# Chronic Caffeine Consumption Exacerbates Hypertension in Rats With Polycystic Kidney Disease

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● **Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited disorder frequently associated with renal failure, hypertension, and other abnormalities. The present study determined whether chronic caffeine intake in an animal model of this disease would affect renal structure and function and blood pressure. Heterozygous male Han:Sprague-Dawley rats with ADPKD and normal littermates were provided with either tap water or solutions of caffeine to drink, starting at 1 month of age. When rats were aged 6 months, glomerular filtration rate (GFR) and mean arterial blood pressure (MAP) were measured under Inactin (Byk Gulden, Konstanz, Germany) anesthesia. Caffeine intake had no effect on GFR or cyst development in rats with PKD. MAP was greater in rats with PKD than normal rats and was increased more by caffeine. The hypertensive effect of chronic caffeine intake could not be ascribed to direct pressor effects of angiotensin II. Based on our finding that caffeine exacerbates hypertension in rats with PKD, it may be prudent for patients with ADPKD to limit coffee consumption to four or fewer cups of caffeinated coffee per day, pending studies of humans.**
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**A**UTOSOMAL DOMINANT polycystic kidney disease (ADPKD) is an inherited disorder that is the fourth leading cause of end-stage renal failure in the world. In this disease, numerous epithelial sacs (cysts) arise from kidney tubules, leading to renal enlargement and insufficiency. ADPKD is a systemic disease. Cysts also are commonly found in the liver and pancreas. Approximately 60% to 75% of adult patients with ADPKD and normal renal function are hypertensive, and more than 80% of patients who developed end-stage renal disease are hypertensive.[1,2]

ADPKD in patients is extremely variable in its expression. This may be caused by the specific genetic defect, genetic background of an individual, and possibly such environmental factors as diet. In studies of animal models of PKD, it has been shown repeatedly that dietary modification can dramatically alter the course of PKD.[3] Evidence to date for such an effect in patients is much weaker.[4]

The Polycystic Kidney Research Foundation has recommended that patients with PKD should restrict their intake of caffeine-containing foods and beverages.[5] This recommendation appears to be based on (1) in vitro data showing that cyclic adenosine monophosphate (cAMP) stimulates fluid secretion and proliferation of cyst epithelial cells,[6,7] and (2) biochemical evidence that methylxanthines (eg, caffeine) inhibit the phosphodiesterase enzyme that breaks down cAMP.[8]

The present study determined whether chronic caffeine intake would affect renal structure and function and blood pressure in an animal model of ADPKD, the Han:Sprague-Dawley (Han: SPRD) rat. Heterozygous male Han:SPRD rats show a slowly progressive form of ADPKD that resembles the human disease in many respects.[9,10] Using clearance methods in the rat, we show that caffeine intake for 5 months did not significantly impair renal function, but exacerbated hypertension.

## MATERIAL AND METHODS

Experiments were conducted in accordance with The National Institutes of Health Guide for the Care and Use of Laboratory Animals. Animals used were heterozygous male Han:SPRD rats with PKD and their normal littermates, bred in our animal care facility from breeding stock originally obtained from the Polycystic Kidney Program at the University of Kansas. All animals were allowed free access to a diet

containing 24% protein and 6% fat (Teklad 6% mouse/rat diet 7002; Harlan, Madison, WI). Rats were provided with either tap water (19 normal rats, 17 rats with PKD) or caffeine solutions at concentrations of 0.1 mg/mL (6 rats with PKD), 0.2 mg/mL (5 normal rats, 5 rats with PKD), or 0.32 mg/mL (5 normal rats) to drink. Caffeine solutions were started at 1 month of age and continued until rats were aged 6 months. Fluid consumption was measured when rats were aged 3 months; we assumed that these values were representative of intake throughout the duration of the study. Caffeine intake was normalized per square centimeter of body surface area (BSA), using the formula[11]:

$$\text{BSA (cm}^2) = 9.1 \times \text{body weight (g)}^{0.66}$$

Clearance measurements were performed in rats anesthetized with Inactin (Byk Gulden, Konstanz, Germany) exactly as described previously, and some experiments were performed at the same time as in our previous study.[12] Briefly, a solution of polyfructosan (a synthetic inulin) in isotonic saline was infused intravenously at 3 mL/h to establish steady plasma levels. Clearance measurements from the left kidney were started 1 hour after cannulating the ureter, and two to three timed urine samples were collected over the next hour. Two to three arterial blood samples were collected. Mean arterial blood pressure (MAP) was measured through a femoral artery cannula and transducer (Gould-Statham, Hato Rey, PR) and continuously recorded on a chart recorder. Polyfructosan concentrations in plasma and urine were measured by an anthrone method, and glomerular filtration rate (GFR) was calculated as described previously.[12]

At the end of 14 experiments on rats with PKD, one kidney (usually the left) was rapidly removed, the cortex and medulla were separated, and wet and dry weights (samples heated in an oven at 120°C for 16 hours) were determined. The contralateral kidney was fixed by retrograde aortic perfusion with a 3% paraformaldehyde solution.[12] Histological sections were stained with hematoxylin and eosin. Four nonoverlapping cortical areas (each, 6.6 mm$^2$) from each of 10 kidneys were photographed using a digital camera at original magnification ×40, and cyst lumen areas were measured using Adobe Photoshop 5.5 (Adobe Systems, San Jose, CA). In sections of normal rat kidneys,[13] 99.7% of tubule lumen areas are less than 6,000 $\mu$m$^2$. Therefore, we defined a cyst as a luminal space surrounded by epithelial cells with an area greater than 6,000 $\mu$m$^2$. We determined the number of cysts per 26-mm$^2$ cortex area, number of cysts with a lumen area greater than 50,000 $\mu$m$^2$, and mean cyst lumen area.

Data are presented as mean ± SD. Data were analyzed by two-way (Table 1) or one-way (Tables 2 and 3) analysis of variance. Multiple comparisons in Table 1 were made using the Bonferroni correction. $P$ less than 0.05 is considered statistically significant.

## RESULTS

Table 1 lists results of experiments on rats that consumed either plain tap water or a high dose of caffeine in tap water from ages 1 to 6 months. Note that the caffeine concentration in the drinking water given to normal rats was 1.6 times that given to rats with PKD because rats with PKD drink approximately 1.6 times more fluid (Table 1) and we wanted to achieve similar caffeine intakes. Rats with PKD given tap water had lower GFRs and greater urine outputs compared with normal rats given tap water. Caffeine ingestion by normal rats did not affect any of the variables measured. However, caffeine intake by

**Table 1.  Effects of Chronic Intake of a High Dose of Caffeine**

| | Normal Rats | | Rats With PKD | |
|---|---|---|---|---|
| | Water | Caffeine (0.32 mg/mL) | Water | Caffeine (0.2 mg/mL) |
| Caffeine intake (mg/d/m$^2$ BSA) | 0 | 400 ± 12  (5) | 0 | 444 ± 58  (5) |
| Body weight (g) | 478 ± 26 (5) | 495 ± 7    (5) | 462 ± 29  (13) | 508 ± 14  (5)* |
| Fluid intake (mL/d/100 g body weight) | 13.4 ± 0.9 (5) | 13.8 ± 0.5 (5) | 21.4 ± 4.9 (9)† | 26.0 ± 3.8 (5)‡ |
| MAP (mm Hg) | 110 ± 3    (5) | 115 ± 3    (5) | 116 ± 10  (13) | 138 ± 16  (5)‡§ |
| GFR ($\mu$L/min/100 g body weight)‖ | 528 ± 41  (5) | 458 ± 40  (5) | 146 ± 67  (13)¶ | 98 ± 39  (5)# |
| Urine flow rate ($\mu$L/min/100 g body weight)‖ | 1.9 ± 1.2 (5) | 2.0 ± 1.2 (5) | 8.4 ± 3.6 (13)¶ | 7.0 ± 1.9 (5)** |

NOTE. Numbers in parentheses indicate number of rats.
*$P$ < 0.01 compared with rats with PKD given water.
†$P$ < 0.01 compared with normal rats given water.
‡$P$ < 0.01 compared with normal rats given caffeine.
§$P$ < 0.001 compared with rats with PKD given water.
‖For the left kidney.
¶$P$ < 0.001 compared with normal rats given water.
#$P$ < 0.001 compared with normal rats given caffeine.
**$P$ < 0.05 compared with normal rats given caffeine.

**Table 2. Effects of Chronic Intake of a Lower Dose of Caffeine**

| | Normal Rats | | Rats With PKD | |
|---|---|---|---|---|
| | Water | Caffeine (0.2 mg/mL) | Water | Caffeine (0.1 mg/mL) |
| Caffeine intake (mg/d/m² BSA) | 0 | 305 ± 32 (5) | 0 | 214 ± 16 (6) |
| Body weight (g) | 464 ± 28 (14) | 491 ± 17 (5) | 467 ± 10 (4) | 499 ± 26 (6)* |
| Fluid intake (mL/d/100 g body weight) | 15.1 ± 2.5 (7) | 17.7 ± 2.0 (5) | | 25.1 ± 2.0 (6) |
| MAP (mm Hg) | 107 ± 6 (14) | 103 ± 4 (5) | 108 ± 9 (4) | 123 ± 7 (6)* |
| Heart rate (beats/min) | | | 327 ± 14 (4) | 335 ± 5 (3) |
| GFR (μL/min/100 g body weight)† | 392 ± 31 (14) | 388 ± 30 (5) | 168 ± 26 (4) | 162 ± 37 (6) |
| Urine flow (μL/min/100 g body weight)† | 6.8 ± 1.7 (14) | 5.8 ± 2.1 (5) | 9.1 ± 3.7 (4) | 9.7 ± 3.9 (6) |

NOTE. Numbers in parentheses indicate number of rats.

*$P < 0.05$ compared with rats with PKD given water.

†For the left kidney.

rats with PKD resulted in greater body weights and greater MAPs than rats drinking tap water. Fluid intake, GFR, and urine output were not significantly affected by caffeine intake in rats with PKD.

Table 2 lists results from experiments with lower doses of caffeine. As with the greater doses, caffeine intake had no significant effect on any of the measured variables in normal rats, but it produced significantly greater body weights and blood pressures in rats with PKD.

Figure 1 shows the relation between MAP and caffeine intake from all experiments in Tables 1 and 2. Even with no caffeine intake, rats with PKD had significantly greater MAPs than normal rats. The slope of the line relating blood pressure to caffeine intake is significantly ($P < 0.001$) higher in rats with PKD than normal rats, suggesting that rats with PKD are more sensitive to the blood pressure–increasing effect of caffeine.

To determine whether the greater blood pressures observed with chronic caffeine intake were caused by increased activity of the renin-angiotensin system, we examined the effects of angiotensin II blockers (losartan, saralasin) at the end of some experiments. Injection of 10 mg/kg of body weight of losartan intravenously, a dose that resulted in 89% ± 15% inhibition of the pressor response to a bolus injection of 100 ng/kg of angiotensin II, produced a decrease in MAP of 5 ± 3 mm Hg (n = 5) in normal tap-water–drinking rats and 6 ± 4 mm Hg (n = 4) in normal high-dose caffeine-consuming rats (Table 1) after 5 minutes; these responses are not significantly different. In three rats with PKD that consumed a low caffeine dose (Table 2), losartan produced a 3 ± 2 mm Hg decrease in MAP. In rats with PKD (Table 2), intravenous infusion of saralasin at 10 μg/min/kg for 40 minutes, a dose that resulted in 100% inhibition of the pressor effect of an angiotensin II bolus,

**Table 3. Effects of Caffeine Intake on Kidney Weight, Water Content, and Histological Characteristics in Rats With PKD**

| | Water | Caffeine (0.2 mg/mL) |
|---|---|---|
| Left kidney weight (g) | 2.88 ± 0.62 (17) | 2.96 ± 0.24 (5) |
| Cortex (% water) | 87.5 ± 0.6 (9) | 87.3 ± 0.4 (5) |
| Medulla (% water) | 85.0 ± 0.7 (9) | 84.8 ± 0.3 (5) |
| No. of cysts/26 mm² of cortex | 321 ± 28 (5) | 282 ± 57 (5) |
| Large cysts/26 mm² of cortex* | 20 ± 3.7 (5) | 20 ± 13.6 (5) |
| Mean cyst lumen area (μm²) | 1,449 ± 158 (5) | 1,518 ± 285 (5) |

NOTE. Caffeine intake did not result in a statistically significant change in any of these variables. Numbers in parentheses indicate number of rats.

*Large cysts are defined as those with a lumen area greater than 50,000 μm².
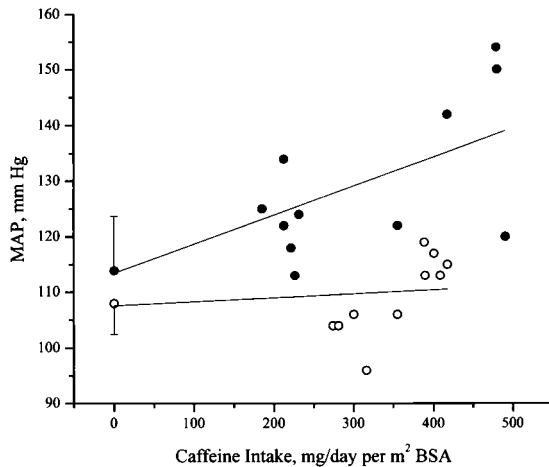
**Fig 1.   Relation between MAP and caffeine intake in normal rats (○, lower line) and rats with PKD (●, upper line). Each circle for rats given caffeine presents blood pressure data from a single 6-month-old rat. With no caffeine intake, MAP averaged 114 ± 10 mm Hg (n = 17) in rats with PKD and was significantly (_P_ < 0.05) greater than that in normal rats (108 ± 5 mm Hg; n = 19). Rats with PKD showed a steeper relation between blood pressure and caffeine intake than normal rats (_P_ < 0.001). Equations for least-squares lines are y = 0.007x + 108 (_r_ = 0.20; _P_ = not significant) for normal rats and y = 0.052x + 113 (_r_ = 0.68; _P_ < 0.001) for rats with PKD.**

produced an increase in MAP of 4 ± 1 mm Hg (n = 4) in water-drinking rats and 1 ± 3 mm Hg (n = 3) in caffeine-solution–drinking rats; these values are not significantly different. We are forced to reject the hypothesis that the vasoconstrictor effect of angiotensin has a role in the hypertension produced by caffeine intake because angiotensin II blockers did not produce a greater decrease in blood pressure in caffeine-consuming rats.

Table 3 lists kidney weights, water content, and histological characteristics in rats with PKD drinking either water or a 0.2-mg/mL caffeine solution. Caffeine intake produced no significant difference in any of the measured variables. Notably, the number and size of cysts did not differ in rats drinking tap water versus caffeine solution.

## DISCUSSION

The major finding in this study is that chronic caffeine intake exacerbates hypertension in rats with ADPKD. Our initial studies were performed using a caffeine solution containing 0.2 mg/mL

because this concentration has been widely used in studies of rats.[14] The average intake in rats with PKD of this solution was 444 mg/d/m² of BSA (Table 1). If we assume an average cup of brewed coffee contains 85 mg of caffeine[15] and an average human adult man has a BSA of 1.73 m², then the intake of caffeine by rats was equivalent to a human intake of approximately nine cups of coffee per day. With the lower dose of caffeine, 0.1 mg/mL of drinking water (Table 2), the average caffeine intake by rats with PKD was equivalent to human consumption of four cups of coffee a day. Coffee intake varies widely: in Denmark, the average daily intake by adults is 7 mg of caffeine/kg of body weight, or approximately six cups of coffee.[15] Caffeine doses used on this study of rats are high, but not unreasonably so.

Caffeine intake led to a significant increase in body weight in rats with PKD (Tables 1 and 2). In normal rats, there was a tendency for a greater body weight with caffeine intake, but this did not reach statistical significance. It is possible that the weight gain is a consequence of a stimulating effect of caffeine on activity and food intake, but we did not measure these parameters.

Excess body weight or obesity is the major risk factor for hypertension in humans, but the mechanisms by which obesity increases blood pressure are not fully understood.[16] In rodents, obesity is not universally associated with an increase in blood pressure.[17] It is possible that the modestly greater weights in caffeine-drinking rats with PKD, approximately 7% to 10% greater than in water-drinking rats with PKD, is caused by expanded extracellular fluid and plasma volumes, but these variables were not studied.

We should note that we undertook these studies to determine whether caffeine would affect renal cyst size and renal function in vivo, suggested from in vitro studies.[5] We therefore performed measurements that are routine in clearance studies. The increase in MAP with caffeine intake was a complete surprise. Because a similar effect in patients could be important, we believe it prudent to report this finding, although we were not able to sort out the mechanisms from our measurements. The increased body weight with caffeine consumption may provide a clue for further study.

We observed no statistically significant detri-

mental effects of chronic caffeine consumption on kidney function in 6-month-old rats with PKD (Tables 1 and 2). With the greater dose of caffeine (Table 1), there was a trend toward a lower GFR in rats with PKD compared with rats with PKD drinking tap water. In 6-month-old rats with PKD, GFR averaged approximately one third to one quarter of normal values. In our colony, male heterozygous rats with PKD drinking tap water die of renal failure at an average age of 9 months.[12] If caffeine consumption accelerates the progression of PKD in the Han:SPRD rat, this effect may be noticeable only late in the disease in this model.

There are several possible ways in which caffeine might have produced hypertension in rats with PKD. Caffeine can increase blood pressure by activating the sympathetic nervous system or renin-angiotensin system, exerting positive inotropic and chronotropic effects on the heart, or blocking the vasodilator effects of adenosine.[18,19] Heart rate did not differ in rats that consumed caffeine compared with rats that consumed tap water (Table 2), suggesting that an increase in heart rate or cardiac sympathetic activity does not explain the hypertension. Acute administration of angiotensin II blockers did not affect blood pressure differently in caffeine-treated rats compared with rats that drank water; therefore, it is unlikely that the hypertension produced by chronic caffeine intake is caused by the vasoconstrictor effect of circulating angiotensin II. Further studies are needed to define the mechanisms responsible for caffeine-induced hypertension in rats with PKD.

There currently is no evidence that caffeine directly stimulates cyst growth in vivo. Data in Table 3 do not support the idea that caffeine results in more or larger kidney cysts. Furthermore, it is unlikely for several reasons[20] that caffeine exerts its effects in the body by blocking the breakdown of intracellular cAMP. First, caffeine, in contrast to isobutylmethylxanthine (which was used in the in vitro studies[6,7]), is a weak phosphodiesterase inhibitor. Second, plasma levels of caffeine achieved after coffee drinking are much less than those needed to affect cAMP breakdown. Third, in in vivo studies, investigators have not shown increases in tissue or plasma levels of cAMP after the administration of therapeutic doses of methylxanthines. Actions of caffeine in vivo in doses ordinarily consumed appear to be related mainly to antagonism of endogenous adenosine at the receptor level.[20] Although cAMP might have a role in renal cystic disease,[21,22] we consider it unlikely that caffeine affects this disease by changing cAMP levels.

Effects of caffeine on cardiovascular function in humans have been studied and debated for a long time.[18,19] Chronic caffeine intake is not usually associated with a persistently elevated blood pressure or increased frequency of hypertension, and it usually does not produce lasting increases in plasma levels of catecholamines, vasopressin, or renin. Pincomb et al[23] found that men with borderline hypertension responded to acute caffeine administration with a greater increase in diastolic blood pressure than healthy men. They suggested that regular caffeine use in such persons may stabilize high vascular resistance states and promote the progression of vascular disease. Several investigators[24-27] examined effects of chronic caffeine consumption in various rat models of hypertension. Rats with hypertension caused by renovascular disease respond to chronic caffeine intake with a further increase in blood pressure. Conversely, normal rats, spontaneously hypertensive rats, and rats with genetic heart failure do not show an increase in blood pressure with chronic caffeine intake. Caffeine attenuates an increase in blood pressure in deoxycorticosterone acetate (DOCA)-salt hypertensive rats. Results of the present study support the general finding that some hypertensive or hypertension-prone people or animals may be unusually sensitive to the pressor effects of caffeine.[19,23,24]

Hypertension is a common problem in patients with PKD and may contribute to a decline in renal function.[28-32] The rate of renal disease progression is more rapid in hypertensive versus normotensive patients with PKD. There also is an increased incidence of cardiac valve abnormalities and aneurysms, additional reasons that hypertension should be controlled. It has been shown recently that control of blood pressure with an angiotensin-converting enzyme inhibitor (enalapril) leads to a significant decrease in urinary albumin excretion in patients with ADPKD, and this treatment could delay the onset of renal failure.[32] Studies of Han:SPRD rats with ADPKD have shown that chronic treatment with

enalapril reduces blood pressure, improves GFR and renal plasma flow, and decreases kidney size.[33]

Based on our finding that caffeine exacerbates hypertension in rats with ADPKD, it may be wise for patients with this disease to limit their intake of caffeinated coffee to four or fewer cups per day. This recommendation is, of course, an extrapolation from an animal study; it may not be relevant to humans. Controlled clinical trials or epidemiological studies are needed to determine whether caffeine intake exacerbates hypertension in patients with ADPKD.

## ACKNOWLEDGMENT

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