*Kidney International, Vol. 38 (1990), pp. 1177–1180*

# Renal structure and hypertension in autosomal dominant polycystic kidney disease

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**Renal structure and hypertension in autosomal dominant polycystic kidney disease.** Hypertension has been reported to occur in 50 to 75 percent of subjects with autosomal dominant polycystic kidney disease (ADPKD) prior to the onset of marked renal insufficiency but concurrent with cystic deformation of the renal parenchyma. The present study was undertaken to examine whether the renal structural abnormalities are greater in hypertensive (HBP) versus normotensive (NBP) male and female patients with ADPKD who were matched within gender groups for age, body surface area, serum creatinine concentration (males HBP 1.2 ± 0.02 vs. NBP 1.1 ± 0.03 mg/dl, NS; females HBP 0.9 ± 0.03 vs. NBP 0.9 ± 0.02 mg/dl, NS) and creatinine clearance (males HBP 100 ± 3 vs. NBP 108 ± 3 ml/min/1.73 $m^2$, NS; females HBP 97 ± 3 vs. NBP 96 ± 2 ml/min/1.73 $m^2$, NS). Renal volume was significantly greater in the HBP compared to the NBP group (males HBP 624 ± 47 vs. NBP 390 ± 43 $cm^3$, $P < 0.0005$; females HBP 466 ± 32 vs. NBP 338 ± 24 $cm^3$, $P < 0.002$). Since increased renal volume is due to increased cysts, the results indicate that the early high incidence of hypertension in ADPKD correlates with the renal structural abnormalities in this disorder.

An early and high incidence of hypertension has been well documented in autosomal dominant polycystic kidney disease (ADPKD), often occurring prior to a decrease in creatinine clearance [1–10]. This hypertension in ADPKD may contribute to the high cardiovascular mortality in these patients [11] and also may accelerate the rate of progression of renal insufficiency [11, 12]. The pathogenesis of the hypertension associated with ADPKD, however, has not been clearly established.

Since ADPKD is a systemic disease with several extrarenal abnormalities including hepatic cysts [3], intracranial aneurysms [13], mitral valve prolapse [14], and intestinal diverticulitis [15], the high incidence of hypertension in these patients could reside in some extrarenal and/or intrarenal pathogenetic factors.

An intrarenal pathogenesis of ADPKD hypertension has been suggested by the observation that renal cyst decompression has been associated with a decrease in blood pressure [16, 17]. Long-term persistence of this hypotensive effect of renal cyst decompression in ADPKD has, however, not been documented, perhaps because of renal fluid reaccumulation in decompressed cysts or enlargement of other renal cysts.

The present study was undertaken to explore further the potential role of renal cystic enlargement in initiating hypertension in ADPKD. The results supported this hypothesis. In the sex, age, body surface area, and creatinine clearance-matched normotensive and hypertensive patients with ADPKD, the hypertensive patients exhibited significantly larger renal volumes reflecting greater cystic involvement.

## Methods

One hundred and forty-seven subjects with ADPKD were studied at the Clinical Research Center at the University of Colorado Health Sciences Center from July 1985 to November 1989. All subjects underwent a detailed formalized interview including a complete history and physical examination with determination of blood pressure in all subjects. Hypertension was defined as diastolic pressure greater than 90 mm Hg, a systolic pressure greater than 150 mm Hg in the sitting position, or a known history of hypertension on therapy. Mean arterial pressure (MAP) is reported as diastolic pressure plus one third of the pulse pressure. Study subjects were between the ages of 16 and 45 years with a serum creatinine concentration less than 1.5 mg/dl and creatinine clearance between 75 and 150 ml/min/1.73 $m^2$. Body surface area (BSA) was less than 2.6 $m^2$ for males and less than 2.2 $m^2$ for females. The hypertensive and normotensive groups did not differ in mean age, body surface area, serum creatinine concentration or creatinine clearance.

A complete abdominal ultrasonogram was performed on all subjects utilizing a high resolution real-time scanner (Acuson or ATL with a 35 or 5 mmHz transducer) and a conventional static scanner (Picker 802). These methods detect cysts greater than 2 mm in diameter. Images from the static scan were used to measure renal dimensions. Renal volume was calculated using the following formula for a modified ellipse: $4/3\ \pi$ (length/2) (anterior-posterior diameter/4 + width/4)$^2$. Mean renal volume was calculated from both kidneys. Subjects were considered to have ADPKD if there were bilateral renal cysts totalling five or more.

Serum creatinine concentrations were measured in all patients while on an ad lib diet. Two consecutive 24-hour urine

Received for publication April 24, 1989
and in revised form June 4, 1990
Accepted for publication July 24, 1990

collections were obtained for creatinine; creatinine clearances were calculated and corrected for body surface area. All laboratory determinations were performed by the Clinical Research Laboratory at the University of Colorado Health Sciences Center.

Means of continuous variables were compared using the two sample *t*-test for unequal sample sizes and unequal variances when applicable. Chi-square tests were used to investigate the relationships among categorical variables. All variables are presented as mean ± one standard error. Tests of significance are executed at a significance level of 0.05, however, significant *P* values are also provided.

## Results

Sixty-four male and eighty-three female subjects comprised the study population. Forty-two of the male subjects were hypertensive (HBP) (66%) and twenty-two were normotensive (NBP) (34%). Thirty-four of the female subjects were HBP (41%) and forty-nine were NBP (59%). The frequency of hypertension was significantly greater in the males than in the females in this population ($P < 0.003$).

Fifty-nine percent of the HBP group (45 of 76) were diagnosed with hypertension prior to the study and were taking antihypertensive medications. However, 49% of this group on medication were still hypertensive by the study criteria (22 of 45) with a mean MAP of 114 mm Hg. An additional seven percent of the HBP group (5 of 76) were diagnosed with hypertension prior to the study but were not taking medication and all were hypertensive at the time of the study with a mean MAP of 114 mm Hg. Thirty-four percent of the HBP group (26 of 76) were not aware they were hypertensive prior to the study (mean MAP 112 mm Hg). The mean age of onset of hypertension was 27 years (males 27 ± 1 vs. females 26 ± 1 years, NS).

Age (HBP 32.3 ± 0.9 vs. NBP 31.1 ± 0.9 years, NS), BSA (HBP 1.76 ± 0.03 vs. NBP 1.69 ± 0.03 $m^2$, NS), serum creatinine (HBP 0.9 ± 0.03 vs. NBP 0.9 ± 0.02 mg/dl, NS), and creatinine clearance (HBP 97 ± 3 vs. NBP 96 ± 2 ml/min/1.73 $m^2$, NS) were not different between the hypertensive and normotensive ADPKD females. Similarly, age (HBP 32.7 ± 1.1 vs. NBP 29.6 ± 1.7 years, NS), BSA (HBP 2.03 ± 0.03 vs. NBP 2.00 ± 0.04 $m^2$, NS), serum creatinine (HBP 1.2 ± 0.02 vs. NBP 1.1 ± 0.03 mg/dl, NS), and creatinine clearance (HBP 100 ± 3 vs. NBP 108 ± 3 ml/min/1.73 $m^2$, NS) were similar in hypertensive and normotensive ADPKD males (Table 1).

MAP was higher in hypertensive than normotensive patients of both genders (Table 1). MAP was significantly higher in the men compared to the women in both the HBP ($P < 0.02$) and the NBP ($P < 0.005$) groups. Both HBP and NBP groups had a significant increase in MAP after changing from supine to upright position (HBP 10.5 ± 1.0 mm Hg, $P < 0.0001$; NBP 9.9 ± 1.0 mm Hg, $P < 0.0001$). However, this change in MAP with the assumption of an upright posture was not different between HBP and NBP groups.

Mean renal volume was significantly greater in the HBP males and females versus the NBP males and females respectively (males HBP 624 ± 47 vs. NBP 390 ± 43 $cm^3$, $P < 0.0005$; females HBP 466 ± 32 vs. NBP 338 ± 24 $cm^3$, $P < 0.002$) (Fig. 1).

**Table 1.** Subject characteristics of HBP and NBP groups

| | Male | Female |
|---|---|---|
| Age *years* | | |
| Hypertensive | 32.7 ± 1.1 | 32.3 ± 0.9 |
| Normotensive | 29.6 ± 1.7 | 31.1 ± 0.9 |
| *P* value | NS | NS |
| BSA $m^2$ | | |
| Hypertensive | 2.03 ± 0.03 | 1.76 ± .03 |
| Normotensive | 2.00 ± 0.04 | 1.69 ± .03 |
| *P* value | NS | NS |
| Creatinine clearance *ml/min/1.73 $m^2$* | | |
| Hypertensive | 100 ± 3 | 97 ± 3 |
| Normotensive | 108 ± 3 | 96 ± 2 |
| *P* value | NS | NS |
| $S_{Cr}$ *mg/dl* | | |
| Hypertensive | 1.2 ± 0.02 | 0.9 ± 0.03 |
| Normotensive | 1.1 ± 0.03 | 0.9 ± 0.02 |
| *P* value | NS | NS |
| MAP *mm Hg* | | |
| Hypertensive | 112 ± 2 | 105 ± 2 |
| Normotensive | 99 ± 2 | 94 ± 1 |
| *P* value | 0.0001 | 0.0001 |

## Discussion

Hypertension is a common occurrence in ADPKD prior to the onset of marked renal insufficiency [1–10]. In addition, marked structural deformation usually occurs in ADPKD prior to azotemia [3]. Since less pronounced renal structural abnormalities than those observed in ADPKD have been considered pathogenetic in some forms of hypertension [18–22], it is reasonable to suggest a relationship between structural deformation and hypertension early in the course of ADPKD. This was the major hypothesis examined in the present study.

In order to examine this hypothesis in a study population it was important to consider other factors known to alter blood pressures. Gender is an important determinant of blood pressure, with essential hypertension being more common in males than in premenopausal females [23]. Indeed in our population hypertension was more common in males than in females. Hence for analysis, the groups were separated by gender. As BSA also can affect blood pressure [24], the study populations were matched for this variable. Finally, given the role of impairment of renal function in hypertension, the study groups were matched for renal function as measured by serum creatinine and creatinine clearance and renal function was within the normal range.

In the present study, in both male and female ADPKD patients, hypertension was associated with greater renal structural abnormalities at comparable body surface areas and renal function. Specifically, the hypertensive ADPKD patients exhibited greater renal volumes. These results, therefore, may help explain the observation of Bennett et al [16] and Frang, Czvalinga and Polyak [17] that renal cyst decompression is associated with a decrease in systemic blood pressure. The present results are also compatible with the earlier findings of Milutinovic et al, which were not controlled for age, BSA, or gender [10], that patients with kidneys larger than 15 cm were more likely to be hypertensive.

The mechanism(s) by which renal cysts may initiate hypertension at an early stage of ADPKD is in need of further study.

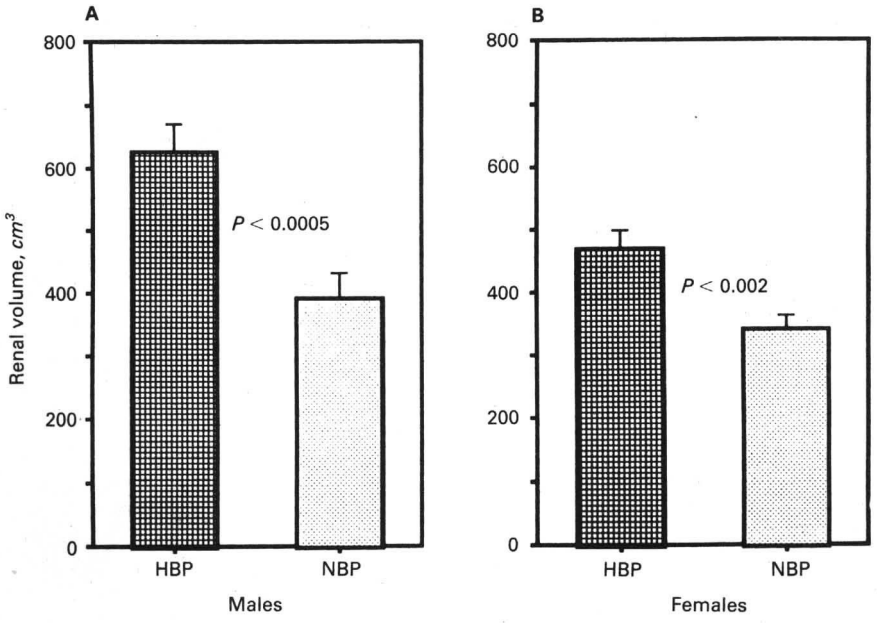


**Fig. 1.** *Renal volume in HBP and NBP ADPKD subjects separated by gender.* The bars are means ± 1 standard error of the mean. Symbols are: (■) HBP; (□) NBP.

Angiographic studies have shown attenuation of peripheral renal vasculature by renal cysts in patients with ADPKD [25, 26]. On the other hand, hormonal evidence of renal ischemia has been less evident. Specifically, plasma renin activity (PRA) has not been found to be consistently elevated in patients with ADPKD [5, 8]. It should be noted, however, that bilateral renal ischemia secondary to cyst enlargement in ADPKD may mimic bilateral renal artery stenosis which also is not consistently associated with an increase in PRA [27]. Moreover, recent preliminary data demonstrated that PRA and plasma aldosterone were significantly increased in hypertensive patients with ADPKD as compared to matched patients with essential hypertension, both before and after converting enzyme inhibition [28]. Thus, the early initiation of hypertension in ADPKD may relate to bilateral renal ischemia secondary to cyst alteration of renal vasculature. Further studies will be necessary to establish this pathogenetic mechanism by which increasing cystic involvement results in hypertension in ADPKD but activation of the renin-angiotensin-aldosterone system appears to be involved.

## Acknowledgments

These data were published in Kidney International 31:297, 1987 in abstract form. This research was supported by Grant 5 P01 DK34039, Human Polycystic Kidney Disease (PKD), awarded by the Department of Health and Human Services, Public Health Service, NIDDK, and the Clinical Research Center, Grant RR-0051 from the General Clinical Research Centers Research Program of the Division of Research Resources, National Institutes of Health.

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