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Biomarkers and the Fontan Circulation

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Although the dramatically improved survival of children with single-ventricle heart disease with Fontan circulation in the recent era is a tremendous accomplishment in pediatric cardiology and cardiac surgery, it has been accompanied by a growing realization that Fontan circulation is largely a state of compensated heart failure at risk for decompensation. Fontan failure occurs in numerous ways with unpredictable timing.[1] Often heart transplantation is the only potential therapy, but patients who have undergone a Fontan palliation are at high risk for posttransplant morbidity and mortality, making it a nonideal therapeutic option.[2] The ability to identify a patient heading for worsening Fontan failure would allow trials of therapy that could slow progression of the failing circulation. Predicting future Fontan failure could also identify patients needing transplant evaluation before the morbidities that accompany Fontan failure worsen their transplant candidacy. Recent attention has turned to how best to identify patients progressing toward Fontan failure before they reach late stages.

With their article, "Galectin-3 Is Elevated and Associated With Adverse Outcomes in Patients With Single-Ventricle Fontan Circulation," Opotowsky and colleagues made a significant contribution to the Fontan failure literature with their investigation into galectin-3 serum levels in Fontan patients.[3] The authors found that Fontan patients with elevated galectin-3 serum levels are at higher risk of nonelective hospitalization or death. In addition, the authors offered fascinating hypotheses that galectin-3 is not only a biomarker for Fontan failure but also is potentially directly involved in the pathogenesis of Fontan-related ascites, which, if true, offers a new therapeutic target in this difficult population. A biomarker that can identify those at risk for poor outcome while helping explain some of the mechanistic reasons for the poor outcome would be particularly useful. This study was unique, relative to other studies of biomarkers in this cohort, in that it included longitudinal follow-up and outcomes data. This addition allows the results to be viewed within a broader context and adds to the importance of the study.

Although the study by Opotowsky et al is sound and insightful, it is challenged by many of the same limitations that other investigations into Fontan biomarkers have encountered: (1) The patient numbers, although reasonable for a Fontan study, are still quite limited; (2) the differences found in serum concentrations between at-risk and standard Fontan patients were small; (3) the outcomes were limited in number; and (4) the serum concentrations were measured only once per patient, severely limiting the ability to understand how these galectin-3 levels vary over time and how they could be used for serial monitoring. Albeit a promising start, the results must be viewed as from an initial pilot study only; further study is warranted.

Many other investigators have sought to identify biomarkers that could predict Fontan failure. Brain natriuretic peptide (BNP), a relatively sensitive biomarker for many other forms of heart failure, has limited utility in the Fontan population. In an analysis of the Pediatric Heart Network's Fontan cross-sectional study, Atz and colleagues found that BNP was within the normal range in the majority of patients with Fontan physiology, and high serum BNP had only weak associations with suboptimal Fontan outcomes. The authors concluded that routine use of BNP as a surveillance tool was not warranted.[4] Similar to BNP, N-terminal pro-BNP has been shown to vary in Fontan patients with levels that are independent of cardiac functional status.[5] Other neurohormonal activity markers have been studied. Kolcz and colleagues found a significant correlation between endothelin-1 serum concentrations and patient exercise performance, which could be used as a proxy for poor tolerance of Fontan circulation but is nonspecific.[6] Kojima and colleagues examined the usefulness of red blood cell distribution width in Fontan patients and discovered a significant negative correlation with mixed venous saturation and positive correlation with central venous pressure.[7] Red cell distribution width may thus be an easy marker for impaired cardiac index

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and impaired Fontan circulation, but no outcome associations were sought in this study. Avitabile and colleagues examined the relationship between insulin-like growth factor 1 and markers of disease severity including BNP and cardiac index.[8] They found a negative correlation of insulin-like growth factor 1 and BNP and a positive correlation between insulin-like growth factor 1 and cardiac index, suggesting a potential relationship between mediators of growth hormone and disease burden.

Fontan biomarker investigations have not been limited to measurements of serum proteins. Endothelial function has been demonstrated to be abnormal in Fontan patients and associated with reductions in patient cardiac output during tilt testing.[9] Endothelial function makes an interesting therapeutic target[10]; however, its variation over time and impact on Fontan failure remains unknown. Liver fibrosis and cirrhosis in Fontan patients is an increasingly recognized and concerning complication of Fontan circulation. Although serum biomarkers and measures of liver function have very limited utility in this disease, noninvasive assessment of liver stiffness as a proxy for fibrosis shows promise and has been associated with unfavorable Fontan hemodynamics.[11,12] The temporal changes in these measurements and their ability to predict Fontan outcomes have yet to be adequately examined. Renal dysfunction is also prevalent in Fontan patients. Kidney-specific biomarkers, such as urine microalbumin/creatinine ratio, may be able to detect renal injury from Fontan circulation in the absence of other evidence of circulatory insufficiency.[13] Again, the ability of these biomarkers to predict kidney or Fontan failure needs further study.

Interest in finding markers for Fontan progression is clearly present in the cardiology community, and the aforementioned pilot and initial investigation studies are only a sample of the potential markers that could be used. These initial investigations are necessary to establish biological and clinical feasibility for each potential measure, but they must be viewed as a first step only. The majority of biomarker studies describe the candidate marker at a single moment in time, often remote from the initial Fontan surgery. Understanding how each of these measures changes as time since Fontan progresses will better elucidate their utility to predict progression to failure and how we should use them clinically to monitor our patients. In addition, most studies of Fontan patients are limited in terms of patient number due to the relative rarity of the diseases. Given this, the ability to study biomarker associations with "hard" outcomes, such as death or transplant, is often challenging. This leads to the use of surrogate outcomes possessing nonspecific associations with actual Fontan failure. Although these initial investigations into biomarkers must continue, the time has come to begin conducting more prospective, longitudinal, and multicenter studies to address the growing problem of an aging Fontan population. Multicenter prospective studies are often thought of as time intensive and costly; however, we believe the current clinical and research climate is right to begin using grassroots multicenter research collaborations and alternative research methods[14] and to leverage existing multicenter infrastructure to mitigate these potential barriers to research. Our great achievement in improving single-ventricle congenital heart disease survival will remain great only if we can learn how to care for the survivors and sustain their survival.

Disclosures

None.

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