ALEXANDER EGBE: Greetings. I'm Dr. Alexander Egbe, an assistant professor of medicine pediatrics. I'll be speaking to you today about it on anticipated consequences of the Fontan Operation. I have no disclosures.

During this presentation, we will talk about the hemodynamic limitations of the single ventricle physiology. And next, we will review the basics of the Fontan Operation. And finally, we'll end by discussing the unanticipated consequences of the Fontan Operation.

So what is a single ventricle physiology? In a normal biventricular heart, the systemic circulation and pulmonary circulations are linked in series. As a result, pulmonary blood flow is equal to systemic blood flow, and the saturation is 100%. In a single ventricle physiology on the other hand, the [INAUDIBLE] intracardiac mixing of systemic venous blood and pulmonary venous blood result in an obligatory right to left shunt and sinuses. So the two primary hemodynamic limitations of the single ventricle physiology are one ventricle volume overload ultimately leading to ventricle failure, and sinuses due to obligatory right to left shunt.

It is because of these two problems that a Fontan Operation became necessary. The Fontan Operation was first performed in 1968, but described in 1971. In a nutshell, this is an operation that directly routes systemic venous return into the pulmonary circulation bypassing the subpulmonary ventricle.

This operation has undergone several modifications since the original description more than four decades ago. On the left part of the screen is the classic atrial pulmonary Fontan that was popular in the early '70s. On the right side of the screen is the extracardiac conduit Fontan, which is the latest modification of the Fontan Operation.

The Fontan Operation completely separated pulmonary and systemic circulations, as shown in the movie. And by so doing it overcomes the problems of the single ventricle physiology, which are sinuses and ventricular volume overload. But it does this at a very high hemodynamic cost.

It turns out at the absence of a subpulmonary ventricle in a Fontan resolves in an obligatory high intravenous pressure and low cardiac output. High CVP and low cardiac output is a definition for heart failure. So although the Fontan Operation solve the problems of the single ventricle, it just created a heart failure model. This operation is just a palliation and not a cure. And we know is because we have longitudinal data showing that the survivals of these

operations are faced with a lot of unanticipated consequences, which I'll go over in the next few slides.

The first unanticipated consequence is atrial arrhythmia. Atrial arrhythmia is present in half of all adult Fontan survivors. It is common in this population because of certain anatomical and physiologic characteristics of the Fontan circulation that predisposes to arrhythmia. These include right atrial dilation that is common in the atrial pulmonary Fontan model, atrial fibrosis from long standing sinuses, and presence of surgical scars in type of Fontan models.

The role of direct current cardioversion for atrial arrhythmia management is well established in cardiology. And also in patients with biventricular heart, we tend not to worry a whole lot about a small thrombus on the right side. This is because if the risk is small pulmonary embolism, the right ventricle is able to mount enough systolic work to overcome the afterload. In a Fontan circulation on the other hand, there really is no subpulmonary ventricle. So even a small pulmonary embolism can result in catastrophic and disastrous hemodynamic consequence.

On the screen is a still frame of a TEE of a patient with atrial pulmonary Fontan connection that was referred to our cardioversion [INAUDIBLE] for DC cardioversion. And just for reference, on the top of the screen is a left atrium. And you can see the huge right atrium. And in the right atrium, you see a thrombus.

Of note, this patient had a therapeutic INR of 2.8. If you go ahead and [INAUDIBLE] this patient and this thrombus breaks off into the pulmonary tree, this patient can collapse and die. So because of the concern about pulmonary embolism and its downstream consequences, there is a general reluctance among congenital cardiologists to perform DC cardioversion in Fontan patients with hemodynamically stable arrhythmia.

So certain question needs to be answered. One, is DC cardioversion effective? How safe is it? And what happens after DC cardioversion with regards to recurrence?

To answer these questions, we reviewed outcomes all 152 DC cardioversions in 86 Fontan patients. We found out that cardioversion was effective in [INAUDIBLE] and presenting arrhythmia in 3/4 of the patients. Those patients who were on a class 1 or class 3 anti-arrhythmic drug had higher success rate. There were no deaths or thromboembolyic complications associated with this procedure.

This is the highest safety profile ever reported in Fontan patients in the literature. And we

attribute this to liberal and meticulous use of TEE guidance prior to DC cardioversion. At Mayo Clinic, we performed TEE before DC cardioversion in all Fontan patients, regardless of what the INR is.

Although we've shown that this procedure is effective and safe, the outcomes of short term follow up was it be disappointing with more than half of them having a [INAUDIBLE] occurrence within three years. This emphasizes the importance of linking your acute management strategy to your long term arrhythmia management strategy. So what are the options for chronic arrhythmia management in Fontans? The options are medical therapy with anti-arrhythmic drug, catheter ablation, or Fontan conversion with anti-arrhythmia surgery.

The question is are all these strategies equally effective? If the answer is no, then at what point should we transition from one strategy to the other? To answer this question, we reviewed outcome of 264 adult Fontan patients with atrial arrhythmia. All patients initially received anti-arrhythmic drug therapy until they had their first arrhythmia recurrence. This patients were then triaged into three different treatment pathways based on the decision of the primary cardiologist.

110 patients continued on anti-arrhythmic drug therapy, 34 patients went for catheter ablation, and 33 three patients went for Fontan conversion with anti-arrhythmia surgery. And indication was primarily for arrhythmia. On follow up we found that the patients who continued the medical therapy had significantly worse outcome, with almost all the patients having arrhythmia recurrence within five years. However, those patients that went for Fontan conversion or ablation had significantly better outcome with the recurrence rate of 50% in five years. Another important observation from this study was that the 40 patients that went for Fontan conversion or catheter ablation, the risk of recurrence was higher the longer you wait prior to performing these procedures.

So take home point for arrhythmia management are one, always think about it thrombus. Perform TE-guided DC cardioversion, regardless of what the INR is, especially in people with atrial pulmonary Fontan. Second point is that ablation for all anti-arrhythmia surgery are the preferred long term arrhythmia management strategy for these patients. The earlier you refer to patients for this procedure, the better the outcome.

Moving onto the second unanticipated consequence, which is thromboembolism. Thromboprophylaxis in Fontan is a very tricky business. Because you're trying to manage to

balance on one hand, the high tendency to clot, vessels a high tendency to bleed in these patients.

So certain questions still remain unanswered. One is, how common is thromboembolism? How do we prevent it? And how do we treat it when it occurs?

To answer this question, we looked at outcome of 278 patients with atrial arrhythmia. 2/3 of these patients received antiplatelet therapy alone for thromboprophylaxis while 1/3 receive anti-coagulation with or without anti [INAUDIBLE] therapy.

We found out that in the subset of patients with atrial arrhythmia, the incidence of thromboembolism was 6.5% per year. Also, those patients that had thromboembolic complications were more likely to die or be hospitalized for heart failure. Also, anti-coagulation with Warfarin and a target INR of 2.5 was superior to aspirin with regards to prevention of thromboembolism without an increase in bleeding or risk. How common is thromboembolism in this population?

So we looked at all comers, nearly 400 Fontan patients. We found out that thromboembolism was present in 1/4 of the patients, and some of them were on Warfarin at a time of thromboembolism. So all patients we treated with Warfarin. So those patients who were already on Warfarin, we increased a target INR to 3.0 to 3.5. Warfarin was effective in treating all cases of thromboembolism without any need for thrombolytics or surgery.

However, at a target INR of 3 to 3.5 required for therapy, there was nearly a 10% bleeding risk. Also, some of the patients whose anti-coagulation were discontinued because of bleeding, they went on to have a second thromboembolic event. So you anti-coagulate them, they bleed. You discontinue anti-coagulation, it clots.

So take home point for thromboembolism management in Fontan, thrombus is common. It's present in 1/4 of adult Fontan patients. And in this subset of patients with atrial arrhythmia, the event rate is 6.5% per year. Warfarin is effective as a prophylaxis agent, and at a target INR of 2.5, it does not increase your bleeding risk. However, you require higher target INR of 3.0 for treatment. And that is associated with a nearly 10% bleeding risk.

Finally, we would touch on liver disease. The hallmark of Fontan hemodynamics is high central venous pressure or low cardiac output. The livers is subjected to chronic hepatic venous congestion and altered hepatic blood flow due to low cardiac output on other regulation within

this flattening circulation. And over time, chronic liver disease results.

Based on Mayo data, we found out as cirrhosis is present in about 1/4 of all adult Fontana patients. And so far, we've identified seven cases of hepatocellular cancer in Fontana patients. Liver disease is important because survival is just 35% within five years of cirrhosis diagnosis. And also, unlike the other consequences that I've reviewed, there is no treatment for liver disease except to perform heart liver transplant, which is not a great option.

In summary, we've talked about hemodynamic limitations of the single ventricle physiology, which are ventricular volume overload and sinuses. The Fontana Operation was invented to overcome these limitations. It is a palliation and not a cure.

Patients who survive this operation are now faced with unanticipated consequences. The only way we can change the clinical landscape of this disease is to focus on understanding the [INAUDIBLE] physiology of these consequences and devising better ways to treat them. Thank you for listening.