Exploring the Spectrum of Pathology and Treatment in Portopulmonary Hypertension: Four Experts Address the Toughest Questions


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This discussion was moderated by Ronald J. Oudiz, MD, Associate Professor of Medicine, David Geffen School of Medicine at UCLA, and Director, Liu Center for Pulmonary Hypertension, Division of Cardiology, Harbor-UCLA Medical Center, Torrance, California. The participants included Michael J. Krowka, MD, Professor of Medicine, and Russell Wiesner, MD, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota, and Michael Ramsay, MD, FRCA, Chairman, Department of Anesthesiology and Pain Management, Baylor University Medical Center, and Clinical Professor, Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, Texas.

Dr Oudiz: How are most patients diagnosed with portopulmonary hypertension? How many patients have their condition discovered "by accident" in the operating room as they're being prepared for liver transplantation?

Dr Ramsay: Up until about 18 months ago we diagnosed about 60% of these patients on the operating room table just prior to transplant. Now, because everybody is looking for it, all our patients are being screened with echocardiography, so we're diagnosing only about 15% to 20% on the operating room table. Those are the patients who have had normal echos sometime in the past year during the work-up, but developed portopulmonary hypertension since then.

Dr Wiesner: We've always been screening. Our pickup in the operating room is probably less than 15%, isn't it?

Dr Krowka: It's fairly low because we've been very aggressive with the screening. We've tried to screen so there are never more than 12 months between echos, but we still miss the few that get to the operating theater. But we have the back-up of their having a Swan-Ganz catheter placed at the time of the operation. So if we missed something during screening, we hope to pick it up at the time of operation.

Dr Wiesner: Most of these have been moderate cases. I don't know if we've missed any severe ones.

Dr Krowka: We have not had to cancel any cases in the last 8 years that I'm aware of.

Dr Wiesner: We're talking about pulmonary pressures of 40 mm Hg or so, or 35 mm Hg.

Dr Krowka: A mean pulmonary pressure certainly greater than 50 mm Hg. We screen routinely for portopulmonary hypertension—every case at our institution, symptomatic or not, gets a screening Doppler echo at the time of transplant evaluation. I'd say 10% of the candidates have a right ventricular systolic pressure estimate greater than 50 mm Hg, and all of those patients undergo a right heart catheterization.

Dr Oudiz: So if the right ventricular systolic pressure is less than 50 mm Hg, you don't necessarily worry about significant pulmonary hypertension?

Dr Krowka: That is correct, but we follow through and probably repeat an echo in 6 months if, let's say, the patient had a right ventricular systolic pressure of at least 40 mm Hg.

Dr Ramsay: That's similar to what we do at Baylor, but I'd like to follow up on one comment about canceling patients on the operating room table. I'd like to change that to "delay" or "defer." We bring everybody back later, having treated them with vasodilators for up to 18 months, and transplant successfully.

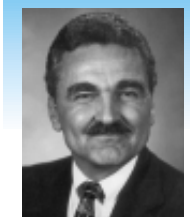
Dr Oudiz: So a good percentage of those who were initially found too risky for surgery were treated, and a good number of them were brought back and

successfully underwent transplantation?

Dr Ramsay: Correct.

Dr Oudiz: Dr Krowka, does your experience match that of Dr Ramsay's with respect to patients who might have had a normal echo a couple of years prior to their transplantation and then developed pulmonary arterial hypertension?

Dr Krowka: Absolutely. We found several cases where there was a normal screening echo, not only in terms of estimated right ventricular systolic pressure but also normal right ventricular size and function, and 12 to 18 months later at least moderate pulmonary hypertension developed by all recognized criteria. So this can change relatively quickly.



I agree that right heart function is absolutely critical. Our anesthesiologists would follow right heart function in the operating room with transesophageal echocardiography. I don't think there's any patient we've let go to liver transplant who has not been covered by at least intravenous epoprostenol, so we want to have a vasodilator on board for those who have a significant pulmonary hypertension situation. —Dr Krowka

Dr Ramsay: We had one patient in whom severe pulmonary hypertension developed in 3 weeks. He had a normal echo 3 weeks prior to coming to transplant, and then had a mean pulmonary artery pressure of about 45 mm Hg at the time of transplant. We went back and reviewed the echo and, maybe in hindsight, we could look at it and say there may have been some signs that the right ventricle was under strain, but not definitely. It was basically a normal echo. There had to be some kind of acute thrombosis or thromboembolic etiology, you would think.

Dr Oudiz: It is fascinating that you have the opportunity to screen a relatively small group of patients that allows you a window into the development of pulmonary hypertension. In patients with connective tissue disease or primary pulmonary hypertension or drug-induced pulmonary hypertension, the denominator is too large to screen them all and assess development, so we don't have a good feel for how quickly pulmonary arterial pressures rise from a baseline of normal. But here you've put a finger on the natural history of patients as they develop pulmonary hypertension, and sometimes catch it before it evolves. Three weeks is really strikingly quick. Even a year and a half is much quicker than what is generally thought to be the time course of pulmonary hypertension development. In portopulmonary hypertension patients we think it takes years to decades.

Dr Krowka: I agree that when these things occur this quickly a strong possibility exists that we're dealing with some in situ thrombosis as opposed to their throwing clots or just obviously missing something on echo. Indeed, we've seen a spectrum of pathology at autopsy. There's no question that platelet aggregates and in situ thrombi have been seen, at least in the setting of post-transplant pulmonary hypertension.

Dr Ramsay: That's an interesting point, Mike. We certainly see 10% to 15% of liver transplant patients who come through for surgery who, despite having a significant coagulopathy on laboratory analysis, when you run a thromboblastogram, they're actually hypercoagulable. This is particularly seen in patients with primary sclerosing cholangitis (PSC) and in some with primary biliary cirrhosis (PBC). This may be a factor that sets them up to present more acutely with raised pulmonary artery pressures.

Dr Wiesner: When we look at our group, there's no etiology that seems to stand out. We see it as often in alcoholic patients.

Dr Ramsay: The numbers of hypercoagulable patients are small. The number of patients with PSC who have the typical hypocoagulability compared with the number of patients who are found to be hypercoagulable in practice is not many.

Dr Oudiz: What happens when a patient is scheduled for liver transplantation and is found either on the operating room table or just with a screening echo? Clearly if the pressure is high, you're going to send that patient to right heart catheterization. And those who by right heart catheterization have significant pulmonary hypertension that precludes surgery will likely be placed on treatment. What percentage of those treated patients with PPH-like disease can actually get their transplant?

Dr Ramsay: So far in our patients we've gotten very aggressive in treating them; we've performed transplantation in everyone we have deferred. We have not lost anyone on the list while they've been receiving therapy. But the thing that we look for is not just mean pulmonary artery pressure and pulmonary vascular resistance. We're also looking at right ventricular function. So they're getting right heart catheterization and echocardiography relatively frequently, every 3 to 6 months. We've had two patients in whom the right ventricle really toughened up. Instead of having a widely dilated ventricle and right atrium, we've seen that ventricle turn in a period of 18 months into a good contracting hypertrophied ventricle. So we took those patients on—we couldn't get their pressures below a mean of 45 mm Hg, but the patients did fine.

Dr Wiesner: What are the ranges at the higher end? Are any of these in the 70, 80, or 90 mm Hg range?

Dr Ramsay: The highest mean pressure in the true portopulmonary hypertension patient (we've seen higher numbers in patients with cardiomyopathy and volume overload) we've seen that I can recall is probably 58 mm Hg. But that was pretransplantation. In that patient, after reperfusion of the new graft, we got a massive increase in cardiac output. That patient's mean pulmonary artery pressure was equivalent to the mean systemic arterial pressure.

Dr Oudiz: The mean pulmonary pressure went up.

Dr Ramsay: Yes. With the increase in flow and relatively fixed pulmonary vascular resistance, the pulmonary artery pressure went up. That was several years ago. We eventually lost that patient. We probably in retrospect could have put a right heart assist device in that patient or something like an atrial septostomy would have been required.

What happens to patients if you go ahead and transplant with significant portopulmonary hypertension? It's twofold. One is that if you have acute right ventricular failure, you may lose the patient. Two, if you just have right ventricular dysfunction, you may lose the graft, which may mean losing the patient too. So there are two downsides to going ahead. It's not just patient survival, it could be graft survival.—Dr Ramsay

Dr Krowka: We've had a few cases also where we identified during the evaluation the mean pulmonary arterial pressure being greater than 50 mm Hg on right heart catheterization and we initiated appropriate therapy with intravenous epoprostenol and had disappointing results. Either there was no significant improvement in hemodynamics over 6 to 12 months or a substantial adverse event occurred, usually related to the hepatic status. They had a bleeding episode, they got infected and died of a nonrespiratory or noncardiopulmonary complication. So not everyone we've seen previously has been a responder. Most of them have responded and we still have several on the waiting list for transplant, but unfortunately other bad things can happen.

Dr Ramsay: When you say they're not responders, have they progressed or have they stabilized at whatever level you saw?

Dr Krowka: That's a good point. They've stayed right where they are. We've not been able to dramatically improve their mean pulmonary artery pressure or their pulmonary vascular resistance. Now, recently we've noted when we followed B-type natriuretic peptide levels that the levels decrease, but the hemodynamic numbers stay about the same, and I'm not sure what that means—that could be favorable—but certainly the hemodynamics by number are not worsening.

Dr Ramsay: That's not the natural history of the disease. If you don't treat it, it's going to continue to progress. Therefore, you have stabilized it. We've seen two patients now with that right ventricle over the course of 18 months that has looked a lot stronger, strong enough that we've elected to take them on and perform transplantation.

Dr Oudiz: Dr Ramsay, in the patients you are treating, are you also treating solely with intravenous epoprostenol?

Dr Ramsay: We have been administering intravenous epoprostenol as our primary therapy until this last year and a half. We have now looked at other therapies that don't require the intravenous route. Some of the patients are getting bosentan despite the fact that it has a reputation for kicking up liver enzyme levels. We've got a pulmonologist who is administering it in preference to epoprostenol. We also have a limited experience with treprostinil.

Dr Krowka: We've used subcutaneous treprostinil rather than intravenous epoprostenol in four patients waiting for transplantation.

Dr Oudiz: Dr Ramsay, I think you mentioned that one of your end points in addition to the standard ones is right ventricular function.

Dr Ramsay: The right ventricle is the critical piece in this. If the pressure is high but the right ventricle is great, that patient ought to do fine.

Dr Oudiz: You will do a transplant in a patient whose right ventricular function has improved but the mean pressure is still over 50 mm Hg?

Dr Ramsay: Yes, but the right ventricle really has to be good, we have to see it really contracting well. In most of those patients, when you initially see them, the right ventricle is widely dilated and the right atrium is widely dilated. So even if they were to survive the surgery, that liver graft gets congested because of the right ventricular dysfunction. And the liver will fail. So we really must have good right ventricular function proven by preoperative and intraoperative transesophageal echocardiography.

Dr Oudiz: Dr Krowka and Dr Weisner, do you have the same criteria or do you have absolute cutoffs in terms of pressures?

Dr Krowka: I think we've used essentially the same criteria. A 50 mm Hg mean artery pressure is the number we've followed with our anesthesia group and we do want to see improvement with epoprostenol and the right heart function. I agree that right heart function is absolutely critical. Our anesthesiologists would follow right heart function in the operating room with transesophageal echocardiography. I don't think there's any patient we've let go to liver transplant who has not been covered by at least intravenous epoprostenol, so we want to have a vasodilator on board for those who have a significant pulmonary hypertension situation.

Dr Wiesner: At least not in recent times.

Dr Krowka: Correct:

Dr Oudiz: What outcomes do you see on average when patients who had pulmonary hypertension were treated with, let's say, intravenous epoprostenol, and had, for example, their mean pressure drop to 40 mm Hg? How do they do postoperatively and how do they do over the longer term?

Dr Ramsay: At Baylor, we've had one patient and this is the last one we lost postoperatively, someone who came in with a mean pressure in the mid to high 50 mm Hg range. We were able to reverse it on the table by just using inhaled

nitric oxide. We brought that patient's mean pulmonary artery pressure down into the low 40 mm Hg range and we felt comfortable that we could transplant safely. The right ventricular function looked reasonable. We transplanted. However, in a very small number of transplant patients in our practice, in about 3%, on reperfusion the cardiac output increases up to 300%. That's what happened in this patient. Cardiac output went up from 6 liters to nearly 18 liters per minute and with that massive increase in cardiac output, the mean pulmonary artery pressures went sky high and the right ventricle failed. So we'd rather back off and take some time to get that pressure down and make sure it stays down and that right ventricular function is good, before we go ahead.

It is fascinating that you have the opportunity to screen a relatively small group of patients that allows you a window into the development of pulmonary hypertension. In patients with connective tissue disease or primary pulmonary hypertension or drug-induced pulmonary hypertension, the denominator is too large to screen them all and assess development, so we don't have a good feel for how quickly pulmonary arterial pressures rise from a baseline of normal. —Dr Oudiz

Dr Krowka: At Mayo we would treat these patients with intravenous epoprostenol or subcutaneous treprostinil for several months before transplantation, continuing the medication through the procedure. After transplantation it's a clinical judgment as to how quickly patients can be weaned off. With the last three patients that I am aware of, we were able to wean off over several months and within one year after the transplant. I'm not sure if we've cured portopulmonary hypertension. I think we've controlled it and improved it, but it's unclear whether we actually normalized the hemodynamics after transplant in everyone. The other benefit pretransplant was not only the pulmonary vasodilator therapy but some pulmonary vascular remodeling, hopefully, and an antiplatelet aggregating effect.

Dr Wiesner: We've had some deaths on treatment too. Early deaths. My feeling overall is that I'm not sure how often liver transplantation per se actually reverses the condition. I know it's been reported. Mike, have we seen anybody where it's been completely normalized?

Dr Krowka: We've dramatically improved patients' hemodynamics, but I'm not aware of any patients at our institution that we've been able to take absolutely off all pulmonary vasodilator therapy, and that includes a calcium channel blocker, after transplantation. The patients we have posttransplant now are being treated either with a calcium channel blocker because they've had some systemic hypertension or with bosentan. No one is receiving intravenous epoprostenol or subcutaneous treprostinil post-transplant at least after a year. We've been able to wean everyone off it.

Dr Ramsay: It's somewhat similar at Baylor. We've had to keep giving some patients intravenous epoprostenol for over a year, for almost 18 months, before we've gotten them off. But we've had a small number of patients whose condition reversed in a matter of days, and you just wonder if it is a different pathology that we are dealing with.

Dr Wiesner: Have you had some deaths?

Dr Ramsay: Yes, before epoprostenol we did. They were mostly postoperative as the pulmonary artery hypertension continued to progress despite transplantation. But once we instituted epoprostenol therapy postoperatively until stabilization or normalization of pressures, we have not had a death as a result of pulmonary hypertension.

Dr Oudiz: That's fantastic. The fact that you can get everyone off prostacyclin therapy, even if it takes a year and a half, is quite different from what we've seen with the pulmonary hypertension patients. That brings us to the last question. Dr Krowka, you had a concern and we all have concerns about what the future holds in terms of therapy. We mentioned bosentan, which is certainly off label in patients who have liver disease, and also sildenafil, which is looking promising and undergoing multicenter trials. What do you think about the use of these as primary agents with respect to initial treatment once the patient has been screened and found to have pulmonary hypertension?

Dr Krowka: There is substantial potential for bosentan if it's given with careful attention to dosing and watching liver function. I would continue to use the prostacyclins, and perhaps combination therapy is going to be a good idea down the road. I have concerns about sildenafil mainly because some patients with liver disease probably have increased nitric oxide effect on the vascular bed already. If one thinks sildenafil is working because of increasing nitric oxide effect even further, I am not so sure that medication is going to be appropriate alone or in combination for portopulmonary hypertension. We would have to do the studies. I think combination management may well be an option and I would not exclude bosentan as Mike Ramsay said.

Dr Ramsay: I think the inhaled nitric oxide issue is interesting. In the first six patients we tried it on we got no response at all. We even looked at exhaled nitric oxide and in some of the patients it was very elevated, but in others it was normal. Then we had a series of five patients where inhaled nitric oxide helped. Inhaled nitric oxide in these patients clearly brought the pulmonary artery pressures down temporarily. I'm wondering if the same thing might be true of using sildenafil. You might find in some patients it works and in some it may not work.

Dr Krowka: That gets back to your comment on pathology. There is probably a spectrum of pathology that we are seeing, not just one pulmonary vascular pathology. And that is something we can hopefully learn more about over time.

Dr Oudiz: Is a heart-lung transplant a viable option in some patients?

Dr Wiesner: It is for certain people. For younger people I think it is a consideration.

Dr Krowka: There have been two adult heart-lung-liver transplants accomplished in the United States. Both were done in the Mayo Clinic system for primary biliary cirrhosis and severe pulmonary hypertension. We have not done any more because multiorgan transplantation is just such a major undertaking and it's so hard to pick the right recipient. Our selection criteria have required that the patient had to be under 50 years of age. So right way you've narrowed such transplantation down to a very few patients.

Dr Oudiz: What are your thoughts on the possibility of a small, multicenter trial looking at initially the use of bosentan vs Flolan or Remodulin in patients who were screened and deemed to be inoperable because of their pulmonary hypertension?

Dr Krowka: I agree that it should be done. Anecdotally, several institutions are using the medication carefully but we've not been able to conjure up enough support to provide the medication in a multicenter trial. Perhaps we need to revisit this again as other investigators present their case-by-case successes. A case report from the United Kingdom will be published in *Transplantation* regarding the beneficial effects of bosentan after transplantation in a patient who did not respond to intravenous epoprostenol.

Dr Wiesner: Mike, are enough data published to put ours together with other groups? There are only anecdotes in this literature, right?

Dr Krowka: You'd really have to have a multicenter study where the inclusion criteria and outcome variables are well defined.

Dr Ramsay: I think now enough people are screening ahead of time that maybe we could get the numbers in a multicenter study and do this.

Dr Oudiz: Is there anything else that you think is critical or at least useful that we haven't discussed?

Dr Ramsay: What's the downside of going ahead? What happens to patients if you go ahead and transplant with significant portopulmonary hypertension? It's twofold. One is that if you have acute right ventricular failure, you may lose the patient. Two, if you just have right ventricular dysfunction, you may lose the graft, which may mean losing the patient too. So there are two downsides to going ahead. It's not just patient survival, it could be graft survival.

Dr Krowka: I think all the centers need to continue to be very aggressive with their screening because new medication options are coming down the road. Even inhaled iloprost may be a therapeutic option. The door is open for us not only to consider these options but also to initiate a multicenter approach toward therapy.