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Primary aldosteronism: Higher volume load, cardiac output and arterial stiffness than in essential hypertension

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Abstract. Choudhary MK, Värri E, Matikainen N, Koskela J, Tikkakoski AJ, Kähönen M, Niemelä O, Mustonen J, Nevalainen PI, Pörsti I (Tampere University, Tampere; University of Helsinki, Helsinki; Tampere University Hospital, Tampere; and Seinäjoki Central Hospital, Seinäjoki, Finland). Primary aldosteronism: Higher volume load, cardiac output and arterial stiffness than in essential hypertension. *J Intern Med* 2021;**289**:29–41. https://doi.org/10.1111/joim.13115

Background. The diagnostics of primary aldosteronism (PA) are usually carried out in patients taking antihypertensive medications. We compared haemodynamics between medicated PA, medicated essential hypertension (EH), never-medicated EH and normotensive controls (n = 130 in all groups).

Methods. The hypertensive groups were matched for age (53 years), sex (84 male/46 female) and body mass index (BMI) (30 kg m^{-2}); normotensive controls had similar sex distribution (age 48 years, BMI 27 kg m^{-2}). Haemodynamics were recorded using whole-body impedance cardiography and radial pulse wave analysis, and the results were adjusted as appropriate. Radial blood pressure recordings were calibrated by brachial blood pressure measurements from the contralateral arm.

Results. Radial and aortic systolic and diastolic blood pressure was similar in PA and never-medicated EH, and higher than in medicated EH and normotensive controls ($P \leq 0.001$ for all comparisons). Extracellular water balance was ~ 4% higher in PA than in all other groups ($P < 0.05$ for all), whilst cardiac output was ~ 8% higher in PA than in medicated EH ($P = 0.012$). Systemic vascular resistance and augmentation index were similarly increased in PA and both EH groups when compared with controls. Pulse wave velocity was higher in PA and never-medicated EH than in medicated EH and normotensive controls ($P \leq 0.033$ for all comparisons).

Conclusions. Medicated PA patients presented with corresponding systemic vascular resistance and wave reflection, but higher extracellular water volume, cardiac output and arterial stiffness than medicated EH patients. Whether the systematic evaluation of these features would benefit the clinical diagnostics of PA remains to be studied in future.

Keywords: arterial stiffness, cardiac output, extracellular water, hypertension, primary aldosteronism.

Introduction

In 2015, the prevalence of elevated blood pressure (BP) in adult females was around 20% and in males around 24%, affecting ~ 1.13 billion people worldwide [1]. Several studies have indicated that the prevalence of primary aldosteronism (PA) exceeds 5% amongst hypertensive patients [2,3]. Aldosterone excess predisposes to sodium retention, increased extracellular water (ECW) volume, hypokalemia, alkalosis and hypertension [4]. Accordingly, increased ECW volume was reported in patients with PA versus controls in small previous studies (≤16 participants per group) [5,6].

Aldosterone excess promotes oxidative stress, inflammation, endothelial dysfunction, impairs vasorelaxation, promotes fibrosis, and causes vascular, renal and cardiac damage [7,8]. Supporting these views, carotid intima–media thickness was

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higher in patients with PA than in essential hypertension (EH) [9,10]. In patients with EH, increased aortic stiffness, measured via the recording of pulse wave velocity (PWV), is an independent predictor of cardiovascular mortality [11]. According to a review, PA patients (n = 272) had higher aortic PWV than EH patients (n = 240), whereas no significant difference was found in the variables of wave reflection, augmentation index (AIx) and AIx adjusted to heart rate 75 beats per minute (AIx@75) [10]. Recently, the forward and backward wave amplitudes were reported to be higher in medicated PA than in medicated EH, possibly reflecting vascular damage in PA patients [12,13] (see Supplementary Table S1).

Typically, patients with PA have higher BP and they need more antihypertensive medications than patients with EH [14]. Independent of the level of BP, increased incidence of myocardial infarction and stroke, and increased prevalence of atrial fibrillation have been reported in patients with PA [15]. According to the German Conn's Registry, patients with PA are at a higher risk of cardiovascular mortality than patients with EH [16]. However, higher BP does not seem to entirely explain the increase in cardiovascular morbidity and mortality in PA patients.

The suspicion of PA most often arises because of a poor response to antihypertensive medications [14]. Subsequently, in general the clinicians carry out the diagnostics of PA in patients who are ingesting BP-lowering agents [14]. At present, PA is probably less severe and better treated than previously [3,15], whilst the range of the haemodynamic changes in contemporary PA is still not entirely known [12]. Also, limited information exists about how parallel changes in systemic vascular resistance and ECW volume could influence wave reflections in PA [17]. To gain insight about the principal haemodynamic features of PA, our objective in this cross-sectional study was to examine cardiovascular function in patients with medicated PA, medicated EH, never-medicated EH and normotensive controls.

Methods.

Participants

All subjects participated in an ongoing study with the primary aim to examine haemodynamics in primary and secondary hypertension (Eudra-CT 2006-002065-39, ClinicalTrials.gov NCT01742702). Patients with confirmed aldosteronism from all five university clinics in Finland are referred to Tampere University Hospital for adrenal vein sampling. These patients were invited to participate in noninvasive haemodynamic recordings. The other participants were enrolled by announcements from the employees of, and patients treated at, Tampere University Hospital, and from staff of Tampere University, and clients of Varala Sports Institute and local occupational healthcare providers. Participants were recruited in the order in which their contact information reached the research nurses.

The 520 subjects of the present study were chosen from 1260 hypertensive and normotensive subjects recruited during 2006-2019. The groups were normotensive controls, never-medicated EH, medicated EH and medicated PA (Table 1). The study included 336 men and 184 women aged 21-80 years. The three hypertensive groups were matched for age (53 years), sex (84 male/46 female) and body mass index (BMI) (30 kg m^{-2}). Additionally, the medicated PA and medicated EH groups were matched for the use of beta blockers, or beta + alpha blockers (Table S2). The normotensive controls were matched for sex (n = 130, age 48 years, BMI 27 kg m^{-2}).

The exclusion criteria were the following: history of (1) coronary artery disease, (2) stroke, (3) heart failure, (4) valvular heart disease, (5) chronic kidney disease, (6) secondary hypertension other than PA, (7) alcohol or substance abuse, (8) psychiatric illnesses other than mild depression or anxiety and (9) heart rhythm other than sinus rhythm. The study complies with the Declaration of Helsinki and was approved by the Ethics Committee of the Tampere University Hospital (study code R06086M). Signed informed consent was obtained from all participants.

The never-medicated EH patients had elevated office BP (≥140/90 mmHg) [18]. The diagnosis of PA was based on screening and confirmatory testing [3]. Screening of aldosteronism (n = 130) was defined as serum aldosterone (pmol L^{-1}) to plasma renin activity (ng mL^{-1} h^{-1}) ratio > 750, with serum aldosterone concentration ≥ 280 pmol L^{-1} [3,19]; or serum aldosterone (pmol L^{-1}) to plasma renin concentration (mU L^{-1}) ratio > 30, with serum aldosterone concentration ≥ 280 pmol L^{-1} [3,20,21]. Most of the patients (n = 82) had

Table 1. *Basic clinical characteristics and laboratory results*

	Normotensive controls (n = 130)	Never-medicated essential hypertension (n = 130)	Medicated essential hypertension (n = 130)	Medicated primary aldosteronism (n = 130)
Male/female	84/46	84/46	84/46	84/46
Age (years)	47.9 (0.9)	53.5 (0.8)*	52.9 (1.1)*	53.0 (1.0)*
Height (cm)	175.6 (0.8)	174.7 (0.8)	173.7 (0.8)	173.8 (0.8)
Weight (kg)	82.5 (1.1)	91.8 (1.4) *	89.0 (1.4) *	92.1 (1.7) *
Body mass index (kg m^{-2})	26.7 (0.3)	30.1 (0.5)*	29.5 (0.4)*	30.3 (0.5)*
Number of type 1 diabetics	0	0	1	1
Number of type 2 diabetics	1	3	21*†	31*†
Office systolic BP (mmHg)	126.3 (0.8)	161.7 (1.6)*	145.2 (1.8)*†	154.1 (1.5)*†‡
Office diastolic BP (mmHg)	81.9 (0.5)	99.3 (0.8)*	90.9 (1.2)*†	91.6 (1.0)*†
Hypertension duration (years)	0.0	1.6 (0.5)	11.2 (0.9)*†	14.9 (0.9)*†‡
Office heart rate	65 (1)	70 (1)*	66 (1)	69 (1)*
Smoking status (never/present/previous)	67/23/40	64/15/51	70/15/45	68/22/40
Alcohol (standard drinks/week)	4.3 (0.5)	5.7 (0.7)	5.6 (0.6)	4.0 (0.4)
eGFR (ml min^{-1} 1.73 m^{-2})	96.2 (1.3)	89.5 (1.1)*	88.5 (1.6)*	86.8 (1.8)*
Sodium (mmol L^{-1})	140.5 (0.2)	140.7 (0.2)	140.0 (0.2)†	142.8 (0.2)*†‡
Potassium (mmol L^{-1})	3.80 (0.02)	3.82 (0.03)	3.75 (0.03)	3.48 (0.03)*†‡
C-reactive protein (mg L^{-1})	1.5 (0.2)	2.5 (0.4)	2.5 (0.3)	3.1 (0.6)*
Creatinine (μmol L^{-1})	76.6 (1.2)	75.7 (1.2)	77.1 (1.3)	80.7 (2.9)
Cystatin C (mg L^{-1})	0.87 (0.01)	0.93 (0.01)*	0.95 (0.02)*	1.0 (0.02)*
Uric acid (μmol L^{-1})	303 (6)	336 (6)*	349 (8)*	327 (7)
Total cholesterol (mmol L^{-1})	5.1 (0.1)	5.6 (0.1)*	5.1 (0.1)†	4.7 (0.1)*†‡
Triglycerides (mmol L^{-1})	1.07 (0.05)	1.53 (0.08)*	1.49 (0.07)*	1.48 (0.09)*
HDL cholesterol (mmol L^{-1})	1.60 (0.04)	1.45 (0.04)*	1.41 (0.04)*	1.36 (0.04)*
LDL cholesterol (mmol L^{-1})	3.04 (0.09)	3.54 (0.08)*	3.20 (0.09)†	2.96 (0.08)†
Glucose (mmol L^{-1})	5.42 (0.05)	5.81 (0.06)*	6.33 (0.14)*†	6.55 (0.13)*†
Cornell voltage-duration product (mm*ms)	1569 (50)	1917 (47)*	2017 (98)*	2163 (75)*

Results shown as mean (standard error of mean); eGFR, estimated glomerular filtration rate (CKD-EPI cystatin C creatinine formula).
*$P < 0.05$ versus normotensive.
†$P < 0.05$ versus never-medicated essential hypertension.
‡$P < 0.05$ versus medicated essential hypertension.

presented with hypokalemia (Table 2), and confirmatory testing was performed in the majority (n = 113), showing urine aldosterone excretion > 33 nmol day^{-1} during oral sodium loading [3,19]. Seven subjects who had borderline screening tests for PA were included, as they were hypokalemic (plasma potassium < 3.3 mmol L^{-1}), presented with elevated serum aldosterone (range 513-1290 pmol L^{-1}) in control samples and showed elevated 24-hour urine aldosterone excretion (range 44-132 nmol day^{-1}) during oral sodium loading (Table 2) [3].

Office BP measurements and laboratory analyses for elevated BP were performed according to the guidelines of the European Society of Hypertension

[18]. The participants were examined by a physician, and medical history, lifestyle habits, dietary supplements, medicines, smoking status and alcohol consumption as standard drinks (~12 grams of absolute alcohol) per week were documented. Leg oedema was classified clinically: no oedema, cuff part of the socks made impressions in the ankle region (mild), pitting in the feet and ankles (moderate), and oedema extending to the proximal parts of the calves (severe).

Altogether 362 (69.7%) participants used medications, and the BP and lipid-lowering medications are shown in Table 3. Amongst 130 PA patients, spironolactone was previously used by 51 subjects, but was discontinued in 47 of them 6 weeks before the recordings. Prazosin and calcium channel blockers were prescribed by the treating physicians when needed. Four PA patients continued spironolactone for safety reasons (Table 3). Other regular medications are listed in Supplementary Table S3.

Laboratory analyses

Blood and urine sampling were performed after ~ 12 hours of fasting. Plasma sodium, potassium, glucose, cystatin C, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, C-reactive protein, uric acid, and creatinine concentrations, and urine sodium and potassium concentrations, were determined using Cobas Integra 700/800 (F. Hoffmann-Laroche Ltd., Basel, Switzerland) or Cobas 6000, module c501 (Roche Diagnostics, Basel, Switzerland), and blood cell count by ADVIA 120 or 2120 (Bayer Health Care, Tarrytown, NY, USA). Plasma renin activity (PRA) was initially determined using radioimmunoassay (DiaSorin, Saluggia, Italy), but this method was replaced by the analysis of plasma direct renin concentration (LIAISON immunoanalyzer, DiaSorin, Saluggia, Italy) [20]. In patients with very low renin values, the concentrations were given as the following low detection limits: 0.2 ng mL^{-1} h^{-1} for PRA and 2 mU L^{-1} for direct renin concentration. Plasma and urine aldosterone was quantified using liquid chromatography–mass spectrometry (LC–MS/MS) on API 4000 (Sciex) as described earlier [22]. To exclude patients with renal diseases, automated urine dipstick refractometer analysis was performed (Siemens Clinitec Atlas or Advantus, Siemens Healthcare GmbH, Erlangen, Germany). Glomerular filtration rate (eGFR) was estimated using the CKD-EPI creatinine–cystatin C formula [23].

Pulse wave analysis

Continuous pulse wave and radial BP were captured using an automated tonometric sensor (Colin BP-508T, Colin Medical Instruments Corp., USA) recordings from the left radial artery. The radial BP signal was calibrated twice during the 5-minute period by contralateral brachial BP measurements. Aortic BP, AIx (augmented pressure/pulse pressure*100) and AIx@75 were determined using the SphygmoCor software (SpygmoCor PWMx®, AtCor medical, Australia) [17,24].

Whole-body impedance cardiography

Beat-to-beat heart rate, stroke volume, cardiac output, ECW and PWV were recorded using

Table 2. *Laboratory characteristics of 130 patients with primary aldosteronism*

		95% confidence interval			
	Mean	Lower bound	Upper bound	Number[a]	Normal range
Lowest plasma potassium (mmol L^{-1})	3.14	3.06	3.21	130	3.3–4.8
Serum aldosterone (pmol L^{-1})	822	720	925	130	<520
Plasma renin activity (ng of Ang I mL^{-1} h^{-1})	0.32	0.24	0.42	79	1.5–5.7
Plasma renin concentration (mU L^{-1})	13.3	9.2	17.4	51	4.4–46
Ratio of aldosterone to renin activity	3234	2727	3740	79	<750
Ratio of aldosterone to renin concentration	119	79	158	51	<30
Urinary aldosterone (nmol/24h)	100.5	55.3	145.6	113	<40
Urinary sodium (mmol/24h)	223	205	242	89	130–240
Urinary potassium (mmol/24h)	113	104	122	78	60–90

[a]Number of subjects with available result of the laboratory determination.

whole-body impedance cardiography (CircMon®, JR Medical Ltd., Tallinn, Estonia). The electrode configuration has been previously reported [25]. Systemic vascular resistance was calculated from the tonometric BP and cardiac index measured by CircMon®: normal central venous pressure (4 mmHg) was subtracted from mean arterial pressure, and the value was divided by cardiac output. Systemic vascular resistance, stroke volume and cardiac output were related to body surface area (cardiac index, stroke index and systemic vascular resistance index (SVRI), respectively). The stroke volume values measured using CircMon® correlate well with 3 dimensional ultrasound [26], and the cardiac output values correlate well with values measured using thermodilution (bias 0.00 L min^{-1}, 95% confidence interval (CI) −0.26 to 0.26) and direct oxygen Fick method (bias −0.32 L min^{-1}, 95% CI −0.69 to 0.05) [25].

The CircMon® evaluates ECW volume by the formula ECW = k*(H^2/Z), coefficient k (Ω*cm) derived from blood resistivity and the relation between the distance of voltage electrodes, H is body height (cm), and Z is the recorded impedance of the body. The bioimpedance-derived ECW volume correlates well with ^{51}Cr-EDTA dilution-based ECW measurement (n = 15, r = 0.74, bias 0.2 ± 1.1 L, mean ± SD) [27]. The ECW balance is calculated as ECW/$ECW_{predicted}$. The formula for predicted ECW is 2.4 * (0.0236 * $H^{0.725}$ * $W^{0.423}$ – 1.229) in males and 2.6 * (0.0248 * $H^{0.725}$ * $W^{0.423}$ – 1.9549) in females [28–30]. In the current results, the ECW balance of the normotensive group was adjusted to 1.0.

To measure PWV, the CircMon® software records the time difference between the onset of the decrease in the impedance of the whole-body signal and the signal from the popliteal artery region [31].

Table 3. *Number of subjects using antihypertensive or lipid-lowering medications*

	Normotensive controls (n = 130)	Never-medicated essential hypertension (n = 130)	Medicated essential hypertension (n = 130)	Medicated primary aldosteronism (n = 130)
Number of antihypertensive medications (median)	0	0	2	3
ACE inhibitor	0	0	42	22*
Angiotensin II receptor blocker	0	0	52	65
Beta blocker	0	0	65	64
Beta and alpha blocker	0	0	4	6
Calcium channel blocker	0	0	60	115*
Thiazide	0	0	53	15*
Furosemide	0	0	6	5
Spironolactone	0	0	7	4
Amiloride	0	0	8[a]	0
Nitrate	0	0	2	0
Moxonidine	0	0	5	18*
Minoxidil	0	0	0	1
Potassium supplement	0	1	4	82*
Prazosin	0	0	6	23*
Statin	5	3	46	36
Ezetimib	1	0	1	0
Fibrate	0	0	0	1

Statistic is only about the differences between primary aldosteronism versus medicated essential hypertension; spironolactone was previously used by 51 patients with PA, and this medication was discontinued in 47 of them 6 weeks before the recordings.
*P < 0.05.
[a]in 7/8 combination with hydrochlorothiazide.

PWV is calculated from the time difference and the distance between the electrodes. As the whole-body impedance cardiography slightly overestimates PWV, a validated equation was utilized to calculate values that correspond to the ultrasound method (PWV = PWVimpedance * 0.696 + 0.864) [31]. With this equation, the PWV values recorded using CircMon® show good correlations with values measured using SphygmoCor® (r = 0.82, bias 0.02 m s^{-1}, 95% CI −0.21 to 0.25) [17] or ultrasound (r = 0.91) [31].

Experimental protocol

Research nurses recorded haemodynamics in a noiseless temperature-controlled laboratory. Prior to the recordings smoking, caffeine-containing products and heavy meals were to be avoided for ≥ 4 hours, and alcohol consumption for > 24 hours. The subjects rested supine, and the left arm with the tonometric sensor was abducted to 90 degrees in a support. After getting accustomed for about 10 minutes, supine haemodynamics were recorded for 5 minutes. For the statistical analyses, the mean values of each 1-minute period of recording were calculated. The good repeatability and reproducibility of the measurement protocol has been demonstrated previously [32].

Statistics

The demographic and laboratory data were analysed using analysis of variance (ANOVA). The homogeneity of variances was tested with the Levene's test. Haemodynamic differences between the groups were examined using generalized estimating equation (GEE) analyses. This method enabled the analyses of repeated measurements over the 5-minute recording period to compare differences between the study groups in the haemodynamic variables. Linear scale response was applied, and the autoregressive option was chosen for the correlation matrix, as successive serial measures of haemodynamic variables in individual participants are autocorrelated. The Bonferroni correction was applied in all post hoc analyses. The groups presented with differences in age, BMI, proportions of diabetic subjects, eGFR; plasma uric acid, triglycerides, HDL cholesterol, LDL cholesterol and glucose (Table 1). If any of the above variables correlated with the haemodynamic variable of interest with $P < 0.1$ (Pearson), they were included in the GEE analyses as covariates. The PWV analyses were additionally adjusted for mean aortic pressure [33]. As changes in plasma sodium, potassium and C-reactive protein probably reflect true effects of aldosterone [3,15], no adjustments were performed for these variables. Lean body mass was used instead of BMI in analyses concerning ECW volume and balance, as lean body mass is more suitable for normalization of body fluid volumes [34]. The results were presented as mean and standard error of the mean (SEM), or as mean and 95% CI of the mean, and $P < 0.05$ was considered statistically significant. SPSS version 26.0 (IBM SPSS Statistics, Armonk, NY, USA) was used.

Results

Study population

Altogether, 336 (65 %) male and 184 (35%) female subjects participated in the analyses (age range 21–80 years) (Table 1). Sex distribution was equal in all groups, whilst the normotensive subjects were ~ 5 years younger with ~ 3 kg m^{-2} lower BMI than in the other groups. The number of type 2 diabetic subjects was higher in the medicated EH and PA groups than amongst the never-medicated EH and normotensive groups. Office systolic BP was ~ 10 mmHg higher in PA versus medicated EH, whilst office systolic and diastolic BP was highest in the never-medicated EH group (Table 1). There were no differences in clinically evaluated lower extremity oedema between the groups: even in the PA group 91% were without oedema, 6% had mild oedema, whilst 3% had moderate oedema.

Average alcohol intake and smoking habits were not different between the groups. Patients with PA had the longest known hypertension history (Table 1), whilst the median number of antihypertensive medications was not different between PA and medicated EH ($P = 0.135$, Table 3). Although 82 PA patients were taking potassium supplements, plasma potassium concentration was lowest, whilst plasma sodium concentration was highest, in the PA group (Tables 1 and 3). Amongst the PA patients 36 subjects and amongst the medicated EH patients 46 subjects, were taking statins (Table 3). Plasma total cholesterol was lowest in the PA group, and LDL cholesterol was highest in the never-medicated EH group (Table 1). Plasma triglycerides and glucose were higher, and

HDL cholesterol was lower, in the 3 hypertensive groups than in normotensive controls. Fasting plasma glucose was slightly higher in the PA group and the medicated EH group than in the never-medicated EH group. Cornell voltage product did not differ between the 3 hypertensive groups and was higher than in normotensive controls (Table 1).

Noninvasive haemodynamics in the laboratory

Radial systolic and diastolic BP, calibrated from contralateral brachial BP signal, and aortic systolic and diastolic BP were not different in medicated PA and never-medicated EH, and were higher than in medicated EH and normotensive controls ($P \leq 0.001$ for all comparisons). BP was also higher in medicated EH than in normotensive controls ($P < 0.001$ for all comparisons) (Figures 1a-d).

When adjusted for confounding variables, ECW volume was higher in PA patients than in medicated EH and normotensive subjects ($P < 0.05$ for both) (Figure 2a). Also, the bioimpedance-derived ECW balance was ~ 4% higher in PA than in all other groups ($P \leq 0.009$ for all) (Figure 2b).

Aortic-to-popliteal PWV, adjusted for mean aortic pressure in addition to demographic and metabolic factors, was higher in medicated PA than in medicated EH and normotensive subjects ($P \leq 0.033$) (Figure 2c). However, PWV was highest in never-medicated EH ($P \leq 0.004$ for all comparisons) (Figure 2c). Aortic-to-popliteal PWV without conversion to values that correspond to the ultrasound method is presented in Figure S1. Aortic pulse pressure was higher in all hypertensive groups than in normotensives ($P < 0.001$ for all), and it was also higher in medicated PA than in medicated EH ($P = 0.008$) (Figure 2d).

Never-medicated EH patients had higher heart rate when compared with PA, medicated EH and normotensive subjects ($P < 0.05$ for all) (Figure 3a). Stroke volume related to body surface area (stroke index) did not differ between PA patients and normotensive controls and was higher than in medicated and never-medicated EH ($P \leq 0.033$ for all) (Figure 3b). Despite similar beta-blocker use, cardiac index was ~ 8% higher in medicated PA than in medicated EH ($P = 0.012$) (Figure 3c). SVRI was similar in the PA and both EH groups, and higher than in normotensive controls ($P < 0.001$ for all) (Figure 3d).

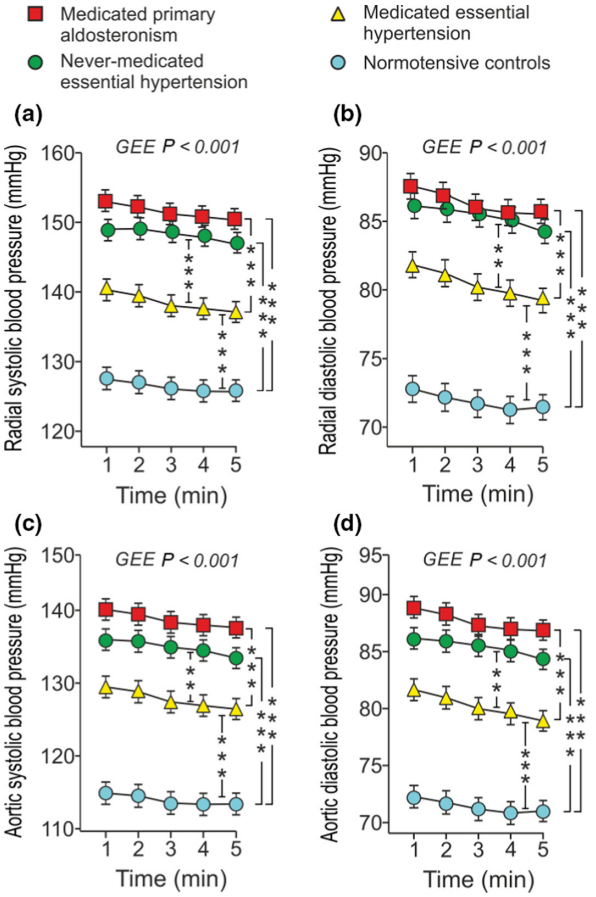

Figure 1 *Radial systolic (a) and diastolic (b) blood pressure calibrated from brachial blood pressure measurements, and aortic systolic (c) and diastolic (d) blood pressure in medicated primary aldosteronism (n = 130), never-medicated essential hypertension (n = 130), medicated essential hypertension (n = 130) and normotensive controls (n = 130) during 5-minute recordings in supine position; mean ± SEM; statistics by generalized estimating equations (GEE) adjusted for age, BMI, presence of diabetes, eGFR; and plasma triglycerides, HDL cholesterol, LDL cholesterol, uric acid and glucose (see Methods);* **P < *0.01*, ***P < *0.001*

The forward wave amplitude (FWA) did not differ between PA and never-medicated EH, and was higher in PA than in medicated EH and normotensive controls ($P \leq 0.002$) (Figure 4a). AIx@75 was corresponding in all hypertensive groups, and higher than in normotensive controls ($P < 0.001$ for all) (Figures 4b). A summary of the main haemodynamic findings of this study is presented in Table 4.

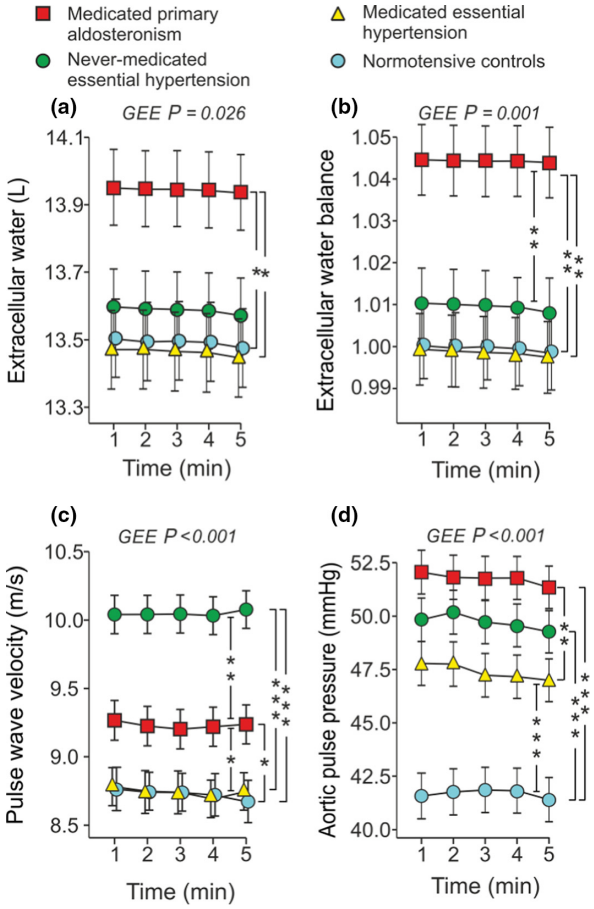

Figure 2 *Extracellular water volume (a), extracellular water balance (b), aortic-to-popliteal pulse wave velocity (PWV) (c) and aortic pulse pressure (d). Groups and statistics as in Figure 1, except that in extracellular water analyses, BMI was replaced with lean body mass, and in PWV analyses, the results were also adjusted for mean aortic blood pressure;* *P < *0.05*, **P < *0.01*, ***P < *0.001*

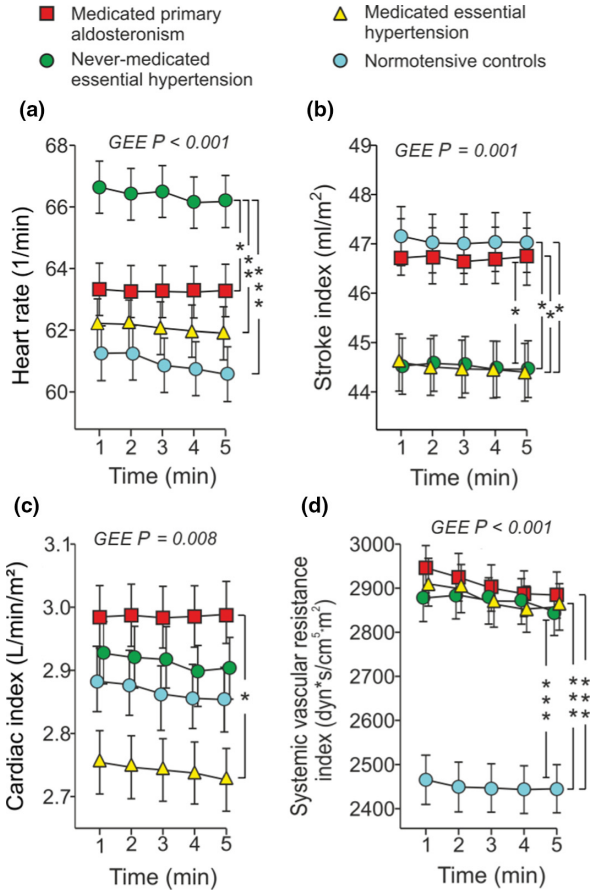

Figure 3 *Heart rate (a), stroke index (b), cardiac index (c) and systemic vascular resistance index (d). Groups and statistics as in Figure 1;* *P < *0.05*, **P < *0.01*, ***P < *0.001*

Adrenal vein sampling was successful in 114/130 subjects with PA. Lateralization to either adrenal was detected in 63/114 patients. However, no significant haemodynamic differences were detected between subjects with bilateral versus unilateral aldosterone excess. Amongst the PA patients, serum aldosterone to plasma renin activity ratio correlated with radial and aortic diastolic BP ($r_S = 0.23$, $P = 0.04$ for both), and 24-hour urine aldosterone excretion correlated with radial and aortic diastolic BP ($r_S = 0.20$, $P = 0.04$ for both), but not with other haemodynamic variables.

Discussion

Rather few studies have examined haemodynamic differences between PA and EH patients carefully matched for confounding factors. Here, we compared haemodynamics between patients with medicated PA, medicated EH, never-medicated EH and normotensive controls. The PA group presented with the typical characteristics of aldosterone excess [3], and only four PA patients and seven EH patients were taking spironolactone during the recordings. In addition to age, BMI, sex, plasma lipids and glucose, the medicated groups were matched for the use of beta adrenoceptor blockers, as this class drugs interferes with both cardiac function and regulation of systemic vascular resistance [35].

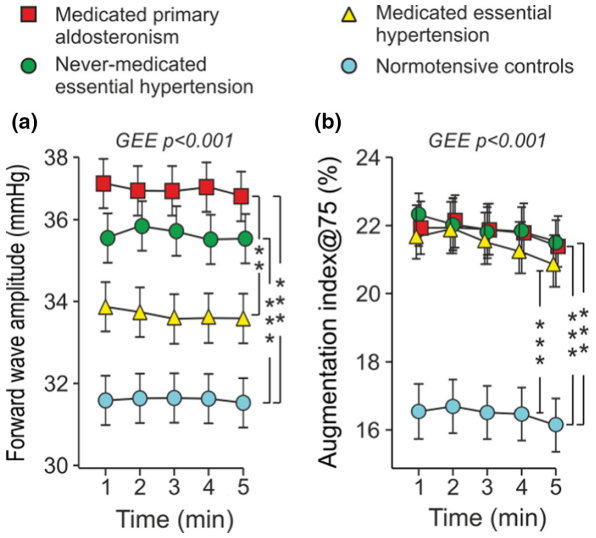

Figure 4 *Forward wave amplitude (a) and augmentation index adjusted to heart rate of 75 beats per minute (b). Groups and statistics as in Figure 1;* **P < *0.01,* ***P < *0.001*

In separate previous reports, PA has been associated with increased ECW volume [5,6], increased cardiac output [36] and increased large arterial stiffness [9,10,37] (see Supplementary Table S1 for a summary of haemodynamic findings in PA). Our results showed that SVRI and AIx@75 were corresponding in all hypertensive groups, whilst medicated PA patients had higher ECW balance, cardiac index and PWV than medicated EH patients.

Largely due to elevated aldosterone-to-renin ratio [14] and elevated plasma natriuretic peptide concentration [38], the PA patients are considered to have volume overload. In 279 patients with resistant hypertension, plasma natriuretic peptide and aldosterone concentrations, and aldosterone-to-renin ratio, were higher than in 53 subjects with normotension or controlled hypertension [39]. ECW volume, estimated by means of radioactive sodium sulphate injections, was higher in 11 PA patients than in 11 normal controls (16.8% vs. 14.6% of body weight, respectively) [5], and in 10 PA patients than in 7 EH patients [6]. When compared with the manufacturer reference values, Wu et al. reported ~ 4% overhydration in 41 patients with PA by bioimpedance spectroscopy, a method widely used for the evaluation of volume status in dialysis patients [40]. In the present study, ECW balance was also ~ 4% higher in the PA group than in all other groups (Figure 2b), indicating fluid overload.

In the current study, stroke index was higher, and cardiac index was ~ 8% higher, in medicated PA patients than in medicated EH patients (Figure 3c). Already in 1973, 16 patients with PA were found to have higher heart rate and cardiac index than 30 patients with EH, without differences in total peripheral resistance [36]. Cesari et al. found increased cardiac output in PA versus normotensive controls using ultrasound [41], whilst Kusunoki et al. reported higher cardiac output in medicated PA than in medicated EH based on waveform analyses form the brachial artery [42]. When examined using magnetic resonance imaging, 37 patients with high aldosterone had ~ 9% higher left ventricular end diastolic volume than 71 patients with normal aldosterone, indicating intracardiac volume expansion [38]. In contrast, in an echocardiography analysis, no differences were detected in stroke volume or cardiac output of 17 PA patients versus 10 EH patients [43] (see Supplementary Table S1). Aldosterone excess has also been associated with thicker left ventricular walls when compared with EH patients [44,45], which was attributed to deposition of extracellular matrix and collagen in the heart [44,45]. However, in the present study the hypertensive groups demonstrated corresponding increases in Cornell voltage product when compared with normotensive controls.

High aldosterone levels and high aldosterone:renin ratio predispose to increased arterial stiffness [46]. Increased intima–media thickness and fibrous tissue content were reported in the carotid artery of 23 PA patients versus 24 EH patients [9]. In small arteries, PA patients had higher type III collagen content than EH patients, indicating increased fibrosis [47]. Accordingly, several studies have reported increased large arterial PWV in patients with PA, although in all investigations the analyses were not adjusted for BP and other confounders [9,10,37]. In the present study, PWV was higher in patients with medicated PA than in medicated EH. However, PWV in the never-medicated EH patients was highest amongst all groups. This indicates that although they had not been diagnosed with hypertension previously, they must have had long-standing untreated high BP. Our results agree with the view that unawareness of hypertension is a major problem [48], and stress the importance of early diagnosis and treatment of hypertension. Of

Table 4. *Summary of the noninvasive haemodynamic results in the laboratory*

	Normotensive controls (n = 130)	Never-medicated essential hypertension (n = 130)	Medicated essential hypertension (n = 130)	Medicated primary aldosteronism (n = 130)
Radial systolic blood pressure (mmHg)[a]	126.7 (1.1)	148.0 (1.6)*	138.7 (1.4)*	151.8 (1.7)*
Radial diastolic blood pressure (mmHg)[a]	71.9 (0.8)	85.2 (1.0)*	80.4 (0.8)*	86.8 (0.9)*
Extracellular water balance (%)	0.0 (0.7)	0.9 (0.7)	0.0 (1.0)	4.6 (0.9)*
Pulse wave velocity (m s^{-1})[b]	8.7 (0.1)	10.1 (0.2)*	8.8 (0.1)†	9.3 (0.1)*
Cardiac index (L min^{-1} m^{-2})	2.89 (0.05)	2.93 (0.05)	2.76 (0.04)	2.97 (0.05)‡
Systemic vascular resistance index (dyn*s/cm^5·m^2)	2467 (45)	2850 (51)*	2861 (53)*	2922 (58)*
Augmentation index adjusted to heart rate 75 beats per minute (%)	16.3 (0.8)	21.8 (0.7)*	21.1 (0.8)*	21.8 (0.7)*

Results shown as mean (standard error of the mean).
[a]Calibrated from contralateral brachial blood pressure.
[b]Adjusted for age, BMI, presence of diabetes, triglycerides, HDL cholesterol, LDL cholesterol, uric acid, glucose, eGFR and mean aortic pressure.
*$P < 0.05$ versus normotensive.
†$P < 0.05$ versus never-medicated essential hypertension.
‡$P < 0.05$ versus medicated essential hypertension.

note, PWV measured by the present method is an independent predictor of incident hypertension [49].

In many studies, patients with PA had higher AIx and AIx@75 than normotensive subjects, but these variables of wave reflection were found to be similar in patients with PA and EH [10,37]. These results correspond to our findings showing similar AIx@75 in all hypertensive groups. Recently, the amplitude of the forward and backward waves were found to be higher, although the AIx values were not different, in medicated PA patients than in medicated EH patients [12]. This was suggested to reflect dysfunction of the arterial system, but information about central BP, or the effect of volume load on pressure waves were lacking. The proportion spironolactone users was also higher in the PA group than in the EH group (15% vs. 2%), and office BP and wave reflection were recorded sequentially [12], not simultaneously like in the present study. The FWA depends critically on the level of BP [50], and we found no differences in FWA between never-medicated EH and medicated PA patients with comparable laboratory BP values. We evaluated peripheral arterial function by the recording of SVRI that was not different between the EH and PA groups.

In our study, 82 of the PA patients were hypokalemic at screening and they were treated with potassium supplements. However, mean plasma potassium concentration was still lower amongst PA patients than in the other groups, whilst the PA group also presented with elevated plasma sodium concentration. Previously, increased plasma sodium concentration was reported in PA [51], and Steichen et al. have discussed the inclusion of plasma sodium and potassium concentrations in the diagnostic algorithm of PA [51]. The 24-hour urine collections are unreliable and depend largely on the intake of electrolytes, whilst urine sodium excretion is also variable due to water-free sodium storage in the body [52].

Without treatment with mineralocorticoid receptor antagonists or adrenalectomy, PA increases the risk of cardiovascular events and death [15]. However, the diagnosis of PA is not straightforward [3,4,51,53,54]. Early PA detection depends on screening, but under-diagnosis is characteristic in primary care [54]. High heterogeneity in the diagnosis of PA was even revealed in specialized care in Germany [53]. Considering the high prevalence of hypertension in the population [48], and the high prevalence of PA amongst hypertensive individuals [2,3], reliable, easy-to-perform, and

cost-effective diagnostic tests for PA are welcome. Whether screening and diagnosis of PA would benefit from information about the haemodynamic characteristics and ECW volume makes an interesting research topic in the future.

The current study has limitations. Screening for aldosteronism by serum aldosterone and plasma renin analyses was not performed in the EH groups. However, we can assume that ≥ 90% of the participants in these groups had primary hypertension [2,3], and the inclusion of subjects with unrecognized PA would have reduced the haemodynamic differences between PA and EH. The present methods have been validated against invasive measurements, three-dimensional ultrasound and tonometric PWV recordings [17,24–26]. Yet, noninvasive evaluation of stroke volume is based on mathematical analyses of bioimpedance with a formula containing body height, and a coefficient including BMI [25]. Similar heights in all study groups ($P = 0.314$) and similar weights and BMIs ($P = 0.285$ and 0.377, respectively) in the hypertensive groups should increase the analysis reliability. The haemodynamic recordings were performed in voluntary subjects, which make a source for selection bias, and lasted for five minutes, which gives a rather short window of observation. Still, the analyses were based on average from ≥ 300 cardiac cycles in each subject. For patient safety, the antihypertensive medications in the PA group were not being discontinued. For this reason, we included both never-medicated and medicated EH groups in the study. Previous spironolactone treatment may also have influenced the haemodynamic results in 47 subjects of the PA group. Finally, the cross-sectional design does not allow conclusions about causality. However, a strength of this study is the large number PA patients.

Conclusions

In this study, we examined noninvasive haemodynamics in patients with PA and EH versus normotensive controls. The inclusion of never-medicated and medicated EH groups allowed us to conclude that aldosterone excess *per se*, not only the aldosterone-induced elevation of BP, invoked changes in haemodynamic variables that may contribute to the reported excess cardiovascular risk in PA [16]. Whether the routine determinations of extracellular water volume, cardiac output and arterial stiffness would benefit the clinical diagnostics of PA remains to be studied in future.

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Conflict of interest

The authors declare no conflicts of interest with respect to this manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Summary of haemodynamic findings in primary aldosteronism versus essential hypertension, normotension and secondary aldosteronism; and effects of treatment in primary aldosteronism.

Table S2 Number of subjects using beta blockers or beta+alpha blockers.

Table S3 Number of subjects using other than anti-hypertensive or lipid-lowering medications.

Figure S1 Aortic-to-popliteal pulse wave velocity (PWV) presented as unprocessed raw data without conversion to values that correspond to the ultrasound method (see Methods) in medicated primary aldosteronism (n = 130), never-medicated essential hypertension (n = 130), medicated essential hypertension (n = 130), and normotensive controls (n = 130) during 5-minute recordings in supine position; mean±standard error of the mean; statistics by generalized estimating equations (GEE) adjusted for age, BMI, proportions of diabetic subjects, eGFR; and plasma triglycerides, HDL cholesterol, LDL cholesterol, uric acid, glucose, and mean aortic pressure (see Methods); *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

