

JEFFREY GESKE: Greetings I'm Dr. Jeffrey Geske, assistant professor of medicine and cardiologist at Mayo Clinic. During today's Trending Topics video we'll be discussing reverse order liver transplantation. That's liver transplant before heart transplant. I'm joined by my colleagues, Dr. Sudhir Kushwaha, professor of medicine and the director of our heart transplant clinic, as well as Dr. Rocky Daly, professor of surgery and surgical director of the heart transplant clinic. Welcome.

ROCKY DALY: Good morning.

JEFFREY GESKE: Recently you've experienced successful reverse order liver heart transplantation. When are some times when you might actually think about combined organ transplant, either the reverse or the kind of more traditional combination?

SUDHIR KUSHWAHA: Well as you know, Jeff, there are certain situations where the heart and the liver are both affected sometimes by a systemic disease process which requires a combined organ transplant. Other times when the severity of the heart failure is such that the liver ends up getting cirrhosis, and we're familiar with that in conditions particularly where there's severe right heart failure. And then there are other diseases where there might be a concomitant liver process going wrong and we're considering heart transplant because the patient has heart failure, as well. And so those are the situations where we might consider doing a combined operation.

And we have several patients who we've done over the years who have undergone combined heart liver transplant in the normal order, which is heart first, followed by liver. And so we have quite an experience as an institution in doing this. Rocky might want to comment a little bit about that.

ROCKY DALY: So when the patients have failure in both organs, then we consider them for combined heart liver transplant. When we normally do the surgery if they need this-- and actually, we have quite a bit of experience with combined heart liver transplant. We've done about 35 cases which turns out to be the most in the world. So it's not a real common operation but there are some patients that obviously benefit from it.

The heart doesn't tolerate the ischemic time as well as the liver does. So normally in these operations, we do a heart transplant and then they immediately begin the liver transplant. And

they're doing the liver transplant then with a stronger heart, a better heart, because we've just put it in and hopefully that heart has tolerated the ischemic time and the surgery. So obviously we have to select the donors properly so the heart will be good for a liver transplant. In these cases, for immunologic reasons we considered reversing the order of the surgery to deal with the immunology.

JEFFREY GESKE: Well, tell me a little bit about that immunology. How do the elevated antibody levels-- how does that end up affecting this process?

SUDHIR KUSHWAHA: Well, transplantation has become very successful over the last several years largely because we have very good immunosuppressives. Now, those immunosuppressives are good at suppressing what we call cellular rejection. And in those situations, we have predominantly t-cells which can attack the newly transplanted heart and cause damage and ultimately rejection. But the drugs we give actually suppress that quite well such that severe cardiac rejection-- cellular rejection, I mean-- is actually quite rare.

Now, there are patients who have very elevated antibody levels. And these are what we call pre-formed antibodies. And quite often younger women, by virtue of having been pregnant previously, will have preexisting pre-formed antibody levels. Patients who have had previous transfusions can sometimes have circulating antibodies, which under normal circumstances don't do them any harm. But when it comes to transplantation, we have these very high levels which we can measure now and quantify using the current technology which gives us an idea of what would happen if there were antibodies to particular antigens on the donor heart.

So if you have very high antibody levels and the donor heart expresses a certain antigen, then those antibodies will really create a lot of damage and cause severe rejection, which is very, very difficult to treat because these antibodies, you can try and remove them, but they always come back because the b-cells which make them are still there in the recipient.

And so it creates a situation where we are unable to transplant certain patients because we're unable to find an appropriate match for them because they have very high circulating antibodies. And we have to make sure that the donor we get doesn't express the antigens to which that patient has antibodies.

So I hope that's reasonably clear. But with this concept of reverse order really came about as a result of our experience with combined heart liver transplantation, and we noticed that these

patients, we have the largest series, as Rocky just stated, really didn't suffer much in the way of rejection or even antibody mediated rejection. So I'll let Rocky comment a little bit more about that, actually.

ROCKY DALY: Right, we noticed in our experience that the incidence of rejection in the patients who had combined heart liver was much less than the rejection in the patients who had just isolated heart transplant. So that got us to thinking that this is obviously a immunologically favorable state. And we have the opportunity to collaborate with our colleagues in other areas of transplant through the transplant center here, which is a multi-disciplinary undertaking.

And the kidney transplant team was having the same experience when they were involved with combined liver and kidney transplant. And they also noticed this and noticed that the antibody titres went down-- just the antibodies to that donor, not all the antibodies, but just the antibodies to that donor didn't seem to be as high.

So we had this group of patients who are young patients and have become sensitized. They have a lot of antibodies and had the need for both heart and liver transplant. So many of them are congenital heart disease patients that have developed cardiac cirrhosis from their congenital disease, often Fontan physiology. So they've had multiple operations, multiple transfusions, but still they're young people in their 30s and 40s. And you're trying to find a way to help them.

We had really very little success with just reducing the antibodies with various medical means, which is consistent with other reports. And so it occurred to us that we might consider transplanting the liver prior to putting the heart in. And that might follow through, as Sudhir said, in terms of reducing the antibodies. So we proposed doing that.

JEFFREY GESKE: What sort of technical challenges did you run into now you've identified this issue and you've come up with a novel solution? As you began to approach it, what are some of the considerations in that regard?

ROCKY DALY: Well, from a surgical standpoint it's intimidating. Because if the patient has had multiple cardiac surgical procedures, and then we're considering doing the liver transplant while the heart, which has also been procured from the same donor, is just kind of waiting on ice in the corner of the operating room, ischemic time for the heart gets very long. And then we still have a heart operation where there are multiple previous surgeries and pretty massive adhesions along the section.

So we have to work carefully with our liver surgeon colleagues, and we kind of work back and forth. Ideally we do as much of the cardiac dissection as possible without having to go on bypass. And then they come and do as much as they can do. And they actually remove the liver while the organs are in transit so that as soon as they arrive, they can sew the liver in, which is a little different from what they normally have to do.

SUDHIR So timing is everything.

KUSHWAHA:

ROCKY DALY: Timing is everything. It's like this choreography that has to happen, because the patient won't tolerate hepatectomy for a long time. But on the other hand, we don't want to have the organ sitting in the corner while we're still working. We want to be really, really ready for them when they arrive in the operating room.

SUDHIR So we end up being limited, I suppose, by having organs which are close by. So some of the
KUSHWAHA: organs we might take from further afield because of the ischemic time, as Rocky already mentioned, is a limiting factor, we're really confined to having fairly local donors for this sort of situation, wouldn't you say, Rocky?

ROCKY DALY: Yeah, we need donors that are not too far away and obviously vigorous enough to tolerate what's going to be a longer than usual cardiac ischemic time. The other challenging thing is that we don't know how effective the liver will be, to what degree it will remove antibodies for some of these patients that have some massive levels of antibodies. And so we have some criteria that we've developed to try to select patients with situations where at least the liver has a chance. And we do that with the prospect of crossmatch which we accept as positive, but Sudhir might want to comment on the--

SUDHIR Yeah, we try and limit the degree of mismatch, to put it in simple terms. I mean, you can get
KUSHWAHA: high degrees of mismatch and low degrees of mismatch, and we try and minimize so that we get the best match possible in terms of antigen and antibody matching so that-- the fact of the matter is that I'm thinking back to the first patient we did. I mean, she had a lot of circulating antibodies, very high levels. But in fact, the major mismatches were only in three antigens. So that allowed us to limit the exposure to the donor liver.

We were very concerned. We went into this with some trepidation, obviously, because the price of failure would have been a bad outcome for that patient. And I think we thought about it

and formulated this strategy, and we minimized the degree of mismatch. And luckily the appropriate donor came up. Actually, the donor was at St. Mary's institution, so that also minimized the ischemic time issue which Rocky was just talking about.

JEFFREY GESKE: So it sounds like a lot of moving pieces between the antigen matching, having the organs close enough to have the timing right, minimizing the ischemic time. What's the Mayo experience been like so far, and where do you see it going next?

ROCKY DALY: Well, we've done four cases so far. They've all been successful. We are still limited by some patients having a much higher reaction prospect and the prospect of crossmatch where we haven't been able to always do the surgery. We have a kind of limit. We accept a positive crossmatch, but we won't accept a positive crossmatch that's extremely high. Because that tells us that perhaps the antibody activity is more than the liver will deal with. So we've developed a protocol where we will accept a positive crossmatch up to a certain level, a channel shift level.

Whether we could expand that, I don't know. At some point we'll have a problem. And as Sudhir said, the patients will be the people that will suffer from pushing the frontier maybe a little bit too hard, so we're being careful with that. There isn't really data to help us. The limiting factor is getting the donors. And that's the limiting factor, of course, in transplantation is having donor availability. So we have a large heart transplant waiting list. We have a number of patients on the waiting list waiting for this procedure. And it's very challenging and disheartening.

SUDHIR KUSHWAHA: The wait time can be very lengthy, unfortunately. It's very difficult for these patients. And we really feel for them, because they're very limited because they have such severe cardiac failure and liver failure, as well. But there's nothing we can really do to speed the process up. I mean, as Rocky said, perhaps we could consider changing our criteria. But then we're also exposing a greater degree of risk, as well.

JEFFREY GESKE: Great. I'd really like to thank you both for joining me today. It's been fantastic learning about some of these new groundbreaking approaches to both heart and liver transplant, or liver and heart transplant as it may be in this case. I'd really like to thank you both, Rocky and Sudhir, for a fantastic discussion. And I'd like to thank you as well for joining us today on this Mayo Clinic heart.org Medscape topic review. Thank you so much.