Transcript Details
This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/prosecutions-arguments-holding-court-in-ph-should-all-adult-fontan-patients-be-placed-on-pah-group-1-therapy/14244/

Released: 10/28/2022
Valid until: 10/28/2023
Time needed to complete: 54m

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Prosecution's Arguments - Holding Court in PH: Should All Adult Fontan Patients Be Placed on PAH Group 1 Therapy?

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCME curriculum.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Krasuski:
Dr. Aboulhosn, you may call your first witness.

Dr. Aboulhosn:
Thank you, Your Honor. The prosecution calls Dr. Sasha Opotowsky to the stand. Dr. Opotowsky, in an average year when you're not in prison, how many adult patients with single ventricle physiology do you see?

Dr. Opotowsky:
Our program follows over 250 adults living with a single ventricle circulation.

Dr. Aboulhosn:
Would you say most of these patients have a Fontan?

Dr. Opotowsky:
Yes.

Dr. Aboulhosn:
And what is the major issue that you see with adult Fontan patients with respect to the pulmonary circulation, Sir?

Dr. Opotowsky:
As it pertains to the question of vasodilators, the major issue is that with aging there's an increase in pulmonary vascular resistance, PVR. PVR is one of the main determinants of cardiac output in the Fontan circulation. Based on fundamental physiological considerations, there's a direct relationship between central venous pressure and pulmonary resistance and flow. Central venous pressure is invariably elevated even in asymptomatic individuals functioning well with the Fontan circulation. This high venous pressure presumably causes ongoing injury and carries an inherent risk of complications related to chronic venous hypertension and circulatory failure. The inability to increase pulmonary blood flow with exertion when the tissues require more oxygen that is to increase pulmonary blood flow and therefore be able to deliver oxygen to the tissues is limited. There's no single accepted hemodynamic definition of pulmonary vascular disease or elevated pulmonary resistance in patients with univentricular hearts in the Fontan circulation. However, in this context, we still tend to measure transpulmonary gradient defined as the difference between pulmonary artery pressure and left atrial pressure and cardiac output as being done in the biventricular circulation. While there's no specific number for any of these variables that defines elevated versus normal, it goes without any question or controversy that lower pulmonary vascular resistance is better. That said, there is no clear cutoff in this circulation. I will say that there are some numbers that have been put forth in the

literature such as a transpulmonary gradient of less than equal to six millimeters mercury or a pulmonary vascular resistance less than three wood units times meter squared. But I think it's more important to think about the principle that lower is better because it allows the little pressure to overcome the resistance of the pulmonary circulation to allow the circulation to supply the tissues with oxygen.

Dr. Aboulhosn:
Well, thank you for that. And why is the cutoff for pulmonary vascular resistance so different for Fontan patients when compared to other PAH patients who have a biventricular circulation?

Dr. Opotowsky:
Well, single-ventricle system requires that low pulmonary vascular resistance to maintain the preload of the single ventricle. That is the blood coming back from the body augmenting the filling of the systemic ventricle. And with that, with high resistance to the pulmonary circulation, you really wouldn't be able to get blood back to the ventricle and therefore wouldn't be able to be pumped to the body to supply the tissues.

Dr. Aboulhosn:
Would you start all failing Fontan patients on PAH therapy to lower this dangerous pulmonary vascular resistance that can cause such problems in the Fontan circuit? And if so, can you explain why?

Dr. Opotowsky:
For legal reasons, I'm going to answer your question with a question and that is, why would you deprive these patients of lower pulmonary vascular resistance? With that said, there's several lines of evidence suggesting that vasodilator therapy may benefit the failing Fontan circulation. Let's look at the overall picture first though. As I stated a moment ago, systemic venous hypertension is necessary to drive blood flow through the pulmonary vasculature with the systemic venous pressure typically five millimeters of mercury or so higher than the pulmonary venous atrial pressure. Pressures in the hepatic veins are therefore higher than normal, the same as central venous pressure. That's also true about the lung, excuse me, the kidneys, and the systemic veins such that there's ongoing damage to those tissues. With that abnormal hemodynamics such as in the liver, this predisposes to late complications such as liver fibrosis and cirrhosis.

As you can see in this somewhat complicated slide, the pulmonary vascular resistance right at the top in the center is a key part of this cycle but is only one part of it. So, we can't expect when somebody argues that these medications don't cure the circulation, don't provide an enormous benefit. We can't expect with these multiple parts that could be dysfunctional that addressing one of them will necessarily solve the problem. But what you can see here is that without low enough pulmonary vascular resistance which can be assisted by pulmonary vascular therapy, blood can't return from the Fontan pathway through the smaller pulmonary arteries around the systemic atrium to provide preload to the ventricle, and therefore it can't be ejected to provide blood to the body.

Phosphodiesterase-5 inhibitors are one type of medication that have been studied both acutely and in case series with promising preliminary results. In the acute setting, Sildenafil, for example, has been shown to improve peak oxygen uptake in adult individuals with a Fontan circulation as you can see in this example shown on this slide.

In unselected cohorts of individuals with a Fontan circulation, Sildenafil has been shown to improve some exercise parameters. But in selected failing Fontan circulation, Sildenafil truly appears to improve symptoms and sometimes seems to reverse, to some degree, Fontan circulatory failure. This effect does appear to be related and dependent on reducing the pulmonary vascular resistance rather than on direct effects of ventricular function or other off-target effects. It would appear that targeted pulmonary phosphodiesterase-5 inhibition may be a benefit to the Fontan circulation. Although admittedly, adequately powered clinical trials are still lacking in this regard.

In the stable Fontan circulation, there is some evidence for efficacy of pulmonary vasodilators.

A recent study, the fuel trial demonstrated the treatment with Udenafil was not associated with an improvement in oxygen consumption of peak exercise which I will admit was the primary outcome selected, but it was associated with improvements in multiple measures of exercise performance at the ventilatory anaerobic threshold and also physiologic parameters suggestive of improved vascular function, et cetera.

Dr. Aboulhosn:
And let me ask you this, do we see similar effects from other classes of Group 1 PAH medications, not just PDE-5 inhibitors? How about other medications?

Dr. Opotowsky:
Yes, we do. The effect seems to be consistent. Both endothelin receptor antagonists and prostanoids that have been evaluated for efficacy and safety in the Fontan have shown similar effects. Although there have been subtle differences in the patterns. The use of

endothelin receptor antagonist in the Fontan circulation appears to have an acceptable safety profile and may be effective.

For example, the TEMPO trial looked at 75 adolescents and adults randomized 1:1 to 14 weeks of treatment with bosentan, an endothelin receptor antagonist, versus placebo. As you can see in this figure, peak oxygen consumption increased significantly by two milliliters per kilogram per minute and 28.7 to 30.7 in the bosentan group compared to an increase of 0.6 milliliters per kilogram per minute and 28.4 to 29.0 milliliters per kilogram per minute in the placebo group. This was statistically significant with a P value of 0.02.

Two studies have also evaluated the use of inhaled iloprost prostanoid in the management of the Fontan circulation. Inhaled iloprost was well tolerated and led to symptomatic improvement and improved improvement of peak VO2. Although one of these studies, admittedly, was a short-term study. The use of these medications, however, is not widespread given the challenges in administering them. And requires further clinical trial data and efficacy to recommend their routine use in particular.

Dr. Aboulhosn:
Thank you, Dr. Opotowsky. Now, do you consider all lines of agents that we just discussed to be safe in adult Fontan patients?

Dr. Opotowsky:
There is very little suggestion of substantive harm from these medications. Of course, the studies had stringent exclusion criteria. And one would have to use one's clinical judgment in a patient who has very low blood pressure at rest and is already lightheaded. One wouldn't start any medication that could decrease blood pressure. But in general, these medications are not only safe, but they're very well tolerated. Yes, there are some adverse effects, and some individuals may not tolerate it or have an allergy like any medication including a placebo, but in general, they're very well tolerated and safe.

Dr. Aboulhosn:
Well, I think that makes our case. Thank you so much, Dr. Opotowsky. No further questions from the prosecution, Your Honor.

Dr. Krasuski:
Dr. Kay, you may cross-examine the witness.

Dr. Kay:
Thank you, Your Honor. Dr. Opotowsky, how many Group 1 PAH medications are known to reduce pulmonary vascular resistance and which one of them appears to be most potent?

Dr. Opotowsky:
All of the medications for Group 1 PAH that are pulmonary vasodilators reduce pulmonary vascular resistance. In general, prostanoids, inhaled or intravenous, have had the most potent effect clinically and on pulmonary vascular resistance.

Dr. Kay:
And you just stated that the prostanoids are seldom used in the Fontan patients. And there's a lack of clinical data supporting their use in this patient group. If that is the case, why are the PDE 5 inhibitors and the endothelin receptor antagonists, the medication you speak of is having so much benefit in the Fontan patients?

Dr. Aboulhosn:
Objection, Your Honor. The defense is asking the witness to conjecture here. Come on!

Dr. Krasuski:
Objection, sustained. Dr. Kay, please stick to questions that the witness is able to factually answer.

Dr. Kay:
I will rephrase, Your Honor. Dr. Opotowsky, do you personally use the medications you referred to in your Fontan patients, failing or otherwise? And do you see any changes in PVR that would suggest they can reduce the pressure gradient across the lungs, and better facilitate venous-powered pulmonary flow? Have you seen patient improvement or improvement in the transpulmonary gradient or pulmonary vascular resistance? And if so, is it uniform across all patients?

Dr. Opotowsky:
Thank you. You asked if I personally use the medications. And no, I do not. But I do use them in my patients. And I have seen improvements in exercise performance and patient quality of life in a good number of those individuals.

Dr. Kay:
I see. And in your experience, are there any circumstances where application of Group 1 vasodilators has produced a negative result?

Dr. Opotowsky:

Yes. There have been some studies that have failed to demonstrate any improvement in primary outcome when these medications have been studied such as a phosphodiesterase-5 inhibitor or an endothelin receptor antagonist.

I can think of the 2013 study of Bosentan where there was no significant improvement in primary endpoint exercise capacity, or the secondary endpoints of peak oxygen consumption, or the ratio of minute ventilation to carbon dioxide, the VE/VCO2 ratio, as shown here.

Dr. Kay:
So, Dr. Opotowsky, have there been any studies showing that this extends the life of our Fontan patients?

Dr. Opotowsky:
No.

Dr. Kay:
So, Dr. Opotowsky, even from the testimony you have provided, can you say that Group 1 medications are effective in all Fontan patients?

Dr. Opotowsky:
No, I cannot.

Dr. Kay:
Thank you, Dr. Opotowsky. No further questions, Your Honor.

Dr. Krasuski:
Thank you, Dr. Kay.

Announcer:
You have been listening to CME on ReachMD. This activity is jointly provided by Global Learning Collaborative (GLC) and TotalCME, Inc. and is part of our MinuteCME curriculum.

To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.