Heart Transplant

Announcer: Welcome to the Mayo Clinic Cardiovascular Continuing Medical Education podcast. Join us each week to discuss the most pressing topics in cardiology and gain valuable insights that can be directly applied to your practice.

Dr. Bell: I'd like to welcome our viewers and our listeners again today for another in the series of Interviews with the Experts. My name is Malcolm Bell I'm the vice chair for the Department of Cardiovascular Medicine here at Mayo Clinic, Rochester. And it's my great pleasure today to introduce our guest Dr. Mauricio Villavicencio, who's an associate professor of surgery here at at Mayo and director of a heart transplant program. Welcome, Mauricio.

Dr. Villavicencio Theoduloz: Well, thanks very much for the warm welcome and I'm delighted to be here, talk to you about this important topic, for me is a passion. So I'd love to talk about it.

Dr. Bell: Yeah, well, we're thrilled to have you here and I'm sure that we'll be hearing lots of very interesting information from you. So really we're here to talk about what's happening in the world of cardiac transplantation today. And maybe I'll just start off asking you a very simple question. We're aware of many advances in assessment and treatment and outcome after cardiac transplantation, but what do you consider to be the single greatest advancement in heart transplantation in the last decade?

Dr. Villavicencio Theoduloz: Well, I think it would be, probably, I would think about two very hard contenders, for that first place. I would say in the single advancement, I think overall I think heart transplantation for me, the two most important things, the last day it has been the introduction of the DCD heart transplantation which we didn't have before, that was done by the pioneers in Australia and then moved to the United Kingdom and then a few years later here in the US, probably that will be-

Dr. Bell: Let's just perhaps interrupt you, some of our viewers and listeners may not be familiar, what DCD stands for.

Dr. Villavicencio Theoduloz: Yeah, DCDs is the donor after circulatory death. So essentially, we have to be clear that we have had a traditional type of donor, the donor after brain dead, that the brain is injured the donor is brain dead and is the legal system dead. So we could go after, beating heart, assess the beating heart and take it out on transplant. That's our traditional donor. But now more and more has increased, reached about 30% in the us the DCD donors which is those that have some sort of neurological injury, but they're not brain dead. So they're not dead. And obviously from ethical research you cannot take the heart. But what happens is, because the neurological prognosis is very poor then is decided to withdraw care, the family withdraw care and then this is done in a control fashion in the operating room. And the donor will go hypotensive with the saturation. The heart will stop will be five minutes after declaration of death and then we could open up the donor and take out the heart. And it's a heart that is stopped, that it's tended, looks terrible. So you say, "Why would you have interest in transplanted that organ so that Dr. Mauricio might be crazier trying to do that." But this was pioneer, as I said in Australia and then move here. And then you have to think that it's around 30% of our donors are now DCDs. And then in other countries, like in UK 50% of the donors are DCD donors. So it's

still underutilized, but it has opened a door of greatly increasing the availability of organs. That's what I would rank it, number one in the greatest advance, going back to what we were talking about. And then only maybe the second one for me, the ex vivo heart perfusion, that has been replacing cold storage in certain situations in heart transplantation. So those are the two probably, DCD I think it has more an importance in terms that, for the wide impact that can have in reaching many patients, that are in need of heart transplant.

Dr. Bell: Okay, well we'll come back to DCD here in in a moment. Maybe in just another very simple question to ask, are there increasing numbers of patients now or awaiting transplantation? And I'm asking that because we now have durable VADs that many patients receive and has the donor pool increased significantly, particularly now prior to DCD options? And so we know that there has been a very small donor pool. Has that increased significantly and is it gonna match perhaps the increased number of people waiting for cardiac transplants?

Dr. Villavicencio Theoduloz: Well, it has increased the donor pool so through several initiatives. So the units here, here in the US has been done a great job that every year we have had increased number of heart transplant, that come from increased donor pool. One other significant example is that for example, the hepatitis C donors, as you know, hepatitis C, it was a disease difficult to treat before but with the advent of the direct antivirals, that was kind of five years ago that we are able to treat aggressively the recipients for that have donors from hepatitis C. So what it turns out that currently in the US, 20% of the donors are from drug overdose and from those around 18% are hepatitis C donors. So it is a significant contribution. You don't have to increase the donor pool. Then we have been getting way more aggressive look at some donors that previously we wouldn't. And the DCD is part of that reality.

Dr. Bell: So before we, again before we move back to DCD, we've also heard about xenotransplantation, in the press recently. Is xenotransplantation having a resurrection here, a lot of interest in this years ago but it didn't seem to have gone very far. So is there renewed interest and hope in that field?

Dr. Villavicencio Theoduloz: Well, I had to confess that I wasn't a skeptical about xenotransplantation, special, there's some great transplant surgeons that have said, "Xenotransplantation now is the future and always will be." And then I work with Chris McGregor here at the Mayo Clinic, several years ago when he was doing, xenotransplant and he was looking forward to have it in the clinic, in three or four years and it is been 18 years and then we still don't have it, clinically available. However, this a recent one that was done by the Dr. Griffith and his team, and I have look into the case deeply and explain on the discuss with him in one of our cardiothoracic meeting and actually was quite inspiring. And I'll tell you what, at least for me very inspiring because they did a, so a xenotransplantation from a transgenic pig into a human recipient that didn't meet criteria for transplant and had a very extremely, I mean, if you would've put it on the list, you wouldn't have extremely high risk because the patient was the condition wasn't been arterial ECMO, was stuck on the ICU for a long time. And the patient had had no compliance in the past but it was very categorical about that. So there was a lot of ethical dilemmas in there, but I would cut to the point in terms that, they transplanted it, they faced significant problems, put in the heart in their recipient. 'Cause they took a big heart to put it into a big man. But actually once they opened the pig the heart was kind of small. So they had to

modify somewhat their technique and do some of the older biatrial heart transplant technique to be able to sew the heart and then they had an terrible interpretive complication that is very uncommon. But it happened on this patient, there was an aortic dissection and so they had to do replacement of the aortic arch with a frozen elephant trunk. So in spite that of all of that the heart looked hyperdynamic after them. So you got an eject fraction for around three weeks of around 80%, I would say. And a patient was able to get off the vein arterial ECMO and then there has some complications with the viruses. And then in week four or five, can't remember exactly what was it the heart started getting thickened and then apparently they took several biopsies and there were no rejection. So I found that quite remarkable. But it happened at kind of, the heart started getting thick, but it was not like kind of myocardial hypertrophy, looked like two or three times the thickness of the wall and then the function deteriorated and the patient passed away and then on the pathology was demonstrated essentially there were red blood cells, circulating within the myocardial fibers. So you would say it was kind of the endothelium was the sort of destroyed lately but there was no evidence of cellular rejection or humoral rejection. So I found that very attractive the concept and breathtaking, to see. But certainly we're not there and I think there's gonna have to be the more experienced system maybe brain data recipients and see how it goes. But it's not ready for a clinical trial. Anywhere near that, so-

Dr. Bell: Well thank you for those comments. So let's move back to the donation after circulatory death. So as you said earlier, these are patients who've had serious neurologic injury but technically are not brain dead. They have circulatory or cardiac respiratory failure. So presumably they're on inotropes suppressors and events later. But then you are presumably waiting to withdraw that support, in a appropriate donor. And as you said, then you wait for that circulatory arrest or death and you're gonna wait, I think you said five minutes the maximum but of course typically, I mean that patient's about to die or that heart's gonna die. And so there's that warm ischemic insult and so that's why you said, five minutes. Could you just maybe just briefly explain then what you do? I mean it sounds to me that you're going to basically be resuscitating that heart again with perfusion ECMO perhaps but maybe you just explain exactly what you do there. Because again, technically the patient isn't brain dead.

Dr. Villavicencio Theoduloz: Yeah, so lemme tell you a little bit what it happens before because we have to start with the donor that we are a little bit more selective with the donor. So the donor has neurological injury and then but the heart has to have normal function and a normal echocardiogram and then hopefully no inotropes. So we in very good circulatory condition. But what is the problem is the neurologic condition. So when they take the breathing tube out, in a controlled fashion in the operating room the donor blood pressure will go down but it will go down secondary to the neurologic and respiratory problem and then, lack of ventilation if you would. And then of course, there's a one period of ischemia, that we say, whenever the pressure starts, whenever the pressure on the door goes below 50, you start having warm ischemia to the heart. So the injuries starts there and then moreover, when it has stopped the heart and you have to wait five minutes. So essentially you have to resuscitate that recently previous very good heart in a way. And there's where it comes, the modern techniques of procurement that are essentially two, one is normothermic regional perfusion and the second one is ex vivo heart profusion. And I'll explain both for those I haven't heard about them. The normothermic regional perfusion, essentially, you go with a harder lung bypass machine or an ECMO machine to the donor and once the heart has a stopped and that has been declared, you open the chest and you quickly

cannulae the patient for cardiopulmonary bypass and then you occlude the cephalic vessels the vessels that go to the head. So to avoid re-establishment of the flow to the brain. So essentially you clamp the innominate, the left carotid, the left subclavian, and you go on bypass. So you go on bypass most of the time for around 45 minutes something like that. And then you come off bypass and then you take a look at the heart and see how that heart looks after being in bypass for 45 minutes and then you like it you take it out in the same way that you do a brain dead. So you give, cold blood cardioplegia and then you go ahead and transplant it into your patient. How'd that sound? Was that clear or, and then any-

Dr. Bell: No, it's very clear and obviously this is done under very controlled conditions. You've got an open sternotomy and you've got everything under control. But I think one of the important points you made but then the procurement at that point is the same as if it were coming from a brain dead patient

Dr. Villavicencio Theoduloz: Correct, correct.

Dr. Bell: And then you talked about the ex vivo system and so this is that so-called heart in a box. And I know you talked about this just recently, one of these sessions but maybe you could just briefly remind our listeners what that entails.

Dr. Villavicencio Theoduloz: Yeah, well this is kind of fascinating technology because it essentially is kind of portable ECMO especially design to procure a heart so that it is kind of device that the size of the dishwasher you take it on the plane and what happens is the DCD donor when the heart has stopped you take out the heart and put it on the OCS device and with intention of resuscitating the donor showing in that sense we will call it, sort of a direct DCD donation, without going in normothermic regional perfusion. So you put it directly into the ex vivo sort of ECMO circuit. So there's a pub, there's oxygenation you control the temperature, you see the hematocrit you see the pressure in the aortic root. But so you inject the blood through the aortic root that comes out through the coronary sinus and then you close the IVC and SVC and then the blood goes to the right ventricle PA and then you collect it again and then pop it again into the aortic root. So essentially you kind of provide a circulatory system within that device.

Dr. Bell: And you potentially then could combine that with your your normothermic regional perfusion as well in terms of, 'cause you're talking now, about transportation of that heart.

Dr. Villavicencio Theoduloz: Yes, so you are able now with this technique you're able to put the heart in the box and transport the heart and you transport it, in a normothermic fashion meaning 36 degrees with the heart beating. So you're able to hook it on the device, perfuse it and then get the heart beating. So what happens is that heart that was arrested, but it was a few minutes ago, a good function in heart you resuscitated on the device and essentially what you get at the beginning and what you monitor is the lactate levels. So you monitor the lactate levels during transport and when you're arriving to your recipient hospital and then you want your lactate levels, be kind of stabilizing or going down because as you know, the heart, has this unique capability of metabolizing the lactate. Not only when the heart is in shock, producers lactate, but when it's functioning well, it's metabolizing the lactate so it should start coming down. So if your lactates are coming down, with the heart on the device and then you see your heart is looking

good, with good contraction on the device then you go ahead and transplant it. And then in this case you sort of minimize the ischemic time because you are profusion all the time with the blood. I forgot to tell that when you have a DCD donor you put the cannula in the right atrium and drain all the blood from the donor to put it on the circuit of the OCS device. So that is what it produces the heart to recover on it and then you transplant. So for far there has been a US trial and then it has been approved for FDA use on DCD donors, the device. And then it's quite remarkable because the survival of those heart transplanted patients is the same that in a brain dead donor and provided that you probably were more selective, with the type of donors that we choose. And then there's a little bit of more primary graft dysfunction sort of meaning the need of vein arterial ECMO or a balloon pump or inotropes right after with this technique. But I think it is kind, in the way I see it is that the heart needs a little bit more time to recover completely because you might perfuse it, you take out the heart from the DCD donor and then you might peruse it, for four or five hours but probably the heart will need after the period of cardiac arrest a little bit more time to recover. So sometimes you put your recipient on on ECMO and then take it out really quickly and I have transplanted many patients at the heart after I implanted it, that doesn't work. And then that's what we need to kind of put our research on see what are the factors that lead to that that some of the hard, doesn't work but then you put your recipient on V-A ECMO and the reality is that it recovers very fast. So all those that I have done, they have recovered very quickly and then you pull out the vein arterial ECMO in your recipient in two or three days, is really amazing.

Dr. Bell: Yeah, it's really fascinating. And maybe just one quick question. Does this allow you then a longer window of time between the procurement and then the transplanting into the recipient? And I guess I'm thinking about transportation from does that allow longer distances for transportation or is it, are you still limited in terms of the time that you can keep that heart?

Dr. Villavicencio Theoduloz: Well we have prolonged quite a bit because with the cold storage method, we had kind of four hours and some people, especially the guys from Australia or ones that are Seattle, they have to travel longer, to get a donor maybe. And so, but in this case, I have easily gone eight, nine hours total out of the body time, so with five six hours of perfusion and then the beauty of it that you take it out the heart and then you sew it in and then it works perfectly well. So it's kind of, for me it's a game changer because all long ischemic times the dysfunction that have to withstand and then this makes the heart quiet strong. So here we go from Rochester, Minnesota we have taken hearts from New Mexico, from the east coast, from way west and then there's no problem. And then if the donor is brain dead you could use it is brain dead so the donor is brain dead and then you take it and then the heart works quite well on the OCS device and then there's less primary graft dysfunction than a DCD donor. As I said, the DCD donor has more primary graft dysfunction recovers quickly, but you travel long distances, you get at least four more hours. And then we need to have a little bit of a caveat here because the longer you perfuse it, I think on the device the hard sense to get edematous and I really don't know why is that, maybe it's not in the intrathoracic cage or what is going on, but it just gets a little bit of kind of petechiae and edematous and sort of, it will take a while. I mean, we as a cardiac surgeon would like, to put the heart on the device and then come at seven in the morning and do the heart transplant and then most of the team, the team would love that. But I don't think we're yet there because probably we have doubled the time but it's not forever.

Dr. Bell: Yeah, I actually, your transplant teams do not seem to be a service that is is done at convenient time. So you don't work by convenience, at least by at this point. Well, this is really fascinating and we didn't even really start talking about some of the ethical issues with DCD but presumably that's all being, I mean it's an approved, approach here. And if I'm remembering my history correctly I think the very first transplant that was done by Christian Barnard I think it was back in the sixties, that that actually was a circuitry failure, circuitry death and not a brain death patient. But correct me if I'm wrong but that's certainly something I remember, reading a number of years ago.

Dr. Villavicencio Theoduloz: Yeah, I believe it was a DCD donor, actually we didn't know, I mean, it didn't have that label at that time, because we didn't know what was DCD donor, but it was like that, the heart hat stopped but I believe, they put it really quickly on the recipient and then resuscitated on the recipient because obviously we didn't have a normothermic regional profusion or ex vivo heart profusion and then it worked quite well. So that's the way it started, I think in heart and lung, both first transplants were sort of DCD donors and then later on, kind of the conventional definition of brain dead was written.

Dr. Bell: Once again history, recycles itself. But also now we've just gone a little bit over time. I think we could be here talking about these advances for some time yet, but we'll have to stop there. Thank you so much for sharing your views and your experience on this and these remarkable developments in the world of cardiac transplantation. So thank you so much, Mauricio.

Dr. Villavicencio Theoduloz: Pleasure to be here. Thanks very much for the invite.

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