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# Focus on CTEPH/CTED

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**Dr. Channick:**
So yeah, so we have some typed-in questions, and we say we want to make this interactive. We have a great panel. We have Dr. Goel from Cedars. We have Michael, who you met, our fellow, Dr. Troy and then Dr. Jasuja. So I think what we'll do is, again, get your questions out, I think we'll, you know, try to take it in a little bit of order, and maybe make it based on the case a little bit.

So we had a case of a patient who, you know, we suspected had some acute clot. Now, many of our patients already present with chronic disease. But, you know, what - how do you - I guess, Khushboo, how do you make that distinction? Because you get - I think you guys get, you know, tons of PE's, if I remember correctly, I'm not sure why you have so many PE's at Cedars? We don't have, you know, maybe, I don't know, we can speculate on that. But, you know, you must face that acute versus chronic decision all the time. And what's your approach over there?

**Dr. Goel:**
Yeah. So I think the first thing is, it rains a lot of PE's probably because we also make sure that we get consulted for every PE as part of our PERT service. So I think every PERT service is structured a little bit differently. But we like to get consulted for any pulmonary embolism, what even if it's low risk PE, not just intermediate and high risk PE's because what we've learned, and this kind of points a little bit towards what Dr. Jasuja was saying was that PE's are complex, and they can have different lasting effects, both kind of in the acute and the long-term setting.

So I think one of the important things that we keep in mind is, yeah, you can have purely acute clot, you can have purely chronic clot that comes through the door, or you can have a mix of acute on chronic. And so I think really, going back to the basics, really getting a really good history. What is the chronicity of these symptoms? How acutely did they develop? Is there an acute-on-chronic, you know, component to when the symptoms developed? Really getting a sense for is it provoked or unprovoked? And if so, when those, you know, those factors are occurring. Also, really radiographically, I think keeping an eye out for all the findings that you mentioned, are really important. If you have old CT scans, like if they've had a PE in the past, I'll really look at both, because sometimes you realize that, oh, this clot that I'm seeing today is actually in the exact same distribution as it was 5 years ago. That that's been, you know, several cases that we've come across that. Also looking at the Echo, you know, echocardiogram and how that correlates to the hemodynamics, I think, in the acute phase is helpful. You know, do they have a terrible blown RV? And are they compensated or not compensated, kind of make me think is this purely an acute process versus they've actually been living with this for a while? So I think between history, imaging, and correlating the echo findings to the acute presentation is a good starting point.

**Dr. Channick:**
And, Mike, just to add on to that a little bit. So, you know, the question is how long you - some of these people have never been on

anticoagulation, they're rolling through the door, you know, they got maybe some acute clot, maybe some chronic, something in between. The history is, you know, they've been symptomatic for awhile, then maybe they got acutely worse, something happened, they pass out. So what is the - I can't remember in this case, how long you give anticoagulation and try? And what was your approach?

**Dr. Troy:**
Yeah, this is actually a great case to illustrate that point of just like historical imaging, because this person had presented to the Southside Hospital 7 years prior. And her re-presentation,CAT scan had clearly some acute component, but those eccentric clots inductor, and Dr. Saggar can attest to this as well, a lot of it was very similar to how it looked previously. And she had actually undergone a lot of other extensive stuff previously. She already had a negative prothrombotic workup.

But having that previous CAT scan I think had played a major role in our services ability to say, we think that there is some serious chronicity here, aside from just the features of eccentricity. And so, my suspicion is that this was really an acute-on-chronic presentation.

**Dr. Channick:**
Yeah, it's always hard to know and there is some guidance on this, you know, the in terms of guidelines, in terms of, quote, how long you wait, although I'm not sure I always agree with that.

**Dr. Jasuja:**
So technically, our guidelines are for patients who present with an acute PE before you can determine that they have an official diagnosis of CTEPH they must undergo 3 months of anticoagulation. But and as Dr. Channick was alluding to in our group, once we see these findings, you know, on history, as Khushboo mentioned, especially on imaging and based on their echo, if we have an inkling that this is actually acute-on-chronic disease or actually just purely chronic disease, but they've never actually been on anticoagulation before, we'll usually do at least 2 months of anticoagulation before getting a VQ scan and a repeat echo.

**Dr. Channick:**
Yeah, exactly. Okay, so I had – there are a lot - the questions are kind of firing in here. There are a lot of them - trying to group them - kind of related to, you know, how we make this distinction of is there a small vessel disease or more distal arteriopathy? You know, what is truly operable versus inoperable? And like trying to get some detail on how those decisions are made from a diagnostic perspective?

**Dr. Jasuja:**
Absolutely. And I was worried I was going to run out of time, so I didn't - I'm glad someone asked this question. So in terms of operability, really, we use our PA gram or sometimes our dual energy CT or a CT pulmonary angiogram. Now, in an experienced center, and that's qualified as a center that the surgeon has done over

50 cases of PTE, actually, you can surgically access segmental and subsegmental disease, it really depends on the experience of the surgeon. But this is, I think, where the critical aspect of having a multidisciplinary CTEPH meeting with surgeons, pulmonary doctors, cardiologists, hematologists, and IR really comes in because we actually look at the imaging together, we look at the PA gram, we determine, okay, which part is going to be surgically accessible or not?

In terms of the question about the microangiopathy that comes in, obviously CTEPH is a multimodal disease, right? You have your proximal obstruction that results in pulmonary hypertension, but you also can develop this microangiopathy in vessels that are less than 500 micrometers in size. And that really comes with looking at how are these patients doing hemodynamically, when you look at their right heart, cath and looking at, you know, how is their RV function? What is their pulmonary vascular resistance? What is their functional status? And when we really incorporate that into the multidisciplinary discussion on, you know, how safe are these patients for surgery? Is there a certain group of very sick patients that we actually want to use medical therapy going in to sort of optimize them? And so, I think the key point is really using that multidisciplinary discussion.

**Dr. Channick:**
Yeah, we can talk a little bit more about, you know, how we make, you know, the adjunctive therapies along with it, like medical therapy, BPA after surgery or before surgery. We have a lot of those sort of hybrid type approaches. And there's some data on this. I mean, someone asked about medical therapy prior to surgery and what's the role. And it's still somewhat debated. I think there's some data that, you know, medical therapy may improve the function of hemodynamics prior to an intervention, maybe it decreases the risk, although that's debated. What we don't want to do is delay surgery to try medical therapy. And that's been shown pretty clearly that patients who have clearly operable disease, and there was a question that, are less responsive to medical therapy for pulmonary hypertension. It kind of makes sense. It's more of an anatomic problem than an arteriopathy problem. But these, as somebody said, as soon as are our clear, you know, judgments.

There's another question just to kind of keep it moving on to CPET, and you know, clearly, the usual cardiopulmonary exercise testing, which we'll hear more about from our esteemed experts in a little bit, but maybe I'll ask Khusboo, because I mean, we do quite a few of

the invasive CPET's. But you know, you see a lot of these patients, they have some residual dyspnea on exertion, maybe they have some chronic clot, you know, there may - they may not have overt severe pulmonary hypertension. How do you approach those? And maybe specifically, as it relates to, you know, provocation testing, exercise testing?

**Dr. Goel:**
Yeah, I mean, I think, you know, cardiopulmonary exercise testing is a very, very thorough test that we do, even if it's, you know, not a full invasive CPET with a Swan, because it really gives you so much hemodynamic data and can really help put you in a direction of where do - what do I think the, you know, the limitations are coming from. And so, I think strategically using and timing the CPET is important. So I think in your case, this was a really good example of, you know, we - had a diagnose this upfront, we've, you know, initiated medical management. Now, the functional status has improved, but it's still not perfect. And I think that's kind of the spot where I think it can be helpful to us start with a CPET. And say, am I seeing signs, you know, that this could be a pulmonary vascular disease process? And I think in this case, that really helped push you from now that she's – this patients behaving like a CTED patient but with exercise, that's really when you unravel that this person has a lot of limitations, and then you're able to push the case to say, hey, maybe we should actually remove that clot. So I think it can be helpful to answer the question - the piece of that puzzle to say, how much of that clot is actually contributing to PAH either at rest or with exercise, and therefore - and you know, symptom-wise as well.

**Dr. Channick:**
Yeah, no, we have, you know, a world of CPET expert, Dr. Cooper is sitting in the audience, and you know, he could chime in, although we may hear about it a little bit later. But, you know, the question becomes, you know, what are we looking for on a CPET, even a non-evasive, to indicate that this patient's exercise intolerance after a PE has been contributed to by, you know, or is by the clot as opposed to, let's say deconditioning or obesity. And I think that's still sometimes a challenge, because we have a lot of patients who have some residual thrombus after a PE and a lot of patients who are still short of breath. I know, Tim Mars in San Diego has done some studies looking at, you know, dead space as a good predictor of exercise capacity after PE and patients with chronic clots. Obviously, if you have overt exercise-induced PH, you know, we at least think that may be the cause of the persistent dyspnea, though we can't say for sure. You know, maybe we'll call you out, minding your own business in the audience. What do you think about that? You know, you're the - you know, you're the guy. The rest of us are just faking it with CPET.

**Dr. Cooper:**
Well, thanks, Rich, it's a pleasure to be here, firstly, and thank you for including me in this marvelous program. So, you know, the thing about cardiopulmonary exercise testing is we do get a lot of data. I mean, the starting point is to define the degree of aerobic impairment, if you like, and, you know, that can be used in risk stratification. But specifically, with regard to chronic thromboembolic pulmonary disease, you know, we want to know what the gas exchange abnormalities are. And then so we need some degree of invasive CPET. At minimum, we need to measure the alveolar arterial oxygen partial pressure gradient at maximum exercise, and calculate the VD/VT. And when we can look at VD/VT indirectly in the slope relationship between ventilation and carbon dioxide output, but it's better to have arterial blood gases and actually measure it, and then you get two endpoints of that tell us about high VQ and low VQ gas exchange abnormalities. And then the crucial question is, while they may or may not be present, do they contribute to exercise limitation? And, you know, that's very nuanced in the way we kind of unravel all of that, but better to have the data and be informed. I think, even though it's sometimes quite complex to interpret.

**Dr. Channick:**
Yeah. Michael, would you? Yeah. Oh, sorry, Mike.

**Dr. Lewis:**
You know, so, you know, I think that, you know, cardiopulmonary exercise testing, you know, has, you know, definite endpoints that are compatible with, you know, PAH compatible with heart disease, compatible with deconditioning. And I think there's a tremendous overlap. So I think it's going to be very difficult to pinpoint. I agree with Chris, that, you know, looking at, you know, VD/VT may be helpful. But on the other hand, the other parameters that we look at, which is, you know, the ventilatory equivalent for CO2, you know, slope, and values also reflect, you know, dead space. And we see that with all the conditions that I mentioned. So I think, you know, coming to a definitive diagnosis based on cardiopulmonary exercise test, is, you know, there's no definitive way to say, one way or other, just your Gestalt, along with all the other clinical and other variables.

**Dr. Troy:**
Yeah, I guess just to piggyback on that, the difficulty - one of the difficulties in this case is - that I glossed over, was she had some true cardiomyopathy in addition to all this other stuff. And so, you can look at that pulmonary angiogram and there's these huge areas where there's clearly defects, you know there's going to be a dead space problem. But her exercise issues were really somewhat subtle for someone with that VQ scan and that PA gram. But this is a young person with a very, you know, active lifestyle, traveling back and forth very commonly between the coasts. And so, you know, the question really becomes if we're - if our goal as doctors is to optimize this

person's quality of life for the next 40 years, then maybe, you know, it really is important to get into the nuances in a way that you can't without doing a CPET.

And, you know, as you mentioned, as part of the Gestalt, that just adds another piece of data along with all the other things to suggest that this is a pulmonary limitation, not a pure cardiac or mixed cardiac pulmonary problem.

**Dr. Channick:**
Yeah, this is the classic case where you need to trend it or you get serial data. Chris, do you want to say something else?

**Dr. Cooper:**
If this time, you know the thing about high VD/VT, your wasted ventilation, it's an issue if someone has mechanical problems in breathing and has potentially ventilator limitation, but most people don't have that so you can have high VD/VT that isn't necessarily consequential or impairs exercise performance.

At the same time, you know, although pulmonary vascular diseases obviously make us think about a high VQ abnormalities, but the blood is diverted elsewhere, and you get low VQ abnormalities, and it's often the hypoxemia that is more critical in limiting exercise performance. So we have to look at that as well.

**Dr. Channick:**
You know, I wrote this exactly, I think it remember your case of a marathon runner I saw. This was when I was in Boston, and she, you know, had had a baseline peak VO2 of like 125% predicted, she had a clot in her right lower lobe, normal echo, normal resting pressures. But on repeat CPET, she only got to like 88% predicted peak VO2, so you had two datapoints showing this big drop, although she still was, quote, normal. And now I used that as a decision to intervene on that clot. And she had, you know, dramatic symptomatic benefit and went back to running the marathon. So having serial data is critical. Yeah.

**Female:**
Chronic pulmonary hypertension happens because of unresolved clots despite being on anti-coagulation. What's the story on the pathophysiology?

**Dr. Channick:**
Yeah, great question. Why this develops? Do you want me to answer? Okay. We don't know. That's easy. So yeah, it's why acute becomes chronic in some patients, and it's more extensive, we don't know. We think of it as a failure of clot lysis, rather than overt hypercoagulability. In other words, these patients don't usually have measurable hypercoagulable or thrombophilias, with a few exceptions, a lupus anticoagulant is present, a little bit more commonly, about 14% of them, versus 8 or 7% of the normal population. But all the other clotting factors, are not really any different with few minor exceptions.

**Dr. Channick:**
So say that again? Yeah, well, certainly, as it organizes, you can't do much about it, because it's really fibrous tissue. When you look pathologically, this is fibroproliferative material, doesn't even look like a clot anymore. But why they developed this fibroproliferation? We don't really know. There are some risk factors, as Sonia said, like chronic inflammatory conditions, maybe the size of the initial clot. Somebody asked here about whether intervening more acutely will decrease the likelihood of a chronic clot? And maybe, do you guys think that way, Khushboo, over at Cedars? Like, as a justification for thrombectomies?

**Dr. Goel:**
I don't think that would be the justification for using it.

**Dr. Channick:**
Yeah. I've heard it before, though.

**Dr. Goel:**
But just to quickly, like actually piggyback off of your question was another way that we figure out like, is it chronic clot or acute clot? Because a lot of times people come in thinking it's an acute clot, they think it's intermediate risk PE, they go in for a pulmonary thrombectomy, or catheter-directed thrombolytics, and they go in there, and they say, 'Oh, this is actually chronic clot. This is not acute.' And so that's another way that now that, you know, we're using more interventions, people find out and that there really is a difference. You can't use those procedures on, you know, more chronic organized clot.

**Dr. Channick:**
And it's - they've been tried believe me, we hear that a lot. Mike?

**Dr. Lewis:**

Yeah, just with regard to the pathobiology of, you know, CTEPH, you know, Sudar Rajagopal, you know, at Duke, I've been working with him in terms of, you know, advanced proteomics and genomics, etc. And he's got a nice paper that's out in the *Blue Journal*, looking at some of the things that we've, you know, worked on. So, I mean, inflammation, fibrosis, impaired, you know, clot resolution, are all signal transduction pathways that seem to play a role. There are specific cell types and, you know, macrophages and all sorts of other kind of cells that seem to be involved that are distinctly different from acute clot.

**Dr. Channick:**
Yeah, no, that definitely, I know Sudar has worked as well, again, the group in San Diego found some abnormalities in the fibrinogen gene, you know, maybe they create clots that are more resistant to lysis to this mutation and fibrinogen. But that's only in some of the patients.

One last really quick one, because they had a million questions on this one. The DOAC versus warfarin in patients with chronic thromboembolic disease. Maybe, Sonia, you could give us the party line on that.

**Dr. Jasuja:**
Yeah, absolutely. So party line, and what has been most studied is the use of warfarin in these patients with CTEPH, especially patients who are post-surgery; we prefer to use warfarin in that group. But you know, more recently, of course, with the development of DOACs and the ease and feasibility of use of those medications, you know, in certain patients, we are sometimes considering the use of DOACs a year after surgery. Now there are certain groups that you want to make sure that you, you know, they must be on warfarin. So for example, patients with triple-positive antibody APLS, these patients must be on warfarin, patients with known hypercoagulable states, Factor V Leiden, prothrombin, you want to generally keep those patients as well on warfarin. But it's an area where we're hoping that we can kind of study more and see, you know, if DOACs can be used.

**Dr. Channick:**
Yeah, I mean UCSD published, and quite interesting, and we will have to wrap up. But I thought it was sort of cool. They looked at the specimens of the PTE patients in a blinded way. And they looked at the amount of acute material versus this chronic material, because a lot of the specimens have both acute and chronic. And they found that the patients who had been on DOACs prior to surgery, had a higher incidence of acute material in the specimen, suggesting maybe they had been laying down clot more than the patients who were on warfarin where they were almost all chronic lesion. So again, retrospective data. But I thought that was kind of interesting, but the jury's still out, I would say. I think it'll evolve over time, but we'll see.

**Dr. Lewis:**
So Rich, what would you recommend?

**Dr. Channick:**
So we typically do warfarin postop for at least 6 months, very arbitrary. And then we can talk about switching to a DOAC with certain patients. Certainly, as Sonia said, patients who are having trouble getting therapeutic INRs, we'll switch them earlier. And I can't say we've seen a big difference anecdotally.

Alright, so I guess we're done. Thank you, everybody. That was a great session. We have about a 10- or 15-minute break.

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