I’m Hunter Champion with the UPMC Cardiovascular Institute in the Department of – Division of Pulmonary and Critical Care Medicine, and I recently moved here about a year ago to work with Mike Mathere to setup a comprehensive pulmonary hypertension program. Today I’m really going to just discuss primarily the role of pulmonary hypertension in heart failure and what we think we may be able to do about it prior to transplantation.

This slide simply outlines the relative, the survival in patients if they have a pulmonary vascular resistance of 1 to less than 3 Wood units compared to those who have 3 to 5 Wood units or 5+ greater Wood units per pulmonary vascular resistance. And this in large part, these data have really you know pushed the envelope a little bit in terms of restrictions that a lot of institutions will move with regard to pulmonary vascular resistance. At Hopkins they wouldn’t transplant people unless their PVR was less than 3. And it was pretty- they were pretty staunch about that. But I think that there may be ways we can be a little bit more aggressive in the future, particularly if we are able to better diagnose the pulmonary vascular disease and then think about treatment.

So this is the call that we get often times, we hear Mr. Jones needs a heart transplant but he has pulmonary hypertension. And the answer is not then yes or no, the answer is really what kind of pulmonary hypertension does Mr. Jones have? And so this is what we, what I’ll try to outline today for you briefly. First defining some terms.
Pulmonary hypertension is just an elevated pulmonary pressure. If we want to think about it broadly we generally think about it as, as being a mean pulmonary artery pressure of greater than 25 millimeters of mercury, or having a pulmonary artery systolic pressure of greater than 40. And left heart disease certainly you don’t need me to give you the definition, but it certainly is just a syndrome of exertional limitation, congestive symptoms that may be from abnormal left heart structure, valvular disease, both systolic and non-systolic heart failure.

But when we think about pulmonary hypertension in the left heart we often times need to think about what the cause is. And we often times discuss this as being pulmonary venous hypertension, and you know classically in medicine if you are not able to treat something you just classify it a lot, and so that’s what they did for many years in pulmonary hypertension, they just classified it and they came up with these classifications and pulmonary venous hypertension is generally considered WHO Group 2 PH. Now this is not the group of patients that have FDA approval to treat with Endothelin blockade or PD5 inhibitors of Prostacyclin, this is that which is Group 1 disease, this is the left heart disease group and we are currently doing studies to evaluate these therapies in this, this group.

Pulmonary hypertension with left heart disease, as I mentioned before, systolic heart failure, diastolic heart failure, valvular disease and certainly we see it in restrictive or constrictive cardiomyopathy; but I think even more important, if the only thing that you get out of this few minutes with me is really the big question when you see an elevated pulmonary pressure is whether or not it’s passive in nature, meaning is it proportionate to the elevated wedge pressure that these
patients would have, or they wouldn’t be thinking about transplant. Is it reactive? Meaning is it disproportionate of elevated filling pressures, or is it intrinsic or what we often times call fixed pulmonary hypertension and vascular remodeling? So we’ll touch on these just briefly.

Now in medical school they always talk about pulmonary arterial hypertension as being something which is incredibly rare, you never see it. It’s somewhere between pheochromocytoma and Wegener’s on your, on your list of things that you would check off in medical school; but in reality it is relatively common and we see it most commonly in a number of pulmonary diseases like interstitial lung disease, like COPD and that type of thing. And this type of condition is characterized by a mean PA pressure of greater than 25 at rest with a wedge pressure of less than 15, and a concomitant increased PVR of greater than 3. This type of disease is characterized by a pre-capillary vasoconstriction and vascular remodeling, and this leads to a marked increase in pulmonary vascular resistance.

Now if we think about pulmonary venous hypertension this is a little bit different. Even though the mean PA pressure is the same at 25, in general these patients have a wedge pressure of greater than 15, and typically the PVR is less than 3. This is the type of PH that the vast majority of our heart failure patients have. How does that happen?

Well, we know that increasing the – or when you produce – when you have left ventricular dysfunction you increase the N diastolic pressure, you end up with an activation of neurohormonal
factors such as endothelin, such as brain natriuretic peptide and a decrease is Prostacyclin and Nitric Oxide signalling, you increase Cytokine formation locally, this then leads to pulmonary endothelial dysfunction, particularly with regard to the increased pulmonary vascular – or increased pulmonary venous pressure. You have to remember that these, these lungs are trying to adapt to not going into flash pulmonary edema, so they are increasing their thickness of the vessels and you actually get an arterialization of the venous system. This then leads to further pulmonary vasoconstriction and pulmonary vascular remodeling and then eventually you end up with the, the final end product as, as was mentioned earlier, white ventricular dysfunction and that is really what is often times linked to the increased morbidity and mortality in these patients.

The one thing we also have to remember, and this is why we call our PH program a comprehensive pulmonary hypertension program is that you are willing to think about the concomitant diseases. Do these patients actually have preexisting left heart disease, do they have sleep disordered breathing and John Lee in our clinic is a sleep expert and he actually is evaluating not only the role of sleep disordered breathing in producing PH but what effect left heart disease has in actually causing sleep disordered breathing. Does this patient have prior PEs? We’ve actually in the past we’ve done a pulmonary embolectomy and have been able to take a patient who was not considered adequate for transplant and bring them down to actually being adequate for transplant. And do they have concomitant hypoxic lung disease, do they have some interstitial lung disease, are they obese, these types of things.
So very briefly, in most heart failure patients, and I need to stress this, in the majority of heart failure patients the PA pressure simply tracks with the wedge. If you diurese them or mechanically support them and bring their wedge pressure down you’ll actually see a reversibility of their pulmonary hypertension. This comes from Lynn Horder Stevenson’s paper in 1995 where she essentially highlights what the hemodynamics are in these patients at admission. And here we had a wedge pressure of 26 and a mean PA pressure of 52 on admission. This was similar in the, in the between 89 and 90, and then at the time of discharge when she considered these patients “dry” wedge pressure went down from 26 to 16 on average and the mean PA pressure dropped from 52 down to 40. So in general if you can treat these patients and bring their wedge pressure down you can actually reduce their PA pressures, and this is actually quite important. We’re going to talk in just a second about what happens with that and, and when it may become fixed and you may need to think about something else.

If we are going to determine the heart transplant candidacy for these patients we need to think about whether or not they can acutely vasodilate. Often times we’ll use inhaled nitric oxide or other factors in the cath lab to see if their lung pressures will come down with inhaled NO. Subacutely we can do this in the, in the intensive care unit with sodium nitroprusside challenge. We also do this chronically with L-VAD implant. We also then needed to determine our treatment strategy, can we identify any reversible causes of their pulmonary vascular disease like valve surgery or heart failure or working with their heart failure regimen, add on vasodilator therapy. And I’m going to talk about some of the investigational studies that we are doing right now utilizing agents like Sildenafil and
Endothelin blockade. Chronic agents and then certainly we know that inodilators like Milrinone and Dobutamine in low output states can give you a significant amount of pulmonary artery pressure lowering.

So when we think about pulmonary hypertension as a true disease in left heart disease, this is really the less common form. And I do believe that there is a subgroup of our patients that we consider for transplant each year that have essentially what we call “fixed pulmonary arterial hypertension” as a result of their, their venous congestion. And I’ll show you some data in just a second what happens when we use L-VADs in these patients.

So in many of these patients you really can’t explain just on the basis of their wedge pressure alone, these patients will have an elevated transpulmonary gradient of greater than 15 and also have a higher PVR. This is the group of patients that actually ended up having the higher mortality in, in our UNOS data.

This simply shows the difference between idiopathic PAH and pulmonary venous hypertension on the effect on the arterial system. If we think about the classic idiopathic pulmonary arterial hypertension you think about plexogenic lesions, you think about medial hypertrophy and you think about intimal fibrosis and essentially a small clot in the lumen of these tiny remodeled vessels.
Well what we see with pulmonary venous hypertension, and these are lessons we’ve really learned from mitral stenosis cases, right. We take these patients who we say you are going to feel so much better after you get your mitral valve replaced, and they come back, their PA pressures are exactly the same after you replace the valve and they don’t feel any better. And that’s because in a lot of these patients this is what has happened, you actually have what should be a very thin pulmonary vein, a very thin pulmonary artery system and in fact what’s done is it’s actually remodeled. Now if you can support them and if you haven’t gotten yourself into trouble with RV dysfunction, if you can support them through that time, I do believe that you can get reverse remodeling. And classically if you do take care of the valve in these patients they do anecdotally respond to traditional pulmonary hypertension therapies.

This is one of our old animal models where we looked at pulmonary vein occlusion, we essentially take a surgical clip and put it on the pulmonary veins of rats and we show that the – you get this arterialization, you, you increase the artery size in the lung but then you also see this further arterialization of the venous side as well because of the elevated pulmonary venous pressure.

We published a paper in 2008 in the circulation Heart Failure where we looked at this, the specific phenotype of pulmonary vascular disease. These are 58 patients who underwent L-VAD implant. At the time of L-VAD implant, as you would imagine, the cardiac output increased significantly from around 2.2 to upwards of 4, mean PA pressure did not change even though you had a significant drop in pulmonary wedge pressure. Now as a consequence of this concomitant increase in flow and
decrease in wedge pulmonary vascular resistance didn’t really even change in this patient population, and it’s true that a lot of these patients will drop their PA pressures either within a few days, a few weeks, but there is this subgroup, and we localized a subgroup of these patients who remain and have persistently elevated pulmonary vascular resistance.

This was a group that we treated under an investigational study using Sildenafil and we got these patients up to about 50 milligrams 3 times a day of Sildenafil. And here we show pre-L-VAD pulmonary vascular resistance, post-L-VAD pulmonary vascular resistance and then we have a control group. Now granted you have to be careful with historical controls, these were his – these were patients who did not change their pulmonary vascular resistance over 12 to 15 weeks in an era before Sildenafil. So the patients that were on Sildenafil did have the smaller pump, they were using a Thoratec pump at that time, but what we did see and observe was that within a few weeks we saw a significant drop in PVR in the Sildenafil treated group.

What’s even more interesting I think is using invasive human dynamic analysis we were able to look at RV function and when we look at RV systolic function as measured by a relatively low independent measure of DPDT max, normalized for instantaneous pressure, we saw that after starting Sildenafil we saw a significant increase in RV systolic function compared to the patients that did not receive therapy. So I think this at least points to the potential utility of these vasodilator agents in patients in whom you’ve actually dropped the wedge pressure and remember, these patients here, until their PVR at Hopkins would get down below 3, they weren’t even eligible for
being listed. Whereas once these patients dropped down to the 3 range they were able to potentially be listed for transplant.

Very briefly, I wanted to just discuss a few other studies, not just my own. This comes from Mark Simongrand’s group, looking at the efficacy and safety and Sildenafil and the evaluation of PH with severe heart failure. This is fantastic, Mark exercises these patients before and after treatment, and what he found was that after therapy – well he started off with a wedge of 25 and after therapy he had an average wedge of 18 and cardiac index increased from 2.4 to 2.8 in his treatment group.

They even looked at pulmonary vascular resistance and systemic vascular resistance, he had what they called a balanced effect, which was a drop in not only systemic vascular resistance but also a drop in pulmonary vascular resistance, suggesting that it may also be beneficial in left heart disease, much like our Nature Medicine paper showed that Sildenafil and PDE5 inhibitors can prevent heart failure in an animal model.

This is another study looking at 34 subjects with class 2 through 4 heart failure, the primary end point on this was exercise capacity and hemodynamics. In general this was a, a pretty basic group of patients, they were relatively sick and on their way to potentially transplant. And what Mark found in his group with Sildenafil treatment, this was a PDE5 inhibitor, remember that increases cyclic GMP and helps enhance the nitric oxide and natriemic peptide system by inhibiting PDE5. It’s not
just for erections any more. But Sildenafil significantly increased the peak VO2 in these patients, and peak cardiac output at the time of exercise, comparing pre and post-therapy.

I’m going to pass through this, but essentially he confirmed some of the data that we had showing improved RV function in his treatment group with Sildenafil, significantly greater than placebo, this decrease in PVR and improvement in stroke, stroke volume.

Now why don’t we use all these medicines for heart failure? Well, there have actually been disappointing results in the past with heart failure. In fact, if you remember, Epoprostenol, which is also known as Flolan was initially tried in heart failure patients before it then became an orphan drug and started treating an orphan disease called pulmonary arterial hypertension. And the first trial took 471 patients in class 3 and 4 heart failure and randomized them to IV continuous Epoprostenol or placebo. And even though they had a significant reduction in systemic vascular resistance, which you would think would be pretty good, they had a marginal drop in pulmonary vascular resistance, which you also would think would be pretty good, and you did have an increase in cardiac index with therapy. Patients actually had less survival. So this a little bit analogous to our ________ studies, at least with, with Inamrinone, but here we saw conventional therapy, granted the mortality curve in this isn’t great but it was even – it was worsened by the Epoprostenol. Now one caveat to this is nothing was done about wedge in these patients. It was literally thrown in as hey, let’s take these patients on usual therapy and see what happens. I would love to see another study like what we
did in our L-VAD population with Epoprostenol to see if we could see similar results to what we saw with, with our Sildenafil group.

Endothelin blockade has been equally frustrating simply because we’ve had a significant number of negative trials in heart failure. Remember this was the first neurohormonal blockade blocking agent that actually did not change mortality in patients with heart failure. Ace inhibitors worked, aldosterone antagonists worked, ARBs worked, but Endothelin significantly elevated in heart failure, but in the Reach Study, now granted they used a massive dose of Bosentan 500 milligrams BID, which is about 2 to 3 times what we normally use in our PAH patients, but they stopped the trial early due to increased LFTs. Enable 1 and 2 used a lower dose, but had no effect on mortality, and then the Earth Study with Darusentan, another Endothelin receptor antagonist did not have any effects on LV remodeling, heart failure progression or mortality.

So the conclusion here is really we don’t know what Endothelin means in this patient population. It may just very well be a marker but maybe not a mediator. I’m not really necessarily buying that. Our work with knockout animals has, has proven that otherwise. It just may be that, that we are not picking the right patients. Adding to the level of frustration is the fact that Reach and Enable were never published. These were only published in abstract form, so all we have are the presentations that were given at the, at the meetings and the, the one paragraph abstract. So we really need to do more with regard to Endothelin blockade in this patient population.
So in conclusion, pulmonary hypertension is certainly prevalent, it’s clinical significant but it is under-appreciated in many of our patients with left heart failure both systolic dysfunction as well as diastolic dysfunction. The most important thing, if I – if you take home anything from this is that you really need to find the lesion, find what the problem is. Do they have reactive pulmonary vasculature? Do they not? Do they have sleep apnea? Do they have something else that you need to work up and actually examine for treatment? You need to appreciate the pros and the cons of diagnostic tests. I didn’t focus on diagnostic testing here. But suffice it to say don’t just go by echo, you need echo and right heart catheterization to evaluate these patients. Their RV dysfunction may be altered – may alter your pulmonary pressures and certainly portends of poor prognosis. We are currently working on new and novel ways of assessing right ventricular function in our – in our cath and echo labs. And then provincial interventions, think about that, heart failure drug titrations, limited treatment options, limited treatment options other than vasodilators may very well be, be promising. But I have to caution everyone that’s not yet FDA approved for, for therapy in heart failure. And so with that I’ll leave you with my email address, please don’t hesitate to get in touch with us. Our PH program is comprehensive so we see patients with heart failure as well as the traditional patients with lung disease. So please don’t hesitate to, to get in touch.