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Review

Protein Losing Enteropathy after Fontan Operation

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Protein losing enteropathy (PLE) is a potentially lethal complication of the modified Fontan operation. PLE can occur in up to 10% of patients after a Fontan operation. It is characterized by fatigue, peripheral edema, ascites, pleural effusions, growth delay, and/or diarrhea. The etiology is not well understood and many mechanisms for the development of PLE have been proposed. These include elevated systemic venous pressure, elevated thoracic duct pressure, elevated levels of brain natriuretic peptide (BNP), small bowel inflammation, elevated mesenteric venous pressure, and low cardiac output. A thorough cardiovascular investigation should be undertaken once PLE develops to identify potentially reversible important hemodynamic abnormalities. Despite more than 25 years of research, no universal or curative treatment has been identified. Overall, management is aimed at decreasing edema and increasing serum protein levels. Other treatment strategies include: nutritional therapy, atrioventricular pacing, diuretics, heparin, steroids, albumin infusion, and cardiac transplantation. Further investigation is needed to enhance our understanding of PLE and to define improved treatment.

Introduction

Fontan and Baudet, in 1971, described a surgical technique for palliation of tricuspid atresia.[1] Modifications of this procedure are utilized to treat most forms of functional single ventricle. This technique diverts vena caval blood directly into the pulmonary arteries, bypassing the heart. Over the years, patient selection and surgical techniques have improved resulting in early and late mortality of approximately 2% and 5%, respectively, in the recent era.[2]

Protein losing enteropathy (PLE) is a potentially lethal complication of the modified Fontan operation. It was first described in a patient with single ventricle after Fontan operation by Crupi, et al. in 1980.[3] PLE may be characterized by decreased energy level, peripheral edema, ascites, pleural effusions, growth delay, and/or diarrhea. These patients may exhibit low serum albumin, low serum protein, hypocalcemia, acquired hypogammaglobulinemia, and elevated fecal alpha-1-antitrypsin.[4–8] In some cases, onset of symptoms may be related to a recent nonspecific illness. PLE occurs, on average, 3.5 years following Fontan operation.[9] However, it can occur immediately after operation to as long as 16 years postoperatively.[5, 7] The prevalence of PLE is approximately 1–11% for patients who have had a non-fenestrated Fontan operation.[5, 7, 10–12] The incidence of PLE among patients who initially had a fenestrated Fontan operation is not well defined. The "true" overall incidence may be underestimated because of asymptomatic or transient cases.[13] In 1996, Feldt, et al. described the five-year survival in patients who developed PLE after a non-fenestrated modified Fontan operation to be 46%.[5] This data was based upon early PLE experience after Fontan operation and, the current survival may be better due to improved medical and surgical management.

Etiology

Many mechanisms for the development of PLE have been theorized over the years. Yet, the cause of PLE remains

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poorly understood.

1. Elevated systemic venous and thoracic duct pressure

A number of cardiovascular conditions are associated with PLE including superior vena cava obstruction, constrictive pericarditis, nonfenestrated Fontan operation, tricuspid valve stenosis or insufficiency, and restrictive cardiomyopathy. All of these conditions share the common feature of increased venous pressure in the tributaries of the superior vena cava. In patients with constrictive pericarditis, tricuspid valve disease, restrictive cardiomyopathy, or the Fontan operation, there also is increased venous pressure in the tributaries of the inferior vena cava. Thus, it is quite clear that a major determinant of cardiac associated PLE is increased systemic venous pressure. However, there are many patients with elevated systemic venous pressures after Fontan operation that do not develop PLE and are no different than patients who develop PLE.[7] Hence, additional factors must contribute to the development of PLE. Other determinants of PLE include longer cardiopulmonary bypass time, right ventricular morphologic forms of single ventricle, longer hospital stay, and postoperative renal failure.[5]

There have been several intriguing studies that may provide insight into the etiology of PLE in patients with cardiac disease. In 1861 Ludwig and Tomsa demonstrated that venous congestion of the gut greatly increased lymphatic production in the gut.[14] One could speculate that if a patient had increased systemic venous pressure that produced increased portal venous pressure and venous congestion of the gut, associated with reduced flow through the thoracic duct, that this could produce PLE. Furthermore, it has been shown that thoracic duct lymph flow is increased with cirrhosis but PLE is uncommon in cirrhosis alone. There is also increased gut lymph production with portal hypertension. Patients with cirrhosis can develop PLE in the presence of portal hypertension if there also is obstruction to thoracic duct flow.[15] This situation is very similar to that in patients after Fontan operation assuming that systemic venous hypertension leads to portal hypertension coupled with drainage of the thoracic duct into a vein with high pressure.

Blalock, et al. demonstrated that occlusion of the superior vena cava can produce chylothorax.[16] In 1963, Wegria, et al. demonstrated that increased venous pressure from occluding the left innominate vein in dogs resulted in decreased flow of lymph in the thoracic duct which led to an accumulation of lymph in the lymphatic system and the intracellular spaces.[17] This reduction of lymphatic flow is consistent with Starling's laws and can lead to obstruction of lymph flow in the gastrointestinal system. In 1965, Marshall, et al. demonstrated that dogs with ligated thoracic ducts had increased losses of I-131 labeled polyvinyl-pyrrolidone into the gastrointestinal lumen in the absence of elevated venous pressures.[18] A number of investigators have demonstrated that it is possible to produce chylous pleural effusions and PLE in rats after ligation of the thoracic duct.[19, 20] However, these complications do not occur in all animals and it may be due to the fact that lympho-veno collaterals develop in some of the animals that decompress the lymphatic channels.[21, 22]

2. Inflammation

Inflammatory bowel disease can also lead to inflammation of lymphatics and lymphangiectasia.[23] Ostrow suggested that elevated inflammatory markers such as tumor necrosis factor alpha and C-reactive protein, which have been reported in adults with congestive heart failure and in response to low cardiac output, may contribute to the development of PLE after Fontan operation.[24] Bowel inflammation could result in loss of intestinal wall integrity and loss of lymph into the gut lumen.

3. Low cardiac output and increased mesenteric resistance

It is well known that relatively low cardiac output occurs after Fontan operation. Mertens, et al. reported that patients with PLE after Fontan operation have a mean cardiac output of 2.4 l/min/m^2.[7] Others have demonstrated low cardiac output at rest and failure of cardiac output to increase normally with exercise after Fontan operation.[25] Rychik, et al. suggested that reduced cardiac output is an additional determinant of PLE. They also demonstrated that patients who had a Fontan operation and who developed PLE have higher mesenteric resistance than patients who had a Fontan with no PLE or normal subjects.[26]

4. Brain natriuretic peptide

Clinicians have used brain natriuretic peptide (BNP) and its derivatives as serum markers for impaired cardiac function. There is some data that suggests that BNP is increased after the Fontan operation.[27] However, others have failed to show increased levels of BNP after Fontan operation.[24] Ohhashi, et al. demonstrated, using bovine mesenteric

lymph vessels, that elevated levels of BNP inhibits lymph transport through a reduction of spontaneous contraction and marked relaxation of lymphatic smooth muscle.[28] Thus, elevated BNP levels after Fontan operation could also contribute to the development of PLE.

5. Congenital lymphatic malformations

It is interesting that patients can develop chylous pleural effusion after chest operations. However, only a minority of patients who have a chest operation do develop chylous pleural effusion. It is rather fascinating that after the Fontan operation only a small number of patients develop PLE. One wonders if patients who develop chylous pleural effusion and patients after a Fontan operation who develop PLE have an unrecognized congenital lymphatic malformation. This is an interesting hypothesis but difficult to prove because of our inability to define precisely the anatomy and physiology of the lymphatic system.

Thus, the potential determinants of PLE after the Fontan operation include elevated systemic venous pressure, elevated thoracic duct pressure, elevated levels of BNP or other inflammatory markers, elevated mesenteric venous pressure, and reduced cardiac output.

Treatment

Management should be aimed at decreasing edema and increasing serum albumin and protein levels.

1. Hemodynamic considerations

Upon initial PLE diagnosis, it is critical to exclude important hemodynamic abnormalities that could be responsible for development of PLE. This may require cardiac catheterization. The presence of significant obstruction to pulmonary blood flow can cause PLE and relief of these obstructions, in some cases, can cure PLE. Several investigators have reported improvement in PLE with transcatheter stent placement or operation to relieve areas of stenosis.[29, 30] If no significant hemodynamic abnormalities are found, other causes of PLE such as nephropathy, liver failure, etc., should be excluded and optimal medical management should be initiated.

2. Fenestration

A number of investigators have performed fenestration after PLE has developed in patients who previously had a nonfenestrated Fontan.[31–33] Theoretically, fenestration could improve PLE by increasing cardiac output albeit with lower than normal systemic arterial blood oxygen saturation. Vyas, et al., created 16 fenestrations in 7 patients in post Fontan operation patients with PLE. After the fenestration, cardiac index increased from 2.5 to 2.9 l/min/m^2, Qp/Qs decreased from 0.97 to 0.79, and systemic arterial blood oxygen saturation decreased from 95.6% to 89.6%. These findings suggested a meaningful fenestration was created. Unfortunately, decreased ascites was observed only after 9 of 16 procedures and 10 of 16 fenestrations spontaneously closed. Three patients experienced long term stabilization of clinical course while two patients required eventual Fontan takedown and one patient died.[33] Fenestration has been shown to lessen PLE after 2–3 months but it also appears to be temporary and not a cure. Fenestration may make PLE easier to manage in some patients.

3. Diet therapy

A diet high in protein and low in fat but augmented with medium chain triglycerides may be beneficial. However, this diet is not particularly palatable and there are no controlled studies that demonstrate its utility in PLE associated with the Fontan. Because hypocalcemia has been associated with PLE, calcium supplementation may be useful.[34]

4. Atrioventricular pacing

Atrioventricular pacing has also been reported to reduce signs and symptoms of PLE.[35] Theoretically, this may be helpful by increasing cardiac output for patients with bradycardia or atrioventricular dissociation. However, reports of pacing success have been quite limited.

5. Pharmacologic therapy

1) Diuretics

Diuretics may be helpful to control edema secondary to hypoproteinemia. In addition, spironolactone, a nonselective aldosterone receptor antagonist, also has been demonstrated to reduce proteinuria.[36] Ringel and Peddy subsequently demonstrated high-dose spironolactone to be effective medical management of PLE.[37]

2) Albumin infusion

For patients with marked edema, particularly in the presence of severe hyponatremia, the infusion of albumin can be useful to reduce the degree of edema. Unfortunately, the effects are quite short lived and the infusions are quite expensive.

3) Drug therapy to improve ventricular function

Since relatively low cardiac output may be one of the determinants of PLE, measures to increase cardiac output may be beneficial. Also, it has been reported that there is increased systemic vascular resistance after Fontan operation. Hence, afterload reduction may be useful to treat patients with PLE.[38, 39)]

4) Steroids

Inflammation seemingly is an important component of PLE. Rothman, among others, have reported success using steroids.[40–42)] Rychik has described some success in treating PLE with budesonide, a steroid that has been helpful in treating inflammatory bowel disease.[43, 44)] Two different histologic patterns of the small bowel have been described in PLE; one is lymphatic congestion, and the second is a sprue-like pattern in which the gastrointestinal lumen becomes denuded and replaced with granulation tissue. One can speculate that lymphangiectasis with leakage of lymph into the interstitial spaces produces an inflammatory reaction leading to the sprue-like pattern and steroids may be effective in this setting by decreasing inflammation in the gastrointestinal wall. Surgical resection of localized intestinal lymphangiectasia has also been shown to be successful.[45)]

5) Heparin

Donnelly, et al. reported that heparin could ameliorate PLE.[46)] The improvement of PLE after administration of intravenous or subcutaneous heparin could be due to several mechanisms. Heparin inhibits mast cell degranulation in the intestine. Stimulation of intestinal mast cells is thought to cause nausea, abdominal cramping, and may be associated with protein loss.[46)] If heparin inhibits mast cell degranulation, this process could be halted. After Fontan operation, thromboembolic events occur in approximately 20% of patients.[47)] The anticoagulation effects of heparin could decrease the development of mesenteric microemboli leading to damaged gastrointestinal cell wall and contributing to enteric protein loss. Heparin also has been shown to possess anti-inflammatory effects and may act in a manner similar to steroids.[48)] Finally, heparin is a known component of the basement membrane of the intestinal wall. Heparin sulfate stabilizes the gastrointestinal luminal wall and by that mechanism could decrease protein loss.[49, 50)] Of note, low molecular weight heparin in has been reported not to have the same effect as unfractionated heparin.[46)] However, Bhagirath and Tam recently reported low molecular weight heparin to be effective for treating PLE in an adult patient.[51)] Not all patients respond to heparin and there are a number of adverse side effects of heparin which make long-term treatment with heparin problematic.

6) Somatostatin

Somatostatin has been effective in the management of primary intestinal lymphangiectasia. It decreases thoracic duct lymph flow in dogs and reduces splenic blood flow in animals. Somatostatin also slows gastrointestinal transit time and inhibits gastrointestinal motility. In addition, it inhibits absorption of triglycerides and acetylcholine release in the gut. Acetylcholine raises capillary infiltration pressure gradient which augments gut lymph flow by 100 to 600%. Therefore, limited evidence may suggest that somatostatin may be helpful in patients with PLE.[52)]

7) Pulmonary vasodilators

In patients after Fontan operation with elevated pulmonary vascular resistance, administration of nitric oxide can lessen PLE.[53)] Based upon this experience, sildenafil has been used to treat patients with PLE. Presumably, sildenafil works by reducing pulmonary vascular resistance improving cardiac output and, potentially, reducing systemic venous pressure. It also has been shown to decrease mesenteric arterial resistance and increase mesenteric arterial blood flow.[24)] Uzun, et al. further demonstrated sildenafil to have a positive impact on PLE by decreasing mesenteric vascular resistance.[54)] However, there have been no randomized trials using sildenafil for treatment of PLE.

8) Cardiac transplantation

Cardiac transplantation has been shown to be successful in eliminating PLE. Bernstein, et al. reported a study involving 32 patients listed for cardiac transplantation with PLE after Fontan operation.[55)] Twenty-five patients (78%) had transplantation and seven died waiting for transplantation. Nineteen of the 25 patients survived greater than 30 days after transplantation and PLE resolved in all twenty-five. The other six patients died less than 30 days postoperatively.

Conclusion

PLE can cause significant morbidity and mortality after the Fontan operation. The etiology is not well understood and could be multifactorial in nature. An extensive cardiovascular investigation should be undertaken once symptoms develop. The management of these patients can be very difficult with no single treatment strategy being successful in all patients. Further investigation is needed to enhance our understanding of PLE and to improve our treatment strategies.

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