Sympathetic Activity Is Increased in Polycystic Kidney Disease and Is Associated with Hypertension

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Abstract. Hypertension is common in patients with polycystic kidney disease (PKD). This study addresses the hypothesis that sympathetic activity is enhanced in hypertensive PKD patients, not only when renal function is impaired but also when renal function is still normal. Muscle sympathetic nerve activity (MSNA, peroneal nerve), plasma renin activity (PRA), heart rate, and BP were studied in PKD patients with normal and with impaired renal function and in matched controls. In hypertensive patients with normal renal function, MSNA and mean arterial pressure (MAP) were higher than in normotensive patients (23 ± 5 versus 15 ± 7 bursts/min; 110 ± 10 versus 90 ± 3 mmHg; P < 0.05), whereas PRA and heart rate did not differ. In PKD with chronic renal failure (CRF) (creatinine clearance rate, 39 ± 19 ml/min), MAP, MSNA and PRA were higher than in controls (resp, 116 ± 7 versus 89 ± 9 mmHg; 34 ± 14 versus 19 ± 9 bursts/min; 405 [20 to 1640] versus 120 [40 to 730] fmol/L per sec; all P < 0.05). Heart rate in PKD CRF did not differ from controls. MSNA correlated with MAP (r = 0.42; P = 0.01) and age with MSNA (r = 0.45; P < 0.01). Regression line of age and MSNA in patients was steeper than that in controls. This study indicates that MSNA is increased in hypertensive PKD patients regardless of renal function. The data support the idea that sympathetic hyperactivity contributes to the pathogenesis of hypertension in PKD.

Hypertension is common in patients with autosomal dominant polycystic kidney disease (PKD). The prevalence is 50 to 62% when renal function is still normal and increases to almost 100% in patients with chronic renal failure (CRF) (1–3). Renal structural changes play an important role in the pathogenesis of the hypertension. Renal arteriograms of end-stage PKD nephrectomy specimens demonstrated marked attenuation of the vasculature due to extrinsic compression and replacement by cysts (4). Angiographic images of kidneys of hypertensive PKD patients (from mild to advanced renal failure) show a large amount of avascular renal substance peripheral to the outermost branches of the arterial tree (5).

Renal ischemia can lead to sympathetic activation. During renal ischemia, adenosine is released. This adenosine evokes an increase in afferent renal nerve traffic, as can be shown during adenosine infusion in the renal artery of uninephrectomized dogs (6). In rats, induction of renal artery stenosis (7), partial renal ablation by arterial ligation (8), or intrarenal phenol injection (9) cause excitation of the renal afferent nerves, which results in neurogenic hypertension. Even a small injury in one kidney, not affecting GFR, leads to hypertension in association with an increased central sympathetic activity (10). In these animal models, hypertension can be prevented or reduced by rhizotomy or ganglionic blockade. Thus renal injury in experimental conditions can lead to sympathetic overactivity and hypertension, and this overactivity is associated with activation of renal afferent nerves.

In hypertensive CRF patients, hyperactivity of the sympathetic nervous system is often present. Dialysis patients who have their native kidneys still present, show an increased muscle sympathetic activity (MSNA), whereas MSNA in anephric dialysis patients is comparable to that of controls (11). We showed that MSNA is increased in CRF patients who were not yet on dialysis and that this overactivity was reduced by chronic angiotensin-converting enzyme (ACE) inhibition (12). These clinical data indicate that in humans the diseased kidneys are also critically involved in the pathogenesis of increased central sympathetic outflow.

Based on these observations, we hypothesized that sympathetic activity, quantified by measuring MSNA, is enhanced in hypertensive PKD patients, not only when renal function is impaired but also when renal function is still normal.

Materials and Methods

Subjects

We investigated three groups of subjects: PKD patients with normal renal function (PKD-N), with CRF (PKD-CRF), and healthy controls. PKD patients were eligible when they had a positive family history for cystic disease and a positive ultrasound (bilateral renal involvement). The plasma creatinine in PKD-N was less than 110 μmol/L. PKD-CRF patients had a creatinine clearance rate between
20 and 75 ml/min and a stable plasma creatinine in the previous 3 mo. Diabetic patients and patients with clinically manifest heart disease (congestive heart failure and/or coronary heart disease) were excluded.

Healthy controls were gender, age, and body mass index (BMI) matched to either the patients with PKD-N or PKD-CRF.

Protocol
The institutional committee for studies in humans approved the protocol. All subjects gave their written informed consent. All patients and controls underwent an identical set of measurements in supine position in a quiet room with an ambient temperature of 22 to 24°C. The protocol included supine BP, heart rate, MSNA, baroreflex sensitivity, extracellular volume (ECV), and PRA. Any antihypertensive drugs, except diuretics, were discontinued at least 2 wk before the study. Subjects collected 24-h urine on the day before the MSNA measurement.

BP and heart rate were measured in a recumbent position with a standard mercury sphygmomanometer. Measures of five infusions were used. The baroreceptor sensitivity measurements, BP and heart rate were recorded continuously by finger plethysmography (Finapres; Datex-Ohmeda, Louisville, CO). The Finapres device is especially suitable for analysis of changes in BP during short-term interventions (13). Measurement of MSNA was recorded with a unipolar tungsten microelectrode that was placed in a muscle nerve fascicle of the peroneal nerve using the technique of Wallin and described previously (12, 14). The electrode positioning is evaluated during a Valsalva maneuver. The patient is asked to blow into a mouthpiece of an aerod bipolar meter to 40 mMg for 15 s while BP, heart rate, and MSNA are continuously recorded. The BP overshoot after the restart of breathing is associated with a short pause in neural activity. The neural signal during the BP overshoot is considered to be the background noise. This procedure is done at the beginning and at the end of the study session. The success rate of obtaining an adequate neural signal is approximately 85%. The interbeat intervals were measured from the electrocardiogram. The sample frequency is 200 Hz. The heart rate is computed from the interbeat interval. An intravenous cannula for infusion and blood sample collection was inserted into an antecubital vein.

After instrumentation, the subjects rested for 20 min. Baseline measurements for BP, heart rate, and MSNA were obtained, blood was sampled for PRA and bromide. Next, baroreflex sensitivity was assessed as the response of MSNA and of heart rate to changes in BP induced by subsequent continuous infusion of sodium nitroprusside and phenylephrine. Infusion of sodium nitroprusside (333 μg/ml in glucose 5%) started at a rate of 33 μg/min and was individually increased (in 3-min steps) to obtain a reduction of MAP of at least 12 mmHg. After a second 20 min rest period, a continuous infusion of phenylephrine (333 μg/ml in saline 0.9%) was started at a rate of 33 μg/min and individually increased (in 3-min steps) to increase MAP by at least 12 mmHg.

Sympathetic bursts were identified by inspection of the mean voltage neurogram and counted for every min. The means of 5 min recordings are presented. During the baroreceptor sensitivity assessments, MSNA was counted for 1 min during each infusion step.

Laboratory Analyses
Bromide distribution volume as an index of extracellular fluid volume was calculated from plasma bromide concentration in blood samples that were obtained at 90, 120, and 150 min after injection of 4 g of sodium bromide. Plasma bromide was measured colorimetrically at 440 nm by the gold bromide technique and corrected for plasma bromide before injection. The distribution volume was corrected for bromide penetration into erythrocytes, for plasma water content, and for the Donnan equilibrium effect and expressed as ml/kg lean body mass (15). Lean body mass, estimated from weight and height, is the most suitable index for normalization of body fluid volumes in humans and allows comparison of men with women (15, 16). The normal range in our laboratory is 273 to 334 ml/kg of lean body weight. PRA was measured by RIA (17).

Data Analyses
Data are mean ± SD, unless indicated otherwise. MSNA was expressed as the number of bursts of sympathetic activity per min or as the number of bursts per 100 heartbeats to correct for differences in heart rate. During the sodium nitroprusside and phenylephrine infusion, MSNA was counted for 1 min during each infusion step. The results of the continuous registration of MAP and heart rate were averaged per min. Baroreflex sensitivity was expressed as changes in MSNA and interbeat interval versus BP. It was calculated for each subject by least squares analysis of the linear part of the baroreflex curves that included the baseline value and expressed as the number of bursts per min per mmHg and the R-R interval per mmHg, respectively.

Statistical Analyses
PRA was analyzed after logarithmic transformation. Baseline parameters analysis was performed with Student’s unpaired t test between patients and healthy controls. Pearson correlation coefficients were calculated followed by stepwise linear regression when significant correlations were found. Only independent variables were included in the regression analyses. Slopes of regression lines were compared by analysis of covariance. Statistical significance was defined as P < 0.05.

Results
PKD Patients with Normal Renal Function
Eighteen patients with PKD-N (plasma creatinine <110 μmol/L) were studied. Average BP (office BP using mercury sphygmomanometer) was 135/87 mmHg (SD 13/9). Four patients used an ACE inhibitor or angiotensin II (AngII) antagonist, which was stopped at least 2 wk before the study. Patients were divided into hypertensive (BP >140/90 mmHg three times) and normotensive groups based on their untreated office BP.

In hypertensive patients, MSNA was higher than in controls. In contrast, PRA did not differ between groups. In normotensive patients, MSNA did not differ from controls. Table 1 and Figure 1 show the characteristics of these two groups and those of the controls. Baroreceptor sensitivity did not differ between the two PKD-N groups and was identical to that in controls.

PKD Patients with Impaired Renal Function
Twenty PKD-CRF patients were studied. Their characteristics are presented in Table 2 and Figure 2. All patients were on antihypertensive drugs (ACE-inhibitor or AngII antagonist), in 11 cases combined with diuretics. Their office BP (using mercury sphygmomanometer) was 135/85 mmHg (SD 13/8). After stopping the antihypertensive medication, BP increased in all patients, but no patient became severely hypertensive


Table 1. Characteristics and baseline values of PKD patients with normal renal function and healthy controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PKD HT $n = 9$</th>
<th>PKD NT $n = 9$</th>
<th>Controls $n = 18$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>36 ± 7</td>
<td>33 ± 6</td>
<td>33 ± 7</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>6/3</td>
<td>5/4</td>
<td>10/8</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>23.1 ± 2.9</td>
<td>24.3 ± 3.2</td>
<td>24.5 ± 3.0</td>
</tr>
<tr>
<td>Creatinine clearance rate (ml/min per 1.73 m$^2$)</td>
<td>101 ± 7</td>
<td>98 ± 15</td>
<td>103 ± 14</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>110 ± 10$^{bc}$</td>
<td>90 ± 3</td>
<td>88 ± 11</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>66 ± 10</td>
<td>59 ± 6</td>
<td>62 ± 9</td>
</tr>
<tr>
<td>PRA (fmol/L per sec)</td>
<td>310 (170–830)</td>
<td>355 (150–610)</td>
<td>235 (40–690)</td>
</tr>
<tr>
<td>MSNA (bursts/min)</td>
<td>23 ± 5$^{bc}$</td>
<td>15 ± 7</td>
<td>14 ± 5</td>
</tr>
<tr>
<td>MSNA (bursts/100 bpm)</td>
<td>36 ± 11$^{bc}$</td>
<td>25 ± 11</td>
<td>24 ± 8</td>
</tr>
<tr>
<td>Baroreceptor sensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>for MSNA (bursts/min per mmHg)</td>
<td>−2.1 ± 0.8</td>
<td>−2.1 ± 1.0</td>
<td>−1.9 ± 0.9</td>
</tr>
<tr>
<td>for heart rate (ms/mmHg)</td>
<td>12.0 ± 5.1</td>
<td>15.2 ± 5.1</td>
<td>16.1 ± 6.5</td>
</tr>
<tr>
<td>ECV (ml/kg LBM)</td>
<td>326 ± 21</td>
<td>323 ± 25</td>
<td>313 ± 26</td>
</tr>
</tbody>
</table>

$^a$ Results are expressed as mean ± SD; PRA is expressed as median (range). PKD, polycystic kidney disease; PKD HT, patients with hypertension; PKD NT, patients with normotension; MAP, mean arterial pressure; PRA, plasma renin activity; MSNA, muscle sympathetic nerve activity; ECV, extracellular volume; LBM, lean body mass.

$^b$ $P < 0.05$ compared with controls.

$^c$ $P < 0.05$ compared with PKD NT.

(dioisolic BP >120 mmHg). Diuretics were continued to maintain normovolemia. Vitamin D supplements, phosphate binders, and/or HMG-CoA-reductase inhibitors were continued as well.

PKD-CRF patients were older than patients with PKD-N. BP and MSNA in PKD-CRF was higher than in controls ($P < 0.01$) and higher than in hypertensive patients with PKD-N ($P < 0.05$). PRA in PKD-CRF was higher than in controls, whereas ECV was not different.

Baroreceptor sensitivity was not different between patients and controls. Additionally, baroreceptor sensitivity in PKD-CRF was not different from that in PKD-N patients.

**Correlations**

In all PKD patients ($n = 38$), MSNA correlated with MAP ($r = 0.42; P = 0.01$) (Figure 3), and age correlated with MSNA ($r = 0.65; P < 0.001$), creatinine clearance rate ($r = −0.66; P < 0.001$), and PRA ($r = 0.45; P < 0.01$).

In all PKD patients, age and PRA were predictive for MSNA (MSNA = −11.48 + [0.81 × age] + [0.01 × PRA]; $r^2 = 0.53; P = 0.01$).

In all controls ($n = 38$), MAP did not correlate with MSNA but MSNA correlated with age (MSNA = 0.93 + (0.4 × age); $r^2 = 0.50; P < 0.01$). Regression lines of MSNA and age in all PKD were steeper than in controls ($P < 0.01$) (Figure 4).

**Discussion**

In this study, we show for the first time that hypertensive PKD patients have increased MSNA regardless of renal function. Hypertensive PKD patients with normal renal function do not have increased PRA, although the levels may be considered too high for the level of BP. The data support the idea that sympathetic hyperactivity contributes to the pathogenesis of hypertension in PKD.

Few studies have addressed the question of whether the sympathetic nervous system is activated in PKD by measuring plasma noradrenaline levels. In one study, no difference was found between normotensive and hypertensive patients with (near) normal renal function (18), whereas others reported increased levels in comparison with patients with essential hypertension (19). It is generally agreed that plasma noradrenaline levels are poor indicators for sympathetic activity. There is also clear evidence that the degree of sympathetic activity to various organs may differ (20). MSNA is the directly measured sympathetic nerve activity. The signal is highly reproducible and represents the sympathetic tone to the peripheral resistance vasculature, which is the main determinant of BP (21,22).

Therefore, these data provide firm evidence that hypertensive PKD is characterized by sympathetic hyperactivity, whereas it is normal in normotensive patients. MSNA correlates with BP, which supports the idea that sympathetic overactivity is involved in the pathogenesis of hypertension in PKD.

Experimental studies have come up with at least two pathophysiologic mechanisms for the increased sympathetic activity in renal disease patients. First, inappropriate renin secretion in relation to the state of sodium-volume balance has long been recognized (23). There is clear evidence that high circulating AngII levels can stimulate central sympathetic outflow by a direct effect on the vasomotor center in the brainstem (24), which in humans can be quantified as increased MSNA (25).

Second, the diseased kidneys can command the brain to increase sympathetic outflow by increasing renal afferent nerve activity. During ischemia, adenosine is released. Direct infusion of adenosine into the renal artery, induction of renal artery


stenosis, partial renal ablation by arterial ligation, or intrarenal phenol injection cause hypertension, which is prevented by renal afferent denervation (8–10).

Both mechanisms that underlie the sympathetic stimulation are related to intrarenal ischemia. It is, therefore, difficult to differentiate between the contributions of these two mechanisms in human disease. In this study, PRA correlates with MSNA. This may indicate a common origin. PRA in hypertensive and normotensive PKD-N was identical. In these patients, MSNA is already significantly increased. This seems to argue against a cause and effect relation. In both patients and in controls, MSNA increases with age, which indicates that the increase in MSNA in the renal patients is partially explained by mechanisms also present in the normal population. Some have suggested that a decrease in arterial or cardiopulmonary baroreceptor sensitivity with advancing age is the cause of the increase of MSNA in healthy persons (26). However, using the MSNA technique, others found no difference in baroreceptor sensitivity in older compared with younger persons (27, 28). A decrease in $\alpha$-adrenergic responsiveness may explain increase in MSNA with age (29). Although these studies and our study do not contain longitudinal data, they do not support the hypothesis that baroreceptor sensitivity for MSNA changes with advancing age. In this study, the regression line of age versus MSNA in the patients was steeper than it was in controls. It seems likely that the progression of renal damage results in the further increase of MSNA. In line with this hypothesis is the study that indicates that MSNA in dialysis patients is even higher than in the patients of this study (11).

An inverse relation between ECV and renin has long been recognized (23). Fluid overload suppresses and volume deficit stimulates renin production. Although the relation between sympathetic activity and ECV has not been studied, it is conceivable that an identical relation is present. An important feature of this study is that we maintained the patients in normovolemic condition. In many cases, this meant that di-

### Table 2. Characteristics and baseline values of patients with PKD-CRF and healthy controls$^a$

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PKD-CRF $n = 20$</th>
<th>Controls CRF $n = 20$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>48 ± 7</td>
<td>46 ± 13</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>18/2</td>
<td>18/2</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>26.1 ± 3.0</td>
<td>24.7 ± 2.6</td>
</tr>
<tr>
<td>Creatinine clearance rate (ml/min per 1.73 m$^2$)</td>
<td>39 ± 18$^b$</td>
<td>91 ± 8</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>116 ± 8$^b$</td>
<td>89 ± 9</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>60 ± 8</td>
<td>61 ± 11</td>
</tr>
<tr>
<td>PRA (fmol/L per sec)</td>
<td>405 (20–1640)</td>
<td>120 (40–730)</td>
</tr>
<tr>
<td>MSNA (bursts/min)</td>
<td>35 ± 13$^b$</td>
<td>19 ± 9</td>
</tr>
<tr>
<td>MSNA (bursts/100 bpm)</td>
<td>58 ± 20$^b$</td>
<td>31 ± 13</td>
</tr>
<tr>
<td>Baroreceptor sensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>for MSNA (bursts/min per mmHg)</td>
<td>−2.2 ± 1.2</td>
<td>−1.9 ± 1.0</td>
</tr>
<tr>
<td>for heart rate (ms/mmHg)</td>
<td>13.6 ± 7.3</td>
<td>14.2 ± 4.9</td>
</tr>
<tr>
<td>ECV (ml/kg LBM)</td>
<td>317 ± 28</td>
<td>301 ± 28</td>
</tr>
</tbody>
</table>

$^a$ Results are expressed as mean ± SD; PRA is expressed as median (range). CRF, chronic renal failure.

$^b P < 0.05$ compared with controls.
uretic therapy was continued while other antihypertensive drugs were stopped before the study. Both in the patients with normal renal function and in those with CRF the ECV were not different from controls, indicating that differences in PRA and MSNA were not explained by differences in fluid status. ECV were not measured while the patients were on active drug treatment. However, body weight did not change after stopping antihypertensive treatment (data not shown). The fact that the patients were normotensive while on ACE inhibitor or AngII antagonist (in many cases combined with diuretics) supports the idea that the hypertension in PKD is caused by mechanisms affected by these interventions.

Sympathetic hyperactivity adversely affects the cardiovascular risk profile by its effect on BP. However, independent of this effect, it is also associated with the development of left ventricular hypertrophy, arterial remodeling, arrhythmias, platelet aggregation, and poor prognosis in heart failure (30). Indeed, left ventricular hypertrophy is often present in hypertensive PKD, even early in the course of the disease (31). We have shown that chronic ACE inhibitor treatment reduces both BP and MSNA, whereas chronic calcium channel blocker reduces BP but increases MSNA (12). In one study, an ACE inhibitor reverses left ventricular hypertrophy in end-stage CRF patients with various renal diseases more effectively than a dihydropyridine calcium channel blocker (32). Our data suggest that ACE inhibitor treatment should be started early in the course of the disease. Recent data show that enalapril effectively reduces left ventricular hypertrophy in hypertensive PKD patients with moderate CRF (33). No comparison was made with other classes of antihypertensive treatment.

Although this study does not contain longitudinal data, the results suggest that in PKD with normal renal function a transition takes place from a condition with normal MSNA to one with increased MSNA that is parallel to the increase in BP. Hypertensive PKD patients with normal renal function do not have increased PRA, although the levels may be considered too high for the level of BP. Others have shown in PKD patients with normal renal function that hypertension is associated with greater renal volume than normotension (34). Furthermore,
cyst size reduction results in a decrease in BP (35). In this study, we have no data on kidney or cyst size. It is conceivable that the expansion of the cysts will result in stimulation of the mechanisms that lead to sympathetic and renin activation.

In conclusion, our data add to the recently reviewed present knowledge on the pathogenesis of hypertension in PKD patients (36). The study shows that hypertensive PKD patients have increased sympathetic activity regardless of renal function. This sympathetic hyperactivity contributes to the hypertension, but it may also increase cardiovascular risk independent of BP. Treatment to normalize BP and sympathetic activity should be started early in the course of the disease.

Acknowledgment

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References


