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Exploring Xenotransplantation: Is the Future of Heart Transplants Now?

Dr. Sorrentino:
In a groundbreaking procedure, a 57-year-old man with life-threatening heart disease received a heart from a genetically altered pig. Surgeons at the University of Maryland Medical Center performed the 8-hour operation, making it the first successful transplant of a pig's heart into a human being. And while much is still uncertain, what could this achievement mean for the future of organ transplantation?

You're listening to *Heart Matters* on ReachMD. I'm Dr. Matthew Sorrentino. And joining me to talk about this groundbreaking event is my fellow ReachMD host, Dr. Javed Butler.

Dr. Butler, it's great to see you today and chat with you today. Could you just start by telling us a little bit about your background, your career, and what you do in cardiology?

Dr. Butler:
Yeah. So I'm a heart failure transplant cardiologist, so this is interesting to me not only from a general cardiology perspective but from a transplant perspective as well. And in the earlier part of my career, I was working with a cardiac surgeon who did a lot of research in this field as well, so great to be at this point in the history.

Dr. Sorrentino:
You know, it really was an amazing report in the news when it came out. I think we were all really surprised that there was a successful xenotransplantation. I remember in the past with chimpanzee transplants, it was really not going very far and not working.

The patient, he's a 57-year-old patient, David Bennett. He's doing well the first few days after the transplant. I know he's being closely monitored. What are the potential things that we need to worry about at this point? What could happen that's different from a human transplant?

Dr. Butler:
Yes, it is a lot of things, right? There were some genes and some other pathways that were modified in this genetically engineered animal, so that's great. That's all for sort of the hyperacute rejection and the short-term complications, but obviously any animal heart has a lot of proteins that are being expressed, so the long-term rejection and what it means is something to be discovered. Now remember, these animals are 4-footed animals. Human beings are 2-footed animals. So how does that adapt to the human physiology, not only at rest but also under stressful conditions? And how the afterload and all of those sort of circulatory physiology works we will learn. We have been told that a cardiac growth-determining gene was actually disabled in this heart, but in this new environment, how will that play out in order to adapt to different human stresses? We don't know. We actually don't know how the xenoimmunology will look. Will the rejection be the same for histopathology? Will it be different? And how will we evaluate that? So certainly a lot to learn, but so far so good. Things are going well.

Dr. Sorrentino:
You know, in this day and age of COVID with viruses jumping from animals into humans, one of the concerns I wondered about using a

xenotransplantation, using drugs that certainly suppress the immune system, could that bring out any infections that we don't know about from the animal transplant? Is there any concern that you're aware of about that?

Dr. Butler:
Yeah, a hundred percent, right? The two big reasons for which the xenotransplantation has been delayed and so much research has gone on, one is obviously rejection, especially hyperacute rejection, but the second is xenosis and transmission of animal viruses into human, so that has certainly been the concern, but that has been specifically addressed in this case. Now the genes that were disabled that encode for porcine endogenous retroviruses, how comprehensive it is or that there are some other things that are missed, I mean, we will learn, but we are at least told that the pig genes that encode for porcine endogenous retroviruses were disabled as part of this genetically modified pig heart.

Dr. Sorrentino:
For those just joining us, you're listening to *Heart Matters* on ReachMD. I'm Dr. Matthew Sorrentino, and I'm speaking with fellow ReachMD host Dr. Javed Butler about the first successful transplant of a pig's heart into a human being, which was conducted by the team at the University of Maryland Medical Center.

Dr. Butler, I want to ask you some questions about some of the genetic alterations. I understand that there were some knockout alterations which I guess were trying to get rid of carbohydrates that would cause rejection, but also there were some human genes that were put into the transplant. Do you know a little bit more about what was actually done?

Dr. Butler:
Not everything at least to my knowledge has been disclosed, but there are sort of 4 layers of modification that has been done for this to be successful. So the first is something that you already sort of mentioned, and which is that there are 3 major carbohydrates that are supposed to be the main reasons for hyperacute rejection, and this is a triple-gene knockout animal model where those 3 carbohydrates are silent, so the chances of hyperacute rejection goes down.

The second issue is complement and coagulation pathways, right? So then you can have a lot of thrombotic factors that can get activated, and then you can have thrombotic microangiopathy. So with the CRISPR Cas9 technique, that has also been silenced, so the complement system in thromboregulation pathways have been silenced with the use of the CRISPR technique.

The third issue is the xenosis transmission and infection issue, and we talked about disabling the pig genes and coding for porcine endogenous retroviruses.

And then the fourth is how to manage these patients posttransplantation. So generally speaking, we only use sort of T- and B-cell immunosuppression, but again, from what we have heard is that there is an anti-CD40 monoclonal antibody that has been added to the regimen of the typical T- and B-cell immunosuppression as well to maintain long-term tolerance and quiescence of the risk of rejection. So this is sort of a 4-step process to make this thing successful, and that's where we are.

Dr. Sorrentino:
I understand that last year was pretty much a record year for heart transplants. There were over 3,800 heart transplants in the country that were done, which is a remarkable achievement. But when you think of 3,800 transplants, and I think of all the patients right now in my hospital with advanced heart failure, this is only really the tip of the bucket, I think. Do you think this will make an impact, that we'll be able to get many more patients treated instead of just waiting and waiting on a list for a transplant?

Dr. Butler:
So on one hand, you're absolutely correct that the number of people with advanced heart failure, the number of people who die awaiting transplantation, the number of times that we are forced in a situation where we take less than ideal donor just because the patient is really not doing well, will this sort of revolutionize all of that? Well first, we have to see whether the survival of the transplanted organ rivals that of routine usual transplantation, so we don't know that.

I would say that even if it is better to rivalthe suboptimal donors, even that is a big advance, but if it rivals the usual donors that we use,

then you can sort of farm these animals specifically for the purposes of transplantation. I'm sure that there are ethical concerns about sort of farming animals for the need for transplantation, and I'm sure that some of our ethics colleagues have global views on that that I don't totally understand.

But then the second thing is that if we can be successful in that, can we be successful in other organ transplantations, and can we have xenorenal transplantation and xenoliver transplantation? And are we also now entering into an era where at least the living donor transplantation will just go away because living donor kidney, living donor liver, has a lot of morbidity and risk for the donor organs as well, so at least if that can go away. But will the wait time shrink and will a lot of this just become sort of genetically farmed animals that are transplanted? So we are going into a whole new world with this transplant.

Dr. Sorrentino:
And I think it's going to be a lot more than just coming up with farms that have these animals. I mean, these were genetically modified animals. I'm sure this was an unbelievable undertaking just to get these 10 genes modified. And who knows? It might be 20 genes, it might be 50 genes we have to modify before we'll get a transplant that can be viable. So it seems to me we have to set up a whole system where this technology can be successfully done.

Dr. Butler:
Just think about it that first you have to study which are the major determinants of hyperacute rejection, what are the major determinants of infection transmission, of complement, of thrombosis, then develop a way where you can successfully modify the pig heart so that these things are reliably and to an adequate degree suppressed. We are at the first experiment, but we'll learn a lot because even in the most successful manner, we don't know how many of the proteins that the body will react against, and we will learn all that, so the process will continue to evolve, and sort of the next generation of these genetically modified animals will be a whole lot more complicated, not that this is not complicated enough.

But I will still say twenty years down the road, what a simple balloon angioplasty did and look where we are right now, so we'll figure all this out. The arc of human success will just continue to move forward.

Dr. Sorrentino:
Well, this has been a fascinating look into the first successful transplant surgery using a genetically altered pig heart, and I'm sure there will be much more to discuss about this in the future. But for now, I want to thank my fellow ReachMD host, Dr. Javed Butler, for joining me today. Dr. Butler, it was really great speaking to you about this today.

Dr. Butler:
What a pleasure. Thank you so much.

Dr. Sorrentino:
For ReachMD, I'm Dr. Matthew Sorrentino. To access this and other episodes in our series, visit ReachMD.com/HeartMatters, where you can Be Part of the Knowledge. Thanks for listening.