prognosis,⁷ some may have considered such aggressive care with multiple reoperations to be futile or unwarranted, a sentiment that may have hindered the opportunity for repeat surgery in some cases. This study appears to argue instead for an escalation of care and for a greater willingness to perform serial operations; it advocates for staying in the fight. Hippocrates long ago counseled that extreme disease calls for extreme measures.⁸ In this case, relentless disease may call for relentless measures.

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See Article page 387.

Commentary: Total anomalous pulmonary venous connection, heterotaxy and pulmonary vein obstruction: The relentless pursuit of imperfection

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Spigel and colleagues¹ describe the medium-term outcomes among patients with total anomalous pulmonary venous connection (TAPVC) over nearly 25 years at their

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CENTRAL MESSAGE

Complex statistics can provide increased understanding of CHD patients but must be coupled with optimum research methodology to ensure we are not in relentless pursuit of an imperfect understanding.

institution. Their objective was to examine time-related mortality and reintervention in those with and without heterotaxy, with each group stratified by the presence or absence of pulmonary vein obstruction (PVO). The population consisted of 118 patients with heterotaxy (of whom 49 had PVO) and 218 patients without heterotaxy (of whom 87 had PVO). Not surprisingly, the authors found that patients with heterotaxy had greater mortality than those without and that those with PVO had worse survival than those

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without in both the heterotaxy and non-heterotaxy groups. Patients with both heterotaxy and PVO had the greatest number of pulmonary vein interventions (median of 2.0 at 6.5 years). This well-written paper originates from a thoughtful and experienced investigative team, and the subject matter is highly impactful in that outcomes among patients with TAPVC with heterotaxy remain suboptimal. However, despite this, there remain flaws inherent to the inferences, study design, and data quality—problems encountered by many investigators using retrospective data.

As stated, the primary objectives articulated by the authors were to study mortality, the rate of reinterventions, and the factors associated with reintervention. The comparative groups created by the authors to do this imply that the features of importance with respect to reintervention are heterotaxy and PVO. However, isn't this a *fait accompli* that perhaps implies that only these 2 features are important, without exploring any others? Also, wouldn't we expect that heterotaxy and PVO affect both mortality and reinterventions? Should we instead be more interested in the morphology of the veins, location of the obstruction, or the pattern and type of reinterventions, as targets of new knowledge?

Interestingly, in the perspective statement, the authors state that "...many patients will achieve a steady state enabling a lasting freedom from intervention." However, a median follow-up of 6.5 years is too abbreviated to determine the steady state of any patient group. Of note, one of the authors of this paper published a study some years ago attesting to the "relentless" nature of recurrent PVO following repair of TAPVC.² Do we think it is less relentless in 2021, or are we more facile salvaging patients despite successive procedures?

One of our primary concerns related to study design is that this was a retrospective study with unequal follow-up, as those with heterotaxy and those with single ventricles had a specialized follow-up program to monitor them. An example of how this may introduce bias was that in the last year, 53% of those with heterotaxy were seen, whereas only 38% of those without heterotaxy were seen ($P = .01$) at about 6.5 years of follow-up. It is unclear, however, if the rigor of surveillance was equal for both heterotaxy and single-ventricle patients, including the potential for increased reinterventions. While the authors bring this to attention in both the methods section and within the limitations, the manner in which this affects reintervention is a significant issue in the study. In our opinion, it would have been better to apply a matching algorithm or restrict the comparison to those patients followed for similar

intervals. In addition, while techniques such as modulated renewal can allow us to reset the clock back to time zero, it is unclear in a scenario such as PVO whether patients are truly reset to the same starting point. PVO is a finicky problem, and not all lesions can be ameliorated to the same degree, so it is hard to appreciate whether patients are reset to the same baseline. If PVO is only improved a little bit with a reintervention, we are not really resetting the clock, and perhaps modulated renewal is not an appropriate methodology. Finally, we support the use of competing risks to analyze the competing events of reintervention, death, and transplantation. However, supporting figures and the extension of these analyses to the parametric realm may have allowed elucidation of multiple risk factors within each pathway.

There were also several key pieces of data lacking from this analysis that seem as if they could have easily been provided. First, the authors did not enumerate the specific numbers of patients reintervened upon based on each criterion. In other words, how many were reintervened upon based on a pulmonary vein gradient ≥ 4 mm Hg or for pulmonary venous congestion on chest radiograph, etc. How many had a combination of more than 1 of these features? These data would add immensely to our understanding of the presentation and prevalence of different causes for reintervention—also very valuable knowledge to relay to families and providers. A formal risk analysis would have been helpful to provide clinicians with an understanding of the features for which one should keep an eye out with respect to mortality and reintervention. Cardiac catheterization data (pulmonary vascular resistance, cardiac index, right ventricular pressures) in this group would have also been useful. The authors discuss mechanistically that increased Qp relative to Qs is potentially causative for PVO, but there are no objective data to support this contention.

Ultimately, although complex statistics can provide increased understanding of our patients with congenital heart disease, they must be coupled with the optimum research methodology to ensure we are not in relentless pursuit of an imperfect understanding.

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