Korean Circ J. 2022 Aug;52(8):621-622
https://doi.org/10.4070/kcj.2022.0166
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Editorial

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Protein-losing Enteropathy: A Big Challenge in Fontan Circulation

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▸ See the article "Long-term Outcome of Fontan-Associated Protein-Losing Enteropathy: Treatment Modality and Predictive Factor of Mortality" in volume 52 on page 606.

OPEN ACCESS

Received: Jun 8, 2022
Accepted: Jun 21, 2022
Published online: Jul 5, 2022

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Funding
The author received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest
The author has no financial conflicts of interest.

Data Sharing Statement
The data generated in this study is available from the corresponding author upon reasonable request.

Protein-losing enteropathy (PLE) is a serious complication in patients with a Fontan circulation, which is an 'acceptable' palliative strategy to save patients with various kinds of the functionally single ventricle. The pathophysiology of PLE in Fontan patients is unknown and thought to be multifactorial; a genetic background, abnormal anatomy of the lymphatic system, altered mesenteric circulation, or association with Fontan hemodynamics, including high central-venous pressure, a chronic low cardiac output state, or systemic ventricular dysfunction.[1] Therefore, the treatment strategy is still complicated. Various kinds of medical, interventional, and surgical modalities have been tried, but a universally accepted effective treatment strategy has not been identified yet, and the long-term outcome is still poor.

In this issue of the *Korean Circulation Journal*, Yoon et al.[2] performed a retrospective review of patients with a Fontan-associated PLE at 2 institutions in Korea from 1992 to 2018, aiming to investigate the clinical characteristics, treatment response, and outcomes of Fontan-associated PLE. A total of 38 out of 832 patients with Fontan circulation were diagnosed with PLE, an incidence of 4.6% at 26 years. Various medical and/or surgical therapeutic modalities were used. Fourteen patients (37%) died during the study period, with freedom from death of 81.6% at 5 years and 76.5% at 10 years after the diagnosis. Types of treatment did not affect survival or death, though Fontan conversion was associated with mortality in this cohort. Independent risk factors of mortality were New York Heart Association functional class III or IV, low aortic oxygen saturation (<90%), and ventricular dysfunction. Ten patients (26%) showed a resolution of PLE, which was defined as normal laboratory tests and no clinical symptom associated with PLE lasting for at least 3 years, 6 patients with medical treatment alone and 4 with surgical or interventional treatment.

They concluded that although there is no definitive treatment, the survival rate of patients with Fontan-associated PLE has improved.

This study showed again a gloomy picture of Fontan-associated PLE with a low resolution rate and high mortality. The authors' conclusion of improved survival is not based on their data but based on the historical comparison. The survival rate of patients is significantly higher in this study than in the report by Mertens et al.[3] in 1998, which reported a 5-year survival of 59% and a total mortality rate of 50%. However, the mortality is worse than in the study by John et al.[4] in 2014, which reported a survival rate of 88% at 5 years. Recently, Schleiger et al.[5] reported a survival rate of 96.1% at 5 years, but 70.5% at 10 years, still showing high long-

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term mortality rates. In another study by Sharma and collegues[6] using the Australia and New Zealand Fontan Registry in 2021, freedom from death or transplant was 70% at 5 years, 65% at 10 years, and only 43% at 15 years after the diagnosis, with no difference between eras (pre-2000 vs. post-2000). Therefore, the conclusion at present is the outcomes of Fontan-associated PLE are still very poor despite using the full range of medical and surgical treatment options, and a universally accepted effective treatment strategy is not identified yet. The declarative statement, "comprehensive assessment and individualized treatment strategies" is still valid.

In terms of risk factors for mortality, the reported results are still conflicting. John et al.[4] reported that decreased survival was seen in patients with high Fontan pressure (mean >15 mmHg), decreased ventricular function (ejection fraction <55%), and New York Heart Association functional class > II at diagnosis. Schleiger et al.[5] reported medical therapy with budesonide and pulmonary vasodilator therapy in combination was associated with improved survival. In addition, older age at Fontan was the only predictor of poor prognosis.[6] In the present study, Fontan pathway pressure, pulmonary vascular resistance, age at PLE diagnosis, and the era of Fontan surgery were not significant risk factors for mortality. Further study is needed to elucidate this issue. In addition, the risk factors of developing PLE, not mentioned in the present study, is also an important issue to study in the future.

The study has several limitations: the small sample size, a retrospective study with incomplete data collection, and center- or physician-related different approaches to evaluate and treat patients, which might hinder making concrete conclusions. Nevertheless, it is noteworthy that this study provides a comprehensive description of Fontan-associated PLE including clinical characteristics, treatment options and responses, and long-term outcomes for a long study period (26 years) in Korea, firstly. The results will help us broaden the scope of understanding of Fontan-associated PLE and provide an important resource for future study. Recently, the Korean Fontan Registry has launched, and nearly 1,800 Fontan patients were registered from 10 institutions (unpublished data). We may look forward to more insightful understandings of Fontan circulation and associated complications and better care for the patients in the future.

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