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

Announcer:
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Dr. Kay:
The defense calls Dr. Wayne Franklin. So, Dr. Franklin, how frequently do you see adult Fontan patients?

Dr. Franklin:
Really almost every day, or at least five days a week, sometimes on the weekends, so I see them quite a lot.

Dr. Kay:
Of those with single ventricle physiology, how many have had the Fontan palliation?

Dr. Franklin:
Ah, very good question. I'm going to say in our practice, probably 50%, that is, by the time I see them, they've had the Fontan, you know, various stages, Glen shunted circulation, so at the very, you know, I would say about half have had the Fontan operation, so it's quite frequent.

Dr. Kay:
Of those corrected patients, how many are showing evidence of overt or developing pulmonary hypertension? Of those that when you do see the pulmonary hypertension, how often do you initiate this therapy?

Dr. Franklin:
Well, there are a number of reasons that I do not start group one medications. First, we cannot get an accurate measurement of PVR or pulmonary vascular resistance in these patients, so we have to use transpulmonary gradient as a guide to disease progression. In theory, there's a strong linear relationship between central venous pressure and transpulmonary gradient.

As in this figure here, as the PVR increases in Fontans, the transpulmonary gradient will increase if pulmonary blood flow is constant, as noted by the green line. Changes in central venous pressure in relation to pulmonary vascular resistance are dependent on pulmonary blood flow, so small increments in pulmonary vascular resistance can result in significant reduction of pulmonary blood flow, hence the red line. In extreme cases, central venous pressure could be a normal range for Fontan patients with low cardiac output despite elevated pulmonary vascular index, and some Fontan patients with a transpulmonary gradient greater than six and a PVR index greater than three, there's been suggestion of that should be the definition for pulmonary hypertensive vascular disease in Fontan patients.

For patients with single ventricle physiology, efforts to avoid pulmonary vascular resistance really start in the neonatal period. Now, I know we are a group of adult congenital providers, and this is an adult congenital-focused trial. The neonatal management of single

ventricle patients has to aim at optimal preparation of the pulmonary bed for the Fontan circulation, avoiding prolonged periods of pulmonary over circulation, pulmonary hypertension, and subsequent volume load. But at the same time, it has to allow for sufficient pulmonary blood flow to promote pulmonary arterial growth. Then once the Fontan circulation is established and completed, limitation of cyanosis can be a theoretical benefit. In those patients who have fenestration, closure of that fenestration or veno-venous collaterals can reduce cyanosis as we all know, but as we all also realize, it can result in an increase in central venous pressure and Fontan pressure. Once pulmonary vascular disease is considered in patients with a Fontan, pulmonary vasodilator therapies are often initiated. We all do it, we've all seen it, okay? But in Fontan patients, a transpulmonary gradient greater than six and a PVR index of greater than three Wood units has been suggestion as a definition for pulmonary hypertensive disease by the European Pediatric Pulmonary Vascular Disease Network, the oh so elegantly abbreviated EPPVDN. If the EPPVDN definition is applied as data published in 2003 by Khambadikone and coworkers, they showed that one decade after Fontan operation, only a very small proportion of Fontan patients with good functional status have an elevated PVR based on invasive hemodynamic data. In contrast, Mitchell and colleagues, although they are surgeons, found that PVR was elevated in most patients with overt Fontan failure when examined after heart transplantation. So, what do these findings say? Well, what these findings tell me, Dr. Kay, and Your Honor, is that these elevations in PVR are likely not present in all patients, and we would mainly want to use pulmonary dilators in contrast to Dr. Opotowsky's testimony only if the PVR was elevated, consistent with a PAH or pulmonary arterial hypertension situation. So prophylactic use of vasodilators across the board in all Fontans, as I believe Dr. Aboulhosn is arguing, may not always give the benefits for which we are searching.

Dr. Kay:
So let me get this correct, Dr. Franklin. You are telling me and the jury that not all Fontans therefore should be on pulmonary arterial hypertensive therapy?

Dr. Franklin:
Correctamundo, Dr. Kay, I believe so. There were two recently published meta-analyses which yielded conflicting results.

You can see here from 2021, Li et al published, and they concluded from an examination of 13 studies that were both randomized controlled trials and non-randomized controlled trials that also reported patient baseline data along with data for dichotomist and continuous variables, that pulmonary vasodilators appear to not be beneficial in the categories of pulmonary resistance, heart function, or quality of life, and there's no significant evidence to confirm that most pulmon vasodilators improve exercise capacity in Fontan patients. In this analysis, the variables assessed included change in pulmonary resistance, heart function, exercise capacity, quality of life, mortality, you name it, and adverse events after drug administration. A random fixed effects model is used to an assess the mean difference-to-risk ratio with a 95% competence interval, that's pretty high, of 449 Font patients from the 13 studies that were included. They also pooled estimates, and pooled estimates of the change in pulmonary artery pressure, NYHA association class, peak oxygen consumption, short form 36 or SF 46 as we call it, mortality, and any adverse event were not significantly different between the drug and control groups. Likewise, most results of the subgroup analysis revealed no significant between group differences. Pulmonary vasodilator therapy appears to be safe but not beneficial and in the categories of pulmonary resistance, heart function, and quality of life in patients who've undergone a Fontan.

In contrast, Wong and coworkers in 2019, now, just a few years ago in their meta-analysis, and I know we all read all these meta-analyses, they found that there was a significant improvement in NYHA functional class six-minute walk and peak VO2. So again, we have two conflicting meta-analyses published very closely together. In addition, let me also say that in the SV inhibition trial, and it's also known as a single ventricle inhibition trial now in progress, it's a phase three trial looking at the efficacy and safety of PDE5 inhibitor therapy in teenagers 15-year-old and greater, and adults for variation in their VE to VCO2 slope measured by a cardiopulmonary exercise test between baseline and six months of treatment. While some of the early results of this study should be very interesting, and we may hopefully start to settle the issue of whether vasodilators can safely benefit the entire single ventricle population.

Dr. Kay:
So, what does all this mean?

Dr. Franklin:
Well, Dr. Kay, in summary, it means to me that we do not have a definite answer to your original question. Contrary to what my California counselor would say, we do not know if vasodilator therapy is of benefit in every Fontan patient. It may mean that we need to be looking in more detail at all types of Fontan patients who we are assessing for vasodilator therapy. In other words, we need consensus guidance on hemodynamic cutoffs to dictate commencement of therapy.

Dr. Kay:
And moving on, do you have other concerns about the use of vasodilator therapy in the Fontan patients?

Dr. Franklin:

Well, Dr. Kay, I certainly do. You know, one of my big concerns is potential complications that vasodilator side effects may contribute to those Fontan patients. Signs of maladaptation of the Fontan circulation can clearly develop in nearly every organ system. We've all seen that, hepatic, renal, central nervous system being particularly common in Fontan patients in the liver, in the kidney. Let's start with the liver.

Hepatotoxicity is a possible side effect of endothelin-dealing receptor antagonist. We all know that, and that really needs to be considered when choosing pulmonary vasodilator therapy in Fontans, keeping in mind the risk of hepatic dysfunction. The second generation of endothelial receptor antagonist, ambrisentan and macitentan are thought to be considerably less hepatotoxic compared to bosentan, the first generation. And we know that failing Fontan patients are already at an increased risk of protein losing enteropathy, or of PLE as we call it, or liver disease edema and ascites. In the case of bosentan, one of the earliest and probably the longest-studied ETRA, the issue of hepatotoxicity has to be considered. This medication must be discontinued if the transaminase the ALT to AST levels are accompanied with clinical symptom of hepatotoxicity.

It's important to note that reintroduction of this drug also, studies have not really been established, and given that the Fontan patients are already at risk for hepatic issues, this cannot be ignored. But in fairness, in fairness now, I also have to say that in most of these small studies, vasodilator and Fontans usually studying ERAs or PDE5 inhibitors, the medications are well tolerated. To Dr. Opotowsky's point, they're well tolerated, but I think the problem still has to be a strong consideration before therapies are undertaken.

Dr. Kay:
Are there any other issues with using ERAs that come to mind, Dr. Franklin?

Dr. Franklin:
Well, there's always the issue of fetal toxicity, right? Big issue now, ambrisentan and macitentan are contraindicated in females who are pregnant or who may become pregnant. We always have to advocate pregnancy avoidance anyway in these PAH or pulmonary arterial hypertension patients due to fetal and maternal risk, and I think it's important to continuously emphasize this on our female Fontan patients and consider monthly pregnancy testing.

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

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

Dr. Aboulhosn:
As far as this EPPVDN, I'm pretty sure I got a case of it on a trip to Tijuana about a month ago. The other thing I'm going to have to push back on a little bit is this EPPVDN definition of a pulmonary arterial resistance greater than three Woods units times meters squared when it's indexed. I think that is far too high. There's a consensus paper that was recently published in the European Society of Cardiology Heart Failure Journal in 2021 that changes that down to 2.3 Woods units times meters squared. So, they don't even have their definition of pulmonary arterial resistance elevation figured out at this point, so I'm not sure we can even accept any of that, but let's put that aside for a minute. Let me ask you a question, Dr. Franklin. Have you ever used vasodilator therapy in your Fontan patients?

Dr. Franklin:
Have I ever used vasodilator therapy? Yes, yes, doctor, I have, but only in those who are failing.

Dr. Aboulhosn:
And what criteria do you use to determine which patient is failing and which patient's not failing?

Dr. Franklin:
Well, I think you're trying to trick me, but as criteria, you mean there are multiple, I would choose to use criterion, and I think this would be addressed previously. It would be a transpulmonary gradient above five Wood units would make me think towards a medical approach to lowering this transpulmonary gradient.

Dr. Aboulhosn:
So, you would not start any patient on pulmonary vasodilator therapy without catheterizing them first, Dr. Franklin?

Dr. Franklin:
Although I did not talk about catheterization, I would use an alternate means to reduce this transpulmonary gradient first, since the historical evidence is not 100% in support of vasodilator therapy. For example, anticoagulants have been shown to prevent thrombolic thromboembolic events, although I might be more scrutinizing of the use of diuretics in the older Fontan with heart failure. Of course, the ultimate treatment of the failed Fontana is a heart-liver transplant, but I do not think the core of the argument is that today, I believe,

correct?

Dr. Aboulhosn:
So, what you're saying is you would not use these therapies in a patient who is not failing. That's what I'm getting from you here. And that the data showing reduction in transpulmonary gradient by the use of ERAs or PDE5 inhibitors is not compelling to you, so you're going to wait until the car crashes right off the road before deciding that you need to put your hands on the wheel. Is that what I'm understanding there, Dr. Franklin?

Dr. Franklin:
A lot has been staked on those small studies, and perhaps too much on subsequent meta-analyses. And if you look at least one of the meta-analyses that I showed, I think we may need to take a harder look. I mean, honestly, I think there are some legitimate concerns around the meta-analysis by Wong et al. The Wong analysis included data from a limited number of studies with significant clinical and methodological diversity. When substantial heterogeneity exists, pooling data from multiple trials and presenting a single summary estimate can be misleading. You know that I know that the honorable Dr. Krasuski knows that it should be avoided. A second point, two of the included studies were not randomized controlled trials. One was a retrospective design, and one was a prospective design with a historical cohort control group, and thus in fact do not fulfill the author's inclusion criteria of randomized control only studies. Four of the included studies concerned pediatric patients only so they were not even dealing with adult congenital or even teenage patients. And in the five studies that were remaining in the Wong meta-analysis included adult patients at midterm to long-term follow-up after the Fontan procedure. So realistically, I don't think you can compare pediatric immediately post Fontan and adult Fontan patient data. And on another note, of the five adult Fontan studies, three reported only small increases in peak VO2, whereas the other two studies did not show any improvement, these zero to even negative one. So, it seems to me that a lot has been staked on analyses of this sort, but what we truly need is a larger study in adult Fontan patients who are either stable and/or progressing towards failure. And we are all eagerly waiting results from randomized controls trials such as the single ventricle inhibition trial and the RUBATO study with macitentan.

If you look at this table, this was an online publication from the acc.org, and it basically shows that we have no guideline-directed therapy showing that there's any guidelines that are recommended for treating failing Fontans. We're just winging it. We're just driving the car with blinders on, and we're just kind of going for it, so that's how I answer your question.

Dr. Aboulhosn:
Thank you, Dr. Franklin. I have no further questions, Your Honor.

Dr. Krasuski:
Dr. Kay, do you wish to call any other witnesses?

Dr. Kay:
No, Your honor, the defense rests.

Dr. Krasuski:
Dr. Aboulhosn, do you wish to call any other witnesses?

Dr. Aboulhosn:
No, your honor, the prosecution rests.

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