Table 2 Laboratory data of liver function

	No LC	LC	*p*
IV collagen 7 s (ng/mL)	7.3 (5.7–8.0)	6.7 (5.8–7.7)	0.52
Hyaluronic acid (ng/mL)	22 (20–42)	44 (28–82)	0.024*
AST (U/L)	24 (19–36)	27 (22–32)	0.59
ALT (U/L)	24 (18–28)	28 (19–35)	0.34
γ-GTP (mg/dL)	63 (44–87)	115 (84–157)	<0.001*
t-bil (g/dL)	1.0 (0.7–1.5)	0.9 (0.5–1.5)	0.76
Alb (g/dL)	4.6 (4.4–4.8)	4.4 (4.1–4.8)	0.18
Plt ($\times 10^4/\mu$L)	17.9 (14.0–20.8)	14.9 (9.3–19.4)	0.14
Forns index	6.8 (4.4–10.7)	11.5 (8.0–18.6)	0.01*

* $p < 0.05$ considered statistically significant

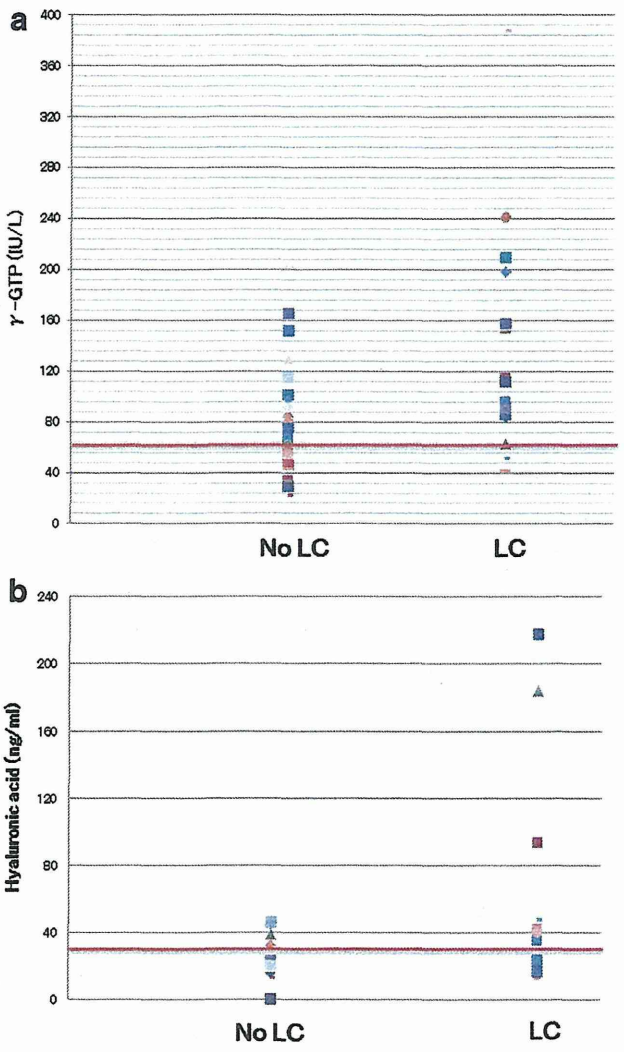

Fig. 1 **a** Distribution of hyaluronic acid. Cutoff value of 40.5 ng/mL had sensitivity of 64.5 %, specificity of 64.1 %, positive predictive value of 75.4 %, and negative predictive value of 64.1 %. **b** Distribution of γ-GTP. Cutoff value of 67.5 IU/L had sensitivity of 85.2 %, specificity of 57.7 %, positive predictive value of 70.2 %, and negative predictive value of 76.4 %

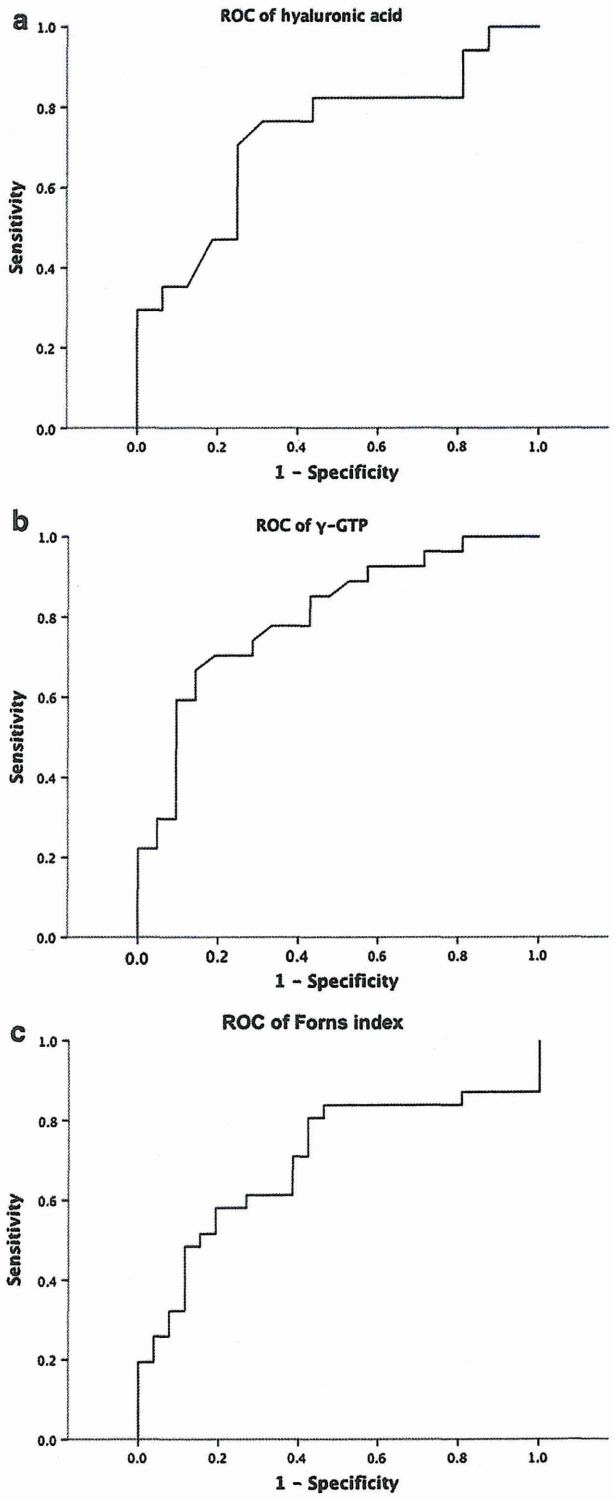

Fig. 2 ROC curve of a model aimed to discriminate patients with LC and without LC. **a** ROC of hyaluronic acid. AUC 0.730, 95 % CI 0.554–0.906, $p = 0.024$. **b** ROC of γ-GTP. AUC 0.802, 95 % CI 0.676–0.927, $p < 0.001$. **c** ROC of Forns index. AUC 0.700, 95 % CI 0.560–0.839, $p = 0.01$

curves of a model aimed to discriminate patients with LC and no LC using these three valuables are shown in Fig. 2.

Multivariate logistic analysis also revealed that duration after Fontan procedure was an independent risk factor ($p = 0.01$, respectively).

There was no patient who had neither hepatitis B nor C in the whole study subjects.

Postmortem study

There were 31 deaths after Fontan procedures carried out between 1974 and 1992, and autopsy specimens of the liver were available for 5 patients. Three of these five patients had undergone a CT scan of the liver and were included in the CT scan study. All but one had undergone atriopulmonary connection (APC)-type Fontan procedure, and Bjork procedure was performed in one patient. Baseline characteristics of the patients are shown in Table 3. The time from Fontan procedure was between 8 months and 24 years and 5 months (15 ± 9.6 years). NYHA functional status was II in 3 patients and III in 2 patients. The central venous pressure was 15 ± 5 mmHg. Correlation between pathology and CT findings is shown in Table 4.

In a patient who died 8 months after Fontan procedure, liver pathology showed mild fibrosis only in the central venous area, suggesting grade 1 fibrosis. All other patients had liver fibrosis greater than grade 2. Two of three patients died after TCPC conversion, and autopsy specimens showed advanced fibrosis that matched the CT findings (Figs. 3, 4). The one who was diagnosed as LC with CT had less severe findings of fibrosis (grade 2) on pathology (Table 4.).

Discussion

There is an increasing evidence of the risk of LC a long time after Fontan procedure. The present study evaluated large number of patients studied to date long term after Fontan procedure. Although liver biopsy is still the gold standard for liver pathology, other imaging modalities including CT, MRI, and, more recently, transient elastography have been widely used in combination with serological markers to evaluate LC [13–16]. We used contrast-enhanced CT in this study because it has been shown that the corresponding sensitivity, specificity, and diagnostic accuracy were better than those for ultrasound [11]. Although CT has been widely used to evaluate liver pathology, diagnosis of LC has been a discussion and it is sometimes difficult to draw a line between LC and no LC based on radiologic findings because it is a gradual process. Radiologists make diagnosis of LC on CT depends more on presence of irregular surface and regenerative nodule formation, compared to left lobe enlargement and dull edge. Disease progression is not uniform, but the first two findings are more prominent in progressed disease. Ginde et al. also showed that all patients they studied had abnormal findings on CT, and heterogeneous enhancement was the most common findings in their study [16].

We examined histopathology of the liver after Fontan procedure and compared it with the CT scan findings. Histological characteristics of liver fibrosis in Fontan patients are different from those seen in hepatitis. Fibrosis starts from the portal area in hepatitis but from the central venous area in Fontan patients. The pathophysiological mechanisms of liver injury in Fontan patients have not been fully elucidated, but may be similar to those in right heart failure [11]. Increased central venous pressure may result in sinusoidal dilatation, collagen deposition, and finally fibrosis. Fibrotic septa extend from the central venous area to other vascular structures to complete bridging in advanced disease. In our postmortem series, we could show that the patient who had Fontan circulation for 8 months had limited fibrosis around the central venous area, whereas 2 patients who had experienced Fontan circulation for more than 20 years had bridging fibrosis (Fig. 3). These findings are in agreement with those reported by Kendal et al. [10]. In our series, CT findings were correlated with the histopathological findings, although in one patient in our series, LC was diagnosed on CT but histology showed less severe findings. Therefore, we think that, although there is a limitation in CT, contrast-enhanced CT could be utilized to evaluate liver fibrosis in Fontan patients. In our study, 86 % of the patients who had experienced Fontan circulation for more than 20 years had cirrhosis. It must be considered that the age at Fontan procedure was relatively late in this series compared with that more recently, the patients of which are still in their late twenties, which is way before the age of onset of non-cardiac cirrhosis that occurs sometime in the mid-fifties [17].

In the present study, although it was significantly higher in LC group, central venous pressure itself had no significant correlation with presence of LC. The only significant contributing factor was time from Fontan procedure. This means that long duration of exposure to high central venous pressure results in fibrosis, cirrhosis, and finally hepatocellular carcinoma, which was also suggested by other studies [11–13, 18]. Annual incidence of HCC is dramatically increased in stage 3 fibrosis or cirrhosis to a level as high as 3–7 % [17]. We had one case with hepatocellular carcinoma that developed by the age of 16, which was successfully treated by *trans*-catheter arterial embolization (data not shown). However, the incidence of HCC before 20 years old is extremely rare; those who have Fontan circulation completion around 2 years of age are at significant risk of developing LC in 20 years time, developing a high risk

Table 3 Patients' characteristics and pathological findings of the liver

Patient	Age (years)	Sex	Diagnosis	Fontan type	Fontan time	NYHA	CVP (mmHg)	CT	Pathology
1	33	F	TA IIb	APC	8 months	III	18	NA	F1
2	37	M	SLV	APC	22 years 3 months	III–IV	20	NA	F3
3	26	M	TA Ib	Bjork/TCPC	10 years 6 months	II	16	LC	F4
4	39	M	SLV	APC/TCPC	16 years 11 months	II	8	LC	F2
5	35	F	DORV MA PA	APC/TCPC	24 years 5 months	II	16	LC	F3

TA tricuspid atresia, *SLV* single left ventricle, *DORV* double outlet right ventricle, *MA* mitral atresia, *PA* pulmonary atresia, *CVP* central venous pressure, *TCPC* total cavopulmonary connection, *LC* liver cirrhosis

Table 4 Correlation between pathology and CT

	Case 3	Case 4	Case 5
Pathology	F4	F2	F3
CT findings	LC	LC	LC
Irregular surface	+	+/−	+
Dull edge	+	+	+
Left lobe enlargement	+	+	+
Regenerative nodule	+	+/−	+

for HCC at a very young age. However, contrast-enhanced CT is a sensitive method to diagnose LC and differentiate borderline HCC [17], radiation and contrast use in patients with kidney dysfunction, which is often present in Fontan patients, may not be ideal for repeating in a short period of time. Baek et al. showed usefulness of Forns index and other indices for evaluation of cirrhosis in Fontan patients [18]. Forns index is calculated using γ-GTP, platelet count, age, and cholesterol level. Our result showed that both no LC patients and LC patients had Forns index higher than 6.9 which had been shown to be a cutoff value for detecting significant fibrosis. [19] This may indicate that most of the long-term Fontan patients had significant degree of fibrosis than normal population. Our data showed that Forns index greater than 7.7 can discriminate LC from no LC, but this needs to be validated with pathology obtained with biopsy which is the gold standard till now.

Evaluation of the extent of liver disease is crucial when one considers major surgery, such as TCPC conversion in failing Fontan patients. The indication and timing of TCPC conversion are still unclear. Those experiencing failing Fontan circulation have multiple risk factors including liver and kidney dysfunctions, and these need to be taken into account for decision making [7, 8, 11]. Kieswetter et al. showed that those with failing Fontan circulation had extensive liver injury, including 7 out of 12 patients with cirrhosis, which is consistent with our result [11]. They also showed that Fontan duration and hepatic vein pressure were positively correlated, but central venous pressure was not. More importantly, they opted for an alternative surgery in 2 of their patients on the basis of the extent of liver disease in combination with other risk factors. In our postmortem case series, we had three patients who died after TCPC conversion. One of the three had suspected cirrhosis and died for rupture of varices. Pathology showed grade 4 fibrosis, which was consistent with CT findings. It is crucial to investigate liver function and associated varices preoperatively for risk stratifications.

Although transient elastography has become available, limited information on this is available in our patient population. Friedric-Rust et al. demonstrated that 36 of 39 children had signs of fibrosis after a mean duration of 5–6 years from Fontan operation, including only one patient with surface nodularity and other signs of cirrhosis. They also showed a significant correlation between serum fibrosis marker and transient elastography [13].

Although liver biopsy could be performed at the time of cardiac catheterization, its complications need to be borne in mind. The risk of significant complications requiring hospitalization is reported to be about 1–5 % [17]. Post-Fontan patients are known to have coagulation abnormality together with liver dysfunction, which may be associated with high risk for bleeding at the time of biopsy [4, 8]. In addition, there have been concerns regarding under-staging of liver fibrosis with needle biopsy. Cirrhosis could be missed in 10–30 % of cases when using single liver biopsy, and this is mainly due to both the size of the biopsy and the number of biopsies taken [20, 21]. Bedossa et al. also showed that biopsy could determine the liver fibrosis stage in only 65 % of cases, and it also depends on the size of the specimen [22]. Laparoscopy-guided biopsy has been shown to be better than needle biopsy but its invasiveness and risk for bleeding in Fontan patients cannot be neglected. Therefore, indication for liver biopsy should be made carefully considering risks of complications and limitations of needle biopsy, including sampling and interpretative errors.

Limitations

Due to retrospective nature of the study, we only evaluated those who had undergone abdominal CT scan between 2008 and 2010. Fontan procedure was carried out in 529

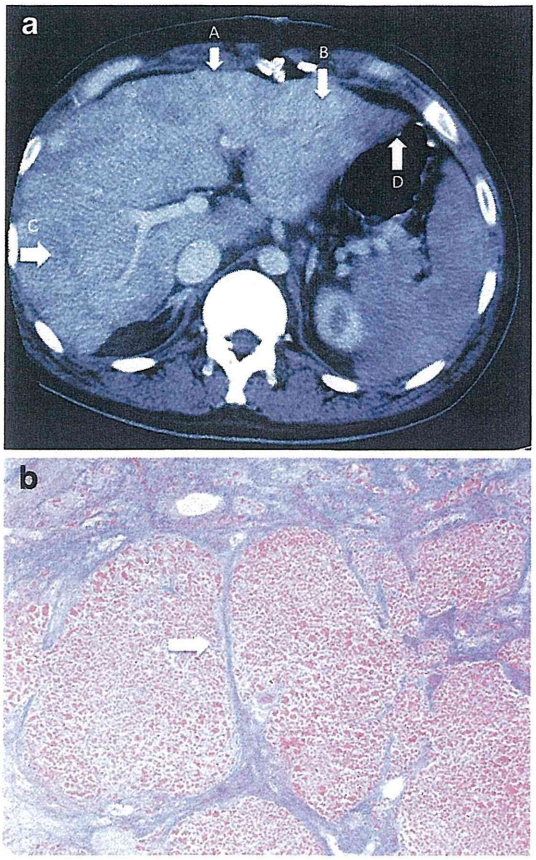

Fig. 3 The patient died from rupture of varices 10 years after Fontan procedure (Bjork type). **a** Abdominal CT revealed liver cirrhosis and esophageal varices. All the 4 findings of cirrhosis are present. *A* irregular surface, *B* left lobe enlargement, *C* diffuse reticular pattern of the liver parenchyma, *D* dull edge. **b** Liver pathology showed complete bridging fibrosis (*arrow*) and hepatocellular degeneration indicating grade 4 fibrosis. Hematoxylin and eosin staining

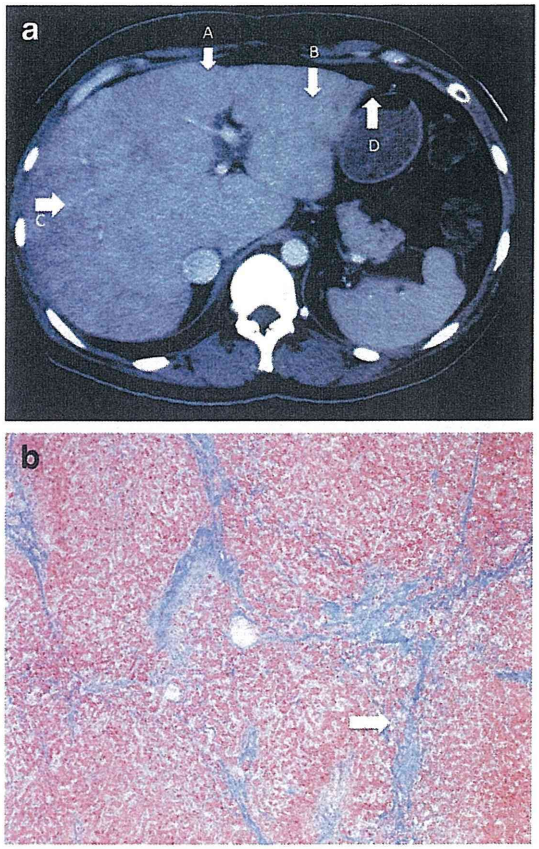

Fig. 4 The patient died of arrhythmogenic shock after TCPC conversion, which occurred 24 years after initial Fontan operation. **a** Abdominal CT showed smooth surface (*A*), enlargement of the left lobe (*B*), dull edge (*D*), and some parenchymal changes (*C*), indicating severe fibrosis/cirrhosis. **b** Pathology specimen showed grade 3 fibrosis with fibrous bridging. Hematoxylin and eosin staining

patients between 1975 and 2002, and 57 patients were reported to be dead by the end of 2007. Of the remaining 472 patients, 209 patients were followed more than 5 years. It is hard to count the patients who were lost of follow up, and how many of them had regular clinic visit during the study period. And CT scan was not routinely taken on all patients in regular basis. This may result in the higher detection rate of cirrhosis in our study population.

Although the cutoff values of hyaluronic (>40.5 ng/mL), γ-GTP(>67.5 IU/L), and Forns index (>7.7) were calculated using Cox proportional regression model, determined by means of Youden index of the AUC on ROC curve analysis shown in Fig. 2, we did not have chance to validate the accuracy of this data. Thus, we did not include this in the text. Hayashi et al. used serum hyaluronic acid concentration of 29.3 ng/mL to separate their study population into two groups based on their median value, and showed significant relationship between hyaluronic acid concentration and portal vein hemodynamics in Fontan patients [23]. Both studies are retrospective and included small number of patients. Further investigations in prospective manner to follow these serological markers together with radiological evaluation in larger population are necessary to determine the clinical significance of our findings.

In summary, we demonstrated that LC diagnosed with CT is as frequent as 54 % in long-term Fontan patients. The likelihood of having LC is increased with time, and failing Fontan circulation. Hyaluronic acid, γ-GTP, and Forns index could be useful markers to monitor the progression of liver fibrosis in Fontan patients.

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Compliance with ethical standards

Conflict of interest None to declare.

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CONGENITAL HEART DISEASE

Management of the failing Fontan circulation

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The 'Fontan circulation' has evolved to include a variety of surgical procedures designed to overcome the absence of two distinct ventricular chambers.[1 w1–w3] Inherent to this circulation is chronic elevation of right atrial and vena caval pressure, and absence of a dedicated power source to serve the pulmonary circulation, making low pulmonary vascular resistance and optimal systemic ventricular function the essential ingredients of a successful Fontan circulation.[2] Originally designed for the single left ventricle, modifications to the original atriopulmonary connections extended repairs to complex ventricular anatomy, and are now most commonly performed for single right ventricular anatomy associated with hypoplastic left heart syndrome. Together with improved perioperative management, creation of the Fontan circulation in two stages (superior cavopulmonary anastomosis followed by later Fontan completion[w4]), and performance of Fontan procedures at a younger age, have led to reduced operative mortality associated with the Fontan procedure of ≤5% (compared with 15–30% in earlier decades); survival at 20 years is presently 85%.[3 w5]

Over the last two decades, the initial survivors of the atriopulmonary Fontan repairs have reached adulthood, bringing a multiplicity of haemodynamic complications and sequelae of their abnormal circulatory status. The atriopulmonary connection is now obsolete as a surgical option, and the current surviving adults with this circulation do not reflect contemporary Fontan outcomes. Nonetheless, their attendant compendium of complications and sequelae provides a daunting array of management challenges, and stigmatises the current perception of long term Fontan outcomes.

The 'Fontan circulation' now encompasses a spectrum of anatomic substrates, staging options, and operative techniques. Problems classified as 'Fontan failure' may represent problems inherent to the morphologic substrate, operative variables, and inevitable sequelae of the Fontan circulation: chronic venous congestion and progressively declining functional status. This review will separate complications into those where intervention may optimise clinical status while maintaining the Fontan circulation—the 'failing Fontan'—and those conditions which have progressed to a 'failed Fontan', where options are limited to cardiac transplantation or attempts to minimise the impact of irreversible functional deterioration. Finally, we will discuss strategies which may alter the incidence and time course of Fontan failure.

THE FAILING FONTAN CIRCULATION

Evaluation of the failing or failed Fontan circulation requires knowledge of the anatomic substrate, surgical intervention details, cardiac imaging and assessment of haemodynamic status, assessment of rhythm status, and evaluation of other organ systems and metabolic function. Late Fontan failure may present insidiously over years. It is a failure of medical management to interpret the absence of overt symptoms or ascites as evidence of optimal haemodynamic status in the functionally univentricular circulation. In contrast to other forms of operated congenital heart disease, Fontan patients have lived with less than ideal cardiac output their entire lives, and may neither recognise nor show overt manifestations of progressive decline in functional status until deterioration is quite advanced (table 1).

Growth

In general, the Fontan patient population is shorter in height than the normal population; there is increased recognition that failure to gain weight appropriately is an early indicator of suboptimal cardiac output in childhood.[4] Growth failure should prompt a thorough investigation of haemodynamic status, with early efforts to optimise haemodynamic status with catheter or surgical intervention for residual obstruction or valve abnormalities.

Exercise capacity is lower in Fontan patients than in other patients with repaired congenital heart disease, and recent studies have reported a 1–3% annual decline in maximal oxygen consumption beginning in adolescence.[5 w6–w8] In Fontan patients, the average peak oxygen consumption ranges from 19–28 ml/kg/min, or 50–60% of predicted consumption for age. Decline in exercise function correlates with the need for hospitalisation and symptom development.[6 w8] Decreased exercise tolerance is more common in single right or indeterminant ventricular morphology, and in patients with lateral tunnel repairs, and may be related to chronotropic incompetence or abnormal pulmonary compliance with exertion.[6 w8 w9] Serial exercise testing may objectively identify changes in haemodynamic or rhythm status, which may be addressed with intervention such as pulmonary stenting, atrial

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Table 1 Failing Fontan circulation

Constitutional	Growth failure	Inadequate cardiac output
	Exercise intolerance	Chronotropic incompetence, pronounced atrial distension
	Depression	Secondary to limitations on functional status
Haemodynamic	Obstruction	Atriopulmonary, pulmonary arterial
	Systemic venous	Pulmonary venous return, atrioventricular (AV) valve inflow
	Systemic outflow	Ventricular outflow, aortic arch
	AV valve function	≥Moderate regurgitation ≥Mild stenosis
	Ventricular dysfunction	Secondary: atrial dilatation/distortion; AV valve or semilunar valve dysfunction, chronic arrhythmias or antiarrhythmic medications; impaired myocardial perfusion due to coronary sinus hypertension
	Thrombosis	Systemic venous, atrial, pulmonary
Rhythm	Arrhythmias	Sinus node dysfunction, predominant junctional rhythm, AV block, supraventricular tachycardia/atrial tachycardia, ventricular tachycardia
Pulmonary	Cyanosis	Intracardiac right to left shunt, veno-venous collaterals, pulmonary arteriovenous malformations (AVMs)
	Pleural effusions	
Gastrointestinal	Ascites	Secondary to portal hypertension related to obstruction, versus cirrhosis
Metabolic	Metabolic markers	Declining albumin; thrombocytopenia; hyperbilirubinaemia; coagulopathy

pacing, pulmonary vasodilator therapy, or Fontan conversion surgery.[5]

Cyanosis

A mild degree of desaturation is present in most Fontan patients, due to coronary sinus drainage to the left atrium or pulmonary shunting. Resting saturations <90% suggest the presence of right to left shunting (either intracardiac or due to veno-veno collateral flow to the left atrium) or pulmonary arteriovenous fistulae. Coil embolisation of collaterals or catheter based occlusion of atrial septal defects may improve saturations, although investigation for a more compelling cause for the development of collaterals may allow more definitive intervention. Patients with discontinuous pulmonary arteries with a classic Glenn to the right pulmonary artery have insufficient hepatic flow to that lung, and would benefit from surgical intervention to provide confluent pulmonary arteries and increased hepatic flow to the right lung. Patients with atriopulmonary connections frequently have 'decompressing' collateral flow or atrial level shunts, and benefit from Fontan conversion.

Pathway obstructions and valve dysfunction

The development of haemodynamic abnormalities may be gradual and insidious in Fontan patients, and detection is complicated by the lack of complaints from most patients until pronounced limitation occurs. Decline in exercise tolerance, resting or exercise desaturation, the presence of a murmur, hepatomegaly, or cardiomegaly on radiography are indicators of haemodynamic abnormalities. Patients with atriopulmonary connections develop marked right atrial distension over time, secondary to anatomic obstructions at the anastomosis, or due to the notable energy loss associated with sluggish flow (figure 1). Decompression of the atrium occurs via coronary sinus dilatation, and atrial communications or veno-veno collaterals from the systemic veins to the left atrium or pulmonary veins may ensue. Distension of the right atrium may result in torsion and narrowing of the connection to the pulmonary arteries, as well as compression of the pulmonary venous return from the right lung; the dilated atrium may impinge on inflow in the setting of a right-sided atrioventricular valve. Anatomic obstructions may exist at the atriopulmonary anastomosis or the branch pulmonary arteries; a gradient of >1 mm Hg in this circuit dependent on passive flow is haemodynamically significant. Patients with valved conduits in place, either atrioventricular or atriopulmonary, invariably develop obstruction over time. Patients with lateral tunnel repairs in general do not develop pronounced atrial distension, but narrowing at the pulmonary arteries may exist. Abnormalities of atrioventricular (AV) valve function result in elevated left atrial pressure, which will harm the pulmonary circulation. Chronic aortic outflow obstruction will result in hypertrophy and diminished ventricular compliance; the volume overload of aortic insufficiency will contribute to ventricular failure.

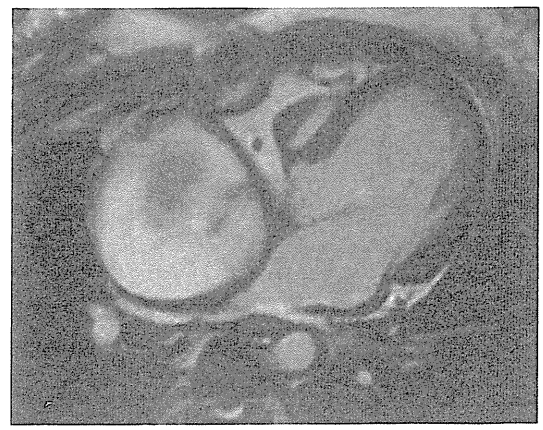

Figure 1 MRI of marked atrial dilatation with impingement on pulmonary venous return in a patient with an atriopulmonary Fontan anastomosis for tricuspid atresia. Right atrium measures 7×7.5 cm. Image courtesy of Cynthia K Rigsby, Children's Memorial Hospital, Chicago, Illinois, USA.

Hepatic and infra-diaphragmatic venous congestion is present in all Fontan patients, to greater or lesser degrees. Sequestration of platelets by the liver and spleen result in thrombocytopenia, present in 15–25% of adult Fontan patients. Mild elevation of bilirubin is common, followed by abnormalities of liver enzymes. The effects of years of venous congestion will result in hepatic cirrhosis, which becomes apparent by approximately 11 years following surgery.[7] Surveillance with abdominal ultrasound may detect hepatic nodules, with more detailed imaging provided by CT. Monitoring of α-fetoprotein may provide early detection of hepatocellular carcinoma, now reported in a small number of older Fontan patients.

Arrhythmias

This broad term includes sinus node dysfunction, predominant junctional rhythm, atrioventricular block, supraventricular and ventricular arrhythmias, and the risk of arrhythmic sudden death. Modifications to the Fontan procedure have resulted in a decreased incidence of sinus node dysfunction and atrial arrhythmias. Sinus node dysfunction is reported in 40% of patients with atriopulmonary connections, and is reported in up to 25% of lateral tunnel and extracardiac cavopulmonary connection surgeries.[8 9 w10 w11] Reassurance based on an 'adequate overall heart rate', which is usually junctional, is a disservice to the patient, as the haemodynamic consequences of junctional rhythm in the Fontan circulation are profound, including acute elevation of atrial pressure with each ventricular contraction. Non-sinus rhythm has been associated with increased risk of atrial arrhythmias, as well as an increased risk of hepatic fibrosis[w12]; these data warrant vigorous attempts to maintain regular atrial rhythm in Fontan patients.

The incidence of atrial arrhythmias during long term follow-up has decreased with surgical modifications of the Fontan procedure, from as many as 60% of atriopulmonary patients to approximately 12% of extracardiac total cavopulmonary connection patients.[9–13 w5 w13] Atrial reentrant tachycardia accounts for approximately 75% of supraventricular tachycardia, with focal atrial tachycardia in up to 15% of patients.[w13 w14] In lateral tunnel patients, the reentrant circuit may reside in the pulmonary venous atrium. Atrial fibrillation is becoming increasingly common in adult Fontan patients, and is present in almost half of patients referred for Fontan conversion. Risk factors for the development of atrial tachycardia include an atriopulmonary connection, preoperative bradycardia, lack of sinus rhythm, older age at Fontan and longer postoperative interval, greater than mild atrioventricular valve regurgitation, and heterotaxy syndrome.[3 9 11 w11] As the incidence of atrial tachycardia increases with the postoperative interval and is a major source of morbidity,[8 10] regular surveillance of rhythm with ambulatory 24 h monitors, event monitors and exercise testing becomes more important during long term follow-up.

Termination of an acute episode of atrial tachycardia within 24–48 h from onset is recommended whenever possible, due to the rapid deterioration in haemodynamic status associated with tachycardia in the single ventricle circulation. Figure 2 summarises an algorithm for management of atrial arrhythmias.[w15] Development of atrial tachycardia is commonly associated with haemodynamic abnormalities which will require more extensive haemodynamic, functional, and metabolic evaluation. Catheter ablation for atrial tachycardia in Fontan patients has considerably lower success rates than in other forms of repaired congenital heart disease. Acute success rates from catheter ablation in the Fontan patient range from 40–75%, with recurrence of tachycardia in 60% of patients during the first year.[14 w14] Catheter ablation in this

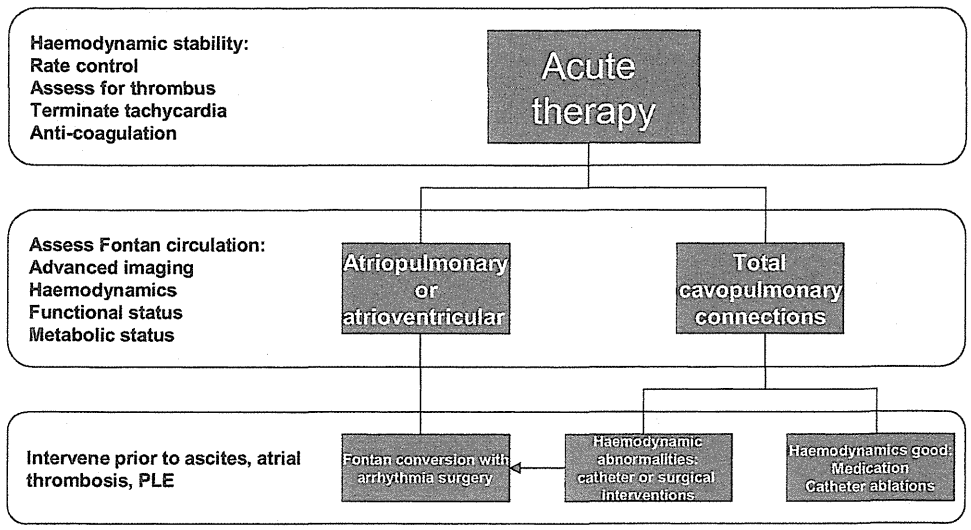

Figure 2 Management of atrial arrhythmias in Fontan patients. PLE, protein-losing enteropathy.

Heart 2012;**98**:1098–1104. doi:10.1136/heartjnl-2011-301133

population is best suited for patients with lateral tunnel repairs and focal atrial tachycardia, or atriopulmonary repairs who are not suitable candidates for Fontan arrhythmia surgery. The development of significant arrhythmias in the atriopulmonary or atrioventricular Fontan modification, when coupled with signs of heart failure, is associated with a 3 year mortality rate of 25%.[6]

Fontan conversion with arrhythmia surgery

Recognition that atriopulmonary Fontan patients have associated haemodynamic limitations in addition to atrial tachycardia led our group to incorporate arrhythmia surgery into Fontan conversion to an extracardiac total cavopulmonary connection, beginning in 1994.[15 w16] In addition to right atrial reduction, performance of a modified right atrial maze procedure eliminates right atrial macro-reentrant tachycardia, but is not intended to treat focal atrial tachycardia or other mechanisms without targeted resection (figure 3). Left atrial macro-reentrant tachycardia or atrial fibrillation is treated with an additional left atrial Cox Maze III, which effectively eliminates atrial fibrillation, but we have noted recurrence of a slower organised atrial reentry tachycardia in about 15% of such patients.[w16] Implantation of epicardial dual chamber anti-tachycardia pacing systems is performed for virtually all patients, predominantly relying on atrial pacing at rates of 70–80 beats/min chronically, without ventricular pacing. Our centre has performed over 135 Fontan conversions with arrhythmia surgery at a mean interval of 15.5±5.2 years following initial Fontan procedure, with acute mortality of 1.5%; other centres have achieved relatively comparable results.[16] Analysis of intermediate outcomes in the initial 110 patients undergoing such surgery at our centre showed freedom from death or transplantation at 15 years of follow-up was 80%, with freedom from recurrent tachycardia of 85%. Risk factors for poor outcomes in this population include right or ambiguous ventricle, presence of right atrial thrombus at time of surgery, older age at Fontan conversion, longer post-Fontan interval, or ascites. Patients with protein-losing enteropathy are not considered candidates for Fontan conversion surgery, and patients without correctable causes of poor ventricular function, or multiorgan system disease, may be better treated by transplantation. We have recently demonstrated improved functional status at 5 years of follow-up in a subset of patients undergoing paired pre- and post-Fontan conversion exercise testing, with an average 17% increase in maximal oxygen consumption. These results suggest that aggressive efforts to improve flow dynamics and associated haemodynamic abnormalities, eliminate arrhythmias, and maintain chronic atrial rhythm may favourably alter what has been considered as an 'inexorable decline' in functional status in many Fontan patients.

In addition to atrial arrhythmias, atrioventricular block occurs, either due to intrinsic conduction abnormalities as seen in patients with L-transposition, or as a consequence of surgery. The incidence of pacemaker implantation in most series ranges from 3–18%, without stratification as to implantation for AV block versus sinus node dysfunction.[3 w5 w17] Limitations of venous access to the atrium, the risk of endocardial lead thrombosis, and the morbidity of repeat sternotomy to place epicardial leads, support a preemptive strategy of atrial lead placement at the time of primary Fontan repair, although not a class I or II indication for pacing by current recommendations. With improved survival, it is becoming apparent that ventricular arrhythmias are noted in 3–12% of adult patients.[17 w5 w17] The contribution of ventricular arrhythmias to late sudden death, reported in 9% of patients, is not yet known.[18]

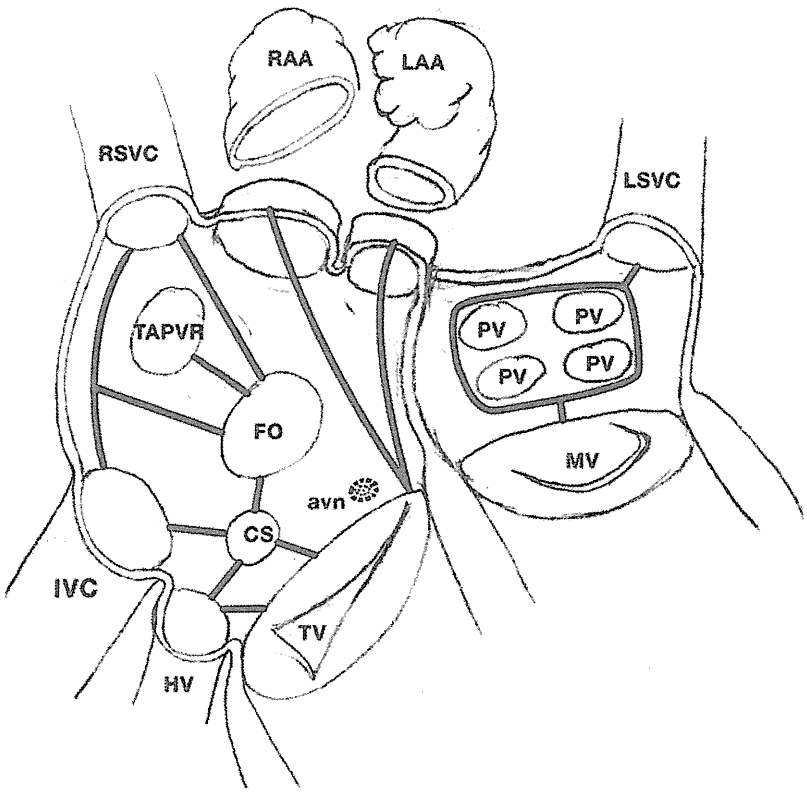

Figure 3 Surgical modifications of atrial maze procedure in complex anatomy. Solid black lines indicate sites of cryoablation. avn, atrioventricular node; CS, coronary sinus; FO, foramen ovale; HV, hepatic vein; IVC, inferior vena cava; LAA, left atrial appendage; LSVC, left superior vena cava; MV, mitral valve; PV, pulmonic vein; RAA, right atrial appendage; RSVC, right superior vena cava; TAPVR, total anomalous pulmonary venous return; TV, tricuspid valve. Reprinted with permission from Mavroudis C, Deal BJ, Backer CL, Tsao S. Arrhythmia surgery in patients with and without congenital heart disease. *Ann Thorac Surg* 2008;**86**:857–68.

Ascites

Ascites may develop as a consequence of elevated right atrial pressure, protein-losing enteropathy or hepatic dysfunction, and requires clarification of the aetiology with aggressive evaluation and treatment. Ascites may occur without hypoalbuminaemia, but is an advanced indicator of a failing Fontan circulation; in this setting, Fontan conversion with arrhythmia surgery may be feasible, although with increased risk of later

Fontan failure. A small number of patients have persistent or recurrent ascites late after Fontan conversion, without evidence of Fontan circulation obstruction. In this setting, ascites is thought to be related to hepatic dysfunction. Diuretic therapy and optimisation of medical therapy may minimise ascites; regular evaluation of cirrhotic changes with abdominal ultrasound, CT or MRI, and monitoring of liver function, is recommended. When advanced cardiac liver cirrhosis changes are noted, the risk for hepatocellular carcinoma increases.[7] Combined cardiac and liver transplantation for a Fontan patient has been performed successfully.[w18]

THE FAILED FONTAN

In the unusual setting of early postoperative failure, a failed circulation requires early takedown of the Fontan surgical circuit. Late failure, discussed here, includes haemodynamic or multiorgan system complications of the Fontan circulation which are not reversible by surgical or catheter interventions at acceptable risk. Strategies to minimise/palliate complications or consideration for cardiac transplantation are the limited therapeutic options. Table 2 summarises the conditions associated with a failed Fontan, which are discussed in several excellent reviews.[19 w19] Most studies report early operative mortality for Fontan patients undergoing cardiac transplantation at approximately 30%, higher than that reported for other forms of congenital heart disease,[20] although one recent study showed no difference in early mortality among Fontan patients.[w20] Problems specific to the Fontan patient undergoing transplantation include multiple prior surgeries with increased sensitisation rates between 20–60%, with preformed antibodies to donor human leucocyte antigens (HLA), complexities of venous anatomy, malnourishment associated with protein-losing enteropathy, and acute graft right heart failure. After the early transplant period, there is no difference in long term survival compared with other forms of congenital heart disease, with survival rates at 10 years of around 54%.[w21 w22] Due to the significant mortality on the waiting list and elevated early mortality, there is interest in developing implantable mechanical assist devices in Fontan patients as either a bridge to transplantation, or 'destination therapy'.[w23 w24]

FAILURE OF MEDICAL CARE

At this stage in our knowledge of the natural history of the Fontan circulation, several concepts have become clear, including: (1) the unique challenges of the functionally univentricular circulation with progressive multiorgan system impact; (2) the inability to definitively treat a truly 'failed' Fontan with measures other than cardiac transplantation; (3) the inadequacy of traditional cardiac follow-up visits to reliably detect subtle changes in circulation before advanced stages; and (4) the challenges in 'cardiac' management that present unlike any other repaired congenital cardiac anomalies. In addition,

Table 2 Failed Fontan circulation

Condition	Incidence	Manifestations	Aetiologies	Treatments
Early failure	3%	Low cardiac output, pleural effusions, chylothoraces, ascites, hepatomegaly	Pulmonary vasculature abnormalities Incessant/refractory atrial tachycardia Residual obstruction related to surgical technique	Early evaluation to correct obstructions, terminate tachycardia Fontan takedown Recreate systemic to pulmonary blood flow Cardiac transplantation
Late failure Lymphatic dysfunction Protein-losing enteropathy (PLE)	2–13%	Ascites, peripheral oedema, pleural effusions, diarrhoea, malabsorption of fat, hypoalbuminaemia	Unknown, but associated with: Low cardiac output Mesenteric vascular flow abnormalities Intestinal cellular wall damage Autoimmune reactions Intestinal lymphangiectasia *Risk factors:* prolonged postoperative chest tube drainage, systemic right ventricle	Nutritional support with protein and medium chain triglycerides Optimise cardiac output: atrial rhythm, pulmonary vasodilator therapy, afterload reduction, atrial fenestration Enteric steroids Diuretics Heparin High dose aldactone Intravenous albumin and γ-globulin infusions Immunosuppression Cardiac transplantation
Plastic bronchitis	<2%	Tachypnoea, cough, wheezing, expectoration of bronchial casts	Unknown; associated with leakage of proteinaceous material into the airways resulting in bronchial casts	Urgent bronchial lavage Pulmonary vasodilators Cardiac transplantation
Primary ventricular dysfunction	~7–10%	Progressive exercise intolerance, AV valve insufficiency, hepatomegaly, ascites	Chronic hypertrophy, abnormal ventricular morphology (systemic right or indeterminate ventricle), older age at repair, prolonged cyanosis or volume overload, myocardial perfusion abnormalities	ACE inhibition Pulmonary vasodilators Calcium channel blockers for diastolic dysfunction β-blockers Multisite pacing Cardiac transplantation
Progressive increase in pulmonary resistance	Unknown	Hypoxaemia	Pulmonary arteriovenous malformations, inadequate hepatic vein effluent, lack of pulsatile flow	Pulmonary vasodilators; stenting of pulmonary arterial narrowing
Hepato-renal insufficiency			Low cardiac output, sepsis	Supportive care, optimise cardiac output, high mortality
Hepatic failure	Unknown	Hepatomegaly, ascites; hepatocellular carcinoma	Progression of chronic cardiac cirrhosis	Cardiac and liver transplantation