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EDITORIAL COMMENT

"Doc, Am I a Good Fontan?" Well, I Guess We Don't Really Know…*

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Appointments with patients post-Fontan and their families often bring up discussions about their resilience and capacity to overcome multiple hurdles. As patients age, the parents' concerns regarding the tenuous prepalliation period and procedural risks are soon replaced by the individuals' own fears and questions regarding their future. Heart failure, liver disease, arrhythmias, need for transplantation… With so many potential long-term complications, it is natural that providers are frequently asked by patients about their prognosis. Despite >50 years since the inception of the Fontan procedure, this vital question remains very difficult to answer.

In this issue of *JACC: Advances*, Elder et al[1] seek to assess our ability to predict 1-year major adverse event (MAE) in a cohort of predominantly adolescents and young adults post-Fontan among 9 New England congenital heart centers. Providers were asked a very simple question: "Would you be surprised if your patient has a MAE in the next year?". Their definition of MAE was broad, ranging from more predictable (such as the need for transplantation or new-onset ascites) to more idiosyncratic metrics (eg, sustained ventricular tachycardia or development of protein-losing enteropathy). The results are sobering. Despite the highly experienced sample of clinicians (21 ± 12 years post-fellowship), the ability to predict outcomes was only 17% better than random chance.

As typically seen in cohorts of patients post-Fontan, there was heterogeneity in the underlying anatomical diagnosis and types of Fontan connection. In spite of the young and predominantly asymptomatic (eg, 51% with NYHA functional class I) population, 12% of patients experienced a MAE within 1 year. Most MAEs were related to unplanned cardiac hospitalization and arrhythmic events. Astoundingly, approximately 40% of these patients had been labeled as "good Fontans" by their providers. Noteworthy laboratory, cardiopulmonary exercise testing (CPET), and cardiac catheterization data were not presented, and it is unclear how often clinicians had those at their disposal when assessing risk.

The only factor independently associated with the perception of being at risk for MAE and the outcome itself was the need for diuretics or beta-blockers. This observation is unsurprising since it is intuitive for beta blockers to be used in those with a history of or at high risk for developing arrhythmias. Although not individually included in the model, the univariable analyses suggest the use of diuretics to be a stronger predictor of MAE than beta-blockade. Diuretics are commonly used in adults with congenital heart disease, but their initiation should not be taken lightly. The current observations agree with prior studies demonstrating diuretic requirement being associated with increased mortality in adults post-Fontan.[2,3] Therefore, leg edema and/or ascites requiring decongestive therapy might be an early clue that advanced therapy (ie, transplantation) should be considered, assuming no other obvious culprit (eg, significant Fontan pathway stenosis) is present.

Interestingly, clinicians associated the presence of ventricular systolic dysfunction with a higher risk for MAE. Despite the natural focus on ventricular ejection fraction by patients and providers, lessons from acquired heart failure have taught us not to be falsely reassured by normal systolic function. As highlighted by the authors, data demonstrating worse prognosis

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in those with systolic dysfunction in the setting of Fontan palliation are conflicting. The lack of association between systolic dysfunction and MAE might simplify our assessment given the challenges in determining normal systolic function in this population due to variable ventricular anatomy and absence of well-established cutoffs for reduced ejection fraction. The current results emphasize the importance of assessing the entire clinical picture (instead of solely focusing on ventricular [dys]function) and reinforce the irreplaceable role of history-taking—a prior unplanned cardiac admission was the strongest predictor of MAE.

Their observation regarding the association between ≥ moderate atrioventricular valve regurgitation and MAE deserves attention. As reflected in the study's demographics, this is particularly topical in current cohorts, given the growing number of patients with hypoplastic left heart syndrome and/or right ventricular morphology. Increased mortality in those requiring atrioventricular valve intervention early in life has been demonstrated.[4] The current findings underscore the deleterious impact of atrioventricular valve regurgitation in Fontan patients even extending to their later years. The problem is that the outcomes of atrioventricular valve intervention in symptomatic adolescents and adults are unknown. This is a critical knowledge gap given the inherent risks of the procedure, and this aspect in care of Fontan patients desperately warrants further investigation.

But why is it so difficult to prognosticate patients post-Fontan? First, albeit cliché, the reality is that all Fontans are different. The numerous permutations according to underlying anatomy, surgical history, timing of Fontan palliation, and current age make a standard approach exceedingly difficult. A simple example is the interpretation of serum biomarkers. N-terminal pro-brain natriuretic peptide (NT pro-BNP), an integral component of the evaluation and management of biventricular heart failure, has been suggested to vary according to the type of Fontan connection. Moreover, the influence of ventricular morphology on its secretion is unclear. Accordingly, how do we interpret NT pro-BNP levels in a patient with tricuspid atresia and atriopulmonary connection vs one with hypoplastic left heart syndrome with an extracardiac conduit? CPET, another widely used tool in cardiomyopathies and valvular disease, might also be challenging to interpret in Fontan patients. A peak VO_2 of 60% predicted might warrant surgery in a young individual with bicuspid aortic valve-related aortic regurgitation but represents an expected value even among post-Fontan patients who are doing well.

The unknowns are also the result of evolution in surgical techniques. The burden of atrial arrythmias was evident immediately after the introduction of the atriopulmonary connection, becoming essentially universal in those reaching adulthood. Due to the timing of total cavopulmonary connection introduction, the incidence of late atrial fibrillation/flutter in this population still requires better understanding. Lastly, even if long-term data *are* available, they might not be of help to the patient in front of us. The 30- or 40-year survival rates postpalliation are paramount when initially considering the procedure but might be of little use when counseling a 50-year-old adult post-Fontan about their 5-year survival.

Prognosticating Fontan patients might require an individualized approach and thinking outside the box. This is particularly important given the limitations of echo-Doppler in this population. We demonstrated that liver fibrosis scores might provide prognostic information and insight regarding unfavorable underlying hemodynamics.[5] We have also noted a direct correlation (albeit modest) between systemic venous pressures and spleen size (William R. Miranda, C. Charles Jain, Patick S. Kamath, Christopher J. Francois, Heidi M. Connolly, Luke J. Burchill, Alexander C. Egbe; unpublished data; November 2023). Lastly, we reported that, despite its uncertainties, NT pro-BNP levels >300 mg/dL and/or a peak VO_2 <50% predicted on CPET were associated with higher Fontan and ventricular filling pressures during cardiac catheterization.[6] The future of outpatient Fontan evaluation may involve a score incorporating all these (and potentially other) metrics—an approach that has been highly successful in heart failure with preserved ejection fraction.

The answer to this complex dilemma might be a much simpler one. Fontan (or systemic venous) pressure has invariably been associated with clinical outcomes. Its measurement, however, typically requires cardiac catheterization, which is onerous and carries obvious risks. Peripheral venous pressure (PVP) has been shown to accurately reflect Fontan pressures.[7] Moreover, resting and exercise PVP values correlated with Fontan-related outcomes.[8] Accordingly, we have incorporated measurement of PVP in the outpatient evaluation of our Fontan patients and during their catheterization to document the correlation with centrally measured values. An elevated PVP might, therefore, alert the clinician of a suboptimal milieu.

The care of Fontan patients is humbling and poses endless challenges to patients, families, and providers. Regardless of the method proving itself optimal for prognostication of Fontan patients, Elder et al have shown us that it will likely be superior to our clinical gestalt. The first step—acknowledging our limitations—has been taken, and now it is our job to tell our patients if they are "good Fontans" in an objective and evidence-based manner.

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