Unique Features of Hypertension in ADPKD

Robert W. Schrier, MD
Professor of Medicine
University of Colorado Denver
School of Medicine
Disclosures

Dr. Robert W. Schrier serves as an Advisor to Novartis, Janssen, Ikaria, and Otsuka Pharmaceuticals.


P < 0.001


The Progression of Renal Disease in Hypertensive and Normotensive ADPKD Patients

1.5
1
0.5
0

0.67
1.0
2.0

Normotensive
Hypertensive

1/Scr
Scr (mg/dl)

Age (years)

P<0.001

Mean Renal Volume is Significantly Higher in Hypertensive versus Normotensive ADPKD Patients

Relationship between GFR and Renal Volume in 229 ADPKD Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NBP (N=30)</th>
<th>BBP (N=27)</th>
<th>HBP (N=28)</th>
<th>P-value for ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>13/17</td>
<td>15/12</td>
<td>17/11</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>12.0 ± 0.8</td>
<td>11.8 ± 0.8</td>
<td>13.6 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>151 ± 5</td>
<td>151 ± 5</td>
<td>160 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (mg/100 ml)</td>
<td>0.66 (0.57–0.70)</td>
<td>0.69 (0.62–0.77)</td>
<td>0.74 (0.68–0.81)</td>
<td>NS</td>
</tr>
<tr>
<td>24-h creatinine clearance (ml/min/1.73 m²)</td>
<td>135 (127–145)</td>
<td>127 (117–138)</td>
<td>130 (120–141)</td>
<td>NS</td>
</tr>
<tr>
<td>Urine microalbumin excretion (mg/day)</td>
<td>31 (19–51)</td>
<td>22 (14–35)</td>
<td>23 (16–33)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>109 ± 2</td>
<td>119 ± 2</td>
<td>130 ± 3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>64 ± 1</td>
<td>68 ± 1</td>
<td>72 ± 2</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

Note. SBP: NBP vs BBP (P=0.0122), NBP vs HBP (P<0.0001), BBP vs HBP (P=0.0022); DBP: NBP vs BBP (P=NS), NBP vs HBP (P=0.0003), BBP vs HBP (P=NS). Data presented as mean ± s.e. or geometric mean (95% CI).
Correlation between systolic blood pressure and renal volume in 85 ADPKD children

\[ \text{Ln(Renal Volume)} \] vs. Systolic blood pressure (mm Hg)

- Borderline
- Hypertensive
- Normotensive

\[ r = 0.70 \]
\[ P < 0.0001 \]

Correlation between diastolic blood pressure and renal volume in 85 ADPKD children

$$\text{Ln}[\text{Renal Volume}] (\text{ml})$$  $$r = 0.52$$  $$P<0.0001$$

- **Borderline**
- **Hypertensive**
- **Normotensive**

NORMAL RENAL VASCULATURE
RENAL VASCULATURE IN ADPKD
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-aldosterone system.
The Effect of the RAAS in the Development of Hypertension and Progression of ADPKD

The diagram illustrates the relationship between bilateral renal cysts and the development of hypertension. The RAAS (Renin-Angiotensin-Aldosterone system) is involved in this process. Here’s how the interaction occurs:

1. **Bilateral renal cysts** lead to an increase in **Renin**.
2. **Renin** results in an increase in **Angiotensin II**.
3. **Angiotensin II** leads to the following effects:
   - Increased secretion of **Aldosterone**
   - Increased renal sodium retention
   - Increased **vascular resistance**
   - Increased **fibrosis**
   - Increased **mitogenesis**
4. The end result is **hypertension**.

*Source: Eder, Schrier: JASN, 12:194-200, 2001*
Blood Pressure Responses to Saralasin in Hypertensive patients with PKD and Renal Vascular Hypertension (mean ± SEM)

* P < 0.05 Pre- vs Post- Saralasin

Anderson et al. (1979).
MAP response to All Inhibitor in 1K1C HBP Rats

Gavras, 1973

Angiotensin II Inhibitor 270 µg (9 µg/min i.v.)

24-hour sodium repletion

Sodium depletion

Gavras, 1973
Plasma Renin Activity (PRA) Response to Captopril During High Sodium Diet in ADPKD (300 mEq/day)

Bell, Schrier, et al. KI, 34:683-690, 1988
The Renin-Angiotensin-Aldosterone System is Stimulated in ADPKD as Compared to Essential Hypertension

The Renin-Angiotensin-Aldosterone System is Stimulated in ADPKD as Compared to Essential Hypertension

The Renin-Angiotensin-Aldosterone System is Stimulated in ADPKD as Compared to Essential Hypertension

ANGIOTENSINOGEN (AGT) EXPRESSION BY ADPKD KIDNEY

Renal Cyst

Renal Tubules

RENIN EXPRESSION BY ADPKD KIDNEY

ADPKD Kidney

Normal Kidney

ANGIOTENSIN II EXPRESSION BY ADPKD KIDNEY

PLASMA CATECHOLAMINES IN ESSENTIAL HYPERTENSIVES (EH) AND IN HYPERTENSIVES WITH ADPKD DIVIDED IN TWO GROUPS ACCORDING TO RENAL FUNCTION

* p<0.001 and ** p<0.01 vs. ADPKD

Kidney section from a 39-yr-old patient with typical ADPKD (H and E stain)

Immunohistochemical staining using an ET-1 antibody

EVIDENCE FOR IMPAIRED ENDOTHELIAL FUNCTION IN ADPKD

<table>
<thead>
<tr>
<th></th>
<th>Hypertensive ADPKD Patients (n = 15)</th>
<th>Essential Hypertensive Patients (n = 16)</th>
<th>Healthy Subjects (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>39.6 ± 7.2</td>
<td>40.8 ± 4.8</td>
<td>38.1 ± 8.8</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>4/11</td>
<td>7/9</td>
<td>8/16</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>25.5 ± 3.5</td>
<td>26.0 ± 3.2</td>
<td>24.7 ± 3.5</td>
</tr>
<tr>
<td>Smokers (n)</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>138 ± 18 *</td>
<td>134 ± 14 *</td>
<td>119 ± 14</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>85 ± 11 **</td>
<td>77 ± 13</td>
<td>75 ± 9</td>
</tr>
<tr>
<td>CrCl (ml/min/1.73 m2)</td>
<td>91 ± 29</td>
<td>112 ± 14</td>
<td>105 ± 12</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>195 ± 23</td>
<td>179 ± 29</td>
<td>180 ± 30</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>121 ± 37</td>
<td>115 ± 35</td>
<td>114 ± 37</td>
</tr>
<tr>
<td>LVMI (g/m2)</td>
<td>132 ± 23 ***</td>
<td>111 ± 16 ****</td>
<td>95 ± 17</td>
</tr>
</tbody>
</table>

* P < 0.01 vs. healthy subjects; ** P < 0.005 vs. healthy subjects; *** P = 0.02 vs. essential hypertensive patients, P < 0.0001 vs. healthy subjects; **** P < 0.005 vs. healthy subjects
Percentage of LVH in ADPKD Patients

Correlation Between Blood Pressure and Left Ventricular Hypertrophy in Polycystic Kidney Disease

Mean Arterial Pressure (mm Hg)

Renal volume was markedly increased in hypertensive (HBP) as compared to borderline hypertensive (BBP) and normotensive (NBP) children with ADPKD.

Effect of ACE Inhibitors on Left Ventricular Hypertrophy in ADPKD

MAP mmHg

Baseline  Year 1  Year 7

110  94  94

LVMI (g/m²)

0  20  40  60  80  100  120  140  160

* P < 0.05 versus baseline; ** P < 0.01 versus year 1 and baseline

Introduction

In a 7-year prospective randomized study, 79 hypertensive ADPKD patients with left ventricular hypertrophy (LVH) were randomized to standard blood pressure control (135-140/85-90 mm Hg) or rigorous blood pressure control (< 120/80 mm Hg).

With angiotensin converting enzyme inhibitor or calcium channel blocker, amlodipine
Mean Sitting Systolic BPs from the 4th month through year 7 of ADPKD Patients Randomized to Rigorous (<120/80 mm Hg) or Standard 135-140/85-90 mm Hg) BP Control

Mean Sitting Diastolic BPs from the 4th month through year 7 of ADPKD Patients Randomized to Rigorous (<120/80 mm Hg) or Standard 135-140/85-90 mm Hg) BP Control

Effect of Rigorous versus Standard BP Control on Left Ventricular Mass Index in ADPKD Patients Over 7 years

Effect of BP Control with Amlodipine versus Enalapril on Left Ventricular Mass Index in ADPKD Patients Over 7 Years