Del Nido Cardioplegia—Not Just Kids Stuff

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Good morning. It’s nice to be here. I’m thankful to the program committee for inviting me. I really appreciate it. Yes, it’s going to be bittersweet leaving New York Presbyterian Hospital, Columbia University Medical Center (NYP-Columbia). I’ve been there for 30 years and I grew up there and it’s kind of sad, but you know, I’m moving on to working at home and doing some new things, and I’m looking forward to those endeavors.

So with that, I have no disclosures. However, I am freezing in this room. One disclosure I’ll make, and I’m sure all the other ladies are as well.

Just to briefly remind you of myocardial oxygen consumption, you can see in this table that in the vented beating heart at 37 degrees, it’s about 5.5 mL/100 g/min, but when your temperature drops to 22 degrees, oxygen consumption decreases to 2.9 mL/100 g/min. The fibrillating heart consumes the most oxygen, and at 22 degrees, again the consumption decreases to about 2. But cardioplegia provides the most effective myocardial preservation. At 37 degrees, when cardioplegia is given to the heart, consumption is 1 mL/100 g/min, and with temperature lower than 22 degrees, it is further reduced to .3 mL/100 g/min. So cardioplegia really provides a very good protection.

I’m not going to go through the cardioplegia history because we had a fine review of that in one of the speaker’s slides. In 1972 though, you can see we had hyperpolarizing solutions (Bretschneider and Kirsch). In 1978, 4:1 Buckberg solution was introduced, and then in 2003, single-dose cardioplegia from Dr. del Nido. At NYP-Columbia, our cardioplegia strategy was a combination of Plegisol and albumin crystalloid solution for many years. Then for a very, very long time—I can’t even remember how many years, but it seemed like almost in the whole history of my career there, we just used crystalloid cardioplegia 4:1 blood. And then in an effort to join the blood conservation, we decided to completely switch to Quest Medical whole blood Microplegia, and we eliminated that liter of crystalloid and we thought that’s where we can contribute toward solutions and, in addition, modifications to shrink our circuit.

Then almost at the same time, we switched to single dose del Nido 1:4 cardioplegia, but incidentally there are very, very few publications for its use in adult surgery. Dr. Bacha who had worked with Dr. del Nido in Boston came to Columbia University at that time. He had started using the single dose del Nido. So all of the other surgeons started asking “well, if it works for adult congenitals and the kids, why shouldn’t it work for valve, adult valves at least?” And I said I have absolutely no idea, you know, but here we go again. I have to think about what’s going to happen with cardioplegia. Del Nido solution is used in kids. It’s used in adult congenital surgery. It could be used in valves, valve/coronary artery bypass grafting and maybe even in procurement, but nobody really knew.

So of course, I was challenged, trying to find for my surgeons—this became my job solely—a publication on del Nido use in an adult. So I went through the literature and this is what I found, this article by O’Blennes et al., “Protecting the aged heart during cardiac surgery: The potential benefits of del Nido cardioplegia.” I did not reveal to my surgeons that this paper referring to delNido use and adults was used in adult rats. So I kind fibbed to them about the reference, but this was really all I could find. The objective of this information was looking at aged heart. The method used isolated the cell model of cardioplegia arrest and reperfusion in senescent rat hearts. But what they did was a very, very elaborate study. They isolated 3- or 4-month-old myocytes and then they measured the sodium current in single myocyte strands. They looked at the mechanism of voltage activation and inactivation in the presence and absence of lidocaine. They also tested this on 24-month-old rats, which incidentally are equal to a 70-year-old patient, and they looked at isolated working hearts.

And the hearts were arrested with cardioplegia 60-minute ischemic periods and then reperfused, and troponin
was assayed. So what they found was that elderly hearts are not well protected by some cardioplegia solutions and that the aged heart was similar to the immature heart, more susceptible to ischemia reperfusion injury, poorly equipped to handle intracellular calcium overload. They hypothesized that a cardioplegia strategy developed for immature hearts may also provide superior myocardial protection for the aged heart. And you can see that the del Nido cardioplegia solution was associated with less activity—here—during the arrest and lower intracellular calcium in the aged myocytes (1).

The return of the rhythm after reperfusion was much longer in the del Nido group as well. You can see here. The inactivity during early reperfusion may improve myocardial recovery. Also they found that during reperfusion coronary resistance increased with the standard solution but not with the del Nido solution. The return of spontaneous rhythm may be due to the lidocaine, which can promote coronary arterial vasodilation, or alternately may be when 4:1 standard solution with a higher hematocrit was used, which could cause microvascular obstruction related to hypothermia or induce sludging.

They concluded that del Nido cardioplegia prevented spontaneous activity during cardioplegia arrest, reduced myocardial injury, and resulted in superior myocardial function after reperfusion in these aged hearts, and that del Nido had the potential to provide superior myocardial protection for older patients undergoing cardiac surgery. That’s why we went on to move it into our clinic.

Another article and this is by O’Brien et al.—I think they’re in the same lab as O’Brien—the pediatric cardioplegia strategy resulted in enhanced calcium metabolism and lower serum troponin as you can see here. Practically nothing in the del Nido group (2). And the compelling finding was that there was no action potential that could be stimulated in the del Nido-infused myocytes, but the modified Buckberg-infused myocytes could be stimulated soon after.

So with that, Kevin Charette, who now works at Seattle Children’s Hospital, used to be one of the chief perfusionists in our Children’s Hospital in New York did this study using single-dose myocardial protection technique using del Nido cardioplegia during cardiac or congenital heart surgery procedures. He looked at 34 patients, pediatric patients, with cross clamps greater than 90 minutes, and they were grouped by modified adult cardioplegia solution vs. a del Nido solution. So here he was—even though we began using it he wanted to look back and study what was happening before use of del Nido.

So as you can see here, del Nido is this recipe. And the modified arrest dose for an adult was 1:1, 15 mL/kg, and then 5 mL given at every 30-minute intervals. The results of that study were simply that the intraoperative glucose was less because there was no glucose in del Nido and the number of doses was also less because it was given once. And del Nido is safe to use for all types of congenital heart surgery compared to our modified adult solution. So that was just a simple study that was done.

The question is, which solution is best? There are a number of studies that show conflicting results as to which method provides better protection, multidose or single dose. Multidose solutions are St. Thomas, adenosine, plegiisol, and Buckberg. You need to give these—they need to be replenished every 20–30 minutes. And so the question really is, what we’ve been talking about all morning, “what if you could just give them once with the same degree of protection?” And the single-dose solutions are Bretschneider, del Nido, and Custodial. One dose is required for up to 2 hours of cross clamp.

So close the gates and stop the pumps. The real story is it does not usually need to be redosed because sodium and calcium exchanges are inactivated with lidocaine, which blocks sodium, magnesium and calcium channels. So what is the best strategy, multidose, multi-clear, adenosine, continuous warm, single-dose Bretschneider, del Nido? What’s in the literature? So I did a review and I found a lot of conflicting evidence. And basically all these articles, each study, you know, has merit for what they studied but there’s not really anything that’s letting us know what’s the exact solution we should use.

Hyperpolarizing with cardioplegia is beneficial according to this article by Wei He and Yang, “The superiority of hyperpolarizing to depolarizing cardioplegia in protection of the coronary endothelial function.” They said that depolarizing solutions impair the coronary endothelium, and also that blood is good (3). After the clinical comparison study between crystalloid-based St. Thomas solution, they concluded that addition of blood to an established crystalloid cardioplegia solution significantly enhanced myocardial protection. So what is good (4)? And this one says—and this is 5576 patients—blood isn’t necessary. We found evidence that argues against any superiority in terms of the heart outcomes between blood or crystalloid cardioplegia. OK, now if you’re not getting confused, let me go further (5).

Bretschneider is good. In both single-dose, high-dose volume. This cardioplegia preserved the heart in the same manner as blood cardioplegia, and this is very convenient method as we only have to infuse once (6). Surgeons really like the idea of giving their solution once and then not having to stop what they’re doing and continuing with their surgery. This article says Bretschneider is bad. The effect of cardioplegia solution induced fluctuations in sodium level on postoperative seizures in patients, pediatric cardiac patients. Hyponatremia is associated with postoperative seizures (7). But then, it says del Nido is good because del Nido actually has less association with postoperative seizure as it has low sodium concentrations. So it goes on and on and on and on and
on. And that’s the way cardioplegia has been, you know, my whole 37 years in perfusion.

And I’m sure with many of you as well. So, Dr. del Nido came to our institution. I was so happy because it was very timely in that I was going to be able to ask him some questions about giving cardioplegia for adults, but my surgeons informed me before we went to grand rounds that “you will say nothing.” He does not like to it would be better not to discuss del Nido in this forum. And the reason was because Dr. del Nido did not really study his own solution. Only others have studied it.

Dr. del Nido has a vast amount of research in other areas such as: improving right ventricular ejection fraction, anatomic variants, and surgical reconstruction, valve reconstruction. He’s a master of surgery and that’s what he does. Nonetheless, I got up and asked him a couple of questions, and he said to me that I really think we just got lucky with the recipe. And I asked how long between doses and he said he does not give another dose until he sees activity, and Rich had mentioned that’s what they do with their group. Why does too frequent dosing cause a sluggish heart? So he thinks that it takes the heart a while to metabolize the direct shot of lidocaine.

Then I wondered “if it would not only work for valves, would it work for CABG surgery,” and he said my research did not look at this but it should work just as well. Give some retrograde to ensure full coverage and do not be tempted to give too much cardioplegia solution. So that was a precaution that we kept in the back of our minds. For short cross clamps such as atrial spectal defects or simple repairs, we gave 10–15 mL/kg for adults and only give 10 mL as a redose, otherwise the heart will be sluggish for a few minutes after the clamp removal. But even if that happens, you should not try to attempt to continually defibrillate, which surgeons really like to do because they want the heart beating again. Just usually wait, and it’s unnecessary for defibrillation.

Again, no studies, no protocols, no methods. We wanted to have our standard solution available to us once we switched to del Nido just in case some of the surgeons weren’t in favor of the change or if something happened we would have a fail-safe way to go back and deliver our standard solution. Ken Fung is one of my chief perfusionists in charge of extracorporeal membrane oxygenation (ECMO) at our institution, at Columbia, and we were pondering over how we were going to easily change our circuit from delivery of del Nido, and still have available our other solution. And he came up with this, a schematic, and we had Sorin build it for us. And we also measured every which way that you can give cardioplegia with every kind of retrograde cannula: olive tip, mushroom tip, blue metal, and we recorded all the pressure gradients. We came up with a protocol to use 4 del Nido and 4:1 blood and again, it was custom made.

We also had a surgeon that did not bulldog the mammary artery when he was doing reoperative CABG surgeries, and he was worried about having the patent mammary graft, constantly washing out the heart after initial dose of cardioplegia, so we also had to find a way to deliver continuous cold crystalloid through the coronary sinus or blood. Once we started using del Nido cardioplegia for our adult patients, everybody wanted to come and visit. After Cleveland Clinic visited our hospital, Kuna Kim wrote a really beautiful article of how they deliver their del Nido cardioplegia in the Journal of ExtraCorporal Technology. It’s published, and they just modified our technique, and they were very nice to also acknowledge us that they had visited our hospital and that we shared all of our information and protocols with them.

Looking at the adult patient reports going forward, Rich mentioned, at the AATS Mitral Conclave Symposia there was a poster session where Ramanathan said that del Nido cardioplegia adult surgery requires fewer cardioplegia doses and defibrillations and the potential benefits of minimally invasive surgery (8). And the data are really soft. I mean the cross clamp time mean number of cardioplegia doses and mean number of defibrillations were significantly less. I mean that’s not really robust information. Nonetheless, we have used del Nido solution now exclusively in over 5000 cases. We had planned to use antegrade single dose technique for a liter and then, if the ventricle really was hypertrophied, we would give it an additional liter. Some of our surgeons do measure myocardial temperature, which is really helpful because then you know that it is everywhere around the heart and that the myocardium is cold. And then, one of my surgeons still said he was going to give it every 30 minutes anyway with his CABGs.

We were able to find few publications on this series of patients, “Short-term outcomes in adult cardiac surgery in the use of del Nido” by Ota et al (9). He compared existing multidose strategy using whole blood cardioplegia with Quest to del Nido and found that we may expedite critical portions of the surgery by repeat cardioplegia doses and eliminating the use of a retrograde cannula. And you can see on this graph that there was significant difference in cross clamp bypass time, doses of retrograde because no doses were given, and then total cardioplegia is less because you’re not redosing every 30 minutes. So we only gave a liter of del Nido cardioplegia compared to >2500 L at times of standard solution. And then, we found that the exogenous blood was less and that’s probably due to the less dosage of clear fluid.

Then another article with the same series of patients, “Myocardial protection using del Nido cardioplegia in adult reoperative aortic surgery.” The analysis of the patients undergoing reoperation for aortic valve replacement demonstrated that del Nido cardioplegia offered equivalent outcomes when compared to whole blood with
regard to short-term postoperative survival (10), ejection fraction, need for hemodynamic support and complications, and in addition, a lower total cardioplegia volume was required. And as a result of our findings presented here, in all adult case operations, our institution now use del Nido cardioplegia for myocardial protection.

And then we looked at specifically del Nido cardioplegia safely administered in high-risk coronary bypass patients and del Nido in isolated CAGB following acute myocardial infarction, and it was associated with morbidity, complications, and preservations comparable to whole blood cardioplegia; a reduced bypass and cross clamp time and lower total volume of cardioplegia may shorten the length of stay and improve outcomes (11). In preparation of this meeting, I wanted to look at the data (n = 5580 patients) just for all-comers since we began using del Nido. We collected all of our information from Spectrum Viper (Charlotte, NC). It’s our electronic medical record. So I queried it and I just put it into an EXCEL sheet and there were hundreds of data points, some blank due to user input. We learned that going forward, we need a better way to figure out how to collect our data more precisely, not just randomly, and be more diligent. This retrospective review had 3100 patients that were analyzed.

There were no specific protocols for the delivery method, although we wanted there to be the end, though the surgeons, you know, decided to do what they want and no matter what they do and what you ask them to do, they always have to be different from one another, and I think you all probably find that as well. So we’re supposed to be giving just antegrade, but as you can see we’re giving antegrade-retrograde, retrograde-retrograde, left coronary, right coronary, but in the end, we really are giving mostly antegrade. We had many variations for delivery of solution.

The other thing that you worry about when you give cardioplegia and potassium is what are your potassium levels going to be, and you can see here that of the 3100 patients, the average potassium after cross clamp was only 4.6. So there was no worry there. And then spontaneous defibrillation are recorded on the x axis as well as number of cardio versions. Then as you can see the frequency of cardio versions is 2650 of the 3100. There were fewer cardioversions with most patients having spontaneous defibrillation.

The heart spontaneously defibrillates, and you can’t believe it until you use it, but it does happen. You just need to wait for the heart to wash out after you take the cross clamp off. And some of my surgeons have become a little impatient, can’t even wait that 30 seconds, 40 seconds, and now they’re choosing to pace the heart to have it start beating. I thought we were going to wait until the heart defibrillates on its own. So a lot of lessons to learn. Also again, as I said we learned that we need to be more mindful of the data collection in future, and as you can see here a graph of the frequency of the number of doses: 1, 2, and 3, are all really one dose because it would be given antegrade and then left coronary, right coronary, but it is single antegrade dose given as a first dose.

And then finally, to conclude, we now have used del Nido solution in over 5000 patients. Our aim of administration of del Nido was single dose after 60 minutes of cross clamp, and the next dose amount is decided by the surgeon based on the anticipated length of the rest of the cross clamp and how much more surgery he needs to perform. After retrospective review of the data, we found the following trends: the average cross clamp time was 58.7 minutes, total volume of del Nido was 913 mL, the number of cardioversions was an average of 0.18, and potassium after cross clamp was an average of 4.8. del Nido cardioplegia for adults is being used for all patients undergoing cardiac surgery at NYP-Columbia, and in addition, the use of del Nido solution requires lower total and retrograde cardioplegia volumes to achieve adequate myocardial protection. Thank you very much.

REFERENCES