

PLE 時の大体の総蛋白() ALB () g/dl

口調査時現在もあり だいたいの発症西暦 昭和 平成 年 月

PLE 時の大体の総蛋白() ALB () g/dl

5. 抗凝固、抗血栓の有無

抗凝固は ワーファリンのみが調査対象

抗血栓は アスピリン または 他の薬物でも可

次の どれに該当するか Oをつけてください。術後 2年の間は 問いません

P0 と W0 : 術後 1-2 年間は抗血小板薬 ないし ワーファリンを内服していたが以後 中止
または 術後からずっと内服していなかった

P1 と W1 : 術後から 現在まで大部分の期間、 抗血小板薬 ないし ワーファリンを内服して
きた

P2 と W2 : 術後から 2 年以上 抗血小板薬 ないし ワーファリンを内服していたが、途中で中
止

P3 と W3 : 術後 1-2 年間は抗血小板薬 ないし ワーファリンを内服していて中止、または 術
後からずっと内服していなかったが、途中から内服開始。しかし、また中止した。経過中、何
回か断続している場合も P3, W3 とします。

P4 と W4 : 術後 1-2 年間は抗血小板薬 ないし ワーファリンを内服していて中止、または 術
後からずっと内服していなかった。途中から内服開始。現在まで内服継続。

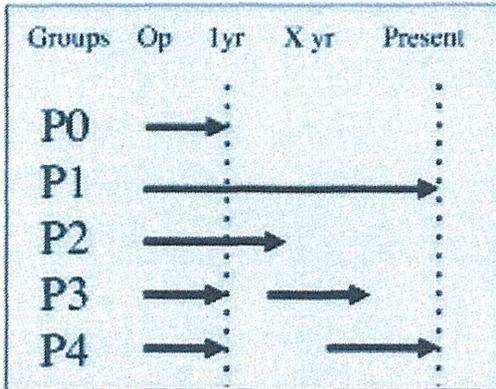
P2 の場合、大体の薬の中止時期 (術後年数でも、年月 ででもよいので 記入してくださ
い

P4 の場合、大体の薬の開始時期 (術後年数でも、年月 ででもよいので 記入してくだ
さい

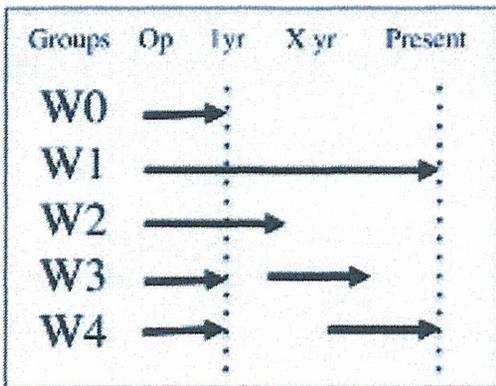
W2 の場合、大体の薬の中止時期 (術後年数でも、年月 ででもよいので 記入してくださ
い

W4 の場合、大体の薬の開始時期 (術後年数でも、年月 ででもよいので 記入してくだ
さい

Anti-Platelet



Warfarin



ワーファリンを使用例では 大体の INR は？（変動があるでしょうから、大体の値で結構です）

1.5 未満、 1.5-2.5, 2.5 以上

6. 出血イベントの有無 無し

喀血

発生時期 西暦 昭和 平成 年 月 （複数回起こったら 最初の時期）

脳出血（血腫）

発生時期 西暦 昭和 平成 年 月 （複数回起こったら 最初の時期）

腹腔内, 腹腔内臓器出血

発生時期 西暦 昭和 平成 年 月 （複数回起こったら 最初の時期）

7. 血栓、塞栓の有無

血栓

血栓 無し（有りの診断がないかぎり、推定で無しとします）

経胸壁エコー で無しと診断

その最終時期 西暦 昭和 平成 年 月

以下は有りの場合です

血栓があったことがある（塞栓症状があった場合でもまず血栓について記載してください）

有の時期 西暦 昭和 平成 年 月

場所（複数） フォンタン導管 右心房 肺動脈 体心房 体心室 その他
()

発見契機 定期検査 塞栓症状 その他 ()

診断法（複数） 経胸壁エコー 経食道エコー CT MRI RI

処置（複数） 放置 ワーファリン内服 溶解薬点滴 手術 その他 ()

転帰 内科管理で生存 血栓が一因で死亡 手術で生存 手術死亡

塞栓や梗塞 無

有 以下は有りの場合

場所 肺 脳 その他の臓器 ()

有の時期 西暦 昭和 平成 年 月

処置（複数） 放置 ワーファリン内服 溶解薬点滴 カテーテルで吸引 手術
その他 ()

転帰 予後に変化無し 塞栓が誘因となって予後悪化 塞栓が誘因となって死亡

血栓または塞栓発症時前後の臨床所見

右心房拡大（APCの場合など） 無 有 測定していれば右房容積() ml/m² または
右房最大横径 () cm

主心室収縮機能低下 なし 軽度（EF55-45%） 中等度（EF45-30%） 高度（EF30%
以下） 不明 {エコー、カテーテル、MRI など}

8. 治療薬

次の図の どれに該当するか ○をつけてください。術後 2年間は 問いません

P0：術後 1-2年間は薬を内服していたが以後 中止

または 術後からずっと内服していなかった

P1：術後から 現在まで大部分の期間、薬を内服してきた

P2：術後から 2年以上 薬 を内服していたが、途中で中止

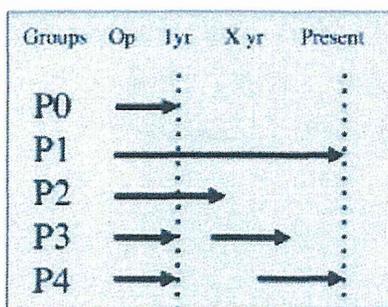
P3: 術後 1-2 年間は薬 を内服して中止、または 術後からずっと内服していなかったが、途中から内服開始。しかし、また中止した。経過中、何回か断続している場合も P3 とします。

P4: 術後 1-2 年間は薬 を内服して中止、または 術後からずっと内服していなかった。しかし途中から内服開始。現在まで内服継続。

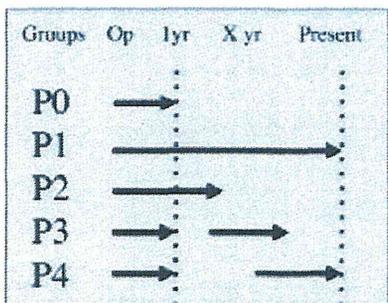
P4 の場合、大体の薬の開始時期 (術後年数でも、年月 でもよいので 記入してください

該当のものに○をしてください。P4 の場合、開始時期を記入してください。

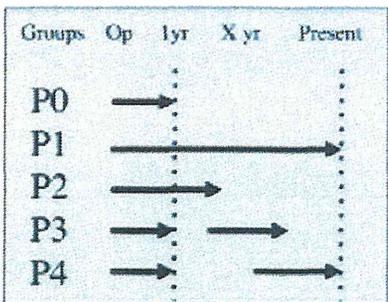
1) ACE inhibitor・ARB



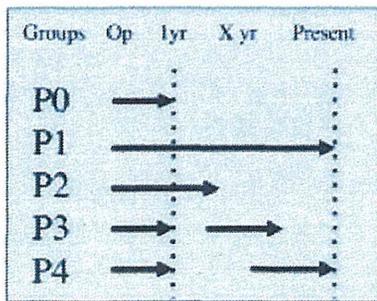
2) 利尿薬



3) beta-blocker



4) 肺血管拡張薬



6. チアノーゼ出現 (SP02 80% 以下のもの) 有 無 不明

時期 (治療していれば治療前のデータ) 西暦 昭和 平成 年 月 頃

SP02 () %

右-左短絡の原因 バツフルリーク fenestration 側副血管 換気血流不均衡

肺動静脈瘻 不明

チアノーゼに対する治療 無し

外科的短絡閉鎖 TCPC conversion Embolization (カテーテル治療)

7. 肝臓 病変

肝硬変、肝線維症、肝がん、結節性病変 (arterialized nodules) : エコー、CT, MRI, 生検、剖検で専門医が診断したもの

無し 最終診断時期 西暦 昭和 平成 年 月

肝線維症 大体の診断時期 西暦 昭和 平成 年 月

肝硬変、大体の診断時期 西暦 昭和 平成 年 月

肝がん 大体の診断時期 西暦 昭和 平成 年 月

結節性病変 (arterialized nodules) 大体の診断時期 西暦 昭和 平成 年 月

8. 妊娠 (女性のみ)

妊娠無 :

ワーファリンが理由で避妊

ワーファリンとは無関係に妊娠せず

妊娠有 : 妊娠時 年齢 () 歳

ワーファリンを使用していたので人工中絶

ワーファリンの使用とは無関係に人工中絶

自然流産

妊娠継続

抗血小板薬服用の有無 無し 有り

ワーファリンを服用していても妊娠継続

ワーファリンを中断して（他の薬に変えて）妊娠継続

その場合、他の薬は？ ヘパリン、抗血小板薬、新抗凝固薬

妊娠中の合併症 無し 有り 心不全悪化 チアノーゼ悪化 性器出血

その他 ()

分娩した場合

経膣分娩

ワーファリンを服用していても経膣分娩

ワーファリンを中断して経膣分娩 (ヘパリンにかえてもよい)

ワーファリンを服用しておらず経膣分娩

帝王切開

ワーファリンを服用していても帝王切開

ワーファリンを中断して帝王切開 (ヘパリンにかえてもよい)

ワーファリンを服用しておらず帝王切開

児の状態 出生週数 ()、 出生児体重 () g

児に異常なし

異常有り その内容(未熟児、低出生体重は除く)()

ワーファリンに起因すると思われる児の異常あり

その内容 ()

II. 資料

Risk factors and serological markers of liver cirrhosis after Fontan procedure

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Received: 31 October 2014 / Accepted: 4 September 2015
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Abstract Liver cirrhosis (LC), which may result in hepatic failure or cancer, has been reported in patients after Fontan procedure. The purpose of this study was to clarify the frequency and histological characteristics of LC, and to evaluate the risk factors and serological markers of LC with Fontan circulation. Retrospective review of contrast-enhanced CT scans (CT) of the liver was carried out in 57 patients after Fontan procedure. Patients were divided into two groups: LC group ($n = 31$) and no LC group ($n = 26$). Age at Fontan procedure, duration after Fontan procedure, catheterization data, and history of failing Fontan circulation were compared between groups. Serological data including γ -GTP and hyaluronic acid were compared. Histology of autopsy specimens was assessed when available. Duration after Fontan procedure was significantly longer in LC group than no LC group. History of failing Fontan circulation was more frequent in LC group than in no LC group. There was no correlation between type of procedure (APC/Bjork/lateral tunnel/TCPC) and LC in this series. Serum hyaluronic acid, γ -GTP, and Forns index were significantly higher in LC group. Significant risk factors for LC were duration after Fontan procedure (>20 years). In

autopsy specimens, histopathological changes of LC were observed predominantly in the central venous area. LC diagnosed with CT is frequent in patients long after Fontan procedure, especially after 20 years. Hyaluronic acid and γ -GTP could be useful markers to monitor the progression of liver fibrosis in Fontan patients.

Keywords Fontan procedure · Failing Fontan circulation · CT scan · Liver cirrhosis · Serological marker

Abbreviations

Fontan patients	Patients who had undergone Fontan procedure
LC	Liver cirrhosis
TCPC	Total cavopulmonary connection
APC	Atriopulmonary connection

Background

Fontan procedure for tricuspid atresia was performed for the first time in 1971 by Fontan and Baudet [1], and has been subsequently applied for other patients with single ventricle physiology. Over time, many modifications of the Fontan procedure have been applied, and its long-term result has been substantially improved. Recently, the main interest has shifted from short-term survival to long-term morbidity [2]. The hemodynamic characteristics of Fontan circulation, involving passive circulation of blood from the central vein to the pulmonary artery, result in relatively high central venous pressure, impaired structural and functional properties of the peripheral vessels [3], impaired cardiac function [4], and depressed cardiac output [5]. There is increasing evidence of liver dysfunction associated with these hemodynamic characteristics [3–11]. More recently,

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hepatic cancer was reported in patients who had undergone Fontan procedure (Fontan patients) at a relatively young age [12], which has become a major concern in this population. However, little is known about liver cirrhosis (LC) in patients a long time after Fontan procedure. Therefore, this study was conducted to determine the frequency of LC, characteristics of histopathological changes of the liver, the risk factors of LC, and the serological markers of LC a long time after Fontan procedure.

Materials and methods

Retrospective cohort study to assess the development of liver cirrhosis after the Fontan procedure was carried out at Tokyo Women's Medical University. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, and approval by the institution's human research committee.

Liver cirrhosis: CT scan study

Those who had undergone Fontan procedure and were followed at our institute for more than 5 years, and who had undergone CT scan of the liver between 2008 and 2010, were included in this study. Retrospective review of CT scans of the liver was carried out in 57 consecutive patients. Those who had undergone CT scan but for which the image quality was not sufficiently clear to diagnose pathological change of the liver were excluded from the study.

Diagnosis of liver cirrhosis Two radiologists who were blinded to the clinical courses and laboratory characteristics evaluated CT images and made diagnosis of cirrhosis. In this study, LC was diagnosed using contrast-enhanced CT scan based on the following four findings: irregular surface, dull edge, presence of diffuse reticular pattern of the liver parenchyma (regenerative nodule), and left lobe enlargement of the liver. Diagnosis of LC was made when regenerative nodule formation was observed with other three findings.

Groups

Patients were divided into two groups: LC group and no LC group, on the basis of the diagnosis made on CT scan of the liver. Patient history, including age at Fontan operation, duration after Fontan operation, central venous pressure, which was measured within 6 months of CT scan, and history of failing Fontan circulation resulting in total cavopulmonary connection (TCPC) conversion, was compared between LC and no LC groups. Our institutional indication of TCPC conversion for APC Fontan is sign of failing

Fontan circulation which included the presence of heart failure, arrhythmia, and/or significant thrombus formation.

Baseline characteristics of the patients and laboratory data were then compared between groups. Fontan procedure includes classic atrio-pulmonary connection (APC), Bjork procedure, lateral tunnel, and total cavopulmonary connection.

Laboratory data including AST, ALT, gamma-glutamyl-transferase (γ -GTP), total bilirubin (t-bil), albumin, type IV collagen 7 s, hyaluronic acid, and platelet counts were collected when available within 3 months of CT scan and compared between groups. Forns index was calculated using a following formula:

$$7.811 - 3.131 \times \ln(\text{platelet count}) + 0.781 \times \ln(\gamma\text{GTP}) + 3.467 \times \ln(\text{age}) - 0.014 \times (\text{cholesterol}).$$

Postmortem study

In addition to the CT scan study, we also reviewed all the patients who had undergone Fontan procedure at our institute and died. Those for whom autopsy specimens were available were identified to evaluate pathology of the liver. Clinical records and catheterization data were also reviewed.

We classified the degree of fibrosis based on the new grading system. Degree of fibrosis was divided into 4 categories; no fibrosis (F0), mild fibrosis (F1), moderate fibrosis (F2), severe fibrosis (F3), and cirrhosis (F4). F1 includes pericentral and perisinusoidal expansion of fibrosis. F2 includes perisinusoidal and periportal expansion of fibrosis with some bridging. F3 includes fibrosis with complete bridging (porto-central septa), and cell irregularity. F4 is cirrhosis, which includes rearrangement of lobular architecture. Of note, this has some differences from the standard classification of fibrosis, which is made for liver fibrosis due to inflammations such as hepatitis. Fibrosis after inflammation usually starts from the portal area, but that observed in Fontan patients, owing to long-standing high central venous pressure, starts from the central venous area.

Statistics

Statistical analysis was performed with Statistical Package for the Social Sciences (version 19.0, SPSS Inc., Chicago, IL, USA). Clinical and laboratory data are expressed as median (IQR = interquartile range), and mean \pm SD where appropriate. Difference between two groups was assessed using Mann-Whitney *U* test. *p* value was calculated using Fisher's exact test. Cox proportional regression model, determined by means of Youden index of the area under the curve (AUC) on receiver operating characteristic (ROC) curve analysis, was used to discriminate patients with LC and no LC. Relationships between risk factors for LC such

as age, age at Fontan procedure, duration after Fontan procedure, type of Fontan procedure, history of TCPC conversion, cardiac diagnosis, and diagnosis of heterotaxy syndrome were evaluated using multivariate logistic analysis. A p value of less than 0.05 was considered significant.

Result

CT scan data

Baseline characteristics, clinical profiles, and cardiac catheterization data are shown in Table 1. There were 31 patients (54 %) in the LC group and 26 patients in the no LC group. Age at CT scan study and age at Fontan procedure were significantly older in the LC group than in the no LC group ($p = 0.02$, and $p = 0.003$). And duration after Fontan

procedure in the LC group was significantly longer than that in the no LC group ($p = 0.003$). There were 14 patients who had Fontan circulation for more than 20 years. Among those 14 patients, 12 patients (86 %) had cirrhosis. Central venous pressure in the LC group was significantly higher in LC patient ($p = 0.023$). There were 24 patients in total who underwent TCPC conversion in this series. TCPC conversion had been performed significantly more frequently in the LC group (23/31, 74 %) than in the no LC group (1/26, 4 %) ($p < 0.001$). There was no correlation between type of procedure (APC/Bjork/lateral tunnel/TCPC) and LC in this series.

Hyaluronic acid and γ -GTP were significantly higher in the LC group ($p = 0.024$ and $p < 0.001$, respectively) (Table 2). Distribution of the serum hyaluronic acid and γ -GTP is shown in Fig. 1a, b. Forns index was significantly higher in LC group than in no LC group ($p = 0.01$). ROC

Table 1 Clinical profile

	No LC ($n = 26$)	LC ($n = 31$)	p
Gender female/male	14/12	17/14	
Age (years)	19 (12–24)	25 (22–35)	0.001*
Age at Fontan procedure (years)	3 (2–7)	8 (4–13)	0.0015*
Fontan duration (years)	15 (10–17)	17 (15–22)	0.003*
Diagnosis of heterotaxy syndrome	6	5	
Cardiac diagnosis			
Tricuspid atresia	7	16	
Double outlet right ventricle	6	4	
Transposition of the great arteries	1	2	
Corrected transposition of the great arteries	2		
Single left ventricle	2	3	
Single right ventricle	5	4	
Atrioventricular septal defect	1	1	
Pulmonary atresia intact ventricular septum	2		
Ebstein's anomaly		1	
Type of Fontan procedure			
Atriopulmonary connection	18	20	
Bjork	3	10	
Total cavopulmonary connection	2	1	
Lateral tunnel	3		
CVP (mmHg)	13 (12–15)	14 (11–17)	0.023*
TCPC conversion	2	23*	<0.001*
Aortic saturation (%)	96 (94–97)	95 (92–96)	0.096
Cardiac index (L/min/m ²)	2.2 (1.8–2.6)	2.2 (1.8–2.4)	0.462
AV valve regurgitation trivial/mild/moderate	5/17/1	2/21/6	0.384
Medications			
Warfarin	2	20*	<0.001*
Diuretics	5	22*	<0.001*
ACE inhibitor/ARB	6	12	0.574

LC liver cirrhosis, CVP central venous pressure, TCPC total cavopulmonary connection, CTR cardiothoracic ratio

* $p < 0.05$ considered statistically significant