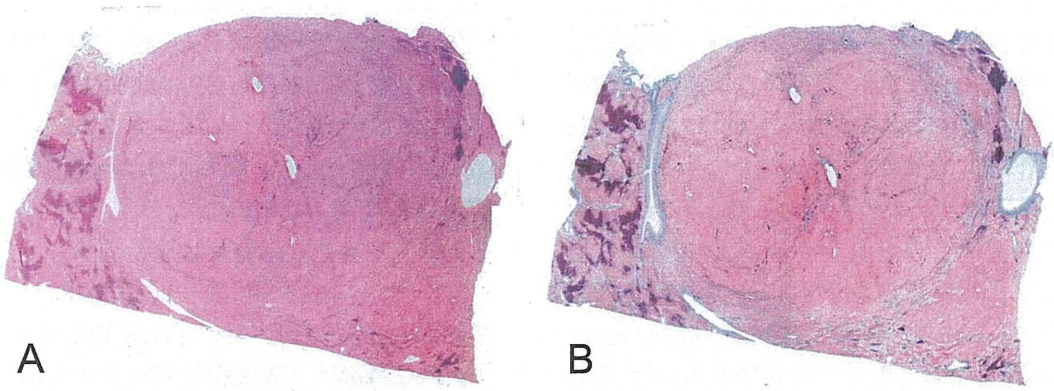

Fig. 3 Histopathological findings of the caudate lobe
A: Vasculature was observed in the nodule, and the congestion in the nodule was milder than that of the perinodular lesion.
B: The nodule was surrounded by fibrous septa. However, the fibrosis in the nodule was milder than that in the perinodular lesion.
(Original magnification, ×12.5, A: hematoxylin-eosin staining; B: Masson's trichrome staining)

みられ1例でHCCの発症が認められたと報告している[5]．Fontan術後のうっ血性肝硬変は，Fontan術後に生ずる体静脈圧の上昇に伴い肝静脈圧が上昇し，これが肝の中心静脈圧の上昇につながることから惹起されると考えられている[3]．慢性障害肝である肝硬変を背景に有する肝には種々の結節性病変の発生が報告されており，これらの結節性病変は特に高分化型HCCとの鑑別が重要である．鑑別診断には

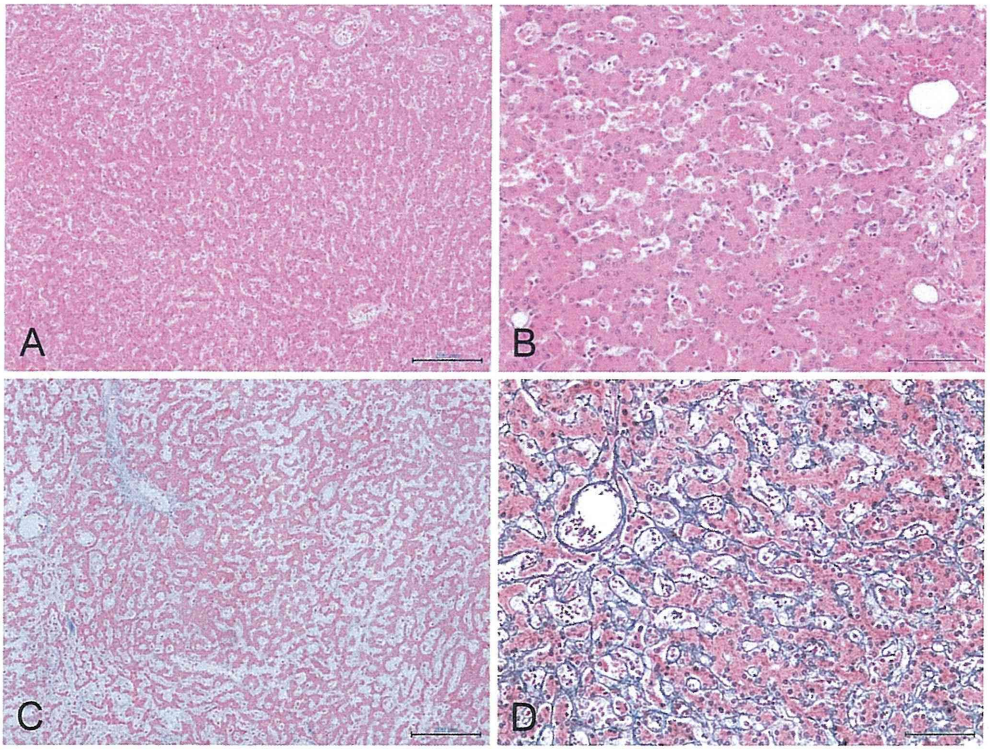

Fig. 4 Histological findings of the nodule in the caudate lobe
A: Hepatic sinusoidal dilatation was observed.
B: The parenchymal cells did not display cellular or structural atypia.
C: Liver section showing mild hepatic fibrosis.
D: Fibrosis was observed in the pericellular area. The sinusoidal structure was maintained.
(A: original magnification, ×100, hematoxylin-eosin staining; B: ×200, hematoxylin-eosin staining; C: ×100, Masson's trichrome staining; D: ×200, silver impregnation staining.)

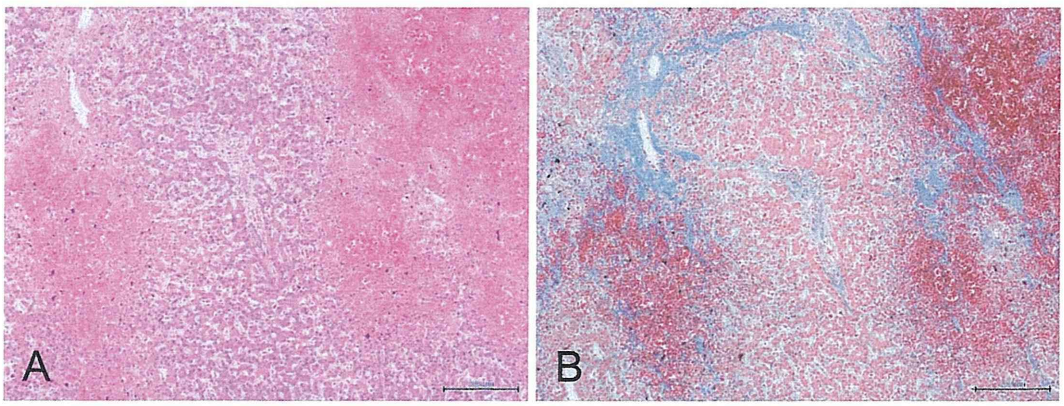

Fig. 5 Histological findings of the perinodular lesion
A: Hepatic sinusoidal dilatation and severe hepatic congestion were observed.
B: Bridging fibrosis was observed in the liver section.
(A: original magnification, ×200, hematoxylin-eosin staining; B: ×200, Masson's trichrome staining.)

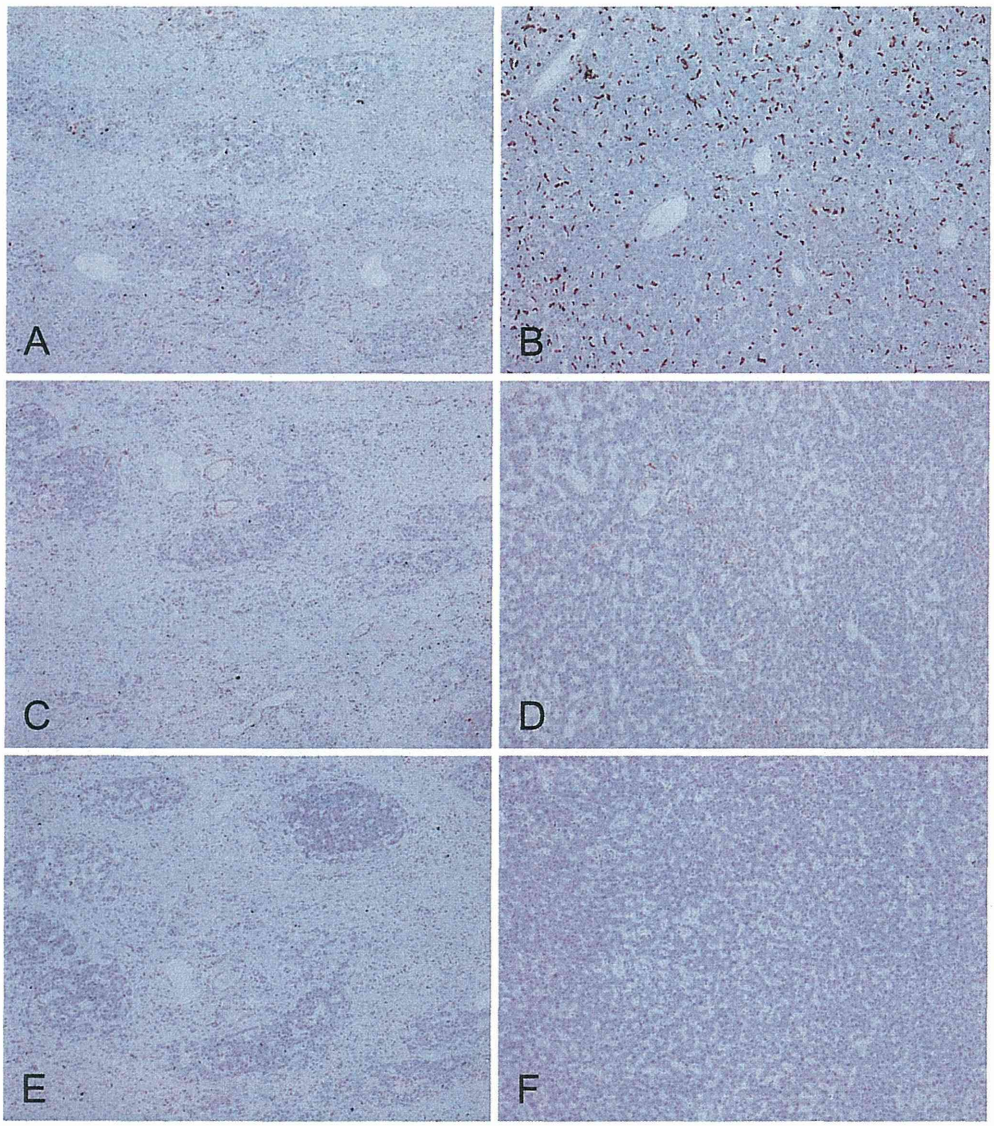

Fig. 6 Immunohistochemical staining for CD68 (A and B), CD34 (C and D) and Glypican-3 (E and F), showing the perinodular lesion (A, C and E) and nodule (B, D and F) in the caudate lobe (original magnification, ×100)
A, B: CD68-positive cells were observed in both the perinodular lesion and nodule.
C: Only the blood vessels in the portal tracts and sinusoidal spaces were CD34-positive.
D: The sinusoidal spaces were CD34-positive, whereas the central sinusoidal spaces were CD34-negative.
E, F: Negative staining of Glypican-3 in both the perinodular lesion and nodule.

腹部造影CT検査や腹部超音波検査，腹部MRI検査などの画像診断が有用である．特に，gadolinium ethoxybenzyl diethylene triamine pentaacetic acid（Gd-EOB-DTPA）造影MRIが肝腫瘤性病変の鑑別診断に広く用いられているが，確定診断に肝生検や手術材料が必要な場合も少なくない[6]．

本症例では，超音波検査において結節は増大傾向を伴っておりHCCが疑われたが，腎機能障害や全身状態の不安定さがあるため造影CT検査を施行することは困難であり，生前診断には至らなかった．剖検材料の組織所見では結節内の肝細胞に異型性はみられず構造も正常に近くGlisson鞘も存在しHCCは否定的な所見であった．

本症例のような良性の肝結節性病変は，原発性肝癌取扱い規約；第5版補訂版（2009年）では上皮性腫瘍の項目内の肝細胞腺腫あるいは腫瘍類似病変として記載されている[7]．肝細胞腺腫（hepatocellular adenoma：HA）は慢性肝炎や肝硬変などを合併しない肝臓に発生することが多く，女性が90％を占めており経口避妊薬の内服との関与が知られている．

Table 1 Classification of Hepatocellular Nodules*

1. Regenerative lesions
  1.1 Monoacinar regenerative nodule
    1.1.1 Diffuse nodular hyperplasia without fibrous septa (nodular regenerative hyperplasia)
    1.1.2 Diffuse nodular hyperplasia with fibrous septa or in cirrhosis
  1.2 Multiacinar regenerative nodule
  1.3 Lobar or segmental hyperplasia
  1.4 Cirrhotic nodule
    1.4.1 Monoacinar cirrhotic nodule
    1.4.2 Multiacinar cirrhotic nodule
  1.5 Focal nodular hyperplasia
    1.5.1 Focal nodular hyperplasia, solid type
    1.5.1 Focal nodular hyperplasia, telangiectatic type
2. Dysplastic or neoplastic lesions
  2.1 Hepatocellular adenoma
  2.2 Dysplastic focus
  2.3 Dysplastic nodule
    2.3.1 Dysplastic nodule, low-grade
    2.3.1 Dysplastic nodule, high-grade
  2.4 Hepatocellular carcinoma
    2.4.1 Small hepatocellular carcinoma (less than 2 cm)
      2.4.1.1 Early HCC
      2.4.1.2 Progressed HCC

*According to the International Working Party[8] and International Consensus Group for Hepatocellular Neoplasia[9].
HCC; Hepatocellular carcinoma.

組織学的には異型のない肝細胞のシート状～索状増生がみられ，腫瘍内には門脈域を欠くことも特徴としてあげられる．本症例では背景に肝硬変を有していることや結節内に門脈域が散見されることより，肝細胞腺腫は否定的であった．

他に鑑別すべき疾患として，限局性結節性過形成（focal nodular hyperplasia：FNH）やその他の過形成性結節があげられる．これらは前述の原発性肝癌取扱い規約では腫瘍類似性病変（tumor-like lesions）に分類されるが，規約内で詳細は記載されていない．原発性肝癌取扱い規約の他に，肝の過形成性結節の詳細な分類として International Working Party（IWP）分類が知られている（Table 1）[8]．IWP 分類では肝細胞結節を regenerative lesions と dysplastic or neoplastic lesions に分類し，FNH や今まで多種類の診断名で呼ばれてきたその他の過形成性結節は前者の regenerative lesions に分けられている．FNH は肝細胞腺腫と同様に慢性肝炎や肝硬変などがない正常肝に発生し，結節内には中心性瘢痕や不規則な線維化が観察される．大きさは肝の一葉を占める大きな結節の報告もあるが，多くは 5cm 以内とされている．本症例においては背景肝が肝硬変であることより FNH は否定的である．本症例の結節性病変は両葉にびまん性に結節が多発し径が 3.5×5.0 cm 大と大きい結節を含むこと，異型性に乏しいこと，結節内に複数の門脈域がみられることより IWP 分類の multiacinar regenerative nodule に合致するものと考えられた．

以上は一般染色からの鑑別点であるが，免疫染色を用いた肝腫瘤性病変鑑別の試みがなされている．後藤は結節内と非結節内の CD68 陽性細胞の局在が結節の異型度や分化度に依存し，結節内の CD68 陽性細胞の減少の度合いが大きいほど結節の異型度が高いことを報告した[10]．また，近年では CD34 染色および Glypican 3 染色が高分化の HCC と良性の肝腫瘤性病変の鑑別に有用であるとされ，頻用されている．Wanda らは 142 例の肝腫瘤性病変における CD 34 染色と Glypican 3 染色の染色パターンを報告検討し，腫瘤内のほぼ全体の類洞内皮に CD34 陽性を呈する症例は全例高分化の HCC であり，HA あるいは FNH などの非悪性病変では門脈域の血管や門脈域に接する類洞内皮の一部で陽性所見を認める“incomplete CD34 staining pattern”であったこと，Glypican 3 染色は 88% の HCC において陽性を呈し，全ての非悪性腫瘤性病変で陰性であったと報告した[11]．本症例の結節性病変においては，結節内の

CD68陽性細胞数は結節外と比して減少はみられない．また，結節内におけるCD34染色所見は“incomplete CD34 staining pattern”であり，Glypican 3染色陽性肝細胞は観察されない．これらの点からも低悪性度を示唆するといえる．

結　論

今回，生前にHCCと鑑別を要する肝多発結節性病変を呈したFontan術後の1剖検例を経験したので報告した．Fontan術の手術成績の向上とともに今後Fontan術後遠隔期における肝硬変症例と硬変肝を背景にした種々の結節性病変の発生の増加が注目される．症例の蓄積によりFontan術後の肝病変の現状や発生機序の検討が必要であると考えられる．

開示すべき利益相反状態はありません．

文　献

1) **Asrani SK, Asrani NS, Freese DK et al**: Congenital heart disease and the liver. Hepatology **56**: 1160–1169, 2012
2) **白石　公**：【循環器疾患　最近の話題】成人期を迎えた先天性心疾患患者の諸問題．京府医大誌 **119**：247–258, 2010
3) **藤澤知雄，田中靖彦**：Fontan循環における肝合併症．日小児循環器会誌　**29**：162–170, 2013
4) **Stanton RE, Lurie PR, Lindesmith GG et al**: The fontan procedure for tricuspid atresia. Circulation **64**: II140–II146, 1981
5) **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 **129**: 1348–1352, 2005
6) **Döhr O, Hofmeister R, Treher M et al**: Preclinical safety evaluation of Gd-EOB-DTPA (Primovist). Invest Radiol **42**: 830–841, 2007
7) **日本肝癌研究会**：「臨床・病理　原発性肝癌取扱い規約」，第5版補訂版．金原出版，東京（2009）
8) **International Working Party**: Terminology of nodular hepatocellular lesions. Hepatology **22**: 983–993, 1995
9) **International Consensus Group for Hepatocellular Neoplasia**: Pathologic diagnosis of early hepatocellular carcinoma: a report of the international consensus group for hepatocellular neoplasia. Hepatology **49**: 658–664, 2009
10) **後藤　清**：肝結節性病変におけるCD68陽性細胞の局在に関する組織病理学的検討．肝臓　**38**：19–26, 1997
11) **Coston WM, Loera S, Lau SK et al**: Distinction of hepatocellular carcinoma from benign hepatic mimickers using Glypican-3 and CD34 immunohistochemistry. Am J Surg Pathol **32**: 433–444, 2008

Impact of Liver Disease After the Fontan Operation

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Liver disease is being reported with increased frequency in survivors of the Fontan operation. The clinical impact of structural hepatic abnormalities in these patients remains largely unknown. We sought to assess if, and how, cardiologists are screening for hepatic disease in these patients to evaluate for clinical or laboratory correlates of structural hepatic disease and determine the prevalence and clinical impact of such disease. Retrospective data analysis from tertiary institutions was performed. Hepatic imaging studies and serology performed over the last decade were reviewed and clinical and laboratory correlates of structural hepatic alterations on liver imaging or biopsy were sought. Outcomes were determined. In this cohort study, 53 of 60 adult survivors (88%) underwent hepatic imaging with computed tomography, magnetic resonance imaging, or ultrasound with a median number of 2 (0 to 10) studies over the past decade. The frequency of hepatic imaging varied widely with 70% of patients undergoing serial studies. Cirrhosis with or without abnormal hepatic nodules was seen in 29 of 53 patients (55%) at 18.4 ± 5.6 years after the Fontan procedure. Adverse hepatic-related outcome occurred in 22% of the entire patient cohort and was unrelated to time from Fontan operation. In conclusion, there exists significant variability in the type and timing of testing for hepatic complications after the Fontan procedure. Structural hepatic alterations are common and can be associated with significant morbidity and mortality. Routine imaging, and serologic evaluation, is recommended in all Fontan survivors. **(Am J Cardiol 2015;115:249–252)**

Hepatic cirrhosis after Fontan palliation for single ventricle cardiac anatomy has been well described in small patient cohorts.[1–5] The evolution of anatomical hepatic derangements in these patients remains ill-defined thereby making it difficult to know whom to screen and how often.[4–6] We sought to characterize the frequency and modalities of hepatic screening used for evaluation of these patients and identify the type, severity, prevalence, and clinical impact of anatomic and physiologic hepatic derangements present. We also sought to assess for laboratory or clinical correlates of cirrhosis or other significant hepatic pathology in an adult cohort of patients surviving the Fontan procedure.

Methods

An institutional review board approved review of data on all patients evaluated during the past 10 years who had undergone the Fontan procedure in childhood and survived to ≥18 years was performed. Serologic and clinical correlates of "significant" hepatic pathology were assessed for. Significant hepatic pathology was defined as the presence of advanced fibrosis, cirrhosis, hepatocellular carcinoma, hepatic adenomatosis, or dysplastic hepatic nodules on imaging and biopsy. This definition was chosen as it was believed that these particular findings, in contrast to isolated portal hypertension and/or early fibrotic changes, carried significant potential to alter long-term outcome. The presence or absence of protein losing enteropathy (defined by an elevated stool α-1 antitrypsin and associated hypoalbuminemia) was recorded. Cardiac catheterization data were recorded if performed within 1 year of imaging and/or biopsy evaluation for cirrhosis. Data from routine outpatient laboratory evaluation performed in adolescence and adulthood were reviewed. Testing was performed at the discretion of the primary cardiologist. The frequency and absolute number of times routine outpatient testing was performed were recorded. Values from routine out-patient testing performed at or near the time of hepatic imaging were recorded for the purposes of data analysis. International normalized ratio values were not recorded as most patients were on warfarin therapy. Several scores found to be predictive of hepatic fibrosis in other patient populations[7–9] were calculated including aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio,[7] APRI (AST to platelet ratio)[8] and FIB-4 score (age × AST/platelet count × ALT).[9]

Evaluation for liver pathology was performed at the discretion of the primary cardiologist. Imaging of the liver was performed through ultrasound with Doppler, dual phase computed tomography with contrast, or magnetic resonance imaging. Liver biopsy was performed at the discretion of the hepatologist involved in the patient's care and was triggered

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See page 252 for disclosure information.

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Table 1
Demographic data for the entire patient cohort

Clinical Variable	N=60
Male/female	31/29
Age at last follow-up (years)	28 (18-43)
Age at Fontan (months)	66 (14-324)
Type of Fontan	
Extra cardiac conduit	20 (33%)
Lateral Tunnel	20 (33%)
Atriopulmonary connection	14 (23%)
Bjork modification of atriopulmonary connection	6 (10%)
Atrial arrhythmias	29 (48%)
Pacemaker	24 (40%)
Asplenia	12 (20%)
Protein Losing Enteropathy	13 (22%)
Peak Oxygen consumption (ml/kg/min ± SD)	60.8 ± 12.8

Table 2
Liver imaging per patient (N=53)

Maximal severity of Liver Disease On Imaging	Number of patients
No hepatic abnormalities	4 (7%)
Congestion only	20 (38%)
Cirrhosis without nodules	19 (36%)
Cirrhosis with nodules	10 (19%)

by imaging findings consistent with cirrhosis and progressive serologic abnormalities, suspicious hepatic mass, or consideration of cardiac transplantation.

Cirrhosis was defined on biopsy using the Metavir grading system[3] or in those patients without biopsy, as computed tomography or magnetic resonance imaging findings of parenchymal heterogeneity with irregular undulating liver margins, and caudate hypertrophy with or without enhancing nodules.[3] Hepatic imaging was assigned a score out of 4 with[1] representing no identified hepatic abnormalities,[2] minor changes believed to represent congestion or early fibrosis,[3] consistent with cirrhosis and[4] cirrhotic changes with enhancing nodules. Patients with a score of 3 or 4 were deemed to have cirrhosis whereas those with a lesser score were said to not have cirrhosis unless there was evidence to the contrary on liver biopsy. Frequency of an adverse hepatic outcome was calculated and defined as clinically symptomatic synthetic hepatic dysfunction including gastrointestinal pathology with bleeding requiring treatment, hepatic encephalopathy defined as altered level of consciousness in association with an elevated ammonia level, hepatocellular carcinoma or adenomatosis, hepatorenal syndrome in the face of normal systolic function, or progressive change in dysplastic hepatic nodules required listing for liver transplant in association with listing for cardiac transplant.

Statistical analysis was conducted using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina). Continuous data were expressed as means with SDs or medians with ranges as appropriate and categorical data were tabulated. A 2-sided p value of <0.05 was considered statistically significant. Demographic, clinical, and serologic variables for those patients with versus without significant liver pathology and those patients with versus without adverse clinical outcome were compared using a chi-square test for dichotomous or categorical variables and *t* test or Wilcoxon rank sum for continuous variables depending on their normality. Correlates of cirrhosis, and the presence of adverse clinical outcome were sought using a logistic regression model and odds ratios calculated. Using a logistic regression model, the area under the curve was determined to calculate the sensitivity and specificity of each laboratory test.

Results

Sixty adult patients who had undergone the Fontan procedure during childhood, and who were evaluated as adults in either a pediatric cardiology clinic or adult congenital cardiology clinic within the last 10 years, were identified. Clinical characteristics of the patient cohort are outlined in Table 1. At the time of last follow-up, 45 (75%) were alive without listing for heart transplantation, 1 alive awaiting heart transplantation, 3 (5%) alive and awaiting combined heart and liver transplantation, 6 (10%) alive after heart transplantation, and 5 (8%) deceased. Age at death was 24 ± 5 years. Of the 53 (88%) patients who underwent hepatic imaging for evaluation of cirrhosis (Table 2), initial hepatic imaging was performed at 24 ± 7 years occurring 18 ± 5 years after the Fontan procedure. Serial imaging was performed in 37 patients (70%). Patients underwent a median of 2 (0 to 10) studies during adolescence and adulthood. Patients with a normal initial study were less likely to undergo repeat imaging (33% vs 75%, $p = 0.003$). Of the 8 patients who had a normal first study and underwent repeat study, 4 (50%) had new abnormalities on repeat imaging 2.8 (1 to 10) years later. Of the 29 patients undergoing serial imaging who had abnormal findings on first study, 25 (86%) had new abnormalities on repeat scan 2 (1 to 7) years later. Comparing those patients who underwent hepatic imaging ($n = 53$) versus those that did not ($n = 7$), evaluation with hepatic imaging was not related to current age (25 ± 5 vs 26 ± 6, $p = 0.6$), age at Fontan procedure (7 ± 6 vs 6 ± 4 years, $p = 0.8$), interval from Fontan procedure (20 ± 6 vs 21 ± 5 years, $p = 0.8$), type of Fontan procedure (modern day vs atriopulmonary connection 69% vs 66%, $p = 0.4$), clinical symptoms, or presence of an abnormal liver function test (70% vs 57%, $p = 0.4$) but was related to whether the patient was seen in a pediatric cardiology versus adult congenital cardiology clinic (48% vs 100%, $p = 0.001$). Liver biopsy was performed in 19 of the 35 (54%) patients noted to have cirrhosis on imaging and demonstrated Metavir F1 stage (no fibrosis) in 0, F1 to F2 stage (portal fibrosis and/or bridging fibrosis with few septae) in 4 (21%), F3 stage (bridging fibrosis with many septae) in 4 (21%), and F4 stage (cirrhosis) in 11 (58%). Esophagogastroduodenoscopy was performed in 23 patients, with findings of varices in 10 (43%), erosive gastric or duodenal ulcers in 5 (26%), and hepatic gastropathy or duodenopathy without ulcers in 9 (39%). Outpatient laboratory evaluation as defined herein was performed a median of 5 (1 to 20) times per patient over the past 10 years. Routine testing in everyone included a comprehensive metabolic panel with assessment of AST, ALT, alkaline phosphatase, protein, and albumin. In addition, 29 (48%)

Table 3
Laboratory correlates of hepatic pathology

Variable	Hepatic Cirrhosis		p
	No (n=18)	Yes (n=35)	
Gamma glutamyl transferase (U/L)	103.9 ± 57.8	129 ± 83.4	0.28
Aspartate aminotransferase (U/L)	37.7 ± 13.6	43.1 ± 15.0	0.07
Alanine aminotransferase (U/L)	33.3 ± 17.6	35.4 ± 14.8	0.33
Bilirubin (μmol/L)	23.2 ± 11.9	22.2 ± 15.3	0.64
Alkaline Phosphatase (U/L)	89.8 ± 34.4	109.7 ± 59.1	0.23
Platelets ($x10^3/\mu L$)	168.2 ± 46.7	184.6 ± 83.9	0.80
α-2 macroglobulin (g/L)	2.61 ± 1.0	3.44 ± 2.0	0.05
Hepatitis C Antibody positivity	1 (5)	0	NS
Aspartate aminotransferase to alanine aminotransferase ratio	1.26 ± 0.44	1.41 ± 0.69	0.47
Aspartate aminotransferase to platelet ratio	0.48 ± 0.28	0.55 ± 0.36	0.52
Age (years) x aspartate aminotransferase/ platelet count x alanine aminotransferase	38.29 ± 27.63	40.62 ± 25.14	0.53

Table 4
Clinical correlates of hepatic cirrhosis

Variable	Hepatic Cirrhosis		p
	No (n= 18)	Yes (n=35)	
Age at Fontan (months)	89.0 ± 65.0	75.0 ± 48.2	0.51
Years after Fontan	20.3 ± 5.4	21.3 ± 5.1	0.71
Systemic left ventricular	10 (58%)	17 (48%)	0.45
Recurrent atrial arrhythmias	43.3	57.7	0.28
Chronic amiodarone use (%)	2 (11%)	4 (11%)	0.90
Pacemaker	7 (39%)	13 (37%)	0.80
Years paced n= 21	5.2 ± 7.5	5.8 ± 7.7	0.83
Resting Sa02	90.4 ± 3.6	89.1 ± 4.3	0.17
Peak exercise Sa02 n= 48	86.6 ± 4.3	83.1 ± 6.2	0.04
Peak % predicted V02 n= 48	62.7 ± 12.5	59.0 ± 13.2	0.33
Fontan pressure n= 31	16.7 ± 3.9	15.9 ± 3.3	0.71
Wedge pressure n= 31	12.4 ± 3.7	10.2 ± 3.9	0.21
NYHA Class III/IV (%)	4 (22%)	18 (51%)	0.03
Ascites	4 (22%)	19 (54%)	0.005
Pleural Effusion	2 (11%)	7 (20%)	0.45
Protein Losing Enteropathy	2 (11%)	11 (31%)	0.12
Original Fontan Type			0.82
Classic APC	5 (28%)	12 (34%)	
LT	6 (33%)	12 (34%)	
EC	7 (39%)	11 (32%)	
Fontan Revision	1 (5%)	7 (20%)	0.14

patients underwent additional routine testing with gamma-glutamyl transferase (GGT), α-fetoprotein, complete blood count, and alpha2 macroglobulin as dictated by provider preference. All patients requiring surgery before 1992 or with findings of cirrhosis on imaging or biopsy underwent testing for Hepatitis C. One asymptomatic patient was hepatitis C antibody positive and did not merit treatment. Thrombocytopenia was present in 18 patients (30%). Patients without a functional spleen (n = 12) had a greater platelet count than those with a spleen (250 ± 77 vs 152 ± 51, p = 0.0006).

Few clinical or laboratory correlates of cirrhosis or other significant anatomic hepatic derangements were identified in this patient cohort (Tables 3 and 4). In patients without protein losing enteropathy, and thus with a normal protein level, an elevated α-2 macroglobulin level was present in 13 of 14 patients (93%) with cirrhosis versus 1 of 11 patients (9%) without cirrhosis (p <0.0001). Using receiver operating characteristic analysis to calculate area under the curve, no other laboratory marker or calculation was found to be a good predictor of cirrhosis with the 95% confidence interval for area under the curve crossing 0.5 in all instances. GGT and alkaline phosphatase correlated with both Fontan and wedge pressure (r = 0.4; p = 0.012, r = 0.5; p = 0.007 for GGT and r = 0.5, p = 0.001; r = 0.5, p = 0.008), respectively. No laboratory parameter was shown to correlate with years from Fontan procedure.

Interval between initial Fontan procedure to diagnosis of cirrhosis was 18 ± 5 years. Time to diagnosis of cirrhosis was explored for surgery type (contemporary Fontan procedure [lateral tunnel or extracardiac conduit] vs atriopulmonary connection), gender, and year of Fontan. Patients with a contemporary Fontan surgery had a shorter interval to diagnosis of cirrhosis than those with an atriopulmonary connection Fontan (17 ± 5 vs 25 ± 3 years, p = 0.01).

Of the 29 patients with significant hepatic derangements on imaging, adverse hepatic outcome occurred in 13, representing 45% of those with abnormal routine liver imaging and 22% of the entire patient cohort of 60 patients. Type and frequency of adverse hepatic outcomes included liver failure with death in 4 (with 1 of these patients having hepatic adenomatosis), recurrent gastrointestinal bleeding in 4, hepatic encephalopathy in 3, and evolving dysplastic nodules in 2 patients listed for cardiac transplantation, requiring re-listing for heart and liver transplants. Adverse liver outcome was not related to age at Fontan (77 ± 49 vs 82 ± 60 months; p = 0.9) or time from Fontan (20 ± 6 vs 21 ± 4 years; p = 0.65). Patients with an adverse liver outcome had a higher AST on routine laboratory testing (48 ± 20 vs 37 ± 10 U/L; p = 0.04) but no other serologic marker or calculated laboratory score differed between those with or without adverse liver outcome.

Discussion

We describe an adult cohort of Fontan survivors who underwent hepatic evaluation and in whom significant hepatic pathology was found in the majority, and in whom, longitudinal testing demonstrated progression of hepatic disease. Although routine hepatic imaging to rule out significant liver pathology in these patients is becoming increasingly frequent, it is still not universal. Even when performed, the type and frequency of testing varies markedly as described herein. Clinicians may be relying on routine liver serology to guide further testing. As noted by others, we found that routine serologic liver tests did not correlate with the presence of cirrhosis. There are several potential reasons for this. GGT and total bilirubin tend to be elevated in most adult patients who underwent Fontan[11] and do not necessarily reflect cirrhotic changes but rather, hepatic congestion. Conversely, hepatic transaminases often remain normal despite the presence of significant hepatic derangements.[10,11] Others have documented the serologic panel FibroSURE (Laboratory Corporation of America, Raritan, New Jersey) to be a good noninvasive marker for liver fibrosis in these patients.[3] The panel includes 6 biomarkers namely haptoglobin, apolipoprotein A1, bilirubin, GGT, ALT, and alpha-2 macroglobulin. In this series, this last biomarker was found to be highly correlated with the presence of cirrhosis, particularly in those patients without protein losing enteropathy who were able to mount an elevated globulin response in the face of hepatic pathology. More recently, investigators have proposed using the VAST score (varices, ascites, splenomegaly, thrombocytopenia) to assess which Fontan patients are at risk for adverse events secondary to portal hypertension.[11] Similar to previous publications[11] we did note a higher incidence of varices and ascites in those patients with cirrhosis and adverse hepatic outcome, but did not find thrombocytopenia to correlate with adverse outcome. This may be due in whole or in part to a not insignificant number of patients with structural or functional asplenia. These patients had significantly higher platelet counts that would prevent using the score universally in this population.

Because the frequency of hepatic imaging varied considerably in this study, the optimal frequency of screening remains unknown. We did demonstrate progressive hepatic anatomical derangements in the vast majority of patients undergoing serial screening with changes occurring over a period of as little as a year. Given that most patients had structural hepatic derangements at the initiation of screening, it appears that we are currently initiating imaging too late and that periodic imaging should be started in childhood or early adolescence and repeated at regular intervals. Timely diagnosis of structural hepatic derangements may allow for curative therapy for hepatocellular carcinoma, or modification to planned operative cardiosurgical interventions to mitigate risk.

This was a retrospective study and thus data collection was limited to that obtained during the process of routine outpatient care. The vast majority of patients had hepatic imaging and no patient in this cohort was lost to follow-up thereby limiting, albeit not eliminating, potential selection bias. Not all patients underwent liver biopsy, and thus the diagnosis of significant hepatic pathology was based on imaging studies that may not reflect the degree of hepatic pathology in these patients.[6] Serial imaging, although universal in those patients seen in an adult congenital cardiology clinic, was not obtained in all adults seen in a pediatric cardiology clinic thus hampering assessment of the average rate of disease progression. Data collection was confined to those patients who had currently reached adulthood and thus the incidence of hepatic derangements in childhood and adolescence cannot be commented on.

Disclosures

The authors have no conflicts of interest to disclose.

1. Schwartz MC, Sullivan LM, Glatz AC, Rand E, Russo P, Goldberg DJ, Rome JJ, Cohen MS. Portal and sinusoidal fibrosis are common on liver biopsy after Fontan surgery. *Pediatr Cardiol* 2013;34:135–142.
2. Kiesewetter CH, Sheron N, Vettukattill JJ, Hacking N, Stedman B, Millward-Sadler H, Haw M, Cope R, Salmon AP, Sivaprakasam MC, Kendall T, Keeton BR, Iredale JP, Veldtman GR. Hepatic changes in the failing Fontan circulation. *Heart* 2007;93:579–584.
3. Ginde S, Hohenwalter MD, Foley D, Sowinski J, Bartz PJ, Venkatapuram S, Weinberg C, Tweddell JS, Earing MG. Noninvasive assessment of liver fibrosis in adult patients following the Fontan procedure. *Congenit Heart Dis* 2012;7:235–242.
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;129:1347–1352.
5. Asrani SK, Warnes CA, Kamath PS. Hepatocellular carcinoma after the Fontan procedure. *N Engl J Med* 2013;368:1756–1757.
6. Rychik J, Veldtman G, Rand E, Russo P, Rome JJ, Krok K, Goldberg DJ, Cahill AM, Wells RG. The precarious state of the liver after a Fontan operation: summary of a multidisciplinary symposium. *Pediatr Cardiol* 2012;33:1001–1012.
7. Yang HR, Kim HR, Kim MJ, Ko JS, Seo JK. Noninvasive parameters and hepatic fibrosis scores in children with nonalcoholic fatty liver disease. *World J Gastroenterol* 2012;18:1525–1530.
8. Karlas T, Neuschulz M, Oltmanns A, Güttler A, Petroff D, Wirtz H, Mainz JG, Mössner J, Berg T, Tröltzsch M, Keim V, Wiegand J. Noninvasive evaluation of cystic fibrosis related liver disease in adults with ARFI, transient elastography and different fibrosis scores. *PLoS One* 2012;7:e421–e439.
9. Sirli R, Sporea I, Bota S, Popescu A, Cornianu M. A comparative study of non-invasive methods for fibrosis assessment in chronic HCV infection. *Hepat Mon* 2010;10:88–94.
10. Kaulitz R, Haber P, Sturm E, Schafer J, Hofbeck M. Serial evaluation of hepatic function profile after Fontan operation. *Herz* 2014;39: 998–1004.
11. Elder RW, McCabe NM, Hebson C, Veledar E, Romero R, Ford RM, Mahle WT, Kogon BE, Sahu A, Jokhadar M, McConnell ME, Book WM. Features of portal hypertension are associated with major adverse events in Fontan patients: the VAST study. *Int J Cardiol* 2013;168: 3764–3769.

Liver and Cardiac Function in the Long Term After Fontan Operation

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Background. Patients who underwent Fontan operation have some degree of liver disease. We aimed to assess the long-term liver and cardiac function after Fontan operation.

Methods. Patients enrolled underwent physical examination, biochemical tests (aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, bilirubin, international normalized ratio, coagulation factor V, protein profile, fecal alpha-1-antitrypsin), echocardiogram, and liver ultrasonography. A liver disease score was adopted to compare the degree of liver involvement with hemodynamic features.

Results. The study enrolled 34 patients, median age 14.7 years (range, 4.1 to 26.7), 26 with a residual left ventricle, 8 with a residual right ventricle, affected by tricuspid atresia (17), pulmonary atresia (4), hypoplastic left heart syndrome (5), double-outlet right ventricle (2), single left ventricle (2), and miscellaneous (4), with median follow-up of 1.5 years (range, 1.7 to 23.3). We found hepatomegaly in 18 of 34 (53%), splenomegaly in 9 of 33 (9%), abnormal transaminases in 10 of 33 (30%), elevated GGT in 9 of 16 (61%), elevated bilirubin in 10 of 31 (32%), coagulopathy in 17 of 29 (58%), and protein-losing enteropathy in 4 of 21 (19%). Median heart rate z-score was −1.72. Hepatic dysfunction was strictly correlated to low cardiac index ($r^2 = 0.34$, $p = 0.008$) and to a lesser extent to reduced heart rate ($r^2 = 0.18$, $p = 0.07$).

Conclusions. In children who underwent Fontan operation, hepatic dysfunction is correlated with low cardiac index and reduced heart rate. Maintaining or reestablishing a normal cardiac index might prevent or reduce liver disease in the long-term.

(Ann Thorac Surg 2008;86:177–82)

Over the last 30 years, advances in congenital heart surgery and intensive care medicine have dramatically increased the survival of infants with critical congenital heart disease, especially those with a single-ventricle cardiac malformation [1]. Staged palliation culminating in the Fontan operation has been life-saving to infants with single-ventricle cardiac malformations. Nevertheless, in patients followed up after total cavopulmonary connection, the average central venous pressure is about three to four times higher than normal [2, 3], and this is a well-known predisposing factor for the development of chronic liver disease [4]. Quite a few studies have shown that children with cardiac disease and systemic venous congestion have some degree of liver disease [5], and that after the Fontan operation, liver function tests are commonly abnormal [6–14]. However, no correlation has been found so far between the degree of liver disease and cardiac function indicators in this setting.

We sought to identify the characteristic pattern of liver dysfunction occurring in the long term after a Fontan operation and to determine the hemodynamic factors associated with hepatic impairment in children with a functionally single ventricle.

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Patients and Methods

Study Design

Between December 2003 and September 2004, patients who had previously undergone a Fontan operation at our institution and were attending the follow-up program were contacted on the phone to propose to enter a noninvasive study of cardiac and liver function. Thirty-four of 40 patients accepted to be enrolled in the study. Informed consent was obtained from the patients or their parents, and the Ethics Committee of our institution approved this study. Patients having comorbidities involving the liver such as chronic viral hepatitis were excluded from the study.

Patient Evaluation

The work-up comprised history and physical examination including weight, height, heart rate and blood pressure at rest and in supine position, liver and spleen clinical measurement expressed as distance of the lower border from the costal margin, and presence of ascites. A venous blood sample and a stool sample were obtained for laboratory tests. Liver ultrasonography and Doppler sonography were performed with the patient at rest and in the supine position. Echocardiography to evaluate cardiac function by two-dimensional M-mode measurements was also carried out.

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Table 1. Liver Disease Score

Score of Liver Disease	Score According to Considered Variables[a]		
	0	1	2
Liver size from costal edge	Normal (≤ 1 cm)	> 1 cm and ≤ 3 cm	> 3 cm
Total bilirubin	Normal	> 20 μmol/L	> 50 μmol/L
Clotting indicators[b]	Normal	INR > 1.2 and < 2.0 or factor V < 60% and > 30%	INR > 2 or factor V < 30%
Doppler of the hepatic vein	Normal	Monophasic or diphasic pattern	
Doppler of portal vein	Normal	PR < 0.54	Reversed flow
Doppler of the hepatic artery	Normal RI and PI	RI > 0.70 or PI > 1.64	RI > 0.70 and PI > 1.64

[a] Normal values: total bilirubin < 20 μmol/L; INR = 0.8 to 1.2; factor V > 60%; hepatic veins, triphasic pattern; PR > 0.54; RI < 0.7; PI < 1.64. [b] In patients on warfarin, the activity of factor V has been considered.

INR = international normalized ratio; PI = pulsatility index; PR = pulsatility ratio; RI = resistance index.

Evaluation of Liver Disease

LIVER ULTRASOUND AND DOPPLER. Measurements were made with an Esaote Technos MP (Esaote Group, Genova, Italy) using a broadband convex transducer. Pulsed-wave Doppler recordings of the hepatic vein, inferior vena cava, portal vein, and hepatic artery were performed with each patient breathing quietly in the supine position and after fasting. The transducer was placed in a subxyphoid and right intercostal position. Each result was the mean of three measurements.

The study was carried out according to previously published methods, and the values obtained were compared with normal age-matched subjects, as previously described [15–17]. Doppler data included direction, velocity, and flow pattern in the hepatic vein, inferior vena cava, portal vein, and hepatic artery. Pulsatility ratio (PR = minimal flow velocity/maximal flow velocity [normal value greater than 0.54]) of the portal vein as a marker of hepatic vein congestion [18–21], resistance index (RI = peak systolic velocity − end diastolic velocity/peak systolic velocity [normal value lower than 0.7]), and pulsatility index (PI = peak systolic velocity − end diastolic velocity/mean velocity [normal value lower than 1.64]) of the hepatic artery were also calculated [22].

LABORATORY TESTS. We tested full blood count, alanine aminotransferase (normal values, 10 to 40 IU/L), aspartate aminotransferase (normal value, 10 to 40 IU/L), gamma glutamyl transpeptidase (normal value, 10 to 40 IU/L), lactic dehydrogenase (normal value, 0 to 580 IU/L), total bilirubin (normal vaue, less than 20 μmol/L), total protein, albumin, prothrombin time, international normalized ratio, and partial activated thromboplastin time. In patients taking oral anticoagulants (warfarin) factor V activity was determined for evaluation of coagulopathy (normal activity, greater than 60%) [23]. A stool sample was obtained for alpha-1-antitrypsin measurement (normal value, less than 5 mg/g dry stool).

SCORE OF LIVER DAMAGE. For the global evaluation of liver disease, a score of liver injury was introduced, including clinical, laboratory, and echographic data. The liver score has been formulated upon expert consensus with the aim to assess liver function in patients with potential hemodynamic imbalance. We included synthetic function (international normalized ratio and factor V activity), biliary function (serum bilirubin), and liver blood flow and congestion (liver size and Doppler ultrasonography). The score was then compared with cardiac anatomy, type of intervention, and cardiac function of each patient (Table 1).

EVALUATION OF CARDIAC FUNCTION. Medical records, operative notes, electrocardiograms, echocardiography reports, and recent (within the last 2 years) cardiac catheterization reports when available were reviewed. Blood pressure was measured during echocardiography evaluation. All these patients were studied with a 12-lead and a 24-hour Holter electrocardiogram. None of them had a pacemaker.

After positioning of the subject in a partial left decubitus position, a two-dimensional and M-mode echocardiogram was performed with a Hewlett-Packard Sonos 2500 echocardiographer (Hewlett-Packard Company, Palo Alto, CA) during morning hours. This evaluation was considered reliable only if the left ventricle normal geometry was maintained. Measurements of interventricu-

Table 2. Characteristics of Patients

	Number	%
Male	20	59
Female	14	41
Median age, years (range)	14.7 (4.1–26.7)	
Age at operation, years (range)	3.3 (0.9–14.4)	
Follow-up, years (range)	11.5 (1.7–23.2)	
Diagnosis		
Tricuspid atresia	17	50
Pulmonary atresia	4	11.8
Hypoplastic left heart syndrome	5	14.8
Double-outlet right ventricle	2	5.8
Holmes heart	2	5.8
Miscellaneous	4	11.8
Type of intervention		
Atriopulmonary connection	8	23.5
Total cavopulmonary connection	26	76.5

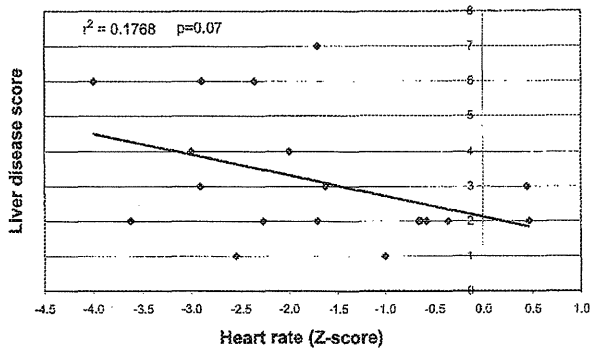

Fig 1. Correlation between increased liver disease score and low heart rate. The equation of the straight line relating liver disease score and heart rate is estimated as: liver disease score = (2.1250) + (−0.5949) heart rate.

lar septal thickness, posterior wall thickness, and left ventricle dimensions were taken at or just below the mitral valve tips by the leading edge-to-leading edge method at the onset of the electrocardiographic Q wave, according to the American Society of Echocardiography [24].

Left ventricular end-diastolic and end-systolic volumes were calculated with the Teichholz correction of the cube formula [25]. Left ventricle chamber volumes and stroke volume determined by this approach have been shown to correlate well with invasive and with two-dimensional and Doppler-echocardiographic volume measurements in a variety of populations with symmetrical left ventricle wall motion [26–28].

The cardiac index (heart rate × systolic output/body surface [mL · min^{-1} · m^{-2}]) and the stroke volume were calculated for each patient, or retrieved from a recent cardiac catheterization in those with a residual right ventricle [29–30]. Heart rate was derived by a 24-hour Holter electrocardiographic recording on each patient.

Statistics

We performed the Student *t* test for paired and unpaired couples of data. Linear regression analysis was used for correlations between hepatic and cardiac values (NCSS 2000 package and Excel for Windows).

Results

Overall, 34 patients accepted to enter the study. Twenty were male, and 14 female; the median age at assessment was 14.7 years (range, 4.1 nto 26.7). Patients' diagnoses and type of Fontan procedure are summarized in Table 2. Eight patients (23.5%) had a morphologic right ventricle, and 26 (76.5%) had a morphologic left ventricle.

Twenty-three patients underwent a total cavopulmonary connection, 11 underwent an atriopulmonary connection. Three patients of the latter group underwent a new operation to convert their original atriopulmonary anastomosis to a total cavopulmonary connection; therefore, in our study, they are included in the former group of patients. None of the patients was taking drugs known to be associated with liver dysfunction.

The median age at intervention was 3.3 years (range, 0.9 to 14.4), with a median follow-up after Fontan operation of 11.5 years (range, 1.7 to 23.2). Patients with an atriopulmonary connection have a follow-up significantly longer (mean duration, 18.7 ± 5.8 years) than those with a total cavopulmonary connection (mean duration, 9.6 ± 11.3 years; $p = 0.00014$, Student *t* test).

Clinical Observations

All patients lead a nearly normal life. Median heart rate was 65 beats per minute (range, 42 to 110). Median heart rate z-score was −1.72 (range, 0.9 to −4); 22 of 34 (65%) had a heart rate less than 1 SD of normal, and 12 of 34 (35%) less than 2 SD of normal. Hepatomegaly was clinically observed in 18 patients (54.5%); liver size from costal edge was equal to or greater than 4 cm in 6 cases (17.6%). Splenomegaly was found in 3 of 33 patients (9%). One patient had asplenia. There was a clear tendency to significance for the correlation between low heart rate and increased liver disease score ($r^2 = 0.18$, $p = 0.07$; Fig 1). In fact, only 3 patients (9%) had a heart rate z-score above zero with respect to normal values for age. A

Table 3. Laboratory Tests

	Normal Value	Number of Patients Tested	Median (range)	Number Abnormal (%)
Aspartate aminotransferase	15–40 U/L	33	35 (20–69)	6 (18)
Alanine aminotransferase	5–40 U/L	33	31 (13–62)	8 (24)
Gamma glutamyl transpeptidase	3–40 U/L	31	44 (3–184)	19 (61)
Total bilirubin	1.7–20 μmol/L	31	17 (1–32)	10 (32)
Direct bilirubin	0–7 μmol/L	29	4.7 (0.1–10)	6 (21)
Total protein	60–80 g/L	30	74.4 (35–92)	> 2 SD: 4 (13) < 2 SD: 2 (7)
Albumin	35–46 g/L	28	45 (16.6–64)	> 2 SD: 10 (36) < 2 SD: 2 (7)
International normalized ratio[a]	< 1.20	23	1.2 (1.09–2.9)	15/23 (65)
Factor V[b]	60%–150%	6	71 (42–104)	2 (30)
Fecal alpha-1-antitrypsin	0–5 mg/g	21	2 (1–72)	4 (19)

[a] Excluded patients on warfarin. [b] Only patients on warfarin.

junctional rhythm was found in 8 of 34 patients (23%). Considering only the presence of coagulopathy or increased bilirubin, the patients with no coagulopathy had a mean heart rate z-score of −1.5 versus −1.8 in patients who had coagulopathy—lower but not statistically different; patients with increased bilirubin had a mean heart rate z-score of −2.1 versus −1.6 in patients with normal bilirubin—still lower but not statistically different.

Laboratory Tests

Results of laboratory tests are reported in Table 3. Ten patients of 31 (32%) showed elevated total bilirubin; 17 of 29 (58%) had an abnormal clotting profile. Total protein was low in 2 of 30 patients (7%), and both showed high levels of alpha-1-antitrypsin in stools (65 and 72 mg/dL [normal value, less than 5 mg/g dry stool]). Elevation of alpha-1-antitrypsin in stool was found in 4 of 21 patients (19%), 2 of whom had clinically overt protein-losing enteropathy.

Severity of liver disease according to the score did not correlate with patient age, age at operation, length of follow-up, residual left or right ventricle, type of surgical repair (atriopulmonary connection versus total cavopulmonary connection), or protein-losing enteropathy. However, patients with an atriopulmonary connection repair had a significantly greater gamma glutamyl tranaspeptidase level (92 versus 44 U/L, $p = 0.01$). The presence of a fenestration, as assessed by echocardiography performed at the time of the study, did not correlate with any indicator of liver function.

Liver Ultrasonography and Doppler

An abnormal flow pattern in the hepatic vein was found in 6 of 33 patients (18%). The diameter of the portal vein was greater than normal in 2 of 34 patients (6%); the median flow velocity was 21 cm/s (range, 9 to 34), abnormally reduced in 9 patients (26%). The flow was hepatopetal in 30 cases (88%), whereas a diastolic reversed flow was recorded in 4 patients (12%). An abnormally fluctuating portal flow with a reduced pulsatility ratio was found in 17 of 34 (50%). However, there was no strict correlation between portal pulsatility ratio and liver disease score ($r^2 = 0.10$, $p > 0.1$), nor between pulsatility ratio and coagulopathy ($p > 0.1$, Student t test). The resistance index in the hepatic artery showed a mean value of 0.74 (range, 0.48 to 0.95), above the normal range in 63% and below in 12%. The mean pulsatility index was 1.38 (range, 0.67 to 3.4), above the normal range in 22% and below the normal range in 13%.

Cardiac Function

Nine patients (26%), including all of those with a morphologic right ventricle, had their cardiac index obtained from a recent cardiac catheterization, whereas the others were studied by echocardiography. Six of 34 patients had an open fenestration when assessed for this study. The presence of an open fenestration did not correlate with the degree of liver dysfunction.

Median ejection fraction was 62%, median shortening fraction was 34%; both were reduced in 5 of 25 patients (20%). Median cardiac index was 2,934 mL · min^{-1} · m^{-2} (range, 1,111 to 6,269 mL · min^{-1} · m^{-2}), reduced in 50%; median stroke volume was 48 mL/m^2 (range, 17 to 81 mL/m^2), reduced in 2 patients (8%). There was an apparent trend to correlation between reduced cardiac index and increased liver disease score ($r^2 = 0.34$; $p = 0.008$; Fig 2). Considering only the presence of coagulopathy, the patients with no coagulopathy had a cardiac index significantly greater than patients who had coagulopathy (mean, 3,591 versus 2,485 mL · min^{-1} · m^{-2}; $p = 0.03$). Considering the level of total bilirubin, patients with an abnormally high value had a lower cardiac index than patients with normal bilirubin (2,087 versus 3,494 mL · min^{-1} · m^{-2}; $p = 0.02$, Student t test).

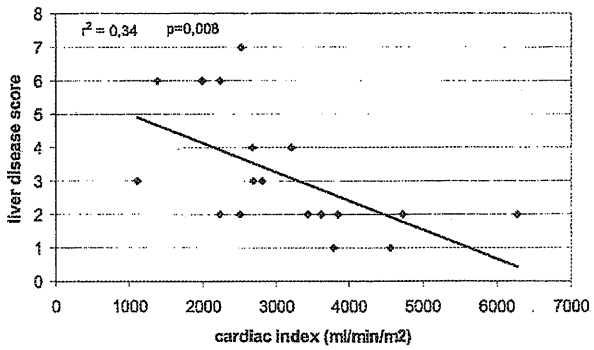

Fig 2. Correlation between increased liver disease score and low cardiac index. The equation of the straight line relating liver disease score and cardiac index is estimated as: liver disease score = (5.8568) + (−0.0009) cardiac index.

Comment

Total cavopulmonary connection is considered the best palliation of complex congenital heart defects with functionally single ventricle. In this condition, several adverse events have been described but strict correlations between long-term complications and type of surgical repair or hemodynamics are lacking, especially as far as liver disease is concerned [31, 32].

The Fontan operation carries features possibly leading to chronic hepatopathy, such as an average central venous pressure about three to four times higher than normal. Venous congestion is a known predisposing factor for chronic liver disease in adults, and has proved to be a feature, confirmed histologically, in keeping with liver dysfunction after Fontan [3, 33–35]. Although venous congestion is the most logical cause of liver dysfunction in a circulation lacking a pulmonary pump, previous findings have suggested that other mechanisms might be implicated and that longstanding increased systemic venous pressure is probably just one of the factors influencing liver function in this setting. Indeed, abnormal coagulation factors levels have been observed in patients after bidirectional cavopulmonary anastomosis, with presumably low splanchnic venous pressure [36], as well as in patients with single-ventricle physiol-

ogy before the bidirectional cavopulmonary anastomosis [37]. It is well known that during a staged Fontan approach, thromboembolic complications may occur, but the cause of perioperative coagulation abnormalities is rather unclear. Procelewska and colleagues [38] recently reported that the hemodynamic status is important as far as coagulation abnormalities and liver dysfunction after hemi-Fontan and Fontan procedures are concerned. The study suggests that elevated concentration of factor VIII and significant influence of hemodynamics on coagulation profile could contribute to postoperative thromboembolic complications [38].

These findings support the hypothesis that, beside venous congestion, other factors may contribute to liver dysfunction in these patients. We have investigated liver venous congestion using the portal pulsatility ratio, a reliable noninvasive test [18–21], and found that 50% of our patients have features of hepatic vein congestion. Nevertheless, there was no correlation between this index and liver disease score or presence of coagulopathy. We therefore hypothesized that other factors might be implicated in the development of liver damage in these patients.

One of the main laboratory features suggesting liver function derangement is the occurrence of coagulopathy, and has previously been described in this setting by several studies [8, 11–14]. Chaloupecky and coworkers [39] observed reduced mean concentrations of factor VII, factor V, protein C, and fibrinogen in patients after total cavopulmonary connection. The same study suggested that the abnormalities in the coagulation profile observed in patients after Fontan operation are related to protein production in the liver [39]. We decided to test coagulopathy using also the measurement of factor V, a vitamin K–independent and therefore also a warfarin-unaffected marker of deranged hepatic synthetic function. This marker is very trustworthy and used commonly in the setting of liver failure [40]. Interestingly, we have found that coagulopathy and liver disease score are correlated with reduced cardiac index and, to a lesser extent, with heart rate, suggesting a probably reduced liver blood flow after Fontan operation.

The same hemodynamic mechanism has been implicated in liver disease of different etiology. Children with portal hypertension due to portal vein thrombosis have a selective impairment of clotting factors and otherwise normal liver function tests [41], similar to Fontan patients [8, 11]; restoring a normal liver blood flow in children with portal vein thrombosis leads to complete normalization of clotting profile [42]. Narkewicz and colleagues [43] found an abnormal galactose elimination in a group of children after the Fontan procedure. This test represents the functional hepatic mass receiving arterial or venous blood flow, being an indirect marker of liver blood flow. Tomita and associates [9] found that Fontan patients' coagulopathy and overall liver function tests were more deranged as compared with a group of patients with increased atrial pressure due to other cardiac diseases, and that prothrombin time correlated to some extent to hemodynamic features, including cardiac index [9]. All these findings support the hypothesis that reduced liver blood flow plays a role in liver disease of Fontan patients.

It is rather well known that most of the children who undergo Fontan operation are bradycardic and have a reduced variability of heart rate [44]. In our study, we have shown that bradycardia is a feature of Fontan's patients with reduced cardiac index. Indeed, there was an apparent trend to correlation between liver disease and low heart rate.

In conclusion, in our study, we have suggested that, in the long-term after Fontan operation, liver dysfunction correlates with reduced cardiac index. The effect of hepatic venous congestion has been demonstrated to be a feature of these patients but could not explain entirely liver disease in this setting. These preliminary findings, if confirmed by a larger prospective study, suggest that the reduction of liver blood flow could affect the hepatic function after the Fontan procedure and that strategies aimed at maintaining or reestablishing a normal cardiac index might prevent or improve liver disease in the long term after a Fontan operation.

References

1. Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax 1971;26:240–8.
2. Kaulitz R, Luhmer I, Bergmann F, Rodeck B, Hausdorf G. Sequelae after modified Fontan operation: postoperative haemodynamic data and organ function. Heart 1997;78:154–9.
3. Stamm C, Friehs I, Mayer JE Jr, et al. Long-term results of the lateral tunnel Fontan operation. J Thorac Cardiovasc Surg 2001;121:28–41.
4. Naschitz JE, Slobodin G, Lewis RJ, Zuckerman E, Yeshurun D. Heart diseases affecting the liver and liver diseases affecting the heart. Am Heart J 2000;140:111–20.
5. Mace S, Borkat G, Liebman J. Hepatic dysfunction and cardiovascular abnormalities: occurrence in infants, children, and young adults. Am J Dis Child 1985;139:60–5.
6. Cromme-Dijkhuis AH, Hess J, Hahlen K, et al. Specific sequelae after Fontan operation at mid- and long-term follow-up. J Thorac Cardiovasc Surg 1993;106:1126–32.
7. Cromme-Dijkhuis AH, Henkens CM, Bijleveld CM, Hillege HL, Bom VJ, van der Meer J. Coagulation factor abnormalities as possible thrombotic risk factors after Fontan operations. Lancet 1990;336:1087–90.
8. van Nieuwenhuizen RC, Peters M, Lubbers LJ, Trip MD, Tijssen JG, Mulder BJ. Abnormalities in liver function and coagulation profile following the Fontan procedure. Heart 1999;82:40–6.
9. Tomita H, Yamada O, Ohuchi H, et al. Coagulation profile, hepatic function, and hemodynamics following Fontan-type operations. Cardiol Young 2001;11:62–6.
10. Rauch R, Ries M, Hofbeck M, Buheitel G, Singer H, Klinge J. Hemostatic changes following the modified Fontan operation (total cavopulmonary connection). Thromb Haemost 2000;83:678–82.
11. Jahangiri M, Shore D, Kakkar V, Lincoln C, Shinebourne E. Coagulation factor abnormalities after the Fontan procedure and its modifications. J Thorac Cardiovasc Surg 1997;113:989–92.
12. Jahangiri M, Kreutzer J, Zurakowski D, Bacha E, Jonas RA. Evaluation of hemostatic and coagulation factor abnormalities in patients undergoing the Fontan operation. J Thorac Cardiovasc Surg 2000;120:778–82.

13. Ravn HB, Hjortdal VE, Stenbog EV, et al. Increased platelet reactivity and significant changes in coagulation markers after cavopulmonary connection. Heart 2001;85:61–5.
14. Odegard KC, McGowan FX Jr, Zurakowski D, et al. Procoagulant and anticoagulant factor abnormalities following the Fontan procedure: increased factor VIII may predispose to thrombosis. J Thorac Cardiovasc Surg 2003;125:1260–7.
15. Ayabakan C, Özkutlu S. Normal patterns of flow in the superior cava, hepatic and pulmonary veins as measured using Doppler echocardiography during childhood. Cardiol Young 2003;13:143–51.
16. Meyer RJ, Goldberg SJ, Donnerstein RL. Superior vena cava and hepatic velocity patterns in normal children. Am J Cardiol 1993;72:238–40.
17. Vocke AK, Kardorff R, Ehrich JHH. Sonographic measurements of the portal vein and its intrahepatic branches in children. Clinical report. Eur J Ultrasound 1998;7:121–7.
18. Duerinckx AJ, Grant EG, Perrella RR, Szeto A, Tessler FN. The pulsatile portal vein in cases of congestive heart failure: correlation of Duplex Doppler findings with right atrial pressures. Radiology 1990;176:655–8.
19. Hosoki T, Arisawa J, Marukawa T, et al. Portal blood flow in congestive heart failure: pulsed duplex sonographic findings. Radiology 1990;174:733–6.
20. Catalano D, Caruso G, Di Fazzio S, Carpinteri G, Scalisi N, Trovato GM. Portal vein pulsatility ratio and heart failure. J Clin Ultrasound 1998;26:27–31.
21. Rengo C, Brevetti G, Sorrentino G, et al. Portal vein pulsatility ratio provides a measure of right heart function in chronic heart failure. Ultrasound Med Biol 1998;24:327–32.
22. Sacerdoti D, Merkel C, Bolognesi M, Amodio P, Angeli P, Gatta A. Hepatic arterial resistance in cirrhosis with and without portal vein thrombosis: relationships with portal hemodynamics. Gastroenterology 1995;108:1152–8.
23. Flanders MM, Phansalkar AR, Crist RA, Roberts WL, Rodgers GM. Pediatric reference intervals for uncommon bleeding and thrombotic disorders. J Pediatr 2006;149:275–7.
24. Sahn DJ, DeMaria A, Kisslo J, Weyman A, for the Committee on M-Mode Standardization of the American Society of Echocardiography. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978;58:1072–83.
25. Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determination: echocardiographic-angiographic correlations in the presence or absence of asynergy. Am J Cardiol 1976;37:7–12.
26. Kronik G, Slany J, Mosslacher H. Comparative value of eight M-mode echocardiographic formulas for determining left ventricular stroke volume: a correlative study with thermodilution and left ventricular single plane cineangiography. Circulation 1979;60:1308–16.
27. Wallerson DC, Ganau A, Roman MJ, Devereux RB. Measurement of cardiac output by M-mode and two-dimensional echocardiography: application to patients with hypertension. Eur Heart J 1990;11(Suppl 1):67–78.
28. Wallerson DC, Devereux RB. Reproducibility of echocardiographic left ventricular measurements. Hypertension 1987; 9(Suppl 2):6–18.
29. Tibby SM, Hatherill M, Marsh MJ, Morrison G, Anderson D, Murdoch IA. Clinical validation of cardiac output measurements using femoral artery thermodilution with direct Fick in ventilated children and infants. Intens Care Med 1997; 23:987–91.
30. de Simone G, Devereux RB, Daniels SR, et al. Stroke volume and cardiac output in normotensive children and adults: assessment of relations with body size and impact of obesity. Circulation 1997;95:1837–43.
31. Driscoll DJ, Offord KI, Feldt RH, Schaff HV, Puga FJ, Danielson GK. Five- to fifteen-year follow-up after Fontan operation. Circulation 1992;85:469–96.
32. Mair DD, Puga FJ, Danielson GK. The Fontan procedure for tricuspid atresia: early and late results of a 25 year experience with 216 patients. J Am Coll Cardiol 2001;37:933–9.
33. Marino BS. Outcomes after the Fontan procedure. Curr Op Ped 2002;14:620–6.
34. 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.
35. Kiesewetter CH, Sheron N, Vettukattill JJ, et al. Hepatic changes in the failing Fontan circulation. Heart 2007;93:579–84.
36. Odegard KC, McGowan FX Jr, Zurakowski D, et al. Coagulation factor abnormalities in patients with single-ventricle physiology immediately prior to the Fontan procedure. Ann Thorac Surg 2002;73:1770–7.
37. Odegard KC, McGowan FX Jr, DiNardo JA, et al. Coagulation abnormalities in patients with single-ventricle physiology precede the Fontan procedure. J Thorac Cardiovasc Surg 2002;123:459–65.
38. Procelewska M, Kolcz J, Januszewska K, Mroczek T, Malec E. Coagulation abnormalities and liver function after hemi-Fontan and Fontan procedures—the importance of hemodynamics in the early postoperative period. Eur J Cardiothorac Surg 2007;31:866–72.
39. Chaloupecky V, Svobodova I, Hadacova I, et al. Coagulation profile and liver function in 102 patients after total cavopulmonary connection at mid term follow up. Heart 2005;91: 73–9.
40. Devictor D, Tahiri C, Rousset A, Massenavette B, Russo M, Huault G. Management of fulminant hepatic failure in children—an analysis of 56 cases. Crit Care Med 1993; 21(Suppl):348–9.
41. Mack CL, Superina RA, Whitington PF. Surgical restoration of portal flow corrects procoagulant and anticoagulant deficiencies associated with extrahepatic portal vein thrombosis. J Pediatr 2003;142:197–9.
42. Superina R, Bambini DA, Lokar J, Rigsby C, Whitington PF. Correction of extrahepatic portal vein thrombosis by the mesenteric to left portal vein bypass. Ann Surg 2006;243:515–21.
43. Narkewicz MR, Sondheimer HM, Ziegler JW, et al. Hepatic dysfunction following the Fontan procedure. J Pediatr Gastroenterol Nutr 2003;36:352–7.
44. Rydberg A, Wiklund U, Rask P, Hornsten R. Serial assessment of variability in heart rate in children with the Fontan circulation. Cardiol Young 2005;15:498–503.

An international multicenter study comparing arrhythmia prevalence between the intracardiac lateral tunnel and the extracardiac conduit type of Fontan operations

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Objective: The study objective was to determine whether the extracardiac conduit Fontan confers an arrhythmia advantage over the intracardiac lateral tunnel Fontan.

Methods: This multicenter study of 1271 patients compared bradyarrhythmia (defined as need for pacing) and tachyarrhythmia (defined as needing antiarrhythmic therapy) between 602 patients undergoing the intracardiac Fontan and 669 patients undergoing the extracardiac Fontan. The median age at the time of the Fontan procedure was 2.1 years (interquartile range, 1.6-3.2 years) for the intracardiac group and 3.0 years (interquartile range, 2.4-3.9) for the extracardiac group ($P < .0001$). The median follow-up was 9.2 years (interquartile range, 5-12.8) for the intracardiac group and 4.7 years (interquartile range, 2.8-7.7) for the extracardiac group ($P < .0001$).

Results: Early postoperative (<30 days) bradyarrhythmia occurred in 24 patients (4%) in the intracardiac group and 73 patients (11%) in the extracardiac group ($P < .0001$). Early postoperative (<30 days) tachyarrhythmia occurred in 32 patients (5%) in the intracardiac group and 53 patients (8%) in the extracardiac group (P = not significant). Late (>30 days) bradyarrhythmia occurred in 105 patients (18%) in the intracardiac group and 63 patients (9%) in the extracardiac group ($P < .0001$). Late (>30 days) tachyarrhythmia occurred in 58 patients (10%) in the intracardiac group and 23 patients (3%) in the extracardiac group ($P < .0001$). By multivariate analysis factoring time since surgery, more patients in the extracardiac group had early bradycardia (odds ratio, 2.9; 95% confidence interval, 1.8-4.6), with no difference in early tachycardia, late bradycardia, or late tachycardia.

Conclusions: Overall arrhythmia burden is similar between the 2 groups, but the extracardiac Fontan group had a higher incidence of early bradyarrhythmias. There was no difference in the incidence of late tachyarrhythmias over time between the 2 operations. Therefore, the type of Fontan performed should be based on factors other than an anticipated reduction in arrhythmia burden from the extracardiac conduit. (J Thorac Cardiovasc Surg 2014;148:576-81)

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The Fontan operation, first described in the early 1970s, revolutionized the management of children with single ventricles.[1] Since inception, the procedure has undergone numerous modifications. Chief among these was the development of the intracardiac lateral tunnel (ILT). First described by de Leval and colleagues,[2] the ILT improved surgical outcomes compared with the original atriopulmonary connection (APC) and was therefore generally adopted. Soon thereafter, Marcelletti and colleagues[3] described the extracardiac conduit (ECC) modification, which, although similar to the ILT, bypasses the right atrium with a conduit from the inferior vena cava to the pulmonary artery.

Arrhythmias, both bradycardia (mainly sinus node dysfunction [SND]) and, more important, tachyarrhythmias (primarily supraventricular tachycardia [SVT] due to atrial

Abbreviations and Acronyms
AFL = atrial flutter
APC = atriopulmonary connection
ECC = extracardiac conduit
ECG = electrocardiography
IART = incisional atrial reentrant tachycardia
ILT = intracardiac lateral tunnel
IQR = interquartile range
OR = odds ratio
SD = standard deviation
SND = sinus node dysfunction
SVT = supraventricular tachycardia

flutter [AFL] or incisional atrial reentrant tachycardia [IART]) have been a challenging problem in patients undergoing the Fontan.[4-6] Bradyarrhythmias are thought to be primarily due to damage to the sinus node or its arterial supply. Tachyarrhythmias are thought to be due to suture lines and pressure and volume overload of the right atrium. Although early bradyarrhythmias and tachyarrhythmias can complicate the immediate postoperative management and increase the hospital length of stay, they are often transient. In the long-term, bradyarrhythmias can be managed by pacemaker implant. However, tachyarrhythmias in this patient population can be a major cause of morbidity and mortality and hard to manage.

The ILT resulted in less late tachyarrhythmia compared with the APC.[4-6] Marcelletti and colleagues[3] proposed that the ECC would be even less arrhythmogenic because it bypasses the right atrium.[7] To date, most studies comparing the ILT with the ECC have been cross-sectional rather than longitudinal and have been inconclusive in determining whether the ECC provides a long-term arrhythmia benefit compared with the ILT.[8-17]

To better evaluate the incidence of arrhythmia in the current era, a multicenter international retrospective study was designed to examine the prevalence and potential difference in early (≤30 days) and late (>30 days) bradyarrhythmias and tachyarrhythmias after the ILT and ECC operations.

MATERIALS AND METHODS

This study was a retrospective cohort study, with The Children's Hospital of Philadelphia serving as the data coordinating center. The study received approval by an institutional review board at each participating institution. All members of the Pediatric and Congenital Electrophysiology Society were contacted and invited to participate in the study.

Study Population

Subjects were identified through a database search and included all patients who underwent an ILT or ECC between January 1, 1998, and January 1, 2008. Patients were excluded from the study if (1) an arrhythmia was documented before their ILT or ECC and (2) follow-up after ILT or ECC was less than 1 year or (3) a previous APC had been performed. A small group of patients (n = 56) at one institution were part of a study of patients with ILT randomized to receive or not receive additional incisions within the right atrium, which may prevent the development of postoperative arrhythmias. We analyzed our data with and without this subset of patients and did not identify any difference; therefore, the data presented include these 56 patients.

Medical Record Review

Standardized data forms were used to extract pertinent data from medical records regarding patient demographics, cardiac anatomic diagnosis, type of surgical repair, electrocardiography (ECG) and ambulatory Holter monitor findings, and presence of rhythm disturbances. When rhythm disturbances were documented, the onset, type, and treatment for the rhythm disturbance were noted.

Rhythm Analysis

Relevant rhythm documentation was reviewed at the individual institutions. If bradyarrhythmias were documented, they were classified as SND or atrioventricular block. If tachyarrhythmias were present, they were classified as SVT or ventricular tachycardia. For the purpose of this study, bradycardia was considered significant if it required pacing. SVT was defined as a rhythm disturbance originating above the ventricles resulting in a fast heart rate causing death or requiring acute or chronic therapy, such as pharmacotherapy, antitachycardia pacing, direct current cardioversion or defibrillation, catheter ablation, or arrhythmia surgery. We did not subcategorize the mechanism of SVT as being due to AFL/IART.

Surgical Procedures

Patients were divided into 2 Fontan groups according to the following: (1) If an external conduit connected the inferior vena cava to the pulmonary artery, patients were classified as having the ECC type of Fontan. (2) If an intra-atrial tunnel connected the inferior vena cava to the pulmonary artery, patients were classified as having the intracardiac lateral tunnel (ILT) type of Fontan. In patients with unusual anatomy, such as heterotaxy syndromes, regardless of modifications used in their surgery, we designated patients using the listed criteria. No patients were excluded from the analysis because of modifications to their surgery.

Surgeries preceding the Fontan operation and the presence or absence of Fontan fenestration were documented. The early postoperative period was defined as the time period 30 days or less after Fontan surgery. The late postoperative period was defined as the period more than 30 days after Fontan surgery.

Study End Points

The primary end points of this study were (1) documented bradyarrhythmia requiring pacing, either temporary or permanent (any patient who received temporary or permanent pacing in the early postoperative period was noted), and (2) documented SVT causing death or clinical symptoms requiring management with commonly used therapeutic options.

Statistical Methods

Descriptive statistics were calculated for demographic and descriptive data, reported as median with interquartile range (IQR) for quantitative variables and number and percentage for qualitative variables. Demographic and clinical variables were compared between the 2 groups (ILT vs ECC) using the Mann–Whitney *U* test, Pearson chi-square test, or Fisher exact test as appropriate.

Multivariate logistic regression models were used to assess the relationship between the type of Fontan (bidirectional Glenn, early arrhythmia, late arrhythmia, hemi-Fontan, and fenestration) adjusting for age at Fontan.

Kaplan–Meier survival curves were generated for time to first late bradyarrhythmia and time to first late tachyarrhythmia. Multivariate Cox regression models were used to assess whether there was a difference between the 2 groups adjusting for age at Fontan. In addition, we also

TABLE 1. Patient characteristics

Variable	ILT (%)	ECC (%)	*P* value
N	602	669	NA
Male	231 (60)	286 (60)	NS
Dominant RV	292 (49)	266 (40)	.007
Dominant LV	165 (27)	219 (33)	NS
Other SV	145 (24)	184 (28)	NS
Norwood*	298	296	NS
Shunts†	190	233	NS
PA band	55	66	NS
Other	21	22	NS
No surgery	38	52	NS
Hemi-Fontan	339 (69)	24 (6)	<.0001
Bidirectional Glenn	58 (12)	296 (70)	<.0001
Fenestration	422 (71)	468 (70)	NS
Age at surgery 1 (d) (median, IQR)	7 (4-30)	8 (3-30)	NS
Age at surgery 2 (mo) (median, IQR)	6.7 (5-11)	6.6 (5-10)	NS
Age at Fontan (y) (median, IQR)	2.1 (1.6-3.2)	3.0 (2.4-3.9)	<.0001
Age at last FU (y) (median, IQR)	11.8 (7.7-16.5)	7.9 (5.4-10.8)	<.0001
FU since Fontan (y) (median, IQR)	9.2 (5-12.8)	4.7 (2.8-7.7)	<.0001

ECC, Extracardiac conduit; *FU*, follow-up; *ILT*, intracardiac lateral tunnel; *IQR*, interquartile range; *LV*, left ventricle; *NA*, not available; *NS*, not significant; *PA*, pulmonary artery; *RV*, right ventricle; *SV*, single ventricle. *Includes all Norwood-type operations. †Includes all varieties of systemic to pulmonary shunts.

performed multivariate Cox regressions adjusting for patient clustering by site with robust sandwich covariance matrix estimation in an effort to see whether patient clustering by center had an effect on results.

RESULTS

Patients

A total of 1500 patient records from 14 tertiary care cardiac centers (10 US, 1 Canadian, and 3 international centers [2 from Japan and 1 from The Netherlands]) were screened for study participation. There were 1271 patients (84.7%) identified as eligible and included in the study. Of these, 602 (47%) were in the ILT group and 669 (53%) were in the ECC group. Table 1 outlines the demographic aspects of the 2 groups. There was no difference in gender between the 2 groups (Table 1). The ILT group had a slightly higher proportion of patients with a dominant right ventricle and a slightly higher incidence of the Norwood-type operation as the initial surgery. Operations before the stage 1 Fontan repair (ie, bidirectional Glenn or hemi-Fontan) were broken down into Norwood type procedures (including Sano modification and Damus–Kaye–Stansel operations), all shunts (mostly Blalock–Taussig shunts but also a few central and other types of shunts), pulmonary artery bands and other surgeries (including coarctation repair without pulmonary artery band), repair of anomalous pulmonary venous drainage, valvuloplasty surgery, and a small number in each group who had undergone no prior surgery.

The majority of the patients in the ILT group had previously undergone the hemi-Fontan operation, whereas most patients in the ECC group had undergone the bidirectional Glenn operation. Patients in the ILT group were younger at the time of the Fontan (median, 2.1 years; IQR, 1.6-3.2 vs median, 3.0; IQR, 2.4-3.9; $P < .0001$) and older at the time of last follow-up (median, 11.8 years; IQR, 7.7-16.5 vs median, 7.9; IQR, 5.4-10.8; $P < .0001$). The interval between surgery and last follow-up was greater in the ILT group (median, 9.2; IQR, 5-12.8; vs median, 4.7; IQR, 2.8-7.7; $P < .0001$).

There were a total of 110 patients with heterotaxy (8.6% of the total), and of these 70 (64%) underwent an ECC and the remaining (30, 36%) had an intracardiac tunnel.

Early Postoperative Arrhythmia

Bradycardia requiring pacing occurred in 97 patients (8%) in the early postoperative period. Of these, 71 patients (73%) had only temporary pacing and permanent pacemakers were implanted in 26 (27% of the bradycardia subgroup and 2% of entire cohort). Of the 26 patients who had permanent pacemakers, 9 (35%) were in the ILT group and 17 (65%) were in the ECC group (Table 2).

Of the 71 patients who had only temporary pacing in the early postoperative period, 7 (10%) underwent implantation of a permanent pacemaker in the late postoperative period.

Tachyarrhythmias occurred early after surgery in 32 patients (5%) in the ILT group and 53 patients (8%) in the ECC group (P = not significant). When bradyarrhythmias and tachyarrhythmias were combined, the burden of arrhythmias in the early postoperative period was 56 in the ILT group and 126 in the ECC group ($P = .0003$).

By multivariate comparison (performed using logistic regression with adjustment for age at Fontan) (Table 3) of arrhythmias in the early period, the ILT group was less likely to be paced compared with the ECC group (odds ratio [OR], 0.35; confidence interval [CI], 0.22-0.57; $P < .0001$), but the incidence of early tachyarrhythmia did not differ between groups (OR, 0.69; CI, 0.43-1.09; $P = .1$).

Late Postoperative Arrhythmias

On univariate analysis (Table 2), both bradycardia and tachycardia were more common in the ILT group compared with the ECC group. Subdividing the tachycardia group into

TABLE 2. Results of univariate analysis

Variable	ILT n (%)	ECC n (%)	*P* value
Early bradycardia	24 (4)	73 (11)	<.0001
Early tachycardia	32 (5)	53 (8)	.063
Late bradycardia	105 (18)	63 (9)	<.0001
Late tachycardia	58 (10)	23 (3)	<.0001

ECC, Extracardiac conduit; *ILT*, intracardiac lateral tunnel.

TABLE 3. Results of multivariate analysis

Variable ILT vs ECC	Odds ratio/hazard ratio*	95% CI	*P* value
Early bradycardia	0.35	0.22-0.57	<.0001
Early tachycardia	0.69	0.43-1.09	.1
Late bradycardia	1.26	0.76-2.1	.38
Late tachycardia	1.32	0.74-2.33	.35

CI, Confidence interval; *ECC*, extracardiac conduit; *ILT*, intracardiac lateral tunnel. *Odds ratios from multivariate logistic regression are reported for early bradycardia and early tachycardia; hazard ratios from Cox regression are reported for late bradycardia and late tachycardia. Age and gender were adjusted in the multivariate analysis.

those requiring acute versus chronic therapy, tachyarrhythmias requiring acute therapy (mostly direct current cardioversion) were identified in 44 patients (7%) in the ILT group compared with 13 patients (2%) in the ECC group ($P < .0001$). Tachyarrhythmias requiring chronic therapy were observed in 38 patients (6%) in the ILT group and 17 patients (3%) in the ECC group. The differences between ILT and ECC observed on univariate analysis were shown to be due to the longer follow-up in the ILT group when multivariate analysis was performed (Kaplan–Meier graphs, Figures 1 and 2).

On multivariate analysis (Table 3), there were 573 patients in the ILT group and 566 patients in the ECC group with data available for multivariate analysis and creation of Kaplan–Meier graphs for bradyarrhythmia. Data were available for 576 patients in the ILT group and 570 patients in the ECC group for analysis of late tachyarrhythmia.

There was no difference in late postoperative bradycardia or tachycardia between the 2 groups. Figures 1 and 2 show the Kaplan–Meier curves for late bradycardia and tachycardia.

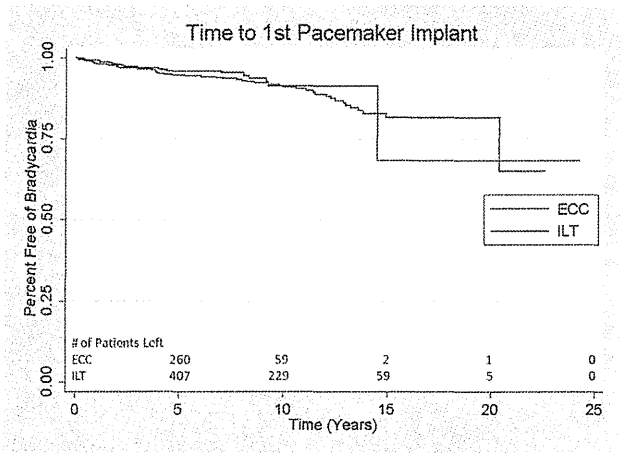

FIGURE 1. Kaplan–Meier curve for late bradyarrhythmia showing time to first bradycardia. $P = .41$; incidence for ILT is 1.1% per year with 5-year cumulative probability of 5.4% (standard deviation [SD], 1.0%); incidence for ECC is 0.8% per year with 5-year cumulative probability of 4.2% (SD, 0.9%). *ECC*, Extracardiac conduit; *ILT*, intracardiac lateral tunnel.

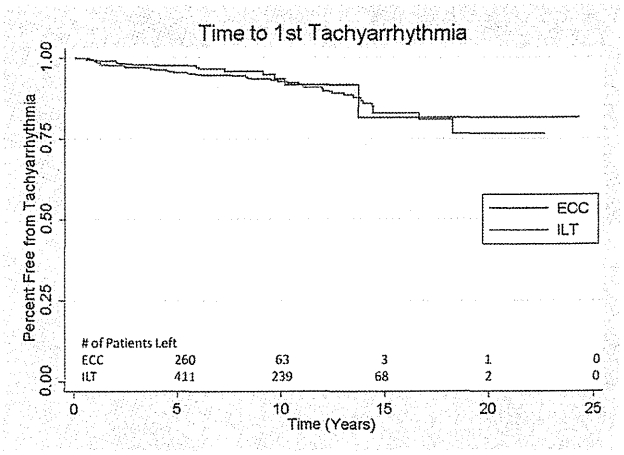

FIGURE 2. Kaplan–Meier curve for late tachyarrhythmia showing time to first tachycardia. $P = .31$; incidence for ILT is 1.0% per year with 5-year cumulative probability of 4.4% (SD, 0.9%); incidence for ECC is 0.6% per year with 5-year cumulative probability of 2.6% (SD, 0.9%). *ECC*, Extracardiac conduit; *ILT*, intracardiac lateral tunnel.

Early arrhythmia did not predict late arrhythmia (ILT vs ECC OR, 1.28; CI, 0.89-1.84) in the whole group and in either subgroup. We observed no "center effect" on the results because of patients clustering in one or few centers.

DISCUSSION

Then main findings of this study were that apart from the ECC being associated with a higher incidence of early SND, the incidence of late arrhythmias (especially late SVT) was similar for the ILT and the ECC when factoring in the duration of follow-up.

Arrhythmias are one of the most frequent and troublesome complications encountered in the population undergoing the Fontan, occurring in the early postoperative period and throughout long-term follow-up. These arrhythmias often are hemodynamically significant, challenging to control, and represent a significant source of morbidity and mortality in this population. When de Leval and colleagues[2] proposed the ILT, their primary purpose was to improve hemodynamics. However, one of their hopes was that it would decrease the arrhythmia burden compared with the earlier APC Fontan.[2] This has indeed proven to be the case.[4-6] However, although it reduces the incidence, arrhythmias have remained sequelae of the ILT.[4-6] The ECC was proposed by Marcelletti and colleagues[3] as a way of completely bypassing the right side of the heart, with the hope that this technique could reduce the risk of SVT.[7] Again, despite these modifications, arrhythmias persist.[8-17]

Factors shown to be associated with arrhythmias in patients undergoing the Fontan include the extent of surgery close to the sinus node and its artery, the extensive suture lines in the atrium, and the presence of pressure and volume

overload of the right atrium.[4-6] Although surgical approaches vary and patients often have had prior atrial incisions for their pre-Fontan operations or for vena caval cannulation, the ILT still requires an atrial incision that may result in damage to the sinus node or its artery and create the anatomic substrate for incisional atrial reentry tachycardia. In addition, the ILT subjects a part of the native right atrium to pressure overload, albeit to a lesser amount of atrial tissue compared with the APC. The ECC does not involve incisions near the sinus node or its artery or placement of incisions or sutures on the right atrial wall. The ECC aims to subject no part of the right atrium to pressure overload. Because of these factors, Giannico and colleagues[7] proposed the ECC as a way to reduce the incidence of arrhythmias in patients with single ventricles. Prior studies on this question have offered inconclusive results, mainly because of the lack of power from small study size.

A number of cross-sectional studies have reported that the ECC is associated with fewer arrhythmias.[8-13] The total number of patients enrolled in these studies have ranged from 51[12] to 165.[11] These studies showed an increased incidence of SND,[8-13] early postoperative SVT,[8,9,12] and late-onset SVT[8,9,12] in the ILT cases compared with ECC cases.

Evidence that the ECC may be associated with worse SND primarily comes from 2 studies from a single center[14,15] that initially reported 36 and then 70 patients. They reported a higher incidence of SND with the ECC in both the early and late postoperative periods.

Third, a few studies have shown no significant difference in arrhythmia prevalence between ILT and ECC.[6,16,17] Most noteworthy among these was a multicenter cross-sectional study of 520 patients from the Pediatric Heart Network Investigators.[6] Their cohort consisted of 306 ILT and 69 ECC cases. They could see no difference in the time-adjusted incidence of clinical SVT between the ILT and the ECC.

To date, the only prospective study on this subject has been by Cohen and colleagues.[17] The examined the incidence of arrhythmia on ECG and Holter monitoring between ECC and ILT using ECG and Holter monitoring. The found an incidence of SND of 13% after both ECC and the ILT.

In another study from the Pediatric Heart Network, Blaufox and colleagues[18] showed that a lower resting heart rate is associated with better functional outcome in patients undergoing the Fontan. They speculated that a lower resting heart rate with consequent longer filling time may be beneficial in the Fontan circulation, which is known to be pre-load dependent.[18]

In contrast to these earlier smaller studies, our larger multi-institutional study shows that early postoperative arrhythmias are more prevalent in patients receiving the ECC compared with the ILT and that long-term arrhythmia burden is not different between the 2 procedures. This study has the advantage of evaluating a large population across numerous centers, reducing the potential effects of institutional surgical and postoperative techniques and arrhythmia management preferences. The most important and troublesome arrhythmia in patients undergoing the Fontan is late-occurring SVT (mainly AFL and IART), which is a source of significant morbidity and mortality, and difficult to manage. The main attraction of the ECC was the hope that it would be associated with a lower incidence of late SVT. This study suggests that the perceived lower incidence of arrhythmias after the ECC is likely due to the shorter length of follow-up in ECC compared with the ILT.

Although this study could not elucidate why the ECC does not result in fewer arrhythmias despite its theoretic advantages, a number of possible reasons can be speculated. The underlying heart defect or operations performed at the pre-Fontan stage may be the true cause of arrhythmias, which are then "unmasked" by the Fontan physiology. Alternatively, the dissection involved in the area of the right atrium to create a space for the ECC conduit as it courses between the inferior vena cava and the pulmonary artery may be more arrhythmogenic than realized. Another possibility is that the ILT, which involves a patch extending from the superior to the inferior vena cava, acts in a manner similar to the Maze operation, thereby reducing its potential arrhythmogenicity lower than expected. Further work is needed to elucidate the causes of late SVT after the Fontan.

Our finding that SVT requiring future management will develop in up to 20% to 25% of patients receiving the ILT and ECC should give cause for concern to all clinicians caring for these patients. Strategies to prevent such arrhythmias and to manage patients with these arrhythmias will likely assume critical importance in the future.

Study Limitations

This study, despite its large size, suffers from the disadvantages of any retrospective data collection. As with most such studies, not all patients had complete data availability for statistical analysis. The follow-up duration in our study is relatively short. Because the length of follow-up has been an important determinant of arrhythmia development in this and prior studies, we plan to revisit this cohort in 5 to 10 years. Our study focused on clinical bradyarrhythmia and tachyarrhythmias. Only those arrhythmias that were treated were included. We did not use any age-specific cutoffs of heart rate on ECG or ambulatory ECG monitoring to diagnose an arrhythmia. Such a stringent definition of arrhythmia likely underestimates the incidence.

CONCLUSIONS

Our study found that the ECC does not confer any long-term arrhythmia advantage over the ILT. Early