

Renal Volume, Renin-Angiotensin-Aldosterone System, Hypertension, and Left Ventricular Hypertrophy in Patients with Autosomal Dominant Polycystic Kidney Disease

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ABSTRACT

The relationship between renal volume and hypertension in autosomal dominant polycystic kidney disease (ADPKD) occurs in childhood. Hypertension is associated not only with increased kidney volume but also with significantly increased left ventricular mass index. Moreover, this increase in left ventricular mass index occurs in children who have ADPKD with borderline hypertension (75th to 95th percentile) and is prevented with angiotensin-converting enzyme inhibitor (ACEI) monotherapy. Progression from borderline to overt hypertension (≥ 95 th percentile) occurs during a 5-yr follow-up in approximately 50% of children with ADPKD and borderline hypertension. Renal cyst enlargement in ADPKD in adults is associated with stimulation of both the circulating and intrarenal renin-angiotensin-aldosterone system. In addition to hypertension, the resultant angiotensin in ADPKD is a pivotal factor in cyst proliferation and expansion, increased sympathetic and endothelin activity, oxidant injury, and fibrosis. There is a close correlation between the level of hypertension, left ventricular hypertrophy, deterioration of GFR, and the progressive enlargement of the cystic kidneys in adult ADPKD. Randomized clinical investigation indicates that ACEI and a BP goal of 120/80 mmHg are associated in a 7-yr study to reverse left ventricular hypertrophy. The effect of renin-angiotensin-aldosterone system inhibition with dual blockade, ACEI and angiotensin receptor antagonists, on renal volume and kidney function is under study in the Halt Progression of Polycystic Kidney Disease (HALT PKD) trial.

J Am Soc Nephrol 20: 1888–1893, 2009. doi: 10.1681/ASN.2008080882

In the past, autosomal dominant polycystic kidney disease (ADPKD) had been termed adult polycystic disease. Now, however, it is clear that many of the features of ADPKD occur during childhood. In fact, ADPKD has been diagnosed *in utero*.¹ Very-early-onset ADPKD has been the designation for infants whose diagnosis is made within the first 18 mo of life.² As compared with children who receive a diagnosis of ADPKD later, the children with very-early-onset ADPKD have larger

kidneys and more renal cysts when adjusted for age.³

CHILDREN WITH ADPKD

The most consistent characteristic of children with ADPKD is the relationship between renal volume and BP. Children with ADPKD and hypertension, defined as >95 th percentile, have significantly larger kidneys than children who have ADPKD and have BP <95 th percentile.⁴

Children with BP between the 75th and 95th percentiles have been designated as having borderline hypertension, whereas BP <75 th percentile is designated as normotension.⁴ Children who have ADPKD and either hypertension or borderline hypertension exhibit a left ventricular mass index (LVMI) that is significantly greater than in children with normotension. Children who have ADPKD with hypertension have the largest kidneys by ultrasonography, and there is a highly significant correlation in renal volume with systolic as well as diastolic BP.⁴ In a prospective 5-yr follow-up study, children with ADPKD and hypertension demonstrated a progressive increase in renal volume and LVMI.⁵ During this 5-yr follow-up, 52% of the children with borderline hypertension developed frank hypertension. Of interest, in contrast to children who have ADPKD with hypertension, who needed more than one antihypertensive agent, the BP in children with borderline hypertension could be well controlled to <50 th percentile by monotherapy with an angiotensin-converting enzyme inhibitor

Published online ahead of print. Publication date available at www.jasn.org.

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(ACEI). Moreover, despite BP control in the children with hypertension during the 5-yr follow-up period, there was a progressive increase in renal volume and LVMI in association with a significant decline in glomerular filtration. In contrast, during the 5-yr follow-up in the children who had ADPKD with borderline hypertension, ACEI *versus* no treatment was associated with control of BP and no change in either LVMI or renal function; however, in the children who had ADPKD and were not treated with ACEI, LVMI increased significantly (66 *versus* 77 g/m²; $P < 0.05$) and renal function declined significantly (135 *versus* 121 ml/min per 1.73 m²; $P = 0.03$) during the 5-yr follow-up period. The renal volume increased significantly in both the ACEI and no treatment groups in children who had ADPKD with borderline hypertension during the 5-yr follow-up period. The renal volume growth, however, was much greater in the children with hypertension than in the children with normotension and borderline hypertension during the 5 yr of the study. Taken together, these preliminary results in children with ADPKD suggest that interventional monotherapy with ACEI to control BP and to prevent increase in LVMI and decline in renal function should begin in children with borderline hypertension.

ADPKD MECHANISMS RELATING RENAL VOLUME, BP, LVMI, AND RENAL FUNCTION

Patient studies of the mechanisms involved in the relationship among renal volume, BP, LVMI, and renal function have been undertaken primarily in adults with ADPKD.⁶ The effect of the increased numbers and growth of renal cysts in ADPKD on renal morphology demonstrates attenuation of intrarenal blood vessels.⁷ This suggests the presence of local areas of ischemia/hypoxia in ADPKD kidneys. Supportive of renal hypoxia, increasing renal erythropoietin concentrations are observed in patients with ADPKD.⁸ This evidence of renal ischemia therefore suggests the renin-

angiotensin-aldosterone system (RAAS) is also stimulated in ADPKD.

RAAS in ADPKD

Initial studies failed to demonstrate increased plasma renin activity (PRA) in patients with ADPKD.⁹ Moreover, an angiotensin receptor antagonist did not alter BP in patients with ADPKD and hypertension but decreased BP in patients with unilateral renal artery stenosis.¹⁰ ADPKD, however, is a bilateral, not a unilateral, renal disease; therefore, any activation of the RAAS would be associated with sodium retention, thereby potentially returning intrarenal renin to within the normal range.

The first evidence of a role of the RAAS in ADPKD occurred in comparing the effect of ACEIs on PRA in patients who had ADPKD and hypertension *versus* normotension.¹¹ The patients with hypertension demonstrated significantly higher PRA in response to ACEI compared with the patients with normotension. PRA, however, is influenced by renal perfusion pressure, sodium intake, and renal function. Studies were under-

taken, therefore, comparing patients who had essential hypertension with patients who had ADPKD and hypertension and were matched for age, gender, BP level, urinary sodium excretion as an index of sodium intake, and renal function.¹² The results demonstrated significantly higher PRA and aldosterone concentrations in the supine position and upright position and with ACEI in the patients with ADPKD (Figure 1). Moreover, after 6 wk of ACEI, a significant decrease in renal vascular resistance was observed in the patients with ADPKD but not in patients with essential hypertension.¹²

Subsequent studies of kidneys from patients with ADPKD demonstrated increased renin activity in renal arterioles outside the juxtaglomerular apparatus and in the cystic epithelium.¹³ The most definitive study to examine the intrarenal RAAS in ADPKD was published by Loghman-Adham *et al.*¹⁴ In that study, all of the major components of the RAAS were identified within ADPKD kidneys, including angiotensinogen, renin, ACE, angiotensin II, and the AT₁ angiotensin

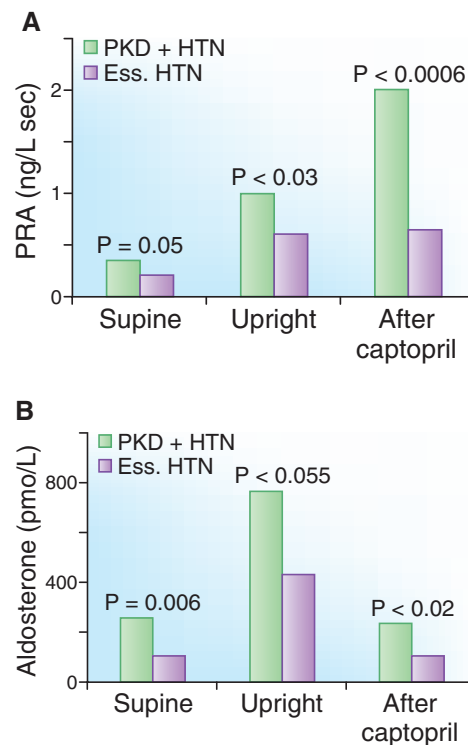


Figure 1. (A and B) PRA (A) and aldosterone (B) are stimulated in ADPKD as compared with patients with essential hypertension. Reprinted from reference¹², with permission.

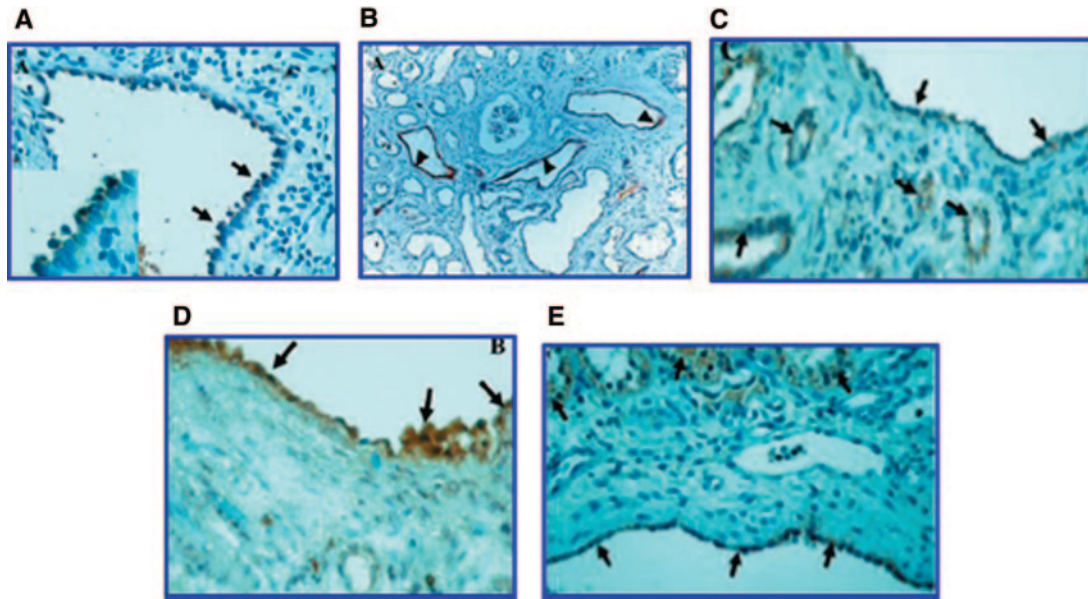


Figure 2. (A through E) Components for RAAS identified in cysts of ADPKD kidneys: Angiotensinogen (A), renin expression (B), expression of ACE (C), angiotensin II (D), and expression of angiotensin II type I receptor (E). Reprinted from reference¹⁴, with permission.

receptor (Figure 2). Thus, there are published results demonstrating both increased circulating¹² and intrarenal RAAS activity¹⁴ in patients with ADPKD.

Renal Volume and LVH in ADPKD

As in children with ADPKD, adults who have ADPKD with hypertension have larger kidneys as compared with patients who have ADPKD with normotension.¹⁵ There is a significant inverse correlation between increasing renal volume and decreasing GFR (Figure 3).¹⁶ Urinary albumin excretion, a surrogate for renal disease progression, was shown in a randomized 5-yr ADPKD study to decrease significantly with ACEI but not with a calcium channel blocker for comparable antihypertensive effects.¹⁷ Moreover, overt proteinuria and microalbuminuria both were associated with increased loss of renal function in patients with ADPKD.¹⁸ The early onset of hypertension in ADPKD, which is frequently undetected and untreated, is associated with left ventricular hypertrophy (LVH) in nearly 50% of patients who have ADPKD and are in their 40s.¹⁹ In the era of renal replacement therapy, cardiovascular complications emerge as the major cause of death in patients with ADPKD.²⁰ Thus, the increased frequency

of LVH and its known association with increased coronary heart disease, cardiac failure, arrhythmias, and sudden death has important morbidity and mortality implications for patients with ADPKD.²¹

Sympathetic Activity in ADPKD

Because activation of the RAAS stimulates the sympathetic nervous system and *vice versa*, studies have been undertaken to compare plasma catecholamine concentrations in patients who have essential hypertension with patients who have ADPKD with and without renal failure.²² Both groups of patients with ADPKD ex-

hibited significantly higher plasma concentrations of norepinephrine and epinephrine than did patients with essential hypertension. There is also evidence of increased renal endothelin 1 (ET-1) in patients with ADPKD using immunohistochemical staining with an ET-1 antibody.²³ This observation is of interest because angiotensin II is known to stimulate endothelin.²⁴ Endothelial function also is impaired in patients with ADPKD as compared with patients with essential hypertension and normal control subjects.²⁵ In this regard, angiotensin II stimulates oxygen radicals, which may

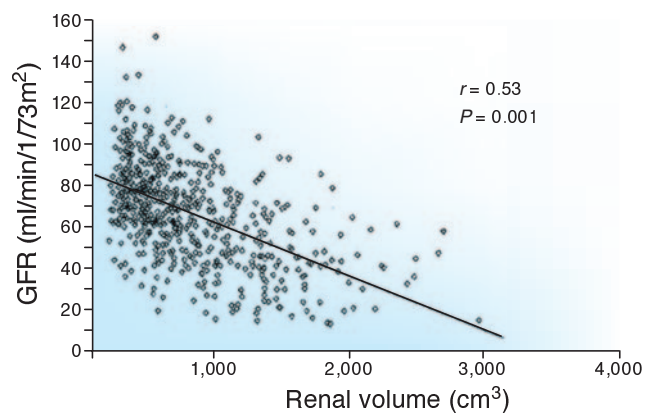


Figure 3. Significant correlation between GFR and renal volume in 229 patients with ADPKD. Reprinted from reference¹⁶, with permission.

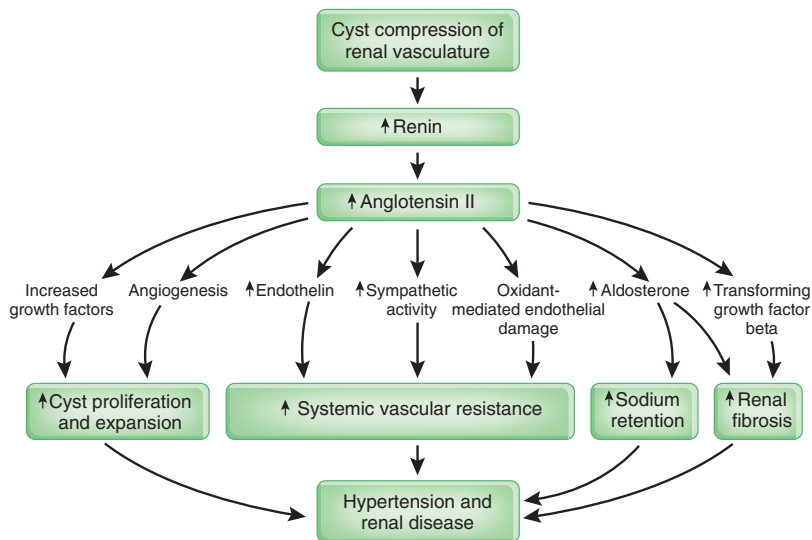


Figure 4. Pathogenic role of RAAS in ADPKD. In addition to its vasoconstrictor effect on BP, angiotensin II is known to increase cell proliferation, angiogenesis, oxidant injury, and fibrosis, known renal components of ADPKD. Potential indirect effects of angiotensin II on causing hypertension include stimulation of the sympathetic nervous system, endothelium, and aldosterone with sodium retention. Angiotensin II also stimulates reactive oxygen species, which could account, at least in part, for the observed endothelial dysfunction in ADPKD. Adapted from reference²⁷, with permission.

exert deleterious effects on the integrity of the endothelium.²⁶

Thus, the pathogenesis of hypertension in patients with ADPKD, which most frequently occurs before any clinically relevant loss of renal function, is multifactorial (Figure 4).²⁷ The relative roles of the RAAS, sympathetic nervous system, sodium retention, and endothelial dysfunction in ADPKD hypertension cannot be ascertained with certainty.²⁸ It is of interest, however, that patients who have ADPKD with normotension exhibit increased total body sodium as compared with unaffected siblings, thus suggesting an early role of the RAAS.²⁹

Hypertension and LVH in ADPKD

The role of hypertension in LVH in patients with ADPKD is relatively firm. As shown in Figure 5, there is a significant correlation between the level of mean arterial pressure and LVMI in adult patients with ADPKD.¹⁹ It is of interest, however, that in the same study, 23% of patients with ADPKD and normotension exhibited LVH. The reason for this observation is unclear, but angiotensin is known to stimulate cellular proliferation.³⁰ Moreover, insulin resistance oc-

currs in patients with ADPKD, and insulin is also mitogenic.³¹ Furthermore, 24-h BP monitoring in patients with ADPKD and normotension showed the absence of nighttime lowering of BP (nondippers), which could contribute to an increase in left ventricular mass.³²

Whereas ACEI reverses LVH in adult patients with ADPKD and hypertension,³³ it was not known whether this effect is specific for blocking the RAAS, the BP-lowering effect, or both. Moreover, the optimal BP level for reversing LVH in patients with ADPKD is not known. A 7-yr prospective, randomized study was

therefore performed in patients with ADPKD, hypertension, and LVH. These patients were randomly assigned to ACEI or calcium channel blockers as well as to a BP goal of 135 to 140/85 to 90 mmHg versus <120/80 mmHg.³⁴ Both ACEI and calcium channel blockers significantly reversed the LVH; however, for the same level of BP, the reversal was significantly greater with ACEI. Although reversal of the LVH occurred at both BP levels, there was significantly greater reversal of LVH at the lower BP goal (Figure 6).³⁴ There were no differences in renal function; however, that study of 75 patients with ADPKD was underpowered to detect differences in renal function.

Results in prospective, observational studies indicated an effect of inhibition of the RAAS on renal progression. In one 5-yr follow-up ADPKD study, patients whose hypertension was treated with a diuretic but not an ACEI were compared with patients who had ADPKD and were treated with ACEI but not diuretics.³⁵ During the 5 yr, the diuretic-treated patients' serum creatinine rose from 1.3 to 2.7 mg/dl, whereas the ACEI-treated patients' serum creatinine increased from only 1.2 to 1.4 mg/dl. Moreover, for comparable BP control, additional antihypertensive medications were needed more frequently in the diuretic group (nine [65%] of 14 versus four [21%] of 19; $P < 0.05$). An epidemiologic study was undertaken to compare progression to ESRD in 612 patients who had ADPKD and were studied between 1985 through 1992 and 1992 through 2001.³⁶

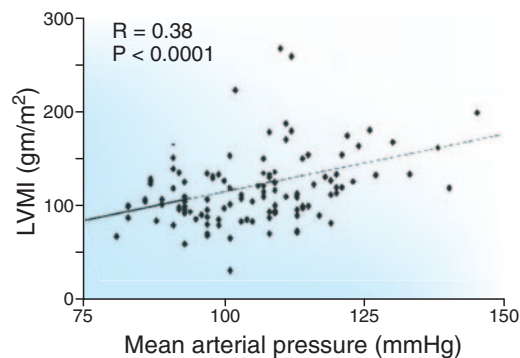


Figure 5. Correlation between BP and LVMI in PKD. Reprinted from reference¹⁹, with permission.

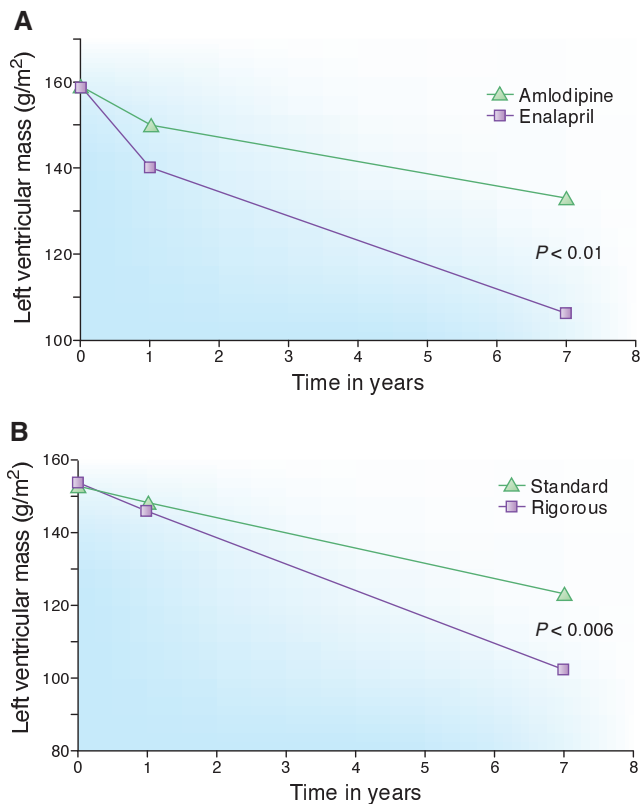


Figure 6. (A) Effect of BP control with amlodipine versus enalapril on LVMI in patients with ADPKD over 7 yr. (B) Effect of rigorous versus standard BP control on LVMI in patients with ADPKD over 7 yr. Reprinted from reference³⁶, with permission.

The baseline demographics were comparable except for lower diastolic and mean arterial BP in the more recent cohort. Also, the more recent cohort of patients with ADPKD was treated much more frequently with ACEI (48.1 versus 13.1%; $P < 0.001$). Most important, the age at time of ESRD was significantly later for men (53 versus 63 yr; $P = 0.0013$) and women (57 versus 61 yr; $P = 0.0021$) in the most recent ADPKD cohort. There are, however, small, underpowered studies of patients with ADPKD in which no beneficial effect of ACEI on renal progression was observed.³⁷ In one ADPKD study, ACEI was compared with β adrenergic blockade on renal progression, and no difference was observed. Both of these agents, however, suppress plasma renin.³⁸

CONCLUSIONS

Although there is substantial published evidence of the importance of renal vol-

ume growth, activation of the RAAS, and hypertension in ADPKD, the effect of a lower BP goal ($<120/80$ mmHg) and inhibition of the RAAS has been shown only in the reversal of LVH. No prospective, adequately powered, randomized study is available to support or refute a beneficial effect of inhibition of the RAAS to slow the progression of the ADPKD renal disease. The National Institutes of Health, therefore, is funding the Halt Progression of Polycystic Kidney Disease (HALT PKD) study (ClinicalTrials.gov, NCT 00283686). Because angiotensin II generation can occur in the presence of ACEI through the chymase pathway,³⁹ the HALT study compares the effect of ACEI plus placebo and ACEI plus angiotensin receptor blocker at various BP levels. The primary end point in study A (GFR >60 ml/min) is change in renal volume by magnetic resonance imaging, which is more sensitive than renal ultrasound.⁴⁰ The same ACEI versus ACEI plus angiotensin receptor blocker

comparison is undertaken in study B with more advanced renal disease (GFR 25 to 60 ml/min) using a combined end point of doubling serum creatinine, ESRD, or death.

Last, there have been important and exciting basic science studies of the pathogenesis and potential interventions in models of PKD. This review, however, is focused on current available information on children and adult patients with ADPKD with respect to the relationship among renal volume, the RAAS, hypertension, left ventricular mass, and renal function.

ACKNOWLEDGMENTS

This research was funded by NIH grants PO1 DK 19928 and 5RO1 DK 058793.

DISCLOSURES

None.

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