Pulmonary vein stenosis: Plea for a multi-institutional registry

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Pulmonary vein stenosis (PVS) in the pediatric patient is a challenging problem for which the cause is frequently unknown, the diagnostic criteria for intervention are uncertain, and the treatments are marginally effective. The 2-year survival in infants with this condition is about 60%. In this issue of the *Journal*, Lo Rito and coworkers¹ from the Hospital for Sick Children in Toronto report the outcomes of 31 patients who underwent surgical repair of multivessel PVS who also underwent preoperative computed tomography or magnetic resonance imaging (MRI). They report that smaller total “upstream” or “downstream” pulmonary vein cross sectional area and greater number of involved pulmonary veins were associated with poorer survival. Lo Rito and coworkers¹ suggest that measurements derived from MRI and computed tomography can be used to predict disease severity and guide postoperative surveillance and “adjuvant” therapy in PVS.

The Toronto group has contributed significantly to our knowledge and management of pulmonary vein stenosis during the past decade, working comparably in the relevant areas of basic science, diagnostic modalities, and surgical techniques.²⁻⁴ This article by Lo Rito and coworkers¹ continues that contribution by reinforcing the value of MRI in imaging the PVs before intervention and by providing a valuable “hint” that preoperative PV size measurements are related to outcome. The task of definitively demonstrating this relationship is daunting for any single institution, however, because (1) PVS is relatively rare, (2) MRI and computed tomography are relatively recently used diagnostic modalities, and (3) MRI is not easily used in an important subset of the cohort, small infants. As such, with only 11 time-related events (deaths) in the cohort, the biphasic parametric risk-hazard analysis used in this study was technically limited to a small number of covariates (2-5, depending on other characteristics of the model). Thus Lo Rito and coworkers¹ could not take into account a myriad of additional covariates commonly associated with survival in complex congenital heart disease—covariates that, if included in a sufficiently large model, could significantly alter the odds ratios otherwise calculated for the included variables. It is prudent to

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Central Message

Pulmonary vein stenosis, a rare but morbid disorder, should be studied with a multi-institutional inception cohort registry.

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consider the results of Lo Rito and coworkers¹ tentative until a larger study can be accomplished.

A Boston Children's Hospital study of PVS recently published in the *Journal* did not escape this dilemma, either.⁵ In their cohort of 49 patients, there were 14 deaths, and the median follow-up period was only 0.5 years. The risk analysis was limited to univariate tests, mostly log-rank tests on pairs of Kaplan-Meier curves. Relative to the Toronto group,¹ the Boston group⁵ found a different set of covariate associations with death. In the Boston study, age younger than 6 months at operation, weight less than 3 kg at operation, and lesser preoperative right ventricular systolic pressure were associated with mortality, but the number of involved pulmonary veins was not. The study did not include pulmonary vein size measurements. As with the Toronto study,¹ and for similar reasons, we should remain circumspect in interpreting these associations.

There are other important differences between these 2 studies. The descriptions of the operative techniques differed. Whereas both institutions pursued a “sutureless” technique, the Boston group⁵ described additional steps such as unroofing atretic veins, debriding all scar tissue out to first-order branches, and tacking vein edges to pericardium. Second, whereas the Toronto group¹ described

only 1 postoperative catheter intervention (1 in 28 operative survivors), Boston group⁵ performed such intervention in 29 of 49 patients (59%), despite similar median ages at operation. Third, the Boston study⁵ used adjunctive chemotherapy in selected patients. Despite these differences, overall time-related survivals at 5 years were similar in the 2 studies—64% in the Toronto study¹ and 58% in the Boston study.⁵

The challenges in studying PVS encountered by these 2 high-volume, research-oriented programs leads us to suggest that PVS should be studied in a different way. Perhaps it is time to consider a multi-institutional mixed or inception cohort registry for PVS. The spring 2015 Society of Thoracic Surgeons Congenital Heart Surgery Database report lists 506 cases of PVS repair as the primary procedure between January 2011 and December 2014. If a study were to enroll just *one-third* of these subjects, it could accrue more than 40 subjects per year. Five years hence, with an anticipated 50 to 80 events (deaths), it would be possible to carry out more robust risk-hazard analyses. Inception cohort registries yield better studies than strictly retrospective or meta-analytic data sets, because subjects are prospectively enrolled and, ideally, all the requested data are acquired. In the early years of the registry, provisional analysis can be used to formulate “best practice” recommendations for nature and timing of diagnosis,

intervention, and follow-up. If the enrolling institutions follow these recommendations, the quality of the registry improves further—the data become, in a sense, more controlled. This is exactly the strategy taken by the Congenital Heart Surgeons Society Data Center for studying anomalous aortic origin of a coronary artery, an anomaly that has an incidence not too different from, and an event rate much lower than, PVS. Perhaps the Congenital Heart Surgeons Society, which has the necessary resources in place, should engage in studying PVS—a rare, but disturbingly morbid, disorder.

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