Venous Properties in a Fontan Patient with Successful Remission of Protein-Losing Enteropathy

A Possible Marker for Venous Stagnation over Central Venous Pressure

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Summary

We present the case of a 1-year-old boy who developed protein-losing enteropathy (PLE) within 2 months of a fenestrated Fontan procedure. His fenestration rapidly closed despite bilateral pulmonary stenosis (BPS). Subsequent to PLE onset, both fenestration and the bilateral pulmonary artery were reconstructed, and the patient's PLE had been in remission, with additive use of medications, for more than 2 years. Notably, although fenestration closed again and central venous pressure (CVP) reduction was minimal, the surrogates of venous return resistance were markedly suppressed as shown by increased blood volume, reduced estimated mean circulatory filling pressure, and suppressed CVP augmentation against a contrast agent. Taken together, dynamic characteristics of venous stagnation, rather than the absolute value of CVP, were ameliorated by the pulmonary reconstruction and use of medications, suggesting a significant role of venous property in the physiology of PLE. In addition, simultaneous measures of CVP and ventricular end-diastolic pressure during the abdominal compression procedure suggested a limited therapeutic role of fenestration against PLE in this patient.

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Key words: Fontan circulation, Venous characteristics, Hemodynamic, Fenestration

Protein-losing enteropathy (PLE) is a critical complication that can occur following the Fontan procedure, which is assumed to be the result of end-organ dysfunction induced by systemic congestion. Although this concept is supported by the fact that creation of fenestration may contribute to PLE remission, some of the patients who developed PLE had fenestration naturally closed despite optimal medications. We experienced a patient with hypoplastic left heart syndrome (HLHS) whose fenestration closed early after a Fontan procedure despite significant bilateral pulmonary stenosis (BPS), who developed PLE as early as 2 months after surgery. His PLE became remission after reconstruction of fenestration and release of PS. Intriguingly, venous characteristics had markedly changed while fenestration closed soon, and CVP was almost unchanged.

Case Report

A male infant diagnosed with HLHS had a fenestrated Fontan procedure at the age of 1 year. Cardiac catheterization prior to total cavopulmonary connection (TCPC) indicated a pulmonary arterial pressure (PAP) of 12 mmHg and a transpulmonary pressure gradient (TPG)

of 3 mmHg, with an estimated pulmonary resistance of 0.92 Um². His pulmonary arterial index was 122 mm/m², and the ventricular ejection fraction was 56%, with mild tricuspid regurgitation.

Within a few days of surgery, the fenestration flow became undetectable despite heparinization. The arterial oxygen saturation (SaO₂) increased to 97% with the percentage of inspiratory oxygen (FiO₂) at 60%, which was 94% with FiO₂ at 100% at the patient's intensive care unit (ICU) arrival after operation. Although ascites and pleural effusion kept the patient in the ICU, he became free of circulatory support using pulmonary vasodilators and diuretics and left ICU on postoperative day (POD) 10. As BPS was suspected by echocardiogram, cardiac catheterization was performed on POD 43. The hemodynamic study demonstrated CVP of 13 mmHg with a cardiac index (CI) of 2.7 L/minute/m². The pressure gradients between bilateral pulmonary arteries and TCPC conduit were 3 mmHg on average, suggesting significant BPS as Fontan circulation (Figure 1A). Percutaneous transluminal angioplasty for the bilateral pulmonary arteries was performed, but it was unable to resolve the stenoses. Coil embolization for aortopulmonary collateral arteries was also performed with the aim of improving Fontan circula-

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Figure 1. **A:** Contrast imaging indicating hypoplasia of bilateral pulmonary arteries. As described in the manuscript, a significant pressure gradient was detected between the conduit and bilateral pulmonary arteries. **B:** The Tc99m scintigram clearly indicated protein leakage to the digestive system, which confirmed the diagnosis of protein-losing enteropathy (PLE).

Table I. Hemodynamic Data

	Post TCPC before PLE	Post TCPC after PLE	Post re-TCPC
SaO ₂ (at cath lab entrance), %	95	95	97
CVP, mmHg	13	14	13
RVEDP, mmHg	8	8	8
CI, L/minute/m ²	2.7	3.4	3.6
Rp	0.7	1.2	0.8
Rs	16.3	10.4	13.2
HR, bpm	105	111	109
PG pull-back			
LPA-conduit, mmHg	3	3	2
RPA-conduit, mmHg	3	4	2

CI indicates cardiac index; CVP, central venous pressure; HR, heart rate; LPA, left pulmonary artery; RPA, right pulmonary artery; PG, pressure gradient; Rp, pulmonary arterial resistance; Rs, systemic arterial resistance; RVEDP, right ventricular end-diastolic pressure; and SaO₂, arterial oxygen saturation.

tion. The TPG was 3 mmHg, and the right ventricular end-diastolic pressure (RVEDP) was 8 mmHg, which was considered to be acceptable at this point, and we decided to follow him up as an outpatient. His medication included flosemide, tolvaptan, sildenafil, and ACE inhibitor.

Two months after the surgery, the patient was brought to the clinic with massive systemic edema. His body weight had increased by 2 kg (+25% of his body weight) as compared with his weight at his latest clinical visit, and serum levels of albumin and total protein were 2.4 and 4.6 g/dL, respectively. No proteinuria was detected, and the 99mTc-human serum albumin scans clearly indicated protein leakage to the digestive system; this convinced us the patient had developed PLE (Figure 1B). After continuous albumin infusion coupled with diuretics, systemic edema disappeared. Cardiac catheterization was performed to assess his hemodynamics (Table I). CI, CVP, mean PAP, and TPG were 3.35 L/minute/m² and 14, 10, and 3 mmHg, respectively. An IVC occlusion test increased the pressure distal to the occluded site from 14 mmHg to 28 mmHg.¹⁾ Blood volume (BV) estimated using Indocyanine Green (ICG) was 64.4 mL/kg. Augmented IVC pressure elevation by the occlusion test, with suppressed BV, implied augmented mean circulatory fill-

ing pressure (mcfP).^{2,3)} Mild abdominal compression implied reduced pressure gradient between ventricle and CVP, thus possibly compromised advantage of the fenestration (Figure 2A). Importantly, the increase in RVEDP was steeper than that of the increase in CVP, and the two pressure amounts became similar at 18–20 mmHg (Figure 2B). Accordingly, we suspected that fenestration closure might have resulted from the suppressed pressure gradient between the conduit and EDP, particularly when ventricular volume was loaded early after the operation.

Since both BPS and fenestration closure were considered to have affected the onset of PLE, surgical interventions to release the BPS and reconstruct the fenestration were implemented. Similarly to the original fenestration, a 4 mm punch-out in the conduit was made, and anti-platelet/coagulation was optimized. As acute increase of EDP could have resulted in another early closure of fenestration, we decided to keep the patient relatively dehydrated to avoid EDP augmentation, as implied by the abdominal compression procedure during previous cardiac catheterization. His SaO₂ was 95% with nasal oxygen supplementation of 3 L/minute. Despite efforts to keep the fenestration open, its signal faded on POD 28. At this point, SaO₂ increased to 97% with nasal oxygen supple-

Figure 2. **A:** Abdominal compression acutely increased ventricular end-diastolic pressure to the level of CVP, which was likely to decrease the pressure gradient between CVP and ventricular diastolic pressure. **B:** The relationship between CVP and EDP during abdominal compression, as indicated by the arrow (A). CVP indicates central venous pressure, and EDP, end-diastolic pressure.

mentation of 1 L/minute. The patient was discharged with macitentan and isosorbide dinitrate tape, in addition to his previous medications.⁴⁾

Cardiac catheterization at 6 months after surgery exhibited the similar CVP with a mildly suppressed BPS gradient (Table I). CI and pulmonary resistance were also similar to those assessed at PLE development. Although augmentation of EDP corresponding to abdominal compression was similar or even suppressed compared with that in previous catheter assessments (Figure 3), BV markedly increased from 64 to 80 mL/kg (Table II). Decreased estimated mcfP, measured by inducible venous stagnation due to IVC occlusion,^{1,2)} suggested a suppressed compensatory force to mobilize the venous pool to the lung, which, in turn, represented decreased venous return resistance and thus organ decongestion. In compliance with this, CVP augmentation after a similar dose of a contrast agent was suppressed compared with the previous one. The contrast imaging of the superior vena cava, innominate vein, and inferior vena cava indicated only a few, tiny veno-venous shunts, similar to those in previous cardiac catheterizations.

The SaO₂ at the latest clinical visit was 97% with FiO₂ at 21%. Notably, the patient has been in remission for more than 2 years without fenestration, implying significant benefits from the efforts, such as releasing pulmonary stenosis and giving additional medications, to reduce venous stagnation, even though the decreases in CVP and the PS pressure gradient were small.

Discussion

Retrospective studies have reported that PLE occurs in 5% to 15% of patients within 2.5 years of undergoing a

Fontan procedure.⁵⁻⁷⁾ Although the mechanisms by which PLE develops in the patients with Fontan circulation have yet to be elucidated, hemodynamic issues, including high CVP, congestion of the superior mesenteric artery, and inflammatory cytokines, are regarded as its plausible causes.^{8,9)} Although fenestration was expected to contribute to venous decongestion,¹⁰⁾ it naturally closed even with significant BPS. Following the onset of PLE, BPS release and fenestration recreation were performed. Notably, no PLE recurrence has been observed for more than 2 years, although the fenestration closed again, and CVP suppression was mild.

The fenestration closed spontaneously again despite intensive use of anti-coagulants; therefore, the regression of PLE was likely to have been a result of the release of BPS or additive medications. Although the pressure gradient of BPS was decreased by only 1 mmHg, and CVP was similar, the venous return resistance, which is the outlet resistance of end-organs, appeared to have been reduced following surgery as evidenced by increased BV with reduced mcfP and suppressed CVP augmentation against contrast imaging (Table II).²⁾ Thus, the release of BPS and use of pulmonary vasodilators coupled with a nitrous oxide donor appeared to have improved the venous property, which suppressed dynamic CVP augmentation against fluctuation in volume conditions. Notably, this finding implied that alternation of the venous property had been activated as the compensation to counteract compromised preload reserve, including a stiffened ventricular property, stenotic pulmonary artery or augmented pulmonary resistance, in the Fontan circulation.

A fenestration should help decongestion if the diastolic function is optimal. The rate for natural closure of fenestration is reported to be between 26% and 40% per

Figure 3. Abdominal compression acutely increasing ventricular end-diastolic pressure to the level of CVP, which was likely to decrease the pressure gradient between CVP and ventricular diastolic pressure (red dotted arrow: before abdominal compression, red solid arrow: after abdominal compression). CVP indicates central venous pressure, and EDP, end-diastolic pressure.

year¹¹⁻¹³) and is considered to be multi-factorial. Surgical issues are one of the primary reasons; however, we employed the baffle punch-out method, which is reported to be robust for maintaining its patency.¹⁴) Traditionally, fenestration has been considered to close naturally when pulmonary circulation is so excellent that the circulation can be sustainable without it,¹⁵) although hemodynamic analyses in the Fontan patients have suggested that the early closure of fenestrations might be associated with a stiffened ventricular property.¹⁶) In the case presented here, abdominal compression during cardiac catheterization indicated a reduced pressure gradient between EDP and CVP at 18-20 mmHg or higher, which suggested that the patient's ventricular end-diastolic pressure volume relationship at relevant preloading was too steep to further increase the preload by a small increment in diastolic pressure. This finding suggested that small increments of ventricular volume loading are likely to augment EDP, and the pressure gradient between CVP and EDP can thus eas-

ily decrease. We speculated that the unfavorable diastolic function coupled with postoperative myocardial edema caused suppression of the pressure gradient between the conduit and the EDP when small fluctuations in volume conditions were loaded, which then contributed to the early closure of the fenestration. The repeated natural closure of the fenestration in this patient despite anticoagulation supports this concept.

Taken together, venous return characteristics, rather than the absolute value of CVP, might be useful dynamic markers of venous stagnation and thus end-organ dysfunction, including PLE. For patients who have a stiffened ventricular property, the exertion of fenestration is barely attained; thus, the release of venous stagnation by means of surgical or pharmacological interventions could be the only solution for PLE.

Table II. Venous Property Before and After Surgical Intervention

	Post TCPC, after PLE	Post re-TCPC, after a year
IVC occlusion		
Mcfp, mmHg	45.1	39.1
ICG		
BV, mL/kg	64.4	80
Contrast imaging		
Pre CVP, mmHg	12	13
Post CVP, mmHg	16	15

BV indicates blood volume; CVP, central venous pressure; ICG, indocyanine green; IVC, inferior vena cava; mcfP, mean circulatory filling pressure; PG, pressure gradient; PLE, protein losing enteropathy; and TCPC, total cavo-pulmonary connection.

Conclusion

The absolute value of CVP alone may not properly indicate venous stagnation in the Fontan patients. Since the release of pulmonary stenosis or medications to reduce pulmonary resistance have provoked alteration in venous characteristics coincident with persistent PLE remission, dynamic venous properties, which are assessed by loading tests including volume loading or depletion, might be the promising guide for preventing Fontan-associated end-organ dysfunction. Although the pulmonary resistance may confound EDP augmentation, the abdominal compression procedure might be effective in detecting a non-responder of fenestration therapy against PLE.

Disclosure

Conflicts of interest: None.

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