

Surgically Curable Pulmonary Hypertension: A View From the Experts



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Five physicians addressed important issues in the diagnosis and management of patients with pulmonary thromboembolic disease. The roundtable discussion was moderated by Victor F. Tapson, MD, Associate Professor of Medicine, Division of Pulmonary and Critical Care Medicine, Duke University Medical Center, Durham, North Carolina, and included William Auger, MD, Professor of Clinical Medicine, University of California, San Diego, Medical Center, San Diego, California; Peter Fedullo, MD, Clinical Professor of Medicine, University of California, San Diego, Medical Center; Eckhard Mayer, MD, Professor of Thoracic Surgery, Department of Cardio-Thoracic Surgery, University Hospital, Mainz, Germany; and Christopher McGregor, MD, Professor of Surgery, Consultant in Cardio-Thoracic Surgery, and Director of the Mayo Clinic William J von Liebig Transplant Center, Rochester, Minnesota.

Dr Tapson: Let's start with a general statement. If we start with the US, how many centers can do thromboendarterectomy for chronic pulmonary embolism?

Dr Auger: It's hard to get a handle on that. It seems some groups are trying to perform thromboendarterectomies on an irregular basis. If you look at the centers that are set up to do these surgeries on a regular basis, one thinks of the Mayo Clinic, and I would probably include the Cleveland Clinic, and the UCSD Medical Center—about three to four centers in the United States.

Dr Tapson: Dr Mayer, how about in Europe? How many centers do this and would you be able to name them?

Dr Mayer: I think there are approximately five to seven centers all over Europe. There is an active center in Paris, one in northern Italy, one in Austria, one in England, and three centers in Germany. In Europe, I think we have the largest experience in Mainz, with approximately 300 cases over the last 12 years, although these numbers are not comparable to the experience in San Diego.

Dr Fedullo: Now that you've raised that question, Vic, I think it raises another question and that is, how many centers should be doing this procedure and how do the other members of the panel feel about the minimum number of cases that are required on an annual basis to optimize outcome? There are good data regarding other high-risk procedures that volume

is related to outcome. The issue is, can the procedure be done with optimal safety? There's a huge learning curve with this procedure. Perhaps Dr Mayer could comment on what he thinks about the volume of procedures and its relationship to outcome.

Dr Mayer: We had a very significant learning curve during the first 5 years of our program when we started in 1989. The results were much worse compared with the last 5 to 8 years. I do believe that a center should have a multidisciplinary team and there should be at least 20 operations per year. That means 30 to 40 patients are referred for surgery and at least 20 patients per year should be operated on to gain enough experience. Even with 20 patients a year, it will take a little time until the results can reach a level comparable to the San Diego results.

Dr Tapson: What do you think about that, Chris?

Dr McGregor: I think I agree with what people have said. Clearly, there is a learning curve. For the first patients, the mortality for us was around 19% and in the subsequent 42 patients it fell to less than 4.6%. I think there are two aspects to this operation in terms of outcomes. I agree totally with Dr Mayer that this operation should be part of a pulmonary hypertension multidisciplinary group. In terms of surgical outcomes, there are multiple reports where people have not gotten over that early learning curve and have a mortality rate of anywhere from 20% to 40% and there's no point in people doing that unless they're going to see it through so that patients down the line benefit from that learning curve. Regarding the number per year, one could argue, but I would say that the minimum of one a month or 12 per year—that kind of number, although the more the better. There is a second issue: once there is significant experience with this surgery the mortality you achieve is dictated by patient selection and how aggressive you will be in accepting patients with distal disease for surgery. There will always be a mortality for this surgery if you are going to be very aggressive in the pursuit of distal disease. I would be interested in what Professor Mayer thinks about that.

Dr Mayer: I totally agree with that. During the first phase of our learning curve we had a mortality rate of approximately 20% to 24%. There was a lot of criticism and all the cardiologists and respiratory physicians told us this procedure is too risky for our patients. Therefore, we changed the patient selection

for a phase of 2 or 3 years and we accepted only patients with proximal disease who were considered surgically accessible. We were able to reduce our mortality rate to less than 5%. But with increasing experience we started to accept patients with very distal disease during the last couple of years and those patients do have a higher risk than 5%. So it's really true that you can influence the mortality rate by changing the patient selection. However, the patients with very distal disease do not have good surgical or medical alternatives so I think someone with adequate surgical experience should also do the high-risk operations in patients with very distal disease.

Dr McGregor: And I would add that if you're not occasionally—and I'm talking about mortality of less than 5% here—if you're not occasionally having a suboptimal outcome, maybe you're not going to help a large number of people with relatively distal disease who could be helped. So I think there's a balance that could be reached here.

Dr Fedullo: I agree completely. There are always those cases that really surprise us in terms of suspecting that the patient had distal disease during their evaluation phase and who have just a wonderful hemodynamic outcome.

Dr Auger: It certainly has been one of our challenges as diagnosticians in selecting appropriate patients to have surgery. What constitutes distal disease? Those of us who see these patients on a regular basis are occasionally surprised by what we have assessed as distal disease turns out to be resectable while patients who we feel have accessible disease can sometimes be very difficult cases. So there are still some diagnostic problems for us in this patient population.

Dr Fedullo: Absolutely. The correlation between the angiographic and hemodynamic findings is a critical part of the referral process. A procedure in someone with distal disease with a PVR of 1500 carries a much higher risk than one in a patient with a PVR of 500, who would probably tolerate the procedure, even if very minimal amounts of clot were removed at the time of surgery.

Dr Tapson: How do you define distal disease? Is it a relative term or fairly absolute?

Dr McGregor: Therein lies the problem, Vic, as Bill just outlined. As a surgeon, I go in sometimes to what is billed as distal disease and it's surprisingly amenable to surgery. At other times I go in expecting to be able to have a good surgical outcome and it turns out to be very difficult, with more distal disease than anticipated. I think there's a certain sort of art to defining distal disease and I don't think diagnostically we're as good as we'd like to be.

Dr Mayer: I completely agree. Even if you think you have a lot of experience it sometimes happens that the operation is a real surprise in a good way and also in a bad way. Sometimes the

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operation and the postoperative course are very difficult in patients who were considered very good candidates preoperatively while other patients considered to have very distal peripheral disease are easily operable. Even with a lot of experience and good diagnostic tools we are never sure before we are at the end of the operation.

Dr Fedullo: It raises two points. First, it's a shame that angiography is not more widely available because we find it useful in determining operability and we've been having a problem obtaining angioscopes. The other issue is that in certain patients this is clearly both a medical and surgical disease. We thought of it somewhat simplistically in the early years as nothing more than mechanical obstruction of the major pulmonary arteries—but it's clear that there can be a small-vessel component to the disease process and the future approach to the disease under that circumstance may involve both surgical and medical therapy.

Dr Auger: I want to underscore what Professor Mayer and Peter have said, that there still remain a number of challenges for us, even in the evaluative or preoperative phase. Peter and I have changed our thinking about how these patients develop pulmonary arterial hypertension over the years. What we once thought was just progressive thrombotic obstruction of the pulmonary vascular bed may indeed not be the major determinant of the severity of pulmonary hypertension over the years. In the unobstructed vascular bed, small-vessel pathology seems to develop over time, eventually leading to a significant rise in pulmonary vascular resistance and cor pulmonale/RV dysfunction. Consequently, our preoperative preparation may sometimes include pulmonary vasodilator therapy for a period of time to improve the hemodynamic profile prior to committing patients to the operating suite.

Dr McGregor: When one has a patient with longstanding thromboembolic primary pulmonary hypertension with a PVR in excess of 1200 or 1300 and one has achieved what you would think is a textbook surgical resection and does not have significant reduction in pulmonary artery pressure—it doesn't happen that often but does occasionally—what do you think is happening under those circumstances? Are those secondary changes in the normal vessels?

Dr Fedullo: I agree with Bill's point of view entirely. I think these people develop a substantial distal pulmonary arteriopathy and despite a good surgical specimen, some of these patients have considerable postoperative pulmonary hypertension.

Dr McGregor: Peter, what happens to the small vessels distal to the obstructive material we remove? Have those vessels been protected or are they subject to the same secondary arteriopathic changes as the unobstructed vessels?

Dr Fedullo: You would think they would be protected but in the series that Ken Moser did a number of years ago, looking at this, he found the arteriopathic changes in both the involved

and the uninvolved parts of the lung. Is that correct Bill?

Dr Auger: What you're stating is absolutely correct, but there were problems with that study. It was very difficult to correlate accurately the areas from which the lung was biopsied to the areas that were angiographically obstructed by chronic thromboembolic disease versus the areas that were unobstructed. In that study small-vessel arteriopathy occurred in both the obstructed and the unobstructed lung regions. What we would have liked to have seen is a difference, more small-vessel changes in the unobstructed vascular bed versus the obstructed vascular bed. However, I think if you look at preoperative and postoperative lung perfusion scans in patients with major-vessel chronic thromboembolic disease, the increase in perfusion in lung regions that have been endarterectomized relative to those that were not endarterectomized would suggest a lesser degree of small-vessel disease in the obstructed vascular bed.

Dr Tapson: What's the latest in the theory of in situ thrombosis? Do we think that a lot of these cases start as embolic disease and then in situ thrombosis develops? What's the theory now?

Dr Fedullo: It's almost impossible to say but the data that we have based on sequential lung scan findings is that progressive pulmonary hypertension occurs in the absence of new perfusion scan defects. This suggests that in situ thrombosis isn't a major problem in the progression of the pulmonary hypertension. Actually the progression is felt to be due to progressive small-vessel changes.

Dr Tapson: Along those lines, do you all have a fairly consistent approach to evaluating somebody for surgery? In terms of evaluating severity, is it fair to say that everyone undergoing this procedure should at least have an angiogram? What about the CT scan? Are we finding cases where the CT is clearly misleading or misrepresenting what's going on? I guess that would be one of the issues, right?

Dr McGregor: We do ultra-fast CT as well as pulmonary angiography in all the patients, and I would not see them as comparative investigations but rather as additive in terms of the information they give. By that I mean the nature of the disease will determine which test is more useful. In other words, if you have a thin transparent veil occluding a segmental pulmonary artery. If that's the nature of the pathology, an ultra-fast CT will miss it totally because of the distance between the cuts. On the other hand, a pulmonary angiogram, if there is circumferential disease, may look better than it should be, considering the extent of the disease and the ultra-fast CT cutting across those vessels at right angles. You will see intimal thickening. So you get different kinds of information from the two tests but I do not believe the ultra-fast CT in any way replaces the necessity of doing a pulmonary angiogram.

Dr Fedullo: I agree completely and also agree completely with the point that the two studies provide complementary information and can be very useful when used together.

Dr Auger: I also agree that the CT angiogram can be very use-

ful. There have been cases of pulmonary hypertensive patients with clearly defined disease on CT angio and major perfusion defects on lung perfusion scans, in whom we feel it was not necessary to do pulmonary angiography. However, there's an increasing tendency to have it replace conventional pulmonary arteriography. I do not believe it has that power as yet. There are still some unanswered questions as to how useful it is in establishing surgically accessible disease. And I would underscore Chris's statement that this disease can appear very different in the pulmonary vascular bed from one patient to the next. This is a surgically heterogeneous disease.

Dr Mayer: Regarding the diagnostics, I completely agree that the combination of CT and angiography is the standard at the moment. However, within the last 2 years we were operating on approximately 30% of our patients without conventional angiography and we do have very good magnetic resonance (MR) angiographies that are comparable to conventional angiographies in most cases. I believe that 2 or 5 years from now MR techniques will replace angiography and CT scanning in many CTEPH patients. MR function tests of the right ventricle can give us even more information than echocardiography. I do believe that there is a future for MR technology in the diagnosis of these patients.

Dr McGregor: I agree totally with that. One of the advantages of MR as well as ultra-fast CT is that one can get an estimate of right ventricular ejection fraction that is much more quantitative and reproducible than that achieved with echocardiography because of geometric considerations. It's very useful to know what the right ventricular ejection fraction is going in. We've just completed a series of 30 or 40 consecutive patients where we did right ventricular ejections before and after PTE. All patients were measured while off of vasodilators. It is interesting that as a group the right ventricular ejection fraction (RVEF) improves highly significantly from before to after, verifying that we've achieved something positive. But also what was very interesting to me was that it didn't matter where you started in terms of EF. In other words, even if your EF was 15 or 10 you improved as much as if it was 30. So that's very encouraging that we did see improvement in the low EF and the higher EF groups preoperatively.

Dr Tapson: Would it be fair to say then that there isn't really an RVEF lower limit with which you couldn't operate? I guess you have to look at the whole patient and the level of other underlying disease, weight, etc. If it were just the RV alone, would an RVEF that was absolutely dismal in a class IV patient ever keep you from doing the procedure?

Dr McGregor: My current take on the thing is that I don't care what the pre-op RVEF is, depending on what the likelihood is of getting a good surgical result. In other words, if the EF is 12% but I'm confident that I can get a good outcome surgically, then the EF does not affect my selection. But if I see an RVEF of 10% or 12%, and the disease is "questionable," I'm a little anxious, and maybe I shouldn't be but I still am.

Dr Fedullo: I couldn't agree more. That is where experience is

crucial to the evaluation of these patients. The anatomic findings must be correlated with the hemodynamic findings. There's no blueprint but you have a sense that the patient with poor RV function and distal disease will not do well. On the other hand, someone with poor RV function and very accessible disease is much more likely to do well. But it takes a certain experiential base to be able to make that determination.

Dr Mayer: I think there's no lower limit of right ventricular function. If the endarterectomy is successful and the findings correlate with the severity of pulmonary hypertension, the preoperative RV function doesn't really make a difference.

Dr Tapson: Dr Mayer, I remember your publishing in the last couple of years a series of cases that included a fairly high number of class IV patients. Those patients would fit into the same category as those with poor RV function. It sounds like you had a good outcome with those individuals.

Dr Mayer: Yes, we have a good outcome in NYHA class IV patients, if angiographic findings and severity of pulmonary hypertension are proportional and a complete removal of the obstructing material is possible. I am in doubt about the surgical indication if there is only minor unilateral distal disease in the angiography and very severe pulmonary hypertension combined with poor right ventricular function. Those are the cases with a very high risk. But if the disease is surgically accessible, I really believe that every right ventricle can recover.

Dr Tapson: What about cases where you have concomitant left ventricular dysfunction or concomitant COPD or other lung disease? How does that play in your decision to do surgery? I guess you have to individualize these cases?

Dr Auger: That's absolutely correct. In days past these kinds of cases concerned us a great deal. Let's just take the case of patients with severe COPD or emphysematous lung disease. This is where CT scanning can be very helpful. If someone exhibits significant occlusive vascular disease to the lower lobes and yet much of the emphysematous lung is in the upper lobes, these patients can be helped with a thromboendarterectomy by improving perfusion to relatively normal lung tissue. In the patients with severe left ventricular dysfunction, an endarterectomy can abruptly reduce right ventricular afterload and consequently increase left ventricular preload, which can precipitate heart failure in the postoperative period. These people are at particularly high risk and do not generally do well following the operation.

Dr Tapson: Is there any way to gauge what someone's ultimate level of function will be preoperatively or do you get really good results in some sick people and maybe not so good results in some people who do not have such significant obstruction? Can you predict the outcome in any way?

Dr Mayer: Not for every patient. For most of the patients we can predict the outcome but there are still some patients in whom

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we are not able to predict the operative and long-term outcome. It can be very difficult to predict the outcome in the individual case.

Dr McGregor: I agree with that. The improvement in right ventricular function is dramatic and early. By a week after surgery their EFs increase 20 points. What is also interesting is that there can be continuing improvement at 6 months and a year when you repeat the test and it's even better. So there's an early acute improvement and there may be ongoing more gradual improvement. When you asked about COPD and patient selection, I think one of the biggest problems we deal with are the patients who

have this disease who are missed and have the possibility of getting surgery. When you think that the prognosis of this disease is so bad when they get to class III or IV and the outcomes of surgery are so good, the frustrating thing is that there are patients sitting around major medical centers who are undiagnosed. I would say a third of the patients I see are labeled as having asthma. We have to try and pick out the disease and secondly, if a group is going to do this surgery regularly and establish a program, they have to have reproducible hemodynamic outcomes not only to confirm operative mortality but the success of the surgery

Dr Fedullo: Even though it appears that patients are being referred earlier, there is still a large group of patients who are carried for years with the diagnosis of asthma, for example. The patients will say, "I've told the doctor, I've never wheezed, I know what asthma is." And yet they'll be treated with steroids for years until somebody finally stumbles upon the diagnosis. Again, getting the word out to the general community that this disease exists and can be confused with other disease processes is very important.

Dr McGregor: I presented at an echo meeting recently and I really made the point that anybody who has an echocardiogram, has elevated pressures, and who does not have morphologic cardiac problems to account for it should have a V/Q scan.

Dr Tapson: Chris is making a crucial point. You first have to diagnose the pulmonary hypertension. As we tell our patients, we have to figure out the cause and the severity and that makes all the difference in the world in terms of what we do. But you've got to rule out curable causes of disease. It's so rare that we find a curable cause of pulmonary arterial hypertension. And to find something surgically curable is crucial. I would absolutely echo that, and no pun intended there, that you've got to evaluate patients with abnormal pulmonary artery pressures and exclude the possibility of acute, subacute, or chronic pulmonary embolism.

Dr Auger: Many of us are at centers focusing on pulmonary vascular disorders that are busier than ever. We can all remember the days when this disease was such an oddity; it was rare when we were operating more than once or twice a month. Now many of us are performing a dozen of these surgeries each month, evaluating anywhere from 10 to 20 patients a month as poten-

tial surgical candidates. However, it is still our impression that there are many more folks out there where the diagnosis has not been adequately explored.

Dr Tapson: When cases are done, how often is reoperation done or how often is transplant ultimately necessary in these cases? It's amazing what all of you have accomplished with this disease over the years, but there are some cases that will deteriorate no matter what you do.

Dr Mayer: I completely agree. Fortunately we have only 1% of PTE reoperations (2 out of 300 patients). In addition I did a lung transplantation 3 or 4 years after primary successful PTE. I don't think that lung transplantation is a good option for patients if they really have CTEPH. However, there are very few patients with primary pulmonary hypertension and in situ thrombosis. We had two cases in the last 2 years in whom we did not have the right diagnosis preoperatively and both patients died. The diagnosis is very difficult if they do have the combination of primary pulmonary hypertension and in situ thrombosis. Lung transplantation is an option for these rare cases.

Dr Fedullo: That has been our experience too. I think some minimum level of pulmonary arterial pressure has to be reached postoperatively to assure a good long-term hemodynamic outcome. Unless that minimum level of pressure is reached, 4 to 5 years later the patient may present with recurrent symptoms. When we reevaluate those patients they have developed recurrent pulmonary hypertension that is not due to recurrent thromboembolic disease. They've progressed as a result of small-vessel disease changes. My feeling is that patients who have an incomplete hemodynamic outcome should probably be reevaluated 3 to 6 months after the surgical procedure. If the patient still has pulmonary hypertension then we should strongly consider medical therapy.

Dr Auger: Two comments, one of which has to do with the rate of reoperation or redo pulmonary thromboendarterectomies. The numbers that have been discussed are consistent with our experience as well—in the range of less than 1% of operated patients. It also appears that if a patient experienced a successful pulmonary thromboendarterectomy the first time and develops recurrent, chronic thromboembolic disease, a second successful thromboendarterectomy is possible. The second comment relates to our experience with a cohort of patients who do not achieve normalization of pulmonary artery pressures postoperatively. Because of the availability of pulmonary vasodilator therapies, we're more aggressively treating those patients who have a suboptimal hemodynamic response from their pulmonary thromboendarterectomy. We have noted that if the pulmonary vascular resistance achieved postoperatively is in the range of 500 to 600, 4 or 5 years down the road their pulmonary hypertension is typically worse. In many cases, based on angiographic and other diagnostic studies, it appears we're not dealing with recurrent thromboembolic disease but rather progression of small-vessel disease.

Dr McGregor: This reemphasizes the point made earlier of why

you need a pulmonary hypertension clinic or center because patients move from the medical site to the surgical site and back to the medical site. This reemphasizes that you need to have multidisciplinary care. Peter and Bill, educate me, what do you think is the hemodynamic outcome in terms of mean PA pressure and PVR that would indicate a good long-term outcome versus naught?

Dr Fedullo: I feel absolutely comfortable when the PVR is below 300 and I'm terribly concerned when it is above 500 and uncertain when it is between the two.

Dr McGregor: And mean PA?

Dr Fedullo: Above 40 I'm concerned, below 30 I'm comfortable and between the two I'm uncertain. These patients have to be evaluated sequentially. If they have a mean PA pressure of 35 after operation, they should undergo repeat right-heart catheterization in 6 months or a year and if there is any evidence that the pulmonary hypertension is progressing then at that point I would initiate medical therapy.

Dr McGregor: And what about PA pressure in the same situation? If the PA pressure is 35 at time of discharge?

Dr Fedullo: I would do exactly the same thing.

Dr McGregor: So anybody who has a mean PA pressure greater than 30 or PVR greater than 300 you would recath them down the line?

Dr Fedullo: Yes.

Dr Auger: It's important to know the numbers we're talking about. The number of patients who are in the category that Peter is discussing is in the range of 5% to 10% of those undergoing surgery.

Dr Mayer: I agree that it's the same numbers, for sure less than 10% of the patients. I think that a less invasive approach for quality control and long-term assessment might be MR angiography and evaluation of right ventricular function. It is a very precise method and you don't have to do a recatheterization.

Dr Tapson: One final question. Any perioperative or postoperative care pearls in terms of management, pressor therapy, anything else someone feels strongly about? I visited the San Diego operation before and Bill and Peter certainly have a superlative operation, and it's very clear that there is a substantial amount of input from surgery and the pulmonary staff.

Dr Auger: It's hard in a moment or two to come up with a successful formula for postoperative management of these patients. The two most formidable problems we have, comprising 50% of our in-hospital mortality, are persistent pulmonary hypertension with RV dysfunction, and reperfusion lung injury. Meticulous supportive care, particularly as it pertains to dealing with reperfusion lung injury, is critical to getting these patients discharged.