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Atherosclerotic Burden and Arterial Stiffness are Not Increased in Patients with Milder Forms of Primary Aldosteronism Compared to Patients with Essential Hypertension

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ABSTRACT

Patients with primary aldosteronism (PA) are at increased cardiovascular risk, compared to patients with essential hypertension (EH). Cardiovascular damage could depend on PA phenotype, potentially being lower in milder forms of PA. Our aim was to assess atherosclerotic burden and arterial stiffness in 88 prospectively recruited patients, including 44 patients with mild PA and EH respectively. All patients underwent a structured study program, including measurements of ankle-brachial index, oscillometric measurement of central pulse wave velocity (cPWV) and vascular ultrasound examination of the supraaortic arteries, the abdominal aorta, and the femoropopliteal arteries. A plaque score was calculated to estimate atherosclerotic burden for each patient. This is a prospective case-control study set at a tertiary care hospital. Patients with PA and EH matched well for age, gender, blood pressure, BMI, and cardiovascular risk factors such as diabetes mellitus and smoking status. Common carotid intima-media thickness (0.77 vs. 0.75 mm; p = 0.997) and cPWV (7.2 vs. 7.1 m/s; p = 0.372) were comparable between patients with PA and EH. The atherosclerotic burden, as expressed by the plaque score, did not differ between the two groups (p = 0.159). However, after initiation of treatment cPWV was significantly decreased in patients with PA (p = 0.017). This study shows that subclinical atherosclerotic burden and arterial stiffness in patients with milder forms of PA is comparable to patients with EH. Nevertheless, specific treatment for PA significantly improved cPWV, which argues for a more liberal use of mineralocorticoid receptor antagonists in patients with arterial hypertension.

Introduction

Primary aldosteronism (PA) is recognized as the most frequent cause of endocrine hypertension and accounts for about 5–15 % of hypertensives [1, 2]. However, it is not so long since PA was considered as a rare cause of endocrine hypertension, characterized by its classic triad of aldosterone excess, metabolic alkalosis and hypokalemia. The higher prevalence in more recent studies is based on the use of the aldosterone-to-renin-ratio (ARR). The ARR allows detecting the normokalemic subtype of PA, which is much more frequent and also considered as a milder form of PA [3, 4].

Aldosterone itself physiologically impacts on water and sodium homeostasis to maintain blood pressure stable. However, in PA long-term exposure to inadequate high aldosterone levels increases cardiovascular risk beyond blood pressure effects [5–9]. Basic research studies suggest that aldosterone may directly impact on vascular function, inflammation and fibrosis and therefore favoring arterial stiffening [10]. Data from clinical studies suggest that arterial stiffness and intima media thickness are increased in patients with PA [11–14]. However, the major drawbacks of these studies often deal with difficulties concerning sample size as well as adjustment for confounders (e. g., diabetes mellitus or smoking status) in addition to an overrepresentation of patients harboring a severe phenotype of PA [10, 12–17]. Furthermore, to the best of our knowledge, data on atherosclerotic burden in patients with PA are still missing. Nowadays, based on increased screening intensity for PA using the ARR, more and more milder cases of PA are diagnosed [4]. In this context it has been speculated that atherosclerosis and cardiovascular risk could depend on PA phenotype and be consequently lower in patients with milder forms of PA [18].

The current study thus aimed on providing data on subclinical atherosclerotic burden but also on arterial stiffness in a large collective of patients with milder subtypes of both unilateral and bilateral PA in comparison to patients with essential hypertension (EH).

Patients and Methods

Patients and controls

The study protocol was approved by the ethics committee of the University of Munich. All patients were prospectively enrolled at the Munich center of the German Conn's Registry and gave written informed consent. To select a cohort with milder forms of PA, only PA patients with baseline aldosterone levels of lower than 200 ng/l, corresponding to the 50th percentile of aldosterone levels in our cohort of patients with PA published before [19], were admitted to study participation. Due to our eligibility criteria patients with a history of carotid artery disease, or peripheral artery disease were also not included in the current study. Based on the eligibility criteria 95 patients could be initially included in the study. Following 1:1 matching for age, gender, BMI and cardiovascular risk factors (markers of lipid and glucose metabolism, body-mass-index (BMI), smoking status and arterial blood pressure) seven participants were excluded from the analysis. The final study cohort consisted of forty-four patients with PA and forty-four patients with EH.

All study examinations followed standard operating procedures. Diagnosis of PA was made according to the Endocrine Society Practice Guidelines [20]. The screening test consisted of a baseline plasma aldosterone-to-renin ratio (ARR; cut-off 12.0 ng/U, sitting position). If elevated, diagnosis of PA was ruled in by an abnormal confirmatory test (e. g. salt loading test, captopril challenge test or both). Antihypertensive medication was stopped before testing, if possible. Otherwise it was replaced by the alpha 1-adrenergic receptor blocker doxazosin or calcium-channel blocker verapamil. The subtype diagnosis between unilateral and bilateral disease was based on adrenal vein sampling in thirty of forty-four PA patients and revealed unilateral PA in seven cases [21]. Baseline examination was performed shortly after testing for PA and before initiation of specific treatment for PA.

Ten patients could be appropriately re-evaluated after a median of two years after initiation of treatment. Seven of these patients were treated with mineralocorticoid receptor antagonists (MRA; spironolactone at a dose of 25–50 mg/d), and three patients with unilateral PA underwent unilateral adrenalectomy with histologic confirmation of diagnosis.

Non-invasive vascular measurements

Settings for non-invasive vascular measurement were standardized (examinations in the morning, room temperature at 18–21 °C, 10 min of resting). At baseline and at follow-up visit, at least three consecutive blood pressure readings were obtained in the sitting position after not less than 10 min of rest using a validated automatic oscillometric device. The measurement was attended by a study nurse or an investigator and the average of the measurements recorded. To ensure proper cuff size for blood pressure measurement the upper arm circumference was measured at each visit. Concerning the ankle-brachial index (ABI) systolic blood pressure was measured bilaterally over the brachial arteries, distal posterior tibial arteries and dorsalis pedis arteries with a hand-held continuous wave-Doppler probe after at least 10 min of rest. The ABI was calculated for each leg as the ratio of the maximum systolic blood pressure of the ankle arteries and the maximum systolic arm blood pressure [22]. For the patient-based analysis, the lower ABI of both legs was taken into account. Peripheral artery disease was defined by an ABI < 0.9 in at least one leg, whereas an ABI > 1.3 was considered indicative of poorly compressible arteries [23].

The measurement of the central pulse wave velocity (cPWV, in m/s) was performed using an oscillometric device and applying the Gesenius–Keller method (AngE Pro 8, software version 1.18.33; SOT Medical Systems, Maria Rain, Austria). Cuffs were placed on both forearms and ankles and ECG-triggered pulse waves were recorded at different cuff pressures [24, 25].

Ultrasound examinations

All patients underwent a standardized vascular ultrasound examination. Ultrasound examinations were conducted using a GE Logic E9 ultrasound machine (General Electric, Munich, Germany) by experienced vascular sonographers with more than ten years in professional experience (AK, CL), blinded to clinical and biochemical information. Except the abdominal aorta which was evaluated with a 2–6 MHz convex probe, all arterial segments were examined with an 8 MHz linear probe. The following arterial segments were examined in the longitudinal and the cross-sectional view: common carotid arteries (CCA), carotid bulbs (CB), external carotid arteries (ECA), internal carotid arteries (ICA), vertebral arteries (VA), subclavian arteries (SA), abdominal aorta (AA), common femoral arteries (CFA), profunda femoris arteries (PFA), superficial femoral arteries (SFA) and popliteal arteries (PoA). Each arterial segment was assessed for the presence of atherosclerotic plaques, stenosis (< 50 %, ≥ 50 %) and occlusion. Atherosclerotic plaque was defined according to the Mannheim Intima-Media Thickness Consensus as focal thickening of the intima-media complex of ≥ 50 % compared to the surrounding IMT and/or focal intimal thickening protruding into the arterial lumen ≥ 0.5 mm [26]. IMT measurements of the

CCA (CCA-IMT) were conducted 1–2 cm proximal to the bifurcation within a region free of plaque. Three CCA-IMT measurements were conducted on each side. Mean CCA-IMT of each patient was calculated as the mean value of all six measurements [27]. The diameter of the AA was measured by using the leading edge method [28]. Absence or presence of aortic ectasia (≥ 2.0 cm) or aortic aneurysm (≥ 3.0 cm) were documented. A modified plaque score was calculated by adding up the number of arterial segments without atherosclerotic changes (0 points), with the presence of non-stenotic atherosclerotic plaques (1 point), arterial stenosis < 50 % (2 points), arterial stenosis ≥ 50 % (3 points) and arterial occlusion (4 points) [29]. Given a total number of 21 segments analyzed, the plaque score could range from 0–84 points.

Statistical analysis

This study aimed to compare (markers of) subclinical atherosclerotic plaque burden between patients with PA and EH. We estimated the sample size on the basis of current literature on CCA-IMT, which also serves as a surrogate parameter for atherosclerotic plaque burden [11]. Assuming a power of 0.8 and a two-sided type I error of $\alpha = 0.05$ we calculated that a total sample size of 71 subjects (sum of patients with PA and EH) would be sufficient to detect a difference of 0.1 mm ± 0.15 mm in CCA-IMT between both groups. To avoid confounding both cohorts were matched for age, gender, BMI, and cardiovascular risk factors (markers of lipid and glucose metabolism, body-mass-index (BMI), smoking status, and arterial blood pressure) as mentioned above. For the follow-up evaluation we calculated based on data of Matsuda and colleagues that a sample size of 8 patients with PA would be sufficient to detect a difference of 0.1 mm ± 0.1 mm in CCA-IMT between baseline examination and follow-up, assuming a power of 0.8 and a two-sided type I error of $\alpha = 0.05$ [30].

All numerical values are expressed as median, 25th and 75th percentile if not mentioned otherwise. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Data between groups were compared using Mann–Whitney U test or chi-square test for numerical or categorical variable, respectively. Within-group changes from baseline to follow-up were calculated by Wilcoxon signed-rank test. Spearman's Rank correlation coefficient was used to perform bivariate correlation analysis. Two-tailed probability values of < 5 % were considered to be statistically significant. Statistical analysis was performed using standard statistical software (IBM SPSS Statistics for Windows, Version 26. Armonk, NY: IBM Corp.).

Results

Clinical and biochemical baseline characteristics of the cohorts

Clinical and biochemical characteristics of the study cohort are shown in ▶ **Table 1**. As expected, according to the study design, patients with PA had higher aldosterone and lower potassium and renin levels compared with EH (▶ **Table 1**). Apart from that patients with PA and EH were well matched for age, gender, BMI, and cardiovascular risk factors such as diabetes mellitus and smoking status. Blood pressure and the intensity of antihypertensive treatment, as measured by defined daily doses of antihypertensives (DDD; both: 1.0; p = 0.688), were also comparable between both subgroups.

Atherosclerotic burden, ABI, CCA-IMT, and cPWV

The amount of vascular plaques was comparable in all 21 arterial segments including the supraaortic arteries, abdominal aorta, and arteries of the lower limbs (▶ **Fig. 1**). Hence atherosclerotic plaque burden, as expressed by the plaque score, was also similar in patients with PA and EH (4 vs. 7; p = 0.159). CCA-IMT was also comparable between both groups with a median of 0.77 mm and 0.75 mm respectively (p = 0.997). While we could not detect any plaques in 16 patients (10 patients with PA, 6 patients with EH; p = 0.269), 12 patients had relevant arterial stenosis (5 patients with PA and 7 patients with EH; p = 0.534). Only 1 patient with PA exhibited segmental stenosis of more than 50 % showing unilateral high-grade stenosis of the SFA (middle segment), also indicated by an ABI of 0.76. Apart from that ABI did not differ between both groups (PA: 1.1 vs. EH: 1.2; p = 0.148). In total 6 patients, 3 patients with PA and 3 patients with EH, had an ABI higher than 1.3, thereof 2 patients with manifest diabetes mellitus type 2. In total seven patients had aortic ectasia, including 2 patients with PA and 5 patients with EH (p = 0.237). Otherwise the measures of the abdominal aorta were in normal range and similar in both subgroups (both: 1.7 cm; p = 0.667). cPWV did not differ significantly in patients with PA and EH (7.2 m/s vs. 7.1 m/s; p = 0.372). In the total cohort, CCA-IMT, cPWV and plaque score (all: p < 0.005) were strongly correlated with each other. Although we could not detect univariate correlation between CCA-IMT, cPWV and aldosterone or renin levels, we observed a significant correlation of the plaque score with higher renin (r = 0.302; p = 0.005) but not with aldosterone levels at baseline (r = –0.013; p = 0.908). Those results were in most part replicable when analyzing PA and EH patients separately (data not shown). However, the latter group showed a strong correlation of the plaque score with renin levels at baseline (r = 0.413; p = 0.006), which was not the case in the PA subgroup (r = 0.137; p = 0.376).

Follow-up

After a median of 2 years following initiation of treatment 10 patients with PA (7 with bilateral and 3 with unilateral disease) underwent reassessment of cPWV and CCA-IMT. At that time systolic blood pressure levels (135 mmHg vs. 167 mmHg at baseline; p = 0.012) and albuminuria had significantly decreased (7.3 mg/d vs. 18.4 mg/d at baseline; p = 0.008), whereas potassium levels had increased (4.4 mmol/l vs. 3.8 mmol/l at baseline; p = 0.005). CCA-IMT was unaltered (0.66 mm vs. 0.70 mm; p = 0.150), whereas cPWV was significantly reduced from 8.2 m/s to 6.5 m/s (p = 0.017; ▶ **Fig. 2**).

Discussion

It is well known that chronically high aldosterone levels in combination with inadequate high dietary salt intake cause cardiovascular damage [5]. In this context there is accumulating evidence that aldosterone impacts on endothelial dysfunction, namely via vascular remodeling, inflammation, alterations in vascular tone and induction of early atherosclerosis at least in patients suffering from a severe phenotype of PA [10–15, 30]. Exemplary, already in 2007

▶ **Table 1** Baseline characteristics of the total cohort.

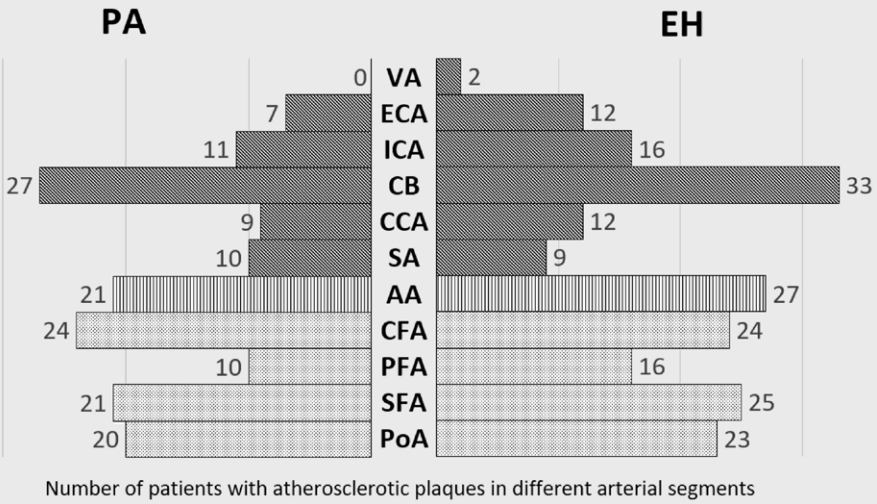
Patient characteristics	Patients with PA (n = 44)	Patients with EH (n = 44)	p
Age [years]	61 [51; 67]	61 [53; 68]	0.622
Sex [f/m]	24/20	23/21	0.831
Current cigarette smoking [n]	3	4	0.717
Diabetes mellitus [n]	6	4	0.502
Duration of hypertension [months]	124 [53; 205]	62 [12; 144]	**0.044**
Statin therapy [n]	8	7	0.777
Cardiovascular events [n]	6	7	0.764
BMI [kg/m²]	27.1 [24.6; 29.7]	26.7 [22.9; 30.1]	0.460
Plasma aldosterone [ng/l]	128 [97; 154]	91 [66; 110]	**< 0.001**
Plasma renin [mU/l]	2.1 [2.0; 3.8]	7.3 [2.0; 21.2]	**< 0.001**
SBP [mmHg]	151 [140; 169]	150 [140; 162]	0.637
DBP [mmHg]	92 [84; 100]	90 [80; 97]	0.169
DDD [n]	1.0 [0.5; 2.4]	1.0 [0.0; 2.6]	0.688
Number of antihypertensive drugs [n]	1.0 [1.0; 2.0]	1.0 [0.0; 2.0]	0.535
Serum potassium [mmol/l]	4.0 [3.7; 4.2]	4.2 [3.9; 4.3]	**0.028**
GFR [ml/min/1.73 m²]	90 [78; 100]	83 [71; 100]	0.246
HDL-C [mg/dl]	58 [48; 66]	56 [47; 69]	0.894
LDL-C [mg/dl]	125 [99; 150]	134 [98; 157]	0.649
Triglycerides [mg/dl]	109 [68; 163]	98 [70; 154]	0.848
Total cholesterol [mg/dl]	199 [176; 230]	206 [166; 238]	0.793
HbA1c [mmol/mol]	36 [33; 39]	38 [36; 38]	0.165
Albuminuria [mg/d]	11.6 [9.3; 15.4]+	9.6 [6.5; 14.6]+	0.088
Pulse wave velocity [m/s]	7.2 [6.0; 8.7]	7.1 [5.8; 7.8]	0.372
Intima media thickness [mm]	0.77 [0.65; 0.90]	0.75 [0.67; 0.85]	0.997
ABI	1.1 [1.1; 1.2]	1.2 [1.1; 1.2]	0.148
Plaque Score	4 [0; 11]	7 [2; 13]	0.159
Supra-aortic plaques [n]	64	84	0.135
Aortic plaques [n]	21	27	0.158
Infra-aortic plaques [n]	75	88	0.399
Aorta [cm]	1.7 [1.5; 1.8]	1.7 [1.5; 1.9]	0.667

Data are given as median, 25th and 75th percentile in square brackets. Significance is marked in bold. Comparisons between baseline values were performed by Mann-Whitney U test and chi-square test. DBP: Diastolic blood pressure; DDD: Defined daily dose; GFR: Glomerular filtration rate; HbA1c: Glycated hemoglobin; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; SBP: Systolic blood pressure. + Owing to incomplete data, the calculations were performed with a reduced number of patients (PA, n = 42; EH, n = 36).

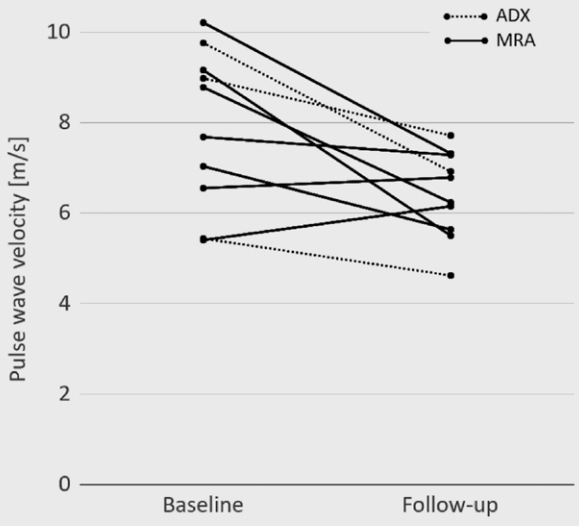
Holaj et al. reported lower CCA-IMT in patients with EH compared to patients with PA. In this study almost 50 % of PA patients had unilateral disease, with another 39 % of patients being unclassified by refusing or unsuccessful adrenal venous sampling (AVS). Mean aldosterone and potassium levels were 389 ng/l and 3.6 mmol/l respectively. Furthermore, those patients still had elevated systolic blood pressure of 160 mmHg, despite receiving a mean of four antihypertensive drugs, altogether illustrating that these patients harbored a severe phenotype of PA.

Over the years we observed a shift to milder forms of PA not only in our center of the German Conn's Registry, presumably due to increased screening intensity using ARR [4]. In the context with Murata and colleagues suggesting lowered cardiovascular risk in patients with mild PA, indistinguishable to patients with EH, our study aimed to compare (subclinical) atherosclerotic burden and arterial stiffness between patients with EH and patients with PA manifesting milder phenotype of PA [4, 18].

The patients included in the present study showed mild phenotype of PA, illustrated by a low percentage of hypokalemia (14 %; n = 6) in the cohort. Further aldosterone levels as well as DDD were lower than reported before (128 vs. 219 ng/l; 1.0 vs. 3.0) in the presence of unchanged SBP (151 vs. 151 mmHg) [19]. As patients with milder forms of PA more frequently show bilateral PA, AVS was only performed in 30 of 44 PA patients, a strategy, which is in agree-



▶ **Fig. 1** Distribution of atherosclerotic plaques in patients with essential hypertension and primary aldosteronism. CCA: Common carotid artery; CB: Carotid bifurcation; ECA: External carotid artery; ICA: Internal carotid artery; VA: Vertebral artery; SA: Subclavian artery; AA: Abdominal aorta; CFA: Common femoral artery; PFA: Profunda femoris artery; SFA: Superficial femoral artery; PoA: Popliteal artery.



▶ **Fig. 2** Changes of central pulse wave velocity (cPWV) from baseline to follow-up in individual patients with primary aldosteronism. Abbreviations: ADX: adrenalectomy; MRA: mineralocorticoid receptor antagonist treatment

ment with current guidelines [4, 20]. Consequently, we could identify only seven patients (16 %) with unilateral disease. Altogether the mild biochemical and clinical manifestation could be the reason that the time to diagnosis in this cohort does not differ from previous studies [31].

Our study results indicate that arterial stiffness as well as atherosclerotic burden in patients with mild PA do not differ from patients with EH, neither using non-invasive vascular measurements (CCA-IMT, cPWV, ABI) nor using plaque score (determined by ultrasound examination of 21 different arterial regions), which in part contrasts findings from patients with PA and a more severe phenotype [11]. However, in the current study markers of atherosclerosis and arterial stiffness strongly correlated with each other but also with cardiovascular risk factors such as presence of diabetes mellitus, high blood pressure levels and male sex (data not shown). When comparing absolute values of CCA-IMT and cPWV with results of other studies, in this study patients with PA are at the lower end of the range, which would be in accordance with a limited impact of mild PA on vascular remodeling [11, 12, 14, 15]. This is further underlined by the fact that CCA-IMT in this study was also lower compared to unpublished data from our Munich center of the German Conn's Registry, collected between 2008 and 2013 and showing CCA-IMT of 1.0 mm in patients with more severe phenotype of PA. In contrast, CCA-IMT and cPWV in patients with EH were midrange compared to recent studies [11].

Moreover, we found a correlation between atherosclerotic burden, measured by plaque score and statin use ($r = 0.315$; $p = 0.003$) and also for CCA-IMT and statin use ($r = 0.235$; $p = 0.028$). Altogether these could be the reasons that in our study CCA-IMT and cPWV in patients with PA were indistinguishable from patients suffering from EH, supposing a less pronounced aldosterone effect in mild cases of PA, which would be in accordance with recent findings [18]. Nonetheless initiation of specific treatment for PA resulted in a statistically significant reduction of albuminuria and cPWV and should be therefore expected to translate into favorable for cardiovascular outcomes (▶ **Fig. 2**). Arterial stiffening itself negatively impacts microcirculation and may be an indicator of premature vascular aging in hypertensive subjects. Improvement of cPWV under treatment, as documented at follow-up in a small subset of PA patients in our study, may be a hint on the effect of aldosterone excess on vascular aging via arterial stiffening. Although it is of note that the reduction of cPWV and albuminuria have also been reported in patients with (essential) hypertension on MRA treatment, which

should promote a more liberal use of MRA in patients with arterial hypertension [32, 33].

Interestingly renin levels correlated positively with plaque score in the total cohort. After splitting into patients with PA and EH we could observe a strong correlation for renin and plaque score in patients with EH ($r = 0.413$; $p = 0.006$), but not in patients with PA ($r = 0.137$; $p = 0.376$). These findings fit well with recent data from us and others, suggesting an association between renin levels and atherosclerotic burden in patients with EH but not in patients with PA [34–37].

Our study has several strengths. This prospective study investigates, for the first time, atherosclerotic burden in a substantial number of patients with PA and controls particularly when compared to earlier studies dealing with CCA-IMT [11]. Patients with mild PA and controls were very well matched with regard to demographics and cardiovascular risk factors. All clinical and sonographic data as well as biomaterial were collected in a standardized manner within the structured diagnostic workup of the German Conn's Registry. In a holistic approach, we studied 21 different arterial regions by high resolution sonography to provide a phenotype of atherosclerotic plaque distribution in patients with PA and EH. It has been shown that plaque assessment of different arterial regions shows stronger association with coronary artery disease than CCA-IMT alone [27, 38, 39].

We acknowledge some limitations of our study. First, mild PA is not yet well-defined. The upper cut-off (200 ng/l) used in our study to define patients with mild PA was chosen deliberately: it defines a collective of patients with aldosterone levels below the 50th percentile in our center and is based on a recent publication [19]. Furthermore, while CCA-IMT is a known surrogate parameter of subclinical atherosclerosis, still no consensus exists on the determination of plaque burden on ultrasound, and most studies are limited to assessment of the carotid arteries [39, 40]. Ultrasound is an investigator-dependent diagnostic method but offers the highest spatial resolution when it comes to detect initial changes of the arterial vessel wall. In our study, sonographers were highly experienced and blinded with regard to the underlying cause of arterial hypertension. Another limitation of the study is the small group of patients in the follow-up. Here, initially 12 patients underwent follow-up. However due to technical problems data of two patients could not be analyzed and we therefore ended up with 10 patients.

In summary, our data show that patient with mild PA do not differ from patients with EH with respect to subclinical atherosclerotic burden as well as arterial stiffness. This does not contradict the previous observation of impaired vascular function in patients with PA but rather sheds light on a second momentum – that of a less pronounced impact of milder PA forms on vascular function and structure. Nevertheless, treatment for PA was followed by an improvement of markers of cardiovascular risk and therefore confirms daily practice to intensify screening for PA and argues for a more liberal use of MRA in patients with arterial hypertension. Further longitudinal studies are necessary to determine whether the long-term risk of mild PA is indeed comparable with patients suffering from EH and to evaluate a specific effect of aldosterone excess on vascular aging.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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