Strategies to arrest and protect the heart have never been more diverse. The session will be comprised of a basic science review of the physiology of the myocardium and the pathophysiology of myocardial injury. The scientific underpinnings of three contemporary cardioplegia solutions will be reviewed and a review of how registries might inform us about myocardial protection.
Discussion

Presented at the Advanced Myocardial Protection Symposium, San Antonio, Texas, October 9, 2015.

Friday 0955–1030 Panel FINAL
Robert Groom, David Fitzgerald, Amanda LeBlanc, Claus Preusse, Rich Ginther, Linda Mongero, Donny Likosky, Tom Kline, Collette Calame, Audience

Robert Groom: Thank you very much. I’m going to start with one question, and then we’ll take questions from the floor. You know, yesterday we spent a lot of time talking about the microcirculation and the glycocalyx and Amanda, you brought us a lot of information about that.

And I was kind of struck by, Jake, one of your—some of the evidence that you brought to us showed that there appeared to be more endothelial dysfunction when blood cardioplegia was used and less with crystalloid solutions. And from what we heard yesterday from Amanda, this just seems absolutely opposite of what one would expect.

So, I was wondering if either of you would like to comment on that. What we saw there from that one study anyway that endothelial function was better with a crystalloid solutions.

Jacob Vinten-Johansen: Yeah. We were a big surprised also on that study, and there was at least a surface correlation of the number of neutrophils in endothelial dysfunction. It’s not a blood vs. a crystalloid thing; I think it’s just hemodiluted blood, less neutrophils that can adhere compared to all blood cardioplegia with more neutrophils. I really don’t think it’s a blood vs. a crystalloid issue.

Amanda LeBlanc: Yeah. I was just going to ask, what exactly is in the blood that you guys are perfusing back in? Is it everything or is it some parts of it which are taken out?

Robert Groom: This is just blood from the oxygenator, and we do it just like you would do it in the operating room, just simply infuse back, and then wean off bypass.

Amanda LeBlanc: Okay.

Dave Fitzgerald: Donny?

Donny Likosky: Thank you all. Just going back to your talk, Bob, where _____ predominantly define low cardiac output as a composite of use of an intra-aortic balloon pump intra or postoperatively return to bypass for hemodynamic reasons, and return to the OR for bleeding, I think. That’s the components of low output.

Robert Groom: Back on bypass, balloon pump –
Donny Likosky: Return to the OR for bleeding.
Robert Groom: No. Two inotropes for –
Donny Likosky: Two inotropes.

Robert Groom: – 48 hours.

Donny Likosky: Exactly right. Sorry. So, in Michigan we’ve had a lot of pushback about that definition as defining low cardiac output. A number of the presenters talked about low cardiac output, and I wanted to know how those studies that you spoke about define low cardiac output because I think if we progress in some data analyses using the three registries that you discussed, we have to be on the same page about how we’re defining the endpoint that might relate back mechanistically to the cardioplegia strategies.

So, we’d like some help and insight about, 1) how have you, some of the presenters, defined low cardiac input, or 2) if we were to study the effect of del Nido or other cardioplegia strategies, what would be the right endpoints for defining, or to study the mechanism underlying cardioplegia?

Robert Groom: Claus, your work referred to low output failure. How was that defined?

Claus Preusse: It was defined in the same way, as you mentioned. There was no difference in our unit. The only thing that is by far more often used in the recent past, is the ECMO system. In Germany, there’s an appropriate trend, while I would prefer the intra-aortic balloon pump, but there’s a trend, being driven by the anesthesiologists to implant an ECMO system as soon or early as possible.

Robert Groom: Do you think there is a good clinical outcome to look at as we evaluate these techniques?

Claus Preusse: We should do it. To my opinion, I do not know a comparative study with intra-aortic balloon pump and ECMO. But, I think nowadays it is necessary to do this.

Dave Fitzgerald: Tom.

Audience: Tom Klein from Vanderbilt Children’s. Great session, lots of good information. I had a couple of questions about the del Nido cardioplegia administration that maybe Linda and Rich could kind of comment on. Can you comment on the delivery pressure that you guys use for the pediatric cases? Was it changed at all when you changed to del Nido?

Rich Ginther: I wouldn’t say we necessarily changed it, but when Dr. Forbess came he’s got an extremely accurate digital pressure monometer on his finger, [laughter] and it’s impressive. Actually, but seriously, when he first came we were directly measuring the pressure in the aortic route with the needle they were handing off to anesthesia because they really wanted to focus on that pressure.
His goal is to achieve some sort of normal mean pressure for that patient and the delivery pressure, so we correlated those pressures with their cardioplegia system pressure, and so as the patients get older, we give it incrementally higher aortic route pressure when we deliver.

But, every single time we deliver they always say, “What’s your pressure? Can you increase the flow?” And they’re really trying to palpate that aorta, and they do it every single case. Did I answer your question?

Tom Kline: Yeah. Actually, that was our exact same experience at Vanderbilt because our surgeons have that same digital pressure.

Rich Ginther: It’s amazing.

Tom Kline: We delivered it a lot slower with a lot lower pressure, and they were really concerned about denuding the aortic intima by delivering at excessively high pressures, and for neonates we’ll end up getting our back pressure that we see on the pump of about 45 mm on a neonate, and we usually arrest from about 3 to 4 mL/kg. So, get a great result.

Linda Mongero: So, for adults we used—we gave cardioplegias just as we do conventionally. We used 100 mm of mercury. We did due diligence and looked at the new solution and on the various cannulas that we used to deliver cardioplegia, but same for antegrade and retrograde, we used the same conventional 40–60 for retrograde.

And the surgeons are really—at least my surgeons—are very impatient when it comes to cardioplegia, and I think it’s one of the most important things we do, and it really gets me upset when we’re in the OR, and they’re yelling, “Hurry up. Hurry up.” I’m like, “This is like the most important thing.” Myocardial protection. Let’s just take our time. They want to get going, they can’t stand there looking at the solution going in.

But, almost within 250 ccs the hard starts when you give del Nido, and then we give the rest of the dose, just 2 a liter, and then again, we wait to see how long the cross clamp is and the surgeon decides, if I still have another half an hour of work maybe I’ll give some more, if not they’ll just continue at that dose. As long as there’s no activity, no more del Nido.

Robert Groom: I want to just take a minute and make a plug for the workshop we did yesterday and we’re going to do today. We had five presenters who presented their techniques, and as Dave mentioned, this is going to be part of a course in AMSEC University. We asked them to give very specific instructions about how they monitor the pressure and how they deliver the solution safely, and I think this is so important, Tom, you said that really is the key. How this is delivered, and we talk about these different solutions that can be delivered in very different ways and different centers.

Audience: I have one other question for Rich regarding calcium, recalcifying the patient. You said you don’t necessarily correct the calciums after you initiate bypass, how low do the calciums get, and then what’s your protocol for recalcifying?

Rich Ginther: Yeah, so it’s a little tough to control. We were really just trying to mimic sort of a Boston protocol for that, and so when we add blood to the prime for maybe a neonatal circuit, we try to have a target resultant ionized calcium on bypass in a range of about 0.8–1. So, it’s a little bit lower, but not really low.

If you have it in that range, when you mix it one part blood to four parts crystalloid, it gets you in—a lot of del Nido’s calcium research, targeted calcium levels at about 0.2–0.5 for the delivery solution, so I think that’s part of the intention of how that’s mixed. And so, 0.8–0.1 going on bypass, you can’t always get that, and it’s hard to actually really accurately get in that range, but that’s the intention.

Audience: So, if it was lower than 0.8 you would recalcify after [crosstalk].

Rich Ginther: We’d give a little bit, yes.

Audience: Oh, okay.

Rich Ginther: We measure gasps on our circuits prior to going on bypass, so we’ll get an idea of what the calcium level is.

Robert Groom: Dr. Preusse, would you like to comment on that? You talked about recalcification after a Custodiol.

Claus Preusse: Generally, there is no need to recalcify, but if there are low blood calcium contents, they administer calcium, but there’s no routine in it. I make a joke on your question concerning the impatience of the surgeons using cardioplegia. I personally know the ideal cardioplegic solution as follows: administration of 10 mL in 10 seconds and have a safe arrest of 10 hours. This is what the surgeons like to have.

Robert Groom: Thank you.

Audience: Thank you very much.

Robert Groom: I was struck by what you shared, Dr. LeBlanc, yesterday about the gender differences, and I’m just wondering, we were beginning to learn more when we look at transfusions that men and women are different. We’re finally learning in 2015 that men are different from women.

I’m wondering if at your center you’ve looked at the differences in—Amanda shared with us yesterday that from her research for women, a lot of the injury is related to the capillary level and low capillary reflow, but with men, the predominant issue seems to be the atherosclerotic process and the ischemia to the tissue –

Amanda LeBlanc: To the large vessels.

Robert Groom: – so there might be a different mechanism. So, I’m wondering if in the future there’ll be a strategy that’s different for men and women. Have you looked at that? Would any of you like to comment on that?

Claus Preusse: We haven’t.

Robert Groom: You haven’t looked –
There is almost no sign of women as we begin to see that, but I found that very interesting from your presentation, Ron?

Audience: Yeah. This would be another question for Rich and Linda real quick. Really more for Linda? We currently run a Buckberg style formula, four to one for our adults and for our pediatrics. For our pediatrics specifically what we do is we give magnesium in the period within about 5 minutes of taking the clamp off. And I would say in 80–90 percent of the kids, we get spontaneous reanimation sinus rhythm.

Robert Groom: That’s 5 minutes after the clamp comes off you give it?

Audience: Five minutes before the clamp comes off.

So, if he’s –

Robert Groom: So, you recalcify before.

Linda Mongero: Magnesium?

Audience: Right.

Linda Mongero: He gave him magnesium.

Robert Groom: Oh, magnesium. I’m sorry.

Audience: Magnesium, yeah. So, and if we don’t get back into sinus rhythm we’ll give a dose of Lidocaine as the clamp comes off and defibrillating. We’re investigating the switch to del Nido, and I was wondering, because you made this kind of a similar switch, do you think I would expect—should I continue to empirically give magnesium? And would I expect my Lidocaine requirements to go up or down moving to del Nido?

Linda Mongero: I would say do not give any out of _____.

Especially to the del Nido solution. Once you add anything to del Nido solution it’s not considered del Nido anymore.

Audience: I’m saying.

Linda Mongero: I know. Afterwards –

Audience: I’m saying to the patient.

Linda Mongero: You will not need to give magnesium, and you certainly will not need to give Lidocaine for sure.

Audience: Thank you.

Robert Groom: Claus, your opinion on the Lidocaine? I’m hearing from my surgeons that use del Nido, they make this argument, they say the half-life of Lidocaine is relatively short. We want you to give a bolus of Lidocaine to the patient before the clamp comes off. How do I argue that –

Claus Preusse: As you may know, Procaine was used in the first, unbuffered Bretschneider solution, and I think there is almost no significant difference between Lidocaine and Procaine concerning their membrane stabilizing effects. But, the problem is if you add a buffer. If the membrane is strongly stabilized, it will influence the permeation of hydrogen ions from the intra- to the extracellular space. It follows, that you will indirectly lose buffer capacity. In other words, the buffer efficiency cannot be fully taken up and that was the reason why we excluded Procaine. We have done measurements and looked at the pH, the interstitial pH and compared this to the same lactate content. If you add Procaine, the lactate pH curve is shifted towards the alkalosis compared with a Procaine-free HTK solution.

That means, if you have an effective buffered solution, Lidocaine or Procaine or other membrane stabilizing agents will negatively influence the buffer capacity. That is a consequence of this.

Dave Fitzgerald: Dr. Baker?

Audience: Amanda, the presentation you gave was fantastic. It strikes me that your epicardial cell patch could be a fantastic adjunct to cardioplegic solution in a patient with recent myocardial damage. I’m wondering whether the panel or yourself would like to comment about that? I have one question. When you said you’ve organized a processing system that takes 70 minutes, but then it has to become three dimensional, and my understanding was that took 14 days.

Amanda LeBlanc: Right.

Audience: So, could you process, apply, and it would sort of build up its three dimensions over time? So you could do it at the time of surgery?

Amanda LeBlanc: Yeah. So, the whole field of bioengineering is trying to make it to where you could get your cell injection and then be able to immediately apply it in a patch-like format right away. So, right now the way that we’re using it, it would not be point of care, but I think that some of the different ways that they’re trying to combine the cells immediately with some delivery solutions that are already FDA approved. I think that it’s definitely within the next couple years that we could have something that would be applied right away.

Robert Groom: Any other panelists want to comment on the patch as an adjunct to protection, future speculation? I think you’re a little over our head. Question over here?

Audience: Yes. One for Linda, then one for the panel. Linda, you allayed many of our fears, I think, with your surgeons just adopting the solution and yet being kind of all over the board of the direction of delivery and even time intervals. With these different methodologies of delivery, do you see differences per surgeon on the reoccurrence of spontaneous work?

Linda Mongero: I haven’t looked at it per surgeon.

Audience: Or even anecdotally?

Linda Mongero: Anecdotally, I would say I’m inclined to say no. Even no matter how they give it, fast or slow, antegrade, retrograde, both. Del Nido works the same every time. It stops the heart. As long as you’re delivering it properly, it stops the heart, and then we give the full liter, and it stays quiet unless there’s washout, and you can actually see that.

And when you first start giving del Nido coming from giving every 20–30 minutes, you get really nervous sitting...
there because you’re used to saying, “Okay, 20 minutes on cardioplegia,” you just get, especially if you really care, which most perfusionists really do, and you really get nervous sitting there going, “Oh my god, I hope everything’s okay.”

And a few times I walked to the head of the table, I was a wreck because I thought, “This is what we do all the time, this is our responsibility. And they’re just ignoring it.” They give it and they’re ignoring us, but it works.

**Audience:** So, even the 30-minute interval shortly before the clamp comes off you still—no more —

**Linda Mongero:** No activity. No activity at all.

**Audience:** And no more defibs or pacing?

**Linda Mongero:** Nothing. And the next MI situation for the perfusionist and everybody in the OR is when they pop the cross-clamp off and nothing happens. Usually you have a period where you take the flow down, take the cross-clamp off and the pressure’s kind of down. As soon as you get your blood pressure back up into the 70s and 80s, boom. Spontaneous defibrillation.

**Audience:** Thank you. Now the panel. I’ve always been blood content fan, and it was interesting for me to find a publication last—well, an article in a publication last year, someone who actually—I think his name is Loberman from Brigham and women’s actually did a modified eight to one del Nido and had some—it was a very small sample size, but I would like the panel’s thoughts on this eight to one modified del Nido.

**Robert Groom:** I think you would hear from this panel, every one of them thinks that their technique is the technique to use. I would mention to you, if you haven’t gone to the workshop, there’s one particular station where a solution that is blood and the additives from del Nido that are used, and there’s a poster on that as well, which might be worth looking at.

**Audience:** Very quick question for Linda. I have surgeons that like to use a syringe of blood when they’re doing their coronary distals to test for leaks. Do yours do that, and is that—

**Linda Mongero:** Yes, our surgeons do that too.

**Audience:** Is there any washout or is there any problem with that?

**Linda Mongero:** No. There hasn’t been. They just take blood from the arterial cannula. We have a stop clot and a pigtail and they’ll take that and they just want to see what the anastomosis looks like. No, there hasn’t been. We don’t do a lot of isolated CABGs at Columbia. We mostly have combined procedures.

**Robert Groom:** I’ll take a question over here. Collette?

**Collette Calame:** OK City OU Medical Center. So, every time I listen to something more about cardioplegia I just get even more confused. Just when I think I’m starting to understand it, I realize I don’t understand it at all. And one of the specific things I had question wise, Dr. Preusse. I know originally the Bretschneider solution had no calcium in it, it was acalcemic HTK essentially? Was that not the case? And then they added the calcium because they had some stone heart?

**Claus Preusse:** No, I’m sorry. I’ve often heard this argument. It has never been a calcium-free solution. Even from the beginning in 1964 it has always been a low calcium solution

**Audience:** I could—

**Claus Preusse:** When Dr. Bretschneider first published his concept for myocardial protection the solution was unbuffered and the sodium and calcium contents were very low.

**Audience:** In the literature there’s something totally —

**Claus Preusse:** Yeah. Yeah.

**Audience:** – and that’s where I got that from.

**Claus Preusse:** Sorry, I have no idea

**Audience:** Thank you for straightening that one out. So, the other question was with the del Nido cardioplegia, and I knew that calcium is important and a small amount of calcium so that theoretically anyway, you don’t get the calcium paradox when you get reperfusion.

And so, del Nido’s got calcium from the blood, now we know Custodiol has calcium, we know four to one cardioplegia has calcium, and then I hear a presentation by a student from Vanderbilt, Tom Klein’s program, and they had a sickle cell patient that needed to have surgery like the next day, and they had blood cardioplegia on the adult side, and del Nido on the children’s side, and this student actually decided to use the del Nido solution without blood.

So, this is now an acalcemic cardioplegic solution, and he gave a presentation at the—it was a Chicago meeting, great results, no issues. It did very well. So, then I’m going. “Wait a minute. I thought you had to have a little calcium in there to prevent the calcium paradox.” So, is that an important thing to everyone in the panel?

**Claus Preusse:** The calcium paradox, we should always keep in mind, it was a wonderful experimental model being developed by Zimmerman and Durrer in the Netherlands. You should always keep in mind, a calcium paradox will be provoked if you have normal physiological sodium concentrations and no calcium.

A calcium paradox will occur immediately after declamping of the aorta, if the heart had been arrested prior to that by a calcium-free solution with normal sodium concentration. A calcium paradox can be reduced or avoided, respectively, by lowering the temperature and increasing the magnesium content. These are two main aspects that reduce the risk. But every solution which contains traces of calcium will never provoke a calcium paradox.

**Robert Groom:** Thank you. I think we’re going to stop there. We’re about 5 minutes over. Please seek out this panel if you have other questions. We’re going to take a break. I’m sorry, Rich, the only beverages we have are coffee and soft drinks; we’ll put them on the list next year, the list that you provided us. So, visit the exhibits and enjoy the flip classrooms this morning. Thank you all.