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Original Article

Rare problems associated with the Fontan circulation

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Abstract The Fontan operation, originally described for the surgical management of tricuspid atresia, is now the final surgery in the strategy of staged palliation for a number of different forms of congenital cardiac disease with a functionally univentricular heart. Despite the improved technical outcomes of the Fontan operation, staged palliation does not recreate a normal physiology. Without a pumping chamber delivering blood to the lungs, the cardiovascular system is less efficient; cardiac output is generally diminished, and the systemic venous pressure is increased. As a result, patients with "Fontan physiology" may face a number of rare but potentially life-threatening complications including hepatic dysfunction, abnormalities of coagulation, protein-losing enteropathy, and plastic bronchitis. Despite the staged palliation resulting in remarkable survival, the possible complications for this group of patients are complex, involve multiple organ systems, and can be life threatening. Identifying the mechanisms associated with each of the rare complications, and developing strategies to treat them, requires the work of many people at many institutions. Continued collaboration between sub-specialists and between institutions will be required to optimise the care for this group of survivors with functionally univentricular hearts.

Keywords: Congenital heart disease; paediatric cardiac disease; hepatic dysfunction; abnormalities of coagulation; protein-losing enteropathy; plastic bronchitis; single ventricle; functionally univentricular heart

The Fontan operation, originally described for the surgical management of tricuspid atresia,[1,2] is now the final surgery in the strategy of staged palliation for a number of different forms of congenital cardiac disease with a functionally univentricular heart. The adoption of the staged strategy has allowed for the survival of thousands of infants and children who otherwise would not have survived childhood.[3,4] However, despite the improved technical outcomes of the Fontan operation, staged palliation does not recreate a normal physiology. Without a pumping chamber delivering blood to the lungs, the cardiovascular system is less efficient; cardiac output is generally diminished, systemic venous pressure is increased, and, as a result, patients with "Fontan physiology" may face a number of rare but potentially life-threatening complications.

The challenges after the Fontan may be cardiac related, as in poor ventricular function or significant atrioventricular valvar regurgitation, or the challenges may be non-cardiac in nature though still related to the underlying physiology. Abnormalities are described in hepatic architecture and function, in the cascade of coagulation, in the gastrointestinal system, and in the lungs. In this review, we will describe some of the rare non-cardiac complications after the Fontan operation and discuss potential therapies.

Hepatic dysfunction

Over the past 5–10 years, as focus has shifted from short-term survival to long-term survival and quality of life, a number of studies have emerged that describe the impact of the physiology of the Fontan on the liver. By definition, hepatic venous

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pressure after the Fontan may be three to four times higher than normal, similar to what may be found in adults with congestive heart failure. The implications of this elevated hepatic venous pressure over the long term are not yet well described, but a limited series of autopsy and biopsy studies have shown hepatic congestion, dilated biliary ducts, hepatic fibrosis, and hepatic cirrhosis.[5–8] Despite the possibility of these findings being mild immediately after the Fontan operation, evidence exists to suggest a correlation in the degree of abnormal hepatic pathology with time from the Fontan, with cardiac output, and with central venous pressure.[5–7]

In addition to hepatic congestion and hepatic fibrosis, there are rare reports of hepatic neoplasm late after the Fontan. Hepatocellular carcinoma and hepatic adenomas have both been described and are thought to result from chronic passive hepatic congestion.[9,10] In one published pathological case, the rupture of a hepatic adenoma led to significant loss of blood and ultimately to the demise of the patient. Despite there being no data about the relative risk of neoplastic transformation following the Fontan operation, the case reports certainly indicate that while rare, the risk of neoplasm is most likely higher than in the general population, and may be associated with the duration of hepatic congestion and degree of hepatic fibrosis and cirrhosis.

The risk of hepatic fibrosis, cirrhosis, and hepatic neoplasm suggests a role for routine hepatic screening. Unfortunately, no current screen has shown utility in this population. A number of screens combining serum markers are suggested for inflammatory disease of the liver, though the applicability of these tests to the unique circulation of the Fontan is unknown.[11–13] Similarly, evaluation of the liver using transient elastography (Fibroscan) is of significant benefit in patients with hepatic dysfunction associated with hepatitis, but may not be an appropriate test in the setting of congestive heart failure or elevated central venous pressures, a condition that is always present following the Fontan.[14–16] Without accurate non-invasive tests or tests of serum to evaluate hepatic function and architecture, biopsy of the liver remains the gold standard. Despite the reported mortality with biopsy being low, the potential for morbidity exists,[17] a potential that might be higher in children who are unwell following palliation for functionally univentricular heart. For now, ultrasonographic assessment[18] of the architecture of the liver, or serial magnetic resonance imaging,[19] may be the most appropriate as baseline testing, with more invasive testing being reserved for those in whom the suspicion of significant abnormalities of the liver is highest.

Unfortunately, even when diagnosed, no direct therapy exists for the elevated hepatic pressure of the Fontan circulation. The elevation is a direct result of the basic physiology following the Fontan operation, and nothing short of a new strategy for treatment of patients with functionally univentricular hearts is likely to have a profound impact. Nevertheless, the potential exists to have at least a modest impact on hepatic pressure through the development of strategies to lower pulmonary arterial pressure. Certainly, the enlargement or creation of a fenestration may allow for a "pop-off" in the setting of elevated pulmonary arterial pressure and is shown to improve systemic delivery of oxygen.[20] Newer medical approaches may also have an impact. In particular, the use of medications traditionally used for the treatment of pulmonary hypertension may lower systemic venous pressure by lowering pulmonary vascular resistance.[21,22] Limited data exist on these medications following the Fontan operation, and no direct measurements exist of their impact on hepatic pressure. Nevertheless, it is certainly reasonable to believe that phosphodiesterase type 5 inhibitors or therapies with prostacyclin that lower pulmonary vascular resistance through their effect on pulmonary vascular resistance may reduce the degree of hepatic congestion.

Abnormalities of coagulation

Abnormalities in the cascade of coagulation remain a vexing problem after the Fontan operation. The precise mechanism by which children are at increased risk for the formation of thrombus after the Fontan is not known and is likely multi-factorial. Certainly, a number of anatomical and physiological risk factors are inherent in the cardiovascular system after the Fontan operation. However, primary abnormalities also exist in the cascade of coagulation following the Fontan that may further impact the risk of thrombosis.

Of the anatomical and physiological differences in the Fontan circuit, those that are likely to play a role in the increased risk of thrombosis include:

- diminished cardiac output,
- abnormal patterns of venous flow,
- prosthetic material used to create the baffle or conduit,
- the presence of blind pouches with low flow of blood, such as rudimentary ventricles and oversewn stumps from the pulmonary artery, and
- in some children, lack of atrioventricular synchrony.

This group of risk factors is characterised by the presence of low-velocity venous flow and the potential exposure of the factors of clotting to prosthetic material.

Despite the possibility of the anatomical and haemodynamic abnormalities after the Fontan being sufficient to explain an increased incidence of

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thrombus, a number of abnormalities in the coagulation cascade also exist following the Fontan that may add to the thrombotic risk. Interestingly, studies have shown abnormalities in both pro-thrombotic and anti-thrombotic factors of coagulation, making a comprehensive understanding of how factors of coagulation impact on formation of thrombus difficult.[23,24] Low levels of protein C, protein S, and antithrombin III are described, which would suggest a hypercoagulable state; meanwhile, deficiencies in numerous factors of coagulation, including factors II, V, VII, VIII, and X, have also been described, which would suggest just the opposite. In an attempt to evaluate the total effect of abnormalities of coagulation on the propensity to form a thrombus, a recent study was performed in which thromboelastography was used in an attempt to determine the net effect of the potential alterations.[25] Surprisingly, in this prospective cross-sectional study, no difference was found between the profiles of coagulation of 25 children following the Fontan operation and 51 age-matched healthy controls.

Whatever the mechanism, the risk of thrombus and thromboembolism following the Fontan operation appears to be significant. In a review at The Children's Hospital of Philadelphia, Coon showed a prevalence of thrombus of 8.8% in children after the Fontan as diagnosed by surface echocardiography.[26] Of the patients with thrombi:

- 48% were located in the Fontan circuit (on the systemic venous side of the baffle/conduit),
- 44% were found in the pulmonary venous atrium,
- one patient had thrombus on both sides of the baffle/conduit,
- two patients had thrombus in their hypoplastic ventricle, and
- one had thrombus associated with an over-sewn pulmonary arterial stump.

Despite the high prevalence of thrombus, the rate of cerebral vascular accident, while not negligible, was significantly lower. Overall, 15% of those with thrombi had concomitant cerebral vascular events.

Despite the risk of thromboembolic events being important and warranting clear guidelines, no consensus exists on appropriate prophylactic strategies. Protocols for management vary, but typically include aspirin or warfarin, although some patients may be on no anticoagulation at all. The reason for this lack of uniformity is most likely related to the relative rarity of significant thromboembolic events and the lack of prospective studies comparing different regimens of anticoagulation. There are a few retrospective studies comparing strategies, but all have a very low rate of events. However, in these retrospective reviews, there does not appear to be good evidence to suggest that warfarin is a useful therapy for all patients:

- In a series of 72 patients started on aspirin on post-operative day 1 following the Fontan, Jacobs et al[27] found no occurrences of thromboembolic events.
- Mahnke et al[2] reviewed the data from the Children's Hospital of Pittsburgh. They reviewed the records of 132 patients with a median follow-up of 7.6 years. In their cohort, they found an event rate for significant cerebrovascular accident of 2.3% with no association between anticoagulation strategy and rate of event.[8]

On balance, enough evidence exists to suggest that some form of anti-thrombotic therapy is useful following the Fontan. However, there are no prospective data to suggest whether an anticoagulation strategy that targets the function of platelets, or a more robust strategy that targets the cascade of coagulation, should be used. Given the low frequency of events, the absence of a proven benefit of warfarin, the significant risks associated with using warfarin, and the relative safety of aspirin at low doses, we believe that treatment with aspirin is sufficient for prophylaxis against thrombosis, unless other risk factors are present or there is a history of a significant thromboembolic event.

Protein-losing enteropathy

Protein-losing enteropathy is an enigmatic and troubling complication seen after the Fontan operation.[29] The disorder is primarily characterised by the abnormal loss of elements of protein into the lumen of the gut, resulting in hypoproteinaemia and hypoalbuminaemia. Loss of vascular oncotic pressure leads to the seepage of fluid into the interstitial tissues and the development of peripheral oedema, ascites, pleural effusions, and pericardial effusions. The break in integrity of the enteric mucosal barrier affects a number of bodily homeostatic systems:

- Loss of albumin leads to abnormalities in the metabolism of calcium.
- Loss of factors of coagulation further upsets an already abnormal cascade of coagulation.
- Abnormal flow in lymphatics, as a result of lymphatic engorgement, may lead to lymphopaenia and a relative immunodeficient state.

Enteric loss of protein after the Fontan operation can be a slow and indolent process, or it can occur with fairly rapid onset. Diarrhoea is seen when there is marked long-standing hypoproteinaemia and the development of oedema of the wall of the gut with

malabsorption; however, diarrhoea is not present in every case of protein-losing enteropathy. Just as many patients complain of constipation and subtle changes in bowel habits, so do those with frank diarrhoea. The most common presenting scenario is a child complaining of shoes feeling tight or clothes not fitting. In young children, peri-orbital oedema upon awakening is common.

Protein-losing enteropathy after the Fontan operation is believed to occur in anywhere from 3% to 10% of patients.[30] As recognition of the disorder has increased, a variety of patterns of manifestation of disease are noted. Some patients manifest the full spectrum of the disorder and remain chronically hypoalbuminaemic unless intervened upon. Then, some patients manifest transient hypoalbuminaemia, commonly 1–2 weeks following a viral syndrome. Within 4–6 weeks, and without intervention, levels of protein in these patients normalise. This phenomenon also suggests that protein-losing enteropathy after the Fontan operation may occur much more frequently than initially thought, as many of these transient periods of mild oedema may go unnoticed by parents, or be ignored by adolescents and young adults.

The diagnosis is made by the presence of low serum levels of protein or albumin in the absence of any other source for loss of protein. Alpha-1-antitrypsin is a protein produced by the liver that remains intact in the circulation. This protein is normally excreted in the stool, and can therefore be used as a marker for abnormal enteric permeability to protein. An increased 24-hour stool clearance of alpha-1-antitrypsin is the "gold standard" assay for diagnosis of protein-losing enteropathy. An increased spot stool concentration of alpha-1-antitrypsin is also diagnostic of protein-losing enteropathy; however, a low concentration does not rule it out.

The underlying pathophysiological mechanism that results in protein-losing enteropathy is still poorly understood. We have postulated it to be due to the confluence of a number of processes:

- First and foremost is the pervasive circulatory insufficiency of the Fontan circulation.[31] To variable degrees, but in essence in all patients with Fontan physiology, cardiac output is diminished and central venous pressure is increased.[32] This state is physiologically similar to a state of chronic low-level congestive heart failure. As a result, gastrointestinal perfusion and delivery of oxygen is diminished. In the presence of low cardiac output, compensatory mechanisms will increase and maintain perfusion to vital organs, shunting blood away from the non-vital mesenteric circulation and further limiting delivery of oxygen delivery to the mucosa of the gut. In support of this notion, we and others have shown increased mesenteric vascular impedance in patients with protein-losing enteropathy after the Fontan operation as measured by Doppler echocardiography.[33,34] We found that patients with protein-losing enteropathy have higher mesenteric vascular impedance than those without protein-losing enteropathy after the Fontan. Both of these groups had higher mesenteric vascular impedance than age-matched normal controls.
- The second mechanistic process that exists in patients with protein-losing enteropathy after the Fontan operation is that of inflammation. Chronic congestive heart failure is an inflammatory disease that results in an increase in inflammatory markers. We showed the presence of increased inflammatory markers such as tumour necrosis factor alpha after the Fontan operation.[35] The phenomenon of new onset protein-losing enteropathy, or a flare of symptoms soon after a viral syndrome, supports the role of inflammation in the pathophysiology.[36]

Experience with response to various treatments supports these two mechanistic concepts as the foundation of the disease. Manoeuvres that increase cardiac output and lower central venous pressure can improve protein-losing enteropathy. Optimising what is a markedly sub-optimal physiology can help alleviate symptoms. Even those who have haemodynamic data that do not suggest a "failing Fontan", such as a pulmonary arterial pressure less than 15 millimetres of mercury, may benefit from actions that improve cardiac output and increase perfusion of organs and delivery of oxygen. Therapies such as creating atrioventricular synchrony through pacing when it is absent[37] and creation of a fenestration[38,39] are reported as successful in improving levels of serum protein. Anti-inflammatory therapies, such as administration of unfractionated heparin[40] or systemic steroids,[41] are reported to be helpful in a select few. Table 1 lists potential therapies for protein-losing enteropathy by disease severity.

At our centre, we have begun using a combination of controlled release budesonide, started at 9 milligrams per day and sildenafil 20 milligrams per day, in an attempt to control inflammation and to improve haemodynamics.[42] Response, defined as a rise in serum albumin from one category of severity of disease to another, has occurred in most of our patients within 4 months of initiation of this protocol of treatment. Once an appropriate level of serum albumin is achieved, typically greater than 3.0 grams per decilitre, controlled release budesonide can begin to be weaned in a slow manner to a low dose of 3 milligrams per day or every other day.

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Table 1. Protein losing enteropathy: categories and therapies

Categories of severity of disease	Therapy	Side-effects or negative aspects
Category I (mild disease; serum albumin 2.5–3.5 g/dl)	Lasix	Electrolyte imbalance, dehydration
	High-dose aldactone	Gynecomastia
	Low-fat, high MCT diet	Poor compliance, commonly ineffective
Category II (moderate disease; serum albumin 2.0–2.5 g/dl)	Atrioventricular pacing	Surgery, effusions, maintenance of the pacemaker
	Heparin	Chronic subcutaneous injections, osteopaenia, commonly ineffective
Category III (severe disease; serum albumin < 2.0 g/dl)	Systemic corticosteroids	Hypertension, hyperglycaemia, adrenal suppression, osteopenia, Cushingoid features
	Sildenafil	Hypotension
	CR-budesonide	Similar to corticosteroids in the face of hepatic dysfunction
	Fontan surgical revision	Complex operation, high mortality
	Heart transplant	Chronic anti-rejection medications, coronary artery disease, likely need for re-transplantation

CR = controlled release; MCT = medium chain triglyceride

To date, none of our patients who had a successful response were able to wean completely off controlled release budesonide without relapse. Hence, it should be anticipated that low-dose controlled release budesonide will be administered long term to keep the disease in check. A caveat to this approach is that while controlled release budesonide has 90% of first pass hepatic metabolism in those with normal hepatic function, patients with Fontan physiology often have abnormal hepatic function, and thus may be at risk for systemic side effects.

Plastic bronchitis

Plastic bronchitis is a rare complication seen after the Fontan operation in which bronchial casts are formed within the airways with potential for obstruction and asphyxiation.[43,44] Two distinctive clinicopathological groups are proposed:

- The cast material may be cellular in nature with inflammatory debris and infiltrate. These types of casts can be seen in patients with severe allergies or asthma.
- Alternatively, casts may be acellular and composed of mucin and fibrin (Fig 1).

Plastic bronchitis following the Fontan operation is most commonly of an acellular cast nature; however, a mixed pathological picture is reported in some patients. The bronchial mucosa typically appears oedematous with dilated lymphatics noted upon histology.

The cause of this complication after the Fontan operation is unknown. In a similar manner to protein-losing enteropathy, it is theorised that unique features of the Fontan circulation predispose to dysfunction of membranes and a break in the integrity of the bronchial mucosa, leading to leakage of proteinaceous material into the airway.

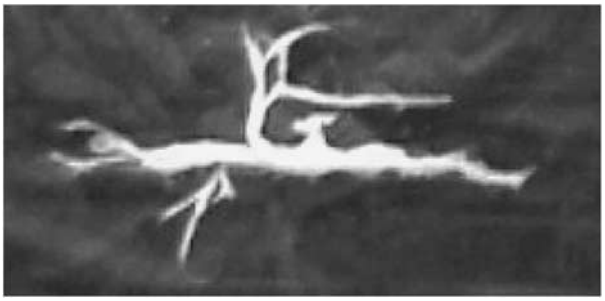

Figure 1.
An example of a bronchial cast from a patient with plastic bronchitis.

Unlike the gut, where large amounts of protein can be continuously lost over long periods of time without fear of obstruction in the bowel, in plastic bronchitis, relatively small amounts of protein lost into the airway can accrete and cause significant obstruction if not expectorated. Hence, in protein-losing enteropathy, the dominant clinical manifestation is hypoalbuminaemia and oedema, while in plastic bronchitis, hypoalbuminaemia is not seen and the dominant clinical manifestation is respiratory distress on the basis of obstruction of the airway.

Interventions that improve cardiac output can result in resolution of plastic bronchitis. This finding also suggests a similar pathophysiology to that of protein-losing enteropathy after the Fontan. Pulmonary vasodilating agents may play a role, by improving ventricular filling and increasing stroke volume and cardiac output.[45] Similarly, anti-inflammatory therapy may be beneficial in reducing severity of disease.[46] Fenestration of the systemic venous pathway has proven effective,[47] as has cardiac transplantation. Plastic bronchitis is a more acute disorder than is protein-losing enteropathy, as it can be life-threatening from the point of first presentation. This fact may explain why there are

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few studies reporting successful chronic medical regimens, as patients either succumb to the disease or receive more aggressive intervention at the outset. Nevertheless, standard care includes maintenance of clearance of the airway through the use of inhaled steroids, albuterol, aggressive pulmonary physiotherapy, and acetylcysteine. Bronchoscopic removal and mechanical clearance of airways can be life-saving.[44,48]

An important therapy that has allowed for improvement in clinical symptoms, but does not alter the underlying origin of plastic bronchitis, is the use of aerosolised tissue plasminogen activator.[43,49,50] Administration of aerosolised tissue plasminogen activator will act to dissolve bronchial casts, which either eliminates the cast or improves the ability for expectoration and clearance of the airway. Long-term therapy as an outpatient is feasible while awaiting a more effective therapy such as cardiac transplantation[51]; however, the agent is very expensive and it has been difficult in the United States of America to convince "third-party payers" to support this strategy.

Future direction

Following the Fontan operation, patients with functionally univentricular hearts have a unique set of long-term challenges. Despite staged palliation resulting in remarkable survival, the possible complications for this group of patients are complex, involve multiple organ systems, and can be life threatening. Identifying the mechanisms associated with each of the rare complications, and developing strategies to treat them, requires the work of many people at many institutions. As long as the Fontan operation continues to be the paradigm for the care of patients with functionally univentricular hearts, we will need to continue to improve our ability to support this circulation. In the long term, a "Fontan pump" or a "Fontan assist device" may usher in a new era of "ventricular replacement", but while work has started on such devices, they remain many years in the distance.[52,53] In the meantime, continued collaboration between sub-specialists and between institutions will be required to optimise the care for this group of survivors with functionally univentricular hearts.

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References

1. Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax 1971; 26: 240–248.
2. Kreutzer G, Galindez E, Bono H, De Palma C, Laura JP. An operation for the correction of tricuspid atresia. J Thorac Cardiovasc Surg 1973; 66: 613–621.
3. Kim SJ, Kim WH, Lim HG, Lee JY. Outcome of 200 patients after an extracardiac Fontan procedure. J Thorac Cardiovasc Surg 2008; 136: 108–116.
4. d'Udekem Y, Iyengar AJ, Cochrane AD, et al. The Fontan procedure: contemporary techniques have improved long-term outcomes. Circulation 2007; 116 Suppl. 11: I157–I164.
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 2005; 129: 1348–1352.
6. Kiesewetter CH, Sheron N, Vettukattill JJ, et al. Hepatic changes in the failing Fontan circulation. Heart 2007; 93: 579–584.
7. Camposilvan S, Milanesi O, Stellin G, Pettenazzo A, Zancan L, D'Antiga L. Liver and cardiac function in the long term after Fontan operation. Ann Thorac Surg 2008; 86: 177–182.
8. Kendall TJ, Stedman B, Hacking N, et al. Hepatic fibrosis and cirrhosis in the Fontan circulation: a detailed morphological study. J Clin Pathol 2008; 61: 504–508.
9. Saliba T, Dorkhom S, O'Reilly EM, Ludwig E, Gansukh B, Abou-Alfa GK. Hepatocellular carcinoma in two patients with cardiac cirrhosis. Eur J Gastroenterol Hepatol 2010; 22: 889–891.
10. Babaoglu K, Binnetoglu FK, Aydogan A, et al. Hepatic adenomatosis in a 7-year-old child treated earlier with a Fontan procedure. Pediatr Cardiol 2010; 31: 861–864.
11. Zhou K, Gao CF, Zhao YP, et al. Simpler score of routine laboratory tests predicts liver fibrosis in patients with chronic hepatitis B. J Gastroenterol Hepatol 2010; 25: 1569–1577.
12. Imbert-Bismut F, Ratziu V, Pieroni L, Charlotte F, Benhamou Y, Poynard T. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. Lancet 2001; 357: 1069–1075.
13. Cales P, Oberti F, Michalak S, et al. A novel panel of blood markers to assess the degree of liver fibrosis. Hepatology 2005; 42: 1373–1381.
14. Lebray P, Varnous S, Charlotte F, Varaut A, Poynard T, Ratziu V. Liver stiffness is an unreliable marker of liver fibrosis in patients with cardiac insufficiency. Hepatology 2008; 48: 2089.
15. Sandrin L, Fourquet B, Hasquenoph JM, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol 2003; 29: 1705–1713.
16. Millonig G, Friedrich S, Adolf S, et al. Liver stiffness is directly influenced by central venous pressure. J Hepatol 2010; 52: 206–210.
17. Jarcuska P, Janicko M, Veseliny E, Skladany L. Circulating markers of liver fibrosis progression. Clin Chim Acta 2010; 411: 1009–1017.
18. Goyal N, Jain N, Rachapalli V, Cochlin DL, Robinson M. Non-invasive evaluation of liver cirrhosis using ultrasound. Clin Radiol 2009; 64: 1056–1066.
19. Huwart L, Sempoux C, Vicaut E, et al. Magnetic resonance elastography for the noninvasive staging of liver fibrosis. Gastroenterology 2008; 135: 32–40.
20. Bridges ND, Lock JE, Mayer JE Jr, Burnett J, Castaneda AR. Cardiac catheterization and test occlusion of the interatrial communication after the fenestrated Fontan operation. J Am Coll Cardiol 1995; 25: 1712–1717.
21. Reinhardt Z, Uzun O, Bhole V, et al. Sildenafil in the management of the failing Fontan circulation. Cardiol Young 2010; 20: 522–525.
22. Giardini A, Balducci A, Specchia S, Gargiulo G, Bonvicini M, Picchio FM. Effect of sildenafil on haemodynamic response to exercise and exercise capacity in Fontan patients. Eur Heart J 2008; 29: 1681–1687.
23. 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: 778–782.

24. 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: 1260–1267.
25. Raffini L, Schwed A, Zheng XL, et al. Thromboelastography of patients after Fontan compared with healthy children. Pediatr Cardiol 2009; 30: 771–776.
26. Coon PD, Rychik J, Novello RT, Ro PS, Gaynor JW, Spray TL. Thrombus formation after the Fontan operation. Ann Thorac Surg 2001; 71: 1990–1994.
27. Jacobs ML, Pourmoghadam KK, Geary EM, et al. Fontan's operation: is aspirin enough? Is coumadin too much? Ann Thorac Surg 2002; 73: 64–68.
28. Mahnke CB, Boyle GJ, Janosky JE, Siewers RD, Pigula FA. Anticoagulation and incidence of late cerebrovascular accidents following the Fontan procedure. Pediatr Cardiol 2005; 26: 56–61.
29. Rychik J. Protein-losing enteropathy after Fontan operation. Congenit Heart Dis 2007; 2: 288–300.
30. Mertens L, Hagler DJ, Sauer U, Somerville J, Gewillig M. Protein-losing enteropathy after the Fontan operation: an international multicenter study. PLE study group. J Thorac Cardiovasc Surg 1998; 115: 1063–1073.
31. Rychik J. Forty years of the Fontan operation: a failed strategy. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2010; 13: 96–100.
32. Gewillig M, Brown SC, Eyskens B, et al. The Fontan circulation: who controls cardiac output? Interact Cardiovasc Thorac Surg 2010; 10: 428–433.
33. Rychik J, Gui-Yang S. Relation of mesenteric vascular resistance after Fontan operation and protein-losing enteropathy. Am J Cardiol 2002; 90: 672–674.
34. Uzun O, Wong JK, Bhole V, Stumper O. Resolution of protein-losing enteropathy and normalization of mesenteric Doppler flow with sildenafil after Fontan. Ann Thorac Surg 2006; 82: e39–e40.
35. Ostrow AM, Freeze H, Rychik J. Protein-losing enteropathy after fontan operation: investigations into possible pathophysiologic mechanisms. Ann Thorac Surg 2006; 82: 695–700.
36. Lenz D, Hambsch J, Schneider P, et al. Protein-losing enteropathy in patients with Fontan circulation: is it triggered by infection? Crit Care 2003; 7: 185–190.
37. Cohen MI, Rhodes LA, Wernovsky G, Gaynor JW, Spray TL, Rychik J. Atrial pacing: an alternative treatment for protein-losing enteropathy after the Fontan operation. J Thorac Cardiovasc Surg 2001; 121: 582–583.
38. Mertens L, Dumoulin M, Gewillig M. Effect of percutaneous fenestration of the atrial septum on protein-losing enteropathy after the Fontan operation. Br Heart J 1994; 72: 591–592.
39. Rychik J, Rome JJ, Jacobs ML. Late surgical fenestration for complications after the Fontan operation. Circulation 1997; 96: 33–36.
40. Donnelly JP, Rosenthal A, Castle VP, Holmes RD. Reversal of protein-losing enteropathy with heparin therapy in three patients with univentricular hearts and Fontan palliation. J Pediatr 1997; 130: 474–478.
41. Rychik J, Piccoli DA, Barber G. Usefulness of corticosteroid therapy for protein-losing enteropathy after the Fontan procedure. Am J Cardiol 1991; 68: 819–821.
42. Thacker D, Patel A, Dodds K, Goldberg DJ, Semeao E, Rychik J. Use of oral budesonide in the management of protein-losing enteropathy after the Fontan operation. Ann Thorac Surg 2010; 89: 837–842.
43. Costello JM, Steinhorn D, McColley S, Gerber ME, Kumar SP. Treatment of plastic bronchitis in a Fontan patient with tissue plasminogen activator: a case report and review of the literature. Pediatrics 2002; 109: e67.
44. DiCindio S, Theroux M, Costarino AT Jr, Cook S, O'Reilly R. Plastic bronchitis: a case report. Paediatr Anaesth 2004; 14: 520–523.
45. Apostolopoulou SC, Papagiannis J, Rammos S. Bosentan induces clinical, exercise and hemodynamic improvement in a pre-transplant patient with plastic bronchitis after Fontan operation. J Heart Lung Transplant 2005; 24: 1174–1176.
46. Onoue Y, Adachi Y, Ichida F, Miyawaki T. Effective use of corticosteroid in a child with life-threatening plastic bronchitis after Fontan operation. Pediatr Int 2003; 45: 107–109.
47. Wilson J, Russell J, Williams W, Benson L. Fenestration of the Fontan circuit as treatment for plastic bronchitis. Pediatr Cardiol 2005; 26: 717–719.
48. Ishman S, Book DT, Conley SF, Kerschner JE. Plastic bronchitis: an unusual bronchoscopic challenge associated with congenital heart disease repair. Int J Pediatr Otorhinolaryngol 2003; 67: 543–548.
49. Zaccagni HJ, Kirchner L, Brownlee J, Bloom K. A case of plastic bronchitis presenting 9 years after Fontan. Pediatr Cardiol 2008; 29: 157–159.
50. Do TB, Chu JM, Berdjis F, Anas NG. Fontan patient with plastic bronchitis treated successfully using aerosolized tissue plasminogen activator: a case report and review of the literature. Pediatr Cardiol 2009; 30: 352–355.
51. Wakeham MK, Van Bergen AH, Torero LE, Akhter J. Long-term treatment of plastic bronchitis with aerosolized tissue plasminogen activator in a Fontan patient. Pediatr Crit Care Med 2005; 6: 76–78.
52. Rodefeld MD, Coats B, Fisher T, et al. Cavopulmonary assist for the univentricular Fontan circulation: von Karman viscous impeller pump. J Thorac Cardiovasc Surg 2010; 140: 529–536.
53. Bhavsar SS, Kapadia JY, Chopski SG, Throckmorton AL. Intravascular mechanical cavopulmonary assistance for patients with failing Fontan physiology. Artif Organs 2009; 33: 977–987.