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Brief Report

High-altitude precipitation and exacerbation of protein-losing enteropathy after a Fontan operation.

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Abstract We describe the development and exacerbation of protein-losing enteropathy after relocating to an environment at an altitude of 3695 feet in El Paso, Texas, in a patient who had undergone a Fontan operation. This report should heighten awareness to the possibility of such patients developing protein-losing enteropathy at high-altitude, with hypoxemia-induced pulmonary vasoconstriction, and subsequent elevation of central venous pressure, the most likely underlying mechanism.

Keywords: Protein-losing enteropathy, Fontan operation, high-altitude

THE DEVELOPMENT OF PROTEIN-LOSING enteropathy following the Fontan operation is an ominous and debilitating complication, which may be refractory to medical therapy.[1–2] Elevation of central venous pressures may predispose to the development of protein-losing enteropathy. The development of protein-losing enteropathy in a patient with a Fontan circulation following relocation to high-altitude has not been previously described. The development of hypoxemia-induced pulmonary vasoconstriction at high-altitude may precipitate this complication in such patients.

Case report

A female patient was diagnosed with double outlet right ventricle, with the aorta rightward and anterior, multiple ventricular septal defects, a straddling stenotic mitral valve, a left superior caval vein to the coronary sinus, and pulmonary stenosis after presenting in the newborn period with cyanosis. She underwent balloon atrial septostomy on the third day of life, which palliated her successfully until 9 months of age, when she required a modified Blalock-Taussig shunt because of increasing cyanosis. The degree of pulmonary stenosis was initially characterized as mild-to-moderate, with a baseline oxygen saturation of 88% when breathing room air after septostomy. The pulmonary stenosis became progressively worse, with the saturation of oxygen decreasing to 66% in room air at nine months of age, hence the placement of the shunt. At eight years of age, cardiac catheterization prior to a Fontan procedure demonstrated mildly elevated pulmonary arterial pressures measured at 20mmHg in the pulmonary trunk and 14mmHg in the right pulmonary artery, with a transpulmonary gradient of 7mmHg. The pulmonary arteriolar resistance was not calculated. The patient subsequently underwent bilateral construction of bidirectional Glenn anastomoses, and creation of a lateral tunnel to produce the Fontan circulation, which was not fenestrated. Following this, she had a stormy postoperative period, with persistent pleural and pericardial effusions.

Cardiac catheterization six weeks after the procedure demonstrated elevated central venous pressures (see Table 1), with an area of stenosis at the bifurcation of the pulmonary arteries between the bidirectional Glenn anastomoses. Angiographically there were no areas of stenosis identified between the inferior and right superior caval veins and the right pulmonary artery, or between the left superior caval vein and left

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pulmonary artery. Six weeks following the Fontan procedure, the patient underwent creation of a surgical pericardial window. Following this, and in conjunction with medical therapy including digoxin, lasix and captopril, the patient made a rapid recovery. She was discharged home two weeks later.

The patient subsequently did well breathing room air, and remained asymptomatic participating actively in gymnastics for four years, until the family relocated to El Paso, Texas, which is situated at an altitude of 3,695 feet. Three months after the move to higher altitude, she complained of peripheral edema, abdominal fullness, and decreased exercise tolerance. She returned to Houston, Texas, situated at 38 feet, where repeat cardiac catheterization was performed two weeks after relocation to sea-level. This study demonstrated mildly elevated central venous pressure, but no obstruction between the right superior and the inferior caval veins and the right pulmonary artery, all pressures being measured at 12 mmHg. There was, however, persistent stenosis between the bidirectional cavo-pulmonary anastomoses, the diameter of which measured 3.5 mm, with a 4 mmHg gradient across the area of narrowing. Angiography in the inferior caval vein demonstrated preferential flow of blood into the right pulmonary artery. A Palmaz 308 stent (Johnson and Johnson, Piscataway, New Jersey) was implanted across the area of stenosis. There was no gradient across the stent following implantation, and the central venous pressures remained only slightly elevated, measured at 11 mmHg after angiography. There was also an improvement in flow of blood to the left lung. The patient reported an improvement in symptoms during her stay in Houston. Three months after returning to El Paso, she complained again of recurrent peripheral edema and persistent diarrhea. Urinalysis was negative for protein, but levels of –1 antitrypsin were markedly elevated in the stools. The serum protein measured 3.3 grams/decileter with the normal range being 6.0–8.0 g/dl, serum albumin 2.0 g/dl with normal range of 3.7–5.5 g/dl, and liver enzymes, including transaminases, were normal. A duodenal biopsy demonstrated markedly dilated lacteals within the villous structures, and expanded lymphatic channels within the submucosa at multiple levels and in each tissue section, consistent with a diagnosis of protein-losing enteropathy (Figure 1). She was treated intravenously with 5% human albumin and lasix with only mild improvement. The family noticed a continued improvement in symptoms, however, while staying in Corpus Christi and Dallas, both situated below the level of 500 feet, before their return to El Paso. Once in El Paso, the symptoms of protein-losing enteropathy occurred once again. The patient was started on oral prednisone 1 mg/kg/day. Three weeks following therapy, her symptoms dramatically improved, with normalization of her biochemical parameters and absence of –1 antitrypsin in the stool (Table 2). She was slowly weaned from steroid therapy over a period of two months. During this time, the family relocated to Dallas, and later Louisiana, and the patient has remained completely free from symptoms on follow-up, with no biochemical evidence of ongoing protein loss for five years following the onset of her protein-losing enteropathy.

Discussion

Protein-losing enteropathy is characterized by intestinal loss of protein associated with hypoproteinemia, loss of body fluids by means of pleural and pericardial effusions, ascites, and peripheral edema, as well as nutritional and immunologic dysfunction. It is a well established complication following Fontan procedure.[1] Although its incidence is relatively rare at 3.7% as reported by the International study group, protein-losing enteropathy remains an ominous prognostic sign, with a 41% five-year mortality rate following its onset.[1] The speculated etiology includes elevated systemic venous pressure resulting in intestinal protein loss by elevation of pressure in the enteric

Table 1. Cardiac catheterization data

Site	6-Week Postoperative Catheterization*	4-Year Postoperative Catheterization**
RSVC	26mmHg	12mmHg
IVC	24mmHg	12mmHg
RPA	20mmHg	12mmHg
LPA	18mmHg	12mmHg

Abbreviations: RSVC represents right superior caval vein, IVC inferior caval vein, RPA right pulmonary artery, and LPA left pulmonary artery.
* Catheterization performed six weeks after Fontan operation.
** Follow-up cardiac catheterization performed four years after Fontan operation while symptomatic with protein losing enteropathy.

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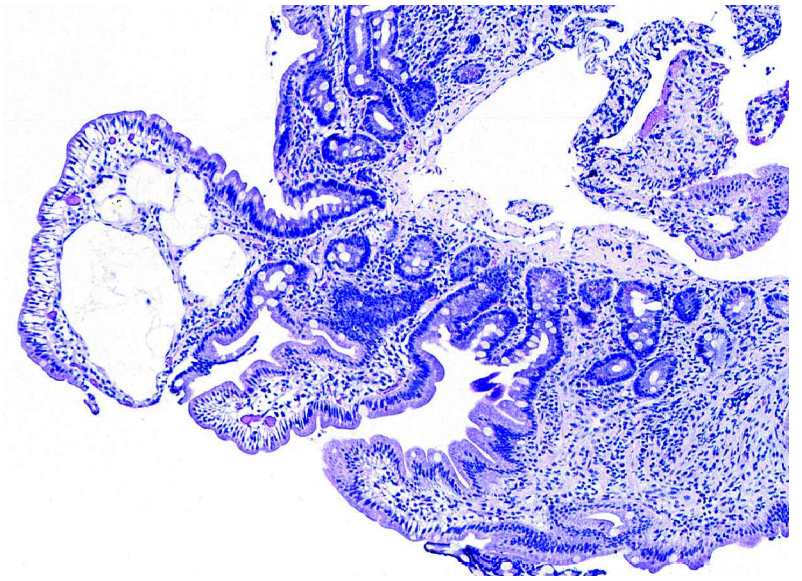

Figure 1.
Duodenal biopsy with markedly dilated lacteals and lymphatics resulting in distortion of the normal villous architecture of the duodenum (H&E stain, original magnification × 40).

Table 2. Biochemical parameters before/after PLE treatment

Variable	Symptomatic PLE	After steroids/relocation
Symptoms	Edema, abdomen distension	Asymptomatic
Serum total protein*	3.3 g/dl	6.2 g/dl
Serum total albumin*	2.0 g/dl	3.9 g/dl
Stool -1 antitrypsin	Strongly positive	Negative

*Serum protein normal range 6.0–8.0 g/dl, serum albumin 3.7–5.5g/dl.

lymphatic system. Once diagnosed, thorough hemodynamic investigation is required specifically to rule out the presence of venous obstruction, severe atrioventricular valvar regurgitation, and ventricular dysfunction as potential causes. Symptomatic therapy includes diuretics and avoidance of fluid overload, but is rarely of long-term benefit.

Symptoms often demonstrate a dramatic response to either intravenous or oral steroids, but the frequency of relapse is high following the withdrawal of therapy.[2] Several authors have reported dramatic improvements in symptoms, marked elevations in levels of albumin in the serum, and quantitative reversal of enteric loss of protein within a few weeks of starting heparin.[3] The exact mechanism of action remains unknown, but may include stabilization of cell-matrix interactions at the capillary endothelial or intestinal mucosal level preventing leakage of protein into the extravascular space or intestinal lumen respectively. Heparin may also alter the architecture of the cytoskeleton in the perivascular space to augment resorption of protein into the lymphatic return.[4] Resolution of protein-losing enteropathy following creation of an atrial fenestration to reduce elevated central venous pressure has also proven effective in treatment of this often refractory condition.[5]

To the best of our knowledge, this case represents the first report describing the onset of protein-losing enteropathy in a patient with the Fontan circulation associated with relocation to a high-altitude environment. We hypothesize that hypoxemia-induced pulmonary vasoconstriction associated with high-altitude led to an elevation of central venous pressure, which then precipitated the onset of protein-losing enteropathy in this patient four years after her Fontan procedure. The fact that she required no palliation other than balloon atrial septostomy in the first nine months of life, and had borderline high pulmonary arterial pressure on catheterization just *prior* to her Fontan procedure, could be indicative of exposure to chronic high pulmonary blood flow in infancy. This increased pulmonary blood flow may have resulted in the development of some degree of obstructive pulmonary hypertension, which in turn could account for the stormy postoperative course she later encountered. Such patients with elevated or borderline pulmonary arterial pressures or resistance could represent a subset of patients predisposed to developing protein-losing

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enteropathy at high-altitude after the Fontan procedure. Alternatively a normal pulmonary vascular resistance might explain how many patients with the Fontan circulation live at high altitude without this complication. Our patient demonstrated little improvement with placement of a stent, yet had a dramatic improvement in symptoms on returning to sea-level after the recurrence of her symptoms, suggesting a reactive pulmonary vascular bed responsive to an increase in ambient oxygen. This patient also had no episodes of relapse following the combination of steroid therapy and the permanent relocation to a sea-level environment. When last seen on follow-up five years following the onset of her protein-losing enteropathy, she remains completely symptom free.

Our report should heighten awareness of the possibility that patients with the Fontan circulation living at high-altitude may develop protein-losing enteropathy. We postulate hypoxemia-induced pulmonary vasoconstriction and elevation of central venous pressure as the most likely mechanism underlying this physiology. Patients with borderline or elevated pulmonary arteriolar resistance may be predisposed to developing this complication.

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