CTEPH Experiences and Expertise

On February 6, 2014, a group of physicians with expertise related to Chronic Thromboembolic Pulmonary Hypertension (CTEPH) met on a conference call to discuss topics related to the disease. The call was hosted by the guest editor of this issue, Richard Channick, MD, the Director of the Pulmonary Hypertension and Thromboendarterectomy Program at Massachusetts General Hospital. Dr. Channick was joined by Victor Tapson, MD, Professor of Medicine in the Division of Pulmonary and Critical Care Medicine at Duke University Medical Center and Director of the Duke Pulmonary Vascular Disease Center; Joanna Pepke-Zaba, PhD, FRCP, Lead Physician and Director, National Pulmonary Vascular Diseases Unit at the Papworth Hospital, University of Cambridge, UK; Vallerie McLaughlin, MD, Professor of Internal Medicine at the University of Michigan; and Bill Auger, MD, Professor of Clinical Medicine and Director of Academic Affairs of the PTE Program at University of California-San Diego.

Dr Channick: Welcome. We really appreciate your joining us from various time zones around the world. It's a pleasure to be joined by several distinguished colleagues to discuss the topic of CTEPH. I'm joined by Drs. Victor Tapson from Cedars-Sinai; Joanna Pepke-Zaba from Papworth Hospital in Cambridge, Vallerie McLaughlin from the University of Michigan, and Bill Auger at University of California, San Diego. We anticipate having quite a lively discussion. I will attempt to frame this topic in different sections and I'll ask each of you to take a section. As usual, we would like the discussion to be spontaneous and animated!

CTEPH is certainly topical given new therapies and our advancing knowledge about the treatment for this disease. But, of course, chronic thromboembolic disease starts with acute pulmonary embolism (PE). Vic, I know you've spent a lot of your career looking at diagnosis and treatment of acute VTE. What would you recommend in a patient who's had a large acute PE? Because presumably that's the patient who could go on to develop this CTEPH. What kind of follow up should these patients get?

Dr Tapson: Well, that's a great way to start, Rich. We don't have a lot of data supporting the fact that patients that have acute PE need repeat studies, such as repeat CT scans or echos. But I think one of the keys is those patients that come back to see us that haven't quite recovered. If somebody's still dyspneic, they come back to see you in a month, a month-and-a-half, where most people with acute PE have recovered, those symptoms could be due to their underlying illness or represent persistent PE. The key is to look for persistent dyspnea, which is going to be the most common symptom. And when someone has those kinds of symptoms present, then further studies are warranted. A number of my colleagues might consider doing a CT scan in someone who had a big saddle embolism and recovered, just to make sure that has resolved completely. But we don't have a lot of data to support these kinds of tests, so a key is symptoms. Are there recurrent, persistent symptoms? And we certainly have to keep in mind that some patients may symptomatically improve or recover from an acute PE, but subsequently present with worsening symptoms and are found to have CTEPH. To follow patients after acute PE, we generally do a six minute walk test, where patients come back, kind of like we do in our pulmonary hypertension clinic. In addition to exercise capacity, we evaluate oxygenation. Because someone may come in, if they're a fairly sedentary person may not have a lot of evidence of persistent problem when, in fact, with exercise they may be hypoxemic. In addition, if the echo previously showed RV strain or PH, I would repeat an echo to make sure it has normalized.

Dr Channick: You mentioned an interesting phenomenon, which is patients becoming asymptomatic following acute PE and then going on to develop chronic disease. Bill, in San Diego, your group has described this as a "honeymoon period." It seems like there is the risk of missing CTEPH in such cases if one is lulled into the false sense of security when patients are "asymptomatic" after 8 weeks. Do you agree?

Dr Auger: That's a really good point. And, yes, we have described this so-called honeymoon period, where after having experienced a large pulmonary embolism, the right heart compensates, even if the thrombus hasn't resolved completely and patients seem to do fine for a period of time. They seem to be doing fine and experiencing a normal course following their acute thromboembolic event on an antithrombotic therapy. And then months, if not years, down the road, they run into problems. The data are not strong enough to support that everybody should have a lung ventilation perfusion scan or echo every six months after they've experienced an acute pulmonary embolism. I agree with Vic, in that I think the evaluative process needs to be based on symptoms.

Dr Tapson: Another key time period is when you're considering stopping their anticoagulation, whether it's 6 months or a year. If you're going to consider stopping it, another time point is to really make sure you know how the patient is feeling. And it may well be that a patient who is on continued anticoagulation might have less of a chance of going on and getting CTEPH, although this is speculative.

Dr Auger: I agree with you, Vic.

Whether or not you keep people on anticoagulants is really a repetitive risk assessment at intervals following their acute event. Do they have a thrombophilic state? Was the clot unprovoked? And so on. What are the ongoing risks that one individual has during their assessment dictates whether or not you need to continue their anticoagulants.

Dr Channick: One other area that gets debated is whether or not more aggressive treatment of massive or submassive PE, i.e., with thrombolysis, will decrease the likelihood of CTEPH. Maybe I'll ask Joanna, do you agree with that view? And at your center, are you more aggressive with the large acute PE in order to prevent CTEPH?

Dr Pepke-Zaba: We do not have much of the acute PE. But generally in the UK, we do not thrombolyse unless the patient is hemodynamically unstable.

Dr Channick: Val, how about your center?

Dr McLaughlin: The same. And there are no strong data that thrombolysis is doing anything above anticoagulation. Vic, are you more aggressive about those with RV dysfunction?

Dr Tapson: Well, like Joanna said, I think really the data support lytics for massive PE. The data don't even unequivocally support that approach. The expert opinion would support that, however. But for submassive PE in the groups we might consider, I think the data are still unclear. The PEITHO study should be published soon; it was presented last year and I think it should be published soon. They met the primary endpoint of decrease in hemodynamic deterioration in the PEITHO study, but we still don't have mortality data that prove thrombolytics improve mortality in our patients with submassive PE.

Dr Channick: It sounds like we can all agree that there really aren't good data that you're preventing CTEPH with more aggressive up front therapy.. Which leads to the next topic, of course, which is why does CTEPH develop? There are data that suggest it's not just the size of the initial thrombus. It's obviously a very complex disease. Joanna – tell us a little bit about why you think people develop CTEPH. Who gets it and why do you think they get it?

Dr Pepke-Zaba: I think that the problem is that there is no animal model of CTEPH disease. And this is why it's so difficult to talk about pathogenesis of disease to understand how the primary insult pulmonary embolism is not fully dispersed and is progressing to the chronic, rigid, and very variable obstruction of the vessel. We know that there are a number of medical risk factors that can contribute to development of chronic thromboembolic pulmonary hypertension. And this would be the history of cancer, thrombophilic disorders, splenectomy. And there are some data suggestive of an inflammation associated to central catheters, such as pacemakers, wires, AV shunts. Blood groups other than O were also a predictor of CTEPH diagnosis and has been reported as a specific feature of the CTEPH patient population. How that affects clot resolution is again very interesting, but the data and our understanding of the pathobiology are limited. I think another interesting issue is how the clots are distributed in the pulmonary circulation. We know that the CTEPH is currently described as a two-compartmental disease of the proximal obstructions, which are suitable for the surgery—treatment of choice, and the distal obstructions are suitable for the surgery with pulmonary endarterectomry and/or secondary small vessel vasculopathy, where the medical treatment can be considered specifically now when potential medical therapy for inoperative CTEPH is available.

Dr Channick: This "two compartment" paradigm has always been very interesting to me. The number of pathophysiologic phenotypes in this condition are striking. For instance, we've all seen patients with very large clots and minimal "small vessel disease" and then vice-versa. Is it one disease with variable responses? Or are they really separate diseases? Bill, what do you think?

Dr Auger: The mechanism for developing CTEPH is still not entirely clear. I think there probably is a spectrum of pathology here. We've felt that in a large percentage of patients who ultimately develop CTEPH that the initial event is, in fact, an occlusive thrombus of the proximal pulmonary vascular bed with the secondary development of a downstream vasculopathy over a period of time. This gets us back to that whole concept of a "honeymoon period." Perhaps the initial clot. . . which can often be a silent PE or wasn't terribly symptomatic, provokes the gradual development of a secondary small vessel arteriopathy. This leads to the development of significant pulmonary hypertension, which becomes symptomatic. That certainly is one theory. Is it possible that folks develop a small vessel arteriopathy first with secondary thrombus development, as a different kind of phenotype for CTEPH? This might be a consideration. . .especially when you start talking about segmental level thrombotic disease. However, this theory is problematic and probably not the typical course of events in CTEPH patients. We still maintain that the initial event is that of a proximal vessel thrombus. This seems more logical when you consider that the endarterectomy surgery wouldn't be beneficial if all you're doing is taking out clot when the basic pathology is that of small vessel disease. But I think you're absolutely right, Rich, when you speak of the wide range of clinical presentation in this disease. In some folks, it just seems to be the proximal vessel clot without much pulmonary hypertension, but they're symptomatic from dead space ventilation issues. You take out the clot and everything gets better. In other patients, there's really severe pulmonary hypertension and a limited clot burden. And so it really is a complex disorder.

Dr Channick: We're certainly not going to discover the pathogenesis today, except to say it is complex. Just one last question on this topic: Do you think the clot grows in situ? Because the material removed at surgery often appears to extend down the branches over time.

Dr Pepke-Zaba: I think that it could. Just looking at what sort of lesions are on the CT scan, the complexity of the webs which are the residual after a previous insult, at least we understand that it can grow down peripherally. But that is rather our interpretation of the findings, not that we have proven it. Additionally, I just want to highlight that it has been shown that different distribution—more central or distal–of obstructions can affect right ventricle function. That might modify the individual person responses and the development of right heart failure contributing to the different phenotypes of CTEPH mentioned already by Dr Auger.

Dr Tapson: My suspicion would be that there has to be a genetic component or susceptibility. Bill could probably tell us his overall feeling about known thrombophilias and how often they occur with this disease. But it just seems to me there's got to be a susceptibility factor, why some people get a clot and it doesn't resolve like it should, assuming that's the major pathophysiology.

Dr McLaughlin: We know, don't we, Vic, that only about 20 percent of patients who have CTEPH actually have a known hypercoaguable state? There are likely many others that we haven't identified.

Dr Tapson: Yeah, that's absolutely right. I think there are probably thrombophilias we haven't discovered or some genetic predisposition, or both, that make patients more susceptible. And as Bill has mentioned, many patients don't have a history of VTE, maybe 50, 60 percent have a history of an acute event. And I think one thing we've found is that the more you talk to a patient, the more you come up with a previous event that sounds like it could have been PE–if they had a "pneumonia" three years ago, in the hospital for four days, and you talk to them about their pneumonia maybe they didn't have that much cough or fever, which is kind of unusual with pneumonia. Or they had, a "cellulitis" in their leg two years ago, so the history does come out. But there must be some susceptibility factor here.

Dr Pepke-Zaba: One more thing: Genetic predisposition for the right ventricle to fail is very important, but that is completely different to the genetic predisposition for development of acute pulmonary embolism or CTEPH. So just for clarification, the most likely genetic factor will clearly distinguish the patient with the chronic thromboembolic pulmonary hypertension, a very rare disease, from those who are developing acute pulmonary embolism, which is common. So we are potentially talking about two completely different genetic diseases.

Dr Channick: Which leads to a very important question: What, in fact is the true incidence of CTEPH? In the literature, we read numbers ranging from less than 1 percent to 4 to 7 percent.

Dr Pepke-Zaba: Well, I think that we don't know. (laughter) I can only tell you that the number of patients with chronic thromboembolic pulmonary hypertension in the UK has grown dramatically since we have started the national program. And now, CTEPH is the second biggest subgroup of the patient with pulmonary hypertension that's seen in the pulmonary hypertension centers in the UK.

Dr McLaughlin: Well, it's one of those things, the more you look for it, the more you're going to find. Sadly, a lot of people don't look for it.

Dr Pepke-Zaba: And we are trying to retrospectively look into the CTEPH population and find out how many – how it relates to the acute PE in the region. But it's very difficult because there are no good data that can estimate acute pulmonary embolism.

Dr Tapson: Yeah, the Pengo data are interesting. You remember that study, of course, in *New England Journal*, probably ten years ago. They had a couple hundred patients. And these patients had a first PE, so they had to have a documented event to be included in this study. They were followed after their acute event and ultimately had a rate of about 3 or 4 percent of CTEPH. But those were patients who had a documented event. So it may be higher than we think and I bet a lot of our colleagues out there and maybe ourselves have patients we follow for PH that may still have unrecognized CTEPH.

Dr Channick: Another limitation of that study was that pulmonary hypertension was diagnosed only by echo.

Dr Tapson: Yeas, that's a good point. So it may have overestimated it.

Dr Channick: Bill, you can attest to the phenomenon that fellows who trained at UCSD start "epidemics" of CTEPH when they'd go out after their training!

Dr Auger: Val makes a really good point. You're not going to make the diagnosis unless you look for it. The experience has always been that when people really start thinking about the possibility of CTEPH, that's when they start picking it up. Studies that attempt to look at the incidence of CTEPH typically follow patients after an acute thromboembolic event or a recurrent thromboembolic event. Unfortunately, there are a number of folks with pulmonary embolic events who don't present symptomatically. So there is a hard-to-define group of patients out there with previously unrecognized PE that ultimately come to you with dyspnea for unclear reasons. It's in these patients particularly, unless you think about the diagnosis of CTEPH and screen for it, you're going to miss it.

Dr Channick: Okay. So if every case of CTEPH was diagnosed that exists in the US, how many surgeries would there be per year? (laughter). For the sake of discussion, we are assuming that all got referred to a center where they had surgery. What would be the number? Five hundred, a thousand, ten thousand?

Dr Pepke-Zaba: The UK population is 64 million. We have performed 153 pulmonary endarterectomies in the last year, previously 150 operations, and we still have a waiting list for the surgery.

Dr Tapson: I think part of the answer to that question lies in the fact that after

starting to see these patients and spending a little time reading CT scans with Bill Auger, that this is an art, reading these CT scans. And I'm convinced, if you're not thinking about it, like you guys have said, you're going to miss it. And even if you're a good radiologist, you can still miss it if you don't see this disease a lot. You may not see the subtle findings. We're not looking for intravascular defects, like acute PE, we're looking for abnormal vessels that have been remodeled and are unusual looking. And boy, I'll tell you, you guys who have spent time at San Diego have seen a lot of these, and it's an art.

Dr Channick: Yes, no about that! So what's the number?

Dr Auger: We just don't know how many endarterectomy surgeries are performed, or how many potential surgical candidates there are in the US. Our best guess is based on what limited surveys we have. Given the small number of specialized centers around the United States, there's probably about 400 thromboendarterectomies being done each year. But that is purely speculative. . .and assuming that all cases of CTEPH correctly identified as operable are having surgery. Which leads to the larger question of how many patients there are with newly diagnosed CTEPH who are not deemed to be surgical candidates for one reason or another. We just don't know.

Dr Channick: So if you are correct regarding 400 PTEs per year in the US, given the number of people surviving PE per year, that would correlate to approximately a 0.1 percent incidence which would be at the low end of the incidence or prevalence estimates.

Dr Auger: What do you think about that, Val, as far as the number of cases?

Dr McLaughlin: The number of cases currently being done? I mean, you guys alone do what, 300 a year?

Dr Auger: No, we did 162 cases in 2013, so, maybe near half of the cases in the United States, I would imagine.

Dr McLaughlin: So that 400 may be a little high, actually. There's you guys', obviously you're the world's leading most experienced center in it. And then there's a modest number of centers that do a modest number of cases. So, I think probably the rest of us combined, maybe we come close to what you do. So I think it's probably less than 400.

Dr Channick: So suffice it to say that we're probably not doing nearly as many PTEs in the US as there are operable patients.

Dr McLaughlin: That's exactly the point. I mean, you know, whether it's 300 or 400, it's still a lot less than what you would expect, based on the epidemiology of the disease.

Dr Channick: Right. Which gets me to the next topic. Val, as someone who has a very large pulmonary hypertension program, how do you do an initial evaluation for CTEPH and at what point do you decide to refer a patient for consideration of surgery? And what is the testing that you do as opposed to allowing the referral center to do?

Dr McLaughlin: With regard to diagnostic testing, I think we've all been involved in discussions, talking about the importance of ventilation/perfusion scan as the study of choice to screen in a patient who has unexplained dyspnea and pulmonary hypertension. While Vic has outlined some of the very nice changes that you see on spiral CT scan, they are sometimes difficult to interpret. You can sometimes miss surgically accessible disease. So the V/Q scan is the screening test of choice. Often, patients will come to us with a spiral CT and we would generally repeat a V/Q scan. There may be a case here or there– and I would love Vic or Bill's opinion on this– for instance a scleroderma patient who has some interstitial lung disease, in whom you think the V/Q's not going to be all that helpful, that maybe we'll look more closely at the CT. But one of the key factors is doing the ventilation/perfusion scan. Unfortunately, this is a practice that is not followed as much as we would like to see. In fact, in one of the registry studies that have been done over the past few years, we see that about half of the patients who ultimately get diagnosed with group 1 PAH do not have a ventilation perfusion scan. Hopefully CTEPH is being evaluated in some other way, but they're not getting the study of choice. Once a patient has a suspicion of chronic thromboembolic disease as we're working them up, be it a patient without a history of PE who has an abnormal V/Q or someone that comes with that history, certainly the pulmonary angiogram is the roadmap. And, at our center, we feel comfortable doing the right heart caths and pulmonary angiograms in these patients. We have enjoyed a wonderful relationship with UCSD over the years. I've sent them many patients over the years and they've been great about initially looking at the films and the records, to see if it's worth a trip. Over the most recent years, we have started doing some thromboendarterectomies at our center. UCSD was gracious enough to host one of our surgeons and some anesthesiologists. As a newer center, you obviously have to pick your initial cases very carefully. And so we've worked together with our surgeon, anesthesiologist, and also with UCSD to help select the appropriate cases for a newer center to do and we've had success, but we still work with UCSD for a lot of these patients.

Dr Channick: Thanks. Bill, I know you get patients referred at all stages of evaluation. Can you add anything to that? I'm sure you're willing to review the V/Q scan or do everything at the center? How do you interact with the referring doctors in this regard?

Dr Auger: Val has appropriately emphasized the need in patients with known pulmonary hypertension to take a closer look at the pulmonary vascular bed, and the recommended screening study for CTEPH would be a perfusion scan. And simply put, the perfusion scan will be either normal or abnormal. If it's normal or showing just kind of a grainy pattern of hypoperfusion, then the chance that that patient will have surgical or operable CTEPH is virtually

zero. If it's abnormal, then the diagnostician needs to move forward and evaluate the pulmonary vascular bed in some other way. Although with appropriate precautions, conventional pulmonary angiography can be safely performed in pulmonary hypertensive patients, and can provide a tremendous amount of information as to whether a patient has operable CTEPH; it is becoming a lost art. Evolving technology is such that examining the pulmonary vascular bed with CT and/or MR . . . and particularly with CT. . . is an increasingly valuable diagnostic tool as long as it's interpreted appropriately. Everyone here can appreciate that even patients with extensive small vessel disease can have an abnormal perfusion scan. So an abnormal perfusion scan, in and of itself, is not enough to say that somebody has surgical CTEPH. You just need to image the pulmonary vascular bed in another way, be it with conventional pulmonary angiography, CT, and/or MR.

Dr Tapson: Bill, can I ask you a question. Given the availability of really good CT scans, do you still feel it's necessary to do a PA gram in all patients?

Dr Auger: Really, it depends on the circumstance. We have observed numerous cases where the CT angiogram has clearly understated the amount of chronic thromboembolic disease present. As surgical techniques have been advanced, particularly both at Papworth as well as at UCSD, where segmental level resection is not only possible, but hemodynamically beneficial, it becomes increasingly important to define operable CTEPH in a region of the vascular bed where CT can sometimes understate the extent of disease. So, particularly in those individuals in whom we're still unsure whether or not they have operable chronic thromboembolic disease, we will do conventional angiography. But in some circumstances where hemodynamic data are available, and we know how sick those patients are, and CT angiography demonstrates a lot of proximal chronic thromboembolic disease, conventional pulmonary angiography is not necessary.

Dr Tapson: Maybe I could just mention one additional aspect of diagnosis, based on something Val mentioned. We do have two scleroderma patients that went through our usual pulmonary hypertension workup when they presented with progressive dyspnea. And we did their V/Q scan, as we always do, and both had high probability scans, had CTEPH, and both have been operated on now. So even if we have a known other cause of pulmonary hypertension, the patient still might have CTEPH.

Dr Channick: I agree. Although our experience has demonstrated the importance of the V/Q scan-and I would certainly classify myself as a "believer"–that belief is not held everywhere. Joanna, at your institution in the UK, are perfusion scans still performed routinely? I know at some European centers they're not as readily utilized.

Dr Pepke-Zaba: No. CT scanning is much more popular than V/Q in the UK generally. Usually, the patient will have a CT scan and if CT scan suggests some degree of pulmonary occlusions, the patient might go to the V/Q scan to look for the sort of wedges which have been already mentioned. And we do like to see perfusion scans with those nice wedges before the surgery. But we also like MRI angiography. And this is a much better way of imaging proximal pulmonary vasculature compared to the CT scan. I totally agree that CT can often underestimate the disease burden and our surgeons like MRI.

Dr Channick: So MRI is typically your confirmatory test?

Dr Pepke-Zaba: Yes.

Dr Tapson: One thing I'd say about MRI, I think you've got a clinician like Joanna, in a center like they have, it's probably a great option. We learned in PIOPED 3, at least for acute PE, that the interpretation of MR really depends on the radiologists reviewing them. I'm sure that would probably hold for CTEPH even more, since it's a difficult diagnosis.

Dr Channick: Let's move on to the next topic: surgery– and I'll turn to Bill, to take us through the referral process and the typical course once the patient gets referred to your center. And then a little bit about the really impressive outcomes after surgery.

Dr Auger: We certainly are available to do as much of the preliminary work in evaluating patients for possible surgery, even prior to their traveling to San Diego. The first step is a request for certain studies that might indicate the patient might have CTEPH, such as an abnormal lung ventilation perfusion scan in the setting of pulmonary hypertension. With an abnormal perfusion scan, a request will go out either for a CT or other imaging modalities to better define what those perfusion abnormalities might be from. Most clinical centers–unless you're coming from a fairly large medical center–don't typically perform conventional angiography in pulmonary hypertensive patients and hence our increasing reliance on CT angiography in order to prescreen patients for possible operative chronic thromboembolic disease. And once it seems that this person is a potential candidate for surgery and it is apparent there's the desire on the patient's part to pursue a surgical option.

Dr Channick: Let me just stop you real quick right there. So let's say I'm a referring physician, and I call and say, "I have this guy. He's in his late 70s. He has some coronary disease." Is he really a candidate for this operation?

Dr Auger: Available data would indicate that age in and of itself is not an exclusion criteria for undergoing endarterectomy surgery. We've operated on patients as old as 88 at UCSD.

Dr Pepke-Zaba: You have beaten us. Our current is 86.

Dr Tapson: It's really remarkable. Of course, these folks have a tendency to select themselves out as being fairly hearty in the first place. To Rich's point, is there an age cutoff? And certainly, what affects perioperative mortality risk

is not so much age but the comorbidities that come with somebody's age. And this particular person at 88 had very few comorbidities that would adversely affect his perioperative course.

Dr Channick: I think it is very important to stress to the readers of this roundtable, some of who may not have diagnosed CTEPH or referred patients for PTE surgery, that this procedure is not "experimental" and has been performed for decades. At large centers of expertise, it is considered almost routine. The postoperative course can be very straightforward, with great outcomes; PTE is a truly lifesaving and life changing procedure. Even at my institution, MGH, when I started the CTEPH program 4 years ago, my esteemed colleagues really didn't have an appreciation for the procedure and its benefits. Now that we are regularly performing the procedure, everyone is a believer! Joanna and Bill, you both have very large programs. Can you elaborate?

Dr Pepke-Zaba: I think the most important is to highlight that mortality now has been dramatically reduced. And in the cases without specific comorbidities, is within the sort of range of any other major cardiac surgery. So we are talking about 2 percent or under 2 percent mortality for the simple cases. I think that's very important to highlight. However, the learning curve at the beginning is very, very steep. The long-term outcomes after the patient recovers from the surgery are excellent. Perioperatively, our average stay on the ICU is 48 hours, patients are walking out from the hospital within 18 days. After 3 months practically, they are back to normal functioning. And good functional status is further improved or maintained for a long time. We've got follow up data with the hemodynamics up to 1 year. And the patients are observed routinely in other PH centers for 5 years-plus. We are currently putting long-term data together, but the mortality of the patients who are surviving the surgery is very good and 5 years' survival is about 95%, which is equal to the one which you expect in this age group, which is around 60-plus.

Dr Auger: And Rich, we're experiencing the same thing. I can underscore that as your experience grows, your mortality rates drop. Over the last five years, we are seeing an overall perioperative mortality of less than 2 percent for our patients, with very little impact now on the level of acuity and/or the severity of the pulmonary hypertension preoperatively. Our median time on the ventilator is a day. Our median time in the ICU is 3 days now. And our median length of stay postoperatively is down to 10 days. But that just comes with doing a greater number of cases. And I think every center that performs this particular operation shares this same experience.

Dr McLaughlin: I think that's true, Bill. But I think the other thing to maybe point out is just patient selection, too. I mean, not all CTEPH is operable. And not all CTEPH that you see is proportionate to the amount of pulmonary hypertension. And so some of those things go into selecting appropriate patients for the surgery.

Dr Channick: Absolutely! There is no question that the outstanding outcomes that we see are due to the multidisciplinary team approach to CTEPH. An experienced medical diagnostician who can interpret imaging and hemodynamics to choose acceptable surgical candidates, an experienced surgeon, and good postoperative care are all critical to success.

Dr Auger: Rich, I'm waiting for you to ask the next provocative question. What constitutes operable CTEPH? Because Val is absolutely right, not every patient with CTEPH is a candidate for the surgery. This is an exciting time in the world of CTEPH with advancements in surgical techniques, and the availability of medical therapies for patients with nonsurgical CTEPH.

Dr Channick: I hesitate to delve into what constitutes operability, because this is a complicated decision that requires extensive experience, something you can't explain in sound bites. Being able to interpret the PA grams in the context of the pulmonary hemodynamics, patient symptoms and comorbidities, is a skill that only comes with time. But suffice it to say that there will be some patients deemed inoperable. Which gets me to the last topic: What is the role of medical therapy? Val, you've been involved in helping develop many of our approved, highly effective medical therapies for pulmonary arterial hypertension. What is the role of medication in CTEPH patients? This question is especially relevant since there is now a medication approved for inoperable CTEPH or post PTE residual pulmonary hypertension.

Dr McLaughlin: Right. So that's a great question, Rich, and Bill, yes, it's an exciting time. I just want to emphasize one thing before we go onto this. That is that every patient deserves the benefit of the doubt and deserves to be at least looked at for surgical evaluation. We're not going to get into the nitty-gritty's of what makes a patient operable or what doesn't. But everybody at least deserves an operability assessment, whether there's a center locally, whether you send films to UCSD, or someplace else. The last thing we want to do is give a medical therapy to someone who could be essentially cured or very well treated with a surgery. So we really need to highlight that, despite all the enthusiasm about the medical therapies that we have. One of the things that may happen to some of these patients is that they have very distal disease and we can't get to it or they develop what we've referred to as a small vessel arteriopathy and they act much more like a pulmonary arterial hypertension, even though they have some amount of distal clot burden. For years, we have occasionally extrapolated PAH therapies to those patients who weren't surgical candidates, just because we had nothing else to offer them. And there are some case reports of that helping and I'm sure we all have experience of patients who had some improvement in their symptoms on PAH-specific therapies.

Rich is alluding to the recently-approved soluble guanylate cyclase stimulator, riociguat, which has been studied in two randomized controlled trials. One was in Group 1PAH and the other in patients with chronic thrombo-

embolic disease that was either not surgical. There was a very intensive surgical operability assessment for those patients, so they were deemed not operable, primarily because of distal disease that was not surgically accessible, or if they had persistent pulmonary hypertension, after an endarterectomy that had occurred at least, I believe, about six months previously. Those patients were randomized to either riociguat or a placebo and followed for a period of 16 weeks. There was an improvement in the primary endpoint of six minute hall walk and some secondary endpoints, including hemodynamics, in those patients. This is really the first good randomized control data of a medical therapy being effective for patients with chronic thromboembolic disease. So there is another option to offer these patients who are not surgical at this point. It's a bit of a complicated drug to use. It has side effects, as all drugs do. It needs to be titrated. One needs to monitor blood pressure. But for those particular patients, it can be an effective means of treating their symptoms of dyspnea and exercise intolerance.

Dr Tapson: I think it's exciting now to have a therapy we can use in those patients who are not operable or who do have problems after surgery. I know we've stressed this point already, but I want to underscore that before using this medication, we've got to make sure that the patient is not a surgical candidate.

Dr Channick: I agree. However, in reality, patients are often placed on medical therapies either in lieu of, or prior to surgery. Bill, you've published on the role of medical therapy prior to PTE and the potential for delaying referrals for definitive treatment.

Dr Auger: Yes, there's that concern. Currently nearly 50% of the patients who come to UCSD who ultimately undergo surgery are on PH medical therapy. So I just suggest that clinicians resist the temptation. . . if it's truly operable disease, the patient's pulmonary hemodynamics are relatively stable and there are no signs of RV failure, to avoid unnecessary medical therapy. I know that there are a lot of things that need to be considered prior to patients' having surgery. . . we don't have the data that say that medical therapy is a good thing to prep patients before a PTE. However, if you have a patient with unstable hemodynamics, treatment of RV dysfunction while awaiting surgery is appropriate, and the referring doctor should work with the center that's going to be doing the operation.

Dr Pepke-Zaba: I think that what probably is happening is that the patients who are treated with a medical therapy are much more complex with more co-morbidities and are much more hemodynamically unstable. Some time ago there was a simple work project looking into removed specimens from the patients on different bridging therapies. Obviously, it's very difficult to compare stiffness, elasticity, compliance of the specimens because we can't apply force to measure it, but there were no obvious differences between the samples assessed by experienced pathologists.

Dr Auger: We're also looking into that, Joanna. There is the sense from our surgeons that perhaps there is a change in the texture of the clot, making it more difficult to remove. A successful endarterectomy is based on adequately creating a dissection plane, such that this chronic, organized, fibrotic-type material can be removed from within the pulmonary vascular bed. The key to a successful operation is removing as much of the clot as possible. If that's more difficult, then the surgeons are in the pulmonary vascular bed a longer period of time. That doesn't mean that it becomes an unsuccessful operation; it's just a more difficult operation. But one is challenged when you're on the phone with referring doctors and they have a patient who is very, very sick, with significant pulmonary hypertension, and very symptomatic. Doctors want to be able to do something for their patients while they're awaiting their surgery. . . what do you do in that setting when you know these drugs haven't been studied for this particular indication?

Dr Channick: In some ways, I'm even more worried about patients at the other end of the spectrum, maybe a little less sick, where physicians may say: "Let's give this medication a try and see how you do for six months or a year before we consider referral for surgery. We've all seen that scenario. In somebody with operable disease who maybe is not as advanced, maybe it's not a good idea to wait. Maybe we're risking more progressive arteriopathy that will be less amenable to surgery.

Dr McLaughlin: And what about more RV dysfunction over time? For these reasons, I would discourage the "wait and see" approach. The cases for whom we've used preoperative medical therapy, as Bill alluded to, are those patients that are really sick, have a lot of RV dysfunction, that we've gotten a bit aggressive with—more to try and improve their hemodynamics, the function of their RV—before a surgery. I would agree that treating someone with a medical therapy just to see how they do, when they have operable disease and could essentially be cured by a surgery is probably not what we should be advocating.

Dr Auger: I don't want my statements to be misconstrued that I'm advocating medical therapy prior to surgery, because Val, you're absolutely right. CTEPH patients with clearly operable disease, outcomes following surgery are far superior compared to medical. You're really not achieving much by putting patients with significant pulmonary hypertension due to chronic thromboembolic disease on a PH medication when the best chance for a cure is surgery.

Dr Channick: Thanks Bill. Well, time is up, so I think we'll stop there. It's certainly been a pleasure and we've had a great interactive discussion of this important topic. Thank you, everybody.