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Editor invite expert opinion: "Pulmonary vein stenosis- novel strategies for a challenging and resistant condition?"

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Please submit your article's Perspective Statement here. The text box will limit you to 405 characters, spaces included	Interventions can be successful in treating proximal pulmonary vein stenosis but ultimate outcome is determined by distal disease not amenable to current treatments. This work is important quantifying severity of distal disease and may provide a tool to monitor the effect of novel medical treatments developed to reduce progression of distal disease.
Please submit the abbreviated legend for your Central Picture. The text box will limit you to 90 characters, spaces included	CT angiogram illustrating proximal left pulmonary vein stenosis.
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Pulmonary vein stenosis- novel strategies for a challenging and resistant condition?

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Picture:

CT angiogram illustrating proximal left pulmonary vein stenosis.

Central message:

A new index presented for assessment of distal pulmonary venous obstruction and a new treatment proposed to ameliorate distal disease.

Perspective statement:

Interventions can be successful in treating proximal pulmonary vein stenosis but ultimate outcome is determined by distal disease not amenable to current treatments. This work is important quantifying severity of distal disease and may

provide a tool to monitor the effect of novel medical treatments developed to reduce progression of distal disease.

Body of editorial:

The fields of paediatric cardiology and cardiothoracic surgery have made significant progress over the last fifty years but despite this there are some conditions which are still extremely resistant to treatment; pulmonary vein stenosis is one such lesion. Over the last five years there have been significant advances in our understanding of this disease and the team from Hospital for Sick Children in Toronto should be commended for their dedication into leading research in this particular field.

Pulmonary vein stenosis is a life-threatening and challenging condition where the pulmonary veins are narrowed, resulting in obstruction of blood flowing back to the heart. It is often progressive, leading to generalised narrowing of the pulmonary veins upstream (distal) from the original site of obstruction and in some cases atresia may develop(1). This results in raised pulmonary venous pressure and pulmonary oedema, often leading to progressive pulmonary hypertension, right heart failure and death. Development of a major venous collateral network can occur and may be associated with improved outcome(1). Neoproliferation of cells(2) is responsible for the pulmonary venous narrowing but the exact pathophysiology remains unknown.

Our lack of understanding of this condition likely accounts for why there are so many different types of surgical and catheter interventions; yet still we have not managed to find the optimal treatment. Introduction of the “sutureless” surgical technique has made some progress in treating proximal disease(3;4), but results remain disappointing when there is distal disease. An aggressive, early combination of both catheter and surgical interventional strategies may be the most effective, particularly in young and small patients, where the disease process can be particularly active(5). However, due to the progressive nature of pulmonary vein stenosis, the most important prerequisite for successful outcome is to achieve complete abolition of the stenosis at an early stage and before there is progression of the disease distally. The optimal initial strategy is likely to depend upon local expertise, but repeated interventions, both surgical and catheter should be contemplated. Mortality and

morbidity are substantial and even balloon angioplasty has recently been associated with significant risk of neurological injury(6).

An understanding of the limitations of imaging modalities is vital when diagnosing proximal pulmonary vein stenosis. Diagnosis can be particularly difficult with echocardiography alone. Indeed in 26% of cases with primary pulmonary vein stenosis, the stenosis were not diagnosed on echocardiogram but rather at cardiac catheterisation or surgery(1). Close observation and a high index of suspicion is required, with further imaging by computerised tomography, cardiac magnetic resonance imaging or angiography recommended if there is any concern of obstruction. Cardiac magnetic resonance imaging is particularly helpful as it not only delineates pulmonary venous anatomy, but also blood flow redistribution in the pulmonary veins and arteries(7).

But how do we know when there is distal disease? It can be very difficult to decide whether the upstream vessels are involved in the disease process; decisions are often made after subjective interpretation of angiography performed in the cardiac catheterisation laboratory. It is vital to diagnose distal disease as this will influence whether surgical interventions, that only really treat proximal disease, are likely to be beneficial. It can also help predict long-term outcome. In this issue Lo Rito and colleagues (8) have suggested a novel technique to make objective measurements of the distal pulmonary venous vasculature using cardiac magnetic resonance imaging and computerised tomography thereby potentially diagnosing patients with diffuse distal disease. This is crucial for identifying patients more likely to respond to current surgical treatments and those that may be candidates for more novel medical therapies for distal disease. This novel and quite complex approach may also be used to quantify response to therapies over time. It would have been interesting to see a comparison of computerised tomography and cardiac magnetic resonance imaging in measuring this new index. Furthermore there would have been additional utility in developing a “cut-off” value of upstream total cross sectional area index defined below which surgical intervention may be considered futile.

Treatment of distal stenosis is not amenable to surgical or catheter intervention and so attention has turned to novel medical therapies to treat distal disease. Previous

studies have investigated the mechanisms responsible for progression of pulmonary vein stenosis. Histological studies have shown a variable manifestation of intimal and medial interstitial fibromuscular proliferation, together with fibrotic displacement of the muscle bundles in the venous wall. This results in occlusion of the lumen of one or more of the pulmonary veins connecting the lungs to the left atrium. Most commonly, the thickening of intimal tissue occurs at the junction where the left atrium meets the pulmonary vein; the narrowing then extends along the pulmonary vein towards the hilum of the lung. Various cell types have been proposed as the source of neoproliferation. In 2000, Sadr(9) studied pulmonary venous tissue from 10 children presenting with congenital pulmonary vein stenosis in a normally connected heart. There was no evidence for thrombosis, inflammation or fibrosis, however there was evidence of myofibroblastic proliferation. Myofibroblasts are a progenitor cell for myocytes and fibroblasts, and retain the ability to differentiate into either cell type depending upon environmental factors. They proposed that congenital pulmonary vein stenosis could be treated with agents that arrest or eradicate the neoproliferative process such as radiation, chemotherapy or gamma interferon. A subsequent study in 2006 by Riedlinger(10) showed that expression of various receptor tyrosine kinases and some ligands raised the possibility of an autocrine or paracrine role for these proteins in the pathogenesis of the intimal occlusive lesion seen in pulmonary vein stenosis. Clearly, understanding these processes would ultimately help develop treatments for pulmonary vein stenosis. Myofibroblastic proliferation also occurs in desmoid tumors of infancy and this led Rehman et al(11) to undertake a chemotherapeutic trial using vincristine and methotrexate in infants and children with progressive multivessel intraluminal pulmonary vein stenosis: success was limited.

Animal models have in the past been used to investigate the pathological changes in pulmonary vasculature that occur with pulmonary venous obstruction. LaBourene(12) in 1990 banded the pulmonary veins in piglets and studied haemodynamic, histological and biochemical changes in the pulmonary vasculature over time. From the Toronto group, Kato et al(13) used a similar animal model in six piglets that underwent bilateral pulmonary venous banding and showed endothelial-mesenchymal transition. Tissues from vessels upstream of the banded pulmonary veins were associated with robust expression of transforming growth factor (TGF-β).

Zhu et al(14) again used the piglet model to investigate the effect of losartan on the progression of the stenotic process. They hypothesised that losartan has an inhibitory effect on TGF-β and hence may modify the progressive stenosis seen in distal veins. They found that losartan significantly lowered the ratio of pulmonary artery/ systemic blood pressure and diminished intimal hyperplasia. The mechanism as to why it helped remains unclear. There was no difference in TGF-β levels between the losartan and non-losartan groups however there was a difference in VE-caderin levels which they thought was indicative of diminished endothelial integrity. Clearly there is still much work to be done in establishing the pathological pathways that lead to progressive distal venous obstruction and translating this to humans. However, this is extremely exciting and innovative work investigating the potential for post-interventional therapies to reduce the effect of distal disease. This would be particularly important in patients considered at high risk of developing post-operative stenosis. Lo Rito's imaging techniques may help identify such high risk groups and monitor the effect of novel therapies. It would be extremely interesting to see whether losartan has a role in reversing established disease and hopefully the research team will go on to investigate this. Future work is likely to involve clinical trials in humans and, due to the rarity of this disease; this is likely to be multi-institutional and multi-national. We sincerely hope that the paediatric cardiac community can come together to make such trials a reality.

In summary, pulmonary vein stenosis is frequently a progressive disease leading to generalised narrowing of the pulmonary veins and in some cases atresia. The best way to prevent progression is to identify and treat the stenosis in the first place so distal disease does not have the chance to occur. In this issue, the team from Toronto proposes a new index of pulmonary vein cross sectional area measured at cardiac magnetic resonance and computerised tomography as a tool to detect patients that are likely to have distal disease and hence worse prognosis. They have previously proposed losartan as a medical treatment which may have a role in preventing distal disease from occurring. This is an exciting development which if confirmed would represent a real advance in therapeutic options. So, are we at a stage where we can prevent progression of pulmonary vein stenosis? There is no doubt we are closer, however there is still much more work needed and clearly collaborative medical trials are the optimal way to progress. For the present,

treatment of established distal pulmonary venous disease remains an extremely challenging and resistant condition to treat.

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