Original Article

End-organ consequences of the Fontan operation: liver fibrosis, protein-losing enteropathy and plastic bronchitis

Jack Rychik,[1,4] David Goldberg,[1,4] Elizabeth Rand,[2,4] Edisio Semeao,[2,4] Pierre Russo,[4,5] Yoav Dori,[1,3] Kathryn Dodds[1]

[1]Division of Cardiology; [2]Division of Gastroenterology; [3]Department of Pathology and Laboratory Medicine at The Children's Hospital of Philadelphia; [4]Department of Pediatrics; [5]Department of Pathology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, United States of America

Abstract The Fontan operation, although part of a life-saving surgical strategy, manifests a variety of end-organ complications and unique morbidities that are being recognised with increasing frequency as patients survive into their second and third decades of life and beyond. Liver fibrosis, protein-losing enteropathy and plastic bronchitis are consequences of a complex physiology involving circulatory insufficiency, inflammation and lymphatic derangement. These conditions are manifest in a chronic, indolent state. Management strategies are emerging, which shed some light on the origins of these complications. A better characterisation of the end-organ consequences of the Fontan circulation is necessary, which can then allow for development of specific methods for treatment. Ideally, the goal is to establish systematic strategies that might reduce or eliminate the development of these potentially life-threatening challenges.

Keywords: Fontan operation; liver fibrosis; protein-losing enteropathy; plastic bronchitis

THE CURRENT STRATEGY FOR MANAGEMENT OF univentricular type of congenital heart disease culminates in performance of the Fontan operation. If nature has provided a congenital heart defect in which only one viable ventricle is present, then that ventricle must be assigned the task of systemic perfusion. Initial newborn palliation is specific to the type of univentricular heart present with the goal of providing balanced flow between the systemic and pulmonary circulations. Ultimately, the two circulations are separated at the Fontan operation. Pulmonary blood flow can be adequately achieved absent a pulmonary ventricle so long as the existing conditions will allow for passive blood flow, first through a superior cavopulmonary connection at a few months of age and then inferior vena caval flow through the Fontan operation at a few years of age.

This strategy is now standard of care and has created survival for thousands of children with a univentricular heart. However, as our experience grows and a greater number of survivors make their way into the second and third decades of life, enthusiasm for this strategy is tempered by the sobering appreciation of its inadequacy as a permanent long-term solution for all. Although mortality early after Fontan operation is quite low,[1] end-organ consequences of the unique physiology generated by the Fontan operation are of significance. Francois Fontan's prescient declaration[2] in 1972 that "this procedure is *not an anatomical correction*, which would require the creation of a right ventricle, but a procedure of physiological pulmonary blood flow restoration, with suppression of right and left blood flow mixing" is quite evident today in the many survivors of the surgery that carries his name.

In this report, we review the circulatory deficiencies of the Fontan operation and discuss its impact on the development of hepatic fibrosis, protein-losing enteropathy and plastic bronchitis.

Correspondence to: J. Rychik, MD, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104, United States of America. Tel: 215.590.2192; Fax: 267.426.5082; E-mail: Rychik@email.chop.edu

Limitations of the Fontan circulation

Upon completion of the Fontan operation, systemic venous return makes its way "passively" from the peripheral veins through the vena cavae into the central branch pulmonary arteries. Once oxygenated, blood returns through the pulmonary veins to a receiving atrium – left or right – then across an atrioventricular valve to the systemic ventricle, before ejection to the systemic arterial circulation.[3]

Without any active force propelling systemic venous return forward, congestion and central venous hypertension follows. A variety of factors influence flow in this system.[4] The type of Fontan connection and the geometry of the connection between the vena cavae and pulmonary arteries influence the kinetics and dynamics of flow as it enters into the lungs.[5] During systemic ventricular diastole, blood normally rushes forward across the atrioventricular valve, emptying the pulmonary venous atrium, which then draws blood forward through the pulmonary veins and capillaries. In a Fontan circuit, this impacts flow upstream in the pulmonary arteries and systemic veins. Abnormalities of ventricular or atrial compliance can negatively influence diastolic filling, ultimately diminishing the impetus for forward flow.[6] Hypertrophy, myocardial fibrosis and dis-coordinate relaxation of the systemic ventricle, common findings in the univentricular heart, can lead to impaired filling.[7] Abnormalities of the pulmonary vasculature, which may occur naturally as a consequences of altered pulmonary flow patterns in utero, or secondarily because of abnormal development as a consequence of initial newborn palliative surgery or lack of pulsatile flow,[8] may contribute to impedance to passive forward flow.

Whereas diastole plays an important role, systole also influences systemic venous flow after Fontan operation. We studied Doppler flow patterns in the pulmonary veins and superior vena cava of patients after superior cavopulmonary connection and found that the predominance of flow during the cardiac cycle appears to occur in systole in both the pulmonary veins and the superior vena cava.[9] As there is no pulmonary ventricle, this cannot be due to ventricular thrust. Thus, what is the impetus for systolic forward flow in the systemic veins after Fontan operation? Atrioventricular valve descent towards the apex during systole is the likely explanation. Systemic ventricular contraction typically involves a downward atrioventricular valve motion, which creates expansion of the pulmonary venous atrium. This is an attempt to fulfil the physiological law of conservation of volume within the heart, in which total atrial plus ventricular volumes remain constant throughout the cardiac cycle.

Table 1. Examples of factors that influence systemic venous forward flow after Fontan operation.

- Geometry of systemic venous connections to the pulmonary arteries
- Size of pulmonary arteries
- Morphological architecture of the distal pulmonary vasculature (arteries, capillaries and veins)
- Pulmonary venous atrial anatomy and compliance
- Ventricular compliance
- Ventricular relaxation and diastolic function
- Ventricular systolic function
- Ventricular geometry and contraction pattern influencing atrioventricular valve dynamics and apical descent
- Atrioventricular valve anatomy and sub-valvar architecture influencing ventricular contraction pattern, systemic atrioventricular valve dynamics and apical descent
- Sinus node function
- Peripheral muscle tone, as a driving force influencing systemic venous return
- Respiratory mechanics as it influences intrathoracic pressure

Negative intra-atrial pressure is generated by this valve motion, which draws blood out of the lungs and pulls systemic venous blood forward.[10] Ventricular geometry and ventricular contraction patterns, highly variable in the univentricular heart, likely influence the phenomenon of systolic atrioventricular valve motion and the impetus for systemic venous forward flow. Additional factors that influence forward flow after Fontan operation are listed in Table 1.

Despite systemic venous hypertension, patients after Fontan operation exist in a ventricular preload *deficient* state.[11] Systemic venous return must obligatorily traverse the pulmonary circuit before filling the ventricle, resulting in low end-diastolic volume and decreased stroke volume. Furthermore, the capacity to increase flow through this system at periods of increased demand is limited, which explains why exercise capacity after Fontan operation is impaired. The chronic conditions of relatively low cardiac output and systemic venous congestion form the basis for an indolent, morbid state that forms the basis for deleterious end-organ consequences.[12]

Impact upon the liver

The liver is positioned in close proximity to the heart and is directly affected by the venous hypertension and congestion generated by the Fontan circulation. The first report of liver fibrosis after Fontan operation occurred in 1983.[13] In some instances, hepatic pathology may pre-exist before Fontan operation as a consequence of haemodynamic instability at initial presentation or at early surgical palliation.[14]

Serious concerns were raised when in 2005 cases of hepatocellular neoplasm were identified after Fontan operation in a 9- and 18-year-old.[15] Since then, a number of reports describe the presence of hepatic fibrosis of varying degrees in almost all patients following Fontan operation.[16–18]

The ostensible cause of liver fibrosis is chronic hepatic venous congestion, although hypoperfusion may play a role as well. Arterialised nodules in the periphery of the liver have been noted on computerised tomography scan, arising in regions of potential watershed hypoperfusion.[19] The liver after Fontan operation is uniquely situated in a vulnerable position. Afferent flow, into the liver, is derived from two sources – the hepatic arterial system and venous return from the mesenteric circulation. Both of these afferent systems are potentially compromised as a consequence of sub-optimal cardiac output to the mesenteric circulation and altered portal venous flow. Efferent flow – exiting the liver – is into the congested systemic venous system directly draining into the Fontan pathway. Tissue perfusion, as reflected by the pressure difference between the afferent and efferent systems of the liver, is limited in comparison to normal.

Although both inflow and outflow into the liver may be affected, the primary pathophysiology is likely related to hepatic venous congestion. Hepatic venous hypertension stimulates liver stellate ganglion cells to transform into fibroblasts, through mechanisms not yet fully delineated. The result is collagen deposition and fibrosis, first in a peri-venular manner, then progressively extending further into the hepatic parenchyma, ultimately leading to bridging fibrosis, broad scar formation and cirrhosis (Fig 1).

Diagnosis and characterisation of hepatic fibrosis after Fontan operation is a challenge.[20,21] Routine blood laboratory testing typically reveals trivial elevation of liver enzyme values in all patients after Fontan operation, findings that do not correlate with the severity of fibrosis. A diminished platelet count may reflect hypersplenism with platelet sequestration, and may be seen in advanced stages of hepatic fibrosis, of any cause. Detection of early stages of hepatic fibrosis is difficult even in the more common settings of alcohol or Hepatitis C-induced liver injury and is often overlooked in Fontan physiology because of the absence of overt signs of liver injury. Non-invasive assays surveying for biomarkers in these conditions have not been extensively studied and correlated with liver pathology seen after Fontan operation. Imaging modalities such as ultrasound or magnetic resonance imaging provide information concerning gross structure, but do not provide adequate information concerning histology, thereby not providing an
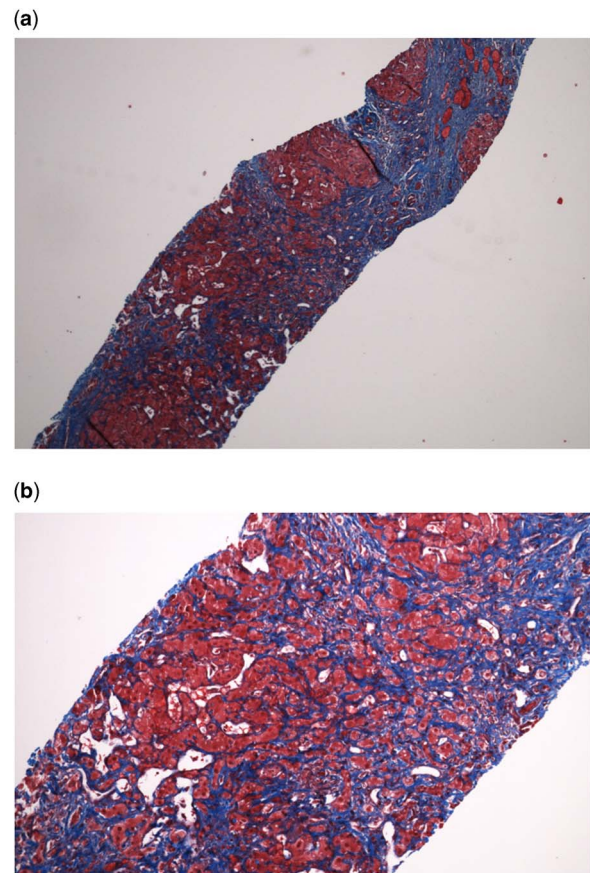

Figure 1.
(*a*) *Core liver biopsy, 10× magnification, trichrome stain from an 18-year-old patient with heterotaxy syndrome, after Fontan operation. There is marked collagen deposition and broad bands of significant fibrosis (blue colour). (b) Increased magnification (40×) shows evidence for cirrhosis.*

accurate means for grading disease severity. Elastography, the analysis of shear wave propagation through biological tissue, can provide information concerning tissue density and holds promise as a means for assessing liver fibrosis in this population.[22] Studies distinguishing liver tissue density characteristics due to venous congestion from that of hepatic fibrosis will need to be performed through correlation of haemodynamic data and liver biopsy material. Unfortunately, at this point in time, liver biopsy is the "gold standard" optimal means available for evaluating hepatic status after Fontan operation.

There is growing evidence that hepatic fibrosis is a ubiquitous complication after Fontan operation. Realising the importance of characterising the health status of survivors after Fontan operation, in order to optimise long-term outcome, and with published data suggesting that no patient is spared this complication, our group at The Children's

Hospital of Philadelphia recently decided to offer systematic, comprehensive evaluation to our patients who are 10 years or more past their Fontan operation.[23] We currently recommend performance of a liver biopsy, with concurrent evaluation of the cardiovascular system through cardiac catheterisation and cardiac magnetic resonance imaging. Although controversial, the decision to undertake an aggressive evaluation of liver status with concurrent assessment of haemodynamics at this 10-year mark provides the best opportunity to identify variables that might be modifiable for the individual patient, leading to a tailored, patient-specific plan for continued care into the adult years.

A number of goals remain concerning management of the liver after Fontan operation. Identifying modifiable variables along the course of univentricular management that may be causative is important. We also need to identify strategies that minimise the conditions that permit ongoing fibrosis after Fontan operation. Understanding the biological basis for fibrosis under conditions of elevated central venous pressure, relative hypoxaemia and diminished arterial perfusion will allow us to develop better strategies of care, and perhaps offer opportunities for treatment aimed at reversal of hepatic fibrosis.

Protein-losing enteropathy

Protein-losing enteropathy is defined as the loss of serum proteins into the gut lumen due to variable loss of integrity of the enteric mucosa. It can occur because of conditions such as inflammatory bowel disease or primary gut lymphatic abnormalities. The incidence of protein-losing enteropathy after Fontan operation is not fully known. The prevalence is believed to be anywhere from 1 to 5%.[24,25] Although a sub-clinical entity is highly suspected,[26] this possibility has not yet been adequately characterised. However, if a sub-clinical entity is present as we suspect, then the frequency of this condition is substantially increased. The clinical manifestations of protein-losing enteropathy are many (Table 2).

Protein-losing enteropathy can occur at any point after Fontan operation. Early onset within weeks to months of surgery is typically related to an acute problem, such as anatomical obstruction of the systemic or pulmonary venous pathways, or ventricular dysfunction. More often, it occurs years after Fontan operation, and without any known trigger or specific cause. Cardiovascular assessment with cardiac catheterisation may indicate a specific problem, but more often than not it typically reveals haemodynamic information that is satisfactory and indistinguishable from other patients with

Table 2. Manifestations of protein-losing enteropathy after Fontan operation.

Pathophysiological consequences

- Hypoproteinaemia
  – Low oncotic pressure
  – Interstitial oedema
- Hypocalcaemia
  – Altered calcium metabolism due to low albumin levels
- Osteopaenia
  – Increased risk of bone fracture
- Hypogammaglobulinaemia
  – Immunodeficiency
- Lymphangiectasia
  – Dilation of gut lymphatics
  – Poor fat absorption (steatorrhoea)
  – Lymphocyte loss (immunodeficiency)
- Loss of clotting factors
  – Hypercoagulability

Clinical sequelae

- Diarrhoea
- Constipation
- Crampy abdominal pain
- Peripheral oedema
- Pleural/pericardial effusions
- Ascites
- Thromboembolism
- Poor growth
- Delayed development
- Failure to thrive
- Death

Fontan circulation who do not have protein-losing enteropathy.

The precise pathophysiology of protein-losing enteropathy after Fontan operation and mechanism of onset is poorly understood. Nevertheless, a framework of understanding has allowed for the development of a useful algorithm for management.[27] As best as we currently understand it, the mechanistic hallmarks of protein-losing enteropathy include the elements of an altered mesenteric circulation and inflammation.

Mesenteric haemodynamics is very much affected by the Fontan circulation. One theory holds that chronic low cardiac output evident after Fontan operation is similar to that of a chronic state of circulatory "shock", with increase in mesenteric vascular tone as compensation. Supporting this notion are data derived from Doppler interrogation of the superior mesenteric artery demonstrating increased mesenteric vascular resistance in children after Fontan operation in comparison to normal,

with further increase in resistance in those with protein-losing enteropathy.[28] Further supporting the idea that haemodynamics play a key role is the resolution of protein-losing enteropathy is what occurs once actions to improve the abdominal circulation are undertaken. Oral sildenafil has been demonstrated to reduce mesenteric vascular resistance and concurrently resolve protein-losing enteropathy.[29] Pacing to create atrioventricular synchrony,[30] fenestration creation[31,32] and heart transplantation[33] have also all led to resolution of protein-losing enteropathy in various reports.

Inflammation is the second mechanistic pillar of protein-losing enteropathy after Fontan operation. A number of clues support this notion. Repeatedly, parents will recount the new onset of protein-losing enteropathy, or worsening of symptoms, within a 2–4-week period of a preceding viral illness. Patients after Fontan operation exist in a relatively increased state of inflammation, with increased levels of circulating tumour necrosis factor α, perhaps related to chronic low cardiac output.[34] Direct inspection of the gut through endoscopy in patients with protein-losing enteropathy after Fontan operation reveals both gross and histological evidence for inflammation (Figs 2 and 3). Furthermore, numerous reports have documented quiescence of protein-losing enteropathy and its symptoms following administration of high-dose systemic corticosteroids.[35,36]

How does altered mesenteric circulation and inflammation lead to enteric protein loss? A rare condition of congenital protein-losing enteropathy has been described, in which there is deficiency of enterocyte sulfated glycosaminoglycan, an essential molecule for maintaining integrity of the intestinal mucosa. To test the role of sulfated glycosaminoglycans in protein-losing enteropathy after Fontan operation, an in vitro model was created.[37,38] Using a monolayer of intestinal cells, albumin flux across was measured. Loss of heparin sulfate, an important intestinal sulfated glycosaminoglycan through addition of heparinase, increased albumin flux across the intestinal monolayer 1.6-fold above resting state. Treatment of the preparation with tumour necrosis factor α to mimic inflammation, in combination with heparanase, further increased albumin flux to sevenfold above resting state. Addition of a small pressure gradient to mimic venous hypertension and complete the pathological picture characteristic of a Fontan circulatory state dramatically increases albumin flux across the mucosa.

Of interest, intestinal sulfated glycosaminoglycan deficiency has been reported in malnourished children with kwashiorkor, a protein-loss state, but not in those with malnutrition and marasmus.[39] This phenomenon suggests a predisposition to altered
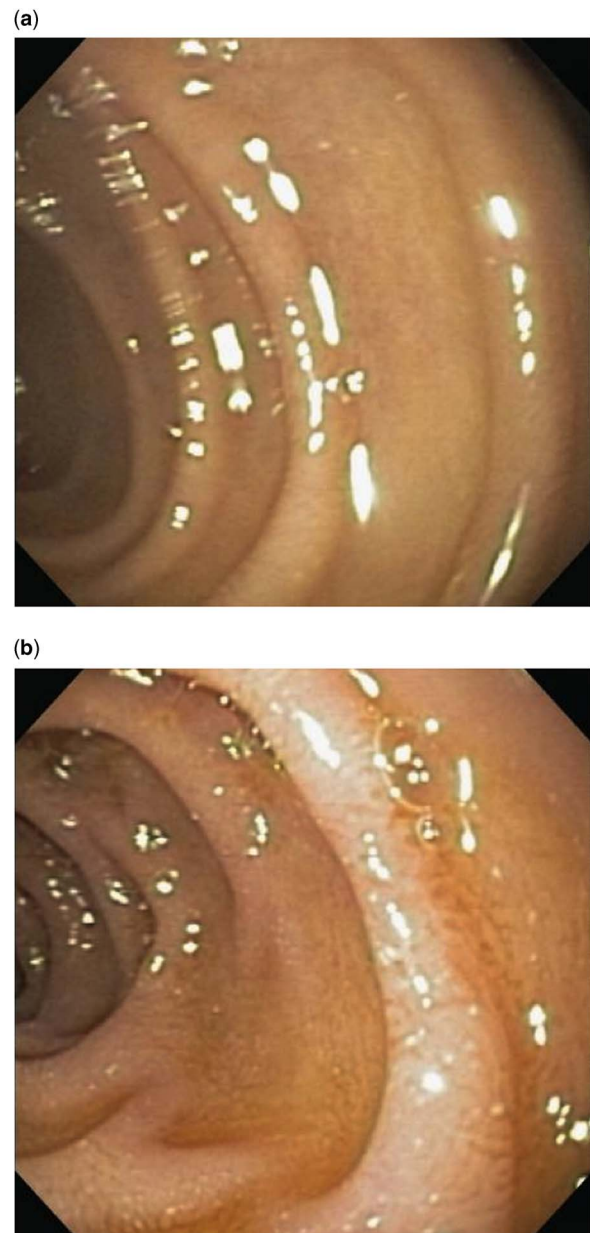
Figure 2.
(*a*) Endoscopic image of a normal duodenum. (*b*) Duodenum of a patient with protein-losing enteropathy after Fontan operation demonstrating hyperaemia and oedema.

sulfated glycosaminoglycan intestinal make-up in a select group, those with Kwashiorkor, but not in all following the stressor of severe malnutrition. In order to assess whether patients with protein-losing enteropathy after Fontan operation may have a similar finding of sulfated glycosaminoglycan deficiency, we have analysed biopsy material from the terminal ileum of 10 patients (unpublished data). Preliminary findings indicate deficiency of sulfated glycosaminoglycan make-up in our patients with protein-losing enteropathy after Fontan operation, but to a variable
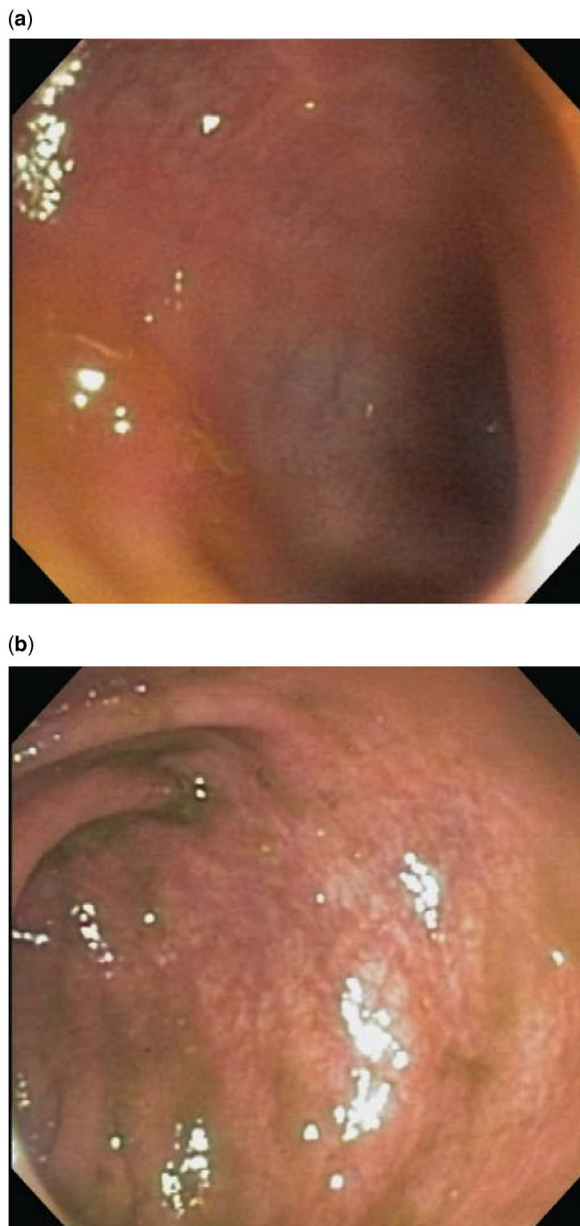
(a)

(b)

Figure 3.
(a) Endoscopic image of a normal colon. (b) Colon of a patient with protein-losing enteropathy after Fontan operation demonstrating hyperaemia and oedema.

degree (Fig 4). This suggests a possible common molecular pathway for protein leak that may exist between various stressor conditions to the gut.

Despite absence of a complete understanding of the pathophysiology, how can we currently manage patients with protein-losing enteropathy after Fontan operation? First, a rigorous investigation for faultiness with the Fontan construct is mandatory through testing including cardiac catheterisation. Pathway obstruction, or other anatomical explanations, which limit cardiovascular functionality should be addressed

if possible (Fig 5). Often, no direct causative explanation can be found, in which case we recommend a two-pronged approach to improve circulation and inhibit intestinal inflammation. Aggressive pulmonary vasodilation through the use of phosphodiesterase inhibition (sildenafil) and/or endothelin-1 blockade (bosentan) can be offered, in order to optimise forward flow through the Fontan circuit. Pulmonary vasodilation should be pursued regardless of the pulmonary artery pressures, as even a small reduction in pressure may significantly influence flow in a venous, low-flow system. In addition, phosphodiesterase inhibition may have a direct salutary effect on intestinal haemodynamics independent of its effect on the pulmonary circulation.[29] In conjunction, oral controlled-release budesonide (entocort) can be used.[40] This agent offers potent anti-inflammatory treatment and is released at the target site of the small bowel. Normally, oral controlled-release budesonide is 90% metabolised at first pass through the liver, therefore minimising systemic side effects. However, as most patients after Fontan operation have some liver changes, which may affect metabolism, side effects are common. Since our centre's initial report on the efficacy of oral controlled-release budesonide, multiple other reports have emerged.[40–44] Experience now shows it to be effective treatment when started in the child or adolescent with new-onset protein-losing enteropathy, but less effective when initiated in the adult patient with chronic, long-standing disease. A trial period of 3–6 months of combination pulmonary vasodilation and intestinal anti-inflammatory treatment is suggested. Positive results are often not seen until a minimum of 3–4 months into therapy, suggesting that perhaps a turnover of intestinal mucosal cells is required under the new treatment conditions in order to prevent protein leak. Protein-losing enteropathy itself leads to calcium loss and bone demineralisation, as can chronic steroid treatment. Hence, once a positive response is noted, slow weaning to a low maintenance dose of oral controlled-release budesonide is indicated.

Failing a response to medical management, other options are available, but each has limitations. Creation of a fenestration may be helpful for some patients.[31,32,45] Mechanism of action is thought to be related to improved cardiac output and possible increase in oxygen delivery to the gut. Although relatively well tolerated in childhood, adolescents do poorly with oxygen saturations in the mid 80% range and are often dyspnoeic, resulting in exchange of one set of problems related to protein-losing enteropathy for another. Heart transplantation is effective when it achieves the goals of reducing central venous hypertension and improving cardiac output.[33,46]
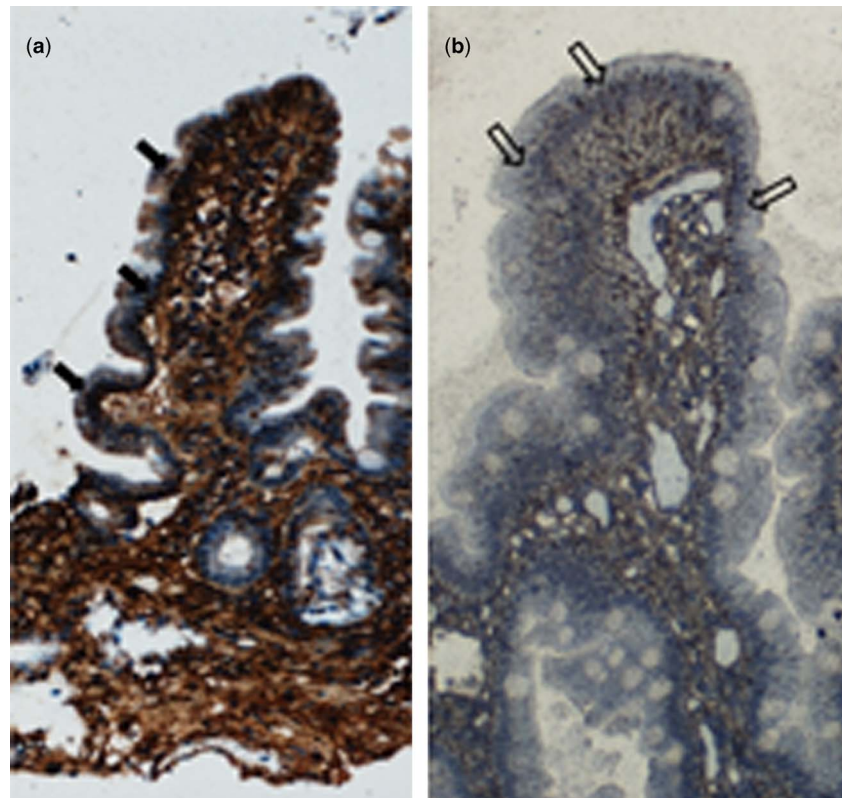
Figure 4.
(a) Silver stain image of a normal intestinal villous with dark band of stain (dark arrows) indicating presence of glycosaminoglycan in the epithelium. (b) Patient with protein-losing enteropathy after Fontan operation in which there is a paucity of silver stain uptake, suggesting a diminution in intestinal epithelial glycosaminoglycan.
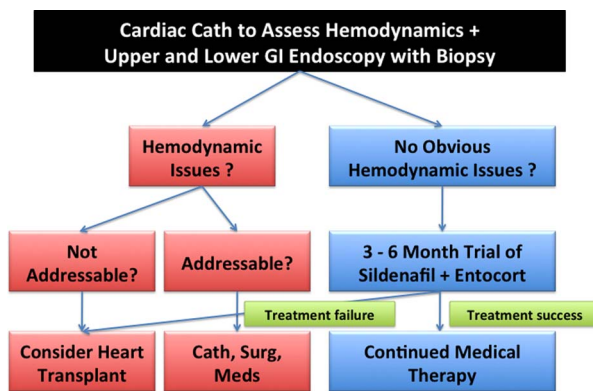

Figure 5.
Algorithm for management protocol of protein-losing enteropathy after Fontan operation.

Improved understanding of protein-losing enteropathy after Fontan operation has provided the ability to develop a working algorithm for treatment. A condition previously reported to have 50% mortality at 5 years from onset of diagnosis[24] is now manageable, leading to a chronic but serious condition in most patients affected. A successful long-term treatment with sustained resolution still evades us.

Plastic bronchitis

Plastic bronchitis is a condition seen after Fontan operation in which proteinaceous material is exuded into the airways leading to cast formation (Fig 6).[47] These rubbery casts are either expectorated or swallowed after mobilisation out of the bronchial tree. Bronchial casts may also remain in situ, leading to lobar atelectasis with subsequent hypoxaemia, or if large enough they can obstruct the airway leading to asphyxiation and death. The condition is believed to be similar to protein-losing enteropathy after Fontan operation in a number of ways.[48] The fundamental problem is a break in the integrity of the bronchial mucosa leading to proteinaceous leak into the airway lumen. Unlike the gut, in which there is rapid transit and hence the potential for abundant loss of serum protein into the stool, in plastic bronchitis the transit time is slow and the space limited; hence, protein accretion and cast formation takes place. Fibrin has been identified as the major protein type making up these bronchial casts.[49] Some investigators believe that there may also be a wide spectrum to the condition, with a sub-clinical entity resulting in

Figure 6.
Bronchial cast from a child with plastic bronchitis after Fontan operation.

the common expectoration of small fibrin plugs and with a prevalence of 4–14% among all survivors of Fontan operation.[50]

Similar to protein-losing enteropathy, the pathophysiogy and mechanism of onset of plastic bronchitis is not completely understood. Amelioration of circulatory haemodynamics either through improvement of the Fontan state[51–53] or through heart transplantation[47,54,55] has been demonstrated to be effective. Pulmonary vasodilation with phosphodiesterase inhibition (sildenafil)[56] or through the use of endothelin-1 blockade (bosentan) has been demonstrated to be effective in some patients.[57] We and other investigators have found great benefit in the administration of aerosolised tissue plasminogen activator as a means for dissolving casts or in limiting development of casts.[58–61] Daily administration of aerosolised issue-plasminogen activator can be life saving as adjuvant therapy when used in combination with a strategy of aggressive pulmonary vasodilation.

Recently, another approach has been proposed to the possible management of plastic bronchitis after Fontan operation. New imaging techniques utilising magnetic resonance imaging, T2 weighted towards high-water content, can offer a means for imaging the lymphatic system. Preliminary findings of magnetic resonance imaging lymphatic imaging suggest the presence of abnormally dilated and tortuous lymphatic vessels in the abdomen of patients with protein-losing enteropathy and the chest of patients with plastic bronchitis after Fontan operation. Interestingly, reduction in lymph production through dietary means[62] or thoracic duct ligation has been reported as a means for treating plastic bronchitis.[63] One plausible hypothesis is that plastic bronchitis is caused by the underlying pathophysiology of the Fontan circulation leading to abnormal lymphatic drainage surrounding the airway.[64] Spillage of lymph-rich, proteinaceous fluid into the airway through mechanisms of overproduction or distal lymphatic channel obstruction results in bronchial cast formation. The risk of leakage of proteinaceous material and cast formation may therefore be present in all survivors of the Fontan operation.

Derangement of lymphatic drainage may therefore be the third component to add to the pathophysiology of plastic bronchitis in addition to an underlying circulatory abnormality and inflammation. Lymphatic leakage alone is unlikely the cause as cast analysis has demonstrated abundant inflammatory cells, and the cytokine profile suggests a pro-inflammatory state.[49] Nevertheless, with this understanding, a strategy for management can be developed. Rigorous investigation for a possible faultiness with the Fontan construct through cardiac catheterisation is required. Pulmonary vasodilation may lower the impetus for airway protein leakage. Use of aerosolised tissue-plasminogen activator will maintain airway patency by reducing cast volume burden. As work in the field of lymphatic imaging after Fontan operation proceeds forward, one may be able to identify specific abnormal lymphatic vessels surrounding the airway. These abnormal lymphatic structures may then become targets for catheter-based interventional techniques to occlude areas of leakage or to divert lymphatic flow away from luminal structures, thereby potentially reducing lymph spillage into the bronchial airway.

Summary

The Fontan operation, although part of a life-saving surgical strategy, manifests a variety of end-organ complications and unique morbidities that are still poorly understood. Liver fibrosis, protein-losing enteropathy and plastic bronchitis are consequences of a complex physiology involving circulatory insufficiency, inflammation and lymphatic derangement, all manifest in an indolent, chronic state. Management strategies are emerging, which shed some light on the origins of these conditions. Continued focused investigation will lead to a better understanding of these complications and allow us to achieve the goal of creating a fully normal duration and quality of life for those born with a univentricular heart malformation.

Acknowledgements

References

1. Rogers LS, Glatz AC, Ravishankar C, et al. 18 years of the Fontan operation at a single institution: results from 771 consecutive patients. J Am Coll Cardiol 2012; 60: 1018–1025.

2. Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax 1971; 26: 240–248.

3. de Leval MR, Deanfield JE. Four decades of Fontan palliation. Nat Rev Cardiol 2010; 7: 520–527.

4. Gewillig M, Brown SC, Eyskens B, et al. The Fontan circulation: who controls cardiac output? Interact Cardiovasc Thorac Surg 2010; 10: 428–433.

5. de Leval MR, Dubini G, Migliavacca F, et al. Use of computational fluid dynamics in the design of surgical procedures: application to the study of competitive flows in cavo-pulmonary connections. J Thorac Cardiovasc Surg 1996; 111: 502–513.

6. Penny DJ, Redington AN. Diastolic ventricular function after the Fontan operation. Am J Cardiol 1992; 69: 974–975.

7. Ho PK, Lai CT, Wong SJ, Cheung YF. Three-dimensional mechanical dyssynchrony and myocardial deformation of the left ventricle in patients with tricuspid atresia after Fontan procedure. J Am Soc Echocardiogr 2012; 25: 393–400.

8. Henaine R, Vergnat M, Bacha EA, et al. Effects of lack of pulsatility on pulmonary endothelial function in the Fontan circulation. J Thorac Cardiovasc Surg 2013; 146: 522–529.

9. Rychik J, Fogel MA, Donofrio MT, et al. Comparison of patterns of pulmonary venous blood flow in the functional single ventricle heart after operative aortopulmonary shunt versus superior cavopulmonary shunt. Am J Cardiol 1997; 80: 922–926.

10. Steding-Ehrenborg K, Carlsson M, Stephensen S, Arheden H. Atrial aspiration from pulmonary and caval veins is caused by ventricular contraction and secures 70% of the total stroke volume independent of resting heart rate and heart size. Clin Physiol Funct Imaging 2013; 33: 233–240.

11. Gewillig M, Brown SC, Heying R, et al. Volume load paradox while preparing for the Fontan: not too much for the ventricle, not too little for the lungs. Interact Cardiovasc Thorac Surg 2010; 10: 262–265.

12. Rychik J. Forty years of the Fontan operation: a failed strategy. Seminars in thoracic and cardiovascular surgeryPediatr Cardiac Surg Ann 2010; 13: 96–100.

13. Lemmer JH, Coran AG, Behrendt DM, Heidelberger KP, Stern AM. Liver fibrosis (cardiac cirrhosis) five years after modified Fontan operation for tricuspid atresia. J Thorac Cardiovasc Surg 1983; 86: 757–760.

14. Schwartz MC, Sullivan L, Cohen MS, et al. Hepatic pathology may develop before the Fontan operation in children with functional single ventricle: an autopsy study. J Thorac Cardiovasc Surg 2012; 143: 904–909.

15. 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.

16. Schwartz MC, Sullivan LM, Glatz AC, et al. Portal and sinusoidal fibrosis are common on liver biopsy after Fontan surgery. Pediatr Cardiol 2013; 34: 135–142.

17. 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.

18. Kiesewetter CH, Sheron N, Vettukattill JJ, et al. Hepatic changes in the failing Fontan circulation. Heart 2007; 93: 579–584.

19. Bryant T, Ahmad Z, Millward-Sadler H, et al. Arterialised hepatic nodules in the Fontan circulation: hepatico-cardiac interactions. Int J Cardiol 2011; 151: 268–272.

20. Friedrich-Rust M, Koch C, Rentzsch A, et al. Noninvasive assessment of liver fibrosis in patients with Fontan circulation using transient elastography and biochemical fibrosis markers. J Thorac Cardiovasc Surg 2008; 135: 560–567.

21. Baek JS, Bae EJ, Ko JS, et al. Late hepatic complications after Fontan operation; non-invasive markers of hepatic fibrosis and risk factors. Heart 2010; 96: 1750–1755.

22. Ferraioli G, Tinelli C, Dal Bello B, et al. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. Hepatology 2012; 56: 2125–2133.

23. Rychik J, Veldtman G, Rand E, et al. The precarious state of the liver after a Fontan operation: summary of a multidisciplinary symposium. Pediatr Cardiol 2012; 33: 1001–1012.

24. 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.

25. Meadows J, Jenkins K. Protein-losing enteropathy: integrating a new disease paradigm into recommendations for prevention and treatment. Cardiol Young 2011; 21: 363–377.

26. Thorne SA, Hooper J, Kemp M, Somerville J. Gastro-intestinal protein loss in late survivors of Fontan surgery and other congenital heart disease. Eur Heart J 1998; 19: 514–520.

27. Rychik J. Protein-losing enteropathy after Fontan operation. Congenit Heart Dis 2007; 2: 288–300.

28. Rychik J, Gui-Yang S. Relation of mesenteric vascular resistance after Fontan operation and protein-losing enteropathy. Am J Cardiol 2002; 90: 672–674.

29. 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.

30. 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.

31. Jacobs ML, Rychik J, Byrum CJ, Norwood WI Jr. Protein-losing enteropathy after Fontan operation: resolution after baffle fenestration. Ann Thorac Surg 1996; 61: 206–208.

32. Rychik J, Rome JJ, Jacobs ML. Late surgical fenestration for complications after the Fontan operation. Circulation 1997; 96: 33–36.

33. Bernstein D, Naftel D, Chin C, et al. Outcome of listing for cardiac transplantation for failed Fontan: a multi-institutional study. Circulation 2006; 114: 273–280.

34. Ostrow AM, Freeze H, Rychik J. Protein-losing enteropathy after Fontan operation: investigations into possible pathophysiologic mechanisms. Ann Thorac Surg 2006; 82: 695–700.

35. 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.

36. Zellers TM, Brown K. Protein-losing enteropathy after the modified Fontan operation: oral prednisone treatment with biopsy and laboratory proved improvement. Pediatr Cardiol 1996; 17: 115–117.

37. Bode L, Eklund EA, Murch S, Freeze HH. Heparan sulfate depletion amplifies TNF-alpha-induced protein leakage in an in vitro model of protein-losing enteropathy. Am J Physiol Gastrointest Liver Physiol 2005; 288: G1015–G1023.

38. Bode L, Murch S, Freeze HH. Heparan sulfate plays a central role in a dynamic in vitro model of protein-losing enteropathy. J Biol Chem 2006; 281: 7809–7815.

39. Amadi B, Fagbemi AO, Kelly P, et al. Reduced production of sulfated glycosaminoglycans occurs in Zambian children with kwashiorkor but not marasmus. Am J Clin Nutr 2009; 89: 592–600.

40. 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.

41. Turner Z, Lanford L, Webber S. Oral budesonide as a therapy for protein-losing enteropathy in patients having undergone Fontan palliation. Congenit Heart Dis 2012; 7: 24–30.

42. Rychik J. Invited commentary. Ann Thorac Surg 2011; 92: 1456.

43. John AS, Driscoll DJ, Warnes CA, Phillips SD, Cetta F. The use of oral budesonide in adolescents and adults with protein-losing enteropathy after the Fontan operation. Ann Thorac Surg 2011; 92: 1451–1456.

44. Schumacher KR, Cools M, Goldstein BH, et al. Oral budesonide treatment for protein-losing enteropathy in Fontan-palliated patients. Pediatr Cardiol 2011; 32: 966–971.

45. 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.

46. Kanter KR, Mahle WT, Vincent RN, Berg AM, Kogon BE, Kirshbom PM. Heart transplantation in children with a Fontan procedure. Ann Thorac Surg 2011; 91: 823–829; discussion 9–30.

47. Larue M, Gossett JG, Stewart RD, Backer CL, Mavroudis C, Jacobs ML. Plastic bronchitis in patients with Fontan physiology: review of the literature and preliminary experience with Fontan conversion and cardiac transplantation. World J Pediatr Congenit Heart Surg 2012; 3: 364–372.

48. Stiller B, Riedel F, Paul K, van Landeghem FK. Plastic bronchitis in children with Fontan palliation: analogue to protein-losing enteropathy? Pediatr Cardiol 2002; 23: 90–94.

49. Racz J, Mane G, Ford M, et al. Immunophenotyping and protein profiling of Fontan-associated plastic bronchitis airway casts. Ann Am Thorac Soc 2013; 10: 98–107.

50. Caruthers RL, Kempa M, Loo A, et al. Demographic characteristics and estimated prevalence of Fontan-associated plastic bronchitis. Pediatr Cardiol 2013; 34: 256–261.

51. Wilson J, Russell J, Williams W, Benson L. Fenestration of the Fontan circuit as treatment for plastic bronchitis. Pediatr Cardiol 2005; 26: 717–719.

52. Chaudhari M, Stumper O. Plastic bronchitis after Fontan operation: treatment with stent fenestration of the Fontan circuit. Heart 2004; 90: 801.

53. Barber BJ, Burch GH, Tripple D, Balaji S. Resolution of plastic bronchitis with atrial pacing in a patient with Fontan physiology. Pediatr Cardiol 2004; 25: 73–76.

54. Laubisch JE, Green DM, Mogayzel PJ, Reid Thompson W. Treatment of plastic bronchitis by orthotopic heart transplantation. Pediatr Cardiol 2011; 32: 1193–1195.

55. ElMallah MK, Prabhakaran S, Chesrown SE. Plastic bronchitis: resolution after heart transplantation. Pediatr Pulmonol 2011; 46: 824–825.

56. Haseyama K, Satomi G, Yasukochi S, Matsui H, Harada Y, Uchita S. Pulmonary vasodilation therapy with sildenafil citrate in a patient with plastic bronchitis after the Fontan procedure for hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 2006; 132: 1232–1233.

57. 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.

58. 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.

59. 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.

60. 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.

61. Lubcke NL, Nussbaum VM, Schroth M. Use of aerosolized tissue plasminogen activator in the treatment of plastic bronchitis. Ann Pharmacother 2013; 47: e13.

62. Parikh K, Witte MH, Samson R, et al. Successful treatment of plastic bronchitis with low fat diet and subsequent thoracic duct ligation in child with fontan physiology. Lymphology 2012; 45: 47–52.

63. Shah SS, Drinkwater DC, Christian KG. Plastic bronchitis: is thoracic duct ligation a real surgical option? Ann Thorac Surg 2006; 81: 2281–2283.

64. Ezmigna DR, Morgan WJ, Witte MH, Brown MA. Lymphoscintigraphy in plastic bronchitis, a pediatric case report. Pediatr Pulmonol 2013; 48: 515–518.