[MUSIC PLAYING]

DR. JAMES T. LUKETICH: This talk I think would not have been a part of this conference 20 years ago, maybe even 10. Maybe it's not a part of the discussion in some centers even today because it wasn't that recognized. We often didn't even equate GERD with asthma, bronchitis. These atypical symptoms of GERD confuse the issue.

I'm not sure where we're going with this because in some of the talks, or some of the studies that I'll show today, it's almost as if, boy, if you're do a Nissen, you're going to just have smooth sailing. You've overcome all the problems. And that's not the case.

And very clearly, from our experience here, just as we've changed who does lung transplants today from whoever is on call to a very dedicated service of lung transplanters. There might be some cardiac surgeons and some thoracic surgeons, but they're clearly dedicated to lung transplant.

Well, I'll have to tell you, the same is true for Nissens. Every Nissen is not the same. And in our group of 22 general thoracic surgeons, really only about five of us are focusing on Nissens and anti-reflux surgery.

And that's for a reason. We have the same issues. So I think some of the studies that I'm going to show today may not be quite so careful in terms of their surgery either. So when you see a patient that got a Nissen that maybe didn't do as well as you thought they should do, well, get that barium esophagram. Be suspicious that the surgery wasn't so perfect.

You might think, maybe something else is going on. Maybe we missed the boat. Maybe it wasn't the GERD that was causing all these problems in the patient. But clearly, you also might have a problem with your surgery that was attempting to eliminate or minimize the GERD.

By starting off, I'd like to educate some of you who may not be aware, that everybody in the room is refluxing 4% of the day, up to 4%. So when you have that pizza and a beer, or you get some indigestion with red wine or peppermint, that's not necessarily a disease. That's gastroesophageal reflux. We all will get it at some point during the day. But many times it's so minor we don't even know it's there, or we take a Tums or a Rolaid. That wouldn't really be considered a disease.

And by studying normals, we know that that 4% mark is not magic. Clearly, there are people that reflux 2% of the time but get a lot of burning. So they just maybe have a more sensitive mucosa.

And then we have some that have very high scores, and you can't convince them that they actually have GERD. They go, mm, no, I don't feel it. Those are the really confusing ones because they may have other manifestations of GERD, the atypical symptoms that are less easy to recognize.

We all know, boy, I got heartburn. I overdid it last night. That's simple. But what about the person who just got an unusual cough or hoarseness but denies any heartburn? Those are the ones you really have to study carefully.

We know the reflux symptoms are very, very common. Transplant, non-transplant, et cetera. And the atypical ones are even harder to figure out.

So when does it become GERD, with the "D" on the end, the disease? Well, it's a matter of the magnitude. When it starts to damage the esophagus, when it starts to cause symptoms to the point of requiring daily medications, clearly, we're going to call it GERD now.

And we might back that up with some studies, like a pH study to determine where is that 4% number, maybe with a barium esophagram to look at the anatomic part. Because you can have very, very near normal anatomy from everything we've used to study the esophagus, and you can still have GERD. So those transient lower esophageal sphincter relaxations may be triggered by medicines, or food, or whatever, things we don't even understand. Certainly stress can do it.

But most of the patients we see, most, have an anatomic correlate. That is, a sliding hiatal hernia. When we see those damaged esophagus without a hiatal hernia, we've got to think of other things.

But clearly, the extra esophageal ones are what we're talking about today. That is, when does that refluxate sneak up high enough into the esophagus, make it up to the larynx, cause not only hoarseness, cough, sinusitis, sometimes ear aches, asthma, bronchitis? I would tell you that any case of adult onset asthma should be considered GERD until proven otherwise. It's just that common.

So we're becoming smarter about this disease. But I don't think we've got it figured out. So lots of these symptoms that are not just heartburn. Once you see that in a non-transplant population, of course, we're going to start the workup.

But in the transplant population, I think, there's evidence today to say that maybe we should be thinking about in every single patient coming for a transplant workup should be considered to be a GERD patient. You've got to at least consider that. Whether it should all be tested, some centers think that. I'm not sure we know, or I'll be able to convince you what the right answer is in that regard.

But these are the things we do. They're not always firmly diagnostic. And they're not necessarily that cheap. And we don't get paid very much to do them. So there is not a lot of reimbursement to cover these studies.

Endoscopy? Yeah, we might see esophagitis in a hiatal hernia. Manometry will tell us what's the pumping status of the esophagus. If it's weak, and we do a valve, we may have caused more trouble than we wanted to because they may not be able to swallow now.

PH testing is the gold standard. The DeMeester score we call it. The Bravo study.

Today we would place a little disposable probe in the distal esophagus. And actually the patient goes home and you see how much acid is sneaking up and hitting that esophagus. And is it GER, physiologic, a little bit of reflux? Or is it GERD?

And I would have to say that in the transplant population we're going to be a little more aggressive calling it GERD because they've got either lungs that are on the way to becoming a replace. Or they've got a new set of lungs, and you certainly don't want to see them damaged. Barium swallow is a very inexpensive test and a good way to assess things.

Gastric damping is important in some patients, especially diabetics that may have gastroparesis. Some of the newer studies, I can't tell you that these have necessarily changed how we do business. But sometimes the more confusing the picture, the more we add these other diagnostic studies. And then we become even more confused. I wouldn't say that any of these have given us one simple test that we know what to do.

What are the symptoms? We talked a little bit about it. But they can be as bad as recurrent pneumonias.

I've clearly had some patients who came to me that were on the transplant list that we've done a Nissen that have actually improved to the point that they came off the transplant list. I'm not at all telling you that a Nissen can cure IPF or end stage lung disease. I'm just saying some patients are in that little teetering between whether they're going to need a transplant or not.

And if you could do something to improve their lungs, you just might delay or even avoid. Especially if you have an obese patient with GERD. Maybe they get a Roux-en-Y. They lose 100 pounds, and now their lungs are improved from no reflux. We've seen that example over and over again. And then you add exercise into that, and avoidance of smoking, and other things. So anyway, those are the success stories that unfortunately aren't so common.

But these are the things that should be the things you'll be watching for when you're reviewing that patient, or considering someone for a transplant, or the patient that has a transplant. Are these things ongoing enough to make you suspicious that GERD is part of it, or that the operation they got to fix their GERD isn't working? That's clearly got to be in consideration.

So this complex relationship between what we call the pump, the esophagus, the valve, the lower esophageal sphincter, and the reservoir, the stomach, it's all working together. And we have to consider all those parts of the reflux picture. I would have to say that the valve is probably the most important part. But you can't just take care of the valve without knowing the status of the pump or the reservoir, or you can get bit on that one.

Then how it gets to the lung, that's complicated. Whether the actual transplant operation predisposes you a little bit more to reflux, or are you damaging some vagal fibers to the lung or to the esophagus? There are some people that hypothesized that just the transplant itself makes the patient more susceptible to reflux. I'm not sure everybody agrees with that, or how important that is. Really the point is, if you get to the point of refluxing, and it's getting into the lungs or the larynx, you have to think about how can we stop that.

A number of studies have shown that a very high percent of patients with asthma have abnormal pH studies. We've seen a very high percentage of patients with just garden variety COPD that have been studied, and a high percentage have reflux. So this is just indirect evidence that our transplant population pre and post have a very high chance of having reflux. So we have to consider that.

Now here is a group of GERD and IPF patients that were studied. And a very high percent, again, with an abnormal pH study, which is our gold standard to tell us we may need a Nissen. Transplant or not, you're getting into the range of maybe needing a Nissen. So all these studies are basically supportive evidence about whether you should consider a patient for a Nissen.

Now are there ways to treat reflux without surgery? Absolutely. Whether it's lifestyle management, avoidance of certain foods, losing a few pounds, had a bed elevated, all of these things can be important. But generally, we're beyond that when we're talking about possible surgery.

And of course, PPIs, which are the gold standard medicine, proton pump inhibitors. So Chrish Fernando, when he was here with our group, looked at a group of patients that were not in the transplant population yet. But the question was, could they be treated just as well with medical therapy versus surgical therapy, and how would they do?

Because we know that medical therapy can neutralize the acid content of the stomach. But we don't have a medication that can keep it there. There are really none.

Reglan doesn't work for that, Propulsid is off the market for a variety of reasons. So we don't have a medicine that improves the tone of the lower esophageal sphincter.

So what happens is, when you neutralize that acid you don't feel the burn so much. But if bile, enzymes, undigested or partially digested food makes it up the esophagus and gets into the larynx, into the lungs, microaspiration, you can have just as bad of problems. Maybe a little less so, some of the studies would say, if you can knock out the acid. But you haven't stopped the reflux.

You've made it less symptomatic, at least from a standpoint of the typical symptoms of heartburn. You can make them feel better. But can you actually improve their quality of life and stop the other symptoms of reflux?

So Chrish did a nice study looking at lap Nissen versus medical therapy. It wasn't randomized, but it was a pretty good study. He matched the patients up well. And Chrish was really good at quality of life studies, and SF36, and something called the HR QOL, which is basically a tool to assess the lifestyle impact of reflux.

And the scores would be in the range of, oh, for a patient without medically treated GERD and minimal GER, maybe we'll call it GER without the "D," your score will be 5, 6. Once you get above 15, you've got pretty severe GERD. So those are the numbers we look for. And of course, our quality of life, if you're familiar the SF36, we'll go over that a little bit.

So anyway, we had 120 patients that had a laparoscopic Nissen. And he matched it up with a medical cohort of 51 patients who were match up as best he could. Their duration of heartburn was similar, their severity of GERD was similar, based on pH studies, et cetera.

Importantly, there are no operative deaths from the Nissen. We can get them home most of the time in an overnight stay today. It was a little longer than one day back then. Right away, back on oral intake. And pretty much, this is cut in half now with the way we're doing Nissens today.

So we can get people in and out pretty quickly. And for the most part, we can operate most lung transplant patients pretty safely. Some are going to be a little frail. But for the most part, we can do it. And we did it in this group.

Anyway, when we looked at the results, clearly, the HR QOL was much better in the surgical group they just summarize. We got them down to a normal score of four. If you looked at the HR QOL in those treated with medicine, they did feel better. But at that same time, when you studied all of the factors of GERD on quality of life, it was very significant residual effects of their reflux. More of the medical patients were dissatisfied with their overall treatment compared to baseline compared to the Nissen And the quality of life SF36 were better in six of the eight domains for the surgical patients.

So I think the point is, while it's easy to put patients on PPIs, and you may make their heartburn better. But the question is, are we protecting their lungs? And that's something that you have to assess on an individual basis.

This is just a summary of the SF36. And I'm going to just conclude to say that you have to consider lap Nissen. And even if you have a good symptomatic response to PPIs, you have not stopped, physically stopped the reflux. So that's really a tough problem because the patients may feel better, and you're thinking about yet putting them through an operation to stop the relatively silent part of the GERD.

Asthma and GERD. No doubt, we talked about a very high percent have the GERD. That is a positive pH studies. Is it from microaspiration it's actually causing the asthma? Or do they have asthma, and the GERD is making it a little worse and a little more difficult to manage?

If the vagus is involved here, and that's impacted by a lung transplant, will it make it worse? All those things are a consideration and indirect evidence that we have to be just very suspicious. Now this was a study that randomized asthma patients with GERD to surgery versus medical therapy. Again, not a transplant group.

But when they looked at those treated with medical management versus surgery, they found that those that got the actual surgery-- let's go to the summary-- there was an immediate reduction in nocturnal pulmonary symptoms, wheezing, coughing, dismia. And at two years, an improvement or cure of asthma in 75% of the surgery patients and only 10% of the medical, 4% of controls. The overall status worsened in half the controls. About a third of the medically treated patients, and only 12% of the surgery. So more indirect evidence, to a degree, that you got to consider going further than just lifestyle changes and medical therapy if you have a transplant population with GERD.

Pulmonary symptoms and GERD. This was another part of that study looking at the actual pulmonary symptoms recorded undergoing fundoplication. And again, evaluated outcomes QOL, HR QOL, and quality of life SF36. And again, we're going to focus on the pulmonary symptoms of GERD in this study.

This is the SF36 again, pre-op, post-op, normals. And then the HR QOL, 20 pre-op down to 2.8 post-op. And the actual pulmonary symptoms, pre-op and post.

There's hoarseness. Pre-op, very high percentage, down to under 20%. Bronchospasm, same. Aspiration almost zero after the Nissen, which I think is very important to the group of people taking care of the transplant population. And of course, laryngitis, a correlate of aspiration, and all of these other things.

So it seems like we can do a better job with fundoplication, at least in a subset of patients by doing the Nissen fundoplication, or a variation of that operation. And overall, with medical therapy, we didn't do quite so well.

I'm going to move on to some other studies looking at the effect of Nissen fundoplication, whether it was done early or late. But this was a study published the *Digestive Diseases* and *Science.* And they looked at, again, patients who were transplanters, pre-transplant. Anti-reflux surgery that was already done, they were excluded.

A total of 188 patients were included in the study. You'd see 155 patients had develop rejection. All cause mortality, 27%. Acid suppression and BMI were associated with rejection in this study.

On multivariate analysis, again, the two things that were associated independently predicted were the acid suppression and BMI. Persistent PPI use was more protective than say the less aggressive medical therapy, like H2 blockers.

Post-lung transplant. Exposure to persistent PPI therapy results in the best protection in the medical therapy group, say compared to H2 blockers. And of course, BMI lowering was important as well.

So this is, I think, telling us that there are things besides surgery we can do to improve upon reflux in the transplant population. Not everybody needs a Nissen fundoplication. Sometimes it is lifestyle management, like weight loss and optimizing medical therapy.

IPF. I think my own experience with patients being referred to me with IPF for a lung biopsy, frequently I annoy my pulmonologist because I'll begin asking the patient, wait a minute, what's your GERD history? I think today, that's not such a common event compared to 20 years ago. Today, most of our pulmonologists, especially in this center, are very well aware of the relationship between IPF.

But it was very common that we would be sent patients with IPF to just do a lung biopsy. We're not asking you to assess them for GERD, or whatever. And really, when we started looking into this, even 20 years ago, we found that many of these patients were actually refluxers.

One of the primary causes of interstitial lung disease may indeed be silent aspiration and GERD. GERD and lung transplant. This is overall five-year survival lung transplant, 55%. And these are some of the things that we think that may lead to that decline in survival. And GERD is being one of the important parts that we may be able to impact on that's affecting this.

In one of the studies, and I'm not going to be able to cover all of these studies today because just for the interest of time. But I did want to go to a very interesting study that was-- well, let me also cover this IPF study.

Because this was just a group of patients with IPF, again, telling us what's the incidence of GERD in an overall group that have IPF, asthma, and bronchitis. Again, a high percentage. But clearly, it's not 100%. So we're not going to impact on everybody by an anti-reflux operation or PPIs.

So let's go to the study I wanted to get to. It's this one. Interesting study out of the Cleveland Clinic, looking at 215 lung transplant recipients.

114 had pre-op pH testing, 32% had evidence of GERD. FEV1 was analyzed. And during their follow up, and what they found is that if they had a group of patients that went to transplantation with no GERD identified pre-transplant, this was their overall FEV1 in terms of its improvement and its relative maintenance. And if you look at the GERD population, significantly worse than the non-GERD.

So I guess the question is, can we turn this line into this? And some studies are going to tell you that even those that said no GERD, they may have some GERD. So it just depends on how carefully they were studied, are you certain that they don't have GERD? But I think these are some of the studies that have just made us so aware of this problem today compared to where we were 20 years ago.

This is another study looking at survival. Same group. Cleveland Clinic looking at what about the impact not just on that FEV1, but survival. It's very clear that the patients with GERD do worse. You can see that significant difference in survival.

Now I was surprised by this part of their study, saying that they didn't see any difference in rejection. Now one of the reasons we often see patients for surgical consultation might be the fact that they're having increased episodes of problems, whether they're true rejection episodes or they're microaspiration that's masquerading possibly as rejection or problems. I don't know if this is true or not. But this particular study couldn't correlate the GERD and non-GERD patients to their rejection episodes.

But I think many of us are suspicious when we see a patient that's struggling. If we're thinking it's rejection, but is it truly just isolated rejection, or is there something going along with their GERD that might be better managed that would impact on this? But it may be clear from this study that it's not a one-to-one, they're all having GERD problems. There's obviously rejection problems unrelated.

I think these questions of is surgery the answer, I think some of the data I've shown you tells us we can impact on the transplantation patient and non-transplantation patient. Anatomically, we can fix the valve. Medically, we can fix the acid. But the medical treatment doesn't stop the reflux. Again, important difference.

What's special about the lung transplant patient? Well, we're not sure that that they are that different from a non-transplant population. But they certainly don't tolerate it very well. So anything that's going to impact upon a newly implanted set of lungs, in addition to the other things that may be going on with that patient, we know that reflux can make it worse.

I don't know about the immunosuppression and the impact of vagal nerve injury during a transplant. We don't really attempt to damage vagus nerves, obviously. But the surgery, you're in close proximity. You're going to lose some vagal fibers, for sure, during a transplant, But I'm not sure that what this impact is and what we can do about that, other than being more careful, and whether we really have an effective immunosuppression on the GERD.

Reflux and injury. We know that acid injury is one thing. We've talked about bile injury. We've talked about pepsin injury. The non-acid components of reflux have been studied, looked at, and clearly are important.

And I think that's my point about treating a patient with PPIs. If you've treated them with PPIs and they're doing better from a heartburn symptoms standpoint, but maybe you're not seeing that improvement in their overall FEV1. Or you think something else is going on with their lungs, whether it's bronchitis, asthma episodes, et cetera, it may be that the aspirate in itself is still getting up into the lungs. And that's why they still may need to consider something else.

This study would tell us that the actual transplantation may make the GERD worse. So they started off with a severity of GERD at one level. Get a transplant. Does it make it worse? Is it the immunosuppression? Is it the vagal injury? I don't know the answer.

But clearly, after transplant, the mean acid contact time increased, which would tell us that if you got acid hitting the esophagus we're worried that it's getting up higher into the oral pharynx and to the larynx. I will tell you that there's no one study that's going to tell us that the reflux patient, that that reflux aid is the cause of their lung problem. We don't have a simple study.

We don't put a probe in the lung, for example. And that may be what's coming next. I don't know. But we don't have an easy way to monitor acid reflux and chronic aspiration.

Whether we can prove that, sometimes we're left with pulmonologists sending the surgeon to us, or the transplant surgeon saying we're not sure. We have a positive pH study, we have a hiatal hernia. We can't figure this out when you're doing this. And that would be in a patient that maybe has no heartburn symptoms.

So it's a tough call because we can make the patient worse with a Nissen from a quality of life standpoint. They can't burp, they can't vomit. And if you make the wrap too tight they may be limited in what they can eat. They may have to change their diet completely from a regular diet to possibly a very soft diet, especially if their esophagus pump is damaged from scleroderma or another related disease.

Sending patients for a Nissen, all of them that have reflux, and thinking, hey, there's not much downside. We might protect their lungs, so let's do the Nissen. Well, that gets into the side effects of Nissen.

And I think that they are there. If they're done carefully they're minimized. But no doubt, we have to take that all into context when we're thinking about patients with acid reflux.

This is the standard operation we do, which is wrapping the esophagus with the stomach. These are the two limbs that are brought around. This should be considered a 360 pretty competent wrap here. This is probably what would be considered the gold standard.

But again, it also has the most impact on inability to burp, vomit, et cetera. Because when you want to keep those contents in the stomach, you're going to impact on the daily ability to burp or vomit. And of course, if it gets too tight, the ability for food to come down.

In some ways, you're always walking that line between too lose and too tight. So if it's too loose, you're going to reflux. And may still reflux after your Nissen if you make it too loose, or if you made this a partial wrap. Versus making it too competent, and the patient's very bothered by gas bloat or dysphasia.

How are we doing for time?

SPEAKER 1: Plenty to go.

DR. JAMES T. LUKETICH: OK. I might have time for one more study. This was another study looking at the role of lap Nissen in protecting the patient after transplantation. Again, lap Nissen being an effective way to stop GERD, and hopefully prevent aspiration. They were looking at alveolar lavage fluids, bowel from patients, and tested it for pepsin, et cetera.

You can see the GERD rate was high. This is the group-- then showing the freedom from [INAUDIBLE]. You can see it's improved compared to the no Nissen group. And this is the GERD positive group without a Nissen. Very high pepsin levels. And this is the group after anti-reflux surgery.

Is this true, true, and unrelated? That is, we can stop it. Does it mean the lungs are going to get better? Well, that's the hope. We can certainly stop the reflux, we can certainly stop the evidence that reflux aid is getting into the lungs by studying the BAL specimens after the Nissen.

And I think that's pretty good evidence from what we've seen in the clinics, that when we get it right we can really improve the patient that's had a transplant by doing a lap Nissen. This is another study looking at the preservation of lung function. This was done by Dr. Job and Dr. Happo when they were with our group.

It's a small study, but it's a nice study looking at end stage lung disease and GERD. Patients, 19 of them had their Nissen pre-lung transplant, 24 post lung transplant. And we'll just get to the summary of it.

What they showed was that before the patients that had the transplant done after, or their Nissen done after the transplant, versus those that had their Nissen done pre-transplant, both groups were actually improved. Is it a little better if you can catch it early and get the Nissen done in the pre-transplant period? I think the answer to that is probably true. But we haven't necessarily proven that in a randomized fashion.

So the question is, should you wait and do the transplant first and then see how they do, and consider the Nissen afterwards? I would say that if you have overt GERD and you're suspicious that it's impacting on the lung function, that you should probably do the Nissen prior. Will they do a little better after their lung transplant because they have obviously better oxygenation? Well, for the most part, we can get patients through a Nissen even in the pre-transplant period.

But not always. You've obviously seen some pretty sick patients that you just may not want to do that. And based on the other studies we've seen today, medical therapy can clearly help. But I would say, either way, we are able to improve the patient, whether we do it before or after. But I think that my vote would be to try to get it early.

Now this was showing the impact of a fundoplication on the actual FEV1. Again, if they had no GERD, this percent predicted at 75. GERD population lower. And with the fundoplication, they're showing that we can actually get it pretty much to a level that's similar to the non-GERD population.

Now this was an interesting study from Duke. I was talking to [INAUDIBLE] about this study this morning and why it's confusing to me. It's this group up here with the dark triangles were those that had reflux and got surgery for the reflux. And this is the group of patients that actually some of them showed no reflux.

So if you look at this group right here, let's say, with the black boxes, they had normal pH studies pre-op, and didn't get a Nissen, obviously. And they went on to still have some relatively significant decline in terms of their freedom from [INAUDIBLE]. So this is the group that was studied that were refluxers, and had early surgery.

And this is, of course, a limited follow up. And [INAUDIBLE] explained the statistics to me a little bit, understanding that this isn't a lifetime. This isn't truly a five-year result. But clearly, those that got the Nissen had a significantly improved period that was freedom from [INAUDIBLE] compared to those that didn't get a Nissen. And even in some of them that didn't have overt evidence of reflux.

So this might be one of those studies that you say, well, we should wrap everybody. I would say that's not the right answer. But clearly, it tells us we need to study them carefully.

Because there may be some patients out there that we are calling non-GERD that still need those more specialized studies to try to determine is it silent GERD, is it subtle GERD? Did you miss it with that one 24-hour pH study, or with the Bravo study? I think this study makes me really wonder about what's going on with this other group?

I'm not so naive to think that the Nissen just was perfection. But if you looked at this group, it would tell you that. And then in addition, this is survival. And it also showed in a limited fashion a far superior survival in those patients that had anit-reflux surgery.

I think we all know, it's not quite that simple. So this study got a lot of criticism. But nevertheless, I think there's some merit to it showing us the potential advantages of an anit-reflux operation, not only on freedom from [INAUDIBLE], but from potentially on long-term survival as well.

So I'm going to stop there, just to say that GERD is a very common disease in the general population, and may be more prevalent in our transplant population. Pre- and post-transplant, we have to think about it. Think about a complete workup for GERD.

Should we be doing it in every patient that walks in the door for a transplant? I'd be interested to see what Bart and others say they're doing at their center in terms of does everyone get a barium swallow? Does everyone get a 24-hour pH study because there are clearly asymptomatic patients from a heartburn standpoint that maybe refluxing.

Anti-reflux surgery can provide graft protection. It's got to be good anti-reflux surgery. And I think patient selection about whether it's a full wrap or partial wrap are important if you want optimal results, and who's doing it, et cetera. But I do think this area needs a lot of further prospective studies. We just don't know all the answers yet. Thank you.

[APPLAUSE]