Extrarenal Manifestations of Polycystic Kidney Disease
Part Two of Three

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Left ventricular hypertrophy
Prognostic importance of left ventricular hypertrophy
Well, how does high blood pressure lead to cardiovascular death? One of the ways is that it causes left ventricular hypertrophy. When the heart has to pump against more resistance, which is what high blood pressure is, it develops more muscles; it becomes hypertrophy; it gets larger.

One might say, "Isn't that great?" Because when you are a weight lifter and you develop your muscles in your biceps, that's not so bad. Well, early it is okay with the heart. But when the muscles in the heart proliferate and the heart gets bigger, which is what left ventricular hypertrophy is, unfortunately the muscle development isn't accompanied by adequate blood vessels. So you have a part of the muscle that is relatively ischemic. If you want a worse prognostic sign for cardiovascular death, it's not cholesterol, it's not even smoking--it is left ventricular hypertrophy.

Left ventricular hypertrophy is associated with an increase in sudden death. Left ventricular hypertrophy is associated with increased heart failure. Left ventricular hypertrophy is associated with an increased irregular rhythms. So left ventricular hypertrophy is not something that a polycystic kidney patient or any patient would want to have.

Now the flip side of the story is that if you aggressively treat the blood pressure, over a period of time one can reverse this left ventricular hypertrophy and decrease the predilection to heart attacks, to arrhythmias or irregular heart rates, to heart failure, and that is what one wants to do in patients who have high blood pressure.

How well do we do in controlling blood pressure in patients with polycystic kidney disease? We said that of the patients who came into our study with polycystic kidney disease, only 28 percent had their blood pressure controlled below 140/90. We just presented an abstract at the American Society of Nephrology that in our group, because of education of patients and nurses and physicians, control of blood pressure has improved drastically, from about 28 percent to 65 percent. We need to be 100 percent. Arlene has already shown you the publication from our group that just came out that over a seven-year period one can keep the blood pressure down and reduce the left ventricular hypertrophy. That is an exciting and very optimistic observation.
LVH is common in PKD patients with hypertension

Here we see that if one actually looks at patients with high blood pressure, 50 percent of men have LVH. If you do an ultrasound of the heart, the heart is hypertrophied. The heart is bigger. The heart is predisposed to arrhythmias, heart failures, heart attacks. And even in females, it is coming close to 50 percent.

So this is something we can do now. We don't need molecular biology. We don't need gene therapy. We don't need to understand the topology of polycystin-1 and polycystin-2, though all of those questions are extremely important. What we can do now is alter the course of polycystic kidney disease by making the diagnosis of hypertension early, preventing or reversing the left ventricular hypertrophy, and improving the #1 cause of death, which is not kidney failure but cardiovascular death, in patients with polycystic kidney disease.
Arlene showed you this. Here is left ventricular hypertrophy. As the blood pressure goes up, the size of the heart, the hypertrophy to the heart, increases.

If one looks at those patients who have left ventricular hypertrophy, they are somewhat older, they weigh more, their blood pressures are higher and, of course, they have more hypertension. They have had hypertension for a longer period of time, and their serum creatinines are higher.
ADPKD patients with LVH have a more rapid fall in renal function
Again, as Arlene showed you, there is a correlation between left ventricular mass or left ventricular hypertrophy of the heart and the rate of fall in kidney function. So the larger the hearts--here is 161 grams/meter squared versus 81--and there is a much more rapid loss of kidney function. So there is an effect on the kidney function, and there is also an effect on the heart and the cardiovascular system.


This is the paper that Arlene referred to that just came out in the journal Nephrology, Dialysis, and Transplantation. This author (Dr. Ecder) is an International Society of Nephrology fellow. Here are Arlene and Godela (Brosnahan). Arlene, unfortunately is down at Emory now rather than Colorado, but we still have good relations.


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Rationale for studying effect of enalapril on LVH in ADPKD
Hypertension occurs commonly and early in the natural history of autosomal dominant PKD disease, affecting both renal and patient outcome, activates the renin-angiotensin-aldosterone system, and, through cyst formation and local renal ischemia, plays an important role in the development of ADPKD hypertension and left ventricular hypertrophy, and it is a known important risk factor for cardiovascular morbidity and mortality. In fact, as I said, it is really the most important predictor of cardiovascular morbidity and mortality.

In fact, I bet if one looked at polycystic kidney patients who have high blood pressure and asked, "How many have LVH?" it would be a small percentage who have ever had their heart size measured with cardiac ultrasound.

Purpose of the study
So we investigated whether this inhibitor of the renin-angiotensin system, enalapril, would affect LVH. We decided not to follow them for just one year but follow them for seven years, as this is a chronic disease.
These patients had their creatinine clearances greater than 50 ml/min, which is not normal but certainly very adequate for a long life. They had left ventricular hypertrophy. We looked at the first patients who finished seven years of the study.

Enalapril study results: effect on blood pressure
One can see here that the arterial pressure went down and stayed down. So blood pressure can be well controlled. A mean arterial pressure of 92 mm Hg is 125/75 mm Hg. We have another hypothesis that needs to be proven, needs to be tested. That is that 140/90 isn't good enough if the kidney is damaged as it is with polycystic kidney disease. Maybe 125/75 is better. We don't know the answer to that question.

We also don't know whether or not any other high blood pressure medicine may work -- perhaps you don't need to block the angiotensin system. Maybe diuretics, which actually stimulate the angiotensin system, are just as good in controlling blood pressure, reversing left ventricular hypertrophy, slowing the progression of kidney failure, and preventing the cardiovascular morbidity and mortality. These are very important clinical questions to be asked, very important clinical questions to be tested.

Enalapril study results: effect on LV mass
So that is the blood pressure, and here is the left ventricular mass, the left ventricular hypertrophy. You can see there was a decrease from 146 grams/meter square to 98 at Year #7. This is where you want to be if you have high blood pressure.

Enalapril study results: effect on kidney function
The kidney function fell, so it is not a total solution. But the rate of fall was at least half the rate that has normally been seen in other studies. So if one has a patient with hypertension and left ventricular hypertrophy which isn't treated, you are going to have end-stage renal disease at about 45 years of age if you're a man. If you aggressively treat it, reverse the left ventricular hypertrophy, not only do you decrease the cardiovascular morbidity and mortality, but one would project end-stage renal disease no earlier than age 70--no earlier than age 70. So we are talking about a very important extra renal as well as renal manifestation of polycystic kidney disease.

Summary

- **After one year of enalapril therapy, there was a significant decrease in MAP which remained stable until the end of the study at seven years.**
- **LVMII decreased significantly after Year 1 and continued to decrease until the end of the study.**
- **Although Ccr remained stable after year 1, a significant decrease was observed after 7 years of follow-up.**

Enalapril study results: summary
In summary, after one year of enalapril, there was a significant decrease in mean arterial pressure which remained stable until the end of seven years. Left ventricular mass index or cardiac hypertrophy decreased significantly after one year and continues to decrease until the end of the study.
Although creatinine clearance remained relatively stable at year one, a significant decrease was observed at seven years, but it was only a little over 3 mls per minute per year. So if you start out at a creatinine clearance of 70 or 80 ml/min, you can do fine until you are down to about 10 ml/minute. You can calculate a 3 ml/minute per year loss is going to take many years before you need dialysis and transplantation. So blood pressure control is not the total answer, but it is a very important factor that needs to be tested clinically.

Proposed 4-arm study of renal protection in ADPKD

We plan to do that study at the University of Colorado, at least if we receive funding from the National Institutes of Health for a PKD study. We are going to have four groups of patients with about 100 patients in each group.

**Group A - triple therapy group: low BP (125/75 mm Hg), ACEi, K Citrate**

Group A... and we use three interventions because in many ways polycystic kidney disease is like a tumor. The cells are proliferating faster than they normally do. And we know in tumors and cancers that one intervention isn't enough, that multiple interventions are better than single interventions. So we proposed that the optimal treatment with three interventions could be proven to be effective. It is not to use 140/90 but to use 125/75, and that the initial high blood pressure medicine to be used would block the renin-angiotensin system with the so-called ACE inhibitors.

**Rationale for use of potassium citrate**

Based on the Tanner results from Indiana University (and I know Dr. Tanner and his wife are here) we plan to use potassium citrate. Why would you use potassium citrate? We know about 20 percent of patients with polycystic kidney disease get kidney stones that cause pain and infection, and we know that many of them have a low citrate concentration in the urine. If you elevate the citrate, you complex the calcium so that it doesn't cause stones. So one could give that therapy just based on kidney stones. But what the Tanner group has shown in animal models is totally independent of the effect of potassium citrate on kidney stones. These animals that normally have a rapid progression of loss of kidney function stabilized with potassium citrate. This has never been tested in humans. So this tripartite approach is Group A.

**Other groups will test if a BP of 140/90 is adequate, or if a diuretic is as good as an**
ACE inhibitor
What would you like to compare them with? 140/90 versus a diuretic, which is a well-known medication for controlling blood pressure, but it stimulates the renin-angiotensin system. So on one hand you block the renin-angiotensin system, and on the other hand, you stimulate it. Then there is a placebo compared to potassium citrate.

Two other groups... because if the multifaceted approach is positive and for the first time one has slowed down if not totally prevented the progression of the cardiovascular and renal morbidity and mortality in polycystic kidney disease, one would like to take it one step further. Is it the blood pressure level? Is it the blockade of the renin-angiotensin system? Or is it the potassium citrate? By having these other two groups, we feel that we can answer those secondary questions.

Comparisons that could be made between four such groups
Let me go back and forth between these two slides: Group A versus Group B. This will compare the triple therapy.
What we mean by that is that all three categories are different—the blood pressure, the drug that is used to control the blood pressure, and the potassium citrate.

But if you want to know about the role of the angiotensin system, you would compare Group B versus Group D. Why is that?
Here are Groups B and D, both 140/90, diuretic versus ACE inhibitor. So that is different, but both of them have placebo. The only difference is the effect on the renin-angiotensin system, assessed by comparing Group B versus Group D.

What if you want to know about the optimal blood pressure with the other two parameters being the same? Compare Group C versus Group D.
Here are Groups C and D -- the blood pressures are different, but the other two parameters are the same.

What if you want to know about the role of potassium citrate independent of the other two factors? Compare Group A versus Group C.

Here is Group A, and here is C. Blood pressure is the same; ACE inhibitors, the same; but the potassium citrate is different.
So one can look at the overall, the triple therapy, and then by the other two groups, as I've shown you, one can test which one of these is having the biggest effect. It might be, for example, that if you get your blood pressure down to 125/75, it doesn't make any difference what drug you use and you don't need potassium citrate.