

Protein-Losing Enteropathy after the Fontan Operation

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In 1971, Fontan and Baudet were the first to describe a surgical technique for the successful separation of the systemic and pulmonary circulations in a patient with tricuspid atresia¹. Soon after, Kreuzer suggested a similar procedure for a patient with the same condition². This innovative procedure became known as “the Fontan operation”, which, especially in the 1970’s and 1980’s, provided a better prognosis for patients with functionally univentricular hearts. Since these early impressive reports, several modifications of the techniques have been described as an attempt to further improve the function of both circulations³⁻⁵.

In the past twenty years, the short-term outcome of this procedure has improved significantly^{6,7}, basically due to better patient selection, progress in surgical techniques and to more adequate immediate postoperative intensive care. However, as time went by and a new group of patients survived, sequelae of Fontan-like operation became apparent, making it less attractive. Hence, complications such as arrhythmias^{8,9}, poorer physical fitness¹⁰, circulatory failure^{11,12}, atrial thrombosis^{13,14} and liver dysfunction¹⁵ are frequent in the follow-up of these patients at outpatients’ clinics and require special care and appropriate management.

A rare complication, although potentially lethal, is the protein-losing enteropathy (PLE) with pathogenesis and treatment still under discussion. The aim of this study is to review the clinical features of patients with PLE, to discuss the reported pathogenic mechanisms and to summarize the published therapeutic options that are potentially applicable to these patients.

Diagnosis

Patients with PLE present with bloating or abdominal pain, diarrhea, edema, pleural effusion, ascites and distress. Laboratory findings usually include hypoproteinemia, low serum immunoglobulins and calcium levels and low lymphocyte count. The onset of EPP may occur from weeks to years after the surgical procedure. In a study by Mertens¹⁶, this interval ranged from one month to 16 years (mean: 2.7 years). The diagnosis of PLE is confirmed by finding high fecal α 1-antitrypsin levels in patients with no other causes of hypoalbuminemia, such as liver disease or malnutrition¹⁷⁻¹⁹. Associated infections may occur due to immune dysfunction confirmed by the low lymphocyte count and immunoglobulin levels²⁰. Some cases may present with no diarrhea and with slight hypoalbuminemia, despite the marked reduction in serum immunoglobulin levels and lymphocyte counts, especially of CD4²¹. According to some authors, transaminases may be increased due to secondary liver congestion²².

Key words

Operation, Fontan, protein loss.

Subclinical gastrointestinal protein loss may occur with no evidence of the classical clinical findings and with normal serum protein levels²³.

Incidence

As far as is known, PLE was first described in 1960 in a 17-year old patient with constrictive pericarditis²⁴. Hypoalbuminemia, hypocalcemia and steatorrhea markedly improved after surgery. After this report, others were published describing patients with similar findings secondary to chronic constrictive pericarditis²⁵, tricuspid insufficiency²⁶, Mustard operation²⁷ and Glenn operation²⁸.

The incidence of PLE after Fontan operation is variable and was first described by Crupi, in 1980²⁹. Shortly after the report of three patients operated by Hess³⁰, Driscoll demonstrated that 10% of 352 cases operated on before 1985 had PLE. This study highlighted the importance of some variables associated with PLE and became an important reference for the Fontan operation¹². The incidence of PLE following the Fontan operation has been reported as 2.5 to 10%^{23,31-34}, but always in studies involving a small number of patients. In a large multicenter study published in 1998 and involving 3,029 patients, PLE was diagnosed in 114 cases (3.7%). This study is a landmark in PLE characterization and demonstrated, among other relevant aspects, the low incidence of this syndrome in patients who underwent the Fontan operation.

Pathogenesis

The mechanisms involved in triggering PLE have been under debate for almost 50 years. As early as 1961, Davidson²⁵ associated the occurrence of the syndrome with high venous pressure and consequent changes in the intestinal lymphatics. Chylous dilatation of small bowel villi³⁵ could cause local edema with secondary protein loss. Curiously, Blalock, in 1936³⁶, induced this physiological change by occluding the superior vena cava of dogs, and caused obstruction of flow in the thoracic ducts and congestion of the intestinal lymphatics. These early studies clearly depicted the role of the small bowel in protein loss, supposedly related to increased central venous pressure. This seemingly obvious concept was challenged by Wilkinson in 1965³⁷, who was the first researcher to perform jejunal biopsy in a patient with PLE and normal venous pressure, demonstrating the characteristic lymphangiectasis. Another important feature described by Strober, in 1968²⁶, was fecal lymphocyte and protein loss, potentially reversible by treating the heart disease³⁸.

In 1984, Hess³⁰ reported three cases of PLE after surgical atriopulmonary connection. These patients had high right atrial diastolic pressure; since antegrade flow in the superior vena cava after the Fontan operation takes place during atrial

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diastole, PLE was allegedly associated to this physiologic variable.

Recent studies have reported cases of protein loss in a circumscribed intestinal region. In 1999, Koch²¹ employed Tc99-labeled albumin and demonstrated a marked reduction in CD4+ lymphocytes of unknown origin in patients with circumscribed intestinal protein loss. According to this author, passive lymph loss secondary to high central venous pressure could not explain the selective loss of CD4+ lymphocytes, suggesting that the primary or secondary disturbance of the immune system could affect the structural integrity and patency of the intestinal wall, thus triggering PLE. In theory, if proven, the circumscribed loss would have definite surgical consequences in these patients. An interesting aspect, recently reported is the possible association of increased mesenteric vascular resistance with PLE³⁹. These authors suggested that the increased resistance would cause mesenteric hypoperfusion, which would be a possible substrate for the development of the syndrome.

Treatment

The five-year survival rate of patients with PLE after the Fontan operation ranges between 46% and 59%^{16,31}. Such figures point out to the extreme severity of this complication, and support the efforts made to optimize the treatments available.

Medical Treatment

In addition to the use of anti-congestive medications, such as diuretics and ACE inhibitors, the replacement by periodic infusion of albumin, immunoglobulins and lymphocytes should be done. Also, patients must be advised to ingest hyperproteic and medium-chain-triglyceride rich diets. In 2003, Chakrabarti²⁰ considered that perhaps these patients had acquired immunodeficiency due to fecal lymphocyte loss and recommended the prophylactic use of antibiotics and the prompt treatment of any infection. Antiviral vaccines and immunoglobulin replacement are also recommended and aim to improve the immunological protection of these patients⁴⁰. Some specific measures have been used with different success rates:

a) Steroids: following Silverman's⁴¹ report on the treatment of intestinal lymphangiectasis, Rothman⁴², in 1991, used prednisone to treat a patient with PLE diagnosed two years after the Fontan operation, with no signs of circuit obstruction and with a mean pressure of 10 mmHg in the right atrium. This innovative experience was soon reproduced with satisfactory result^{43,44} despite the small number of patients. Zellers' experiment was rather interesting, for it clearly demonstrated, though in a single patient, the association between use of steroids and anatomical changes in the duodenal biopsy. With the use of 2mg/kg/day in the first intervention, an improved clinical picture was evident. However, relapse occurred when the drug was discontinued and novel improvement occurred by reintroducing it at 0.5 mg/kg/day. In this case, it was then demonstrated the association of high fecal α 1-antitrypsin and hypoalbuminemia with dilated intestinal villi in the biopsy. It is believed that in addition to its anti-inflammatory effect, steroids may be stabilizing factors of lymphatic and capillary membranes and may reduce the bulk of lymphatic tissue⁴⁵.

Although representing an interesting therapeutic option, the use of steroids is not widely accepted. In the impressive

multicenter trial reported by Mertens¹⁶, 52 patients received single medical treatment with a death rate of 46%. In 16 patients who used prednisone the syndrome resolved in 5, improved in 7 and did not change in 4, thus demonstrating that the drug may be effective. Despite some unfavorable outcomes with this drug reported by other authors, there is evidence of good response in patients with no obstruction in the Fontan circulation. Therefore, this therapeutic option will seem reasonable until prospective studies are carried out. It is worth mentioning that the patient with PLE may be immunosuppressed due to fecal lymphocyte loss; worsening may occur if steroids are used.

b) Heparin: curiously, the mother of a patient with congenital heart disease and PLE observed that the child's diarrhea improved when warfarin was replaced by heparin whenever the child needed surgery. In 1997, Donnelly⁴⁶ reported the successful use of heparin in lower doses than those usually employed in anticoagulation in three patients with PLE. Heparin sulfate is a component of the basal membrane of several organs. When removed from other membranes but preserving proteoglycans, there is a considerable increase in membrane permeability to proteins⁴⁷. The use of exogenous heparin, particularly high molecular weight heparin, may stabilize interactions in the capillary endothelium and the intestinal mucosa, with a consequent decrease in protein loss. In addition, heparin may enhance perivascular protein reabsorption into the lymphatic system.

c) Calcium: in 2004, Kim⁴⁸ prescribed calcium alone, with no steroids or heparin, to a child with PLE, abiding to the patient family's desire. The child improved within four weeks, taking a turn for the worse soon after the drug was discontinued and again improving when reinitiated.

d) Spironolactone: Ringel⁴⁹, in one sole experience, reported the use of spironolactone in three patients with PLE, with considerable improvement.

Percutaneous intervention

In 1994, Mertens⁵⁰ reported the case of a 29-year old patient with refractory PLE after atriopulmonary anastomosis, who responded to percutaneous fenestration in the interatrial septum region. This procedure, even though successful, may be difficult to carry out due to the presence of Goretex or complex baffle in the intra-atrial conduit. Despite its attractiveness, this procedure should not be routinely used, since it was tested in only a few cases. Novel techniques are being tested in some centers and may shortly be included in the therapeutic armamentarium⁵¹. It is noteworthy mentioning that in Mertens' trial¹⁶, carried out in 1998, 13 patients underwent heart catheterization, three of them with associated surgical treatment. Nine patients underwent dilation with balloon catheter with or without stent placement; in that, three to relieve circuit obstruction and six to dilate pulmonary artery obstruction. Eight out of these nine cases had technically successful outcomes, five of whom with improvement of pulmonary obstruction and three with no clinical improvement. Five patients underwent atrial fenestration by means of blade septostomy, three with dilation by balloon catheter, one with interatrial septum puncture and dilation and one with stent placement. Three patients improved significantly while two, only partially. Two patients had stroke and one of them was not on anticoagulants. Other single case studies have been recently reported, such as the azygos vein embolization with Gianturco coil in PLE patients

after the Glenn operation⁵². It is believed that the vein-vein shunt interruption was accountable for the PLE improvement in this case. It is important to highlight at this point that these summarized interventionist options may be of help in treating PLE due to the obstruction of Fontan circulation while, at the same time, they demonstrate the limited efficacy of the interatrial fenestration.

Pacemaker Implantation

An interesting report by Cohen⁵³ was published in 2001 regarding this procedure. In two patients with PLE after the Fontan operation and associated sinus node dysfunction, the implantation of a pacemaker increased cardiac output and resolved the syndrome. After this, pacemaker implantation was considered a possible intervention to treat PLE, even in patients with no arrhythmias.

Surgical Treatment

From the early trials in cases of constrictive pericarditis^{24,25}, tricuspid insufficiency²⁶ and the Mustard operation with vena cava obstruction²⁷, cardiovascular surgery has been an option for treating PLE. In 1980, Crupi²⁹ described the supposedly first case successfully treated by surgery for PLE after the Fontan operation. The insertion of a biological valve in the proximal anastomosis in a patient with previously performed atriopulmonary connection with a valveless conduit and marked regurgitation resulted in great improvement, normalizing the serum protein levels. Fifty-two patients with PLE of the multicenter Mertens trial¹⁶, in 1998, underwent surgery with high mortality rate (61%); among the survivors, 19% still had signs of PLE. Different surgical procedures aiming to optimize the Fontan-like circulation were employed, such as conduit disobstruction, valvuloplasty and septal defects occlusion. Conversion to other types of anastomosis was performed in a small number of patients and the most common was the conversion of atriopulmonary anastomosis into total cavopulmonary connection. Other interventions, including the undoing of the Fontan operation and heart transplantation were carried out in a small number of patients.

It is speculated that delay in surgery and irreversibility of enteric damage, even after postoperative hemodynamic improvement, may be factors of surgical failure. One must also consider that conversion into another Fontan-like circulation may not prevent PLE. Another option is the surgical atrial fenestration, described in 1996⁵⁴. In this interesting study, two cases of PLE refractory to medical treatment had an excellent outcome after a 4.8 mm surgical atrial fenestration. It is noteworthy, as mentioned by other authors, that patients become cyanotic after this intervention, with risk of embolism. In 1997, Rychik⁵⁵ described five patients who underwent lateral tunnel Fontan operation, and had PLE in the follow-up. When treated with surgical atrial fenestration, in three of them protein levels normalized and PLE symptoms subsided two to six weeks after the procedure. In the two patients who did not improve, blood O₂ saturation was greater than 89% and the authors suggested that the clinical improvement seems to be related to the degree of right-left shunt created by the fenestration, and blood O₂ saturation should not be greater than 85%.

In 1998, Barbero-Marcial et al⁵⁶ described an interesting surgical technique in patients with PLE after atriopulmonary anastomosis. In all three cases, conversion into cavopulmonary

anastomosis and diversion of the hepatic veins to the left atrium were performed. Despite technically cumbersome, it seems to be a useful choice, as long as all hepatic veins are excluded from the venous system avoiding that any remaining vein facilitate the communication between the vena cava and the portal system, thus increasing the risk of cyanosis.

Thirty-one patients reoperated after the Fontan procedure were recently reported by Marceletti et al³⁴, most of them due to arrhythmia and heart failure. Three of these patients had PLE, two of whom improved after extracardiac insertion of a polytetrafluoroethylene (PTFE) valveless tube connecting the inferior vena cava to the right pulmonary artery, associated to the reduction of the right atrium. Twenty-seven of the 31 patients are classified as functional class I or II, which confers to this type of anastomosis a hemodynamic efficiency superior to other techniques⁵⁷.

Despite the small cumulative experience, heart transplantation may be an alternative, sometimes the only one, for treating PLE^{58,59}. Brancaccio et al⁶⁰ reported one interesting case of heart transplantation in a patient with PLE. As PLE persisted after such radical surgery, total parenteral nutrition was initiated with improvement after 16 weeks.

Connor⁶¹ has recently described the innovative experience of a 14-year old female patient with PLE refractory to both medication of any type and the Fontan operation revision. The affected small bowel area was localized by means of TC99-dextran scintigraphy. After resection of 135 cm of the jejunum, the PLE gradually improved, despite the demonstration of persisting protein loss on a new scintigraphy. In spite of the successful results of this procedure in patients with PLE and intestinal lymphangiectasis⁶², its benefits to patients after the Fontan operation, as well as the incidence of circumscribed lesions have still to be determined. What would be the determining factor of the enteric lesion in a specific site? What would be the long-term results of cases operated with this technique? Could other lesions appear in different areas of the small bowel after successful resection? These practical questions will remain unanswered until larger studies are performed.

Prevention

The cumulative analysis of patients undergoing the Fontan operation enabled the recognition of some variables possibly related to the worsening of PLE and, thus, the early identification of possible patients at risk. At this point, the classical work by Driscoll¹², in 1992, should be mentioned. This author verified that patients with heterotaxia, polysplenia, systemic venous drainage anomalies, high pulmonary vascular resistance and high left ventricular diastolic pressure had a significantly greater chance of developing PLE after the Fontan operation. These findings were later confirmed, in 1996, by Feldt³¹, who added that right ventricular anatomy, as well as the duration of extracorporeal circulation and of hospitalization were also significantly associated with the appearance of the syndrome. In 2001, Powell⁶³ reported 416 patients who underwent the Fontan operation: 103 (12.6%) cases submitted to extracorporeal circulation for over 140 minutes had PLE, whereas only 313 (0.6%) with extracorporeal circulation lasting less than 140 minutes presented PLE ($p < 0.001$).

This information is relevant for the selection of surgical candidates, as well as for choosing the operative technique to be used. For instance, could patients at risk of developing PLE benefit from atrial fenestration during the Fontan operation?

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One should also consider the possibility of patients with subclinical PLE²³, who have definite protein loss but not the typical findings of the syndrome, and who deserve closer attention. As suggested by Fuji⁶⁴, in 2003, the fecal protein loss precedes hypoproteinemia. One wonders whether these patients would have a better outcome if treated before the appearance of the full-blown syndrome.

Recent data indicate that the immune system has an important role in the genesis of PLE. Patients with low lymphocyte count, especially CD4+ and CD5, seem prone to PLE⁶⁵. Shimilu et al⁶⁶ have recently shown that increased interferon gamma in the intestinal mucosa leads to protein loss not accompanied by epithelial changes under electronic microscopy. Agreeing with Chakrabarti, in 2003²⁰, the information above indicates that determining the immunological profile of the operated patient seems to be important. Prophylactic treatments in patients with immune dysfunction may influence the onset of PLE. The postoperative size of the right atrium may be related to the appearance of PLE³⁵.

Conclusion

Based on the review above, PLE after Fontan operation is a well-known disorder of low incidence but of poor prognosis. Its diagnosis should be suspected in any patient undergoing the Fontan operation and presenting diarrhea and hypoproteinemia with or without edema. Subclinical PLE is well recognized, but its role in the outcome of these patients is

still unknown. Localized obstructions should be sought, as they may cause the syndrome. However, PLE with no obstructions is quite frequent and its pathogenesis is possibly related to complex immune mechanisms. It is mandatory to diagnose acquired immunodeficiency in these patients. Regarding treatment, the patients with circulatory obstruction should be appropriately managed to avoid venous hypertension. The treatment of causes not related to obstruction is still open to debate. Steroids, although not universally accepted, may be used with attention given to possible worsening of an already existing immunodeficiency. Heparin and spironolactone may be useful, although their benefits are yet to be proven. Percutaneous intervention has specific indications, but is not always effective. Surgical optimization of the Fontan-like circulation must be considered whenever possible. Surgical atrial fenestration, conversion into cavopulmonary anastomosis and heart transplantation may be indicated in specific cases. It is important to choose the ideal candidate for the Fontan operation, as PLE seems to be less frequent in certain functional and anatomical circumstances.

Despite its grim prognosis, the recent interest in the elucidation of the mechanisms involved in the syndrome is fundamental to find the ideal treatment. Even though the Fontan operation is a widely practiced procedure in Brazil, few papers were written on PLE pointing to the need of a multicenter Brazilian trial. Such a trial is important to assess the magnitude of the problem, the characteristics of Brazilian patients and the therapeutic options available.

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