

Cardiovascular and Cerebrovascular Comorbidities of Hypokalemic and Normokalemic Primary Aldosteronism: Results of the German Conn's Registry

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Context: Primary aldosteronism (PA) is associated with vascular end-organ damage.

Objective: Our objective was to evaluate differences regarding comorbidities between the hypokalemic and normokalemic form of PA.

Design and Setting: This was a retrospective cross-sectional study collected from six German centers (German Conn's registry) between 1990 and 2007.

Patients: Of 640 registered patients with PA, 553 patients were analyzed.

Main Outcome Measures: Comorbidities depending on hypokalemia or normokalemia were examined.

Results: Of the 553 patients (61 ± 13 yr, range 13–96), 56.1% had hypokalemic PA. The systolic (164 ± 29 vs. 155 ± 27 mm Hg; $P < 0.01$) and diastolic (96 ± 18 vs. 93 ± 15 mm Hg; $P < 0.05$) blood pressures were significantly higher in hypokalemic patients than in those with the normokalemic variant. The prevalence of cardiovascular events (angina pectoris, myocardial infarction, chronic cardiac insufficiency, coronary angioplasty) was 16.3%. Atrial fibrillation occurred in 7.1% and other atrial or ventricular arrhythmia in 5.2% of the patients. Angina pectoris and chronic cardiac insufficiency were significantly more prevalent in hypokalemic PA (9.0 vs. 2.1%, $P < 0.001$; 5.5 vs. 2.1%, $P < 0.01$). Overall, cerebrovascular comorbidities were not different between hypokalemic and normokalemic patients, however, stroke tended to be more prevalent in normokalemic patients.

Conclusions: Our data indicate a high prevalence of comorbidities in patients with PA. The hypokalemic variant is defined by a higher morbidity than the normokalemic variant regarding some cardiovascular but not cerebrovascular events. Thus, PA should be sought not only in hypokalemic but also in normokalemic hypertensives because high-excess morbidity occurs in both subgroups. (*J Clin Endocrinol Metab* 94: 1125–1130, 2009)

Within the last 15 yr, primary aldosteronism (PA) has changed from a rare cause of hypertension affecting approximately 1% of the hypertensive population into the most common secondary cause of hypertension, affecting at least 8% of all hypertensive patients. This increase in prevalence is mainly due to detection of the normokalemic variant of PA (1–5). In a recent large Italian multicenter trial of 1125 unselected patients with hypertension, 4.8% were diagnosed with aldosterone-producing adenoma (APA), whereas 6.4% had idiopathic bilateral hyperplasia (IBH) (1, 6). An increasing body of information about long-term effects of aldosterone excess on the cardiovascular (7, 8) and the renal system (1, 6, 9) has been gathered over the last years. In a small study of 23 patients with PA, left ventricular hypertrophy preceded hypertensive retinopathy and hypertensive renal involvement (10). In another recent report, aldosterone excess caused left ventricular hypertrophy and diastolic dysfunction independent of blood pressure (11). Interestingly, specific treatment of PA decreased cardiac hypertrophy independently of either surgical or medical approaches. These data are endorsed by other studies (8, 12) showing that the prevalence of cardiovascular events was greater in PA than in essential hypertension. Milliez *et al.* (13) also showed an increased number of strokes in patients with PA compared with essential hypertension. Finally, pronounced fibrosis of small resistance arteries was detected in a small series of 13 patients with PA compared with blood pressure-matched patients with essential hypertension (14). Overall, these examples demonstrate that PA is a detrimental state that needs to be detected early in the course of the disease and treated appropriately.

In the study by Milliez *et al.* (13), the occurrence of cardiovascular complications was comparable in both subtypes of PA, in APA and in IBH. Notably, hypokalemia, which can influence the clinical presentation of PA, is present in 50–74% of patients with APA, and only in 5–17% of patients with IBH (1, 15). However, hardly any information is available detailing differences in comorbidities between hypokalemia and normokalemia in PA. Therefore, we used the German Conn's Registry database to compare the extent of cardiovascular and cerebrovascular comorbidities in the hypokalemic and normokalemic form of PA.

Subjects and Methods

The German Conn's Registry (www.conn-register.de) was founded in 2006 by the Section of Adrenal Disease, Steroids and Hypertension of the German Endocrine Society (Deutsche Gesellschaft für Endokrinologie) to study the long-term morbidity and mortality of PA in Germany. In October 2007, nine centers have enlisted, and six centers have included patients. The patients were entered into an electronic database after pseudonymisation using an identification number. Birth date and sex were also recorded. Only the centers are able to identify the individual patient. The database is stored on a server located at the University Hospital Munich. The Ethics Committees of the Klinikum of the University of Munich and of the participating centers approved the protocol. Personal data protection laws are strictly adhered to.

Local data acquisition of the German Conn's Registry was performed in the participating centers based on patients' paper charts or electronic charts, as appropriate. For identification of patients with PA in the cen-

ters, the hospital servers were electronically searched for key words associated with PA. Patients who were diagnosed with PA since 1990 were included in the study.

Because of the retrospective design and the lack of a uniformly accepted diagnostic standard during the study period, the diagnostic criteria for PA varied between the centers. At least three criteria had to be present for inclusion in the registry:

1. Elevated aldosterone to renin ratio, alternatively suppressed renin, and elevated aldosterone concentrations in those patients without aldosterone to renin ratio, relying on the local center-specific assay reference ranges.
2. Serum aldosterone more than middle-normal range.
3. Abnormal confirmatory testing; confirmatory tests varied among the centers, however, all centers used the saline infusion test. The fludrocortisone suppression test and the captopril test were used rarely (<1% of the patients).
4. Adrenal adenoma in histopathology.
5. Blood pressure response to adrenalectomy.
6. Blood pressure response to treatment with mineralocorticoid antagonist.

Mineralocorticoid antagonists and β -blockers had to be withdrawn for 4 and 1 wk before screening, respectively. The diagnosis of PA was verified centrally by review of all available data. Adrenal imaging was performed using computerized tomography and magnetic resonance imaging in all centers. However, only 32% of the patients received adrenal vein sampling.

The extracted patient's data were entered into the access database. The centers received intense training in Munich ensuring high quality of data retrieval and homogeneity of the data entry. The quality of the entered data was validated in October 2007. Possible inconsistencies and missing data were validated and corrected if appropriate. The diagnosis of PA was verified centrally using a diagnostic algorithm.

The following data were collected: patients' demographics, diagnosis, date of initial symptoms and diagnosis; laboratory test results, including hormonal data initially and during follow-up; medication, including potassium supplementation; adrenal imaging; results of adrenal venous sampling; surgical treatment(s); and morbidity related to the disease itself or to the treatment with an indication of the year of first diagnosis. Cerebrovascular events included stroke, cerebrovascular stenosis, transient ischemic attack (TIA), and prolonged reversible ischemic neurological deficit (PRIND). Cardiac events included angina pectoris, myocardial infarction, cardiac insufficiency (more than or equal to New York Heart Association Classification II), coronary angioplasty, and arrhythmias such as atrial fibrillation, atrial arrhythmias, and ventricular arrhythmias. Arrhythmias were counted as such when episodes were documented by either conventional 12-lead surface electrocardiogram or 24 h electrocardiogram recording. Chronic renal failure was defined by the presence of plasma creatinine more than 1.4 mg/dl, or blood urea nitrogen more than 30 mg/dl or glomerular filtration rate less than 50 ml/min. Morbidities of the peripheral cardiovascular system included peripheral arterial vascular disease, fundus hypertonicus, and deep vein thrombosis; sleep apnea included central sleep apnea, obstructive sleep apnea, and pickwickian syndrome. Only single independent events per patient were used and documented in the database.

Study population

By 2007, 712 patients were identified on paper or electronic charts as having PA. A total of 640 patients were entered into the database. Because of missing data or inconsistencies regarding the diagnosis, 87 patients were excluded from further analysis. After validation and verification, the remaining 553 patients with PA were analyzed with respect to their comorbidities. Patients with PA were stratified into those subjects who never had documented hypokalemia less than 3.6 mmol/liter (termed: normokalemic PA) and those who had current or past hypokalemia or received potassium supplements (termed: hypokalemic PA) (average number of potassium measurements: three).

Statistics

Results are expressed as mean \pm SD in the case of normally distributed data, and as median plus range in nonnormally distributed data, if not stated otherwise. Due to the fact that most of our data were not normally distributed, significance of differences was determined by an unpaired *t* test, Mann-Whitney-Wilcoxon test, or Fisher's exact test where appropriate. $P < 0.05$ was considered significant. The risk of complications was expressed in terms of odds ratio (OR) \pm 95% confidence interval (CI).

Results

Patient's characteristics

Of the 553 patients with PA, 316 (57%) were men and 237 (43%) women. The mean age was 61.0 ± 13.0 yr (range 13–96). The systolic blood pressure in the whole cohort was 158 ± 29 mm Hg, and the diastolic blood pressure was 94 ± 16 mm Hg. A total of 310 patients (56.1%) had the hypokalemic variant of PA. In the cohort of hypokalemic patients, plasma potassium levels were 3.1 ± 0.3 mmol/liter (mean \pm SD), and in the normokalemic cohort, 4.2 ± 0.4 mmol/liter.

Definitive histological diagnosis was available in operated patients ($n = 99$). Among those patients, 65 were diagnosed with APA, three with IBH, four with APA and IBH, and 27 had hyperplastic nodular adrenals by morphological criteria. In the subgroup of patients with histologically diagnosed APA, 44 (68%) had hypokalemia and 21 (32%) normokalemia. Of 65 patients, 27 (42%) received adrenal vein sampling. In the other subgroup ($n = 34$), 12 patients (35%) had normokalemia and 22 (65%) hypokalemia. No significant difference in comorbidities among the subgroups could be found.

Body mass index (BMI) was not significantly different between hypokalemic and normokalemic patients (28.4 ± 5.2 vs. 27.9 ± 4.7 kg/m²).

Distribution of hypokalemia across age

We analyzed the distribution of low potassium levels across age decades and found a nearly equal distribution of hypokalemia (45–65%) in all age decades (Fig. 1), with the exception of patients between the ages of 20 and 29 yr, in whom normokalemia was present more often.

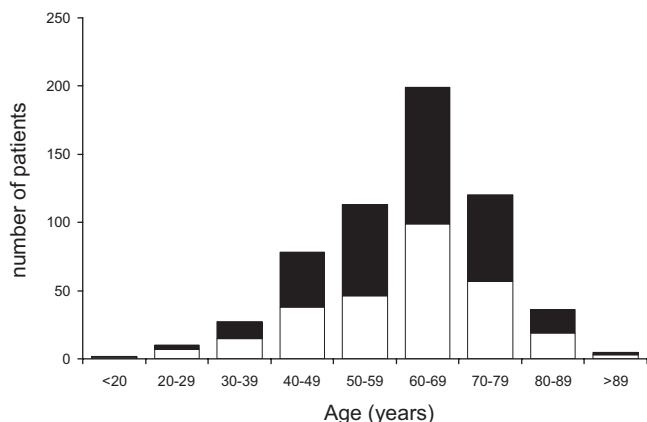


FIG. 1. Age distribution of patients with hypokalemic (black bars) and normokalemic (white bars) primary hyperaldosteronism.

Blood pressure and antihypertensive medication

The systolic blood pressure was significantly higher in hypokalemic PA compared with normokalemic PA (164 ± 29 vs. 155 ± 27 mm Hg; $P < 0.01$). Patients with the hypokalemic variant of PA had also higher diastolic blood pressures (96 ± 18 vs. 93 ± 15 mm Hg; $P < 0.05$). Duration of hypertension did not differ significantly between patients with hypokalemic (mean \pm SEM; 12.9 ± 0.7 yr) or normokalemic PA (11.5 ± 0.8 yr). There were also no differences in the number of antihypertensive drugs between the hypokalemic and normokalemic variant of PA (3.2 vs. 3.1, respectively). The most commonly used antihypertensive drugs before PA testing were calcium channel antagonists, angiotensin-converting enzyme inhibitors, β -blockers, thiazide diuretics, and α 1-receptor antagonists. Only calcium channel antagonists were used more often in hypokalemic than normokalemic patients.

Aldosterone levels

Mean aldosterone concentrations at diagnosis differed between normokalemic and hypokalemic PA, with significantly higher levels in the hypokalemic variant [855 ± 629 vs. 732 ± 538 pmol/liter (308.2 ± 226.8 vs. 263.8 ± 194 pg/ml); $P < 0.05$]. Interestingly, a significant positive correlation was evident between serum aldosterone levels and the prevalence of comorbidities in all PA patients. This correlation was not different between normokalemic and hypokalemic patients. However, whereas the number of events for chronic renal failure was significantly positively correlated with aldosterone levels (Fig. 2), cerebrovascular events showed a nearly equal distribution across the different serum aldosterone concentrations. Dysrhythmia and cardiac disease events showed a trend toward an increased event rate with increasing aldosterone levels. This was not seen in the group with the highest aldosterone levels, probably due to the lower number of patients in this subgroup.

Comorbidities

The overall prevalence of comorbidities was significantly higher ($P < 0.001$; OR = 2.4; 95% CI 1.6–3.6) in hypokalemic than normokalemic PA. No significant difference in the prevalence between normokalemic and hypokalemic PA was found for cerebrovascular events (13.2 vs. 12.6%, respectively), peripheral vascular system events (22.6 vs. 21.3%), sleep apnea (6.6 vs. 6.8%), and chronic renal failure (9.5 vs. 11.6%) (Table 1). In contrast, the prevalence rate for cardiac events was significantly higher in hypokalemic PA (35.2 vs. 20.2%; $P < 0.001$; OR = 2.2; 95% CI 1.5–3.2). Further analysis of cardiac events revealed significantly higher prevalence rates of angina pectoris (9.0 vs. 2.1%; $P < 0.001$; OR = 4.7; 95% CI 1.8–12.4) and chronic cardiac insufficiency (5.5 vs. 2.1%; $P < 0.05$; OR = 2.8; 95% CI 1.0–7.6) in hypokalemic compared with normokalemic PA patients (Table 1). Atrial arrhythmias (12.3 vs. 7.8%) showed a trend ($P = 0.09$) toward higher prevalence in hypokalemic PA. Subgroup analysis of cerebrovascular events revealed a higher, but not significantly different, rate of stroke (7.8 vs. 4.2%; $P = 0.09$; OR = 1.9; 95% CI 0.9–4.0) in normokalemic PA (Table 1). In this subgroup analysis for stroke, no differences in BMI or

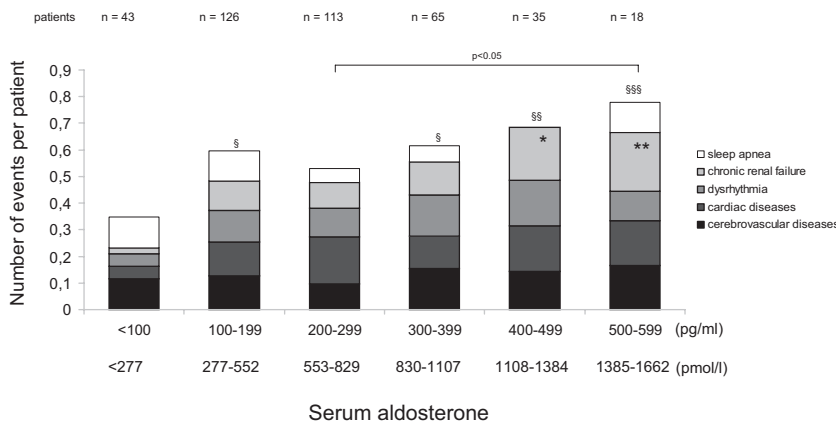


FIG. 2. Number of events per patient of the major comorbidities depending on aldosterone levels in all PA patients. *, $P < 0.05$ and **, $P < 0.01$ for chronic renal failure compared with chronic renal failure events at aldosterone levels less than 100 pg/ml; §, $P < 0.05$; §§, $P < 0.01$; and §§§, $P < 0.005$ for all events compared with all events at aldosterone levels less than 100 pg/ml.

duration of hypertension were found between hypokalemic and normokalemic patients.

Discussion

Thus far this study presents the largest reported cohort of patients with PA. The gender distribution among the sexes in our patient group was similar to that reported in other studies (13). In our cohort more than half of the patients were diagnosed with the hypokalemic variant of the disease, which is in accordance with the recent data by Mulatero *et al.* (15), reporting that 50% of the PA patients studied were hypokalemic. In contrast, other reports have suggested that nowadays the majority of patients that are diagnosed with PA have the normokalemic form (approximately two of three) (3, 4, 16). This discrepancy with our results might be explained by the observation interval of our study, which ranged from 1990–2006, as in the early 1990s, the

hypokalemic variant was still a rather infrequent diagnosis of PA. Second, examination of previous medical records reveals often hypokalemia at some time point in patients who have been primarily diagnosed with normokalemic PA (15). There were subtle differences in systolic and diastolic blood pressure with higher levels in the hypokalemic variant, which was further defined by significantly higher aldosterone levels than the normokalemic variant. However, those patients did not receive more antihypertensive drugs and, therefore, had more frequently poorly controlled hypertension. This stresses the current observation that in patients with resistant hypertension, the incidence of PA is up to 25% (17, 18).

There is no information thus far regarding clinical differences between the hypokalemic and normokalemic variant of PA. Milliez *et al.* (13) divided their cohort into patients with an APA ($n = 65$) and bilateral hyperplasia (IBH $n = 59$). However, this grouping does not separate the patients according to their potassium status, which might be considered as a measure of disease severity. In fact, only three of the total 124 patients with PA were normokalemic (13), and the two subgroups were similar with regard to age, blood pressure, and cardiovascular risk factors. Nevertheless, patients with APA had higher serum aldosterone levels than patients with IBH (13). Our data suggest that the overall number of events increases with higher aldosterone levels.

Cerebrovascular complications

Worldwide about 54% of stroke incidence is attributed to high blood pressure (19). Some studies (12, 20–22) reported an increased prevalence of cerebrovascular disease in PA. In the study by Milliez *et al.* (13), the rate of stroke was significantly increased (12.9 vs. 3.4%) in patients with PA compared with age- and blood pressure-matched controls with essential hypertension. In agreement with these findings, in our study the prevalence for cerebrovascular disease, including TIA, PRIND, stroke, and cerebrovascular stenosis, was 12.8%. However, it should be emphasized that a direct comparison with the study by Milliez *et al.* (13) should be done with caution due to the significant difference in the prevalence of normokalemic PA in the studies. Interestingly, despite the higher blood pressure in hypokalemic PA, the number of strokes tended to be higher in patients with the normokalemic variant of PA. There was no significant difference in BMI or duration of hypertension between the groups.

Although our data provide only indirect evidence, it is intriguing to speculate that aldosterone could have a negative impact on the cerebrovascular system independent of blood pressure. This view is supported by the experimental finding that mineralocorticoid receptor blockade reduced the ischemic defect in stroke-prone rats (23). Interestingly, a high incidence of hypertensive, hemorrhagic stroke was described in individuals with glucocorticoid suppressible hyperaldosteronism (24). Independent of the pathophysiological mechanisms, the high incidence of

TABLE 1. Prevalence of comorbidities in patients with hypokalemic and normokalemic primary hyperaldosteronism (PA)

Prevalence in %	Hypokalemic	Normokalemic
	PA	PA
Cerebrovascular (total)	12.6	13.2
TIA	4.5	3.3
PRIND	1.3	0.8
Stroke	4.2	7.8
Cerebrovascular stenosis	2.6	1.2
Cardiac (total)	35.2 ^a	20.2
Angina pectoris	9.0 ^a	2.1
Myocardial infarction	3.6	4.1
Chronic cardiac insufficiency	5.5 ^b	2.1
Atrial arrhythmia	12.3	7.8
Ventricular arrhythmia	1.9	2.1
Peripheral vascular system	21.3	22.6
Renal insufficiency	11.6	9.5
Sleep apnea	6.8	6.6

The peripheral cardiovascular system includes peripheral arterial vascular disease, fundus hypertonicus, and deep vein thrombosis.

^a $P < 0.001$ compared with normokalemic PA.

^b $P < 0.05$ compared with normokalemic PA.

cerebrovascular events in normokalemic PA emphasizes the need that PA should be sought not only in hypokalemic but also in normokalemic hypertensives.

Cardiovascular complications

Aldosterone has been suggested to be associated with endothelial dysfunction independent of blood pressure, and to produce microvascular inflammation and fibrosis in the brain and myocardium (25–27). Accordingly, mineralocorticoid receptor antagonistic therapy as evaluated in the Randomized Aldactone Evaluation Study (28), Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (29), and 4E trials (eplerenone, enalapril, and eplerenone plus enalapril) (30) conclusively demonstrated a major therapeutic benefit. The only study (12) that has reported prospective data upon treatment of PA found a higher cardiovascular and cerebrovascular risk for patients with PA at baseline, which decreased after operation or medical therapy to levels comparable to those of patients with essential hypertension.

Surprisingly, in former studies cardiac complications (myocardial infarction and arrhythmias) have been reported only sparsely in patients with PA (31–33). Nishimura *et al.* (22) found only one patient with associated coronary artery disease. Milliez *et al.* (13) were the first to show that patients with PA had a significantly increased rate of cardiovascular events, including myocardial infarction (4.0 vs. 0.6%) and atrial fibrillation (7.3 vs. 0.6%), compared with patients with essential hypertension. In accordance with these findings, in our study the overall prevalence for myocardial infarction was 3.8% and for atrial fibrillation 7.1%. A recent study by Catena *et al.* (12) found a three times higher prevalence of cardiovascular events in PA in comparison to essential hypertension. Milliez *et al.* (13) reported that the occurrence of cardiovascular complications was comparable in both subtypes of PA, but this might be due to the very small number of normokalemic patients in their cohort. Also in the study by Catena *et al.* (12), no differences in potassium levels were found between patients with APA and IBH. However, in our larger cohort, we were able to demonstrate a significant difference in the prevalence of cardiovascular comorbidities between normokalemic and hypokalemic PA (20.6 vs. 35.2%; $P < 0.001$). In the hypokalemic variant of PA, the prevalence of angina pectoris and of chronic cardiac insufficiency were especially higher than in the normokalemic variant. One explanation for the finding might be the higher aldosterone levels in the hypokalemic variant. The trend toward higher prevalences of arrhythmias in the hypokalemic variant might also be explained by low serum potassium levels *per se*. In general, it has been suggested that excess aldosterone might be a risk factor for arrhythmic disorders occurring either via left ventricular hypertrophy or via cardiac fibrosis predominantly in the left atrium, or a combination of both (13). In addition, recent data have suggested that higher rates of cardiovascular events in PA might be due to an increased prevalence of the metabolic syndrome in PA (34). Furthermore, the observed difference in blood pressure between hypokalemic and normokalemic patients in our cohort could explain, at least in part, differences in cardiovascular events between the two groups. However, it is surprising that this was the

case for cardiac complications and not for stroke, which is expected to be more dependent on blood pressure levels.

Sleep apnea

Interestingly, we found a high prevalence of 6.7% for sleep apnea in patients with PA. Very recently Calhoun *et al.* (35) published data showing that subjects at high risk for sleep apnea were almost two times more likely to have PA diagnosed and had a higher 24-h urinary aldosterone excretion. In a further study, they detected that a significant correlation existed between plasma aldosterone concentration and the severity of obstructive sleep apnea, suggesting that aldosterone excess may contribute to obstructive sleep apnea severity (36).

Limitations of the study

Limitations of our retrospective cross-sectional study include possible differences in patient and data handling between the participating centers because diagnostic protocols and assays have not been standardized before study start. Furthermore, the lack of a matched control group with essential hypertensive subjects allows no direct comparison between those two entities. Moreover, a possible referral and stratification bias cannot be excluded, which might have underestimated the relationship of PA with fatal cardiovascular events. In addition, definition of comorbidities was based on diagnostic codings at discharge. Finally, in the years between 1990 and 2007, aldosterone assays changed several times, and interpretation of aldosterone levels in correlation to comorbidities might be affected by this fact.

In conclusion, we retrospectively analyzed a large cohort of patients with PA. The incidence of cerebrovascular and cardiac comorbidities was high, and there were some significant differences between hypokalemic and normokalemic PA. Our data highlight the need to identify patients with PA among hypertensive subjects and to treat them adequately either with surgical or medical therapy to potentially prevent the increased risk of comorbidities. PA should be especially sought not only in hypokalemic but also in normokalemic hypertensives because excess morbidity over that seen in non-PA associated hypertension occurs in both subgroups and presumably results from non-blood pressure-dependent effects of aldosterone excess.

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