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Extrarenal Manifestations of Polycystic Kidney Disease Part One of Three



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Dr. Steinman:

Dr. Robert Schrier is Professor and Chairman of the Department of Medicine at the University of Colorado Health Sciences Center. Basically, Dr. Schrier is the father of this entire process and therefore, one of the individuals in the country who has helped move forward much of the research in patients with PKD... again, I say in patients with PKD, in addition to some of the basic research on the pathogenesis and the molecular biology of

polycystic kidney disease. As you all know, obviously, polycystic kidney disease is a systemic disorder. Dr. Schrier is going to address the issue of the extrarenal manifestations of polycystic kidney disease. Dr. Schrier.

Dr. Schrier

With respect to Dr. Steinman's opening comments about Adam and Eve, I am pleased to say that much of what I will present today has been in collaboration with five wonderful women scientists who have been at the University of Colorado over the years: You just heard Arlene Chapman; Aileen Sedman, who works in children's polycystic kidney disease and is now at the University of Michigan; Patricia Gabow, who you probably have heard speak at this conference; also Godela Fick Brosnahan, who is working with us now; and lastly, Pat Wilson, who has done a number of the basic studies. Those five women, academic scientists, have made major contributions to our understanding of polycystic kidney disease.

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Frequency of extrarenal manifestations of PKD	
Manifestation	Freq (%)
Hypertension (?)	78
Hepatic cysts	75
Diverticulosis coli	70
Cardiac valve disorders	25
Intracranial aneurysms	10
Ovarian cysts	40
Inguinal hernias	15

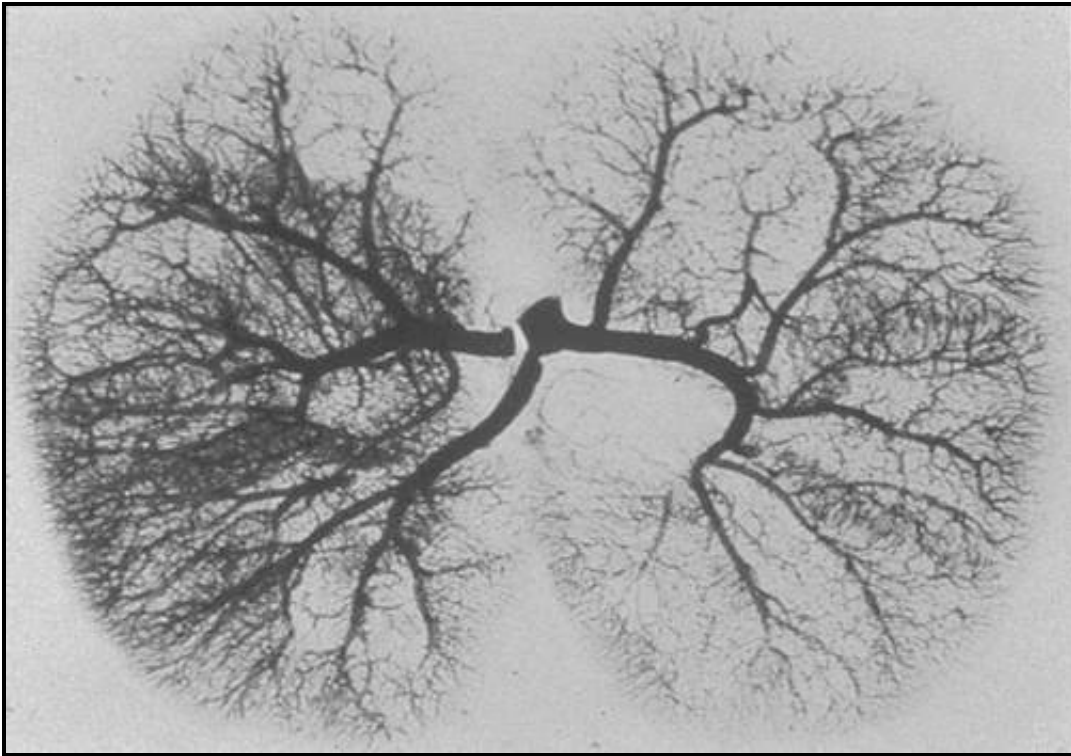
Extrarenal manifestations of PKD and their prevalence

I will talk about the extrarenal manifestations of PKD. There are a number of such manifestations, and they are shown on this slide.

- The question mark by hypertension is because probably the origin of high blood pressure is within the kidney, but the effects of high blood pressure are not only on the kidney but outside the kidney on the cardiovascular system. With dialysis and transplantation available, the number one cause of death in polycystic kidney patients is cardiovascular. One of the major risk factors for cardiovascular death, including heart attacks and strokes, is high blood pressure. I will use high blood pressure and hypertension interchangeably because they are the same.
- In addition to high blood pressure, we know that cysts develop in the liver as well as in the kidney. Hepatic cysts mean liver cysts.
- Also we know that there are outpouchings of the intestines. Those are called diverticula.
- We know that there are some abnormalities in the valves in the heart, the so-called cardiac valve prolapse disorder.

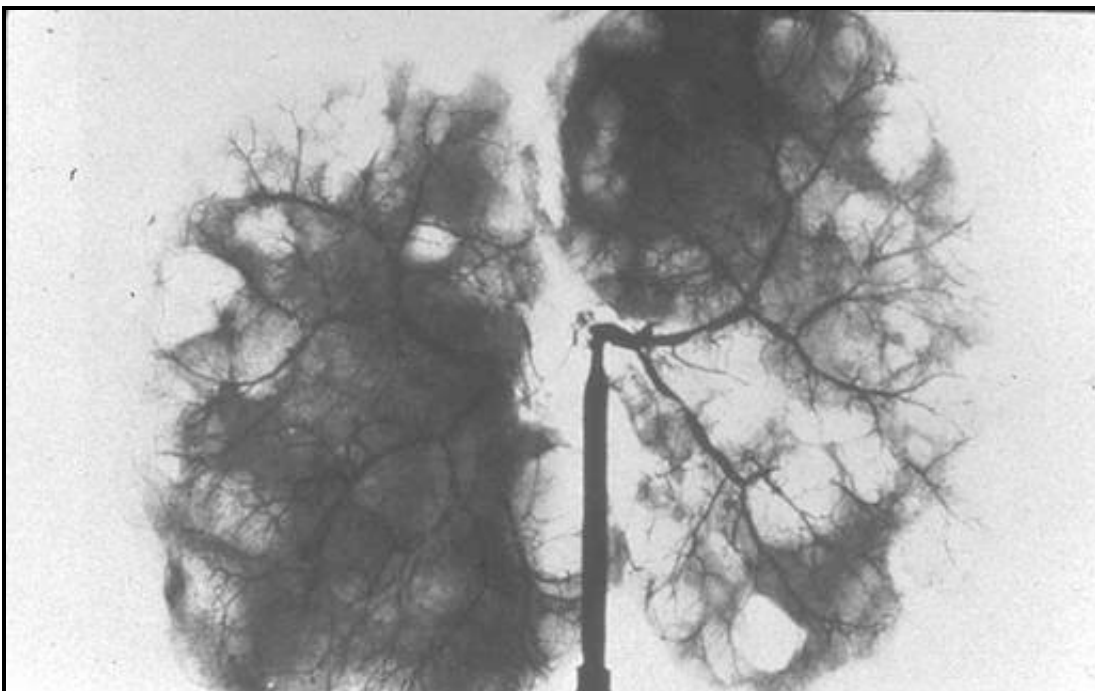
- We also know that there are little outpouchings of the blood vessels in the brain and that sometimes these outpouchings or aneurysms rupture and lead to fatality in patients with polycystic kidney disease.
- There are also cysts in the ovary, which generally do not have any consequences.
- There is further evidence of the systemic nature of polycystic kidney disease that in addition to outpouchings in the intestine, that is, diverticulosis, there is also an increased prevalence of hernias in patients with polycystic kidney disease.


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If one takes the kidney and injects a material that outlines the circulation of the kidney, that is, the blood vessels in the kidney, one will see this type of picture. This is the normal architecture of the blood vessels to the kidney.

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In contrast, if one injects that same substance to outline the blood vessels to a polycystic kidney, this is what one sees. You can see that there is a distortion of those blood vessels that are feeding the oxygen and the nutrients to the polycystic kidney disease.

There is an effect of cysts on erythropoietin and renin.

We know that the kidney is an organ that produces these hormones. When there is a decrease in blood flow or oxygen delivery to the kidney, the release of these hormones is stimulated. You have heard of erythropoietin, which is a hormone made in the kidney that stimulates the bone marrow to make red blood cells. Now there is recombinant erythropoietin so that patients with renal failure can be given the drug and increase their hematocrit.

Another hormone that is stimulated in the kidney, when there are portions of the kidney that are hypoxic (that is, receiving inadequate blood flow) is renin. This hormone acts on a protein that is made in the liver to produce a substance called angiotensin. Angiotensin is one of the most important hormones in the body. It constricts blood vessels. So if you have a heart that is pumping against constricted blood vessels, then the blood pressure goes up. It is like thinking about when you turn on a hose. If you put a clamp around the hose and then upstream you put a hole in the hose--the tighter the clamp, the higher the water would project out, the higher the pressure would be. That is what one sees when you have blood vessels that are constricted by angiotensin.

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Hypothesis

- **Bilateral cyst enlargement causes compression of adjacent parenchyma and stretch of arterioles lining cyst cavities, leading to intrarenal ischemia and activation of the renin-angiotensin system.**

Hypothesis: renin-angiotensin may be involved in the hypertension associated with PKD

It seemed possible that activation of this renin-angiotensin system was involved in the high blood pressure that afflicted patients with polycystic kidney disease. If that were the case, then one could be more specific in treating that high blood pressure because there are drugs that interfere with the generation or the action of angiotensin.

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How small blood vessels might be constricted by PKD cysts

Here you can see again these cysts throughout the kidney and how the small blood vessels could be constricted and thus be stimulated to release renin and to release erythropoietin.

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Hypertension in PKD

Frequency of hypertension *	79/135	59%
Age of onset (yrs)	30 ± 1	
Men	45/79	57%
Women	34/79	53%
Previously diagnosed	53/79	67%
Undergoing treatment	46/79	58%
Controlled with treatment	22/79	28%

*BP > 150/90, CrCl > 70 mL/min/1.73 M²

Frequency of hypertension in PKD

How frequent is high blood pressure in patients with polycystic kidney disease? These are patients with polycystic kidney disease. We have a large number at the University of Colorado. But these are patients who have normal kidney function. So if they went to their

doctor and they measured their serum creatinine, the doctor would say, "You have normal kidney function." So prior to deterioration of kidney function, blood pressure is elevated in 59 percent of patients who present with polycystic kidney disease.

Age of onset is early

Normally if you are among the 50 million Americans who have essential hypertension, that is hypertension that is not associated with kidney disease, it starts in the 40s. With polycystic kidney disease, the high blood pressure starts much earlier. The age of onset is 30 years of age.

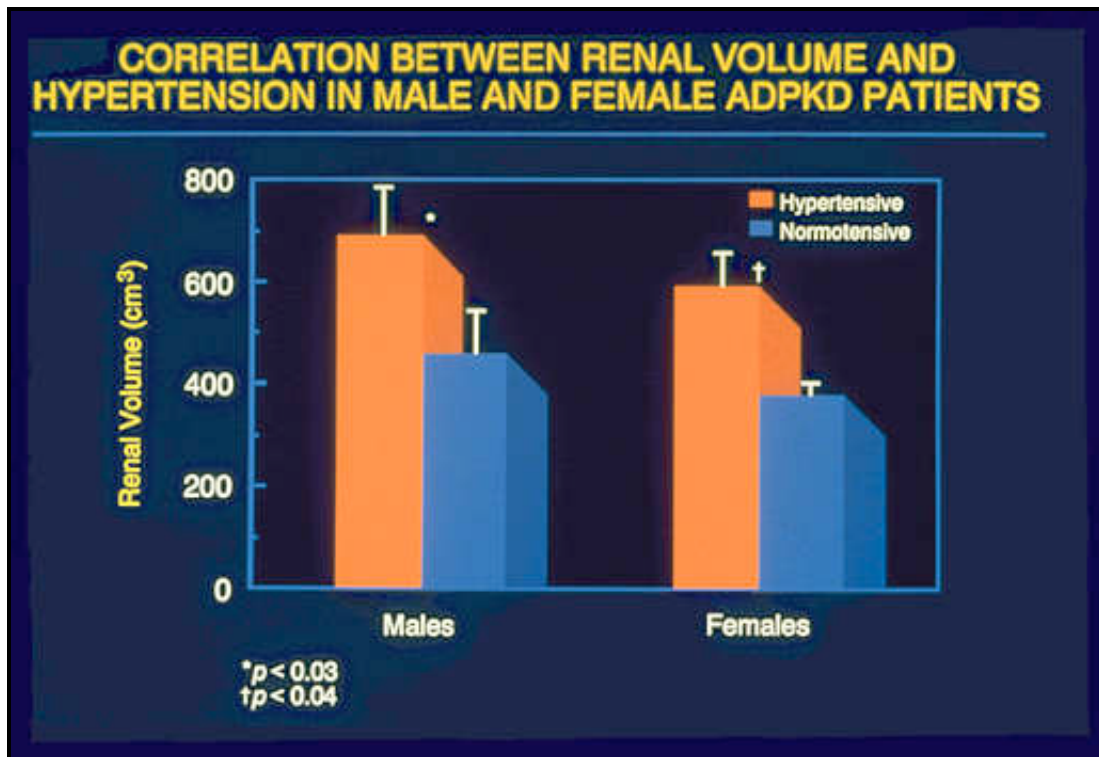
Hypertension in PKD is more common in males and is under-recognized and undertreated

It has a higher frequency in males than females. Only two-thirds were previously diagnosed. A little over a half were being treated. If one uses a very liberal goal for control of blood pressure, and that is to have it less than 150/90 mm Hg or 140/90 mm Hg preferably, look how many patients had their blood pressure controlled--28 percent of all of these patients with polycystic kidney disease had their blood pressure controlled below the accepted range of 140/90 mm Hg. So we have a long way to go with respect to educating patients and their physicians about the importance of control of blood pressure in polycystic kidney disease.

It is well established that high blood pressure predisposes to strokes. It is well established that high blood pressure predisposes to heart failure. It is well established that high blood pressure predisposes to atherosclerosis, and atherosclerosis predisposes to heart attacks.

So should we be more aggressive in picking up high blood pressure early in families where 50 percent of the offspring, because ADPKD is autosomal dominant, will have polycystic kidney disease, before there is any detectible evidence of a rise in serum creatinine? The answer is resoundingly yes. In fact, of all of those things that correlate with progression of kidney disease... you can't change whether you are male or female; you can't change whether you are Black or Caucasian; you can change the early detection and treatment of high blood pressure.

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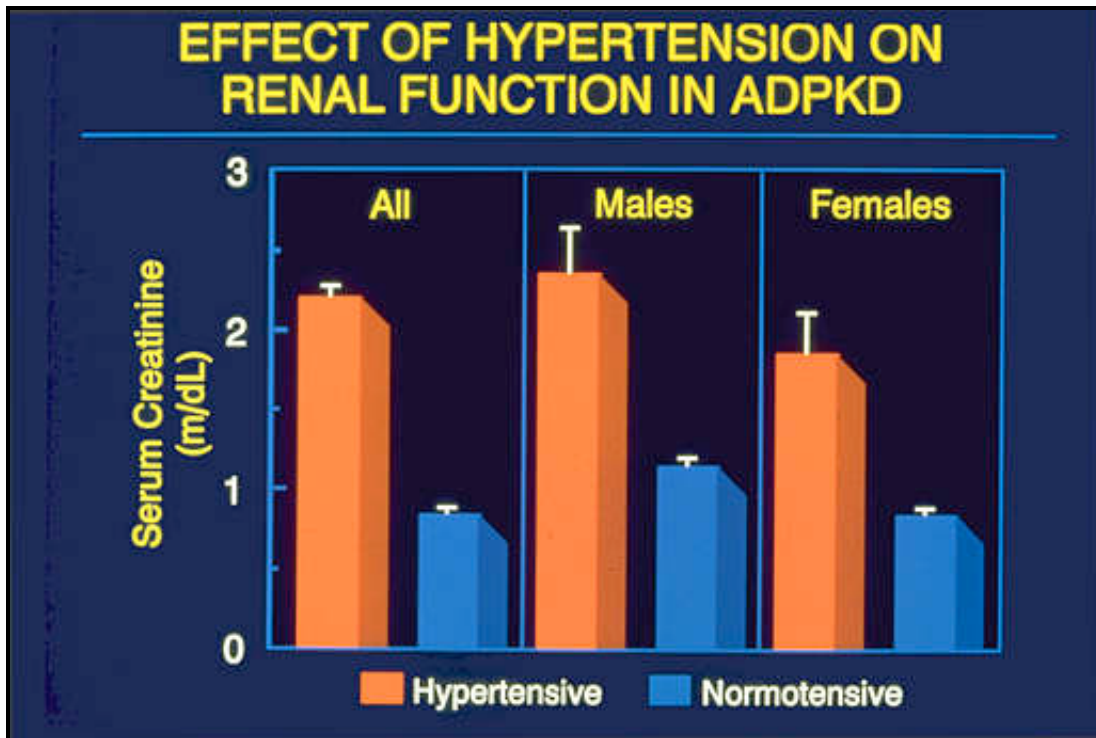
Source: Gabow PA et al, *Kidney Int* 1990 Dec;38(6):1177-80.

Effect of renal volume on blood pressure in PKD

If this intrarenal ischemia, ischemia meaning not enough blood flow getting to the tissues... if this intrarenal ischemia is what is causing high blood pressure, then shouldn't there be a relationship between the size of the kidney, the volume of the kidney, and blood pressure?

Here is a slide that confirms that proposal. Here you have renal volume, the size of the kidney, males on the left, females on the right. The blue bars are those patients with polycystic kidney disease who have blood pressures below 140/90 mm Hg. The orange bars are those patients who have blood pressures greater than 140/90 mm Hg. You can see that there is a significantly greater kidney volume in those patients who have high blood pressure. That would go along with this ischemia hypothesis: stimulating the renin-angiotensin system, causing high blood pressure in polycystic kidney patients.

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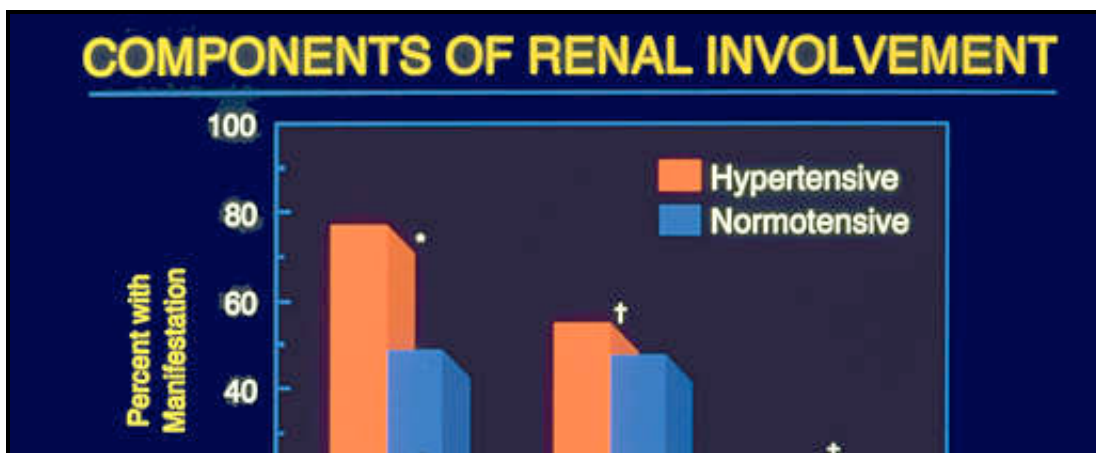


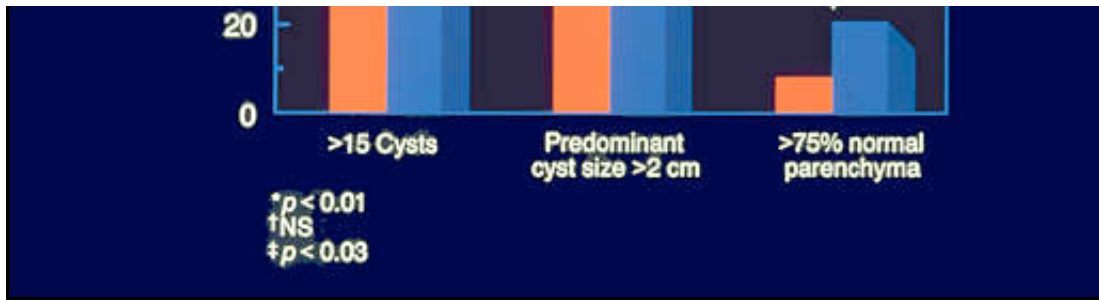
Source: Bell PE et al, *Kidney Int* 1988 Nov;34(5):683-90.

Hypertension in PKD is associated with impaired renal function

Again observational data. If you take a look at serum creatinine, which Dr. Chapman has said is the clinical index of kidney function-- the higher the serum creatinine, the worse the kidney function--and you can see that those hypertension patients, in orange... all patients, male patients, female patients... have higher serum creatinine that those patients with normal blood pressure.

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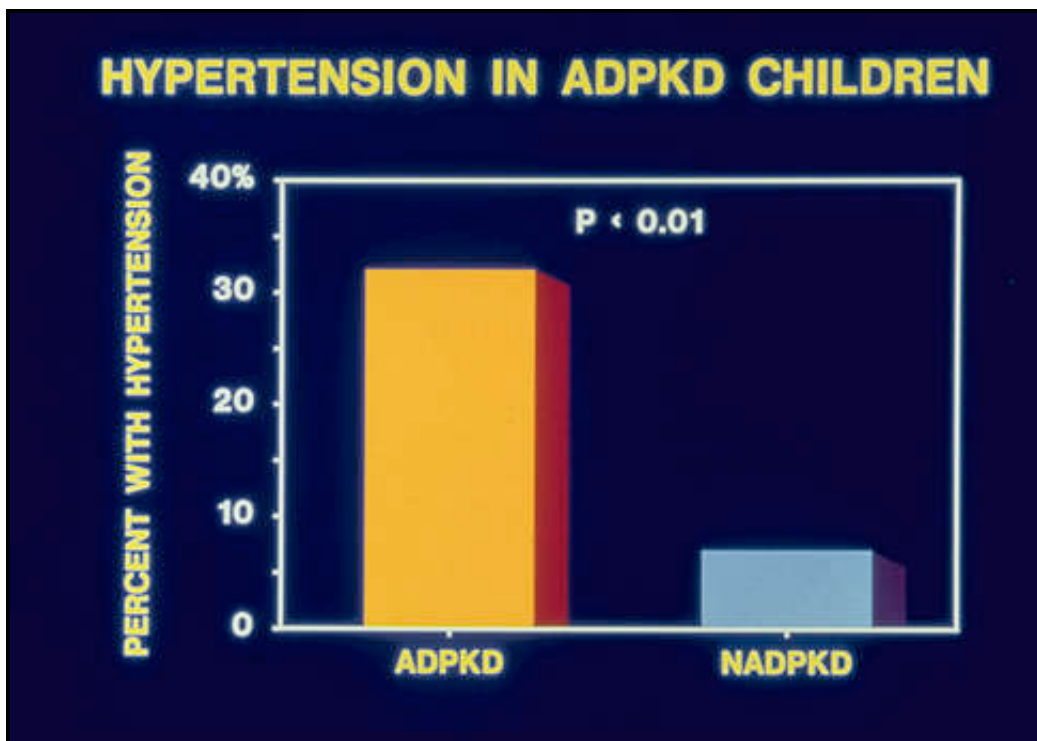


Source: Gabow PA et al, *Kidney Int* 1990 Dec;38(6):1177-80.

More cysts and bigger cysts in PKD patients with hypertension

If one looks further with imaging techniques, like ultrasound, one can extend this observation. The hypertensive patients are more likely to have greater than 15 cysts in their kidneys, and the size of the cysts are more likely to be greater than 2 cm. Those PKD patients who have normotension, are more likely to have 75 percent of their kidney tissue being normal--that is without cysts.

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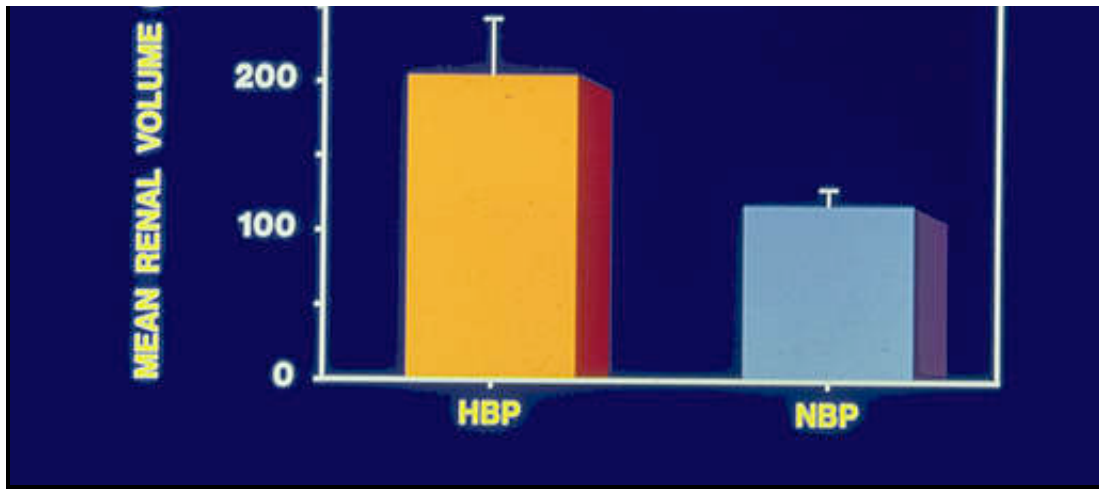
Source: Sedman A et al, *Kidney Int* 1987 Apr;31(4):1000-5.

In children of parents with PKD, those with PKD have hypertension

This is all correlative data. It doesn't prove it. But if one goes from the adult to the child, the story is the same. If one looks at those patients with PKD versus their siblings who do not have PKD, there is a much greater prevalence of hypertension, defined as two standard deviations above normal for the child of that age, than in a sibling who does not have high blood pressure.

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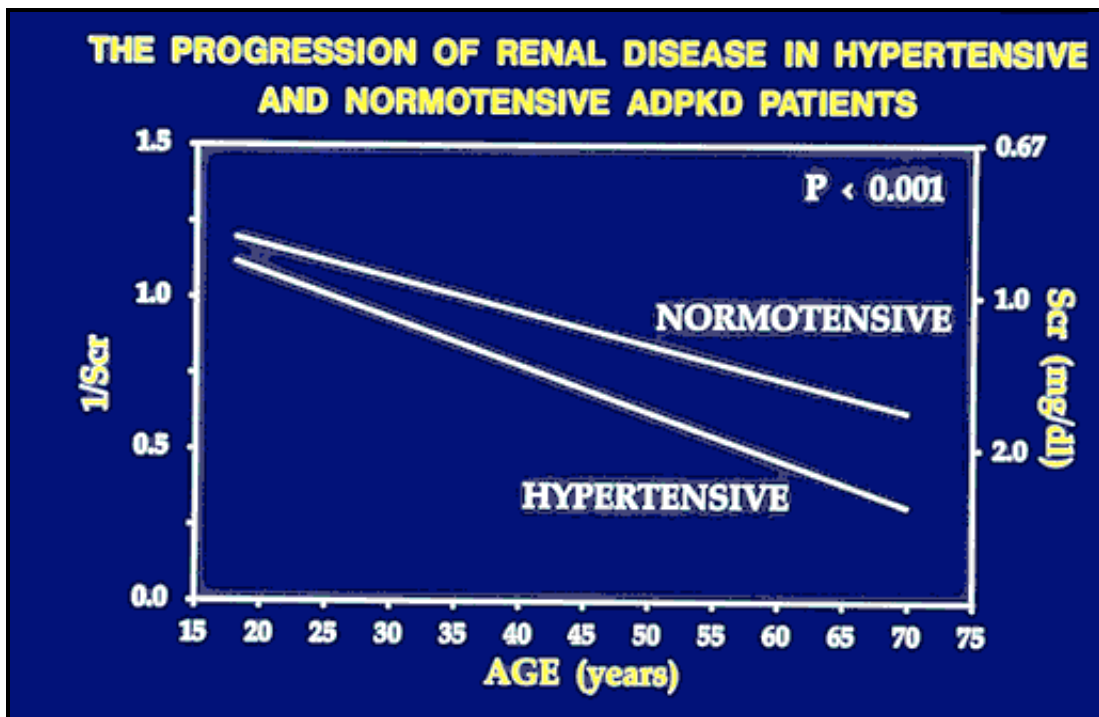
Source: Sedman A et al, *Kidney Int* 1987 Apr;31(4):1000-5.

In children with PKD, renal volume is greater in those with high blood pressure

If one looks at the renal volumes of children, like adults, is renal size greater in those patients who have high blood pressure than in those who don't? And the answer is yes, as you can see.

A P value of less than .05 means that there is less than 5 percent chance that this correlation was happenstance, and thus it is considered statistically significant that there is a real relationship and not a happenstance relationship.

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Source: Bell PE et al, *Kidney Int* 1988 Nov;34(5):683-90.

Rate of decline in renal function greater in patients with hypertension

Arlene showed you this slide or something somewhat similar to this slide. If one projects the rate of progression of loss of kidney function, and thus the rapidity that the patient is heading toward the need for dialysis or kidney transplantation... if they have a normal blood pressure, one could project out that they may never need a kidney transplant or dialysis, in contrast to those patients who have high blood pressure who progress more rapidly. This is an index of how fast the kidney is failing.

What we don't know is if one used high blood pressure medicine, rather than 28 percent

being treated we had 100 percent of patients with polycystic kidney disease whose blood pressures were below 140/90 mm Hg because they were effectively treated and taking their medication, would this line move to the normotensive line? This is an important clinical question which is yet to be studied in patients.

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Hypothesis

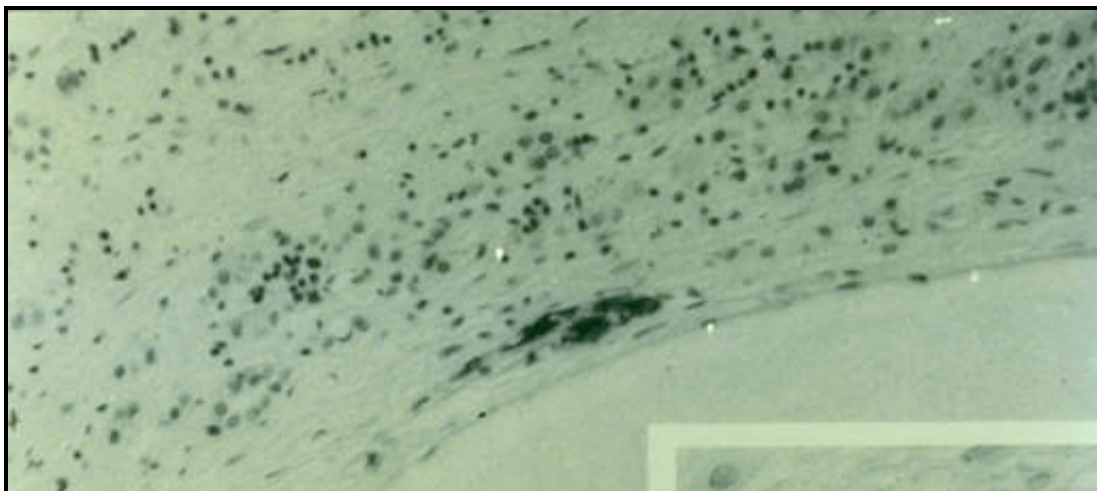
- **Bilateral cyst enlargement causes compression of adjacent parenchyma and stretch of arterioles lining cyst cavities, leading to intrarenal ischemia and activation of the renin-angiotensin system.**

Cause of hypertension in PKD: renal ischemia due to cyst compression?

With this background, one could develop a hypothesis. Now when you do research, be it in animals or tissue culture or humans, you want a hypothesis. Then you design a study to test that hypothesis. Hopefully if it is designed correctly, you will end up with a positive or a negative answer.

This hypothesis states that, as I have discussed, bilateral cyst enlargement causes compression of adjacent parenchyma and stretch the arterioles lining the cyst cavity, leading to intrarenal ischemia, lack of blood flow, and activation of the renin-angiotensin-aldosterone system. So it makes sense, but is it true? What are the data?

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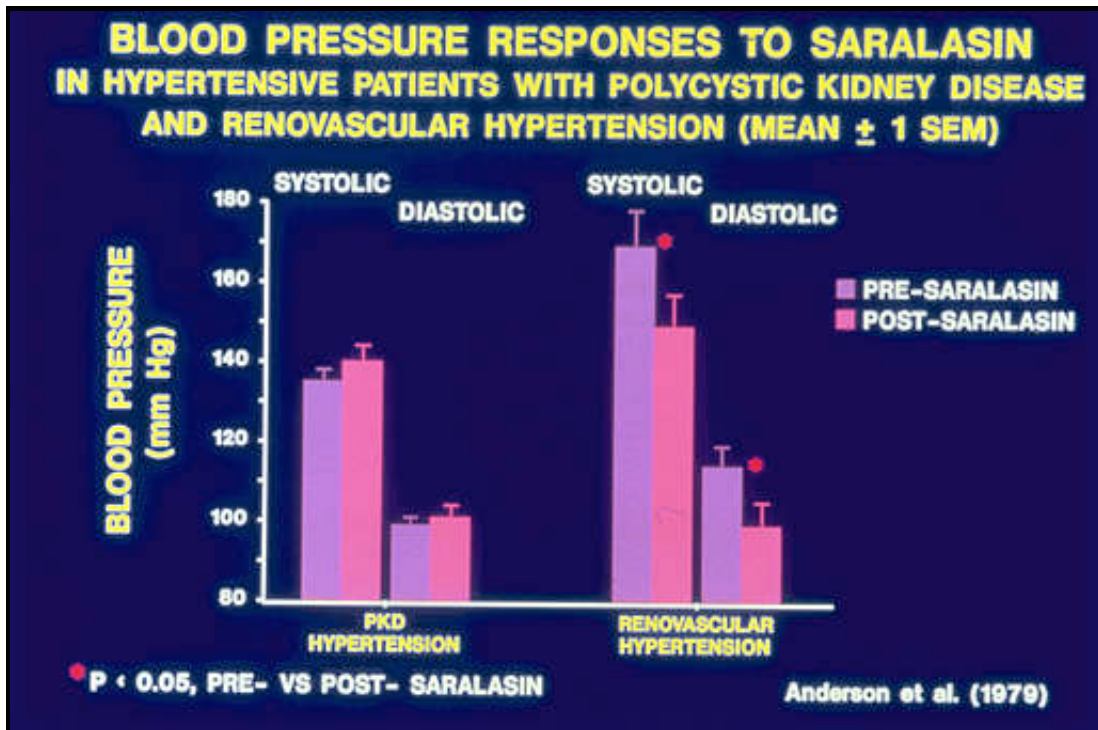




Renin can be demonstrated in cysts walls in PKD

If one stains for renin, this enzyme that is important in producing angiotensin, which elevates blood pressure--if you stain for that, can you see an increased amount of renin in the cysts in patients with polycystic kidney disease? You can see this stain here. This is the cyst cavity. You can see in the lining around it that there is an increased presence of renin.

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Source: Anderson S, unpublished results

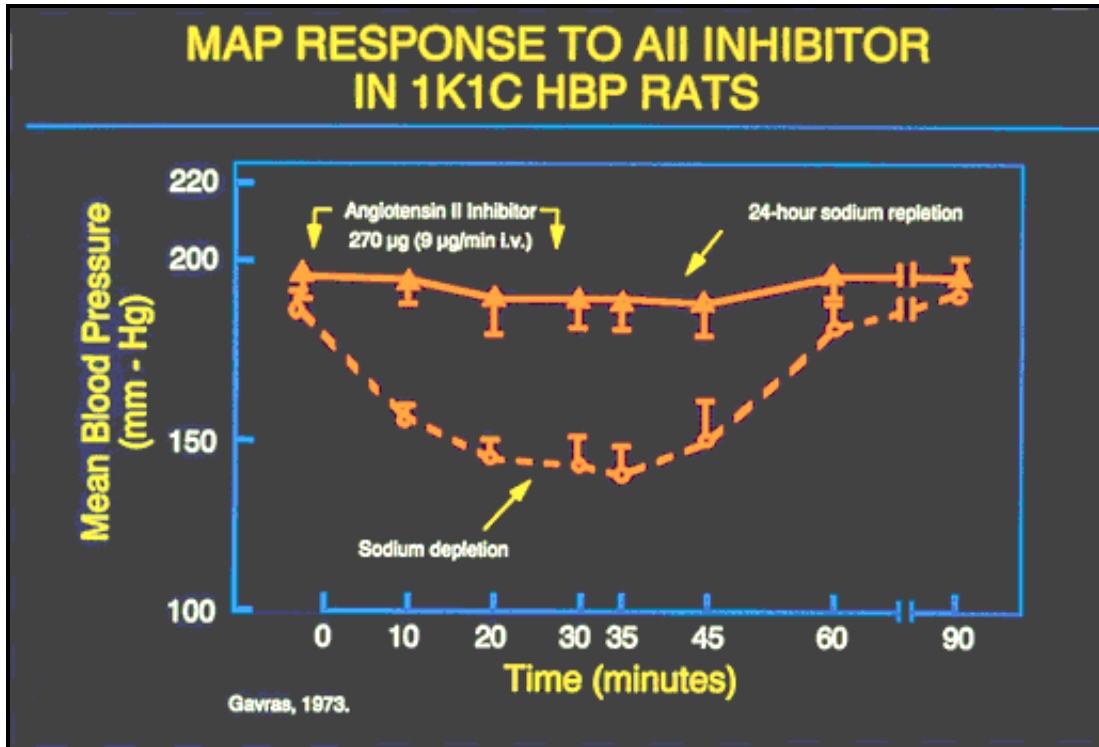
If renin-angiotensin causes high BP in PKD, why does an All antagonist saralasin not lower the BP in such patients?

Very early, a number of years ago, an inhibitor of the renin- angiotensin system was developed. The results were somewhat discouraging because it was known if you have a clamp or a stricture around one renal artery, so-called renal arterial hypertension--which we know is due to the renin-angiotensin system, and you block that system with this angiotensin antagonist called saralasin, that one could have a significant fall in the systolic blood pressure--that is when the heart contracts. The diastolic blood pressure is when the heart is refilling with blood. But when one gave that same amount of saralasin to a polycystic kidney patient, nothing happened. People said, "That hypothesis must be wrong. The renin-angiotensin system must not be involved in polycystic kidney disease," even though all the logic that I presented to you would suggest that it is a reasonable hypothesis to test.

What people forgot, and if they turn to the animal literature, is that it is one thing to have clamps or strictures around one kidney and the other kidney normal. That is the situation in renal vascular hypertension. But in polycystic kidney disease, both kidneys are affected. So you don't have a normal kidney to excrete the extra salt. With PKD the renin-angiotensin system increases and stimulates a hormone called aldosterone that causes the body to

retain salt. So you have a combination of salt retention and activation of angiotensin, both of which cause high blood pressure in PKD.

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Source: Gavras H et al, Science 1973 Jun 29;180(93):1369-71.

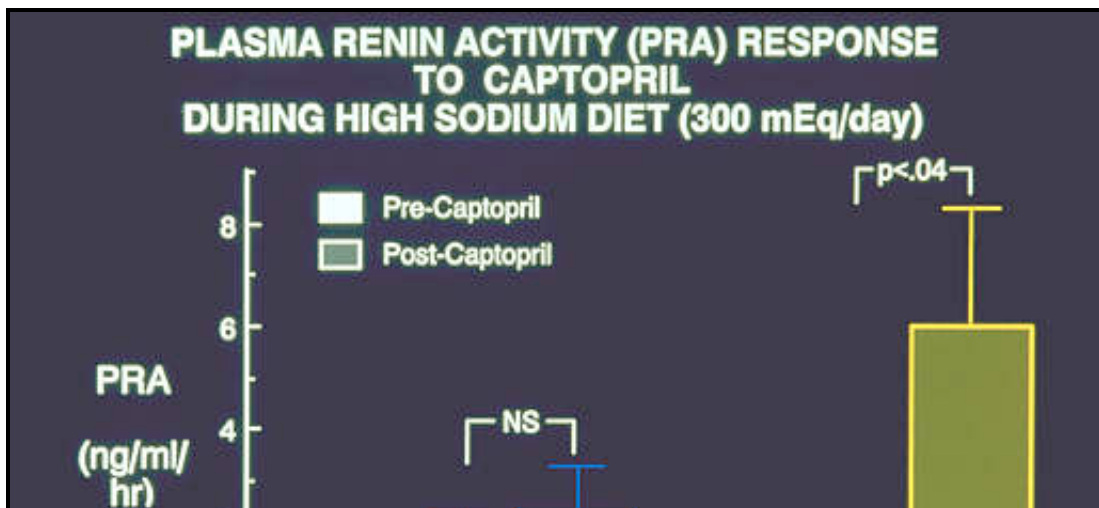
Saralasin only works in an animal model of high renin if there is salt depletion

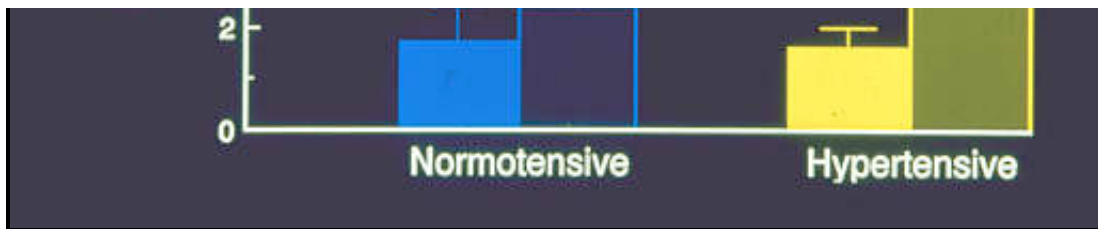
In animals this was pretty clear. If an antagonist was given, an inhibitor was given, nothing happened. This is in an animal that has only one kidney. The other kidney had been taken out. So an analogy of polycystic kidney disease--all the nephrons were ischemic and thus stimulating angiotensin, but they didn't have a normal kidney to get rid of the salt.

With salt restriction and the same inhibitor, look at this big fall in blood pressure. This suggested that that negative study might not be definitive as far as whether or not the renin- angiotensin system is involved in the high blood pressure of polycystic kidney disease.

So we did a large screening study. Actually a sixth female academician, Patty Bell, performed these studies. They all initially looked negative.

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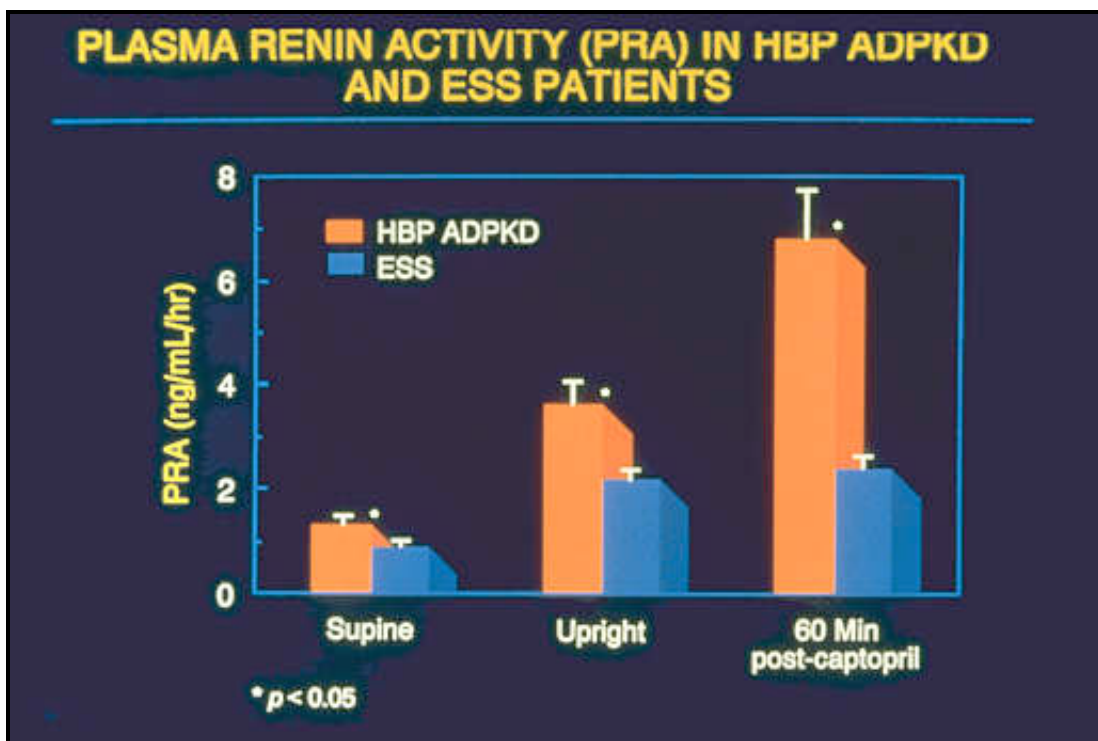
Source: Chapman AB et al, N Engl J Med 1990 Oct 18;323(16):1091-6.

However, captopril, an ACE inhibitor, increases plasma renin activity (PRA) on a high sodium diet in hypertensive PKD patients, but not in normotensive PKD patients

We sat there and looked over this myriad of data, and we stumbled across this observation. This is plasma renin being measured. When one actually gave a drug called captopril, which interferes with this renin- angiotensin system, this renin-angiotensin system normally feeds back and turns off renin. So if you block it and it is already stimulated, the renins might go way up. With captopril, nothing happened in the normotensive group. But they went way up in the hypertensive patients.

So we said, "Wait a minute. Maybe this is bilateral renal artery ischemia due to these cysts, which is stimulating the renin- angiotensin system, which in turn stimulates aldosterone, this sodium-retaining hormone, and that the combination of the salt retention and the angiotensin system led to the high blood pressure, potentially the main cause of death in patients with polycystic kidney disease."

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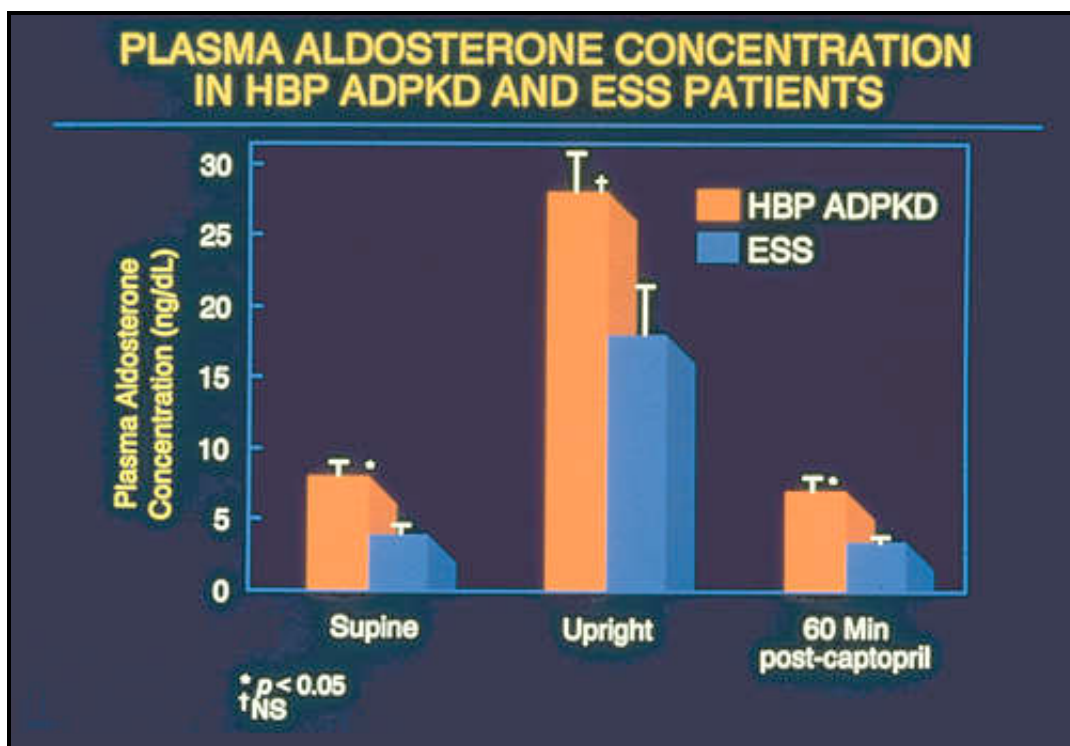
Source: Chapman AB et al, N Engl J Med 1990 Oct 18;323(16):1091-6.

Plasma renin activity is in fact higher in PKD patients with hypertension compared to patients with essential hypertension (ESS)

We did studies with Arlene Chapman, published in The New England Journal, and I think they totally confirmed the role of the renin- angiotensin-aldosterone system in polycystic kidney disease. What one needed was a group of patients with essential hypertension. They didn't have kidney disease. They didn't have polycystic kidney disease. Since the level of blood pressure regulates renin, you can't compare patients who have one blood pressure versus another. You have to have the same blood pressure if you want to bring out a difference between essential hypertension and patients with polycystic kidney disease.

So these are matched patients for gender, for level of blood pressure, for age. You can see that the patients with high blood pressure and polycystic kidney disease versus the essential hypertension--the orange bar, in supine their renins were higher; upright position, the renins were higher; and after the drug, captopril, they were all still higher.

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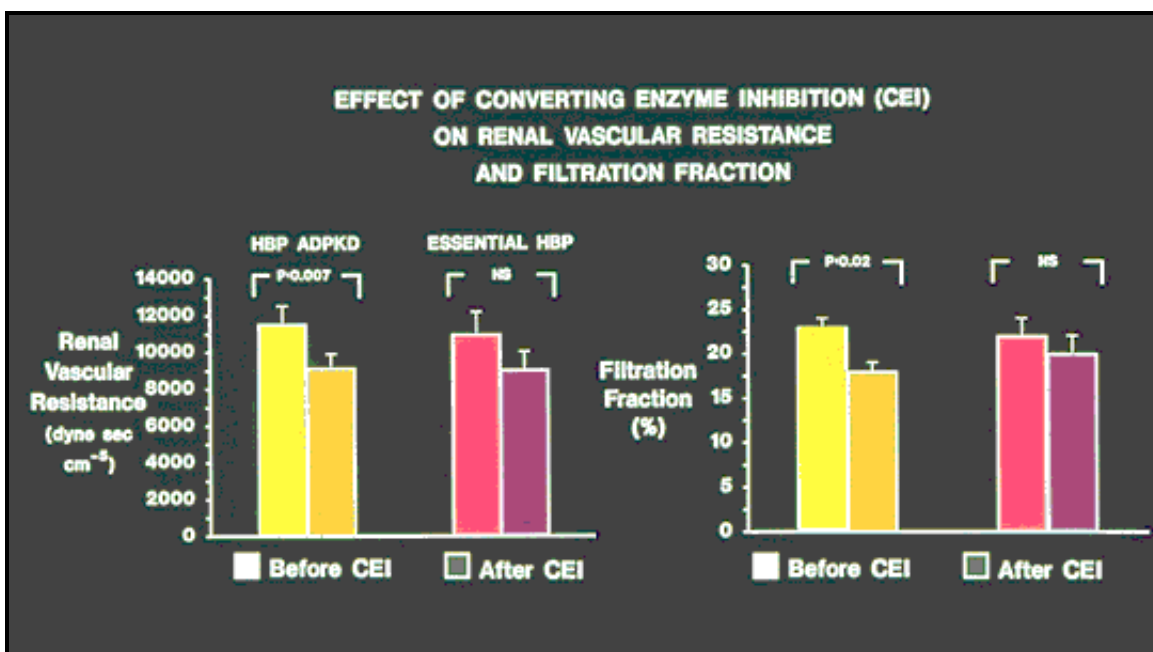


Source: Chapman AB et al, N Engl J Med 1990 Oct 18;323(16):1091-6.

Plasma aldosterone levels are also higher in hypertensive PKD patients vs. patients with essential hypertension (ESS)

If one looks at aldosterone... now remember, angiotensin not only constricts blood vessels but it stimulates aldosterone, which tells the kidney to retain more salt. Retention of salt also increases blood pressure. You can see that aldosterone in the PKD patients was higher in the supine position, higher in the upright position, and higher after captopril.

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The ACE inhibitor captopril also lowers renal vascular resistance in hypertensive patients with PKD

This was a somewhat landmark study. It was an acute study, but chronically if one looked at high blood pressure patients with PKD and also gave these inhibitors, the resistance went down significantly in the kidney, that is, the kidney was less constricted, and this was chronic evidence of the effect of the angiotensin system on the kidney.

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Summary

- **Hypertensive PKD patients compared to essential hypertensive patients exhibit**
 - Greater plasma renin and aldosterone concentrations in the supine position and following captopril ingestion
 - Decrease in renal vascular resistance and filtration fraction following 6 weeks therapy with an ACE inhibitor

Hypertension in PKD and renin: summary

To summarize, hypertensive ADPKD patients compared to essential hypertension patients exhibited greater plasma renin activity and aldosterone concentrations in the supine and upright positions and following captopril ingestion. There was a decrease in renal vascular resistance and filtration fraction following six weeks of converting enzyme inhibitors. Filtration fraction is the ratio between glomerular filtration rate and renal blood flow.

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ROLE OF ANGIOTENSIN AND ALDOSTERONE-MEDIATED SODIUM RETENTION IN ADPKD - RELATED HYPERTENSION





This may look complex, but it is complex. This is the kind of process we have to go through in clinical research, research that takes the basic science to the bedside to the patient to alter the course of polycystic kidney disease. It is built on the background of the knowledge in the basic laboratory. You have heard the exciting developments in molecular biology. Because renal ischemia stimulates renin, which then generates angiotensin that increases the vascular resistance, like putting a clamp around a hose, so that blood pressure goes up.

But we also know that angiotensin stimulates the proliferation of cells, the growth of cells. So it might also stimulate the growth of these renal cysts since we know that the renal cysts have increased growth of their cells.

In addition, as I have said, they stimulate this hormone called aldosterone, which causes sodium retention. If you constrict the blood vessels that the heart is pumping against and you add sodium and increase the volume, you're going to have high blood pressure.

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