New Invasive Technologies in Pulmonary Hypertension

This spring, Guest Editor Richard A. Krasuski, MD, Professor of Medicine at Duke University School of Medicine in Durham, North Carolina, convened a group of experts to discuss the present and future of invasive technologies in the diagnosis and treatment of pulmonary hypertension. The guests included Jamil A. Aboulhosn, MD, Professor of Medicine at the University of California Los Angeles David Geffen School of Medicine in Los Angeles, California; Raymond Benza, MD, Director of the Division of Cardiovascular Medicine and Professor of Medicine at The Ohio State University College of Medicine in Columbus, Ohio; and J. Eduardo Rame, MD, FACC, Louis R. Dinon MD Professor of Cardiovascular Medicine and Physiology and Chief for Advanced Cardiac and Pulmonary Vascular Disease at Thomas Jefferson University Hospital in Philadelphia, Pennsylvania.

Dr Krasuski: I'd like to welcome everyone to today's roundtable discussion. This is a real honor and pleasure for me; I've had the chance to invite what I consider to be some of the best people around to discuss this particular topic, new invasive technologies that are in use in the pulmonary arterial hypertension (PAH) catheterization lab.

Obviously, we've seen a lot of changes over the last decade. The field has moved forward tremendously, and we're doing a lot more therapeutically, certainly with medications. Some of the things that we now have available to us in the catheterization lab have also advanced in a pretty rapid fashion, and that's the topic of this particular issue of *Advances in Pulmonary Hypertension*.

The group I've put together probably needs no introduction, though I will do so anyway. We have one of the real gurus in the field of pulmonary hypertension (PH), Dr Ray Benza. We have a leader in the field of adult congenital heart disease and innovative interventionalist, Dr Jamil Aboulhosn. And last, but certainly not least, one of the great minds in heart failure and PH, Dr Eddie Rame. I'd like to start our discussion with this question: With all the technological advances that have occurred over the last few decades, how has your approach to catheterization of patients with PH changed?

Dr Benza: That's a really good question, because the advancement in imaging modalities has really called into question the necessity of continuing invasive monitoring in patients with PH. As a cardiologist, I feel very comfortable with hemodynamics, and I still believe that hemodynamics help paint the entire picture of risk profiles in this disease. I am still a very big proponent of routinely monitoring patients using hemodynamics and taking them to the cath lab to see if we have their disease adequately controlled, that it's not progressing silently, which we know this disease can do. We are still taking people to the cath lab to do their initial risk stratification diagnosis, and usually again the first 4 to 6 months after new therapy introduction to make sure that hemodynamic profiles are moving in the right direction. Finally, we continue to bring stable patients back to the cath lab to assess hemodynamics on a yearly basis as part of their annual risk stratification process.

Dr Krasuski: I follow a very similar strategy. In terms of follow-up catheterization, we probably perform it a little bit less. I do think that it's very important, especially when considering adding therapies or changing therapies, that you have accurate hemodynamic data. I think we all know that echocardiography is a nice, noninvasive way to assess pulmonary pressure and get a sense of how the right ventricle (RV) is doing over time, but there are times that it is just not good enough or can even be misleading. I think there is no substitute for accurate hemodynamics.

Jamil, I know your practice has expanded mostly into transcatheter valves and other interventions in congenital heart disease. Do you still find yourself doing catheterizations for patients with PH? What are you doing differently now than you did in the past?

Dr Aboulhosn: The main focus of my practice at this point, frankly, is the congenital heart population, many of whom have PH. As far as the yearly diagnostic catheterizations on pure PAH patients, those are done by many of my other colleagues, pulmonologists and cardiologists. In the work that I do, to answer your question as to how things have changed in the last decade with the use of new technology, I have incorporated a number of things over the last 10 or 15 years that we weren't using in the past as much. For example, the use of intracardiac echocardiography in helping to figure out sites of shunting and helping to guide any interventions that we're doing.

Take as an example a patient with PH who is desaturated and may have a pulmonary-level shunt versus an atrial-level shunt versus a combination of both. That's where I find intracardiac echocardiography during a cardiac catheterization to be extremely useful, and that's become quite standard for me to use.

I also incorporate stress catheterization much more than I did in the past, as a means of helping me figure out what happens to people's hemodynamics at rest and with exercise. Often I'm doing these studies not just with the right heart catheterization and checking pulmonary artery (PA) and wedge pressure and such, but using 4 or 5 transducers, checking central venous pressure (CVP), PA pressure, wedge pressure, systemic arterial pressure through a radial arterial line, and even occasionally going as far as putting in a dual lumen pigtail into the left ventricle (LV) and checking simultaneous LV and ascending aorta pressure in those whom I suspect are going to develop gradients with exercise.

It's much more sophisticated hemodynamic assessment and imaging guidance.

You brought up the transcatheter valve work, and that's really taken off as far as pulmonary valve replacements initially in purely congenital patients, but increasingly now in those with acquired pulmonary valve regurgitation, many of whom have PH. The latest is tricuspid valve interventions with the use of the MitraClip in the tricuspid location to try to decrease the degree of tricuspid regurgitation as well as the placement of valves into the cavae, both the inferior and superior vena cava.

I'd say those are probably the main changes that I have seen in my personal practice in the way I approach patients with complex PH. Many of them are structural or congenital.

Dr Benza: I think in the world of noncongenital PH, the advances in the catheterization lab really fall into 3 areas. One was already mentioned, and that is exercise hemodynamics. The second is the rechallenging of patients with selective pulmonary vasodilators, like nitric oxide, to determine if reactivity has reemerged. Lastly, the incorporation of high-fidelity catheters to our workflow to generate pressure-volume (PV) loops in order to give us a better understanding of ventricular-vascular coupling is being applied in several centers.

I think there are emerging data that bringing people to the cath lab and exercising them does add an element of additional information with which you can project a patient's risk and outcome. As all of us know, we typically measure hemodynamics at rest and in the supine position. We do this even with the recognition that people are not flat on their backs all day and thus resting parameters are not reflective of the hemodynamic load our hearts see most of the day. Adding exercise information really tells us more about the hemodynamic burden of the disease during a patient's normal experiences in the ambulatory environment. Presently, there's a lot of work going on with exercise hemodynamics prognostically and diagnostically, and I think we're moving into an area of more comfort with those. Although, again, performing exercise hemodynamics in a busy cath lab is not always logistically possible and they are not always simple to perform. Exercise protocols in the cath lab require some special equipment and they are not standardized from lab to lab. Some labs use upright bicycles, some supine bicycles, and others arm ergometry. In addition, some labs incorporate gas exchange studies. This variability makes results difficult to interpret and incorporate into our prognostication schemes. I think that it's something we definitely need to watch, because more consistent data are coming out suggesting that this is the right thing to do prognostically for patients.

Dr Krasuski: I find that the information I get from exercise catheterization can be very helpful for patient management. One of the biggest challenges in exercise right-heart catheterization is which technique to utilize and as you mentioned, Ray, the room setup. We often are adopting equipment that may not have been designed for that particular purpose. Other challenges include how to measure cardiac output accurately during exercise. While we might do a thermodilution initially at rest, use of the same equipment and technique during exercise often gives automated error messages. Fick technique, on the other hand, is only accurate if oxygen consumption is carefully measured using a metabolic cart. Also, the hemodynamic tracings can get rather noisy and challenging to interpret. Speaking of tracings and ways to clean up their appearances and get more accurate data, Eddie, you've done some seminal work with high-fidelity catheters, PV loop collection and RV-PA coupling. Could give us some background on that?

Dr Rame: Before I comment on that, let me just say that I think the role of exercise catheterization is an important matter to consider. Just 15 to 20 years ago, colleagues would perform exercise catheterization in the low-risk patients to see if they actually had PH by provoking a higher PA pressure and a higher pulmonary vascular disease metric like a pulmonary vascular resistance or diastolic pulmonary gradient. Actually, many of us discovered that the patients with exercise-induced PH would not often progress to more severe disease states and so a "positive" test would not capture prognostic value other than that the patient would have to be followed over time to determine if disease progression occurred.

In the current era, we see the role of exercise catheterization or invasive cardiopulmonary exercise test (CPET) studies in PH quite differently. These tests are often performed to answer the question: Do you have right heart failure or do you not, upon the demand of exercise? We know that everybody with PH has a risk for right heart failure because of the potential for RV-PA uncoupling, but not everybody has bona fide right heart failure, elevated central venous pressure, congestive right-sided indices, and diuretic requirements, which is clearly a significant marker of disease state—both in terms of how these patients are neurohormonally activated and how they respond to pulmonary vascular disease–targeted therapy. We know these patients with right heart failure and diuretic resistance or significant volume retention and variability in weight are often on a very different trajectory in terms of disease progression.

If you have someone with right heart failure and PH, just to your point, Rich, I think that's where it's helpful to consider an exercise catheterization as opposed to using the usual right atrial pressure and cardiac output. I think an exercise catheterization, especially over a time period of years in which you see these patients, could instruct to the fact that they're declining. And maybe if you don't do exercise catheterization, if you're able to start using PV loop measurements, our experience with it has been mostly in patients with PH in the setting of left heart disease and with, let's say for example, a left ventricular assist device (LVAD). We're able to see how the RV responds to both changes in the pulsatile load from the LV, from left-sided heart failure as we change the LVAD speed, and we're also able to measure how the RV may actually respond to volume changes acutely with left-sided unloading or even with a vasodilator challenge; all of that, which

as you know is basically more clinical research.

I think we are seeing now an era where several centers, some with a protocol and some that are just trying to get their hands around the technology, are using the PV loop catheter technology that's out there, and the FDA approved of this PV loop system which is being used to secure an assessment of RV function. In terms of clinical application in PAH and PAH associated with congenital heart disease, I think it's early, but the enthusiasm is definitely there to investigate how it might provide more insight than the current tools we have to understand the transitions of the RV which correlate with disease progression. As far as PAH, I have not used PV loops yet to assist in the guidance of risk stratifying our patients.

In our program here at Jefferson we're already starting the CPET program with invasive hemodynamics in order to estimate RV function and reserve in patients across the spectrum of pulmonary vascular disease. The invasive CPET program has just been launched with our colleague Mahek Shah leading this effort in various clinical states where RV function needs to be better phenotyped. With the PV loop systems, we're still trying to sort out how that's going to differentiate what you do next, but I think it's going to be hugely instructive to know that your patient has an RV that may be more compliant, more responsive, versus an RV that's much more stiff, chronically ill from years of pressure overload hypertrophy, and maybe even more dysfunctional than what the echocardiogram shows.

Dr Krasuski: A specific challenge with collecting PV loops is that you need to have ventricular volumes collected in relatively close proximity to the time that you do the catheterization. Coordinating an MRI, the "gold standard" for volume measurement, and a heart catheterization on the same day can be very difficult.

Jamil, we both have patients who are sent to us with large atrial septal defects (ASDs) and PH. The task we face is determining which ones are potentially and safely closeable. When you have someone lying flat on their back and at rest, as Ray pointed out, it doesn't really truly reflect what happens when they're active. Occasionally I have exercised these patients in the cath lab and been surprised that moderate PH becomes severe. Some of them even developed right-to-left shunting across the ASD, in which case I started worrying about whether it was wise to take away a pop-off valve with device closure. Whereas we traditionally balloon-occlude their defects and say, "Now I know what is going to happen after I close the defect." In fact, you still don't know what will happen with exercise after closure. I'm curious to hear how you personally handle this situation.

Dr Aboulhosn: That is a bit of a challenge. Ideally, if I could have my dream cardiac cath–CPET lab–stress echo lab, what I would love to be able to do is have multiple transducers so I could measure all of these pressures simultaneously, to be able to do stress echo simultaneously, to be able to get cardiopulmonary exercise measures, and be able to occlude a shunt, say a patent foramen ovale or an ASD, while having someone actually do bicycle or ergometry. This would mean that you're going to have to occlude the atrial-level communication with a balloon coming from the neck, not from the leg; therein lies the challenge. In the absence of that ideal, what I will often do is bring someone to the cath lab and do the following.

Let's just take an example of somebody with an ASD and some degree of PH, and you're not sure whether it's appropriate to close or not. In that setting, what I'll do is put in multiple venous sheaths as well as an arterial sheath—I use the femoral approach here—and I'll go ahead and get a baseline arterial blood gas on the patient, and I'll go in and get baseline pressures and baseline saturations on room air. Then I will go ahead and do upper extremity exercises, where we give the patient weights, usually 5- or 10-pound weights in each arm and basically have them do fly presses. It does not mimic the exercise that someone is doing when walking or running, but at least it is increasing the heart rate and causing some increase in blood pressure and giving us some information about the changes that may occur with that level of exertion. We do that and repeat a lot of those same measurements. Then I'll go in and balloon-occlude the defect and get baseline measurements with the defect balloon occluded. I've even gone so far, and this is where the cath lab staff and everybody is like, "Oh my God, please stop," to do another phase with inhaled nitric oxide, with the shunt open and the shunt balloon occluded. You can do so many variations on this. In the end, I find that if somebody desaturates with exercise, that is concerning. If somebody has an elevated PA resistance that is beyond 50% systemic, that is generally a hard stop for me as far as closing an interarterial-level shunt unless there's a really good reason to do it.

You can do all sorts of variations on the scene, but I do believe it is important to balloon-occlude these defects before closing them if there is a question as to whether or not to close them. If I balloon-occlude an atrial-level shunt and I find that the systemic arterial pressure drops, the RV pressure jumps up, the CVP jumps up, those are very concerning findings for me. I will generally then either not close the defect, or if I'm considering closing it, I'll fenestrate an atrial septal device, or use a fenestrated device to basically downsize the defect. That's the way I go along and do it. It's relatively time-intensive.

Dr Krasuski: Great point. You probably won't make the technicians and nurses in charge of a busy lab too happy when you go through so many steps. But I often find that when you explain why you are going through all of these steps, they all appreciate the fact that you are being so thorough. The other point worth mentioning is the use of complementary medical therapy. When I put in a fenestrated device or I completely close a shunt that may be pushing the limits, the fallback is that I can start or add on the many different and new advanced medical therapies for PAH. The other thing that I do is if the pulmonary vascular resistance is borderline prohibitive, I'll first treat them medically with a plan to bring them back and reassess

hemodynamics at a later time with the hope that we've reversed the disease to the point that the shunt can be safely repaired.

Dr Aboulhosn: There's one quote from an old mentor of mine, Dr John Michael Criley, who taught me how to catheterize back in the good old days at Harbor UCLA, one of the county hospitals that UCLA faculty and trainees staff. He used to say, and now I borrow his saying all the time, that it's called the cardiac cath *lab* for a reason. It's actually a laboratory. It's not just a place that we bring patients to in order to do an intervention and then get them out. In my mind, it's actually a place where we can figure things out and can alter the baseline state in such a way as to help us make the right decision. I think this is really the art of medicine. It can still be practiced in the cardiac cath lab, and we should treat it more like a laboratory than just a technical location with some equipment that allows us to do an intervention.

Dr Krasuski: I couldn't agree more. Ray, tell us a little bit about your experience with implantable hemodynamic monitoring. I think you already alluded to this. We get a chance to assess what happens hemodynamically when people are in the community doing what they normally do.

Dr Benza: I think that it's a really appropriate time to bring that up in the conversation, because as I listened to this, some of the things that are emerging in my mind are, again, why are hemodynamics so important? They're important because really they're the earliest things that change in this disease, and assessing hemodynamics on an ongoing basis really gives you a very complete picture of how the patient is responding to the disease. Remember, we're not at a point now where we have molecular markers that tell us when the disease is progressing at a very early level, and beyond that, hemodynamics are the first things that change as the disease progresses. All the other things that we measure—neurohormones, the 6-minute walk test, imaging—are all later down the line. At present, hemodynamics really give us the earliest warning signals about when this disease is changing.

The beautiful thing about the implantable hemodynamic monitors is that they add to that knowledge. They add to that knowledge by giving us multiple different touchpoints to assess hemodynamics over a period of time. It's not an isolated point when a person is lying supine on a cath table. It's multiple pieces of prognostic information that can be obtained every single day, which you can then plot and mark the course of a patient's disease state. Changes in these cumulative plots can then warn a clinician if a patient is straying off course. The importance of this is that many of these hemodynamic changes can occur weeks before a change in symptoms, such that it serves as an early warning signal of decompensation. You can also get the benefit of both resting hemodynamics and some ambulatory hemodynamics with these devices. They are relatively easy to implant in patients. The congenital patients that we've been talking about, though, are probably the one situation where it might be a little more difficult to implant. In the normal PH patients, it's easier.

Dr Aboulhosn: Can I ask you a question about that? When it comes to, say, the CardioMEMS device and the utility of getting PA pressures, we all think it's very useful, but do you think that is sufficient when it comes to the treatment of patients and figuring out what's going on with them? I'm always worried that a drop in PA pressures is not necessarily a good sign in somebody with decompensated heart failure. I always wonder whether I should take a CardioMEMS and put it into somebody's vena cava so that I can end up getting regular CVPs, which seem in my mind to be probably more useful than PA pressures alone. Can you talk a little bit about site of pressure measurement and the importance of maybe adding flow measurement to just pressure measurement?

Dr Benza: Yes, in fact, you took the words right out of my mouth. I was about to say that the current clinically available pressure readings that you get from the CardioMEMS device aren't going to be as useful in PH without the additional stroke volume information, which is presently only available for research. Stroke volume determination with these devices is a hot new area of research.

In the studies that we've conducted, we have looked at the stroke volumes that we calculate with the CardioMEMS device and compared them with those we derive from cardiac MRI, which as you know is really the "gold standard" for stroke volume, and they're pretty accurate. In the NIH-funded studies we conducted in PH using the CardioMEMS device, we had a plethora of hemodynamics that we were able to derive using the stroke volume information and heart rate, including cardiac output, cardiac index. In addition, because you have the pressure measurements, you can also calculate cardiac power, cardiac efficiency, total pulmonary resistance, and elastance.

Thus, the addition of stroke volume information from the device is a very powerful tool that can then be applied in the area of prognostication in pulmonary vascular diseases. We've gone even so far as to look at these combined hemodynamics before and after 6-minute walk tests, and we have found very, very clearly that patients with PH are stroke volume–limited with activities of daily living and that they only maintain cardiac output by increasing their heart rate. That's a very novel finding found using this device.

The addition of stroke volume and the ability to do these types of hemodynamic challenges in patients in the ambulatory situation and not on a bicycle or in the cath lab have really added to our knowledge about these patients. Using the sum total of these events, you really see trends in hemodynamics very clearly over time. When a patient's cardiac output is dropping because their stroke volume's dropping and that's coupled with a drop in pressure, as you mentioned before, it's a bad sign. It's quite different from when the stroke volume stays flat with rising pressures. That means the heart's still able to maintain

stroke volume to some degree during this patient's disease state.

I think with the advancement in technology that we just reviewed, the CardioMEMS device may serve as a very useful tool in the management of people with this disease.

Dr Krasuski: That's really taking the cath lab hemodynamic data collection outside of the cath lab, so that's a great diagnostic advance.

Dr Benza: Yes, and there are people that we haven't had to repeat a right heart catheterization for in years. There's very little hemodynamic drift with the devices, and as I mentioned, the stroke volume calculations are pretty good, particularly when you do them at rest.

Dr Aboulhosn: Ray, could you touch upon the potential for the use of the CardioMEMS device or any other devices that you're aware of for also measuring CVP? Requiring 2 devices, obviously, but if you're going to have one in the PA and one somewhere in the systemic venous circuit, do you think that is something that would be useful to you, that would add additional information over and above what we're getting from a PA pressure and stroke volume and all of the important measurements that you mentioned already?

Dr Benza: Yes, I think that's the one piece of information that we do not get from the device, and in right heart failure it's so critical to know what that CVP is. I think the addition of the stroke volume information really has advanced our knowledge in how this device is good for predicting outcome. Knowing the right atrial pressure would obviously be very, very helpful. This sensor was originally developed for deployment in the aorta. They have sensors of different sizes and they certainly can be applied to the venous system. They haven't done that now, but I know that these have been conducted in animal studies. The only issue with the device in the venous system could be early migration when the device is deployed. Once the devices are endothelialized, however, they will not move, but prior to that, I think that early migration would be the only issue to worry about from a venous deployment of the device.

Dr Krasuski: Let's shift gears just a little bit and talk about the patient who is failing advanced medical management and potentially heading toward a need for lung transplantation. But maybe that patient is either not a great candidate for transplant due to social reasons or has an unusual blood type or antibodies that are not going to get them transplanted quickly. Or maybe they need some assistance to stabilize them until we can get them safely transplanted. Eddie, could you talk a little bit about some of the newer techniques for right ventricular support? What is new and in in what direction do you think the field is heading?

Dr Rame: Let me talk a little bit about what I think is a very early phase right now of having several centers beginning to look at a paradigm for 2 different types of patients. You talk about the patient refractory to medical therapy, who is basically failing, and as we know, right heart failure has a lot of overlap with left heart failure as far as neurohormonal activation, with high levels of circulating neurohormones, including adrenaline and noradrenaline, which induce a metabolic adaptation in these more advanced patients that leads to mobilizing lipids to a state of cachexia due to fat and muscle wasting. That's what we see with these patients. The question is, of course, changing the natural history of that end-stage disease into some survivable endpoint with better quality of life. There's a group right now that's basically putting together a protocol that we are sharing in terms of patient selection for these refractory-to-medical-therapy PAH patients. We're talking about PAH predominantly, solely Group 1 PH, and predominantly idiopathic familial along the spectrum right now, only because right now it's more of a proof of concept. But just to be clear, one paradigm is the idea of long-term support devices that can be built for the right side.

Right now, what do we have? We have LVADs that are very much designed by engineers for generating continuous flow against a left-sided systemic afterload. They are geared for that purpose. When you put them on the right side, you can get away with it in a limited number of patients, but it's not ideal, especially in patients with elevated pulmonary vascular resistance. There are several interested industry partners that are engaging in a long-term project to build a long-term right ventricular assist device (RVAD). This bridge to transplant, or even more of a short-term bridge to getting on PH therapies, is a really interesting question, because how many times are we actually seeing refractory patients? Unlike left heart failure, blood pressure could be an absolute limiting factor for getting people titrated aggressively on PH meds. Often our patients just run out of time. They're getting too sick or having just too much RV failure.

I think that a second paradigm of patients who could be more completely treated with PAH therapies in congenital heart disease is one where they could benefit from temporary to midterm support devices, and there are several companies looking to see if they can use what they have developed. There's one paradigm of a surgical RVAD. The right-direct VAD, which was actually put on the shelf by AbioMed, worked very well, but was not developed since the percutaneously implanted Impella RP was more preferentially used with increasing demand by shock interventionalists. This surgical intermediate RVAD paradigm could allow some patients to be effectively supported, unloading the RV while patients can be more aggressively treated if they are more naïve to PH meds. Maybe that's the paradigm of the bridge to recovery for these patients who are really, really sick. Like you said, these patients are low output, with marginal systemic blood pressure and progressing in terms of end-organ ischemic injury from a deficient cardiac output. In terms of the exercise capacity and the physiology of how flow-adaptive these pumps can be designed, this paradigm is so new that we have no idea how these patients will do in terms of ambulatory or exercise-induced demand.

Dr Krasuski: There are so many challenges to developing RV support, not

the least of which is that you're trying to pump blood through a very-high-resistance circuit, which requires very high flows. As an institution, Duke is very experienced in using veno-arterial extracorporeal membrane oxygenation (VA ECMO), and we utilize it a lot for support, not only in patients who are critically ill with PH, but also in the perioperative period after lung transplantation to help medical stabilization

The other technology worth mentioning is the Novalung, which allows you to bypass the pulmonary circuit by returning blood back to the left atrium. It's an interesting idea because you utilize the high right-sided pressure to passively drive blood through the oxygenator, so no pump is necessary. One of the problems I've encountered with salvage VA ECMO is that we get to patients too late and there's not enough reversible disease to allow the patient to survive to transplant before a lot of other organ systems start to fail.

Ray, I know you are also very involved with transplantation. Could you share your experience for us?

Dr Benza: This is something that we have certainly tried to approach very carefully in the PH patients. I was part of the writing team for the World Symposium on PH looking at RV support for the PH patient. The discussions during that committee meeting were very lively around this issue. I am in support of trying to develop right heart support systems for PH patients. I think that's the right thing to do. However, with the current technology, the delivery of blood flow from the device is still to the pulmonary circulation. In light of that, we have to be very careful with the flows that we put through the lung because shear damage to the pulmonary architecture with high flow can result in very significant hemorrhagic problems. Now, as long as you can keep the flow low, I think that is something that will certainly help with a lot of these patients as we bridge them to transplant, although it may not be a good long-term solution for those patients who are not eligible for transplant. Flows devices that can give you low flows, like 2 L, 2 1/2 L, like the CircuLite device, might be a very appropriate device for a patient with right heart failure related to high pulmonary vascular resistance.

Dr Rame: Just to weigh back in, and following up on what Ray has said—truly, the current roadmap for these companies is the design of a low-flow, partial-support device. I just want to point to the work of Bart Meyns from the medical center in Leuven, Belgium, and his team. They have done a number of studies with large-animal PAH models and demonstrated the ability to support them in the acute postimplant and intermediate term. It's important to note exactly what Ray said—the low flow has been demonstrated to be so imperative because of the absent autoregulation that you actually have in the pulmonary bed when these patients are so acutely and chronically ill. Not only do you risk pulmonary hemorrhage, but you can probably induce more angiopathic changes in the pulmonary vasculature, and these patients are more likely to get worse and not better if this design element is not well incorporated.

But the good news is that so far these models have actually shown both pathologically and clinically that they can actually get better with low-flow paradigms. The idea is to relieve the low cardiac output state, decongest, and assist the right side. I think these patients could do well with low flow, partial assist, and achieve decongestion. This is the hypothesis. Just to be very clear, very few people have achieved a long term with an isolated RVAD, especially in patients with RV pressure overload. These RVADs have a tendency to clot. They see a very high dynamic resistance and the devices thrombose.

The other reason that RVADs tend to clot is because once you assist the RV, even partially, and it recovers function, you then have a parallel circuit with native competitive flow and the devices will thrombose as RVAD flows drop. I think there is a lot to learn in this area. The good news is, like Ray said, there is some enthusiasm to try and support these patients who are truly the "walking wounded," who are crippled with end-stage right heart failure due to PAH.

Dr Benza: The current designs of VADs are meant for supporting the left-sided circulation, not the right side, although they're structurally small enough and can support the right heart in the absence of severe PAH. As these devices are meant to run at 4 L, you can have issues when you reduce the flow down to 2 L, as we were just mentioning, because thrombosis can become a big issue. I think we have the right idea. I don't know if we have the right design yet, and that's what we really have to work at, getting the right design to develop a pump that can deliver low flow without clotting off, that doesn't increase shear stress, and doesn't progress the angiopathic changes in the pulmonary circulation.

Dr Krasuski: There are a lot of challenges involved, but I think we've made great advances in this area and there certainly remains a lot to think about.

Stepping back for a second, Jamil, I'd like to apply our congenital knowledge to other patients with PAH. Although it may be a little controversial, patients with Eisenmenger syndrome appear to have better clinical outcomes than patients with other types of PAH. There are obviously a lot of embryologic RV adaptations that may be beneficial, but one of the hemodynamic benefits may be the presence of the shunt to serve as a "pop-off valve." Septostomy has been around for a very long time. Personally, I've done a few, but they were performed as a last-gasp effort and although initially successful, the longer-term outcome was poor. We recently published a meta-analysis of the studies of septostomy and found short-term outcomes to be fair, but long-term outcomes to be poor. It's a dangerous procedure and you're exchanging one set of problems, a low cardiac index, for another, hypoxia.

The use of the percutaneous Potts shunt, where the right-to-left shunt is from the left PA to the descending aorta, may be more favorable. The shunt is beyond the coronary and brain blood supply, so you are not creating cyanosis at the neurological and heart level. It's a little bit more appealing to think about improving cardiac output but not dropping the systemic saturation to the most vital organs. Can you give us a little bit

of background on this shunt? Have you had any experience with it?

Dr Aboulhosn: The first time I became aware of a percutaneous Potts shunt in a human being was actually by reading about the work that was being done by the great James Lock at Boston Children's. They ended up publishing a case series of Potts shunts that they did in patients and they were successful. They did have some technical issues, but they were successful in doing them. I think the concept is an interesting one. It goes back to this, that patients with Eisenmenger syndrome who have patent ductus arteriosis (PDA) tend to do a lot better than patients, say, with Eisenmenger-type physiology who have a pretricuspid valve shunt. Those who have ventricular septal defects and PDAs seem to do better, but the PDAs seem to do best out of those 3 groups. There are some important reasons for that, and you alluded to the main one, which is that you are not sending highly deoxygenated blood to the brain and, importantly, to the carotid bodies—the chemoreceptors that we have in our carotid bodies that end up driving our respiratory rate and increasing our minute ventilation when there's a detection of hypoxia or elevation in CO_2 levels. It's a nice idea that you would put your right-to-left shunt beyond the subclavian artery and just desaturate your lower body.

As far as the technical aspects of it, it's a very challenging procedure, frankly. What you have to try to do is either use a radiofrequency wire or a transseptal needle, but preferably a radiofrequency wire, and try to go from the descending aorta into the left PA, which is basically what used to be called in the old days, when done surgically, a Potts shunt. That's what you're trying to create here. Then you need to snare the wire on the PA side, create a wire rail, and then put in a short covered stent that doesn't obstruct the aorta and doesn't obstruct flow in the PA. Usually, obstruction of flow in the PA is not an issue here. Why? Because the left PA tends to be severely dilated in a patient with severe PAH who is being considered for this procedure, but in someone with a low cardiac output state who has severe PH, the aorta might be quite small. So how far that stent sticks into the aorta, especially if you're using a covered stent, could be an issue.

Now, one could potentially consider a fenestrated closure device, such as the AFR device, for example. Could something like that be utilized in this space to create an aorta pulmonary window and not have a large stent in the aorta? One of the issues with the surgical Potts shunts in the congenital population, and why they've been completely abandoned as a palliative shunt, is the difficulty with controlling pulmonary blood flow in patients who have low PA resistance. So if you put it into a child, for example, with pulmonary atresia who has limited pulmonary blood flow, you will have torrential blood flow to the pulmonary arterial bed, usually the left PA.

The work of Abraham Rothman in Las Vegas is very applicable here, actually, for the creation of these kinds of Potts shunts in large-animal models. The consequences of uncontrolled pulmonary blood flow into the left PA are that the left PA thromboses, and you accelerate the pulmonary vascular disease process of completely distorting the architecture of the pulmonary vascular bed on that side. Those are the technical issues involved with this.

One case that I did see a few years ago when I was in Europe and at a meeting of the congenital heart society there in Munich was a case where they used a Melody valve in a large PDA. They put it into a PDA in a patient with severe PH, which is a really interesting concept, because what you're doing here is essentially valving this kind of shunt. Oftentimes, if you look at patients with PDAs who have Eisenmenger-type physiology, what you're going to get is a near equalization or equalization in systolic pressures, or maybe the PA systolic pressure would be higher than the aortic systolic pressure. But often you will have a lower PA diastolic pressure than aortic pressure. What's happening there is that you're shunting right-to-left in systole and left-to-right in diastole, but having a valve would prevent that. The valve would close during diastole and you wouldn't end up getting the excess pulmonary blood flow at that point. You'd have a pure right-to-left shunt in that location. I know I'm getting a little bit too technical here, but this is how I think of it: that this would be a fascinating intervention to do, but there are a lot of technical challenges to it. It's not widely utilized, but I do think there are some major advantages to doing it.

There are other areas where you can also create shunts, and these we have done, which is at the ventricular septal level. You can stent the muscular ventricular septum, and you can do that safely, thereby creating a muscular ventricular septal defect as a pop-off for a severely hypertensive RV. It can work well and can decrease the RV systolic pressure. However, it does lead to this issue of more severe desaturation and the consequences thereof, especially the desaturation caused by the right-to-left shunting at the ventricular septal level that is taking place proximal to the cerebral vessels for the reasons I described earlier.

As far as the septostomies go—atrial-level septostomies and the creation of atrial-level shunts—I think that's gotten a lot safer with the advent of radiofrequency wires and needles. For example, the Bayliss systems that are now commercially available are great because if you have a tiny left atrium and a huge right atrium with a septum that is bulging deep into the left atrium, in prior years we would have to use the Brockenbrough needle and try to push until we broke through, and the needle could go through the septum and end up going right through the back wall of the left atrium. Now that risk is much lower with the use of radiofrequency needles and wires. I think performing the procedure is safer and we do have more choices now with the fenestrated devices for attempting to control the size of any fenestration that you create. I do think that the future for these shunts probably lies in the transcatheter Potts shunt, and I think the basic hemodynamic principles and physiologic principles when it comes to the Potts shunt do make it superior to an atrial-level shunt and even to a ventricular septal–level shunt. Really, the key here is going to be the technical details

and making this more widely applicable as opposed to something that's done by a few people around the world who are highly skilled, and done in variable ways at that.

Dr Krasuski: Thank you for that very erudite discussion, Jamil. While you were discussing shunts and fenestrated devices, I thought it would be worth noting that companies are now designing devices that create an atrial shunt for patients with heart failure and preserved ejection fraction. In this case they are decompressing the left atrium into the right to reduce pulmonary congestion. One company in particular, Corvia, is pretty far along now in their clinical trials and may get FDA approval soon. Who knows, maybe this technology may one day be applied in PAH to facilitate the creation of a more effective septostomy. In addition to the problem you noted (perforation of the left atrium), there's also been the issue of the creation of shunts that are just too large, resulting in excessive hypoxia or the septostomy site itself closes afterwards, undoing the benefit and requiring reintervention. The use of such a device may eventually eliminate these problems.

Well, this roundtable has been extremely educational for me, and I hope it will be for our readers as well. I'd like to thank you all for taking time out of your busy schedules to join me. It's certainly a welcome respite from the COVID-19 pandemic, a great chance to sit down and talk about anything other than the coronavirus. Thank you, gentlemen, on behalf of myself and our readers.