Kidney International, Vol. 64 (2003), pp. 1381–1388

Endothelial dysfunction and reduced nitric oxide in resistance arteries in autosomal-dominant polycystic kidney disease

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Endothelial dysfunction and reduced nitric oxide in resistance arteries in autosomal-dominant polycystic kidney disease.

Background. Patients with autosomal-dominant polycystic kidney disease (ADPKD) have defective endothelium-dependent relaxation (EDR). We investigated the relationship between endothelial dysfunction and nitric oxide generation in hypertension and chronic renal insufficiency (CRI) in ADPKD.

Methods. We contrasted acetylcholine (ACh)-induced EDR, 3-morphollinosydnonimine (SIN-1)-induced endothelium-independent relaxation (EIDR) and constitutive nitric oxide synthase (cNOS) activity in subcutaneous resistance vessels and plasma levels and excretion of NO_2^-/NO_3^- (NO_X) in normal, control ($N = 10$) patients with ADPKD or essential hypertension.

Results. EDR was decreased significantly in normotensive ADPKD ($N = 9$), but more severely in hypertensive ADPKD ($N = 6$), or those with CRI ($N = 5$) and in essential hypertension ($N = 9$). The increases in EDR with L-arginine and decreases with L^G-nitro-L-arginine methyl ester (L-NAME) were lost in all groups of patients with ADPKD and in essential hypertension except for a modest effect of L-NAME in normotensive ADPKD. EIDR was unimpaired throughout. Vascular cNOS activity and renal NO_X excretion were reduced profoundly in patients with all categories of ADPKD and especially in those with hypertension.

Conclusion. EDR in resistance vessels from patients with ADPKD is impaired even in the absence of hypertension or CRI, but becomes more marked as hypertension develops. Patients with ADPKD have defective nitric oxide generation from diminished cNOS activity. Endothelial dysfunction and impaired cNOS activity in ADPKD may predispose to hypertension whose occurrence is accompanied by a further sharp deterioration in EDR.

Autosomal-dominant polycystic kidney disease (ADPKD) is a relatively common genetic disorder. Although the kidneys are the major site of clinical disease, it is a multisystem disorder affecting the liver, blood vessels, and heart valves. Large vessels in ADPKD may show vascular ectasia and aneurysms as well as aortic root dilatation [1]. Development of hypertension in ADPKD is succeeded by the onset of chronic renal insufficiency (CRI). The causes of this early rise in blood pressure remain controversial [2].

Endothelium-dependent relaxation of arteries can be induced in vitro by acetylcholine (ACh), which functions as an activator of nitric oxide synthase (NOS) by increasing intracellular calcium [3]. An impaired relaxation response of resistance vessels to ACh has been proposed to contribute to vascular disease in essential hypertension and diabetes mellitus [4–7]. Endothelium-derived nitric oxide plays an important role in maintaining homeostasis of the cardiovascular system [8, 9]. Nitric oxide is generated from the metabolic conversion of L-arginine into L-citrulline by the activity of NOS. The major vascular isoform of constitutive NOS (cNOS) is endothelial NOS (eNOS), which is implicated in endothelium-dependent relaxation with ACh [3]. eNOS knockout mice have an impaired endothelium-dependent relaxation and mild hypertension [10]. These observations have led to the concept that resistance vessels in vivo are maintained in a constant state of vasodilatation by endogenously released nitric oxide.

An impaired relaxation response of resistance vessels to ACh may contribute to vascular disease in essential hypertension and CRI. Recently, we have demonstrated that endothelium-dependent relaxation to ACh and its response to the NOS inhibitor, L^G-nitro-L-arginine methyl ester (L-NAME), are impaired in mesenteric vessels of a rat model of polycystic kidney disease (PKD) (Han:SPRD) [11] and in patients with ADPKD [12].

Since both hypertension and CRI can cause endothelial dysfunction, the first aim of this study is to dissociate the effects of endothelial dysfunction due to ADPKD from the associated hypertension or CRI. We contrasted endothelial function in groups of age-matched normotensive control subjects, ADPKD without hypertension

Key words: chronic renal insufficiency, nitric oxide, hypertension, nitric oxide synthase, arginine.

Received for publication March 22, 2003
and in revised form May 27, 2003
Accepted for publication June 11, 2003

or CRI, ADPKD with hypertension, ADPKD with hypertension and CRI, and in a further group of patients with essential hypertension. Care was taken to characterize hypertension quantitatively from ambulatory 24-hour blood pressure monitoring, and renal function from the plasma clearance of [^{51}Cr]-ethylenediaminetetraacetic acid (EDTA). Endothelial dysfunction could represent defects in endothelium-derived relaxation factor (EDRF) nitric oxide, in responsiveness to nitric oxide in NOS activity, or in endothelium-derived hyperpolarization factor (EDHF). Therefore, the second aim was to investigate the mechanism of endothelial dysfunction in subcutaneous vessels dissected from patients with ADPKD. We assessed the role of nitric oxide from the effects of L-arginine or L-NAME on ACh-induced vasorelaxation, from measurements of NOS activity and from 24-hour excretion of the nitric oxide metabolite, NO_2^-/NO_3^- (NO_X).

METHODS

Patients

The protocol was approved by the Medical Ethics Committee, Copenhagen County, Denmark. All individuals gave written informed consent before entering the study. Ten healthy control subjects, nine normotensive ADPKD patients, six hypertensive ADPKD patients without CRI, five hypertensive ADPKD patients with CRI, and nine patients with essential hypertension were studied. The patients' ages were 23 to 60 years. All subjects were Caucasians and without hypercholesterolemia. All patients with ADPKD were diagnosed by renal ultrasound showing five or more renal cysts distributed in both kidneys. Most patients had a positive family history of ADPKD. The diagnosis of essential hypertension was established by the presence of hypertension and the absence of clinical and laboratory evidence of secondary hypertension or diabetes mellitus and normal serum electrolytes, creatinine, and urinalysis. Inclusion criteria for the normotensive ADPKD patients were that patients consistently had a systolic blood pressure <140 mm Hg and a diastolic blood pressure <90 mm Hg. Patients were considered hypertensive when their clinic systolic blood pressure was consistently >140 mm Hg or diastolic blood pressure was >90 mm Hg or when they were taking antihypertensive drugs. No antihypertensive or other drugs were taken by the patients with normotensive ADPKD or the control subjects. All patients with hypertensive ADPKD and those with essential hypertension were treated with two or more different antihypertensive drugs [angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta blockers, alpha-beta blockers, calcium antagonists, or diuretics]. Vessels for study were harvested as described below 24 hours or more after the most recent drug intake. Plasma creatinine was normal (68 to 105 μmol/L) in eight of nine normotensive ADPKD patients, all hypertensive ADPKD patients without CRI, and all patients with essential hypertension. A Takeda 2420 monitor (Takeda, Tokyo, Japan) was used to measure 24-hour ambulatory blood pressure. Glomerular filtration rate (GFR) was calculated from the 4-hour, one-sample plasma clearance method using [^{51}Cr]-EDTA [13]. All measurements were completed within 1 week of the subcutaneous fat biopsy described below.

Preparation of small subcutaneous vessels

A biopsy of subcutaneous fat of 1.0 × 0.5 × 0.5 cm was obtained from the gluteal region under local anesthesia with 1% lidocaine hydrochloride and placed immediately in cold physiologic salt solution (PSS) (sodium chloride 118 mmol/L, sodium bicarbonate 25 mmol/L, potassium chloride 4.5 mmol/L, calcium chloride 2.5 mmol/L, magnesium sulfate 1.0 mmol/L, and glucose 6.0 mmol/L). Using a dissecting microscope (Olympus SN450, Copenhagen, Denmark), two segments of small arteries (about 2 mm in length with a mean diameter of 200 to 300 μm) were cleaned and frozen in liquid nitrogen for subsequent measurement of NOS activity. Another two segments of the same artery were prepared for functional studies as previously described [14]. Vessels were mounted as a ring preparation on two 40 μm stainless steel wires in an isometric Mulvany-Halpern small-vessel myograph (J.P. Trading I/S, Aarhus, Denmark) [15]. One wire was attached to a force transducer and the other to a micrometer [14, 15]. This arrangement enabled the wall tension to be measured at a predetermined internal circumference. Both dissection and mounting of the vessels were carried out in cold (4°C) PSS. The two segments of resistance vessels from each individual were studied in parallel. One was treated by the experimental protocol described below; the other served as a time control. It was contracted repeatedly with norepinephrine (10^{-5} mol/L).

Vessel experimental procedure

Resistance vessels were warmed in PSS to 37°C, equilibrated for 30 minutes, and the internal circumference set to give a wall tension of 0.2 mN/mm. The myograph chamber was bubbled with 5% CO_2 and 95% O_2 to maintain a pH of 7.4. The resting tension/internal circumference relationship for each vessel was determined. The internal circumference was set to 0.9 × L_{100}, where L_{100} is the calculated internal circumference the vessel would have had in vivo when relaxed and under a transmural pressure of 100 mm Hg [15]. Thereafter, the vessels were incubated for 30 minutes in PSS, which was changed each 10 minutes. Vessels were contracted three times with norepinephrine (10^{-5} mol/L), followed by one exposure to high-potassium solution (KPSS), where sodium chloride was replaced by potassium chloride and finally a repeat exposure to PSS contained norepinephrine (10^{-5}

mol/L). Contractions were maintained for 3 minutes before rinsing with PSS. Thereafter, the vessels were rinsed three times with PSS and left to recover for 20 minutes.

For relaxation studies, vessels were precontracted with norepinephrine (10^{-5} mol/L) and relaxed with Ach (10^{-9} to 10^{-5} mol/L). The bath was rinsed with PSS three times and the precontracted vessels relaxed with 3-morpholinosydnonimine (SIN-1) (10^{-9} to 10^{-3} mol/L). The vessels were rinsed and incubated with L-arginine (10^{-3} mol/L) for 30 minutes after which the norepinephrine contraction and ACh relaxation responses were repeated. Finally, the vessels were rinsed with PSS and incubated with L-NAME (10^{-4} mol/L) for 30 minutes, after which the norepinephrine contraction and ACh relaxation responses were repeated.

All solutions were prepared freshly 1 day before the experiment. ACh, norepinephrine, SIN-1, and L-NAME were purchased from Sigma Chemical Co. (St. Louis, MO, USA). All reagents were prepared in distilled water and diluted to the final bath concentration with PSS.

Pilot time control studies

The time control studies showed that the constriction to norepinephrine was unchanged for the duration of the experiment. We had shown previously that the relaxation responses to ACh were unchanged during incubation in PSS for 30 minutes, 60 minutes, and 120 minutes [12]. Moreover, in a further time control experiment with subcutaneous resistance arteries from normal controls and ADPKD patients, we found that the maximum responses to norepinephrine and the sensitivity to ACh remained stable over a 10-hour period (data not shown).

Measurements of NOS activity of vessels

Frozen vessels were pulverized and solubilized in a homogenization buffer containing 25 mmol/L Tris-HCl (pH 7.4), 1 mmol/L EDTA and 1 mmol/L ethyleneglycoltetraacetic acid (EGTA) at 4°C with a tissue grinder fitted with a motor-driven, ground-glass pestle. Homogenates were centrifuged at 15,000*g* for 5 minutes at 4°C to remove tissue debris without precipitation of the plasma membrane fragments [16]. The supernatant was used for determination of NOS activity and protein mass.

NOS activity of vessels was measured with NOS Detect™ Assay Kit (Stratagene, Alexis Corporation, Lausen, Switzerland) by the conversion of [^{14}C]-L-arginine to [^{14}C]-L-citrulline (Amersham International, Piscatawa, NJ, USA) [17, 18]. NOS activity was expressed as picomoles of citrulline formed per 45 minutes per milligram of protein.

Plasma and urinary NO_X assay

All subjects fasted for 12 hours overnight to reduce diet-related nitrate production [19]. Blood samples were heparinized and plasma separated. Urinary samples were diluted with 2-isopropanol at a final concentration of 10% to prevent bacterial activity [20]. Plasma and urinary samples were frozen at –20°C until analyzed.

NO_X concentration was measured in duplicate using a nitric oxide colorometric assay kit (Griess Reaction, Boehringer, Inc., Mannheim, Germany).

Statistics

Data are expressed as mean ± SD. Statistical differences are evaluated by multiple one-way analysis of variance (ANOVA) or by Newman-Keuls statistics among groups. ACh sensitivity is expressed as pED_{50}, which is the (–log) concentration of the drug required to produce 50% of the maximum response. Relaxation responses to the ACh and SIN-1 are expressed as a percentage decline for the maximum contractile response. The statistical significance is defined as $P < 0.05$. Statistica 5.0 (StatSoft, Tulsa, OK, USA) was used as software.

RESULTS

Clinical characteristics of the subjects

The age and gender of the groups were similar (Table 1). The ambulatory blood pressure was higher in patients with hypertensive ADPKD without CRI and hypertensive ADPKD with CRI and essential hypertension than in controls. The [^{51}Cr]-EDTA clearance was lower in hypertensive ADPKD patients with CRI than in other groups. A modestly decreased GFR of 56 mL/min was found in one normotensive patient with ADPKD, who had a normal serum creatinine concentration and therefore was included in the study.

Endothelium-dependent relaxation (EDR)

The ACh-induced maximum EDR (E_{max}) and pED_{50} were attenuated significantly in vessels from all patient groups. The most severely impaired responses were in vessels from patients with essential hypertension. These defects in essential hypertension were significantly greater than those recorded in both hypertensive groups with ADPKD (with or without CRI), which themselves were significantly greater than in normotensives with ADPKD (Fig. 1) (Table 2). In individuals with normal renal function (GFR 80 to 120 mL/min) from all four groups ($N = 34$), maximum relaxation rate was negatively correlated with the 24-hour ambulatory mean blood pressure ($r = -0.53$, $P = 0.002$) (Fig. 6).

Effects of L-arginine

Incubation of vessels with L-arginine significantly shifted the midpoints of the ACh-dose response curve to the left in normal subjects. However, L-arginine did not significantly change the E_{max} or pED_{50} for ACh in any of the patient groups with ADPKD or essential hypertension (Table 2) (Fig. 2).

Table 1. Characteristics of study groups (mean ± SD)

	Normal control	Normotensive ADPKD	Hypertensive ADPKD	Hypertensive ADPKD-CRI	Essential hypertension
Number	10	9	6	5	9
Age *years*	38 ± 12	43 ± 10	43 ± 10	48 ± 9	46 ± 10
Gender *m/f*	5/5	5/4	4/2	3/2	6/3
Cholesterol *mg/dL*	154 ± 13	155 ± 16	160 ± 15	156 ± 15	167 ± 17
Mean ambulatory blood pressure *mm Hg*	92 ± 6	89 ± 8	110 ± 7[a]	112 ± 8[a]	109 ± 11[a]
[^{51}Cr]-EDTA clearance *mL/min/1.73 m^2*	100 ± 9	84 ± 16	101 ± 10	16 ± 10[a,b]	90 ± 9

Abbreviations are: ADPKD, autosomal-dominant polycystic kidney disease; CRI, chronic renal insufficiency; EDTA, ethylenediaminetetraacetic acid. Mean ± SD values.
[a] $P < 0.05$ compared to normal controls; [b] $P < 0.001$ compared to normotensive ADPKD

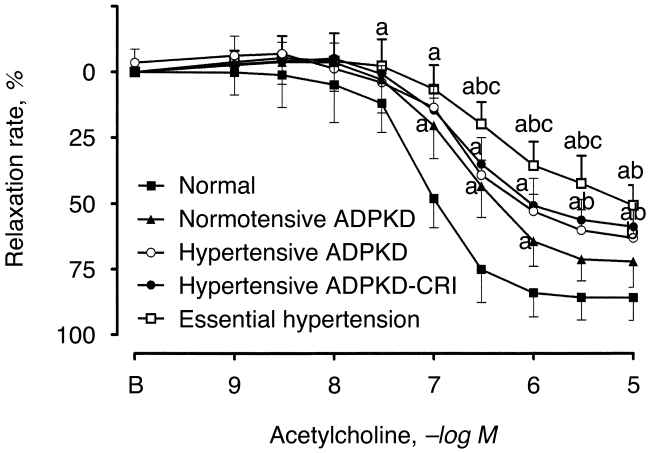

Fig. 1. Mean ± SD values for acetylcholine (Ach)-induced relaxation curves of norepinephrine-precontracted subcutaneous small arteries. a, $P < 0.01$ compared to normal controls; b, $P < 0.01$ compared to normotensive autosomal-dominant polycystic kidney disease (ADPKD); c, $P < 0.01$ compared to hypertensive ADPKD. CRI is chronic renal insufficiency.

Effects of L-NAME

Incubation with L-NAME significantly attenuated ($P < 0.01$) the maximum ACh-induced relaxation response and shifted this to the right in resistance vessels from normal controls (Fig. 2) (Table 2). However, L-NAME did not abolish ACh-induced relaxation in these vessels. Vessels from normotensive ADPKD patients had a mild right-shifted response to L-NAME, but L-NAME did not modify significantly the ACh responses in vessels from any other groups of patients with ADPKD or essential hypertension.

Endothelium-independent relaxation

The SIN-1–induced relaxation responses were similar in resistance vessels from all five groups of subjects (Fig. 3).

cNOS activity in resistance vessels

cNOS activity was decreased profoundly in vessels from all patients with ADPKD. There was a significantly greater reduction in the ADPKD patient groups with hypertension compared to normotension, and a greater reduction still in those with essential hypertension (Fig. 4).

Plasma and urinary NO_X

Compared to normal controls, the plasma concentration of NO_X and the rate of renal NO_X excretion were reduced in all patient groups with ADPKD and essential hypertension, except for plasma NO_X, which was elevated in patients with CRI (Fig. 5).

DISCUSSION

The results confirm previous findings in the Han:SPRD rat model of PKD and patients with ADPKD of an impairment of ACh-induced, endothelium-dependent relaxation of resistance vessels [11, 12]. The major new findings of the present study are that ACh-induced relaxation response of resistance vessels of patients with ADPKD is impaired even in the absence of hypertension or CRI. However, this impairment is exaggerated in ADPKD patients with hypertension, but there appears to be no further impairment in hypertensive ADPKD patients with CRI. The most profound defect in endothelial dysfunction was found in patients with essential hypertension. The endothelial defects in patients with ADPKD and essential hypertension were associated with a loss of an effect of L-NAME on the vessel's response to ACh and a major reduction in NO_X excretion and in cNOS activity of microdissected resistance vessels. During L-NAME, the sensitivity and responsiveness to ACh become similar in the groups with ADPKD or essential hypertension to normal subjects. These results suggest that both ADPKD and hypertension have independent effects to impair endothelial function, and that the effects of these conditions on endothelial function can be ascribed primarily to reduced cNOS expression and nitric oxide generation.

Endothelial function is impaired by dyslipidemia [21] and normal aging [22]. Age and serum cholesterol levels were similar between groups (Table 1), but variation between subjects may have contributed to the response. The profound impairment of ACh-mediated vasodilatation in patients with essential hypertension confirms results in many, but not all, prior studies. Endothelial dysfunction in human hypertension has been documented

Table 2. The maximum relaxation response (E_{max}) and sensitivity (pED_{50}) to acetylcholine of subcutaneous resistance vessels

Index	Normal control	Normotensive ADPKD	Hypertensive ADPKD	Hypertensive ADPKD-CRI	Essential hypertension
Number	10	9	6	5	9
Vehicle					
E_{max} %	85 ± 9	71 ± 12^{a}	$61 \pm 6^{a,b}$	$58 \pm 8^{a,b}$	$50 \pm 13^{a,b}$
pED_{50}	7.15 ± 0.01	6.69 ± 0.03^{a}	6.67 ± 0.05^{a}	$6.64 \pm 0.04^{a,b}$	$6.38 \pm 0.08^{a,b}$
L-arginine					
E_{max} %	92 ± 5^{c}	79 ± 8^{a}	$67 \pm 5^{a,b}$	$63 \pm 9^{a,b}$	$52 \pm 9^{a,b}$
pED_{50}	7.42 ± 0.02^{c}	6.72 ± 0.04^{a}	6.70 ± 0.09^{a}	$6.66 \pm 0.10^{a,b}$	$6.43 \pm 0.06^{a,b}$
L-NAME					
E_{max} %	68 ± 7^{c}	61 ± 9^{c}	63 ± 8	57 ± 7^{a}	$52 \pm 6^{a,b}$
pED_{50}	6.41 ± 0.27^{c}	6.45 ± 0.14^{c}	$6.64 \pm 0.17^{a,b}$	$6.57 \pm 0.19^{a,b}$	6.40 ± 0.14

Abbreviations are: ADPKD, autosomal-dominant polycystic kidney disease; CRI, chronic renal insufficiency. Mean ± SD values.
[a]$P < 0.01$ compared to normal controls; [b]$P < 0.01$ compared to normotensive ADPKD; [c]$P < 0.01$ compared to vehicle

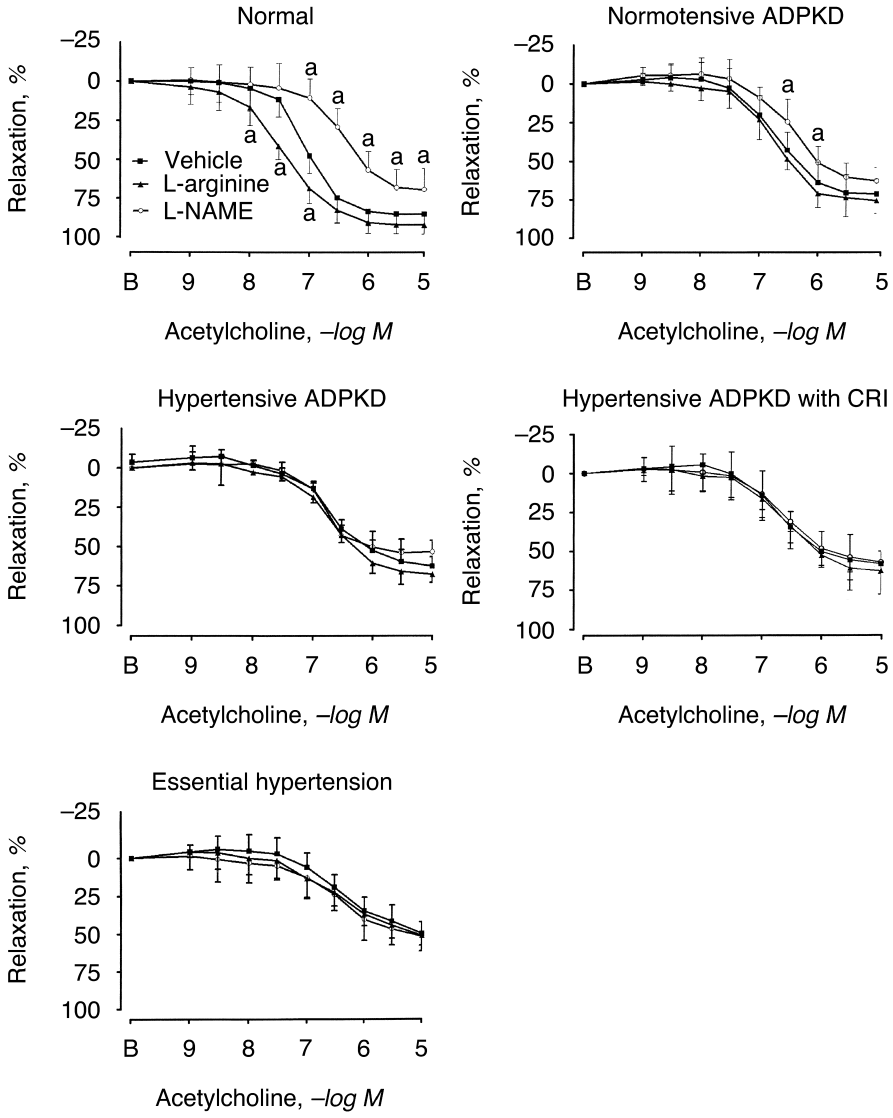

Fig. 2. Mean ± SD values for the effects of L-arginine or L-NAME on the acetylcholine (Ach)-induced relaxation curves of norepinephrine-precontracted subcutaneous small arteries from five groups of subjects. a, $P <$ 0.01 compared to physiologic salt solution (PSS) alone.

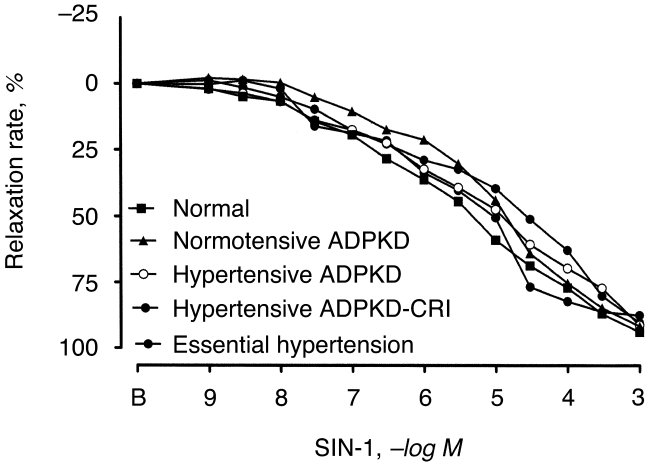

Fig. 3. Mean ± SD values for 3-morphollinosydnonimine (SIN-1)-induced relaxation response of norepinephrine-precontracted subcutaneous small arteries.

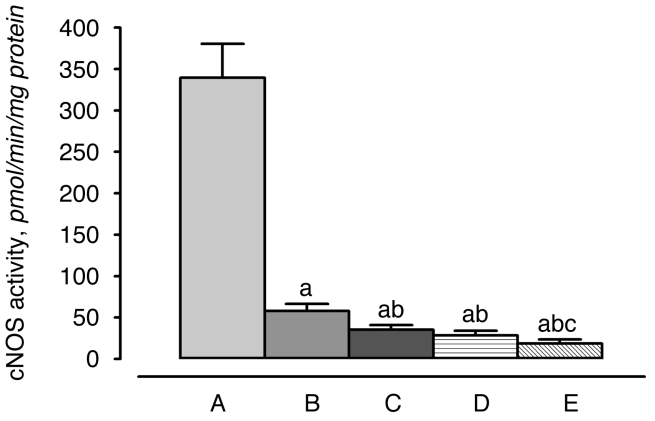

Fig. 4. Activity of constitutive nitric oxide synthase (cNOS) in isolated vessels. Column A, normal controls; column B, normotensive autosomal-dominant polycystic kidney disease (ADPKD); column C, hypertensive ADPKD; column D, hypertensive ADPKD with chronic renal insufficiency (CRI); and column E, essential hypertension. a, $P < 0.01$ compared to normal controls; b, $P < 0.05$ compared to normotensive ADPKD; c, $P < 0.01$ compared to hypertensive ADPKD.

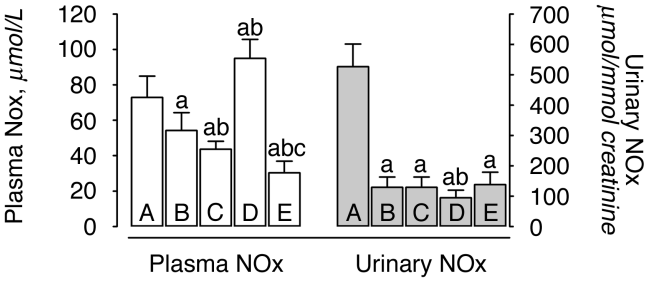

Fig. 5. Plasma and urinary NO_2^-/NO_3^- (NO_X). Column A, normal controls; column B, patients with normotensive autosomal-dominant polycystic kidney disease (ADPKD); column C, hypertensive ADPKD; column D, hypertensive ADPKD with chronic renal insufficiency (CRI); and column E, essential hypertension. a, $P < 0.001$ compared to normal controls; b, $P < 0.05$ compared to normotensive ADPKD; c, $P < 0.01$ compared to hypertensive ADPKD.

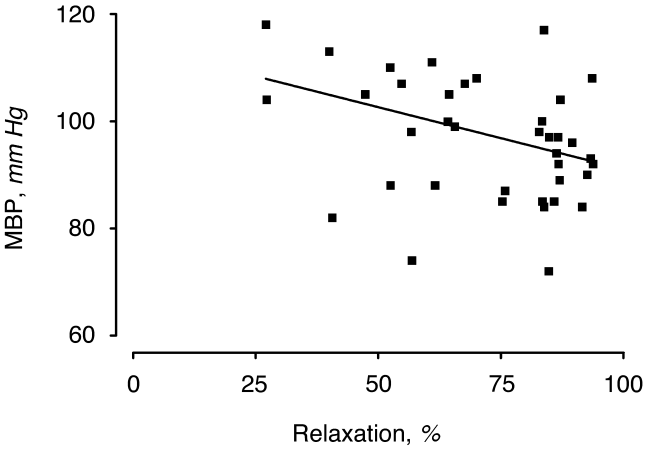

Fig. 6. Linear correlation between acetylcholine-induced maximum relaxation and 24-hour mean ambulatory blood pressure (MBP). Values are $r = -0.53$; $P = 0.002$.

in the peripheral and coronary macro- and microcirculations [23–26] and in the renal circulation [23]. Endothelium-independent relaxation responses to nitric oxide donors are preserved in those prior studies [27–29] and in our present series. The impairment of endothelium-dependent relaxation cannot be ascribed to a decreased ability of vascular smooth muscle to respond to nitric oxide. All hypertensive patients were receiving antihypertensive therapy. The direct effect of the drugs on vascular function was minimized by harvesting the vessels 24 hours or more after the last dose had been taken. However, previous studies have shown that endothelial dysfunction in hypertension is lessened by reduction in blood pressure [30]. Therefore, the treatment that these hypertensive patients received may have masked the full extent of their endothelial dysfunction.

In patients with primary aldosteronism or renal artery stenosis, the ACh response can be restored by correction of the cause of hypertension [23, 31]. This suggests that hypertension per se may contribute to endothelial dysfunction in human subjects. In contrast, an impaired endothelium-dependent vasodilatation appears to be a primary defect in ADPKD. Therefore, there should be additive effects of hypertension and ADPKD, yet endothelial function was impaired similarly in those with essential hypertension and hypertensive ADPKD. This may be a consequence of the almost complete (>85%) inhibition of eNOS activity in the vessels of patients in these two groups (Fig. 4). Hypertension was associated with a worsening of endothelial dysfunction in ADPKD, although CRI did not appear to influence this further. Since these studies were undertaken in resistance vessels, and an inverse relationship was found between the de-

gree of ACh-induced vasorelaxation and mean blood pressure, it is possible that impaired endothelial function contributes to hypertension in these patients.

Impaired endothelium-dependent vasodilatation in essential hypertension is associated with impaired nitric oxide availability [23]. The ACh response of vessels from normal subjects was enhanced by L-arginine and was blunted by L-NAME, indicating an important role for nitric oxide. However, these responses were diminished in normotensive patients with ADPKD and lost in those with hypertension. This could represent an impairment of nitric oxide generation, or an enhanced nitric oxide bioinactivation by superoxide anion ($O_2^{\cdot-}$), which reacts with nitric oxide to form peroxynitrite ($ONOO^-$) [32]. The high pO_2 of the bath solution used in these studies may have enhanced $O_2^{\cdot-}$ generation. We detected a profound decrease in cNOS activity in vessels from all these patients, associated with a decreased rate of NO_X excretion. This implies that a major cause of the impaired ACh response of these patients was an impaired activity of vascular NOS. Indeed, the observation that the ACh-induced relaxation response was little affected by L-NAME suggests that an impaired ability to generate bioactive nitric oxide in the vessels of these patients was the primary cause of their endothelial dysfunction. The defect could not be ascribed to a failure to provide adequate substrate since it was not corrected with L-arginine. The possibility of an additional defect due to enhanced nitric oxide bioinactivation by $O_2^{\cdot-}$ was not studied in these protocols. The elevation of plasma NO_X concentration in patients with ADPKD and CRI likely reflects impaired NO_X excretion [13].

There was a substantial vasorelaxation response to ACh after L-NAME in the vessels from normal subjects and all patient groups. Therefore, the vessels from the patients retained a robust nitric oxide–independent, ACh-induced vasodilator response. This was not investigated further, but likely is mediated by an endothelium-dependent hyperpolarizing factor [33].

Polycystin 1 is the protein that is affected in ADPKD. It is required for the structural integrity of blood vessels [34, 35]. A polymorphism of the eNOS gene (D298 eNOS allele) has been associated with lower vascular NOS activity in PKD1 patients [36]. There is a decrease in the expression of NOS isoenzymes in the kidneys of a rat model of polycystic disease as cyst development progresses [abstract; Wang D et al, XVth International Congress of Nephrology, May 2–6, 1999, Buenos Aires, Argentina]. Induction of NOS with taxol inhibits cyst growth in a mouse model of PKD [37]. These diverse observations may suggest an important interaction between eNOS and polycystin 1 in ADPKD, consistent with our finding of a profound reduction in NOS activity in blood vessels.

CONCLUSION

Endothelial dysfunction predates hypertension and CRI in ADPKD and therefore appears to be a primary defect. However, the development of hypertension leads to a major further defect in endothelial function. These defects in ADPKD can be ascribed to defective cNOS activity.

ACKNOWLEDGMENTS

The authors thank Pia Linne Olsen, Bodil Hellstrøm, Inger Marie Leth, and Britta Vilhelmsen for their meticulous laboratory work during the study. Dr. Wang is supported by grants from the National Kidney Fund, National Capital Affiliate. Dr. Wilcox is supported by grants from the National Institute for Diabetes, Digestive and Kidney Diseases, (DK-36079 and DK-49870) and the National Institute for Heart, Lung and Blood (HL68686-01) and from funds from the George E. Schreiner Chair of Nephrology. We are grateful to Ms. Sharon Clements for preparation of this manuscript.

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