PANEL DISCUSSION

Decision-Making in Submassive Pulmonary Embolism

Insights into the current state of the PE data, how to decide whether to approach mechanically and with what devices, when ECMO may be beneficial, and knowing when extraction is successful and stopping the procedure.

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Dr. Sista, what is the state of the data on submassive pulmonary embolism (PE) currently?

Dr. Sista: We're in a different place than we were 8 or 9 years ago. The fact that a 59-patient, non-United States, randomized controlled trial of ultrasound-assisted catheter-directed lysis (CDL) versus anticoagulation for acute intermediate-risk PE[1] took our small world by storm was an indication of how immature the data were at that time. But, it was a very important study because it showed a positive result—the CDL group had faster right ventricular (RV) recovery than the group on anticoagulants alone. That result, in and of itself, seemed to have value from numerous standpoints, especially given the concern at the time that submassive PE could deteriorate quickly into massive PE. Taking people out of the danger zone, which is what submassive PE was thought to be, was a very good thing.

What's interesting is that until the CANARY trial was published in the last year or so,[2] there were no randomized controlled data after the ULTIMA trial that confirmed or tried to confirm the data reported by Kucher et al. Instead, single-arm studies became the norm for new devices because they were a means toward gaining 510(k) clearance from the FDA, and that steered the direction of data in a way that perhaps wasn't best for the field.

Around the same time that ULTIMA was published,[1] the PEITHO trial showed that systemic thrombolysis had its set of benefits, including a reduction in clinical deterioration, but, it caused too much bleeding.[3] We also learned that submassive PE was not as dangerous as previously suspected, and with prompt anticoagulation, only about 5% will go on to develop clinical deterioration, either fatal or nonfatal.

As a result, we have this situation where we're not totally sure when we're supposed to intervene for intermediate-

risk PE. Some of us have been beating that drum for a while and saying that we need better, more rigorous data to understand exactly in whom and for what reason we should use interventions for submassive PE. This has been the genesis of a couple randomized trials that are going on right now, which is very exciting.

The ELOPE study, which evaluated all comers with acute PE, found that about 46% of patients had abnormal peak oxygen uptake, as assessed by cardiopulmonary exercise testing.[4] This corroborated some observations that patients don't fare well after PE. This post-PE syndrome is characterized by reduced quality of life and exercise tolerance and has influenced the design of the current randomized trials.

There are two trials underway evaluating complementary outcomes, one looking at short-term outcomes from submassive PE and the other looking at medium- to long-term outcomes. The HI-PEITHO trial (NCT04790370), which is sponsored by Boston Scientific Corporation, is a global trial randomizing participants to CDL with the Ekos ultrasound-assisted catheter (Boston Scientific Corporation) or anticoagulants alone. HI-PEITHO is evaluating the intermediate-risk PE population, but it's also looking at patients who have a higher risk of clinical deterioration by a couple of criteria to determine if catheters actually reduce that risk. The study will analyze 7- and 30-day outcomes and follow patients for 1 year.

PE-TRACT (NCT05591118), for which I am the Principal Investigator, is a National Institutes of Health–funded study evaluating medium- to long-term outcomes.* The trial is comparing catheter-directed therapy (CDT) versus anticoagulants alone. There are two primary outcomes. The first is the peak oxygen uptake at 3 months, and the second is the New York Heart Association class at 1 year. PE-TRACT is seeking to assess whether CDT improves cardiopulmonary health (measured by these two primary outcomes) over anticoagulants alone in the year following PE.

At the end of these two trials, we'll have a much better understanding of whether catheters can impact both short- and long-term outcomes. Of note, an important difference between the two studies is that PE-TRACT is allowing mechanical thrombectomy as well as CDL. So, only devices that are specifically cleared for catheter-based PE treatment are currently allowed in the trial.

I would continue to encourage all PE physicians—pulmonologists, cardiologists, hematologists, interventional radiologists—to really remember that this is our disease and these are our patients, and that we have perhaps allowed the research direction to slip away from us a little bit. There are opportunities to control this narrative. And, in that sense, PE-TRACT is wholly unique, in that it is the only non–industry-sponsored PE clinical trial of its size and scope. There is likely going to be a subset of patients that benefits from CDT, but the faster we get to that understanding with data that noninterventionalists perceive as unbiased and rigorous, the better. I would ask the PE community to continue to strongly support and prioritize PE-TRACT.

In a submassive PE case, how do each of you decide whether to approach mechanically?

Dr. Lakhter: At our institution, the PERT (PE response team) is activated for the majority of patients presenting with submassive PE. Through discussion with our interdisciplinary team (which includes pulmonary, interventional radiology, interventional cardiology, and sometimes cardiovascular surgery), a decision is made whether an intervention beyond anticoagulation therapy alone is indicated. We generally consider treatment for hemodynamically stable patients with objective evidence of RV dysfunction and biomarker elevation. Adjunctive findings from transthoracic echocardiography can also help identify those patients who may have reduced cardiac output/cardiac index and may thus be more likely to benefit from interventional therapies. These parameters include reduced RV outflow tract (RVOT) and left ventricular outflow tract (LVOT) velocity time integral, as assessed on pulsed wave Doppler.

As many patients in this PE risk category substantially improve with anticoagulation alone, PE intervention is usually offered to patients who fail to improve despite an initial trial of anticoagulation. These patients can have one or more of the following clinical features: significant dyspnea, markedly reduced functional capacity, persistent tachycardia, hypoxemia, and elevated lactate levels. Another unique group of patients in whom early PE intervention can be considered are patients who developed acute PE within the pulmonary artery (PA) leading to a previously transplanted lung. Due to the lack of bronchial collaterals, these patients are thought to be at a higher risk of pulmonary infarction and graft failure. It is also important to note that shared patient decision-making is an important aspect of PE intervention. Given lack of hard endpoints in prior PE intervention trials, patients need to clearly understand the full spectrum of risk and benefit associated with any intervention.

For patients with submassive PE who are determined to potentially benefit from intervention, my general approach is to offer CDT unless there is a contraindication. There is a variety of available options for CDT including single-lumen infusion catheters (Fountain, Merit Medical), ultrasound-assisted thrombolysis (Ekos), and pharmacomechanical multilumen thrombolysis (Bashir endovascular catheter, Thrombolex). Over the last several years, I have personally transitioned away from single-lumen infusion catheters and instead have been using the Bashir endovascular catheter. With the use of the multilumen infusion basket, we can

limit the total dose of tissue plasminogen activator (tPA) and shorten the duration of tPA infusion to about 5 hours.

For patients in whom thrombolysis is contraindicated (eg, recent surgery, concern for bleeding, recent head trauma, prior stroke, severe hypertension), I would consider mechanical thrombectomy. Other patients in whom I'm cautious about CDT are elderly patients aged > 80 years and very thin patients with low body mass index. Finally, for patients who present with submassive PE but are teetering on the verge of massive (relatively hypotensive but have been stabilized after intravenous fluid administration), I would elect mechanical thrombectomy to speed up the treatment effect rather than performing CDT over the next several hours.

Dr. Ranade: All patients with submassive PE under consideration for CDT are discussed in our institutional PERT. We evaluate CT and echocardiographic imaging studies, factors such as signs of RV dysfunction, thrombus burden, location of thrombus, and the patient's ability to tolerate tPA. The clinical picture, including patient age, anatomy, medical comorbidities, are also important factors in decision-making regarding modality of treatment selected such as CDL versus catheter-directed thrombectomy.

Dr. O'Sullivan: There are no good data (yet) as to whether mechanical thrombectomy is superior to CDT. Often, my decision is based on bed availability in the high-dependency unit, which can be a real problem for us. To be honest, I tend to go for mechanical thrombectomy most of the time.

Dr. Sista: It would be great to know the results of these trials now so we could make decisions based on them. In the meanwhile, we have to use our best judgment, use local expertise, and proceed when one feels a threshold is met. That threshold is different for different practices. I come from maybe initially an aggressive practice, followed by a more conservative practice. Overall, we found that the conservative approach toward submassive PE does not clearly confer a higher risk of deterioration or mortality, somewhat reflecting what we found in the PEITHO trial, and if you promptly anticoagulate most submassive PE patients, they're not going to clinically deteriorate.

There is a subset of patients who still have difficulty getting out of bed, still look dyspneic, tachypneic, tachycardic (heart rate > 110 bpm), and have a soft blood pressure (BP) (< 110 mm Hg) if they're on 12 to 24 hours of heparin. An echocardiogram shows RV distress, and they have a mild lactate elevation, and even worse, they might have a slight elevation of their liver function tests, suggesting cardiac-induced hepatic congestion. Any and all these signs will make me concerned that this is a submassive PE patient who might be at risk for deterioration and that they need some sort of reperfusion. This is when the risk-benefit starts to be in favor of intervention with the data we have currently, but even this population's prognosis is not fully characterized.

The PEERLESS trial (sponsored by Inari Medical) is comparing CDL to mechanical thrombectomy with the FlowTriever device (Inari Medical), so we will have some data on the merits of each after its completion. At this time, there are more data overall on the safety and efficacy of CDT, both randomized and nonrandomized. So, if a patient has some time tolerance, meaning they're not actively about to decompensate, I have a preference toward CDL in my current practice. However, if there's any evidence of hypotension or impending hypotension, RV failure, and there's a need to remove thrombus quickly, that's when I will strongly consider a mechanical option. Thrombolysis is just not an option in some patients (eg, elevated bleeding risk), so certainly mechanical thrombectomy is a very good option if the patient is decompensating.

If opting for mechanical thrombectomy, how do you decide which device and size is best for the case?

Dr. O'Sullivan: I have no sensible answer to this question. The two devices that I tend to choose are either the FlowTriever (Inari Medical) or Lightning 12 (awaiting Lightning 16, Penumbra, Inc.). Both devices are simple to use, work well, and in my experience, yield similar technical and clinical results quickly.

Dr. Lakhter: In our institution, the two most commonly used thrombectomy devices are the Indigo system (Penumbra, Inc.) and FlowTriever system. To decide between the two devices, we consider several important anatomic factors, including body habitus, symptom duration, presence of baseline anemia, and severity of RV enlargement. The main patient-specific factor to consider is body habitus. The Indigo catheter is smaller compared with FlowTriever (12/16 F vs 16/20/24 F) and therefore requires a smaller-bore venous access. In patients at extremes of body weight, the smaller-bore Indigo device may therefore be preferred.

Although all patients with submassive PE have RV dysfunction, in some cases, this is associated with severe RV enlargement. Therefore, it may be difficult to navigate a 24-F FlowTriever catheter across the RVOT without adjunctive techniques such as telescoping over a smaller FlowTriever device (ie, 16 or 20 F) or escalating to a stiffer wire (eg, Lunderquist).

When adjunctive maneuvers are required for catheter delivery, the risk of procedure-related complications increas-

es. Therefore, a smaller-bore device such as Indigo may be more easily navigated across the RVOT. Furthermore, you generally do not need as stiff of a wire to deliver the Indigo, which further reduces the risk of wire-related pulmonary vascular injury.

In patients with longer symptom duration, some of the clot may be partially organized, making it more difficult to extract, in which case, the 24-F FlowTriever device is more likely to be successful. With the FlowTriever, the operator can return the blood back to the patient after aspiration, which occurs after the aspirated blood is filtered through a filter. A similar filter does not currently exist for the Indigo device. Therefore, for patients with baseline anemia and others in whom excessive blood loss may not be well tolerated, FlowTriever thrombectomy may be a better option.

Given these considerations, we use both devices fairly equally. Up to very recently, I would use the 12-F Indigo catheter; however, we are slowly transitioning over to the 16-F device. In the case of FlowTriever, I always try to reach for the 24-F device to improve the chance of an effective thrombectomy. For the left PA, a Triever20 Curve device (Inari Medical) is sometimes needed to navigate shorter and more tortuous anatomy.

Dr. Sista: The currently available devices seem to be much better than earlier-generation devices at removing thrombus; both the FlowTriever and the Indigo CAT device (Penumbra, Inc.) have large lumens and are very good at aspirating thrombus. I think more important than which specific device is how you handle each one, looking at the pitfalls of each, traversing that right ventricle carefully with the right tools (eg, pigtail catheter, balloon-tip catheter), avoiding distal branches of the PAs, understanding that the PA is a fragile structure that causes major complications when disrupted, and that these are powerful devices that should be used with care.

Dr. Ranade: This decision is made based on patient factors such as age, anatomy, medical comorbidities. We visually assess the patient (the "eyeball test")—can the patient handle this procedure? We look at the location of clot within pulmonary vessels: Do we need to debulk large central clot or need to get into the lobar and segmental vessels? For access, we consider internal jugular versus femoral and choose the device that can be used best in the given situation, being safe and efficient and limiting estimated blood loss.

How do you determine the optimal timing and role of extracorporeal mechanical oxygenation (ECMO)?

Dr. O'Sullivan: Unfortunately, I don't have access to ECMO.

Dr. Sista: Everyone is very excited about ECMO, with a lot of time dedicated to it at conferences, but when you poll around the room how many times ECMO has been used for PE patients in the past year, the number is usually on one hand. I don't want to diminish the importance of ECMO or its potential to save lives. The ability to get time back on your side is a very attractive part of ECMO, meaning you can put a patient on ECMO, and then you can reassess, even for 12 to 24 hours, and make a decision whether further reperfusion is needed and how you're going to reperfuse based on circulatory parameters. Most likely, you're not going to lean to systemic thrombolysis or even CDL, but mechanical thrombectomy and open surgical thrombectomy are likely options. Ideally, any practice that has CDT in its offering should be able to recognize the patients who may need ECMO, either on the table or before coming to an interventional suite, and have that conversation with whatever team does the ECMO.

Dr. Ranade: ECMO can play an important role for patients in cardiogenic shock from massive PE. It may serve as a bridge, facilitating RV recovery while providing time for other definitive advanced therapies. We follow a similar practice to that described by Al-Bawardy et al.[5] ECMO can be used as a "bridge-to recovery" or to a "bridge-to-advanced therapy" such as intravenous thrombolysis, CDT, or surgical embolectomy

Our perfusion team is typically on stand-by for high-risk interventions. ECMO may be indicated in settings where a patient with massive PE has had a cardiac arrest, severe hemodynamic compromise without cardiac arrest, has a contraindication to systemic thrombolysis, failed systemic thrombolysis, failed catheter-based clot extraction, or if the patient is too unstable for catheter-based treatment or severe hypoxemia.

Dr. Lakhter: In general, most patients with submassive PE do not require upfront ECMO support. However, the treatment algorithm is very different for hemodynamically unstable patients or those undergoing active CPR. In these patients, early ECMO support may be lifesaving. Nevertheless, there are specific scenarios during which an otherwise stable patient with submassive PE undergoing a catheter-based intervention can develop acute hemodynamic decompensation and thus require escalation to advanced hemodynamic support. Identifying factors associated with hemodynamic decompensation upfront can allow the operator to prepare for possible ECMO.

Patients at highest risk for intraprocedural hemodynamic decompensation have a poor cardiopulmonary reserve. These include patients with severe underlying lung disease (significant hypoxemia and/or require bilevel positive airway

pressure [BIPAP]), preexisting RV dysfunction (pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension), and super morbid obesity. Other factors include the presence of a saddle embolus, severe RV dysfunction, and significant lactate elevation. In these cases, it may be a good idea to notify the ECMO team prior to the start of PE intervention to facilitate a quicker response. For patients at highest risk (ie, patients on BIPAP), the operator may elect to place a small-bore femoral arterial access (ie, 4-F sheath) before starting PE intervention. The arterial sheath can serve as a placeholder to allow for faster venoarterial ECMO cannulation in the event of an emergency.

During the procedure, what indications are you looking for to determine successful extraction is taking place?

Dr. O'Sullivan: We obtain a formal preoperative echocardiogram, and then I personally obtain my own basic echocardiogram using our ultrasound machine to determine the movement of the RV wall. In my experience, this is pretty accurate but not quantifiable. At the start of the procedure, we measure PA pressures (PAPs). These are not perfect and can often be falsely low. Assessment of vitals (systemic BP, oxygen saturation, heart rate, respiratory rate) are key. Although not measurable, patients often have a very anxious look in their eyes. We rarely sedate. As the procedure progresses, there is often one point at which things improve substantially and "everything" settles down—the overall level of concern in the room between the nurses and physicians also lightens considerably.

Angiography is not a big portion of this assessment. We usually do one angiographic run at the start, then little puffs of contrast during the procedure to attack resistant thrombus, and one run at the end. An echocardiogram is obtained the following morning.

Dr. Ranade: We look for signs such as improved oxygenation (improved oxygen saturation and decreased oxygen requirement, improved hemodynamics including heart rate and BP, and improved PA and RV pressures. Some practices obtain additional cardiac output or cardiac index, and some routinely look at mixed venous blood gas.

Dr. Sista: You'll see signs of better perfusion and circulation, improvements in oxygen saturation, a decreased oxygen requirement, a heart rate reduction without a decrease in BP, a slight increase in BP, and perhaps pulmonary systolic or mean pressure goes down while their BP remains stable or improves and the heart rate goes down. However, don't be falsely reassured—there could be a reduction of PAP if the right ventricle starts to fail. Some use the cardiac index to determine if there has been adequate thrombus removal, and it may become an important measure of efficacy going forward.

Dr. Lakhter: I think that there are several different aspects to successful extraction. The first is the actual ability to physically remove thrombus out of the PA. The second is the positive hemodynamic effect of thrombus removal. Given that the lower lobe PAs have the least physiologic dead space, I consider thrombus extraction to be successful if I can angiographically demonstrate reperfusion of previously occluded lower lobe PAs. Give the limitations posed by the size of the large-bore thrombectomy catheters, reperfusion of the lower lobes can be achieved by debulking the interlobar PAs. Selective thrombectomy of individual lower lobe segments is generally difficult to achieve and usually not necessary once interlobar artery is cleaned out. Similarly, if a saddle component is present, specific care is taken to extract that clot as well.

In terms of hemodynamic success, we monitor baseline and postthrombectomy cardiac output/cardiac index, mean PAP, and baseline oxygenation. Postprocedural improvement in these parameters is also considered a sign of successful extraction.

How do you know when to stop the procedure?

Dr. Ranade: Given the dearth of data providing good guidelines for when to stop, the current practice is to evaluate for improved patient hemodynamics as well as extraction of majority of clot burden that can safely and efficiently be extracted, as demonstrated by visual assessment and angiographic confirmation.

Dr. Sista: I've mentioned some of the parameters in the previous answer, and there is certainly some uncertainty of when to stop. That's something we'll be looking at in PE-TRACT. We have to correlate on-table results with short- and longer-term clinical outcomes.

Dr. O'Sullivan: It's a summation of all previously mentioned. The patients have often settled considerably; they will tell you they feel better, their vitals are better, color improves, oxygen saturation improves, as well as work of breathing, etc. On the rare occasion the clinical picture hasn't improved, we switch to CDT and transfer to the intensive care unit. This usually occurs when patients have very poor cardiopulmonary reserve and are acidotic before we start.

Dr. Lakhter: This is a very important question. As with any intervention, we are always balancing the risk and benefit. Unlike in the realm of coronary artery intervention where an operator is looking to achieve an "angiographically

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excellent" result, the same is not true for PE intervention. As a result, it is important to understand that percutaneous mechanical thrombectomy will not get all of the clot out of the PA. A perfect result should therefore not be the goal of the procedure. Instead, enough clot needs to be removed to restore perfusion to key areas of the lung such as the lower lobes. Saddle thrombus should also be removed if possible.

Although thrombectomy works well in extracting acute central PE (saddle and interlobar clot), selective debulking at the segmental level is very difficult and may result in a pulmonary vascular complication with repeated attempts. CDT likely has an advantage over thrombectomy in treatment of the segmental/subsegmental branches because tPA can be distributed to the more distal PA circulation.

Based on these considerations, the operator can consider being done with the procedure once enough of the interlobar and/or saddle clot is successfully extracted. Further confirmation comes via hemodynamic parameters mentioned (cardiac output/cardiac index, mean PAP, oxygen saturation). Finally, with the Indigo device, we also consider blood loss and stop the procedure once we reach an estimated blood loss of 500 mL. ■

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