I think we’re going to be really talking about Del Nido today, because of its observed effectiveness. It kind of went viral. A lot of surgeons wound up leaving Boston and going through other centers and taking it with them and it sort of spread like a little virus and other surgeons wanted this single-dose cardioplegia. The idea of operating uninterrupted sounds pretty appealing. Like Bob (Groom) mentioned—let’s see here, if I could—yeah, I’m going to just go out here. I’ve been using this—well, we’ve (Children’s Health Dallas) been using this solution, excuse me, at our institution for about 10 years on over 3700 congenital surgeries. You know, we do pediatric and adult congenital procedures and we use a solution for everything.

We were recently assigned three stars in the Society of Thoracic Surgeons (STS) based on the mortality risk models. Only 6 of 116 centers were assigned that rating and though I don’t think cardioplegia is the reason you get a high rating, I think to get really good results you do need to protect the myocardium. And when I asked around on the six centers and they were well represented on microplegia, custodial, Del Nido. It was across the board, so there was no inconsistency there.

We’ve been using this solution for so long and presenting it at these meetings, we constantly get asked what’s your protocol, what’s your cardioplegic circuit, because we have this mini (cardioplegia) circuit. If you were at the myocardial workshop you got to see that, and we recently published our experience with the solution a couple of years back in JECT.

I’m going to start off with just a real quick overview in just pediatric myocardial protection and then we’ll get into the Del Nido part of the talk. First, I think most of you know that cardioplegia is just a part of myocardial protection. When we most often talk about myocardial protection we talk about cardioplegia, but myocardial protection is really anything that reduces metabolic demands in activity. Cardioplegia prolongs the tolerance to ischemia.

Excuse me. I’m doing two things at once here and I’m not doing a good job of that. All right.

When you look at all of these techniques that everyone uses, it’s kind of crazy. They’re all across the board. There’s really no consistency and it’s really a mess. There’s a lot of conflicting techniques and some are actually literally the opposite of each other. I know I remember being a student and going on clinical rotations and we had surgeons going cold, continuous, and warm. It really was like working with a bunch of bartenders with their own little cocktail. If you really think about it, cardioplegia actually is quite literally almost a cocktail. Maybe your surgeons like a Sazerac style cardioplegia, but you know, we used to do beer and alcohol during these sessions in here a long time ago. I don’t know why they stopped doing that, but alcohol was a very important part of these talks.

Let’s see here: to even complicate it even further is now you have these differences of the immature heart. As the myocardium develops the myocytes and myofibrils elongate, the number of mitochondria increases, and it’s responsible for adenosine triphosphate (ATP), of course, and also, the structure and amount of sarcoplasmic reticulum change, which, you know, is responsible for calcium management.

For the physiologic differences, basically, it can be broken down into how the myocardium manages a calcium energy consuming processes, and we’ll keep this in mind later in the presentation when we talk about the different formulations. If you could actually address these differences in the anatomy and physiology, it would be a great way to create a very special, specific cardioplegia for a very specific subgroup of patients. But, unfortunately, it’s actually unclear when the transition happens from immature to mature. You don’t really know, so to actually tailor a cardioplegia for a pediatric patient is actually
very difficult, and we’re just going to talk about booze today. [Laughter]

Our peers have questioned the evidence. We have a couple of articles up here that just question and also look at the data that we have. Really, it’s such an empirical nature of all of these different techniques and the answer is that the amount and quality of the scientific evidence actually suggests that myocardial protection is experience based. One of the articles up here, the second from the top, our student faculty (Ashley Risso) will be describing that information in a poster session today, so please check that out. But the general consensus here is that we need more significant resources to move away from single center of studies and may do more clinical trial-like approaches, like blinded, randomized, multi-center studies. It’s been done. It’s difficult to do. Maybe these registries that we’re being more involved with will be helpful and Bob will touch on that a little bit later.

The STS does a nice job of collecting some of this data and they organize cardioplegia in a couple of different categories. Depolarizing solutions are just potassium based. Del Nido is a modified depolarizing solution, because it uses magnesium and lidocaine. In fact, yesterday at the myocardial workshop, a lot of you mentioned in your microplegia and other solutions that you use, your cocktails, many of you contain all of these different additives. We just heard a nice talk about hyperpolarizing cardioplegia, so I don’t need to get into that.

Then, with depolarizing solutions, if any have used them many years ago, just the simple solutions, they worked, but they really weren’t that good. You didn’t really have a very complete arrest and specifically in pediatrics, it’s important to recognize—let me go back—that the intracellular sodium and calcium overload, and also the energy expenditure, because of the differences of the mature and immature myocardium that needs to be addressed.

Here’s a nice little schematic that just shows how the various additives affect the sodium, calcium, potassium channels and their effect on the action potential. You can see that the depolarizing solution works on those fast sodium channels and it’s just important to note that many of the ion pumps require ATP and will continuously expend energy. So sometimes, if you just choose to depolarize the heart, which could actually leave the heart electrically and mechanically excitable, especially if you don’t control calcium.

Let’s see—let’s move on to the next one here. We touched on this a little bit earlier in one of the other talks about effective cardioplegia, but whether it’s an immature myocardium or a mature myocardium, the solution needs to give you a quick arrest. It needs to protect the myocardium. It needs to be reversible, of course, and also it should have no toxic effect on the heart or other organs. That’s actually been brought up with giving large doses of Del Nido over, and over, and over again, and actually giving too much lidocaine.

So, some of these solutions are new. Some of them have been around for a long time, but we’ve been talking about these for a while and they’re gaining interest, especially at these conferences. It’s also interesting to note that whether or not—maybe cardioplegia should be tailored for individual patient needs. Also, these single shot formulas, are they safe? Sometimes it’s unclear what the actual safe range is for those, especially with Del Nido. We get that question all of the time.

As I mentioned earlier, we’ve been using it for about 10 years. Our surgeon, Dr. Forbes, trained with—actually, not trained, worked with Dr. Del Nido in Boston, and when he traveled to Dallas he brought that formula with him. We were using Buckberg solution for many years, actually, with very good results. Also, we used a modified solution that was from Toronto. Dr. Ivan Rebeyka was a researcher up there and he did many—did much research on cardioplegia. Actually, that solution we were using then, that Toronto formula, was very similar to the Del Nido solution and that’s actually because Del Nido was a researcher there with that group and so maybe had some influence in developing this solution. Dr. Del Nido is from Chile, so maybe his cocktail of choice is a little Pisco Sour.

I don’t think he just threw together a little cocktail. Actually, Dr. Del Nido is no newcomer to—if I get—oh, did that not work? No. The animation was so awesome. [Laughter]. That was—oh, man, I had this awesome scrolling list of like the 100 publications he had specifically on myocardial protection. How dare that not work?

But, he really researched a lot of this blank slide. He was a researcher in Toronto in the mid-1980s and then actually in Toronto, and then he moved to Pittsburg to be a clinician there and also, he did a lot of research on cardioplegia there; then moved to Boston in the mid-90s. And if you look at his body of work, he spends a lot of publications on buffering, calcium management, reprofusion injury. When he was in Pittsburg, they actually even patented cardioplegia solution and some people confuse that the Del Nido solution was that solution. It’s actually not. The Del Nido solution is a modification of that patented solution from Pittsburg, which did actually expire. That solution actually used histidine, and so we heard the benefits of the histidine as a buffer (from Dr. Preusse), and I think when he was developing a solution I think at the time, from what I understand, histidine was very expensive and he was looking for a way to sort of mimic that patented solution. So he added blood to the solution for maybe some of its buffering properties, even though it’s a small part of blood, but it’s very similar to that patented solution. He did spend a lot of time developing it and so I think the (drug) concentrations are very intentional.
When you look at the actual research and the publications specifically addressing Del Nido, there’s really only about 16 that I could find. The ones that are in blue are specifically related in some way to pediatric profusion. The ones in purple are specifically related to adult publications. Linda Mongero will be talking about those. But, even when you look at the pediatric literature, there really isn’t much. Most of them are single-center studies.

One of the studies is from our institution, number 16. I don’t know if the laser pointer works here. It’s not going to show up there, but on the bottom right here, one of the original publications—by the way, these are in chronological order, but the last publication, actually, maybe the original publication, found that the Del Nido solution actually effectively controlled myocyte calcium levels in the energy dependent processes, which I think was exactly the intention of the solution as Del Nido designed it.

When you look at the cocktail recipe, you can see that it’s a plasmaLyte-based solution. I think he used that because it’s calcium free. It uses potassium bicarbonate as a buffer, probably not as good as histidine. It has some blood in it, so maybe you get some buffering properties there, although I’m sure it’s minimal. What makes this a modified depolarizing solution is the lidocaine and the magnesium. In our institution, we have our pharmacy compound the solution for us, they keep it refrigerated. It has a beyond use date of 7 days. The compounding pharmacist told me that the approximate cost for the material is about $91.00, so I think it’s relatively cheap compared to some of the outsourced solutions you could buy on the market.

Here’s that schematic again, except this time I’m just illustrating where the Del Nido additives work at the certain pumps. Remember, if you depolarize with potassium, protecting the myocardium also heavily depends on sodium and calcium management. This is where Dr. Del Nido focused so much of his research. The lidocaine gives you electrical inactivity by preventing sodium shifts; this in turn prevents calcium accumulation to the myocyte. With the additive magnesium, mechanical inactivity is also achieved. Magnesium reduces intracellular calcium accumulation, possibly by its calcium antagonist effects. It also inhibits L-type calcium channels, sodium calcium exchange, and competes with calcium binding to troponin.

Here’s our single-dosed technique. In Dallas, I sometimes don’t like calling it a single dose. We like to call it a long and strong dose, because we don’t always give it as a single dose. Our longest single shot is 206 minutes. We surveyed our data for over 10 years and 206 is a long time. It’s given 1:4, blood:crystalloid. We have a water temp in our system at two degrees and we typically get a delivery temp usually around four to six degrees when we deliver. Also, it’s volume based. It’s 20 mL/kg up to about a liter and we’re very vigilant on monitoring the aortic root pressure and we deliver usually to mimic normal physiologic mean pressures.

Now, I mentioned that we don’t always give a single dose, but we found that when we surveyed our data about 90% of the time we do. That usually gets for those really complex arch repairs, switches, complex Tetralogy of Fallots (TETs). We’re giving single doses.

The most common question we get is, “Well, when do you give a second dose? How do you know when to give it?” For the most part you really don’t give it unless there’s electrical activity. Do we see that (electrical activity)? Usually we don’t, but when you have a lot of washout in the coronaries, I don’t care how good the cardioplegia is, if you have washout, the heart is going to beat, especially if you start warming.

So we broke down some of our data. If you could just look at the blue range data. That’s the cross clamp time in minutes here of our shortest cross clamp times where we actually multi-dose. Then we have these upper limits of our longest doses and we’re typically multi-dosing for when there’s lots of collaterals, double switches. When we know the aortic cross clamps can be much longer than 120 minutes, we actually consider giving those doses maybe every 60 minutes, primarily actually to keep the myocardium cool. Here, on the gold line here, by year I have our longest single-dose cardio shots and for the most part we don’t get re-dosed unless we see an electrical activity.

Here is just a blood gas of when you mix the cardioplegia. The calcium level is pretty low, but that’s also intentional, so we actually don’t correct calcium when we go on bypass. We actually intentionally let it drop a little bit, because, you know, we prime with blood and fresh frozen plasma (FFP).

Let me just move on here for the sake of time. Some of the extra points here that everyone always asks us about the multi-dose, I kind of covered that a little bit. I think patient core temperature is a factor, because when you’re only giving the one dose and if you’re doing warm surgery, which I’ve heard many centers doing, I think that the protection isn’t as good. When we give our very long doses, like 3 hours on a single dose, we’ll cool to the mid-20s to low 20s. Also, time vs. volume: if you’re giving a 20 mL/kg on a patient weighing 1 kg, which we’ve done, that dose could go in fairly quickly, so sometimes we’ll try to really get that delivery time at around a minute to really at least insure that we’re at least cooling the myocardium. Sometimes we use it as irrigation. If we’re irrigating, let’s say, for atrioventricular canal, if we’re irrigating the mitral valve a lot, a lot of that will wash out into the aorta and rinse through the coronaries, and so we use just a crystalloid component (of Del Nido) as an irrigation.

We also try to minimize our FFP and packed cells in the prime simple because of the citrate-phosphate-dextrose (CPD) and it has such a high binding coefficient with magnesium and that could actually chelate the magnesium...
in the cardioplegia, so we try to at least minimize that. We have a target hematocrit on bypass of 30.

We do use a solution as our transplant solution. The take-home points are just that it is nice, because it allows you to operate uninterrupted. It’s primarily done as a single dose. That’s why we’re talking about it. It does control the myocyte calcium levels in energy-dependent processes. We found that in the original Del Nido study. We don’t know how long a single dose is effective. We’ve done it over 3 hours and those hearts snap right back. It’s empirical, but at our institution we have good results with giving a single shot over 3 hours. Although it’s designed and the research was done on immature hearts, we use it on all our patient sizes, not just the immature myocardium, and as you know, many adult centers are beginning to use it.

Thank you so much for your time. I really appreciate it. If you have any questions we’ll take it at the end.