Pulmonary Hypertension and Right Heart Failure in the ICU: Tackling Difficult Issues

A group of thought leaders in management of pulmonary hypertension gathered by phone on January 27, 2015 to discuss their approach to difficult issues encountered when PAH and RV-failure patients are in the ICU. Read on to learn their perspective as guest editor Deborah Levine, MD, medical director of the PH Center at University of Texas Health Science Center in San Antonio moderates a discussion among Jeffrey Sager, MD, director of the Cottage Pulmonary Hypertension Center in Santa Barbara, California; Stephen Mathai, MD, MHS, assistant professor of medicine at Johns Hopkins University and member of the pulmonary hypertension program; and Todd Bull, MD, director of the Pulmonary Vascular Disease Program at the University of Colorado and member of the pulmonary and critical care and cardiology sections.

Dr Levine: Thank you for taking the time to join our discussion today. This issue of *Advances* is dedicated to the challenges we face while taking care of our patients with PAH and those with RV dysfunction/failure in the ICU setting. Our roundtable today will focus on our experience and challenges with issues that are not covered in the rest of the journal.

Dr Levine: Much of what we discussed in the articles in this issue focuses on patients with PAH (sepsis, RV dysfunction relating to the PAH patient, etc). But one topic that we do not discuss, which is a major problem for intensivists, is patients with Group 3 PH–patients who are admitted to the ICU with chronic lung disease, who may have some PH and/or RV dysfunction, related or as a complication of their lung disease, who are acutely decompensating in the ICU. How do we go about evaluating and treating these patients? Do these patients undergo RHC? Do we initiate PAH medications? How do we treat them differently from our Group 1 PH patients? Todd?

Dr Bull: I think what you're asking is how we manage patients with an underlying parenchymal lung disease who also have some associated right ventricular dysfunction. That's kind of a tricky group to start out with, in that I think many of us recognize that pulmonary hypertension is associated with this patient population. This is one of the lung parenchymal categories of pulmonary hypertension or WHO Group 3 PH. It's unclear, though, how specifically to deal with the pulmonary hypertension in that group, other than correcting the underlying lung disease or hypoxia. Now, that being said, there are those patients who have certainly more significant RV dysfunction, which in the past has been termed "pulmonary hypertension out of proportion" to their lung disease. And I think many of us in the field think that at least that's a group that may merit consideration of treatment, though it's certainly an area of debate right now. Now, how to deal with them in the ICU setting: my personal thought on this topic in general is that patients go as their RV goes. The RV in a way is a window to the soul, if you will. So, if their RV is severely dysfunctional, based on their underlying lung disease or another problem, then that can really determine or impact their outcomes in the intensive care unit–or at least can play a big role in that. If their RV function is relatively good, then I think their underlying process, whether that be parenchymal disease, may more accurately determine how they do. Launching into treatment, again, I really pay more attention to what the RV size, RV function, what their hemodynamics are in that scenario, as to whether I would consider thinking about other PH specific therapies. But I think you have to be really careful of adding any of our medications to that patient group, because you can certainly induce V/Q mismatch.

Dr Sager: I completely agree with Todd. One aspect is that these patients with pre-existing parenchymal disease or cor pulmonale have very little reserves. Usually an acute event such as infection or pulmonary embolism leads to rapid decompensation. They may have chronic right ventricular compensation for many years until this acute event occurs. When this happens, the right ventricle that is in a chronically compromised situation leads to a spiral of death. The focus of ICU management is to try to reverse the acute reason for decompensation and support the right ventricle. I am extremely cautious about using PAH-specific therapies. Before considering these PAH-specific therapies, I try to maximize right ventricular afterload reduction. For example, focus on improving patient's oxygenation, optimize fluid balance, and deal with arrhythmias. There is the risk of using PAH-specific therapies in patients with parenchymal lung disease due to potential worsening oxygenation and V/Q mismatch. I will use, for example, in the intensive care unit, inhaled epoprostenol as salvage therapy for refractory acute hypoxemic respiratory failure not responding to more conventional therapies. Presently, we do not have enough data to be using PAH-specific therapies upfront in patients with WHO Group 3 disease who had decompensated in the ICU.

Dr Mathai: I also agree with everything that's been said. Some specific things that I might do a little bit differently for patients who have pulmonary hypertension in the setting of parenchymal

lung disease in the ICU compared to other patients is maybe set my goals for oxygenation a little bit higher. Not be satisfied with a saturation of 90% or a PaO_2 of 60, looking for actually reducing some of the vasoconstriction that may be induced by the hypoxia. I agree with the sentiment that we should be aggressive about diuresis. Then also think supporting right ventricular contractility with specific ionotropic agents might be another potential intervention that could be helpful in these patients. Obviously, the impact of mechanical ventilation on cardiopulmonary interactions, either with intubation or even positive pressure ventilation, should be considered strongly in the evaluation and management of these patients, recognizing that the hemodynamic impacts of these interventions may further worsen an already impaired RV.

Dr Levine: Thanks Steve, I completely agree. Often we have patients with lung disease in our ICU or transferred from other facilities to the PH center who are so hypoxemic that the question becomes, if you initiate PAH therapy, will you be able to improve their significant hypoxemia? What has been your experience and what are your thoughts using these agents in these very sick hypoxemic patients (many of whom are ventilated)?

Dr Mathai: One thing that I would like to raise is the possibility of increasing right-sided pressures leading to a PFO and a right-to-left shunt, which could be contributing to the general hypoxemia that's being observed in these patients. I think that's something that should be checked whenever a patient seems to have hypoxia that is markedly worse than prior. Then the management strategies that we proposed regarding supporting the right ventricle and diuresis would be potentially very effective and helpful in reducing shunt and perhaps improving hypoxia. I'll let Jeff and Todd talk about the particular vasodilator agents.

Dr Sager: I would add that physiologically it seems reasonable to use inhaled therapies in patients who have ARDS or acute hypoxemic respiratory failure. It makes sense that you would be getting a drug to an area that is ventilated and reduce problems related to V/Q mismatch. It would make sense to try and use vasodilators in areas that are being perfused and ventilated. Additionally, there is less systemic hypotensive effect. Although it sounds good, it doesn't always bear out in the literature. For example, inhaled nitric oxide in ARDS has been studied and although it improves oxygenation in the first 24–48 hours, hospital mortality and long-term outcome data were no different. I believe that although the long-term outcome data may not be significant, being able to buy the patient improved oxygenation for 24–48 hours allows you time to improve oxygenation and hopefully get the patient to turn the corner. Many times we struggle to get patients through the first 24–48 hours of the acute hypoxemic respiratory failure. If you can get them over the hump with using agents like this, they may actually survive. So although the primary outcome of that particular study didn't show mortality benefit with using inhaled nitric oxide, I believe there is potential benefit for these agents. The other potential benefit of inhaled agents is the ability to use PEEP levels that keep the lung in a low stretch protective strategy. In my practice, I don't use inhaled agents up front but rather as salvage modality. I hope that this can be further studied to help guide clinical practice.

Dr Bull: Yes, my take on that is similar. I think, as I mentioned at the beginning of this discussion, how I decide whether I'm going to go after an agent to treat the pulmonary hypertension or pulmonary vascular disease in my mind really relates to what the RV looks like. What is it doing? How is it functioning? All the better if I have invasive hemodynamics, if that's what I think might be going on. But I think the echo in these scenarios can be useful. And really, I think where people get led astray is just looking strictly at the pressure. In my mind, the pressure is always the least interesting variable; it is how the right heart is responding to the pressure that is important. We know that parenchymal lung disease is one of the things that can make an accurate read on right ventricular systolic pressure by echo inaccurate. Also, if the patient is on the ventilator, then estimating right atrial pressure becomes difficult as you cannot rely on IVC dilation as an indicator of RA pressure in that setting. Now, I guess the topic we brought up here is inhaled therapy, which in theory could improve V/Q matching by improving perfusion to areas of good ventilation, which is the beauty behind nitric oxide. And it is pretty clear that inhaled nitric oxide initially works to improve oxygenation acutely, as Jeff mentioned, as salvage therapy in severe ARDS; but as he stated, it has never been shown to improve long-term outcomes. There's a strange tachyphylaxis that occurs once it's applied that, after 24–48 hours it quits working, which I've always found kind of fascinating. Whoever can figure out why that is and figure out how to keep that from happening is going to be really onto something, because then it would become potentially a lot more useful. We've also been looking at inhaled prostanoids in this scenario, and in particular, inhaled epoprostenol just because of the expense of inhaled nitric oxide. I know other centers have used that, as well. But to me, again, it really comes back to is the problem the right ventricle? And is there really an RV function problem or are you just reading off a pressure? I always caution our house staff: don't just read the pressure on the echo report without looking at RV size and function–ideally, look at the echo yourself. But at least read the report on the RV size and RV function, because that will give you a better idea of what's happening.

Dr Levine: Thank you Jeff. Moving on to evaluation in the ICU. Many of these patients may have echocardiograms, but many do not have previous RHC. Is your experience to place PA catheters in these patients? Have you found it assists you in initiating or choosing the correct therapeutic options?

Dr Bull: That's always kind of tricky. A lot of what we're going to end up discussing in this scenario is from the

ARDS literature, because that's where most of our trials in critical care literature reside because of the ARDSNet. The FACTT trial (Fluid and Catheter Treatment Trial),[1] which wasn't addressing pulmonary hypertension, showed no benefit to a PA catheter as opposed to a central line in terms of patients' outcomes with ARDS. So, in this particular patient population, we no longer grab a PA catheter. Because there were 1,000 patients in that study and 500 of them had PA catheters, we looked at that study and said, "Oh, what a great opportunity to look at what the incidence of pulmonary hypertension is in patients with ARDS." We reported that 70% of the patients had pulmonary vascular dysfunction defined as an elevated transpulmonary gradient and these patients had an increased mortality. There was a dose effect with the worse the pulmonary vascular dysfunction, the higher the mortality.[2] To go back to your question, I would consider a PA catheter in certain scenarios, but usually we find it not necessary in this group. I would do it when I really think the RV is involved and I'm trying to decide if I need to add PH treatment. I'd be curious to hear what Steve and Jeffrey think on the use of PA catheters in this situation.

Dr Mathai: So I rarely use a PA cath in the ICU. I agree with Todd that there may be cases in which it could be helpful. My concern is that if these patients have multi-organ involvement, are on the ventilator, and have underlying RV dysfunction, while serial data such as serial measurements of right atrial pressure and looking for changes in right ventricular function, etc., might be useful, I think most of the time we can manage these patients based on an echocardiogram and what we're seeing with systemic hemodynamics along with oxygenation and ventilation. However, there definitely are cases in which you're kind of confused by the clinical picture and data gathered from the Swan can be helpful.

Dr Bull: Yeah. Now, specifically we're talking – or I think we're sort of leaning back to ARDS or other parenchymal lung diseases in the ICU, because that's how we started off this conversation. And I definitely agree with Steve, it's pretty unusual that we'd need to put a PA catheter in those patients. And again, FACTT shows us that it didn't really help. Though there were problems with FACTT, I would argue. But I think now if you expand our discussion to patients with PAH, severe pulmonary arterial hypertension, and we're trying to add pressors and/or inotropes, etc., I have to say I find PA catheters useful in that situation. So I don't know if we're going to break this talk away from the parenchymal lung disease or sort of stay there for the moment. But I do think there are indications where the PAH patient comes in and is quite sick that I like a PA catheter to help me decide what to do with inotropes and pressors volume.

Dr Sager: Todd, we know that ARDS can cause pulmonary hypertension and, in fact, it can be one of the reasons for significant RV failure in these very sick patients. I agree with you, in those situations we do not routinely place pulmonary artery catheters because we are able to look at the echo and other parameters to help guide therapy. I think the most difficult areas are with patients who have chronic right ventricular dysfunction, for whatever reason, who get into trouble. These patients can be a challenge to figure out the fluid status and filling pressures and often will need a pulmonary artery catheter to help guide therapy. There are significant limitations with using a pulmonary artery catheter in patients in the ICU on ventilators and interpretation needs to be done cautiously with experience. There are hemodynamic changes from the ventilator itself.

Dr Levine Thanks everyone for your thoughtful comments on this challenging issue. Unless anyone had anything else to add on this subject, let's move on to surgical issues in the ICU in patients with chronic PAH. This has become a more a frequent ICU scenario, especially in PH centers, as we often have these patients transferred to us. There is a lot of planning and discussion among anesthesia, surgery, PH physician, and the intensivist which should occur prior to surgery, peri-operatively and post-operatively. Jeff, what is important when looking into these situations? Besides getting a multi-disciplinary team together, what other issues are important?

Dr Sager: This is a timely question as I gave an update to the anesthesia department this week on peri-operative pulmonary hypertension issues. The key to successful operation in patients with pulmonary hypertension results from a multi-disciplinary approach and clear, concise pre-operative, peri-operative, and post-operative plans. A frank discussion is needed among the surgeon, anesthesiologist, and PH specialist. The best type of anesthesia is no anesthesia! One needs to decide on type of surgery and if surgery could be avoided by other therapies. If surgery is needed, a pre-operative assessment of the right ventricle to ensure its stability is paramount. We know from a registry looking at risk factors for mortality in patients with pulmonary hypertension that emergent surgery was one of the highest risks for death in these patients. So if emergent surgery can be avoided in these patients, clearly that's the way to go. Having a surgical plan for both intra-operative and post-operative management of pulmonary hypertension will likely provide the best outcomes for these patients. You need to anticipate post-operative hemodynamic changes.

Dr Mathai: Yeah, I agree. I think other factors to include are the location of the surgery, above the diaphragm, below the diaphragm. Is it vascular? Also, the duration in addition to the type of anesthesia that's planned. I completely agree with Jeff, that while no anesthesia is the best strategy, if there's a way to do a local anesthesia for any elective procedure, that is also preferred over systemic.

Dr Levine: Agree completely, and really the main reason to meet and develop a plan is so that all know what back up plans are available.

Dr Bull: I would add to Jeff's point regarding elective versus emergent. Jeff, you had mentioned Dr. Meyer's publication in the *ERJ* in 2010. We contributed patients to that registry. An important point of that study was that the mortality was not actually near as high for PAH as had had been put forward in a previous case series, where mortalities were listed as high as 50%. The overall mortality was only about 3.5 percent. But if the case was emergent, which was only a small subgroup of about 4 patients, the mortality was 15%. So it went up dramatically when the case became emergent.

The other key point, I think, to that study was that these were all centers expert in the management of patients with pulmonary arterial hypertension. These were centers where you had expertise in pulmonary hypertension; you likely had expertise in cardiac anesthesia, and surgical and critical care expertise. I do agree that the team is a key aspect. One of the things we always stress is that we need cardiac anesthesia involved, because they are most familiar with the potential hemodynamic changes that can occur during induction, during intubation, following intubation–which in my mind are the most dangerous times.

Dr Mathai: So to echo that and just to give one example, we have a cardiac anesthesiologist here who is quite interested in the peri-operative management of patients with pulmonary hypertension. He has agreed to see all of our patients in pre-operative evaluation. He contacts us after he evaluates them. We go over the most recent hemodynamic data, echo data, functional data, and then come up with a plan jointly, prior to surgery. Importantly, we decide whether or not cardiac anesthesia is absolutely required for the surgery or procedure. I think it gives some structure to a program where we all have people who are living longer and develop other complications from general medical conditions that require surgical intervention. I've recently cared for a patient with long-standing iPAH who developed lung cancer that needed resection. That's obviously a complex scenario to undertake. But at the same time, with these kinds of approaches that Jeff and Todd have mentioned, I think we can be successful in managing these patients through these surgeries.

Dr Levine: Agreed, these conversations between each team and the patient are exactly what needs to happen for these cases to be successful. This includes, as Steve noted, to discuss if the benefit of the surgery is greater then the risk. Patient involvement in these conversations is imperative.

Dr Sager: Debbie, just one point to add is about patients who need semi-elective surgeries who appear stable and are often referred to outpatient surgery centers. An example would be a simple cholecystectomy in a PAH patient who is "looking good" should always have this surgery done in a facility where complete management of post-operative pulmonary hypertension can be performed. I do not believe these patients are good candidates for outpatient surgery centers. It's this cohort of patients that are not recognized as being potentially catastrophic cases for whom there's no preparation when you do these cases at an outpatient surgery center.

Dr Bull: I think that's a great point. Again, we have cardiac anesthesia involved when the PA, PAH is severe. And then we mandate, really, that even "simple" (if there is such a thing) operations are placed in the ICU afterward and are managed by our pulmonary hypertension team, because our understanding of the hemodynamic shifts that can occur peri-operatively is important. Because this is what we do for a living, we know what to watch for. Also frequently they're on therapies like prostanoids that can't be interrupted. You had asked earlier, what do we do with their therapies around pulmonary hypertension? Of course, that's part of our education is that we've got to keep the PH medications going, if that means moving to IV PDE-5's, for example, that's what needs to happen, or making sure the prostanoids aren't stopped.

Dr Levine: Very important point. These surgeries/procedures should all take place at a center that is recognized in being able to handle the situations that may occur.

Dr Bull: Yeah, and I suspect that's, you know, from that Mayer *ERJ* paper that we were mentioning from 2010. The mortality is so much lower than what we've seen in previous case series and this may relate to the fact that all the enrolling centers in this registry were major PH centers and were taking these precautions.

Dr Sager: Yeah, I agree.

Dr Mathai: Can we talk about management of arrhythmias?

Dr Levine: Absolutely, this is one important area, that both affects the patients while in the ICU and brings the patient to the ICU.

Dr Mathai: One of the questions that commonly come up I think from others who are managing patients with pulmonary hypertension in the ICU is the development of arrhythmias. I think it's a particularly challenging scenario in a patient with pulmonary arterial hypertension, due to the impact on outcomes and the potential for adverse outcomes related to the standard therapy for arrhythmias. If we look back at the literature and look at arrhythmias that occur at cardiopulmonary arrest in PAH, what you see mostly is bradycardia. This is from a paper by Marius Hoeper back in 2002, describing arrhythmia at the time of a cardiopulmonary arrest in patients with PAH. But if you look into the ICU realm in patients with PAH–and we went back and looked at this in our cohort of patients who ended up in the ICU with PAH– a significant proportion of those patients, nearly 40% of those patients, ended up in the ICU because of new onset atrial fibrillation or flutter. So atrial arrhythmias were the precipitant for ICU admission due to hemodynamic instability or frank right ventricular failure. And I think that's supported if we look though the literature again at the cumulative incident of SVTs in PAH, which is about 25%. So I think it's a significant issue. I'm curious about how the other panelists approach

the evaluation and management of these patients when they present to the ICU.

Dr Bull: I definitely agree that of the things that bring our patients to the intensive care unit, arrhythmias–in particular atrial arrhythmias– is very high on the list. In fact, I've been over the last couple weeks dealing with this over and over again in a number of different patients with PAH with very severe RV dysfunction. And it's the sort of thing that as soon as we see it, we're moving them over to the intensive care unit because it can be such a dramatic occurrence. As you lose your atrial kick, you drop an already depressed cardiac output even further, and then when you're in a rapid ventricular rate scenario you don't have filling time. Hemodynamically, they can really unravel. And so our approach is the use of amiodarone up front, assuming again that we're not in an ACLS type scenario where we have profound hypotension. In that case, ACLS trumps all and electrical cardioversion becomes necessary. . But when we can, we like to use amio. I've had a fair amount of success with that agent. We strictly avoid beta blockers and calcium channel blockers because of their effect on already depressed RV function. And again, I've had luck with amio boluses and amio loading. Digoxin can be thrown in there, but really do we do not find it very useful for the acute scenarios. So that's our approach. I'd be curious to hear what you do in the face of a fast A-fib or A-flutter.

Dr Sager: This is a great question. It's something that we see very frequently in our PH patients. It is often a dramatic finding with significant worsening in the symptoms when it occurs. When the patient's go into an acute arrhythmia, particularly supraventricular arrhythmias, they often decompensate pretty rapidly. I agree with everyone on the panel that we move them to the ICU. We are very reluctant to use calcium channel blockers and beta blockade and often will start with amiodarone. I'm fortunate here in Santa Barbara, where we have very well-trained EP cardiologists who are willing to perform high risk cardiac ablations under direct intracardiac echocardiogram. I have seen several patients turn around quite dramatically as soon as we can get the supraventricular arrhythmia ablated.

Dr Bull: I've become very aggressive about seeking A-flutter ablation. We're not doing this in the acute scenario either. We either have controlled with amio or, if we can't control, then we'll look at electrical cardioversion. But following that, we have some great electrophysiologists here as well who are getting a lot of experience with this because I've been calling them more and more about ablation, in particular for A-flutter We have not been as aggressive about A-fib. But in typical flutter, our success rate is good.

Dr Mathai: And I agree with all that's been said. You know, I think one of the things that really dictate our management and how aggressive we are is the fact that we believe, although there's little data to support this, that rate control is insufficient. So it's not just getting the heart rate below 100 beats per minute, but actually restoring sinus rhythm, which is the key to improving RV function overall. This is based on some observational data looking at studies of right ventricular function in the setting of atrial fibrillation. In the normal right ventricle, you can expect 20–30% of RV function to be dependent upon normal atrial contraction. If you get to someone who's got pulmonary hypertension, about 40–50% of RV function is dependent on normal atrial contraction. You can see this clinically if you look at the impact on outcomes. Two studies looking at this recently within the past 3 years have shown a 2- to 5-fold increased risk of death for those PAH patients who remain in atrial arrhythmia, compared to those who have no atrial arrhythmia. Another study by Marius Hoeper's group showed significant improvement in functional capacity, assessed both by WHO functional classification and six-minute walk distance with restoration of sinus rhythm. So I think for us, it really is an aggressive push, not only to get rate control but to get rhythm control. I think ablation is usually necessary in patients who have flutter, as Todd mentioned.

Dr Bull: Yeah, that was great. And, you know, your comments on outcomes jives well with the 2010 *ERJ* paper by Humbert[3] showing that, arrhythmias, in particular atrial arrhythmias, was one of the markers of bad outcomes in PAH patients in the ICU. It was not a huge study but it was one of the factors that fell out.

Dr Mathai: I think one other thing that we run into sometimes when we were consultants on a case and not primary attendings, we get into the issue of amiodarone toxicity. Many physicians are concerned with the possibility of amiodarone toxicity, but I think this is a bit overblown. I've recently gone back and looked at the literature to try to get a better understanding of what kind of proportion of patients actually have adverse side effects directly related to amiodarone and it's pretty low. I mean, aside from corneal deposits which will develop in the vast majority, most of the side effects occur in less than 5% and less than 1% in many cases of the things we typically think of, like interstitial lung disease. Specifically, the incidence of that is on the order of 1–2%, if someone's on less than 400 mg a day, which I think is the upper limit of the dose that we would all advocate for long-term management of these types of patients. So I don't know what your thoughts are, if you've run into that situation also in your management of these patients.

Dr Sager: One thing that Steve mentioned, worth emphasizing, many cardiology colleagues will be very happy with rate control of these patients, yet they remain significantly dyspneic. It's not just about rate control but rhythm control in patients with underlying right ventricular dysfunction and pulmonary arterial hypertension. These patients are volume dependent and rely on the filling pressures of the atria more so than patients with no pulmonary hypertension.

Dr Levine: Are any of you using cardioversion to restore rhythm?

Dr Bull: We do it when we need to. I mean, again, if you're moving toward a hypotensive scenario or you have a perfusion problem or we're not getting on top of them or the amio is not working– though again, it's my experience.

Dr Levine: Our time is up and I would like to again thank all of you so much for participating in this discussion. I look forward to continuing the conversation on all of these topics.

References

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