Discussion to: Chronic in utero mitral inflow obstruction unloads left ventricular volume in a novel late gestation fetal lamb model

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Dr. Sunjay Kaushal (Chicago, IL):

Good morning. Your surgical team needs to be applauded for the surgical results as well as the technical abilities of this model, which was amazing. You had a very low mortality rate once you got over your learning curve. Your study investigated the use of twin pregnancies for your control, which is very, very valuable as you investigated variables for the other fetus. And also, the LA balloon gradual increase was very critical because other investigators showed that there was a lot of mortality associated with arrhythmias. And lastly, you used echo as well as hemodynamics to understand what was happening to the fetus.

I have three questions. The first deals with your title. You said that there’s a chronic in-utero mitral inflow obstruction. I don’t think it’s a chronic model. I have to question that and challenge you on that one. Also, you said in your title you said there is hypoplasia of the left ventricle. I didn’t really see data for that and also would like to challenge you on that claim. My second one is related to the inflow and growth. You definitely clearly show that there was a difference in volumes, right? And that’s kind of obvious when you increase your balloon in the mitral position, you’re going to have less volume. But I didn’t see any data that showed that there was a growth change. Could you comment about that? And lastly, you created a nice model here for understanding the fetuses’ physiology. What is your next set of experiments that you would do in this setting? Thank you very much.

Dr. Daisuke Onohara (Atlanta, GA):

Thank you. First, I apologize that I just sent you the manuscript a week ago and appreciate your thoughtful comments and the important feedback that needs to be discussed. I totally understand that you have some concerns or suspicions about how we describe our animal model in the title and the conclusion part, so I would like to share my opinion to answer your questions. First, is this experiment an acute study or a chronic study? This relates to the definition of the terminology, acute or chronic study. In my understanding, when we call acute study, it indicates a one-day experiment, meaning we have to euthanize an animal on the same day that we perform the procedure. So, I agree with you that this is too short to be called chronic, but at the same time, I think this is not acute. I should pick another term to describe it, to fit this title.

To your second question: Did this animal have hypoplastic LV or not? As you mentioned, we did observe a significant change in the LV volume but not in the LV structure, meaning in the LV weight or histopathology data, which didn’t support that this animal had a hypoplastic left ventricle. However—I’m going to show the previous slide—as you can see here, we confirmed some morphological changes in the LV. On the control group, it’s showing a longitudinally longer LV compared to the experimental group, which shows a little bit shorter LV. So, we did confirm some change in this animal model, but we shouldn’t say this is hypoplastic left ventricle yet, but we do believe if we continue this animal study longer, we can prove “no flow/no grow theory” can be reproducible in the large animal experiment.
And the third question would be “What is our next step to conduct this experiment?”. In the conclusion slide, I noted that we did confirm some changes in this animal model, and to progress this animal much closer to the HLHS condition, we definitely should conduct this animal experiment at a much earlier gestational age and also a much longer duration of the mitral inflow obstruction. And at the same time, I’m also interested in seeing another technique. Right now, we only inserted the inflatable balloon to occlude mitral inflow, but I’m interested in what could happen if I add banding ascending aorta or ductus arteriosus. It might also impact the lung maturity as well. That’s what I’m going to try as a next step.

Dr. Kaushal:

Yeah, I agree that you need to have a little bit longer duration. But I think you’re going to be crippled a little bit because of the arrhythmias that did occur in your patient population as well as the bradycardia that was setting in at two weeks, so I understand there may be limitations of this study or this model. But clearly, I think you’re onto something that could provide us input of how we can actually intervene during the fetus’ life. Thank you.

Dr. Onohara:

I appreciate it.

Moderator:

Thank you very much.