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Update in Pediatric Pulmonary Hypertension

Announcer:
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Dr. Krasuski:
Welcome to CME on ReachMD. I'm Dr. Richard Krasuski, and today I'm reviewing the latest evidence in pediatric and adult congenital pulmonary hypertension and what it means for your clinical practice.

Single ventricles comprise approximately 8% of congenital heart defects. They are a challenging group of patients and often we are faced with a lot of uncertainty regarding the management of these patients. In 1968, Fontan and Baudet performed the first Fontan procedure to palliate tricuspid atresia. As you can see on the diagram on the right side, the Fontan consists, in this case, of a conduit, a tube that goes from the inferior vena cava up to the pulmonary artery and therefore leaves no subpulmonic ventricle. Survival of these patients has improved after the Fontan was introduced from less than 5% at 1 year to greater than 80% at 25 years.

In the US from 2001 to 2014, there were 16,000 patients who underwent the Fontan procedure. 70,000 post-Fontan patients are believed to be alive worldwide and may double in the next 20 years.

Unfortunately, the Fontan is not the last procedure that these patients will have, and there's approximately about a 10% mortality per decade in adulthood. Now, if you look at the diagram on the right of this slide, you can see that this is the atrial pulmonary Fontan, in which case the atrium was attached up to the pulmonary artery. This was the original Fontan, or what's known as the classic Fontan. Unfortunately, with this type of a connection, what happened is you ended up with a lot of arrhythmias and thrombosis, and so they switched then to the next 2 pictures here. One is the patient with a lateral tunnel Fontan, in which case there's a fenestration here, also, that allows the perioperative outcomes to improve. And then, finally, the extracardiac Fontan, which is a tube, again, that goes from the IVC directly to the pulmonary artery. Now, this resulted in fewer arrhythmias and thrombosis, but they still had other complications that can develop, including systolic and diastolic dysfunction of the single ventricle, chronotropic incompetence and heart block requiring pacemaker placement, cardiac arrhythmias, thromboembolism is still an issue, liver cirrhosis from congestion that's chronic, chronic kidney disease, venovenous collaterals, and pulmonary AV malformations, protein-losing enteropathy, and plastic bronchitis.

Now there's Fontan failure and we define this as, really, 4 different groupings. One is reduced systemic ejection fraction. This resembles acquired systolic heart failure seen in the general population. It's the most common type seen in pediatric patients.

The second type is preserved ejection fraction, but elevated end diastolic pressure, so this acts like diastolic heart failure. Then there's normal end diastolic pressure, but elevated Fontan pressure and multi-organ system dysfunction, and this is where pulmonary vascular disease is prevalent. And then finally, abnormal lymphatic function, which is what results in protein-losing enteropathy and plastic bronchitis.

Now, there are many management strategies far beyond this particular talk, but really what we're going to focus on in those patients that

develop pulmonary vascular resistance issues, since this is a circuit that's really dependent on passive flow, it's obviously not conducive to good output if the pulmonary vasculature is not working properly. So in these patients, the central venous pressure has to be high, in fact, very sky high with exercise. Atrial pressures will reach central venous pressures as high as 40 mmHg, considerably higher than the normal 0 to 5 mm that we often will quote for normal.

Pulmonary blood flow is nonpulsatile, so the cardiac output is really dependent on the low pulmonary vascular resistance as there is no subpulmonary ventricle. Lacking an effective ventricle, even slight increases in the PVR could result in a low cardiac output that could have devastating consequences. And then, depending on the anatomy, some single-ventricle patients are overcirculated early in life.

So there are some controversies in assessing the pulmonary circulation in Fontan patients. First of all, it's hard to understand abnormal when there's a lack of agreement for what normal is in an adult Fontan patient. The prior paradigm that cardiac output decreased over time in Fontan patients because of failure of the systemic chamber has been shaken by recent studies, suggesting that many adults have actually high-output states as they get older, and this is probably the impact of hepatic cirrhosis on these patients.

Another point is, we cannot accurately measure pulmonary vascular resistance in Fontans. MRI could be of assistance to catheterization. There is variable lung perfusion in these patients. There're venovenous collaterals and arterial venous malformations in the lung. These can obviously impact that pulmonary blood flow. And most pulmonary vasodilators, remember, started as unsuccessful heart failure medications before finding success in PAH.

So very early on in the literature here. This goes back to 2008. There was a study looking at response to exercise after being given sildenafil. So these were 27 patients with Fontan. They underwent a cardiopulmonary exercise test [CPET] with noninvasive measurements of their cardiac index and their pulmonary blood flow. And then they were randomly assigned to receive either sildenafil or no treatment.

After 1 hour of rest, they did a second CPET and they looked at this and saw improvements in peak VO_2, the cardiac index, and pulmonary blood flow and really no adverse effects. So really, very exciting data that something was there that could potentially improve cardiac index without any side effects.

Then, they proceeded on to the TEMPO study, which was the only trial to date that showed substantial improvement in the primary endpoint. These were 75 adolescents and adults randomized 1:1 to 14 weeks of bosentan or placebo. Their peak oxygen consumption increased. You can see from 28.7 to 30.7 with bosentan, where they changed much less with placebo. This was statistically significant. The cardiopulmonary exercise time also improved, and 9 patients improved 1 functional class with bosentan versus or 0 of the patients in the placebo group, which, again, was statistically significant.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Richard Krasuski, and I'm reviewing the latest evidence in pediatric and adult congenital pulmonary hypertension and its application in clinical practice.

Well, a similar trial was published around that same time, which was prospective multicenter, 42 patients. Bosentan for 6 months versus no steady medication for 3 months, and then bosentan for the additional 6 months. And you see primary endpoint of VO_2 max at 3 months was not met, neither was there a change in NT-ProBNP level. There was no change in cardiac output. The SF-36, we're looking at quality of life, NYHA function class. None of these improved with the sildenafil versus placebo.

There was a meta-analysis of a number of these trials that was published by Wang, which looked at 9 studies and 381 patients. This suggests a small benefit but had serious methodologic flaws. The meta-analysis was then redone and was 449 patients and 13 trials and published by Lee. And you can see that, really, everything crossed the line of unity here with the exception of a trial that was done with iloprost, suggesting perhaps some benefit with drug. But really, when you combine everything, it crosses the line of unity, so no improvement in exercise capacity in all these trials when they're pooled.

The next large study that was published was the FUEL study, really the largest study published to date. This was done through the Pediatric Heart Network. Thirty clinical sites in the North America and South Korea randomized 400 Fontans to 26-weeks of udenafil, another PDE5 inhibitor, versus placebo. You can see the average age on entry here was adolescent years, 15.5. Most of these patients were male. The majority of them were Caucasian. The peak oxygen consumption, which was the primary endpoint, increased a slight amount with udenafil, and you can see this did not reach statistical significance. Now, they did look at multiple other exercise parameters by cardiopulmonary exercise testing, and there was some increase in oxygen consumption here, increased ventilatory equivalence of carbon dioxide, and an increase in work rate, but no change in mortality or clinical events, myocardial perfusion index, or serum brain natriuretic peptide levels.

But, to focus on one positive, the drug was very well tolerated in this population. I think before this, there was concern about hypotension and other complications that could be a problem in these patients, but it was not seen.

Next was the RUBATO trial. And RUBATO was a 52-week, multicenter, randomized, double-blind, placebo-controlled trial of 10 mg of macitentan, and this was in 137 Fontan patients. These were all total cable pulmonary connections, and no atrial pulmonary Fontans. They had to be over the age of 12, and New York Heart Association functional class II or III. No CPET limitations and no signs of Fontan failure or clinical deterioration within 3 months of screening. The primary endpoint here was to look at the VO_2 max, which, again, in this study, did not change compared with placebo. They also looked at multiple secondary endpoints, including change in peak VO_2 from baseline to 52 weeks, which was not changed. They also looked at daily physical activity to see if that would have improved. Once again, the drug was well tolerated. So pulmonary vasodilators appear well tolerated but could not demonstrate improvements in exercise.

So my summary critique of all the studies that have been published to date. The main criticisms really are based on the size and lengths of follow-up. But there's lots of study design variability. Multiple ages have been included all the way from the pediatric years into the late adult years. Patients on some studies were sick and some studies were well, and we still have trouble, in fact, defining who's sick and how to identify those particular patients for these studies.

Outcomes monitored were mostly cardiopulmonary exercise testing. Perhaps, we want a little bit more in terms of looking at not just quality of life and exercise capacity, but also at clinical outcomes. And are we targeting the correct population? I believe that we really want to be looking at ways to improve how patients do in preventing clinical events, so maybe we should be looking at sicker patients.

Similarity to studies of pulmonary vasodilators and heart failure with group 2 pulmonary hypertension in these trials. So again, I think identifying people who have an elevated pulmonary vascular resistance is essential since that's what we're really looking at the clinical effect of.

So the last hope here is the SV-INHIBITION study. This is done by the Parisian group. Prior studies have suggested that some patients experience an increase in end diastolic pressure with pulmonary vasodilators, which could be confounding the results, so therefore, excluding these patients is important. So this is a multi-center, double-blind, placebo-controlled trial of sildenafil that's sponsored by the French Ministry of Health. In this case, they're looking at patients over the age of 15 and those that are able to perform cardiopulmonary exercise testing.

And then they have to have a heart cardiac catheterization where there's a mean pulmonary artery pressure greater than 15, Fontan pressure greater than 15, and a transpulmonary gradient greater than 5. And these folks get randomized to sildenafil or placebo, and they're looking at a change in the VE/VCO_2 slope after 6 months of treatment, so that's the primary endpoint. And they have a number of secondary endpoints looking at exercise capacity. So this is now targeting patients who truly have physiology we believe is PAH, and I think that's our real final hope as far as these trials go.

So in summary, pulmonary vasodilators appear unlikely to be a wonder drug for Fontan patients, unfortunately, either those that are stable or failing. Pulmonary vasodilators appear surprisingly safe in this population, but they are expensive with limited, if any, benefits. Perhaps the Single Ventricle (SV) INHIBITION study will find that those patients that have identified PAH specifically benefit from this class of therapies.

And until now, unfortunately, no major medications have been proven to be a game changer for these patients, so we're really hoping for something to be positive like this. Physicians should encourage exercise because in this case, exercise has been shown to be beneficial in pretty much every study that's been done in patients with Fontan. So really encouraging your patients to be active is probably the best good long-term goal.

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