

**PROPOSAL FOR PREVENTION OR ALLEVIATION
OF PROTEIN/LYMPH-LOSING ENTEROPATHY (PLE/LLE)
AFTER FONTAN CIRCULATION TREATMENT OF
UNIVENTRICULAR HEARTS: RESTORATION OF LYMPH BALANCE
WITH A “LYMPHATIC RIGHT-TO-LEFT SHUNT”**

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ABSTRACT

In Fontan circulations created for univentricular hearts, systemic venous return is diverted to the lungs before returning to the heart. The Total Cavopulmonary Connection (TCPC) is often the preferred surgical procedure whereby a 4-way anastomosis is created with inflow from the superior vena cava (SVC) and inferior vena cava (IVC) and outflow to the right and left branches of the pulmonary artery. In this arrangement, the systemic venous pressure must be elevated sufficiently to perfuse the lungs passively without the normal boost of the right ventricle. Hence, unlike surgical corrections for other congenital heart conditions, the systemic venous pressures in a Fontan circuit must be elevated to make the circulation work. It is proposed here that the incidence of PLE/LLE is directly related to elevated venous and lymphatic pressures, which cause leakage of proteins/lymph into the gastrointestinal tract (GIT) and expulsion from the body. It is commonly held that elevated venous pressures are relatively better tolerated in the upper body, but much less so in the hepatosplanchnic circulation and the lower body. It is also well established that elevated venous pressure increases lymph formation, most of which is produced in the hepatosplanchnic

region (liver and intestine). It is further argued here that the increase in lymph filling pressure arising from the higher lymph flow, in association with the backpressure exerted by elevated venous pressure at the main drainage point into the venous system, results in a substantial increase in pressure in the thoracic duct. This pressure is transmitted back to the intestinal lymphatics, causing dilatation with lacteal rupture and protein or bulk lymph leakage into the intestine. We propose in this paper a new approach, based on experimental evidence, to prevent and/or alleviate this condition by draining or redirecting the thoracic duct (or, alternatively, a more localized intestinal lymphatic vessel) into one of the pulmonary veins or the left atrium, which are typically at near-normal pressure in a Fontan circulation. This “lymphatic-venous right- to-left” shunt maneuver would significantly reduce the venous backpressure on the lymphatics as well as improve lymph circulation, resulting in a decrease in the intestinal lymphatic pressure and thereby prevent or alleviate protein/lymph loss, i.e. lymph balance would be restored. Moreover, the greatly facilitated lymphatic flow would encourage further capillary filtration to relieve excessive venous pressure in the hepatosplanchnic region and protect the liver and kidneys. This paper is

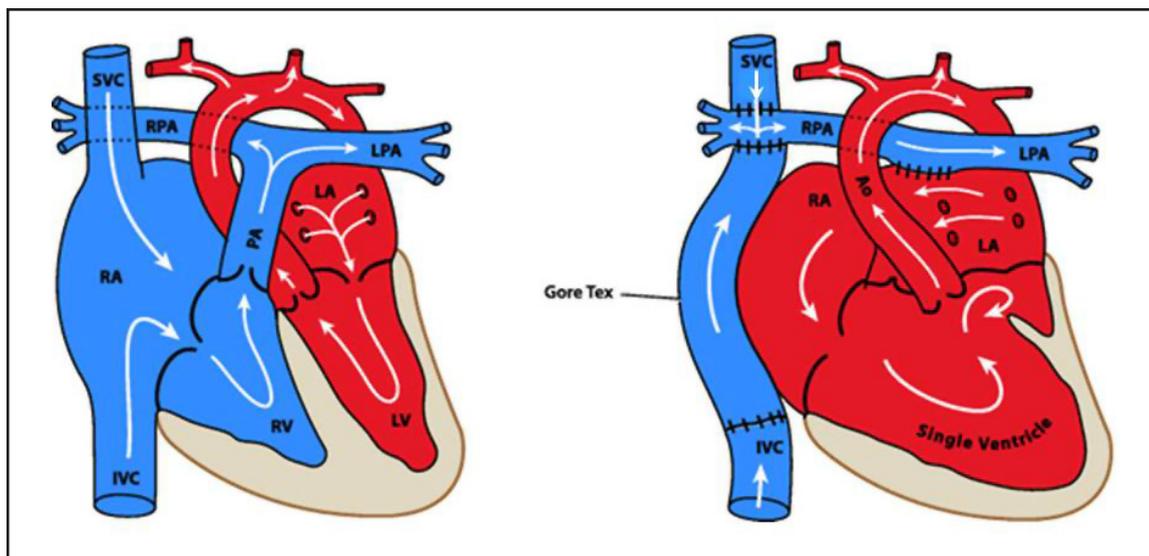


Fig. 1. Diagram of the Fontan procedure. Compared to the normal heart (left), in children born with a univentricular heart driving both the pulmonary and aortic circulation (right), the pulmonary circulation is converted to be driven directly by both the IVC and SVC outside of the heart, and the single ventricle then only drives the systemic circulation through the aorta (right). SVC = superior vena cava; IVC = inferior vena cava; RA = right atrium; RV = right ventricle; PA = pulmonary artery; LPA = left pulmonary artery; RPA = right pulmonary artery; LV = left ventricle; LA = left atrium; Ao = aorta. Modified from Fig. 2 Cannesson et al (27).

intended as a discussion document for elicitation of comments on the soundness and viability of this proposal as well as on technical challenges and steps to explore and advance it.

Keywords: protein losing enteropathy (PLE), lymph losing enteropathy (LLE), Fontan circulation, univentricular hearts, thoracic duct lymph, congenital heart disease, congenital cardiac surgery, chylous reflux, thoracic duct-pulmonary vein shunt, lymphatic right-to-left shunt, heart failure

PHYSIOLOGY, PATHOPHYSIOLOGY, EXPERIMENTAL MODELS, AND PROPOSED APPROACHES

Incidence, Causes, and Treatments for PLE in Fontan Circulations

The incidence of PLE after the Fontan operation (Fig. 1) has been variously reported

as anywhere between 3% and 24%. The widely referenced Mayo Clinic study (1) reported an incidence of 13.4% among 427 patients with a 5-year survival rate after diagnosis of 46%. In spite of multi-factorial analyses (2), the etiology of PLE in Fontan patients is uncertain and hence treatment modalities are diverse. These have included: diet (low fat, medium chain triglycerides, high protein, restricted sodium); systemic steroids (e.g., prednisone) or heparin to stabilize intestinal mucosal cell membranes; diuretics (e.g., furosemide, spironolactone); relief of pulmonary hypertension (e.g., sildenafil); and surgical methods such as baffle fenestration, relief of obstructive lesions, occlusion of aorto-pulmonary connections or resection of localised intestinal lymphangiectasia (i.e., lymph vessel dilatation) (3). In spite of some reported successes, it is agreed that the medical and surgical interventions to date have been generally disappointing, and the incidence

of PLE is unchanged with the outlook for sufferers continuing to be bleak. One international multi-center report (4) states: "We conclude that the current treatment of protein-losing enteropathy after Fontan operation is associated with a very high mortality and morbidity rate. Preventive strategies and new therapeutic approaches are necessary."

On consideration of the treatment modalities listed above, it is probably fair to conclude that most of them are in some way related to the low cardiac output and/or high venous pressure implicit in Fontan circulations. This is supported by the incidence of PLE in congestive heart failure (CHF), which also has these characteristics. In the context of CHF, an article in the British Medical Journal (5) states: "Hypoproteinemia is a rare but serious complication in patients with congestive heart failure, particularly in those with constrictive pericarditis." And: "...in patients with congestive heart failure, studies ... have shown that the protein deficiency is attributable to excess loss of protein in the gut." And, again: "Protein-losing enteropathy is thought to be a functional disorder of the intestinal lymphatics secondary to an increase in central venous pressure."

Fontan Venous Pressures

It is generally acknowledged that, in a 'good' Fontan circulation, central venous pressure (CVP) is in the range 10-15 mmHg (with most Fontan patients > 12 mmHg) and left atrial pressure is in the range 5-10 mmHg (6). In a 'failing' Fontan circulation with abnormal hemodynamics, the pulmonary artery pressure often exceeds 20 mmHg. In a normal biventricular circulation, the CVP is in the range 2-6 mmHg and the left atrial pressure 8-10 mmHg.

Capillary Filtration and Lymph Formation Physiology in Fontan Circulations

Transcapillary fluid exchange between

the blood and body tissues consists of filtration from the arteriolar end of the capillaries into the surrounding interstitium (with the understanding that the vast majority of fluid never escapes the blood circulation) followed by partial reabsorption into the venular end. With this process in balance, the tissue fluid that is not reabsorbed into the blood system enters terminal lymphatics as lymph (some would say the tissue fluid is lymph while others reserve this term for the fluid only within a lymphatic vessel). This fluid is ultimately transported into collecting vessels feeding into two major ducts – the thoracic duct (TD) primarily and the right lymphatic duct, both of which drain into the central venous system. TD lymph, largely from the intestinal lymphatics (and also liver lymphatics), drains into the left venous angle at the junction of the left internal jugular vein and the left subclavian vein.

Capillary filtration and reabsorption are governed by the pressure balance between hydrostatic and oncotic pressures in the intravascular and extravascular compartments. Here, oncotic pressure is the 'pulling pressure' exerted by proteins to keep fluids within their own compartment. This balance is governed by the Starling equation: $J_v = K_f [(P_c - P_i) - \sigma(\pi_c - \pi_i)]$ where J_v = transcapillary fluid flow, K_f = a proportionality constant dependent on capillary surface area and hydraulic conductance, P = hydrostatic pressure, π = oncotic pressure, σ = reflection coefficient, subscript c = capillary and subscript i = interstitial. The reflection coefficient is a factor which represents the permeability of the capillary to the proteins responsible for generating the oncotic pressure where $\sigma = 1$ for total impermeability to proteins and $\sigma = 0$ for free permeability to proteins. The element of the equation in the square bracket represents the net driving force (NDF); if this is positive, filtration of fluid from the capillary occurs, and if negative, absorption into the capillary occurs. As a general example, *Table 1* assumes the following values at the arteriolar

TABLE 1
Starling Forces Governing Capillary Filtration and
Absorption in a Non-Pathological State

	P_c	P_i	π_c	π_i	NDF
Arteriolar end	30	1	25	6	$[(30-1) - 0.9(25-6)] = +11.9$
Venular end	15	1	25	6	$[(15-1) - 0.9(25-6)] = -3.1$

and venular ends of a capillary with a reflection coefficient of 0.9. In this example (Table 1), at the extreme arteriolar end, filtration occurs and at the extreme venular end, reabsorption occurs. Assuming a linear reduction in capillary pressure between arteriole and venule, fluid filtration occurs over most of the capillary length.

In a Fontan circulation, the venous pressures are intrinsically elevated. In the above example of the Starling equation, if the hydrostatic pressure at the venular end of the capillary is increased from 15 mmHg to, say, 20 mmHg due to the elevated venous backpressure on the capillaries, then the NDF at the venular end becomes: $[(20-1) - 0.9(25-6)] = +1.9$. Hence, fluid filtration now occurs over the full length of the capillary with no reabsorption. Thus, increased capillary fluid filtration increases fluid shift from the blood vascular bed to the interstitial space and consequently increases lymph production. The lymph system is therefore burdened with the enhanced filtration quantity causing a volume and pressure increase in the lymphatic vessels. When this burden becomes too great, lymphatic insufficiency results with the excess interstitial fluid remaining as edema. This “third space” (from “lymph imbalance”) further activates the body’s compensatory salt and water retaining mechanisms through the renin-aldosterone system, which aggravates the situation promoting even greater lymph imbalance.

Effects of Venous Pressure on Thoracic Duct Pressure

Wegria et al (7) investigated the effects of increased venous pressure on lymph drainage in dogs. They occluded the left innominate vein in steps by positioning a screw clamp downstream of the entrance of the TD into the venous system. Venous pressure upstream of the clamp (VP), thoracic duct pressure (TDP) and thoracic duct flow (TDF) were measured at control level, followed by a series of incrementally stepped up left innominate vein constrictions. The key findings were that at each step-up, TDF declined with both VP and TDP increasing sharply before falling back slightly over time to settle at an increased value. When the clamp was finally released, VP returned to its control value almost instantly, TDP returned to its control value after 17 minutes and TDF rose instantly to 260% of its control value before falling back more slowly towards it. The authors concluded: “...a rise of pressure in the portion of the venous system into which the thoracic duct enters the venous circulation may interfere with the drainage of lymph from the thoracic duct into the venous system and reduce considerably the flow of lymph in the thoracic duct.” Also: “The fact that, once the venous occlusion is released, the lymph flow rises above the value it had before the venous occlusion then comes back to it gradually, clearly indicates that the rise in innominate vein pressure leads to accumulation of lymph in the lymphatic system and/or the interstitial spaces.” For illustrative purposes here, the data from their Table 1 (7) are shown in graphical form in Fig. 2. This shows the relationship between VP and TDP,

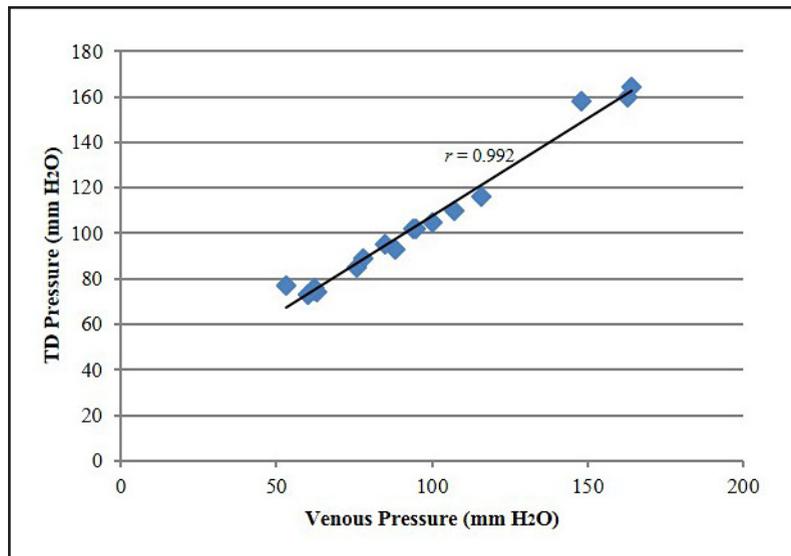


Fig. 2. Correlation ($r=0.992$) between thoracic duct pressure as a result of increased venous pressure produced experimentally in normotensive dogs by occluding the left innominate vein. Graph generated from original data obtained from Table 1 in Wegria et al (7).

including the declining values towards stability after the step-ups. The correlation coefficient (r) of 0.992 is clear evidence that the venous pressure at the drainage point exerts a backpressure on the thoracic duct lymph. Crucially, this experiment was conducted on normotensive dogs, so lymph formation would not have been accelerated by systemic venous hypertension.

Dumont et al (8) performed TD lymph drainage in five patients with severe CHF and found that by openly cannulating the outflow end of the TD the lymph flowed at 4 to 12 times the normal rate and the signs of CHF markedly diminished. However, when the cannula was raised to neck level (to simulate raising venous pressure), TD flow and pressure fell and the signs of CHF reappeared. These findings were subsequently confirmed and extended in a larger cohort of patients (9).

Hence, these studies clearly demonstrate that venous pressure elevation at the lymph drainage point creates a substantial backpressure on TD lymph flow and consequently raises TD pressure.

Components of Thoracic Duct and Intestinal Lymphatic Pressure

Szabo and Magyar (10) investigated the effects of elevated systemic venous pressure and flow throughout the lymphatic circulation in dogs. In one group of dogs, systemic venous hypertension was created by inducing asbestos pericarditis. (In this condition, the pericardium hardens to impair cardiac filling and reduce cardiac output, thus creating generalized venous congestion.) They showed that this maneuver increased capillary filtration and lymph production. In a second group, hypoproteinemia was induced by plasmapheresis, i.e., washing of the blood cells to remove proteins. In this condition, the blood oncotic pressure would be reduced (to increase the NDF), which would also increase capillary filtration but without the hydrostatic effects of generalized venous hypertension. A third group of normal dogs was used as controls.

Recordings were taken of jugular venous pressure (JVP) as a measure of venous pressure near the TD drainage point, and of

TD pressure in the intact lymphatic system. A strong correlation between these parameters was found ($r = 0.812$), thus confirming the venous backpressure in the Wegria study (7). [The correlation coefficient (r) in the Wegria study was even stronger, as the data there were taken from a single animal.] The TD was then cannulated, first with free outflow and then with the cannula connected to a calibrated vertical column. The ascending height of the lymph in the column was taken as an 'outflow obstacle' which represented the JVP when the column height equated with the measured JVP. At flow stoppage the height of the column was taken as the TD end pressure. The lymph free outflow (i.e., formation rate) was increased approximately four-fold over the control group for both the pericarditis and hypoproteinemia groups, and the TD end pressure was elevated for both groups, with that for the pericarditis group being the higher of the two. The increase in TD pressure for the hypoproteinemia group suggests that this is due solely to a forward pressure from the increased lymph formation, as the JVP is assumed normal, so there would be no elevation in the backpressure. For the pericarditis group it is proposed here that the heightened TD pressure increase is due to the combined effect of increased forward pressure from the lymph and the increased backpressure at the JVP.

In the Dumont et al study (8), the authors comment that "the thoracic-duct drainage system is a 'phylogenic late-comer' and transport of unusual volumes of lymph is limited," i.e., the structure of the junction itself provides an obstacle which determines the forward pressure exerted by the lymph flow, regardless of the magnitude of the venous pressure at the drainage point.

The action of the backpressure is also confirmed in a Fontan context by documented evidence of PLE and chylothorax after the intermediate Glenn operation (11) where the SVC is anastomosed to the branch pulmonary arteries but the IVC is not. In this case, the

neck pressures would be elevated but without the increase in hepatosplanchnic capillary filtration which is normally the predominant source of lymph production (12).

Furthermore, Földi and Papp (12) investigated the role of the lymph circulation in CHF in dogs. Venous pressures in the upper and lower body were elevated separately to 20 cm H₂O using adjustable ligatures on the SVC and IVC. Lymph flows were measured using both an open drainage cannula and in the intact closed system (the "true flow"). With no venous pressure elevation, the mean lymph flow rate was 1.35 mL/min into an open cannula and 0.82 mL/min back into the closed venous system. With generalized venous hypertension (i.e. with the SVC and IVC both constricted), the mean open flow rate increased to 6.16 mL/min (a factor of 4.6), whereas the mean closed flow rate increased to 1.48 mL/min (a factor of only 1.8). It is concluded that with generalized venous hypertension, there is a very substantial increase in lymph production, but dynamic insufficiency of the lymphatic system results, with unreturned fluid accumulated as edema. The high systemic venous pressure inherent in a Fontan circulation therefore impairs the efficiency of the lymphatic circulation as a corollary to the increase in lymphatic pressures.

It is concluded from these studies that there are two distinct pressure elements which substantially determine the TD pressure – a forward pressure from lymph formation and a backpressure from the venous pressure at the lymph drainage point. In a completed Fontan circulation, TD pressure would be elevated by both the forward and backward pressure components, and lymphatic efficiency would be impaired. Moreover, in Fontan patients with PLE, capillary filtration, lymph flow, and TD pressure would be further elevated by the oncotic effect of hypoproteinemia (to a variable extent, counterbalanced by a fall in tissue oncotic pressure) as well as the hydrostatic effects of the raised venous pressure.

The investigation by Szabo and Magyar (10) referred to an earlier demonstration that showed an increase in the TD end pressure raised the pressure in the abdominal (i.e., hepatic/intestinal) lymphatics but not in the peripheral lymphatics. A strong positive correlation was shown between the hepatic trunk and TD pressures ($r = 0.931$) and a rather weaker, but significant, positive correlation between the intestinal trunk and TD pressures ($r = 0.600$). In particular, for one dog from the pericarditis group, the intestinal pressure stabilized at 8.0 mmHg (up from 3.6 mmHg at free outflow) for a TD end pressure of 11.8 mmHg (68% of TD pressure).

A series of experiments on sheep was conducted by Drake and colleagues to analyze the effects of raised venous pressure on the intestinal lymphatics. In one of these (13), the neck vein pressure was increased in steps from a baseline of 0.8 cm H₂O to 37.4 cm H₂O. With normal lymph flow volume, the intestinal lymphatic pressure increased from 7.4 cm H₂O to 11.4 cm H₂O but with the infusion of 1 mL/min of Ringer's solution directly into the lymphatics, this increased further to 24.6 cm H₂O. Hence, both of the pressure components identified for the TD were present. In a later experiment (14), neck vein pressure was increased from 1.2 cm H₂O to 17.3 cm H₂O by an intravenous infusion of Ringer's solution. This resulted in an increase in the intestinal lymphatic pressure from 12.5 cm H₂O to 24.6 cm H₂O, thus confirming the earlier findings by Szabo and Magyar (10).

It can be concluded from these studies that with an elevation of venous pressure, any elevated TD pressure would be reflected upstream to the lymphatic vessels; and, furthermore, the same pressure components would apply to the intestinal lymph vessels as the TD.

The study by Witte et al on CHF patients (9) included an examination of the protein content in the TD lymph. They found that the average total protein content of lymph was 46% of plasma compared to 72% in control subjects. Normally, TD lymph arises

mainly from the liver and extrahepatic portal beds. Liver sinusoids have discontinuous capillaries which are freely permeable to plasma protein that produces a low oncotic gradient between the plasma and interstitial fluid. Even a small increase in hydrostatic pressure with little oncotic opposition will therefore produce an increase in filtration with the increased lymph take-up relatively rich in proteins. In contrast, intestinal mucosa has fenestrated capillaries which are less permeable, thus holding relatively more protein in the vascular compartment when fluid filtration is increased, reducing the protein concentration in the intestinal lymph. The dilution of the total protein content in the TD in the CHF patients therefore suggests that with increased systemic venous pressure, a greater proportion of the total lymph arises from the intestinal beds where lymph protein concentration is lower, thus disproportionately increasing the flow and pressure increase in the intestinal lymphatic vessels to intensify their engorgement.

Mechanism of Intestinal Protein Loss

Two distinct mechanisms have been put forward by different sources for the escape of proteins into the gut: 1) the rupture of lacteals or overstretching of their endothelial cells due to lymphangiectasia (2,5), and 2) a breakage in the integrity of the intestinal mucosa to permit seepage through to the gut lumen (15,16). The second of these is well argued in group studies by Rychik and Yang (15) and Ostrow et al (16) who found that: "MVR (i.e., mesenteric vascular resistance) is elevated after the Fontan operation compared with MVR in those with a normal 2-ventricle heart. Furthermore, patients with PLE have increased MVR compared with those after Fontan operation without PLE." (15); and "We found a significantly lower ratio of mesenteric-to-celiac artery flow in the AEPL (abnormal enteric protein loss) group, suggesting that diminished mesenteric flow may play a role in the disease." The logic

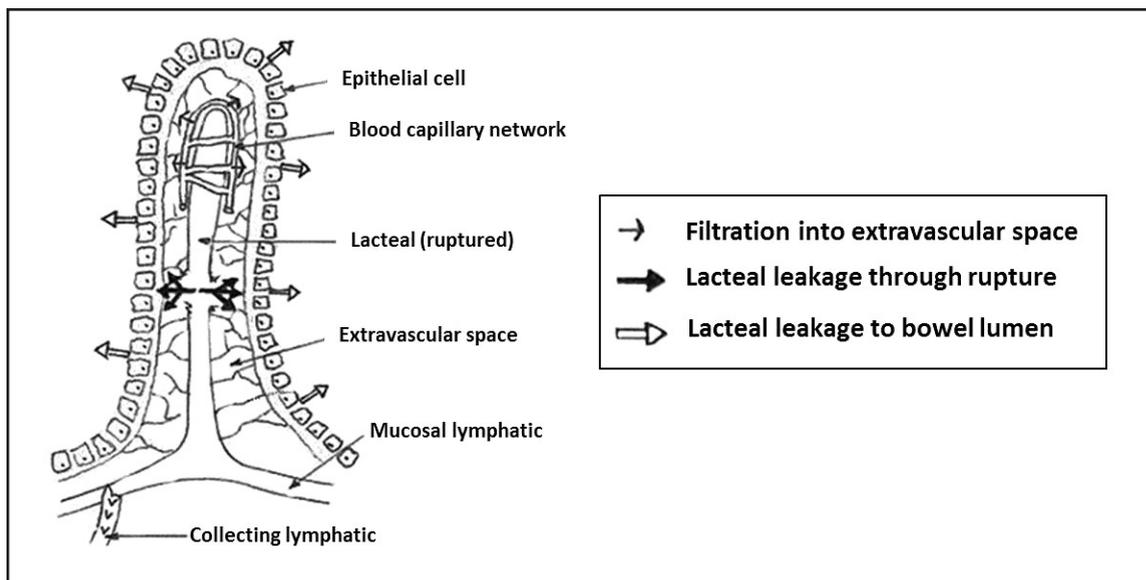


Fig. 3. Potential mechanisms of protein escape at the intestinal lacteals. See text for further details. Modified from Fig. 1 depicting normal anatomy in Miller and Newberry (17).

here is that with the low cardiac output in Fontan patients, a ‘steal phenomenon’ exists whereby some of the mesenteric artery flow is diverted to the celiac artery, which protects the vital organs. The authors conclude that: “Impaired mesenteric perfusion may result in modulation of intestinal cell membrane function and promote cellular apoptosis, factors which contribute to increased intestinal permeability and protein leakage” (16).

The various treatment modalities support this separation, e.g., MCT diets to mitigate lacteal rupture and the administration of heparin and/or steroids to stabilize intestinal mucosal cells. It is proposed here that these mechanisms usually co-exist to explain the complete escape of proteins from the body. This is illustrated in Fig. 3. [adapted from (17)].

Normally, when the tissue fluid volume swells with increased capillary filtration, radial anchoring filaments of the endothelial lacteal wall cells exert a tension, opening up the lumen to permit the inflow of the filtrate, thus returning proteins and other substances via the collecting vessels to the blood. However, when lymph vessels are dilated

under high pressure, the lacteals rupture, with an outpouring of lymph (including its entrapped proteins, lymphocytes and other constituents) into the extravascular space. For escape, the proteins then must pass through the mucosa and/or outer layers of the gut. It is postulated here that the barrier provided by the epithelial cells of the villi is compromised by other factors (15,16) and this, exacerbated by the rupture pressure, permits the seepage of proteins from the extravascular space into the gut lumen and elimination from the body. It is likely that this pressure may well also force out normally filtered proteins from the lacteal blood capillaries. Bulk loss of lymph (i.e., lymphorrhea and lymph-losing enteropathy), including contained cellular elements such as lymphocytes, may occur.

Essence of the Proposal for a “lymphatic right-to-left shunt”

Our proposal for treatment of PLE/LLE in “failing” Fontan circulations is to drain or divert the lymph arising from the intestines

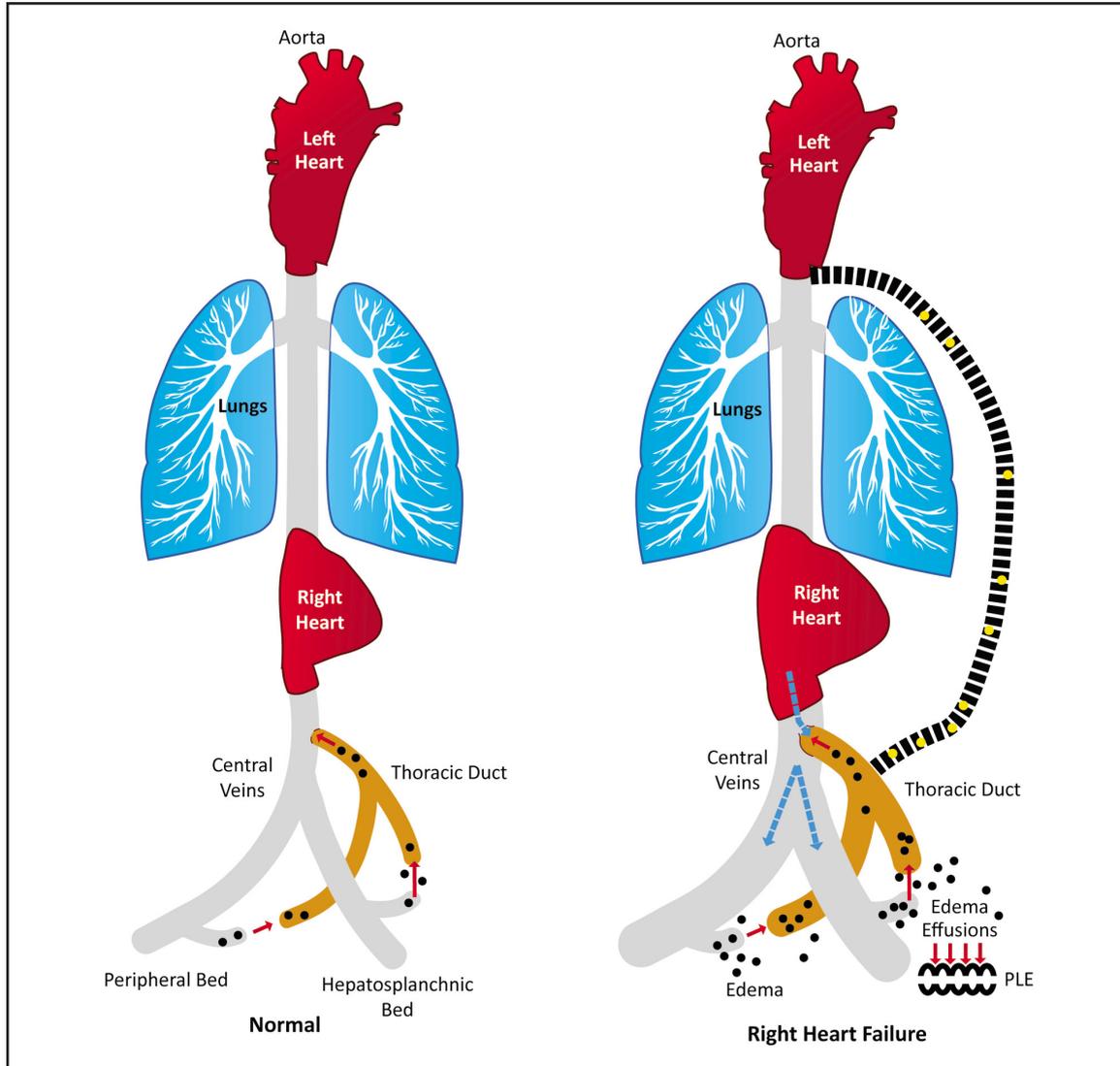


Fig. 4. Schematic comparison of thoracic duct lymph formation and return to the central venous system in right heart failure. Compared to the normal situation (left) where venous pressure is not elevated, lymph absorption/transport balances lymph formation (open circles) and lymphatic pressure is not elevated, right heart failure (right) is associated with generalized venous hypertension, which promotes increased lymph formation (open circles) in both peripheral and hepatosplanchnic beds. At the lymphatic-venous junction in the neck, local resistance combines with the elevated central venous pressure to impede lymph return (dashed arrows depicting higher venous pressure in central veins). When lymph return is inadequate to balance the increased lymph formation, edema appears in the form of tissue swelling/congestion, peripheral edema, visceral effusions, and PLE/LLE. Restoration of lymph balance by reducing lymph formation (lowering venous pressure) or by enhancing lymph transport to match the elevated lymph formation (in this case represented by the dashed connection from lymphatic to left atrium or pulmonary veins) should theoretically lead to resorption of the edema and resolution of effusions and PLE/LLE along with reversal of the associated renal-endocrine compensatory mechanisms. Fig. 5A-D illustrates that this is indeed the case in dogs with pure right heart failure and, we propose here, should be applicable to children with “failing” Fontan circulations by diverting the excess thoracic duct lymph into the left side of the heart (pulmonary veins or left atrium). Note that resulting lowering of central venous pressure and diminishing of edema is not shown in diagram as a functional result of the shunt. A and B modified after Witte et al (9).

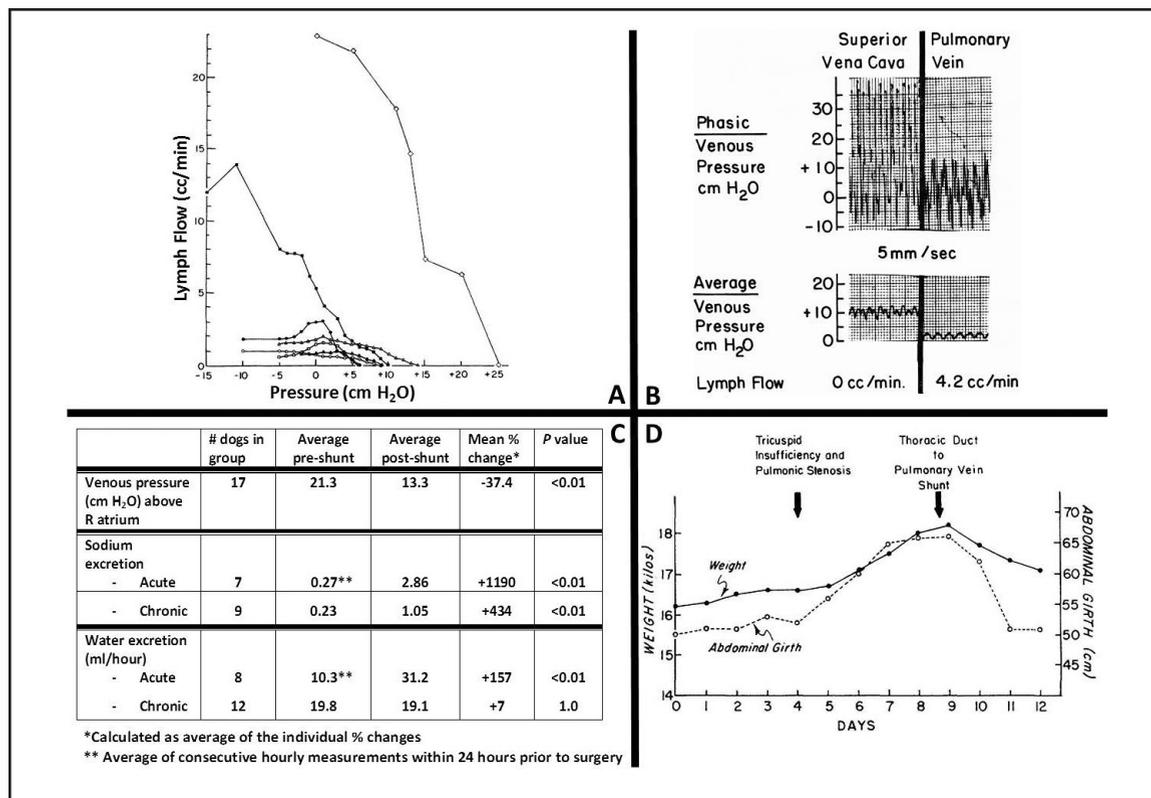


Fig. 5. Relationships between venous pressure and lymph flow in experimental pure right heart failure in dogs and effects of pulmonary vein shunts for treatment. A) Pressure and thoracic duct lymph flow in experimental right heart failure due to tricuspid insufficiency and pulmonic stenosis. Note the animal on the right who required venous pressures of over 25 cm H₂O before lymph flow ceased. B) An example of the relationship between venous pressure (superior vena cava and pulmonary vein) and lymph flow in this model of experimental right heart failure. C) Effects of thoracic duct to pulmonary vein shunts on venous pressure and sodium and water excretion in dogs with right-heart failure. D) Weight and abdominal girth in a typical dog before and after production of experimental right heart failure from tricuspid insufficiency and pulmonic stenosis and after thoracic duct-to-pulmonary vein shunt. Modified and composited with permission from Cole et al (18).

into a lower pressure region than the systemic venous angle, so that both the backpressure and structural obstruction to the outflow are relieved and lymph pressure is reduced, thus preventing or relieving lymph vessel and lacteal damage and protein intestinal leakage (Fig. 4). If lymphatic congestion is relieved by providing an easier drainage passage, sequestered tissue fluid could be expected to be drawn in to the lymphatic system, which would promote further capillary filtration and reduce venous pressure. The clinical studies of Dumont et al (8) and Witte et al (9) clearly demonstrated that external drainage

of thoracic duct lymph (without equivalent fluid replacement) rapidly and dramatically lowers elevated central venous pressure to or toward normal in patients with severe right-sided congestive heart failure. In the study by Dumont et al (8), the systemic venous pressures after open cannulation of the TD fell substantially; and in the follow-up study by Witte et al (9) on a larger cohort, the venous pressure fell from a mean of 32.9 to 14.0 cm H₂O. The fall in venous pressure was attributed to the improved lymph circulation, and it is likely that this would have been experienced to a lesser extent if the outflow

had been diverted to a lower pressure region rather than being openly discharged. Evidence of this is presented in a study by Cole et al (18) (see composite *Fig. 5*), who proposed a TD to pulmonary vein shunt as a possible treatment for right heart failure. This condition was induced experimentally in dogs by creating tricuspid insufficiency and pulmonary stenosis. In one dog typical of the group, mean pressure was 8.5 cm H₂O lower in the pulmonary vein than in the superior vena cava (SVC) (*Fig. 5B*). A lymphatic-venous shunt was created by a direct anastomosis between the TD and left inferior pulmonary vein. There was an immediate fall in systemic venous pressure (average 21.3 - 13.3 cm H₂O) as well as a rise in water and sodium excretion (*Fig. 5C*). Ascites diminished or disappeared in most dogs as exemplified in *Fig. 5D*.

As the CVP in a Fontan circulation must be elevated, it is conjectured that with the salutary fall in systemic venous pressure, the required transpulmonary gradient to passively perfuse the lungs would be maintained by autoregulation. Moreover, any reduction in excessive venous pressure in the hepatosplanchnic region would have an important salutary effect on the protection of liver and kidney function.

Lymphatic Surgery Considerations

The physiologic solution outlined here may present a challenge from an anatomic and surgical perspective, and sustaining the salutary effects longer term is not clear. Nonetheless, the ease, cumulative experience, techniques, tools, and patency rates in lymphatic microvascular surgery have advanced greatly (19) over the years since the experimental studies of Cole et al. A direct lymphovascular anastomosis of the thoracic duct at its terminus or in the mid-mediastinum to the left inferior pulmonary vein (under lower pressure than the central veins – *Fig. 5B*) (18) or the left atrium or alternatively through an interposition silastic

shunt to the left atrium from the thoracic duct, cisterna chyli, or an enlarged tributary could serve to decompress the hypertensive overloaded thoracic duct/hepatosplanchnic lymph system and thereby produce similar salutary changes to those seen in the dog model of right heart failure. This maneuver should relieve the central lymphatic (and also central venous) hypertension by using the systemic ventricle to handle the excess (lymph) fluid load, restoring lymph balance, and promoting excretion of excess salt of water retained, thereby paralleling the findings in dogs with experimental right heart failure (*Fig. 5C*) (18). It is possible that this decompression procedure could be done interventionally under MR-guidance with selective catheterization of the thoracic duct (20,21) without direct exposure in an open procedure, where prior surgery might render the operation and exposure of the thoracic duct technically difficult. In this setting, “gluing” of identified leaking lymphatics (e.g., with lipiodol as a radiopaque contrast and embolization agent) has been accomplished reversing chylous reflux and associated symptoms without necessarily relieving the underlying lymphatic obstruction (21). On the other hand, these procedures could be temporizing, e.g., as a “bridge to transplant.”

In respect to the necessary “lymphatic-venous right to left” connection, a pulmonary vein or the left atrium are the obvious destination points as these are the only sites in a Fontan circulation with normal (or near-normal) venous pressure. The supply point is less clear cut. The most obvious solution would be to sever the TD near the left venous angle and connect the outflow end to the pulmonary vein or left atrium. A prosthetic extension seems preferable to mobilizing the TD to preserve the important lymphatic collaterals to the right lymphatic duct and to the azygos, intercostal, and lumbar veins, which would act as a safety factor in the event of a thrombotic event in the main outflow. This arrangement also has the

advantage that the obstruction to lymph outflow from other regions (e.g., pleural or peritoneal effusions) would also be relieved. This concept is supported by patient #13 with pulmonary atresia and an intact ventricular septum in Dori et al (21) who had a spontaneous (natural) thoracic duct to pulmonary vein shunt that led to a cerebral embolism of the lipiodol (MR documentation in *Fig. 1* in reference 22).

Other more localized supply points could be considered, subject to surgical technicalities, with long-term patency being of paramount importance. Fundamental to these approaches is optimal delineation of the lymphatic anatomy (including normal variations and/or those anomalies possibly associated with congenital cardiac anomalies) and lymph dynamics (pathophysiology) preoperatively by non-invasive bipedal and even 4-limb lymphoscintigraphy (23,24) with SPECT-CT (25) of the chest and abdomen and, more invasively for even better delineation by MR lymphography through the inguinal lymph node (also used for selective gluing of leaking bronchial/intestinal lymphatics) (20,21). In the Fontan situation, the single ventricle function would also have to be assessed and monitored in terms of its ability to handle the increased fluid load. In experimental right heart failure (*Fig. 5*) and patients with “pure” right heart failure (both with intact left ventricular function), this would not present a problem.

With regard to the two elements to the escape mechanism described earlier, this proposal would affect only the accumulation of protein/stagnant lymph under high pressure in the extravascular space around the initial lymphatics. It would not preclude the concurrent administration of agents (e.g., heparin) to stabilize the mucosal epithelial wall.

SUMMARY AND DISCUSSION

In spite of various treatments being tried for PLE in Fontan patients and with

improved aftercare, the incidence of PLE remains considerable and the morbidity and mortality remains high (2,5,7). The emergence of any new treatment modality would therefore be welcome.

It is generally accepted that the etiology of PLE in Fontan patients is not completely understood, but the implicit characteristics of a Fontan circulation of low cardiac output and/or high systemic venous pressure play a dominant role in its pathophysiology (1,7). It is supposed here that the primary cause of PLE in Fontan patients is an excessive TD lymph pressure caused by the combined effect of the forward pressure of increased lymph formation due to elevated systemic venous pressure in combination with the backpressure exerted by the venous system at the TD drainage point. This pressure is transmitted back to the intestines, resulting in lymphangiectasia with lacteal rupture and protein loss through a compromised mucosal integrity.

A “lymphatic-venous right-to-left” shunt – most appropriately between the TD and a pulmonary vein or the left atrium – would enable the lymph to drain into a region of substantially lower pressure thus relieving the venous backpressure and greatly improving the efficiency of lymphatic flow throughout the body. This would relieve the lymphangiectasia and hence reverse or alleviate the PLE, with the retention of proteins and restoration of fluid balance having a profoundly beneficial effect on general health. The proposal would be most effective in patients with the poorest hemodynamics where the pressures are highest (e.g., due to high pulmonary vascular resistance). The underlying pathophysiology and its amelioration could potentially be documented and monitored by advanced lymphatic imaging, non-invasively by whole body lymphangioscintigraphy (23,24) alone or further localized by SPECT-CT (25).

For chronic cases of PLE [infection may trigger episodic cases (26)], usually confirmed by alpha-1 antitrypsin clearance

and hypoalbuminemia, it is recommended that intestinal lymphangiectasia is also confirmed (by biopsy, ultrasonography, or scintigraphy) before choosing lymphatic surgery as the treatment option.

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This research is dedicated to my [HJ] grandson, Henry Bromberg, a 'failing Fontan' patient with PLE who died in July 2016 aged nine years whilst awaiting a heart transplant. It is hoped that new approaches to promote well-being and further prolong life for this condition will be developed in the absence of sufficient pediatric heart donors. We thank Jack Copeland, MD, former Professor and Head of Cardiothoracic Surgery at the University of Arizona for his helpful comments.

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