Cracking the Mystery of Pulmonary Vein Stenosis

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Despite the numerous innovations in all diagnostic and treatment aspects of congenital heart disease, the management of pulmonary vein stenosis (PVS), primary or postoperative, continues to be perplexing, and 1–2-year survival of patients with progressive PVS seems to have stubbornly plateaued at a low range of 50–60%.[1–4] Various medical, percutaneous, and surgical treatment modalities for PVS have been described. Nonetheless, all those options continue to be associated with inferior outcomes due to residual lesions, recurrent stenosis secondary to disease progression in the same or other pulmonary veins, development of pulmonary hypertension, and subsequent right heart failure, all requiring lung transplantation or leading to patient demise.

Despite the rarity of PVS, this challenging lesion is gaining an increased interest among physicians owing to many factors including a growing vulnerable population (eg, infants following surgical repair of total anomalous pulmonary venous connection (TAPVC), premature babies with bronchopulmonary dysplasia), improved detection using advanced diagnostic imaging modalities, and of course lack of consistently effective management strategies.[1–4]

Several prominent centers have recently described their experience and reported their outcomes in the management of PVS using diverse treatment modalities. Most of those reports shared the same limitations due to the small cohort, heterogeneous patient population, and lack of institutional protocols for the diagnosis, management, and follow-up of those challenging patients.[1–4] In the current issue of the Seminars, DiLorenzo et al from the Children's Hospital of Philadelphia report their single-center experience in the management of PVS between 2005 and 2016. They identified 93 children with PVS using ICD codes. Among those, 65 (70%) had significant congenital heart disease and 32 (34%) were born prematurely (<37 weeks gestation). Overall, 65 (70%) underwent PVS intervention with 42/65 (65%) receiving ≥2 interventions. Patients with congenital heart disease were more likely to undergo an initial surgical PVS intervention whereas premature patients were more likely to undergo an initial percutaneous intervention. There were a total of 23 deaths (25%) and 4 lung transplants (4%) at a median follow-up interval of 5.8 months from PVS diagnosis, with 5-year transplant-free survival of 67%. While those results seem to be slightly better from other published reports, their study cohort included patients with less complex PVS forms, explaining the higher survival rates. The authors identified younger age at diagnosis (<6 months) and presence of extensive disease affecting more than one pulmonary vein to be associated with decreased survival. On the other hand, they were unable to demonstrate a significant effect of prematurity or presence of congenital heart disease on survival. While this is a relatively large series from an experienced center, anatomic and intervention details were not provided in this retrospective review and institutional protocols

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Central Message

Collaborative efforts are needed to understand the histopathology of pulmonary vein stenosis, perform necessary research, and guide clinical management of this challenging progressive disease.

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were lacking.[6] As a result, the value of this submission is limited by its descriptive nature of what has been done and consequently the authors were unable to provide solid recommendations that could influence decision-making.

A quote credited to Russian physiologist and Noble prize laureate Ivan Pavlov says "don't be a mere recorder of facts, but try to penetrate the mystery of their origin." For PVS, it seems that we have yet to crack the mystery of this challenging disease and generate a significant impact on the prognosis of those patients. However, several opportunities exist in the prevention, detection, and management of PVS that might positively influence survival of those children. One opportunity is in the prevention of PVS. Postoperative PVS occurs in 10−15% of patients following TAPVC repair and is usually evident within 6−12 months from surgery. Several surgeons advocated for primary sutureless repair of TAPVC and some recent studies have shown a decrease in postoperative PVS, especially in those at higher risk due to preoperative obstruction.[7,8] The potential mechanism of PVS prevention with the sutureless technique is the ability to perform a larger anastomosis that extends into the proximal individual veins, the avoidance of pulmonary vein distortion or scar formation at the suture line with the pulmonary vein wall. I personally believe that this is a superior way to treat TAPVC and while my initial experience with this technique was remarkable, I did recently encounter a few setbacks when I tried a modification of my technique that resulted in a smaller anastomosis and subsequent requirement for reintervention. I believe that by sticking to the principles of creating a wide anastomosis with the sutureless technique, we should be able to decrease the incidence of postoperative PVS. On the other hand, primary PVS is being increasingly reported in neonates and small infants, especially those with history of prematurity, necrotizing enterocolitis, and bronchopulmonary dysplasia.[5] While the cause-effect relationship between prematurity and PVS is not very well understood, it is plausible that the incidence of PVS would decrease if those babies were born at full term with better organ maturation. There is ongoing research to develop artificial placenta and extrauterine systems to support extremely premature fetuses until organ maturity is developed. While this research has been so far limited to animals, it holds promise in the future to be applicable to humans and could potentially eliminate many of the morbidities related to extreme prematurity, including PVS.[9]

The other opportunity exists in the development of novel multimodality strategies in the diagnosis and management of PVS. Because of the progressive nature of this disease and the risk of development of recurrent upstream (distal) obstruction that is resistant to intervention, the key to successfully treating PVS is early detection, early intervention, vigilant follow-up, and timely reintervention for recurrent obstruction. The advances in cardiac imaging including computed tomography and magnetic resonance imaging angiography allow early detection and improved follow-up after intervention. Improved surgical techniques especially the sutureless PVS repair has demonstrated improved treatment results, while improved experience with percutaneous intervention, with or without stent placement, has allowed management of distal and recurrent lesions.[1−4,10,11] New insights on the histopathology of PVS show evidence of myofibroblastic proliferation, activation of tyrosine kinase receptors, elevated TGF-β signaling and activation of Angiotensin II pathways. All of those suggest that therapy targeting myofibroblast proliferation could help prohibiting PVS progression.[12] There are several ongoing research projects examining the effect of targeted medical therapy to slow the progression of PVS that might hopefully reveal histopathologic and clinical benefit in the near future.

Finally, it is obvious that no single institution is going to be capable of creating adequate knowledge of this rare heterogeneous and complex disease, or to formulate a clear and effective treatment strategy. Therefore, collaboration between multiple institutions is clearly necessary to improve the knowledge of this refractory disease and guide clinical management of children with PVS. The University of Toronto group is credited for developing the pulmonary venous stenosis network (www.pvsnetwork.org) that is coordinating enhanced collaboration between multiple institutions to create a registry that would improve knowledge of this disease, to perform research that would help understand the pathology of PVS and examine various experimental medical modalities, and to finally help creating diagnostic, treatment, and follow-up protocols. Obviously, much more work is needed; however, the steps that have been taken in the past few years seem to be in the right direction toward cracking the mystery of PVS in children, hopefully in the near future.

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