Review

Adult patients with Fontan circulation: What we know and how to manage adults with Fontan circulation?

Hideo Ohuchi (MD, PhD, FJCC) *

Department of Pediatric Cardiology and Adult Congenital Heart Disease, National Cerebral and Cardiovascular Center, Osaka, Japan

ARTICLE INFO

Article history:
Received 27 March 2016
Accepted 28 March 2016
Available online 29 April 2016

Keywords:
Fontan operation
Complication
Heart failure
Multiorgan
Prognosis

ABSTRACT

Most of patients after the Fontan operation can reach their adulthood, however, the management strategy for this complex pathophysiology has not been yet established. In general, elevated central venous pressure (CVP) and low cardiac output (CO) due to impaired ventricular preload characterize the Fontan circulation and the ideal hemodynamics could be a combination of a lower CVP with a higher CO. Thus, preserved functional systemic ventricle with low pulmonary artery resistance is thought to be crucial for better long-term outcome. However, on the other hand, because of the unique hemodynamics, these patients have significantly higher incidence of complications, sequelae, and even mortality. The major complications are supraventricular arrhythmias, heart failure, and Fontan-related problems, including protein-losing enteropathy and pulmonary arteriovenous fistulae, both of which are refractory to the treatments, and most of these “Fontan inconveniences” increase as patients age. In addition, one of the recent emerging problems is Fontan-associated liver disease that includes liver cirrhosis and hepatocellular carcinoma. Furthermore, women with Fontan circulation also reach childbearing age and there have been increasing numbers of reports showing a high incidence of pregnancy-associated complications. All these problems may be a part of “Fontan inconveniences” because most of the current Fontan patients are still “young” i.e. in their twenties or thirties and it may be not surprising that more new Fontan-associated pathophysiology emerges as patients age. Recent evidence reminds us of the concept that adult Fontan pathophysiology is not just a cardiovascular disease, rather, a multiorgan disease with many interactions between cardiovascular and non-cardiovascular organs. Therefore, a multidisciplinary approach is mandatory to take care of and anticipate the better long-term outcome.

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* Correspondence to: Department of Pediatric Cardiology and Adult Congenital Heart Disease, National Cerebral and Cardiovascular Center, 5-7-1, Fujishiro-dai, Suita, Osaka 565-8565, Japan. Tel.: +81 6 6833 5012; fax: +81 6 6872 7486.
E-mail address: hohuchi@hsp.ncvc.go.jp

http://dx.doi.org/10.1016/j.jcc.2016.04.001
0914-5087/© 2016 Published by Elsevier Ltd on behalf of Japanese College of Cardiology.
Conventional concept of Fontan physiology

Fontan operation is a final definitive palliative procedure for patients with complex congenital heart disease (CHD) with functional single ventricular physiology due to anatomic difficulties for biventricular correction, such as those with tricuspid atresia, single ventricle, and hypoplastic left heart syndrome. The final goal of the procedure includes elimination of hypoxia (right to left shunting in the heart) and volume overload to the functional systemic ventricle (FSV). The procedure has developed from the original type of atroipulmonary connection (APC) to total cavopulmonary connection (TCPC) where atrial contraction has little impact on the right-sided blood flow in the pulmonary circulation. Significantly improved designs of the TCPC procedures have been made and consist of intra-atrial rerouting (IAR) either using own atrial wall (lateral tunnel) or intra-atrial grafting with xenograft and extra-cardiac rerouting (ECR) with xenograft or with direct anastomosis of the inferior vena cava and pulmonary artery (PA) and the ECR is now a contemporarily main procedure for CHD patients with FSV (Fig. 1) [1].

Because of a lack of subpulmonary ventricle, elevated central venous pressure (CVP), i.e. venous hypertension (VH), and sucking power of the FSV (diastolic function) play pivotal roles for creating driving pressure for the pulmonary circulation, consequently, high CVP, low cardiac output (CO) due to diminished cardiac preload and elevated systemic artery resistance (Rs), and mild but significant hypoxia characterize the Fontan patients with chronic heart failure (HF). In this unique pathophysiology, in addition to low PA resistance (Rp), augmentation of cardiac preload by extremity muscle pump and respiratory sucking also play significant roles for the better circulation (Fig. 2). Fontan patients have limited aerobic exercise capacity, 50–60% of normal, irrespective of the type of procedures, however, some adult Fontan patients did not realize the fact and even overestimate their exercise capacity probably because of the unconscious long-term self-adjustment of their daily life-style. In addition, there are growing concerns of chronic adverse influence of high CVP (HV) on multi-organs, especially the hepatorenal and intestinal functions, and these are summarized in Fig. 3. Of those, major challenging problems are cardiovascular issues, such as arrhythmias and impaired FSV function, including atrioventricular dysfunction, respiratory issues, such as pulmonary arteriovenous fistulae (PAVF) and plastic bronchitis, hemostatic issues, such as pulmonary embolism, stroke, and hemoptysis, protein-losing enteropathy (PLE), and hepatorenal dysfunction. Pregnancy and delivery in young Fontan women are the growing issues and metabolic abnormality is a newly recognized pathophysiology of Fontan circulation. Liver problems are now recognized as Fontan-associated liver disease (FALD) and a significant body of evidence is accumulating, including liver cirrhosis (LC) and hepatocellular carcinoma (HCC) [2]. Deep understanding of adult Fontan pathophysiology as multiorgan diseases due to chronic VH as well as chronic HF is mandatory as to how to manage for expecting better long-term outcome in these patients.

Global clinical characteristics

Prognosis

Mortality-free rate for post 20-year-olds ranged from 69 to 87% [3] and survival rate has dramatically improved mainly due to improved early post-operative survival rate. However,
long-term morbidity and mortality are still high irrespective of the type of surgical procedures when compared with those in other type of postoperative CHD patients with biventricular physiology and the major reasons for the unexpected clinical events are HF, supraventricular arrhythmias, and PLE and its relapses (Fig. 3).

Clinical findings and prognostic variables

Electrocardiography

Conventional electrocardiographic criteria for pathological findings are not applicable because of the underlying anatomical

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**Fig. 2.** Comparison of hemodynamics with patients with biventricular and Fontan (single ventricle) physiology. (a) In patients with biventricular physiology, systemic ventricle (SV) supports the systemic circulation and pulmonary ventricle (PV) supports the pulmonary circulation. Muscle pump (MP) has an additional impact on increase in cardiac preload (venous return). Perfusion pressure is well maintained. On the other hand, (b) in Fontan patients, SV supports the systemic circulation. High central venous pressure (CVP) is the driving pressure of the pulmonary circulation and the muscle and respiratory pumps (MP, RP) play significant role for the pulmonary circulation. Perfusion pressure is diminished due to high CVP and low systemic pressure. VC, superior/inferior vena cavae.

**Fig. 3.** Late complications and sequelae after the Fontan operation. FALD, Fontan-associated liver disease; HCC, hepatocellular carcinoma.

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**1. Psychosocial**
- impaired quality of life

**2. Neuropsychological**
- mental developmental delay

**3. Nutrition**
- cachexia
- obesity

**4. Cardiovascular system**
- abnormal cardiac function
  - systolic, diastolic, dysynchrony
  - impaired AV valve function
  - aortopathy
  - endothelial dysfunction
  - arrhythmias
  - brady and tachyarrhythmias, AV block
- abnormal cardiac autonomic nervous activity

**5. Respiratory system**
- restrictive lung
- pulmonary arteriovenous fistulae
- phrenic nerve palsy
- plastic bronchitis
- hemoptysis

**6. Musculoskeletal system**
- abnormal bone metabolism
- sarcopenia

**7. Reproductive system**
- menstrual abnormality
- pregnancy and delivery

**8. Endocrine system**
- thyroid dysfunction

**9. Metabolic abnormality**
- impaired glucose tolerance, diabetes mellitus
- lipid abnormality (low cholesterol)

**10. Hematology**
- anemia
- lymphocytopenia, thrombocytopenia
- abnormal hematostatic profile

**11. Digestive system**
- FALD (liver congestion, cirrhosis, HCC)
- protein losing enteropathy

**12. Kidney**
- cardiorenal interaction
- hepatorenal syndrome
abnormalities. High amplitude of P wave is seen in APC Fontan patients. Heart rate variability is markedly diminished and wide QRS duration is associated with cardiac dysfunction (dyssynchrony) and reduced exercise capacity [4].

Laboratory findings

Plasma hemoglobin levels are mildly elevated in the stable chronic phase and platelet count is relatively low probably due to liver dysfunction and hypersplenism secondary to portal hypertension. Hyponatremia and hyperuricemia are not uncommon and reflect global HF severity [5]. Plasma levels of total bilirubin and y-glutamyltransferase (GGT) are usually elevated proportional to the liver congestion (40–60%), whereas plasma levels of liver enzymes (alanine aminotransferase, aspartate aminotransferase) are often within normal range and plasma levels of cholesterol are low.

Neurohormonal factors

Plasma levels of norepinephrine and natriuretic peptides are increased and the high levels are associated with poor prognosis in adult Fontan patients [6]. Type of procedure has a significant impact on plasma levels of natriuretic peptides: markedly high in APC patients, followed by TCPC with lateral tunnel and the lowest levels are seen in ECR patients because the secretion is proportional to a stretch of the atria [7].

Cardiopulmonary function

Fontan patients show markedly diminished heart rate response during exercise because of severely impaired cardiac autonomic nervous activity and reduced aerobic exercise capacity as expressed by peak oxygen uptake (VO2, ml/kg/min), which usually ranged from 50% to 60% of normal value. Major cardiopulmonary variables, i.e. heart rate response, peak VO2, and ventilator efficiency, derived from cardiopulmonary exercise testing predict morbidity and mortality. In Fontan patients, peak VO2 rather than ventilator efficiency has strongest prognostic value [8].

Major post-Fontan complications and sequelae

Major complications and sequelae, i.e. Fontan associated “inconveniences”, long after the Fontan operation and the possible management strategy are listed in Table 1 and Fig. 4 for hemodynamic management. Root causes of these inconveniences mostly stem from Fontan circulation itself, therefore, the most important first step for the management is understanding the Fontan circulation. Accordingly, invasive hemodynamic assessment is often required and helpful for the meticulous management.

Heart failure

There have been concerns of failing Fontan circulation due to progressive deterioration of work efficiency of the FSV caused by both impaired ventricular systolic function and sustained high afterload, especially in the non-left ventricular (LV) morphology, i.e. biventricular and right ventricle (RV) as a FSV. In addition, a recent study with cardiac magnetic resonance imaging (MRI) demonstrated a larger FSV (>125 ml/body surface area) was independently associated with low transplantation-free survival [9] irrespective of the type of FSV. QRS duration in non-LV Fontan patients is wider than that in LV Fontan patients and is sometimes associated with dysynchronous contraction of the FSV, resulting in greater hemodynamic deterioration during tachyarrhythmia and reduced exercise capacity [4]. Furthermore, a stiff aorta is now newly recognized as “aortopathy” that has adverse impact on FSV function and coronary circulation due to a high pulse pressure. Endothelial dysfunction is also demonstrated as one of the common features of HF and is related with aerobic exercise capacity, indicating an importance of maintenance of nitric
oxide-associated endothelial function both in the pulmonary and systemic circulation.

Management for HF

No standard pharmacological HF management strategy has been established in adult Fontan patients. Diuretics are effective for inappropriate fluid retention, such as extremity edema, pleural effusion, and ascites. However, on the other hand, diuretic use was one of the independent risk factors for mortality, thus, unjustified use of diuretics should be avoided as demonstrated in adult HF field with non-CHD [3]. As for angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (ACEi/ARB), no clinical benefits have been demonstrated in either child or adult Fontan patients in terms of cardiac autonomic nervous system and exercise capacity for a relatively short study period [10,11]. However, the end-point of the clinical trials was an improvement in exercise capacity, rather than mortality, because of the limited number of patients and low mortality. In addition, most study subjects were classified in New York Heart Association (NYHA) class I or II. So, long-term impact of ACEi/ARB on survival is unknown. As for β blockers, there are only a few case reports for their efficacy. Most post-operative adults with CHD, including Fontan patients, tend to have a slower resting heart rate probably due to the surgery-associated sinus node dysfunction, careless administration of β-blocker may worsen the hemodynamics because the limited stroke volume due to impaired cardiac preload requires higher heart rate for adequate systemic perfusion pressure in the Fontan circulation. In this setting, pacemaker implantation may be required to guarantee adequate minimum heart rate for the management of HF as well as refractory arrhythmias. In case of II or III AV block, special attention should be paid to the pacing site of the FSV to avoid dyssynchronous contraction. Pacing site should be in the longitudinal direction in patients with RV as FSV and opposite sites of both ventricles in those with unbalanced biventricular as a FSV. However, the efficiency of synchronized therapy for FSV is lower in the RV than in the LV [12].

Pulmonary circulation

Better pulmonary circulation is crucial for better long-term outcome in Fontan physiology. High Rp easily collapses the circulation and because of the possible progressive increase in Rp long after the Fontan operation, several randomized clinical trials (RCTs) with PA dilator(s) have been conducted. Regarding phosphodiesterase (PDE)-5 inhibitors, administration of sildenafil (20 mg three times daily) for 6 weeks improved ventilator efficiency and exercise capacity [13] and a single dose of tadalafil (1 mg/kg) for 6 weeks also improved exercise capacity as well as cardiac function. In regard to the mechanisms for improved exercise capacity, improved heart rate response and prevention of exercise-induced elevation of Rp and Rs, rather than increased stroke volume due to improved cardiac preload, are responsible for the benefits [14]. There may be no direct beneficial cardiac effect of PDE-5 inhibitor during exercise. A single dose of iloprost (5.0 μg) improved exercise capacity, especially in those with low baseline exercise capacity (peak VO2 < 30 ml/kg/min). Efficacy of bosentan, an endothelin-1 (ET-1) receptor blocker, was also demonstrated in an RCT [15]. Although there was no improvement in quality of life (short-form 36), administration of bosentan (62.5 mg twice daily for 2 weeks, followed by 125 mg twice daily for 12 weeks) improved exercise capacity and NYHA class when compared with controls (2.0 vs. 0.6 ml/kg/min, p < 0.05). Baseline lower peak VO2 as well as high plasma levels of B-type natriuretic peptide and/or ET-1 may identify the responder. On the other hand, long-term PA remodeling, i.e. decreased medial thickness and increased intimal thickness, may have significant impact on efficacies of PA vasodilators.
Arrhythmia

Supraventricular tachyarrhythmia (SVT), rather than bradycardia, is a major electrophysiological problem. Main mechanisms of the SVT are intra-atrial reentrant tachycardia (IART) and ectopic atrial tachycardia (EAT) and IART is the most common form of SVT (40–60%). SVT is related to increased morbidity and mortality late after the Fontan operation. Although incidence of SVT is higher in AFC patients than in those after TCPC, there has been no clear difference in the incidence between types of IAR and ECR. The prevalence steadily increases irrespective of the type of Fontan procedures, especially in those with heterotaxy syndrome [16]. Incidence of bradyarrhythmia may be high after ECR, especially in those with left isomerism in whom pacemaker implantation is sometimes required.

Management of arrhythmias

Although catheter ablation is effective for managing IART and EAT, the recurrence rate is high (≥50%) because of another new onset of electric circuit. Additional pharmacological management with β-blocker, sotalol, and amiodarone may be needed and effective in some patients with refractory SVT. When drugs of Vaughan-Williams group III were used, careful attention should be paid to side effects of these drugs, for instance, QT prolongation after administration of sotalol and liver and thyroid dysfunctions. TCPC conversion with pacemaker implantation may be effective to control SVT as well as impaired hemodynamics in APC patients, especially in order to manage perioperative arrhythmias as well as hemodynamic adjustment immediately after TCPC conversion. Early intervention for SVT may be preferable for better long-term outcome because SVT is associated with morbidity and mortality, however, the efficacy of early intervention needs further investigations.

PLE

Incidence of PLE after the Fontan operation ranged from 4 to 13% and increases as patients age. The post-10 and 20-year PLE free rate was 92% and 86%, respectively and once PLE occurs, the survival rate 5 and 10 years after the PLE onset was quite low, 50% and 20%, respectively. Owing to recent advances of medical therapy, the 5- and 10-year post-onset survival rates dramatically improved up to 90% and 70%, respectively [17,18]. However, despite a marked improvement in the survival, their quality of life (QOL) remains poor because of the frequent rehospitalizations. Although the precise mechanisms for PLE onset are unclear, HV is closely associated with the onset [17] and infection is sometimes a trigger of the onset and worsens the PLE condition. In addition, some PLE patients have additional major complications, such as arrhythmias (≥30%) and history of thromboembolism (≥20).

Management of PLE

The first step of the management is to check whether active or chronic inflammation exists and the presence of risk factors for raising CVP, both of which are key issues to manage in PLE patients. Much effort should be focused on eliminating any inflammation and the risk factors. The risk factors of raising CVP include excess water intake, stenosis of Fontan route, PAVF, aortopulmonary collaterals, dysfunction of FSV and/or AV valve. Management strategies for each factor are listed in Table 1. After these efforts, oxygen inhalation and PA dilators could be effective to reduce Rp. Surgical and/or catheter fenestration between Fontan route and functional systemic atrium might be one of the options to control PLE pathophysiology. Limited efficacy (44%) by each conventional strategy for PLE patients was reported in an early multicenter study [19]. Transient improvement (76%) could be achieved by heparin administration either intravenously or subcutaneously, however, rates of the PLE relapse and readmission with albumin infusion did not change. Recently, owing to marked advances of vasodilators for PA through three pathways (nitric oxide, prostacyclin, and endothelin), these vasodilators could have an important role for managing PLE patients with a high CVP if they have a high Rp. Although precise mechanisms are unclear, high dose anti-aldosterone therapy and oral steroid administration (budesonide) may be effective in some cases. In addition, subcutaneous administration of IgG (Hizentra, CSL Behring, King of Prussia, PA, USA) has been tried in Japan although the efficacy is unknown at this point [20]. PLE resolves in most failing child Fontan patients after cardiac transplantation, however, early survival rate is lower in these PLE patients than those without PLE. In addition, because of recent marked improved survival rate after the onset of PLE [17,18], it may be difficult to determine the optimal timing of cardiac transplantation.

Thromboembolism and hemorrhagic events

Three prerequisites for thrombogenesis have been recognized as Virchow’s triad: (1) abnormal blood flow; (2) abnormalities in the vessel wall; and (3) abnormalities in blood constituents and this concept can be applicable to Fontan patients to prevent thromboembolic events. In Fontan patients, these three risk factors have been repeatedly demonstrated. In general, several plasma levels of anticoagulation factors, including antithrombin, protein C, and S are low [21]. In addition to increased platelet activity, plasma levels of von Willebrand factor are elevated as a reflection of endothelial dysfunction. Sluggish flow with whirl formations is demonstrated by recent advanced image modalities. Thus, thromboembolic events could occur irrespective of postoperative phase, and the risk may be high in adult Fontan patients, especially in those without anticoagulation therapy [22]. However, there may be significant ethnic differences in coagulation profiles and imbalance between procoagulant and anticoagulant pathways in oriental patients which favor a bleeding, rather than a thrombotic, tendency [23]. Liver dysfunction is, in part, responsible for abnormal coagulation profiles, especially in patients with LC. Although platelet count is commonly low, the platelet activity is increased with aspirin resistance, indicating increased thrombogenesis in adult Fontan patients.

Management of thromboembolic events

Urgent management is required for significant size of thrombus in the Fontan route that could easily collapse a Fontan circulation, however, no standard thromboprophylactic strategy has been established in child and adult Fontan patients. In retrospective studies, incidence of thromboembolic events was significantly lower in Fontan patients with anticoagulation therapy with aspirin and/or warfarin than in those without any anticoagulation although there was no difference in the incidences between those with aspirin and warfarin [22]. On the other hand, the event rate may be higher in sicker patients even if they are treated with warfarin [23]. In one RCT in children, there was no significant difference between aspirin and heparin/warfarin as primary thromboprophylaxis in the first 2 years after Fontan surgery [24]. Although there has been no RCT in adult Fontan patients, it might be rational to prevent thromboembolism by following a notion of Virchow’s triad. In general, thromboprophylactic administration of warfarin should be considered when Fontan patients have some risk factor(s) that include presence of thrombus, high CVP, low CO, significant right to left shunting.
due to veno-venous collaterals, fenestration and PAVF, poor FSV function, dilated right atrium in APC patients, stenosis of the Fontan route, and current and/or history of SVT[22]. Overall coagulation homoestasis, for instance, plasma levels of procoagulant vs. anticoagulant factors, might be as well-balanced in clinically stable Fontan patients as in those with end-stage liver disease, some pathological stress, such as infection, heart failure or hemodynamic deterioration due to arrhythmia, may destroy the delicate balance, leading to hemostatic events. Thus, meticulous thromboprophylactic management should be required in such pathophysiological stressed condition(s). In the presence of significant intracardiac thrombus, immediate surgical removal may be needed as well as medical management with heparin or warfarin. In hemodynamically unstable conditions, the mortality is high (75%) when compared with those with stable hemodynamics (8%). In addition, the prevalence of silent asymptomatic pulmonary thrombosis is relatively high (17%) although the prevalence may depend on the modalities to detect. However, significant ethnic differences also should be taken into account because a prevalence of hemorrhagic events, such as hemothysis, may be high in Japan [23], therefore, significant effort will be needed to establish thromboprophylactic management guidelines suitable for our adult Fontan patients.

PAVF
PAVF could be subdivided into 3 subtypes, diffuse, discrete, and coexistence of both. Incidence of PAVF, mostly diffuse type, is high after Glenn anastomosis and Kawashima’s procedure and the hypoxia is usually progressive. The PAVF often disappears after a completion of Fontan operation probably due to significant hepatic venous inflow that may contain “hepatic factor” into the affected lung. Presence of PAVF may be detected by chest X-ray and lung computed tomography and accuracy of the diagnosis depends on the modalities used and the diagnostic sensitivity by contrast echocardiography with injection of contrast medium is high. Actual incidence of PAVF is unknown, however, the incidence may be high in Fontan patients with left isomerism heart and may occur in the lung with diminished hepatic venous flow due to unbalanced pulmonary flow from the inferior vena cava. PAVF patients have a lower Rp and, therefore, an increased CVP due to the increased cardiac preload may be one of causes for new PLE onset or relapses [17].

Management of PAVF
Surgical re-direction of the Fontan route for aiming at balanced systemic venous pulmonary flow distribution (hepatic factor) to the bilateral PAs may be effective in some child Fontan patients [25]. In addition to oxygen therapy, nitric oxide inhalation may also be effective in hypoxic patients with PAVF. Creating peripheral arteriovenous shunting with an expectation of supplying hepatic factor into the affected lung might be an option. Catheter embolization could be applicable to patients with discrete-type PAVF.

FALD

Chronic congested liver eventually leads to liver dysfunction which is now recognized as FALD and a significant body of evidence has been accumulating [11]. Although the prevalence depends on the diagnostic modalities, according to strict diagnostic criteria with liver imaging and biopsy, 10-, 20-, and 30-year freedom from LC was 99%, 94%, and 57%, respectively, and the survival after diagnosis of LC was 57% and 35%, at 1, and 5 years, respectively [26]. FALD progresses without symptoms although hepatomegaly is commonly seen and ascites becomes evident at the stage of advanced LC with cirrhotic heart failure characterized by systemic vasodilatation. Furthermore, HCC is now one of the emerging issues that care givers have to check long after the Fontan operation [27]. Considering the high mortality of HCC, FALD may be one of the major non-cardiac determinants of mortality in adult Fontan patients.

Diagnosis of FALD
Liver function test has a significant prognostic value in patients with cardiovascular disease, especially, low plasma levels of albumin, high levels of bilirubin, and liver enzymes, such as GGT. Although serological quantitative assessment of liver fibrosis is challenging in Fontan patients, plasma levels of albumin and cholinesterase decrease and plasma levels of total bilirubin, hyaluronic acid, and collagen type IV may increase as hepatic fibrosis develops. In addition, impaired protein synthetic ability leads to abnormal coagulant profiles [21]. Reduction in platelet number indicates fibrotic change in the liver and periportal fibrotic change may be associated with the reduction in Fontan patients. Several studies have addressed the issue of predicting the degree of hepatic fibrosis with conventional predictive formulae: Forms index, Model for End-stage liver disease (MELD), Child–Pugh score, and VAST (varices, ascites, splenomegaly, or thrombocytopenia). However, because these predictions were originally developed for assessing chronic liver disease, mostly for LC secondary to hepatitis, these predictions have significant limitations in patients with FALD. As for image modalities, hepatic ultrasonography has a significant role for screening of FALD. Most Fontan patients showed dilated hepatic and portal veins and an edge angle of the liver is dull. As FALD advances, ascites is frequently seen. Augmented portal flow during inspiration is observed in Fontan patients, especially in those with severe heart failure and/or high CVP, which does not occur in normal subjects. Computed tomography and magnetic resonance imagings are useful to evaluate parenchymal change in the liver. Unlike atrophic liver disease after hepatitis, Fontan patients show enlarged liver with the dull edge angles and irregular surface. In the contrast enhanced imaging, parenchymal reticular pattern in the portal-phase with hypervascular regenerative nodule(s) in the arterial-phase are often observed (=25%) long after the Fontan operation (Fig. 5). Most these nodules are benign, however, careful decision of distinction between benign
and malignant may be required in some cases. Image characteristics for diagnosing HCC are, so far, unclear in Fontan patients. Biopsy findings of the Fontan liver consist of dilated sinusoid and fibrotic change in zone 3 with other global structural changes. Periporal fibrotic change is also observed and these centrilobular and portal fibrotic changes develop before and after the Fontan operation, however, the degree of fibrotic changes are poorly associated with clinical characteristics or outcomes [28]. Establishment of gold standard criteria for evaluating the degree of fibrotic change is desired because of the invasive nature and its potential sampling error in the liver biopsy.

Management of FALD

Because one of the major causes for FALD may be chronic liver congestion due to high CVP, it is crucial to measure CVP for dealing with FALD as well as the other organs and the CVP must be kept as low as possible. Considering evidence of high risk of PLE onset in Fontan patients with a high CVP ≥ 12 (mmHg) and subclinical progression of FALD, early intervention aiming at lower CVP may be mandatory irrespective of their symptoms. In addition, therapy for chronic hepatitis should be recommended because of an increased risk of HCC after post-hepatitis LC. Thus, regular follow-up by a hepatologist may be also mandatory in adult Fontan patients [2].

Pregnancy and delivery

The majority of women with Fontan circulation reach reproductive ages and this issue is rapidly emerging. In one study, contraceptives were not taken by 44% of women with Fontan circulation and, on the other hand, thromboembolic events occurred in some cases with and without contraception (8–11%) [29]. Menstrual disorders are also common in these patients and, therefore, gynecological consultation, including evaluation of ovarian function, may be necessary. There have been several reports on pregnancy in women with Fontan circulation, however, no standard strategy of dealing with this issue has been established. SVT during pregnancy and postpartum is the most common complication (10–20%), followed by thromboembolism or hemorrhagic events [30]. Pre-pregnancy arrhythmias were the only predictor for the arrhythmic events. Heart failure sometimes occurs postpartum. Miscarriage is frequent (30–50%), especially under warfarin treatment, and therapeutic abortions were not rare (9%). In western countries, both vaginal deliveries and C-section were performed with a little higher rate of C-section (50–70%). Fetal/neonatal complications are common. Although gestational age is usually shorter, 33–34 weeks, and the birth weight is low, around 2000 g, recurrence of CHD is low and there has been no maternal mortality despite the high incidence of fetal, neonatal, and maternal complications [29,30].

Other pathophysiology

It has been emphasized that glucose metabolic abnormalities, including diabetes mellitus, have an adverse impact on prognosis in patients with cardiovascular disease and this also holds true in adult Fontan patients. Based on 75 g oral glucose tolerance test, about 40% and 15% of adult Fontan patients have impaired glucose tolerance and diabetic pattern, respectively, and these patients have a significantly higher event rate [31]. Preventive strategies for these metabolic disorders are important to improve the long-term outcome because of the importance of endothelial function in the systemic and pulmonary arteries. In addition, recent study [32] of adult failing Fontan patients revealed that FALD, especially LC, may have significant adverse impact on Fontan circulation that is characterized by a markedly high CVP and low Rs. The abnormal hemodynamics are clearly different from those of conventional concept of low CO with high Rp and Rs.

The evidence strongly reminds us the concept that adult Fontan pathophysiology is not just a cardiovascular disease, rather, a multiorgan disease with many interactions between cardiovascular and non-cardiovascular organs. Fig. 6 shows multiorgan histopathological findings, including the brain (arteriovenous malformation), lung (PAVF), liver (cirrhosis), and kidney (mild change) in our Fontan autopsy case with left isomerism heart who died of multiorgan failure. Therefore, a multidisciplinary approach, including socio and psychological issues, is mandatory to take care of and anticipate better long-term outcome in these particular adults.

Funding

None.