Pulmonary Hypertension Roundtable

Protocols in Heart and Lung Transplantation: An Essential Guide to Preoperative Assessment and Timing to Improve Outcomes


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This discussion was moderated by Victor Tapson, MD, Editor-in-Chief of Advances in Pulmonary Hypertension *and Associate Professor, Division of Pulmonary and Critical Care Medicine, Duke University Medical Center, Durham, North Carolina. The participants included Robert Frantz, MD, Assistant Professor of Medicine, Cardiovascular Division, Mayo Clinic, Rochester, Minnesota; and John Conte, MD, Associate Professor of Surgery and Director of Heart and Lung Transplantation, Johns Hopkins University, Baltimore, MD.*

Dr Tapson: Let's start with a couple of general comments about transplantation and pulmonary hypertension. The first thing that comes to mind is the issue of timing and the severity of PH. When is it the right time to proceed with transplantation or listing?

Dr Frantz: That's a timely topic in a situation where the allocation system for donated lungs may soon be changed by the United Network for Organ Sharing (UNOS). It is sometimes difficult to know when to list patients with PH for lung transplant, especially if they are doing reasonably well with their current therapy. We tend to have to lead the curve by a long way because the waiting times for a lung transplant can be so long. If we don't think about it at least a couple of years ahead of time, the patients may be at risk of dying on the waiting list. The other thing to keep in mind is that the outcomes in general for lung transplantation for PH have been inferior to those for many other diseases, such as COPD, and results seem to vary some from center to center. There is a need to understand why it is that some patients with lung transplants don't do well if they had pulmonary hypertension as their preceding diagnosis. We would like to perform lung transplantation before advanced right heart failure develops because at that point the risk of the operation may rise. So, for us, we're always working on the questions, when is the right time for lung transplantation, is a lung transplant adequate or would a heart-lung transplant be better, and when is it too late?

Dr Tapson: A few years back we would list patients for lung transplantation as soon as they were diagnosed with PH. As their illness progressed, they would end up receiving intravenous prostacyclin, and several or more years would go by. They did well enough with this drug that we'd end up inactivating them. We ultimately realized that we didn't have to list them so soon, and we'd start listing them when they began Flolan therapy, or perhaps a bit sooner. I guess to some degree it may depend on the center and the patient's blood type. If the center has a very long waiting list or a very short waiting list, the listing time may depend on those kinds of things.

Dr Frantz: Yes, no doubt that's true, and it may vary some from center to center. I have been impressed that young patients who have otherwise been healthy can sometimes be surprisingly well compensated until they are about to fall off the edge. And then it can be too late in the sense that sometimes patients can walk 400 or 500 meters with Flolan therapy and look remarkably well compensated, and then 2 years later they are just in disastrous trouble, where you are worried they are not going to survive to transplantation.

Dr Tapson: Because of its clear association with improved survival, we have been inclined to rely heavily on Flolan and sometimes, perhaps, we rely on it for too long. We need to realize that when someone taking this drug is not doing well, that we usually have little else to offer. We don't have enough data on new drugs combined with Flolan, as yet. John, when you approach transplantation and the patient is a pulmonary hypertension patient, is there anything that would particularly concern you or result in any differences with regard to your approach to surgery?

Dr Conte: Definitely. First and foremost, they need to have been evaluated by someone who treats patients with pulmonary vascular disease, just because of the things you've been talking about. Most people will do better in your hands than in my hands. However, oddly enough, the results of transplantation in our program with pulmonary hypertension are better than in any other patient group, but it is not because I do anything differently. I think it has to do with the fact that we have such good pulmonary vascular disease folks around. But I certainly think they should get optimal

medical therapy. Back when many of us started this, there wasn't much, other than calcium channel blockers, to treat these patients. Then the prostanoids came along and boom, we avoid transplantation. Then we kind of looked at medical therapy as a bridge to transplantation, and then as we got better and better at medical management, it became an alternative to transplantation for many patients. So I think patients need to have a thorough evaluation *and* a trial of medical therapy with vasoactive medications. Certainly, it started off with the prostanoids, but we have several other options at this point.

Dr Tapson: John, when patients come to you ready for transplantation, is there anything particularly that disturbs you in terms of hemodynamics? Are there values that make you feel the patient is too sick? Is there a certain cardiac index or severity of disease that concerns you about proceeding?

Dr Conte: We used to say that by nuclear study an ejection fraction of less than 10% was an indication for heart-lung transplantation. At every institution that number may be a little higher or a little lower than that, but I can't say there has been a patient in my experience on whom I regretted doing a lung transplant alone. I had one patient who did require inotropes for a period of time postoperatively, for about a month. But that patient was able to come off inotropes and right heart function has just continuously improved over the last 2 years. If you can get them through the operation, there is no advantage in doing a heart-lung transplant, plus getting a heart and lung is nearly impossible. With the way the UNOS allocation system is currently configured, the need for a heart-lung transplantation is a tremendous disadvantage. To get a heart-lung block you have to be in the same pool as people with just heart disease. Those with the highest priority are all in the hospital on various degrees of support. We currently have a patient who is status 1-A, the highest priority for the heart people, in the hospital sitting around waiting for a donor.

Dr Tapson: John, what about the old single versus bilateral lung argument? Is there a standard now, or is this still center-dependent? Are most people doing bilateral lungs?

Dr Conte: I think most people are doing bilateral lungs, but there are certain places where they have always done single lungs and have had fairly good results, and they are going to continue to do it. I think it boils down to your basic philosophy. Do you want to treat as many people as possible with a limited resource, or do you want to try and get the best results out of every single patient? At about 3 years there starts to be an advantage, regardless of the etiology of the end-stage lung disease, there tends to be an advantage in survival with bilateral lung transplantation. I have always believed that in younger patients I should do bilateral lung transplants. But quite honestly there are many young patients who were near death in whom we did a single lung transplant who have done very well. I think individual institutions will tailor their preferences as they see fit, and you can defend or argue against any position.

Dr Tapson: So timing might be a concern. If you've got someone really running out of time and you can't get a bilateral lung block, but you've got a single lung, might you proceed based on the fact that you've got something available that would be life saving?

Dr Conte: Absolutely.

Dr Frantz: John, I am very interested in your perspective about what it takes to make a pulmonary hypertension patient do well with transplantation. As you know, the UNOS database shows a 1-year posttransplant survival rate for patients with PH to be about 64% compared to about 80% for COPD. This is causing the UNOS subcommittee looking at lung allocation to consider requiring PH patients to be incredibly ill before they receive priority for lung transplantation, and I think at your center and ours that is not our experience. The PH patients are young, they often can do extremely well with transplantation, and it seems that perioperative management must be critical. What do you think explains the problem nationally with outcome in lung transplantation for PH?

Dr Conte: I think most people in this country who do transplantation are general thoracic surgeons. And I think lung transplantation for PH is a cardiovascular disease treatment best handled by people who are used to handling the heart-lung machine. All of these people who have significant PH have to be placed on the heart-lung machine and I think many transplant surgeons try to avoid that, not so much in patients with primary PH, but in those with secondary PH. When you do that you can see severe reperfusion injury when the first lung sees tremendous pressures during reperfusion and it gets overcirculated, pulmonary edema develops, and the spiral starts. So, I think the fact that I am used to the heart-lung machine and am not afraid of it will give me a small advantage in taking care of these patients. Anybody who has a mean pulmonary pressure greater than 40 mm Hg goes right on the heart-lung machine.

Dr Frantz: Well, I think those are very wise comments and it is my perception as well that this is the issue, that cardiothoracic surgeons are used to using cardiopulmonary bypass every day, and thoracic surgeons don't do that every day. They do it maybe when they have a PH patient to transplant. It has made me wonder, though, if we are potentially going to change the lung allocation system in a way that might be detrimental to PH patients because they have the worst outcome nationally. Maybe we should be talking about designating centers of excellence for lung transplant for PH and directing those patients there preferentially.

Dr Conte: I think you can do that at the grass roots organizational level where you can verbalize that people with PH have done very well at these centers. However, from a national and a regulatory standpoint, there is no way that anybody is going to allow that to happen. I mean, just like I may refer someone with a certain disease to a physician who is very good, I can't say every patient has to go to that physician. I don't see how we can set it up nationally that PH patients are treated only at Michigan or Kansas or wherever. Normal referral patterns will be followed. Then if the people at those centers say "We're not great with pulmonary hypertension, you ought to go to Durham, because Vic Tapson and Duane Davis are there," so be it.

Dr Tapson: John, we want to talk about postop management. Do you and the transplant pulmonologists manage these folks together, postoperatively? Do you keep them for a certain amount of time and then gradually turn them over to pulmonary specialists? How do you handle this at Hopkins?

Dr Conte: It's a team effort all the way, starting with preoperative management. As the patients begin to deteriorate a little bit we discuss them more and more frequently, so that what I might accept as a usable lung for patients when they are just being plugged into the system will be different as their condition worsens. We communicate very frequently preoperatively. Postoperatively, it is a joint management effort from as soon as they get back from the operating room until they are discharged from the hospital. It is only after they are discharged from the hospital that the medical transplant team takes over. A couple of things I've learned over the years that I think benefit these patients are maintaining higher peak airway pressures to try and reduce the amount of interalveolar fluid, interstitial fluid, and we also tend to try to keep them a bit dry. If that means they require inotropes or vasoconstrictors, so be it. I think there is probably a 72-hour period in which pulmonary interstitial fluid tends to sequester, and we try to ride patients out through that period with higher airway pressures. I think that helps shift that equation of fluid leaving the vascular space and into the interstitial spaces and alveoli in favor of keeping it in the vascular space.

Dr Tapson: Do you think transplant teams tend to have more rigid criteria or scrutinize PH patients a bit more carefully than other lung transplant candidates because the risk of mortality may be higher? For example, in terms of age criteria?

Dr Conte: From my standpoint, no. We have an age cutoff of about 60 for bilateral lung transplant patients and I really don't think we've looked at whether they would have to have normal PA pressures or not. I operated on a 61-year-old woman about 2½ weeks ago who had sacroidosis, but severe secondary PH, and she did fine. So, I think you have patients who occasionally might not do as well, which might lead you to think you shouldn't do anybody over age 50. But I think we individualize patients no matter what their disease process is, so no, we don't have anything special for PH patients.

Dr Tapson: How about for scleroderma and CREST patients? At Duke we've been fairly rigid about who we will do and we very meticulously screen everyone's esophageal function, for example, since we have felt that reflux and aspiration can be a substantial problem after transplantation, especially with the associated further reduction in gastrointestinal motility that you often see. Bob and John, how do you feel about transplantation in CREST or scleroderma patients?

Dr Frantz: Well, I think that's an area where we have to be extremely careful. These patients may have involvement of the kidneys, which can be an issue in terms of the toxicity of cyclosporin after transplantation. Sometimes they can have coronary involvement as well. They may be undergoing immunosuppression, including sometimes steroids and other agents, and so the ability of their wounds to heal and their tissue integrity may be impaired. Some of them also have substantial problems with ulceration in their fingers and so forth that might be a risk for infection. I think we have to be very careful and certainly more selective in terms of those types of patients than we would be for a patient with primary PH.

Dr Conte: I think we do screen them very thoroughly, but I don't know if we are any more restrictive. I do think cutaneous ulcers, if they are active and are not healing, would rule them out. We've performed transplantation in several patients who had healed ulcers and they had no more wound problems than anybody else.

Dr Frantz: I agree with that. If their ulcers have healed, they should be OK.

Dr Tapson: What are the criteria for esophageal dysfunction? That's what I'm always told is what precludes them from being candidates.

Dr Frantz: If they have a patulous esophagus with very impaired motility on barium swallow, that is a great concern. I think all of us have seen problems with patients who have recurrent aspiration, and in postlung transplantation it can just be a disaster. So we tend to look at esophageal motility and often refer to our gastroenterologist to get a feel for how well the esophagus is functioning. If there is substantial esophageal dysmotility, that would be a concern for us in terms of transplantation.

Dr Conte: I agree wholeheartedly, but I should not even be speaking on this. Vic, you and your colleagues at Duke have led all of us in this regard. At the Society of Thoracic Surgeons meeting a few days ago, one of the Duke residents presented a nice series of patients where postoperatively people had esophageal wraps done and had improved outcomes and decreased OB, am I correct?

Dr Tapson: Yes, that's right. We have seen some significant benefit in that realm and Duane and most of my colleagues here have been very aggressive in that respect. Our transplant pulmonologists scrutinize these folks very carefully, as do your centers. As Bob suggested, if there is a very abnormal esophagus, there is significant concern going into transplant. So all of our patients get a very detailed evaluation with a swallowing study and manometry to make sure there are not substantial abnormalities. I am not so sure there is a clear cutoff point of who is

too severe to be transplanted in that respect.

Dr Frantz: John, I'd like to come back to the issues of heart-lung versus lung transplants and deciding when it is too late to do lung transplantation in patients with PH. For example, patients with ascites developing to a substantial degree, with a low output syndrome, with creatinine levels starting to climb and we are thinking we need to add dopamine on top of Flolan to keep them alive, can patients like that still do well with a double lung transplant? Or, if the right ventricle is really in great trouble, is it too late?

We have tended to list quite early because the waiting times have just been remarkably long for lungs. This may be changing though, in the sense that the one benefit of the new proposed allocation system is that fewer patients with emphysema who have relatively preserved FEV_1, or whose risk of dying is relatively low may undergo transplantation.—Dr Frantz

Dr Conte: Certainly I think the postoperative course is going to be a little bit more difficult and more protracted. But I have performed transplantation in five patients who had PH and were receiving inotropes, mostly dopamine, though two actually had dopamine and dobutamine, and all five of those patients did well. Now, one patient had a very protracted postoperative course and required inotropes for about a month, but I don't think she would have received a heart-lung transplant in time, given our organ allocation system. I think if this were a perfect world and we were taking things off the shelf, a patient like that would, with no question in my mind, be better served by a heart-lung transplant. But that's not reality. So I think if somebody has two lungs that are available and they have right heart dysfunction, they can get through just about anything.

Dr Frantz: In your hands that is probably true, but I am trying to drive at why it is that the national outcomes are not so good. Maybe it has more to do with this issue we talked about earlier in terms of the use of cardiopulmonary bypass and being familiar with it. It would be interesting to look in more detail at the patients who didn't survive lung transplantation and see what happened. Perhaps a multicenter registry effort could help us understand what the issues really are in terms of outcomes.

Dr Tapson: I certainly recall 1990 and 1991 when we performed transplantation in our first PH patients. Although some patients did well, we didn't have much experience with prostacyclin back then. We really respected this disease, as we do now, but we realized the mortality was high, particularly with more severe hemodynamics. I wonder if in some cases we were simply transplanting sooner and that now we have such faith in prostacyclin that we are more reluctant to say it is time. It is clear when someone's condition is deteriorating and hemodynamics are bad in the face of prostacyclin that it is time to transplant, but it would be ideal if there were some way we could recognize a bit earlier that it is time to transplant. I am not sure there is a simple way to do that. Here we are starting to look at the BNP levels in pulmonary hypertension, but we don't really know whether these can help predict if and when someone's condition is going to deteriorate. It would be nice to know when the right ventricle is going to finally buckle and it is time to transplant rather than waiting for someone to clearly worsen with Flolan.

Dr Conte: I don't think we have that. Unfortunately, not enough people are studying that question to have good data. Certainly, we'll never get prospective randomized data, but I think good clinical data looking at those specific markers would be helpful.

Dr Frantz: We do have data from the PH literature published last year by Dr Sitbon indicating that, for example, patients who despite having received IV epoprostenol (Flolan) for at least 3 months can walk less than 380 meters in 6 minutes have a worse prognosis compared to those who could walk farther. These patients who despite several months of IV epoprostenol are still functional class 3+ are clearly ones we have to be careful to move toward transplantation much sooner than somebody who can walk 500 meters with epoprostenol therapy.

Dr Tapson: One thing we haven't touched on is cases, for example, of congenital heart disease, where there are extraordinarily high pressures, but reasonably good right ventricular function. It is difficult to go just by the mean PA pressure, and in terms of timing for transplantation, the same sort of things apply for walk distance, RV function by echocardiography, and clinical right heart failure. We have had a few cases of transplantation based on significant hemoptysis that has developed and been relatively refractory. Any thoughts on congenital heart disease patients and the approach to transplant or timing?

Dr Conte: The teaching I grew up with was that patients with congenital heart disease will live forever and you don't have to rush as much as you would with those in whom disease develops later in life. I don't think I'd do anything markedly different in their evaluation, with one exception. For patients with congenital heart disease, I very frequently get an MRI or an angiogram or an aortogram looking for aortopulmonary collaterals. It's the thing that when you least expect it you're going to get into this friable little vessel that's going to bleed and cause problems, and that's the only thing I do from an evaluation standpoint.

Dr Frantz: Patients with congenital heart disease tend to have more gradual deterioration than primary PH patients in general. Some of it I think is if they have a residual right to left shunt it may offload the right ventricle and allow them to avoid problems with right heart failure for a longer period. So it can make it more difficult to know when to move to transplantation. For some of them the operative risk of transplantation is also substantial if they have had multiple prior operations and, as Dr Conte mentions, have collaterals in the chest so they bleed a lot at operation. They may have received multiple transfusions, so they have high positive panel reactive antibody titers that make it harder to identify suitable organs. It's a complex group that has to be treated in a very individual way, given the complexity and variety of congenital heart disease.

Dr Tapson: I'm sure that it is further complicated by the fact that

some of these patients cannot get by with a bilateral lung transplant and VSD repair, for example. Some require heart-lung transplantation, which makes timing more of a concern as well.

Dr Conte: The data as to which patients require heart-lung transplants and which can receive bilateral or single lung transplants with intracardiac repair are pretty sketchy. I've tended to look at supraventricular problems as repairable (ie, ASV, PDA), those types of things. Patients who have anything other than a very simple membranous VSD are those who need a heart-lung transplant. Those with tetralogy, single ventricles, or even more complex muscular VSDs require heart-lung transplantation.

Dr Tapson: Anything, John, along the lines of right ventricular mechanical assist devices in the surgical realm that might buy time or help postoperatively in these patients?

Dr Conte: We have been looking at a percutaneous right ventricular support system from a company called A-Med that has recently been bought out by Guidant and it's something we certainly will consider, not just for this patient population but for those who undergo regular cardiac surgery and have right ventricular dysfunction.

Dr Tapson: So that is on the horizon?

Dr Conte: Right.

Dr Tapson: Great. I don't think we need to talk about postoperative issues in any detail since eventually these folks tend to be similar in terms of management of immunosuppressive therapy and the like. Any other issues we want to talk about? Anything else about the UNOS allocation or anything else that may be worth mentioning in more detail?

Dr Frantz: I think it's important that we talk a little bit about that because the new guidelines for lung allocation are in flux. I am trying to have some impact on that discussion by bringing to the attention of the UNOS committee that the data they are using looking at outcomes do not reflect outcomes at some centers such as ours and Hopkins. Essentially the UNOS subcommittee has been suggesting that we give priority to patients with PH who can walk less than 150 feet, not meters but feet. That's less than 50 meters. Those patients are moribund. If we went in that direction, we might well cause more harm than good by transplanting in those who are extremely end stage. I am hoping we will be able to work out a recommendation that allocation be made for patients with PH who can walk less than some other distance. We might pick something like 380 meters based on Dr Sitbon's data or 300 meters, or something like that. It concerns me that the current system appears to make it difficult for patients with PH unless they are extremely impaired. I shouldn't say the current system. I should say the current *proposed* system. I don't think it will turn out that way because I think we will be able to modulate the recommendations before they become working recommendations.

Dr Tapson: Are you folks seeing the use of septostomy very often in these PH patients?

Dr Frantz: It is a situation where, if patients are doing poorly, with right heart failure despite epoprostenol, then it is worth thinking about. The issue is that if they have systemic desaturation on a regular basis, then you are going to aggravate that with septostomy. Many patients for whom I have considered it have already had systemic stats that are low, and I worry that I am just going to aggravate their hypoxemia. On the other hand, if the systemic stats are adequate, it can be considered, but in the very patients where we think about it where the right atrial pressure is quite high, the cardiac index is low, it is a higher risk group for not doing well with it. So, honestly, we've not performed it here in any of these patients receiving epoprostenol.

Dr Tapson: Any strong feelings about exactly when to list? I should mention that we usually used to list people when they were initally diagnosed with PH and learned that that is too soon in most cases. We generally list now if someone has to have prostacyclin therapy and sometimes sooner than that.

Dr Frantz: We have tended to list quite early because the waiting times have just been remarkably long for lungs. This may be changing though, in the sense that the one benefit of the new proposed allocation system is that fewer patients with emphysema who have relatively preserved FEV_1 or whose risk of dying is relatively low may undergo transplantation. This might free up some donor lungs to help patients in even greater need. A very large number of patients with emphysema receive transplants at variable times in their disease course, so we have felt the need to list our PH patients very early.

Dr Tapson: Is there any penalty for that? Is there some reason centers might not want to list people and then inactivate and have a large number of patients on their list inactive?

Dr Frantz: Well, it is a bit cumbersome because you have this list that has people on it who aren't really ready to proceed with transplantation. It also makes your waiting times look really long if you are listing people and then deliberately not doing transplants because they are too well. Under the proposed new system there may be listing criteria at the time of listing where those numbers influence priority, so if you list people early who have relatively preserved walk distances, they are going to be low priority for transplant anyway, and you may be better off waiting until they meet higher priority scores. But we need to see how the rules are going to work.

Dr Tapson: Bob, you gave an example of a patient regarding whether you should do a heart-lung transplant or just lungs, someone with advanced right ventricular failure and a lot of ascites. How much does that ascites bother you? Do you worry that at some point it is more than just fluid overload, that it is turning into cardiac cirrhosis and you are transplanting in someone who may now have substantial liver dysfunction, too?

Dr Frantz: This issue does come up sometimes. It probably comes up even more in patients who do not have primary PH. Sometimes other patients who have restrictive cardiomyopathy or are waiting for heart transplantation have ascites for a couple of years and their LFTs are off a bit. In some of those

patients we have done a liver biopsy to make sure it is essentially a noncirrhotic liver, in order to be confident that we weren't going to have a problem in that way. For most PH patients we have found that if we treat them with enough inotropes and really treat them vigorously, we can usually control the ascites. If we couldn't control it, I would be quite worried and might consider liver biopsy in some situations. I have actually not encountered that yet, where I couldn't control the ascites with inotropes and diuretics in a primary PH patient.

Dr Tapson: Bob and John, I'd like to thank you both for taking the time to discuss these issues for *Advances in Pulmonary Hypertension*. I look forward to our future interactions.

Profiles

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strain. We did it by gradually constricting the pulmonary artery with a band, tightening it every week or two until the right heart failed just as it does in the clinical situation. Then we released the band, dropping the pressure to more normal in these dogs and we studied how quickly the right ventricle recovers if you take the load off of it. This was a prelude to considering lung transplant rather than heart-lung transplant and we found that in these dogs there could be very rapid recovery of function in the right ventricle."

This led Dr Cooper and colleagues to rethink their strategy, namely, that they did not need to perform both a heart and a lung transplant. This meant that many more organs would be available for additional patients. "You could do a lung transplant and the heart would recover. We found that the heart undergoes remodeling, the thickened right ventricle returns to a more normal shape and thickness." Dr Cooper recalls that a single lung transplant for PH was performed on November 21, 1989, in a woman who survived and lived for a number of years. "We do have good results for single lung transplant for PH even though a bilateral is done most of the time now. Fortunately, medical management of these patients has greatly improved, so the number of patients coming to transplant has diminished somewhat," he added.

"I've always felt that lung transplantation for PH is the most critical, most demanding surgery—not so much from a technical standpoint, although it does involve the use of cardiopulmonary bypass, but in terms of postoperative care of the patient. Therefore, the best results will be obtained by centers that are very experienced. The problem is, if you have too few centers of excellence, you are not accessible to the patient."

The program at Barnes Hospital, however, is exceptional in that the hospital assumes the responsibility for the patient while he or she is on the waiting list. "In the long term, successful outcomes for lung transplantation, particularly for PH, require an experienced team," said Dr Cooper.

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