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The Need to Define Treatment Goals for Protein-Losing Enteropathy in Fontan Care and Research

We read with interest the recent paper by Itkin et al. (1). The authors are to be commended for their effort. However, the results should be viewed in the context of specific limitations.

First, the serum albumin level is frequently being used as a surrogate endpoint in Fontan patients with protein-losing enteropathy (PLE) (1,2). For a surrogate endpoint to be a meaningful substitute for clinical outcome, the changes induced by a therapeutic intervention (liver lymphatic embolization) on the surrogate (serum albumin level) are expected to reflect alterations in a clinically meaningful outcome measure (remission, major adverse events, survival) (3). As a surrogate endpoint, serum albumin level, however, does not fulfill this important criterion (3). A recent study demonstrated that serum albumin level was not able to discriminate between PLE patients who survived and those who did not (2). Furthermore, PLE in Fontan patients is a complex and heterogeneous disease. Patients often have fluctuating serum albumin levels not induced by an adjustment in their treatment regimen. Although enteric protein loss is the hallmark of PLE, other important cardiac and noncardiac features may all significantly contribute to clinical outcome (2). Even when, in theory, the serum albumin level would be a valid surrogate endpoint in Fontan research, the therapeutic effect on clinical outcome in the study by Itkin et al. (1) would have been overestimated because the effect on the surrogate, although statistically significant, was not of sufficient size and duration (mean change in albumin level 1.50 ± 1.03 g/dl, need for several procedures, duration of 4 months) in those patients with a treatment effect to predict a meaningful alteration in clinical outcome (1,3). Therefore, the results of liver lymphatic embolization should be interpreted with caution, because this surrogate endpoint can yield misleading conclusions. Although the authors also used PLE symptoms to assess the effect of the intervention, it is not clear how symptomatic improvement was quantified. When used subjectively, the results of symptomatic improvement may be biased.

Second, the Central Illustration and Table 3 (1) are somewhat confusing. Table 3 shows that the current albumin level of Patient #5 is 5.2 g/dl. However, the central illustration demonstrates a current albumin level of only 4.0 g/dl, thus showing a significant decrease in albumin over time. In addition, the albumin level of Patient #4 seems lower, and the current albumin level of Patient #1 seems higher (around 2.2 g/dl) than stated in Table 3 (1).

Third, the duodenum as the site of lymph leakage in Fontan patients with PLE has not been reported previously (1). However, duodenal lymphatic abnormalities have been observed in patients with celiac disease and PLE (4). Did the authors exclude celiac disease in their patients?

Taken together, the study by Itkin et al. (1) underscores the urgent need to develop validated outcome measures to assess disease severity and to quantify the true effectiveness of a therapeutic intervention in Fontan patients with PLE.

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REPLY: The Need to Define Treatment Goals for Protein-Losing Enteropathy in Fontan Care and Research

We appreciate the interest of Dr. Dam and colleagues in our work (1) and their thoughtful comments.

The main goal of our study was to describe the pathophysiological mechanism of loss of protein in patients with Fontan physiology complicated by protein-losing enteropathy (PLE). Using the technique of liver lymphangiography, we discovered significant leakage of protein-rich liver lymph into the duodenum, a unique finding not previously appreciated, and a potential area for therapeutic intervention.

The primary goal of embolization of the liver lymphatic ducts in our study was the improvement of patients' symptoms and quality of life, which we demonstrated as being concomitant with a temporally associated increase in serum albumin levels. Serum albumin is recognized as an important marker of disease severity in Fontan PLE, with multiple studies using this measure as an acceptable surrogate ranging from looking at the epidemiology of the condition to treatment responses and end-organ consequences (2–4). In essence, PLE correlates directly with hypoalbuminemia—and any management strategy that improves albumin levels is considered therapeutic. We can only hope that liver lymphatic embolization with a sustained increase in serum albumin levels will increase patients' survival as well; however, only longer-term studies can answer this question. Nevertheless, even temporary reversal of PLE with improved albumin levels can potentially improve the status of such patients by reducing the complications and frailty related to chronic albumin loss.

We agree with Dr. Dam and colleagues that serum albumin level and symptoms can fluctuate. However, in patients P4, P5, and P7 the initial improvement of symptoms and the albumin level increase persist and is sustained to the date of this letter. This is not a random variation phenomenon. The follow-up is now close to 1 year, and we believe we can now refer to the outcome of liver lymphatic embolization treatment as a remission (but not yet a cure).

Lymphangiectasia is a frequent finding in a variety of diseases, including celiac disease, as mentioned. Screening for celiac might be interesting, but statistically would not identify common positivity, and only a very rare celiac has significant protein loss, and not to this magnitude.

In conclusion, we continue to investigate the importance of the liver lymphatic circulation in patients with right-sided heart failure and its contribution to the development of PLE in those with a Fontan circulation. Our hope is that, by identifying the mechanism for protein loss (as we have achieved) and further developing these interventional techniques, we can improve the quality and quantity of life for these patients.

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