I’m Hunter Champion, Co-Director of the Pulmonary Hypertension Program at the University of Pittsburgh, UPMC here in Pittsburgh, Pennsylvania. Today I’m going to discuss pulmonary vascular disease and right heart failure leading towards personalized medicine.

Before we begin with the discussion of pulmonary hypertension I think it’s very important for us to lay out the definition of pulmonary hypertension and the causes that result in the disease. Pulmonary hypertension is defined as a mean pulmonary arterial pressure of greater than or equal to 25 mm of mercury at the time of right heart catheterization. Pulmonary arterial hypertension, however, differentiates itself by having the same definition of a mean pulmonary artery pressure greater than 25 but also having a concomitant pulmonary capillary wedge pressure or LV and diastolic pressure of less than 15 mm of mercury again taken at the time of the right heart catheterization and/or left heart catheterization.

The American College of Cardiology and the American Heart Association guidelines also included definition of a pulmonary vascular resistance of greater than 3 wood units in its definition of pulmonary arterial hypertension.

In our clinic we see a number of different disease states that result in pulmonary arterial hypertension. Although this slide is quite busy, it outlines the majority of the potential causes of
pulmonary arterial hypertension. The WHO at the Dana Point meeting a few years ago helped classify these based on the underlying disease state.

Group 1 pulmonary arterial hypertension includes those patients with idiopathic pulmonary arterial hypertension also known as primary pulmonary hypertension in previous years. There’s an inheritable form, drug and toxin induced, persistent pulmonary hypertension of the newborn and then we have those diseases that are associated with pulmonary arterial hypertension Group I such as connective tissue disease which include scleroderma, rheumatoid arthritis, ____ and other diseases of this type. HIV infection, portal hypertension, congenital heart disease, schistosomiasis, the parasitic disease and chronic hemolytic anemias such as sickle cell disease.

Group 2 pulmonary arterial hypertension is pulmonary hypertension owing to left heart disease. This is the most common cause of pulmonary hypertension and right heart failure that we see in our clinic. It includes patients who have systolic dysfunction of the left ventricle, diastolic dysfunction of the left ventricle and valvular disease.

Group 3 pulmonary arterial hypertension is owing to lung diseases and/or hypoxia. This include COPD and emphysema, interstitial lung diseases and other pulmonary diseases that are of a restrictive or obstructive nature, sleep-disordered breathing, chronic exposure to high altitudes as well as developmental abnormalities that result in hypoxemia.
Group 4 pulmonary hypertension involves valve disease such as chronic thromboembolic disease and Group 5 is a mixed bag of pulmonary arterial hypertension with unclear multifactorial mechanisms such as hemolytic disorders, systemic disorder, metabolic disorders and others.

At our UPMC Comprehensive Pulmonary Hypertension Program we see over 400 new patients per year. Of this almost half of these patients are related to left heart disease. In green we see those patients that have pulmonary hypertension associated with diastolic dysfunction. In yellow we see those patients associated with LV systolic dysfunction, orange, interstitial lung disease, red depicts idiopathic pulmonary hypertension and blue depicts those patients with connective tissue diseases. From this you can see that at our referral Center as well as other, diastolic dysfunction and systolic dysfunction make up the majority of patients that we see.

Pulmonary arterial hypertension is a deadly disease regardless of the cause. This slide shows the mortality curves for patients with congenital heart disease, portopulmonary disease, idiopathic PAH, connective tissue disease and HIV. On the Y axis is percent survival and on the X axis are years from diagnosis. As you can see from this slide, looking at the blue line we see that after 5 years approximately half of patients diagnosed with idiopathic PAH, even in the modern era of treatment, will succumb to the disease.
Those patients with connective tissue diseases depicted in the orange have a much worse prognosis. More than 60% of those patients are passing within the first three years of diagnosis and those with the worse prognosis are those who have HIV associated pulmonary arterial hypertension.

Although there are a number of different diseases that lead to pulmonary arterial hypertension the end for most of these patients is the same and that being hemodynamic collapse. This slide depicts the hemodynamics in patients over time. These hemodynamics are taken at the time of right heart catheterization and we see CO which represents cardiac output in the presymptomatic or compensated phase. We see the cardiac output remains preserved as pulmonary arterial hypertension and pulmonary vascular resistance continued to rise during this presymptomatic compensating phase.

Generally speaking we see very few patients during this phase of the disease. Many of these patients are asymptomatic and it’s not really until they have symptoms that they are seeing their primary care physician, their cardiologist or their pulmonologist complaining of dyspnea on exertion. In the symptomatic or decompensating phase we see the pulmonary artery pressure continues to rise above a symptom threshold. Cardiac output generally will stay the same early but most importantly these patients complain of dyspnea with exertion. When they’re sitting at rest they oftentimes do not have much in the way of symptoms. It’s only when they go upstairs or uphill they really complain of shortness of breath.
As this disease progresses through the symptomatic and decompensating stages we move into what we call symptom classifications 2 to 3 to 4. Class 3 symptoms are those patients who have significant dyspnea with minimal exertion such as doing their activities of daily living. It’s not until patients are really in the declining or decompensated phases that they start having significant symptoms at rest.

On the far right we see that once you pass the symptom threshold particularly at rest cardiac output now begins to drop. We believe the cardiac output drops initially on exertion but then we start seeing that even on resting hemodynamics the cardiac output can be lower. These are patients who are very symptomatic and these are patients who are actually at very high risk. Our goal with current management and diagnosis is to catch these patients if not in the presymptomatic and compensating phases, at least in the very early stages of their disease process. We feel that treating this disease earlier will portent better for patients long term.

This slide shows the mechanism of action of the various therapies for pulmonary arterial hypertension. We currently have 9 FDA approved therapies to treat the condition. Some of which are oral, some of which are parenteral such as inhaled, subcutaneous and intravenous formulations. I’m not going to get into the significant or the differences between the therapies themselves during this discussion. But I wanted to just touch on briefly the various pathways are manipulated in the treatment of the disease.
On the far left you have endothelin pathway, endothelin is a constrictor peptide that is produced by the vascular endothelium. It acts on two receptors endothelin A and endothelin B receptor to produce its effects. The primary receptor for vasoconstriction and remodeling of the pulmonary vasculature is the endothelin A receptor. We modulate this system using oral agents such as Bosentan and Ambrisentan both of which are FDA approved for this therapy or for this condition. Significant data suggests that this peptide is increased in patients with pulmonary arterial hypertension and modulating the release or the receptors for this peptide can have beneficial effects on the disease.

The next pathway in the middle is the nitric oxide pathway. Nitric Oxide is a gas, it’s produced by the endothelium, it acts on the vascular smooth muscle as well as in the cardiac myocyte to increase cGMP. Cyclic GMP then has beneficial effects of vasal relaxation as well as anti-remodeling effect decreasing fibrosis and decreasing heart failure.

Prior to the development of agents like sildenafil or tadalafil we tried to manipulate this pathway from a supply side system, we would give patients more L-arginine or we give them nitroglycerine or nitroprusside but we quickly found that does not seem to have very good long term benefit. Instead by inhibiting the breakdown of cGMP we seem to have a profound effect in a long term manner. Agents such as sildenafil and tadalafil inhibit phosphodiesterase type 5 enzyme which is responsible for breading the cGMP protein. These agents again have been FDA approved for the treatment of pulmonary arterial hypertension.
On the far right we have the prostacyclin pathway. Prostacyclin is an arachidonic acid derivative it is released by the vascular endothelium, it acts on the vascular smooth muscle as well as in the cardiac myocyte to produce cAMP. This arachidonic acid derivative has anti-remodeling effects as well as vasorelaxation effects and more recent data suggests that it also improves right ventricular function in our animal models of disease.

Interestingly enough although all three of these pathways have been exploited in an attempt to vasodilate the pulmonary circuit, more recent data suggests that all three of these pathways are involved in right ventricular function, in maintaining of right ventricular function and exhibiting or promoting these pathways can have varied effects on the right ventricle.

Currently in 2011 I believe that we’re thinking differently about the disease of pulmonary hypertension. Pulmonary hypertension is not just a disease of an elevated blood pressure and elevated pulmonary resistance. These patients don’t die from the high blood pressure in their lungs. I have many patients who live for a very long period of time even though they still have high lung blood pressure. The patients actually die when they're right ventricle is unable to compensate for these pulmonary pressures. This observation has led to a brand new focus on right ventricular function and more importantly how the right ventricle interacts with the pulmonary vasculature. This has been the subject of a recent RFA from the NIH to fund such studies.
We at UPMC have taken a novel approach to how we diagnose and treat this disease state. By combining our clinics and having our clinics be formed by both cardiology and pulmonologists we have the ability to have patients come in and see both the cardiologist and a pulmonologist at the same time. For many years I’ve heard patients say you know my pulmonologist says this is a heart problem, my heart specialist says this is a lung problem, I’m still short of breath and I’m confused. Our new clinic design really helps alleviate that frustration both on the patient’s part as well as on the referring physician’s part in that we can give patients a coordinated set of recommendations and followup patients together.

When we think about how we currently assess the right ventricle it’s been in its infancy for many, many years. Here we see in imaging both noninvasive as well as on the right hemodynamic assessment. And at the top we see traditional measures. So traditionally we’ve measured right ventricular function by more of a looks pretty good to me sort of mentality. There are indirect ways that we have assessed right ventricular function looking at just the right ventricular size, the eccentricity index, the _____ function and that type of thing. However there are some nontraditional methods that we have promoted both in our laboratory here at UPMC as well as with collaborating sites, things such as impedance cardiography, things such as implantable monitors as well as load independent RV function parameters. I’m going to show some of these in the next few slides.
From another standpoint hemodynamics have also been a very significant focus of research here and elsewhere. Traditionally we’ve only measured basic measures, right atrial pressure, mean pulmonary artery pressure, wedge pressure and cardiac index. While we do know that the predictors of morbidity and mortality in these patients primary rest in the hemodynamic parameters such as right atrial pressure, mean pulmonary artery pressure and cardiac index there are a wealth of other newer technologies that are available that we believe will be important in being able to differentiate patients both from a prognostic standpoint as well as being able to assess the response to treatment. Those include things such as augmentation index, stroke volume to pulse pressure, also known as compliance, impedance spectra and pressure volume loop analysis, both directly taken as well as indirectly taken. I’m going to show some of those data in just a second.

Here we see kind of the traditional views of the top two panels, traditional ways of assessing the right ventricle by echocardiography. Echo is nice because it’s readily available at almost every site, we have it in most cardiology offices as well as other imaging centers and it gives us a nice way of being able to visualize the right ventricle. At the top we see traditional 2-D imaging where we see at the top labeled right ventricle compared to left ventricle, in this case this is a patient with severe pulmonary arterial hypertension. We see that the right ventricle is significantly enlarged and it’s even pushing in on the left ventricle. In the middle panel we have continuous wave Doppler. This has been the primary focus of many people with regard to trying to screen patients for pulmonary hypertension. By using Doppler of the tricuspid valve we can estimate the pulmonary artery pressure using a modified Bernoulli equation. On most traditional echo reports it’s only remarked if the
pressure is high. Now we believe though that we have the ability to do more intensive assessment of right ventricular function with traditional echo parameters. On the bottom we see pulse rate Doppler assessment of pulmonary valve flow and pulmonic valve flow, on the left lower panel we see a patient that has severe pulmonary arterial hypertension who has a very low, or I’m sorry, has a very decreased pulmonary artery acceleration time of 70 milliseconds. Compare that then to the lower right panel in a patient who has no pulmonary arterial hypertension, this patient has a pulmonary artery acceleration time of 170 milliseconds, suggesting that they have an appropriate amount of flow in the pulmonary artery. Similar data to these were recently published by Dr. Paul Forfia, a colleague of ours at the University of Pennsylvania and really helped characterize a novel approach with relatively little in the way of need for additional training to assess pulmonary artery hemodynamics.

Moving on to another study spearheaded by Dr. Paul Forfia when he was a fellow in our laboratory at Johns Hopkins we published in 2006 data related to something called TAPSE, TAPSE stands for Tricuspid Annular Plane Systolic Excursion. This was published in the Blue Journal in 2006 and what we did, although we didn’t invent TAPSE, we utilized the measurement of TAPSE to assess right ventricular systolic function. Here you see in the upper panel M mode echocardiography through the tricuspid annulus, and you see the excursion of that during systole. On the left upper panel we see a patient who has a tricuspid annular systolic plane excursion of 2.3 centimeters, which is normal, and on the right we see someone with severe pulmonary hypertension and a much worse TAPSE at 1.5 centimeters. When we assessed this in a number of different patients we were able to then construct mortality curves, which you see on the bottom, for patients who have a low TAPSE,
and a dotted line showing that survival of those patients with a TAPSE of less than 1.8 centimeters of being approximately 60% at 24 months compared to those patients who had a TAPSE of greater than 1.8. Once again this is a novel measure to assess right ventricular systolic function, it can be done anywhere. It can be done through M mode through the tricuspid annulus, but it can also be done with a good trained eye, it can be done with a 4 chambered view of the tricuspid annulus as well.

Moving on to more novel ways of assessing right ventricular function, here we have cardiac MRI, this is the same patient looking through a number of different views, looking at the right ventricular function as well as left ventricular function. It gives us novel measurement, or it gives us good measurement of blood flow through the lungs as well as in the heart. It allows us to assess for congenital abnormalities. It also using weighted T2 imaging it allows us to assess for potential for fibrosis in the hearts of these patients. In the lower right we see a still shot of the left ventricle on the right and the right ventricle on the left. This is another view comparing the prior image to this image, this is a patient with severe pulmonary hypertension and you can see just how large the right ventricle and the right atrium are when compared to the left ventricle.

Moving on to hemodynamics, because next to echocardiography right heart catheterization and hemodynamics is probably the most available thing to most centers with regard to assessing patients and diagnosing pulmonary arterial hypertension. Right heart catheterization in the current state generally are considered by some only for the confirmation of pulmonary arterial hypertension, once
they get the pressures that’s all they, that’s all they really want to examine. Many only consider the mean PA pressure and the pulmonary capillary wedge pressure, most of these are done at rest and remember that I had discussed earlier that a lot of our patients with pulmonary hypertension, especially in the compensated phases are not short of breath at rest, it’s not until they get out and start walking up stairs or walking up hills or walking down the hall that they have much in the way of dyspnea symptoms. Often times the right heart catheterization is not used to track treatment success, to be confused certainly with borderline value. Mean pulmonary artery pressure and wedge pressure can be read differently from group to group, this is an initiative that we have spearheaded with the Pulmonary Vascular Research Institute to try to bring everyone up to speed in terms of how to appropriately interpret hemodynamics. And the resting right heart cath might not help differentiate patients who have diastolic dysfunction between those who have pulmonary arterial hypertension. I’m going to show where I believe exercise and/or fluid challenge may be beneficial in the diagnosis of these patients.

Going back to my previous statement regarding survival in patients with pulmonary hypertension we know that the survival in the NIH Registry of pulmonary arterial hypertension is really dependent on hemodynamics. Where the NIH Registry found that if the mean pulmonary artery pressure was less than 50, the mean right atrial pressure was less than 10 and the cardiac index was greater than 4 liters per minute per liter squared those patients had a much better survival than those patients who had a very high mean pulmonary artery pressure, a high pulmonary – I’m sorry, a high right atrial pressure or a low cardiac index. What you’ll take away from this slide however is that if your mean PA
pressure is between 55 and 85, your mean right atrial pressure is between 10 and 20 or your cardiac index is between 2 and 4 you are kind of left wondering well where does my patient fit? I can tell you that about 90% of our patients fit into that gray zone. And these data are helpful to really kind of define the extreme, but really what we are trying to do is be able to give each patient a good prognosis, an accurate prognosis and an accurate assessment of their likely response to treatment. That is where the personalized care comes in.

Before we can actually get to our personalized medicine though we have to discuss some of our newer techniques that we have available to assess the patients from a prognostic standpoint, the future of cardiopulmonary hemodynamics really in my mind rests in the getting more from the right heart catheterization perspective. Importantly as well I believe is confrontational testing such as exercising patients while you are looking at their hemodynamics, giving a fluid challenge or combining right heart catheterization to the imaging parameters in order to come up with new and novel ways of assessing someone’s prognosis.

This slide shows a patient of mine who has significant pulmonary hypertension with an RV systolic pressure in the 60 to 70 range, and I’ve always wondered why we can’t get more out of tracings like this. This tracing contains a lot of information aside from just the systolic blood pressure and the diastolic blood pressure, this tracing contains a couple of different measurements of systolic function, things like DP DT max, things like diastolic function such as tau or DP DT min. These are parameters that can be derived from these tracings if you put them through the proper algorithm.
When I came to the University of Pittsburgh one of the things that I did was I enlisted the help of an engineer, Tim Bachman, to write a program in which we can take tracings either from a snapshot such as this or from a direct acquisition of cap tracings and digitize those. This slide shows a PA tracing with a lot of catheter work, for those of you who do right heart catheterizations, and I selected this slide because if there was going to be an area where we would find a weakness in our digitizing algorithm it would be in a case such as this. What we do is we import this figure into our MATLAB program, we define the minima, the maxima, the inflection points such as this and once we do this we can then in this manner convert this to a digitized value from MATLAB in which every pixel is given a time as well as a pressure. And this simply shows the example from our patient now in the right bar or the white figure in the middle we see the MATLAB output for that, which matches what we have in the cath tracing, and then we are able to then convert that data to pressure and time. Once we do this, we then import it into our other MATLAB program in which we can get a full characterization of systolic function, diastolic function in a time or pressure domain analysis.

With that in mind we went through and compared in 9 patients, now we have upwards of 30 patients that we compared, but we compare traditional invasive measures, such as Millar micromanometry on the upper left, the leftmost dot with a direct measurement of this one Gans catheter and then with the digitized tracing that we put through our MATLAB program, and what you can see here is that for a variety of right ventricular systolic pressures in the lower bars and lines and for a heart rate range we see that there is good correlation between our digitized tracing values and what we would get from
our micromanometry catheterization techniques. This opens up a huge window of opportunity in which large clinical trials and data from large clinical trials, data from a lot of different centers can then be pulled together, analyzed in a core facility, measure RV systolic function without an expensive capital investment from other groups or other sites, allows us to get contractility data from basic studies and now we are currently validating these methods with archive pressure tracings.

Moving on to the right heart catheterization itself, one of my biggest problems with right heart catheterizations as I mentioned before is the fact that most of them are done at rest. If I have a patient that’s telling me that they don’t – that they are not short of breath at rest but they are short of breath when they exert themselves minimally I’m much more interested in what’s going on with their blood pressure when they are exerting themselves. And as I mentioned before often times disease such as heart failure or diastolic dysfunction can be missed without these types of confrontational studies. In our 2009 circulation paper we outlined the need for this, we also discussed the fact that in patient examples here in the white, on the right side of the bar, right side of the figure you see exercise tracings in which a patient under resting conditions did not meet criteria for pulmonary arterial hypertension. However, with minimal exercise and increasing the heart rate to 100 beats per minute we see now that not only did their PA tracing and their PA mean increase significantly in the upper right panel, but we also saw the wedge pressure increase significantly, thereby making a diagnosis of diastolic dysfunction. This would have been completely missed had only resting pressures been made, resting measurements been made. This patient may very well have been sent home had we not done - without any therapy had we not done the exercise portion of the test.
On the lower we see a similar effect with a patient given a fluid challenge, in which we give ½ a liter to a liter of saline during the catheterization and then measure the response to that fluid challenge both in lung pressure as well as in pulmonary capillary wedge pressure. Dr. David Ishizawar here at our UPMC PH Program has amassed now over 100 patients in whom he has exercised and has been able to really define patients with normal patients here we see in the upper right hand panel, a normal patient with significant exercise and by Stage 1 through Stage 4 we move through an exercise protocol moving from 25 watts per minute all the way to 100 watts per minute, which is a significant amount of exercise. A normal patient should not increase their mean PA pressure or their wedge pressure significantly. However we take a patient who has pulmonary arterial hypertension in the upper right panel, we see the PA mean pressure will increase significantly with exertion and the wedge pressure should stay about the same. This is in contrast to patients who have diastolic dysfunction. In the lower left panel we see patients who have diastolic dysfunction, they increase their mean PA pressure with exercise but they also significantly increase their wedge pressure with exercise. This tends to come down with – when the exercise is stopped. And then in the lower right panel we see a very common condition which is diastolic heart failure associated with PH. Some people call this out of proportion pulmonary arterial hypertension but suffice to say these are patients who not only increase their wedge pressure with exercise but they also increase their mean PA pressure suggesting that likely because of prolonged diastolic dysfunction and increased pulmonary capillary wedge pressure their pulmonary arterial system has remodeled to the point that has been become significantly stiffened.
Moving again toward more novel measures and personalized diagnostics here we have human pressure volume loop analysis. This is a incredible way of fully assessing right ventricular function in patients with pulmonary vascular disease. This is done through a catheterization technique, it involves micromanometry and conductive electrodes and from this catheter we are able to produce the slide that you see to the right which are pressure volume loops in which we have simultaneous measurements of pressure and volume. Here on the left side of the left hand side of the loops we see a patient who has borderline pulmonary hypertension, they have a preserved stroke volume and normal contractility. If we compare that then to the patient on the right we see that the stroke volume here is significantly reduced, the top line, the green line is shifted down and to the right, suggesting reduced contractility and the right ventricular volume is significantly higher than the patient on the left.

We explain these pressure volume loop relationships in this slide. This slide shows as we move through diastolic filling you now have isovolumic contraction in which there is no change in volume but pressure increases. When the pressure increases enough that it forces open the pulmonary valve we then have ejection into the pulmonary vasculature and then once the system has completed ejection you now close the valve and isovolumic relaxation occurs. Once you get diastolic filling you’ve completed the loop. The two points on this figure though that I want to point out are the Ees, which stands for End Systolic Elastance or for a more simplistic definition, RV contractility, and an Ea, which is Effective Arterial Elastance, which is the slope of the line between End Systolic
pressure and volume and diastolic pressure and volume. And the Ea itself is the true afterload on the system. In just a second I’m going to show you how we use RV contractility and afterload in a way to predict morbidity and mortality in this patient population like it’s never been predicted before. I’ve always wondered why we can’t get calculated pressure volume loops, and the answer is we can by using imaging modalities such as echocardiography, CT or MRI we can get the end diastolic volume as well as the end systolic volume. From a right heart catheterization performed on the same day we can then get the end systolic pressure and end diastolic pressure. By having these values we have what we need to complete an Ees and Ea calculation.

This slide shows the data from our – or shows a patient from whom we’ve performed or in whom we’ve performed a gated CT scan. This is a novel way of approaching the traditional CT scan with contrast in which we turn the patient a little bit and we gate it for the ECG signal. By using this CT modality, just like you would use MRI we are able to then calculate our end diastolic and end systolic volumes. On the right of this panel we see a 3-D reconstruction of the right ventricle and the pulmonary artery system. Another way that we are able to get very nice measurements are of pulmonary artery – I’m sorry of right ventricular function is using something called speckle tracking. This speckle tracking is a novel technique developed and really pioneered in the right ventricle by our colleague Mark Simon here in the Heart and Vascular Institute.

On the right – I’m sorry on the left we see a patient with normal ventricular function and what you see with the red crosshatch mark really is your TAPSE as we mentioned before, and you can see how
much the TAPSE there is moving, how vigorous it is. On the left – I’m sorry, on the right we see a patient with severe RV failure. What you can see here is how large the right ventricle is and how the TAPSE is much lower than what we see on the patient on the left. By using these novel ways of assessing right ventricular function we are also able to calculate our end diastole and end systolic volumes in a reliable manner.

This slide shows our comparison of comparison right ventricular and diastolic area by echo on the Y axis with our patient who had their volume calculated by multigated CT scan. And we see that we have a very good correlation between the two. My hope is that eventually we’ll be able to export this technology to everyone so that if you have a reasonable echo in a 4 chamber view as well as a reasonable right heart catheterization then making measurements like this will be doable.

Going back to that Ees/Ea ratio that we discussed this is a forest plot of our cohort of patients with pulmonary hypertension and what we see from this, although it is a busy slide, on the far left hand side we see traditional measures that have been linked with morbidity and mortality in this patient population, baseline 6 minute walk, mean right atrial pressure, cardiac index. But on the right I would like to point out two main features. One, the third bar from the right is Ea or effective arterial elastance or afterload. And what we see there is that having a higher afterload is predictive of morbidity and mortality in this patient population. Granted it does have a wide variance. The second from the right bar is Ees, this is RV contractility. We also see that there is a high correlation between a low Ees and morbidity and mortality. Granted there is a very wide variance among the groups but
if we take for each individual patient and compare the Ees to Ea ratio what we now see is an incredible predictor for morbidity and mortality and this is reflected in the far right figure.

When we take this patient population and subject them to Kaplan Meier analysis, meaning looking at event free survival or of transplant we see that the patients who have a low Ees to Ea ratio, shown in green, I’m sorry a high Ees to Ea ratio greater than .56 shown in green those patients had a very good survival over the course of the next 5 years. However in the patient population who had a reduced Ees to Ea ratio from that initial analysis we see that more than half of those patients were dead within the first year of the study, and the mortality continued to, to worsen such that as a 5 year time point more than 80% of those patients were gone. Now an appropriate question would be Hunter, this probably only reflects cardiac index, what about the patients in whom we don’t, we are really unsure?

We did a further analysis and here we see on the right in patients who have a cardiac index of greater than 2, which tends to be a patient population in whom we are quite concerned, for whom we are quite concerned but often times that are left a little bit in that gray area. We see that those data still hold true. In blue, if the patients had a low Ees to Ea ratio more than half of them were gone within the first year suggesting this may very well be a very profound indicator of morbidity and mortality. My hope is that with further study that we can use this Ees to Ea ratio as a predictor for patients moving on to lung transplant, heart/lung transplant or other advanced support for their disease.
This slide simply shows the ROC curve that we developed for the Ees to Ea ratio. In green we see the traditional measure of mean PA pressure, in red is the right atrial pressure ROC curve, in purple cardiac index and you see that the blue is the Ees to Ea ratio. Suffice to say for those of us who don’t look at ROC curves all the time being up and to the left is better in terms of sensitivity and specificity of finding patients with RV failure. And here we see that this measure is even better than the traditional measures of cardiac index.

So from this, this really does allow us now to serve as a clinical trial hemodynamic core facility, it allows us to have measurements of right ventricular function without expensive capital investment at each site. We are currently validating these methods with our archive measurements as well as prospectively with each patient that comes through our catheterization lab, we are also validating these parameters with hemodynamic acquisition and now we are really determining the treatment response on Ees to Ea ratio.

One of the other features that we offer here at UPMC which is unique is the ability to routinely biopsy the right ventricle of patients with cardiopulmonary disease. In the top panels we have slides from my cohort of patients in which we’ve found significant fibrosis reflected in the green on the left, significant inflammation, other conditions that are potentially treatable such as Plaquenil cardiomyopathy, fibrotic disease, amyloidosis, particularly if it’s reactive amyloidosis in patients with conditions such as scleroderma. Recently we were funded by the NIH to participate in a program called Mapgen and Mapgen is a fantastic program which will really allow us to analyze
these right ventricular samples from a transcriptional analysis standpoint. We’ll be able to compare this transcriptional analysis of the right ventricle with pulmonary artery and whole lung samples and also compare those results with patients who have peripheral blood mononuclear cell transcription analysis. The goal here is to be able to predict what is going on in the right ventricle and in the lung by just using peripheral blood acquisition of transcriptional data. We want to be able to prognose, give a good prognosis of event free survival and we also want to be able to assess treatment response. My goal would be that in the future we don’t have to do biopsies of the heart, that by just taking peripheral blood we’d be able to say yes, you are a patient who would work better with this medication, you would have a better prognosis with this medication over another medication, or we’d be able to pickup and fine tune the ability prognose, give patients a meaningful prognosis of their disease and whether or not they would be heading toward a transplant sooner rather than later.

By using some in-depth analyses as part of Mapgen looking at micro RNA as well as other RNA analysis we want to be able to link the RV biopsies and peripheral samples to outcomes in our patient population, be able to take a genetic footprint if you will and link that then to what patients will respond well from a treatment standpoint and truly personalize the disease. Finally, although there have been a lot of bubbles in this window, I can tell you that traditionally our treatment decisions were only measured based on pulmonary hemodynamics. Now and in the future though we are moving toward being able to make our treatment decisions and our prognoses based on RV hemodynamics, along with pulmonary hemodynamics and then discuss genetic predisposition, peripheral blood mononuclear cell transcriptional profile and RV or lung tissue biopsy transcriptional
profile to be able to then appropriately treat patients. And in conclusion, our RV hemodynamics are the best predictors of morbidity and mortality in patients with pulmonary hypertension of any cause. We do believe that this is going to stimulate new studies of right ventricular function and pulmonary hypertension and also promote studies that combine and validate our noninvasive measures as well as personalize this to the patient by being able to say based on this hemodynamic footprint and based on this genetic footprint and transcriptional footprint we can give you a prognosis of X, Y or Z. And with that in conclusion I’d like to acknowledge my colleagues here at the University of Pittsburgh as well as colleagues at the University of Pennsylvania and Colorado as well as our funding from the NIH, the American Heart Association, the Institute for Transfusion Medicine as well as the Hemophilia Center of Western Pennsylvania. Thank you.