Plasma Aldosterone and Left Ventricular Diastolic Function in Treatment-Naïve Patients With Hypertension

Tissue-Doppler Imaging Study

Cristiana Catena, Nicolas Verheyen, Stefan Pilz, Elisabeth Kraigher-Krainer, Andreas Tomaschitz, Leonardo A. Sechi, Burkert Pieske

Abstract—Aldosterone has hypertrophic and profibrotic effects on the heart. The relationship between plasma aldosterone levels and left ventricular diastolic function in hypertension, however, is unclear. The aim of this study was to examine this relationship in treatment-naïve hypertensive patients free of comorbidities that could affect left ventricular diastolic filling properties. In 115 patients with primary hypertension who were eating a standard diet and 100 matched normotensive controls, we measured plasma aldosterone and active renin levels and performed both conventional echocardiography and tissue-Doppler imaging for assessment of left ventricular diastolic function. Left ventricular hypertrophy was found in 21% of hypertensive patients, and diastolic dysfunction was detected in 20% by conventional echocardiography and in 58% by tissue-Doppler imaging. Patients with left ventricular diastolic dysfunction at tissue-Doppler imaging were older and more frequently men, had greater body mass index, blood pressure, alcohol intake, left ventricular mass index, relative wall thickness, and lower plasma aldosterone levels than patients with preserved diastolic function. Plasma aldosterone correlated directly with left ventricular mass index in addition to age, body mass index, and systolic blood pressure. Plasma aldosterone was also directly related to e' velocity at tissue-Doppler imaging, but this relationship was lost after multivariate adjustment. In conclusion, plasma aldosterone levels are associated with left ventricular hypertrophy but have no independent relationship with left ventricular diastolic properties in hypertensive patients. **(*Hypertension*. 2015;65:1231-1237. DOI: 10.1161/HYPERTENSIONAHA.115.05285.)** ● **Online Data Supplement**

Key Words: echocardiography ■ hypertrophy, left ventricular ■ renin

Diastolic heart failure is detected with increasing frequency in patients with hypertension[1] and is anticipated by changes in left ventricular (LV) filling properties that reflect stiffening of the ventricular wall. These changes in diastolic function can occur even in the absence of hypertension-related LV hypertrophy and are associated with increased hospitalization rate and mortality.[2] Therefore, identification of early LV diastolic abnormalities is critical in patients with high blood pressure to prevent subsequent cardiac functional deterioration heralding cardiac insufficiency.[3] Conventional echocardiographic techniques cannot detect early changes of diastolic function in a relevant proportion of patients,[4] but pulsed tissue-Doppler imaging (TDI) with measurement of myocardial velocities at several segments of the LV wall permits more sensitive[5] and reproducible[6] detection of diastolic dysfunction.

In addition to an increased blood pressure–related cardiac workload, other factors could contribute to the development of structural and functional abnormalities of the heart in patients with hypertension. Evidence obtained in experimental animal studies indicates that inappropriately elevated aldosterone levels and activation of mineralocorticoid receptors (MR) induce profibrotic and hypertrophic responses in the heart.[7–10] Also, studies conducted in patients with primary aldosteronism have consistently reported abnormal LV diastolic properties in association to excess LV hypertrophy in comparison with matched patients with primary hypertension.[11,12] However, results of studies that examined the possible contribution of plasma aldosterone levels to LV diastolic dysfunction in primary hypertension were inconsistent[13,14] and also studies that investigated the effects of MR antagonists on LV diastolic function and clinical outcomes in patients with heart failure and preserved ejection fraction reported controversial results.[15–18] Inconsistencies could be attributed to the use of conventional echocardiography in most of these studies and, most important, to possible interference of drugs used to treat hypertension or heart failure.[19] The aim of this study was,

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From the Divisions of Cardiology (C.C., N.V.) and Endocrinology and Metabolism (S.P., A.T.), Department of Medicine, Medical University of Graz, Graz, Austria; Department of Internal Medicine and Cardiology, Charitè University Medicine, Campus Virchow Klinikum and German Heart Center, Berlin, Germany (E.K.-K., B.P.); and Hypertension Unit, Internal Medicine, Department of Experimental and Clinical Medical Sciences, University of Udine, Udine, Italy (L.A.S.).

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Correspondence to Cristiana Catena, Division of Cardiology, Medical University of Graz, Auenbruggerplatz 15, 8036 Graz, Austria. E-mail cristiana.catena@uniud.it

therefore, to investigate the relationship of plasma aldosterone levels with markers of LV diastolic dysfunction obtained at TDI in treatment-naïve patients with primary hypertension free of comorbidities that might affect LV filling properties.

Methods

Study Population

One-hundred fifteen patients with newly diagnosed and never-treated, grade 1 to 2 primary hypertension, were included in a cross-sectional study. Patients were consecutively recruited at our University clinics in Udine and Graz where patients had direct access. Blood pressure was measured by an automated device (Omron M6; OMRON Healthcare Co, Kyoto, Japan) using an appropriately sized cuff after each subject had been supine for 15 minutes and the average of 3 readings was recorded.[20] Diagnosis of hypertension was based on blood pressure measurements obtained in at least 3 separate visits, according to current guidelines.[20] Predefined exclusion criteria were as follows: age <18 years or >80 years; pregnancy or use of estrogens; body mass index (BMI) >35 kg/m^2; alcohol abuse (daily alcohol consumption of ≥80 g/d); diabetes mellitus; white-coat hypertension; secondary hypertensive disease; impaired LV systolic function (ejection fraction <50%); 24-hour creatinine clearance (glomerular filtration rate [GFR]) <30 mL/min per 1.73 m^2; history of acute illness, stroke, transitory ischemic attack, ischemic heart, cardiac valve, or other types of heart disease, and peripheral artery disease. All patients were white and were representative of the hypertensive population of the 2 geographical areas. Secondary causes of hypertension were excluded in all patients according to established guidelines[20] and as previously reported[21] (online-only Data Supplement). Patients were classified as smokers if they had smoked for at least 5 years, and ≤1 year before the study. Alcohol intake and physical activity were estimated by a questionnaire.[22] Before the study, patients ate a standard diet for 7 days to maintain a sodium intake of ≈150 mmol/d that was checked with measurement of 24-hour urinary sodium excretion.

One-hundred normotensive healthy subjects served as controls. These subjects were selected from the general population of the same geographic areas as the hypertensive patients by frequency matching, after specification of inclusion criteria to avoid age and sex as potential confounding variables. Normotensive controls were not taking any regular medications and did not have any concomitant disease. The study was performed in accordance with the principles of the Declaration of Helsinki, received approval from the Institutional Review Board of the University of Udine and from the Ethics Committee of the Medical University of Graz. Informed consent was obtained from all patients.

Laboratory Measurements

Venous blood was collected in the morning after a 12-hour fast with the patients in the sitting position. Blood was collected into silicone-treated glass tubes containing trisodium citrate and plasma was immediately separated and frozen at −80°C until assay was performed. Plasma aldosterone levels were determined by chemiluminescence using a kit with automatic analyzer IDS-iSYS Multi-Discipline (Immunodiagnostic System Ltd, London, England), with a limit of detection of 37 pg/mL and coefficient of variation between 2.3% and 9.5%, and active renin was assayed by chemiluminescence enzyme immunoassay. Plasma glucose was measured using the glucose oxidase method, and plasma lipids were assayed enzymatically. GFR was assessed by duplicate measurement of 24-hour creatinine clearance and normalized for body surface area.

Echocardiography

Cardiac ultrasound examination was performed as described previously[23,24] by the same experienced investigator who was unaware of the patients' clinical and laboratory characteristics (online-only Data Supplement).

Statistical Analysis

Sample size was calculated to provide a statistical power of >90% in the detection of a 10% difference in plasma aldosterone levels between hypertensive patients with or without LV diastolic dysfunction as detected by TDI, with a probability of <5%. Values are reported as mean±SD for normally distributed variables and as median and interquartile ranges for variables with skewed distribution. Normality of distribution was assessed with the Kolmogorov–Smirnov test, and variables with skewed distribution were analyzed after logarithmic transformation. Pearson χ^2 test was used to compare frequency distributions. Student *t* test was used for comparison between 2 independent groups. Relationships between continuously distributed variables were examined through linear regression analysis, with correlation expressed by Pearson correlation coefficient. Multiple regression analysis was done with variables of LV diastolic dysfunction as the dependent variables and inclusion of covariates according to the level of correlation found in univariate analysis. A multivariate logistic regression model was used to identify which variables are independently associated with indices of LV diastolic dysfunction as detected by TDI. A value of $P<5\%$ was considered to indicate statistical significance. Data analyses were performed using Stata 12.1 (StataCorp LP, College Station, TX).

Results

Between January 2013 and October 2014, we enrolled 115 study participants (age, 48±13 years; 58 men and 57 women). Clinical characteristics, laboratory values, and echocardiographic variables of hypertensive patients and normotensive controls are reported in Table 1, where hypertensive patients are also divided according to the presence or absence of LV hypertrophy. As expected, hypertensive patients had greater LV mass index and worse variables of LV diastolic function, including greater left atrial volume, and *E*/*e*′ ratio, and lower *e*′ velocity than normotensive controls. LV hypertrophy was found in 24 of 115 hypertensive patients (21%), and these patients were older and had higher BMI, systolic blood pressure, and plasma aldosterone levels than patients with normal LV mass. In hypertensive patients with LV hypertrophy, diastolic function was worse than in patients with normal LV mass as demonstrated by significantly greater left atrial volume, lower E/A ratio, *e*′ velocity, and *e*′/*a*′ ratio, and higher *E*/*e*′ ratio. None of the patients had focal defects of LV wall motion.

The patients' characteristics according to the presence or absence of LV diastolic dysfunction as determined by conventional pulsed-Doppler echocardiography or TDI are shown in Table 2. LV dysfunction was detected in 23 (20%) patients by conventional echocardiography and in 67 (58%) by TDI. In all these patients, the pattern of diastolic dysfunction was abnormal relaxation, whereas no pseudonormal or restrictive filling patterns were found. Patients with LV diastolic dysfunction at TDI were older and more frequently men and had greater BMI, systolic blood pressure, daily alcohol intake, LV mass index, and RWT than patients with preserved diastolic function. No differences in smoking habit, level of physical activity, or prevalence of family history of coronary heart disease, or in plasma glucose, plasma lipids, GFR, urinary sodium and potassium excretion, and active renin were found between patients with or without LV diastolic dysfunction, whereas plasma aldosterone levels were lower with borderline significance in patients with diastolic dysfunction. When hypertensive patients with LV hypertrophy (n=24) were removed from analysis, plasma aldosterone levels of patients with (n=51; 121±78 pg/mL) or

Table 1. Clinical Characteristics and Biochemical and Echocardiographic Variables of Hypertensive Patients Who Were Grouped According to the Presence or Absence of LV Hypertrophy and Normotensive Controls

Variables	Normotensive Controls (n=100)	Hypertensive Patients			
		All Patients (n=115)	LV Hypertrophy No (n=91)	LV Hypertrophy Yes (n=24)	*P* Value
Clinical characteristics					
Age, y	51±12	49±13	46±13	54±13	0.046
Men, n (%)	49 (49)	58 (50)	43 (47)	15 (62)	0.184
Body mass index, kg/m^2	25.3±3.2	27.7±4.5*	26.8±4.0	30.6±4.9	0.001
Heart rate, bpm	70±7	72±11	72±10	73±14	0.753
Systolic blood pressure, mm Hg	123±17	150±19*	147±16	159±25	0.034
Diastolic blood pressure, mm Hg	77±8	93±12*	93±10	95±16	0.556
Alcohol intake, g/d	7±13	10±21	8±18	17±30	0.198
Smokers, n (%)	11 (11)	28 (24)†	22 (24)	6 (25)	0.955
Biochemical variables					
Glucose, mg/dL	88±16	92±20	90±18	101±24	0.045
Total cholesterol, mg/dL	205±40	206±41	204±43	211±35	0.464
HDL-cholesterol, mg/dL	55±16	57±15	57±15	58±19	0.784
LDL-cholesterol, mg/dL	127±37	124±34	124±36	126±24	0.798
Triglycerides, mg/dL	102 [72–147]	96 [70–142]	95 [68–126]	100 [81–156]	0.136
Creatinine, mg/dL	0.94±0.17	0.95±0.19	0.95±0.18	0.98±0.21	0.414
Creatinine clearance, mL/min per 1.73 m^2	105±17	98±28	99±27	93±30	0.430
Sodium, mmol/L	139±3	140±2	140±3	140±3	0.977
Potassium, mmol/L	4.3±0.3	4.1±0.3	4.1±0.4	4.1±0.3	0.533
24-h urinary sodium, mmol/d	148±53	164±86	168±92	147±51	0.183
24-h urinary potassium, mmol/d	56±22	62±21	62±22	62±12	0.880
Aldosterone, pg/mL	129±74	143±72	135±67	173±76	0.018
Active renin, μUI/mL	8.9 [4.1–18.8]	10.6 [4.6–20.5]	11.3 [5.2–20.4]	8.2 [3.9–21.5]	0.650
Echocardiographic variables					
LV end-diastolic diameter, mm	49±4	49±5	49±4	53±5	0.001
LV end-systolic diameter, mm	29±4	29±4	29±4	32±4	0.006
Interventricular septum, mm	8.1±1.2	9.5±2.1*	8.8±1.4	12.2±2.3	<0.001
Posterior wall, mm	8.1±1.4	9.2±1.8*	8.7±1.4	11.1±2.0	<0.001
LV mass, g	135±38	168±58*	148±38	246±56	<0.001
LV mass index, g/m$^{2.7}$	32.3±8.3	39.5±11.7*	34.8±7.0	57.4±8.2	<0.001
Relative wall thickness, %	0.334±0.043	0.379±0.082	0.360±0.053	0.450±0.123	0.002
LV ejection fraction, %	68±6	69±5	70±5	69±6	0.669
LV fractional shortening, %	40,4±6,2	40.2±5.7	40.4±5.8	39.5±5.5	0.460
Left atrial volume, mL	42±15	48±16*	44±18	63±14	<0.001
E/A ratio	1.32±0.37	1.25±0.50	1.30±0.53	1.09±0.35	0.027
E-wave deceleration time, ms	203±46	212±49	213±49	210±50	0.816
Isovolumic relaxation time, ms	87±17	91±19	91±17	93±24	0.758
e′ velocity, cm/s	10.7±2.8	9.5±2.7*	9.9±2.8	8.2±1.8	0.001
e′/*a′* ratio	1.29±0.56	1.16±0.59	1.21±0.63	1.00±0.36	0.040
E/*e′* ratio	7.0±2.3	7.6±2.2†	7.4±2.0	8.4±2.6	0.080

Values are expressed as mean±SD. Median and interquartile range in square brackets are shown for variables with skewed distribution. Reported *P* values for the comparison between patients with or without left ventricular hypertrophy. A indicates late-wave transmitral diastolic velocity; *E*, early wave transmitral diastolic velocity; *e′*, early diastolic velocity of septal and lateral myocardial portions at tissue-Doppler imaging; *E*/*e′*, E-wave transmitral velocity to early diastolic velocity at tissue-Doppler imaging ratio; *e′*/*a′*, early:late diastolic velocity ratio at tissue-Doppler imaging; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and LV, left ventricle.

*$P<0.01$ vs normotensive controls.

†$P<0.05$ vs normotensive controls.

Table 2. Clinical Characteristics and Biochemical and Echocardiographic Variables of Hypertensive Patients With or Without LV Diastolic Dysfunction as Assessed by Conventional Pulsed-Wave Doppler Echocardiography or Tissue-Doppler Imaging

	Conventional Echocardiography			Tissue-Doppler Imaging		
Variables	Diastolic Dysfunction No (n=92)	Diastolic Dysfunction Yes (n=23)	*P* Value	Diastolic Dysfunction No (n=48)	Diastolic Dysfunction Yes (n=67)	*P* Value
Clinical characteristics						
Age, y	48±14	50±11	0.497	44±14	52±11	0.001
Men, n (%)	44 (48)	14 (61)	0.263	16 (33)	42 (63)	0.002
Body mass index, kg/m^2	27.3±4.5	28.8±4.2	0.143	26.2±4.6	28.5±4.2	0.007
Heart rate, bpm	71±11	76±9	0.082	73±9	72±11	0.769
Systolic blood pressure, mm Hg	149±19	152±17	0.479	143±15	154±20	<0.001
Diastolic blood pressure, mm Hg	92±11	99±14	0.034	91±12	95±11	0.060
Alcohol intake, g/d	9±20	14±25	0.419	3±8	15±26	0.001
Smokers, n (%)	24 (26)	4 (17)	0.371	11 (23)	17 (25)	0.728
Biochemical variables						
Glucose	91±19	98±21	0.143	88±22	95±18	0.087
Creatinine, mg/dL	0.94±0.18	1.00±0.22	0.251	0.94±0.18	0.96±0.19	0.679
Creatinine clearance, mL/min per 1.73 m^2	100±28	90±24	0.117	99±30	97±26	0.731
Sodium, mmol/L	140±2	140±3	0.804	140±2	140±3	0.673
Potassium, mmol/L	4.11±0.36	4.07±0.31	0.584	4.08±0.32	4.11±0.37	0.607
24-h urinary sodium, mmol/d	166±92	156±58	0.525	155±105	168±71	0.461
24-h urinary potassium, mmol/d	62±22	63±16	0.806	62±24	62±18	0.904
Aldosterone, pg/mL	139±88	160±88	0.313	164±97	129±77	0.046
Active renin, μUI/mL	9.6 [4.3–21.0]	12.8 [5.6–18.0]	0.731	11.2 [5.5–22.2]	10.1[4.4–17.1]	0.385
Echocardiographic variables						
LV end-diastolic diameter, mm	49±5	51±4	0.028	49±5	50±5	0.093
LV end-systolic diameter, mm	29±4	30±4	0.302	28±4	30±4	0.027
Interventricular septum, mm	9.2±1.9	10.6±2.5	0.014	8.6±1.6	10.1±2.2	<0.001
Posterior wall, mm	9.0±1.8	9.8±2.0	0.114	8.6±1.7	9.6±1.8	0.002
LV mass, g	160±49	202±77	0.018	146±46	184±61	<0.001
LV mass index, g/m$^{2.7}$	30.1±11.1	45.1±12.7	0.021	35.4±10.4	42.4±11.9	0.001
LV hypertrophy, n (%)	16 (17)	8 (35)	0.066	8 (17)	16 (24)	0.348
Relative wall thickness, %	0.374±0.085	0.397±0.066	0.178	0.354±0.060	0.397±0.090	0.003
LV ejection fraction, %	70±6	69±5	0.701	71±5	69±6	0.024
LV fractional shortening, %	40.07±5.92	40.96±4.99	0.469	41.04±5.65	39.69±5.76	0.221
Left atrial volume, mL	47±15	50±18	0.370	40±13	54±19	<0.001
E/A ratio	1.38±0.49	0.76±0.17	<0.001	1.54±0.587	1.05±0.32	<0.001
E-wave deceleration time, ms	208±48	228±53	0.116	201±45	221±50	0.027
Isovolumic relaxation time, ms	89±19	99±17	0.029	83±16	97±18	<0.001
e′ velocity, cm/s	9.9±2.8	7.8±1.6	<0.001	12.0±2.3	7.7±1.3	<0.001
e′/*a′* ratio	1.26±0.61	0.78±0.26	<0.001	1.58±0.68	0.87±0.23	<0.001
E/*e′* ratio	7.8±2.3	7.1±1.8	0.145	6.8±1.7	8.2±2.3	<0.001

Values are expressed as mean±SD. Median and interquartile range in square brackets are shown for variables with skewed distribution. LV diastolic dysfunction was defined at conventional echocardiography by transmitral inflow pattern and detection of *E*/*A* ratio lower than normal for the age of the patient and at tissue-Doppler imaging on the basis of *e′* velocities lower than the age-specific cutoff values. A indicates late-wave transmitral diastolic velocity; *E*, early wave transmitral diastolic velocity; *e′*, early diastolic velocity of septal and lateral myocardial portions at tissue-Doppler imaging; *E*/*e′*, E-wave transmitral velocity to early diastolic velocity at tissue-Doppler imaging ratio; *e′*/*a′*, early:late diastolic velocity ratio at tissue-Doppler imaging; and LV, left ventricle.

without (n=40; 155±94 pg/mL) diastolic dysfunction detected at TDI were not significantly different (*P*=0.063).

Univariate regression analysis indicated that LV mass index was significantly and directly related with age (*r*=0.285; *P*=0.002), BMI (*r*=0.518; *P*<0.001), systolic blood pressure (*r*=0.339; *P*<0.001), and plasma aldosterone levels (*r*=0.253; *P*=0.013). All variables of LV diastolic function were significantly related with age (Table 3) and among variables of LV diastolic function measured by conventional echocardiography, the E/A ratio was inversely related with BMI, LV mass index, and RWT and directly with GFR. E-wave deceleration time was directly related with BMI, whereas isovolumic relaxation time was directly related with LV mass index and RWT, and inversely with plasma aldosterone levels. Left atrial diameter was related directly with blood pressure and LV mass index, and inversely with GFR. Among variables of LV diastolic function measured by TDI, *e′* velocity was directly related with GFR and plasma aldosterone, and inversely with BMI, systolic blood pressure, LV mass index, and RWT. The *e′*/*a′* ratio was also directly related with GFR and inversely

with BMI, LV mass index, and RWT and the *E*/*e*′ ratio was directly related with LV mass index and RWT (Table 3).

Multivariate regression analysis was performed including indexes of LV diastolic function as dependent variables and age, BMI, systolic blood pressure, LV mass index, GFR, and plasma aldosterone as independent variables. None of these variables resulted to be independently related with any of the indexes of LV diastolic function except age (β–0.504; *P*<0.001; Table S1 in the online-only Data Supplement). In a multivariate logistic regression model, LV diastolic dysfunction as detected by TDI was included as the dependent variable and variables that were significantly different between patients with or without diastolic dysfunction as independent variables (Table 4). Analysis revealed that age, BMI, and systolic blood pressure, but not male sex, alcohol intake, plasma aldosterone, LV mass index, and RWT, were independent predictors of LV diastolic dysfunction.

Discussion

Because aldosterone might contribute to diastolic dysfunction via its profibrotic effects, we have investigated the relationship between plasma aldosterone levels and LV diastolic properties in never-treated patients with primary hypertension who were free of cardiovascular complications and comorbidities that might affect diastolic filling. Findings indicate that LV diastolic dysfunction detected at TDI is associated with older age, greater BMI, severity of hypertension, and LV mass, and with lower GFR and plasma aldosterone levels. Aldosterone levels are directly related with the *e*′ velocity although this relationship is lost after correction for covariates, suggesting that circulating aldosterone does not affect independently LV diastolic function in primary hypertension.

Diastolic dysfunction is frequently associated with LV hypertrophy in hypertensive heart disease, but it is also detected in patients with normal LV mass, suggesting different causative mechanisms. Clinical evidence obtained in patients with primary aldosteronism and primary hypertension strongly suggests that chronic exposure to elevated circulating aldosterone levels increases LV mass beyond what is needed to compensate for the blood pressure–related hemodynamic load.[9,25] In primary aldosteronism, removal of plasma aldosterone excess with adrenalectomy or administration of MR antagonists decreases significantly LV mass.[12,26] In patients with primary hypertension and LV hypertrophy, addition of eplerenone to angiotensin-converting enzyme inhibitors enhances the effects of treatment on LV mass reduction independent of blood pressure changes.[27] Although in agreement with previous studies this study reports a direct relationship between plasma aldosterone and LV mass, we could not demonstrate an independent contribution of aldosterone levels to diastolic dysfunction even after exclusion from analysis of patients with LV hypertrophy.

MR are expressed in multiple cell types in the heart and elegant animal studies have demonstrated a contribution of MR activation to development of cardiac fibrosis[28] entailing myocardial stiffening and impairment of diastolic properties.[29] However, the clinical evidence supporting a role of aldosterone and MR activation in the development of LV diastolic dysfunction is weak and mostly suggested by findings of studies conducted with MR antagonists in patients with heart failure and preserved ejection fraction or hypertensive patients with diastolic dysfunction. Mottram et al[15] reported beneficial effects of low-dose spironolactone on myocardial relaxation in 30 treated hypertensive patients with exertional dyspnea and abnormal LV filling patterns. In the Aldo-DHF (Aldosterone–Diastolic Heart Failure) trial,[16] spironolactone improved slightly LV diastolic function, but had no effect on maximal exercise capacity and symptoms in patients with heart failure and preserved ejection fraction. Similarly, in

Table 3. Univariate Correlations With Indexes of LV Diastolic Function as the Dependent Variables in Hypertensive Patients

Variables	E/A Ratio		E-Wave Deceleration Time		Isovolumic Relaxation Time		Left Atrial Diameter		*e*′		*e*′/*a*′ Ratio		*E*/*e*′ Ratio	
	r	*P* Value	*r*	*P* Value	*r*	*P* Value	*r*	*P* Value	*r*	*P* Value	*r*	*P* Value	*r*	*P* Value
Age, y	−0.536	<0.001	0.211	0.006	0.354	<0.001	0.176	0.029	−0.605	<0.001	−0.580	<0.001	0.384	<0.001
Body mass index	−0.168	0.029	0.194	0.012	0.006	0.936	0.098	0.226	−0.212	0.005	−0.217	0.004	0.137	0.075
Systolic blood pressure	−0.124	0.107	0.149	0.053	0.041	0.611	0.261	0.001	−0.205	0.007	−0.127	0.097	0.135	0.079
Diastolic blood pressure	−0.038	0.622	0.110	0.156	0.035	0.670	0.173	0.032	−0.044	0.571	−0.052	0.449	−0.091	0.239
Alcohol intake	−0.092	0.253	0.090	0.265	0.130	0.125	0.089	0.239	−0.124	0.121	−0.148	0.065	0.013	0.869
Creatinine clearance	0.247	0.001	−0.130	0.098	−0.114	0.165	−0.209	0.010	0.240	0.002	0.230	0.003	−0.083	0.291
Aldosterone	0.046	0.553	−0.118	0.126	−0.189	0.019	−0.036	0.658	0.168	0.018	0.113	0.074	−0.074	0.336
Active renin	0.044	0.574	−0.189	0.016	−0.100	0.227	−0.119	0.146	0.151	0.052	0.078	0.315	−0.132	0.091
LV mass index	−0.289	<0.001	0.078	0.311	0.234	0.004	0.237	0.003	−0.403	<0.001	−0.284	<0.001	0.382	<0.001
Relative wall thickness	−0.341	<0.001	0.018	0.814	0.226	0.001	0.084	0.300	−0.420	<0.001	−0.325	<0.001	0.315	<0.001
LV ejection fraction	0.025	0.750	0.117	0.131	−0.132	0.103	−0.006	0.944	0.193	0.012	0.046	0.554	−0.042	0.590

A indicates late-wave transmitral diastolic velocity; *E*, early wave transmitral diastolic velocity; *e*′, early diastolic velocity of septal and lateral myocardial portions at tissue-Doppler imaging; *E*/*e*′, E-wave transmitral velocity to early diastolic velocity at tissue Doppler imaging ratio; *e*′/*a*′, early:late diastolic velocity ratio at tissue Doppler imaging; and LV, left ventricle.

Table 4. Logistic Regression Analysis With LV Diastolic Dysfunction as Detected by Tissue-Doppler Imaging as the Dependent Variable

Variables	Odds Ratio	Confidence Interval	*P* Value
Age, y	1.07	1.02–1.12	0.006
Male sex	2.40	0.79–7.29	0.122
Body mass index	1.03	1.00–1.08	0.004
Systolic blood pressure	1.06	1.02–1.10	0.004
Alcohol intake	1.03	0.98–1.09	0.227
LV mass index	1.00	0.99–1.02	0.129
Aldosterone	1.00	0.98–1.00	0.158

LV indicates left ventricle.

the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) study,[17] spironolactone failed to reduce a composite cardiovascular end point in heart failure and preserved ejection fraction. An inverse relationship of plasma aldosterone with *E*/*A* ratio was initially reported in treated patients with hypertension and LV hypertrophy[13] and improvement of diastolic function associated with reduction of LV mass was obtained with spironolactone in hypertensive patients with LV hypertrophy who were already treated with angiotensin-converting enzyme inhibitors and calcium-channel blockers.[30] Conversely, a recent study of hypertensive patients with preclinical LV diastolic dysfunction has reported no change of *E*/*A* ratio and diastolic function assessed by MRI after addition of spironolactone to previous antihypertensive treatment, despite significant reduction in LV mass.[14] Therefore, substantial inconsistencies in findings of clinical studies make it difficult to establish a direct contribution of aldosterone to LV diastolic dysfunction.

Much controversy in the field is generated by the limited ability of conventional echocardiography to detect early changes in LV diastolic function, as opposed to the much more sensitive TDI. In this study, prevalence of diastolic dysfunction was 20% with the use of conventional echocardiography and 58% with TDI. Also, because LV hypertrophy is one of the main causes of diastolic dysfunction, studies on hypertensive patients cannot separate the possible effects of circulating aldosterone or MR antagonists on LV diastolic function from those on LV mass. Last and mostly relevant, effects on LV diastolic filling properties of antihypertensive agents or drugs for heart failure could represent an important confounder.[19] In this study and for the first time, the association of plasma aldosterone levels with LV diastolic function has been examined by TDI in patients who had never received any type of antihypertensive drug and were free of comorbidities that could affect LV diastolic filling properties, such as diabetes mellitus and coronary heart disease. Findings indicate that LV diastolic dysfunction is associated with lower plasma aldosterone levels possibly suggesting beneficial effects of this hormone on LV diastolic properties. However, this association does not persist when covariates are included in a multivariate model, showing that plasma aldosterone levels do not contribute directly to diastolic dysfunction in primary hypertension.

It is important to consider that additional conditions acting as cofactors of elevated local aldosterone might be needed to induce myocardial stiffening and LV diastolic impairment. As suggested by animal studies,[8] these conditions might include inappropriately increased salt status or increased circulating angiotensin-II levels. In this study, patients ate a standard diet for 1 week before examination and no differences in daily urinary sodium excretion were observed between those with or without LV diastolic dysfunction or hypertrophy. Also, active renin levels were comparable between patients with or without LV diastolic impairment or hypertrophy. In this study, we have not assessed additional potential cofactors such as endothelin or markers of oxidative stress, nor measured circulating biomarkers of cardiac fibrosis and this might identify a limitation of the study. Additional limitation is related to the cross-sectional design that does not permit to obtain conclusive evidence on causal relationships although the choice to include only treatment-naive patients would have not allowed a different approach. Also, a type-II error on the association of plasma aldosterone with diastolic parameters cannot be ruled out.

Perspectives

Changes in LV diastolic filling properties are detected early in the course of hypertensive heart disease. Identification of factors that in addition to the hypertension-related cardiac workload could contribute to these changes is crucial for the development of treatment strategies that prevent further cardiac functional deterioration and heart failure. This study, the first conducted in treatment-naïve hypertensive patients free of comorbidities that could affect LV diastolic properties, has examined the relationship of diastolic variables assessed both at conventional echocardiography and TDI with plasma aldosterone levels. Results confirm a direct relationship of plasma aldosterone levels with LV mass but demonstrate no independent association with any of the diastolic variables indicating that aldosterone does not directly affect LV diastolic properties in these patients. Although changes in the salt status and activity of the renin–angiotensin system do not seem to contribute to the present results, the role of other possible cofactors of aldosterone in the induction of myocardial profibrotic changes should be investigated in future studies.

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None.

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Novelty and Significance

What Is New?

- We investigated the relationship of plasma aldosterone with left ventricular diastolic function using tissue-Doppler imaging.
- We studied treatment-naïve patients with primary hypertension free of comorbidities that might affect diastolic filling.
- We demonstrate that despite an independent association with left ventricular mass plasma aldosterone does not directly affect left ventricular diastolic properties in hypertension.
- We highlight the lack of clinical relevance of salt intake in the relationship between aldosterone and cardiac structure and function.

What Is Relevant?

- Impairment of left ventricular diastolic properties herald cardiac failure in hypertension.
- Identification of factors that in addition to hypertension-related workload could contribute to left ventricular diastolic dysfunction is relevant for prevention of heart failure.
- These findings demonstrate that circulating aldosterone does not directly affect diastolic function in hypertension and explain why clinical trials of aldosterone antagonists have not reported any benefit on the cardiovascular outcome.

Summary

Despite a significant association with left ventricular mass, plasma aldosterone levels have no independent influence on left ventricular diastolic function in never-treated hypertensive patients.

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Plasma aldosterone and left ventricular diastolic function in treatment-naïve patients with hypertension: a tissue-Doppler imaging study

Cristiana Catena[1], Nicolas Verheyen[1], Stefan Pilz[2], Elisabeth Kraigher-Krainer[3], Andreas Tomaschitz[2], Leonardo A. Sechi[4], Burkert Pieske[3]

[1]Division of Cardiology, Department of Medicine, Medical University of Graz, Austria

[2]Division of Endocrinology and Metabolism, Department of Medicine, Medical University of Graz, Austria

[3]Department of Internal Medicine and Cardiology, Charitè University Medicine, Campus Virchow Klinikum and German Heart Center, Berlin, Germany

[4]Hypertension Unit, Internal Medicine, Department of Experimental and Clinical Medical Sciences, University of Udine, Italy

Short title: aldosterone and diastole

Address for correspondence:
Cristiana Catena, MD, PhD
Division of Cardiology
Medical University of Graz
Auenbruggerplatz 15,
8036 Graz, Austria
phone: +43 (0) 316 385-12544
fax: +43 (0) 316 385 -13733
E mail: cristiana.catena@uniud.it

Appendix

Study Population

Secondary causes of hypertension were excluded in all patients according to established guidelines [1] after exhaustive testing that included analysis of medical records, physical examination, urine analysis, blood chemistry, duplicate measurements of 24-hour creatinine clearance, plasma aldosterone and active renin, urinary cortisol and catecholamines, electrocardiography, echocardiography, renal ultrasound examination with assessment of the renal resistance index. Renal angio- and adrenal magnetic resonance imaging or computed tomography scan were performed when indicated [1,2]. Primary aldosteronism was excluded after screening by an increased plasma aldosterone-to-active renin ratio of (>20 pg/ml) [3] in the presence of a plasma aldosterone concentration of 150 pg/ml or more, and confirmation of diagnosis by the lack of aldosterone suppression after a standard intravenous saline load (2 liters of 0.9% saline infused over 4 hours) [4] as reported previously [5].

Echocardiography

Cardiac ultrasound examination was performed as described previously [6] by the same experienced investigator who was unaware of the patients' clinical and laboratory characteristics. Measurements of LV diameters and interventricular septum, posterior wall, and relative wall thickness (RWT) were obtained with the patient in the partial left decubitus position with a commercial machine (Aplio CV, Toshiba Medical System, Tokyo, Japan) and a 2.5 MHz transducer, under bi-dimensional cross-sectional control and simultaneous electrocardiographic tracing. LV mass index (LVMI) was calculated by the Penn Convention formula and normalized for body height, with a cut-off value of 50 $g/m^{2.7}$ for men and 47 $g/m^{2.7}$ for women used to define presence of LV hypertrophy [7]. LV systolic function was estimated by the ejection fraction (EF) and endocardial fractional shortening (FS). LV diastolic function was evaluated both with conventional pulsed Doppler trans-mitral flow and TDI in all patients, as previously described [8]. Conventional pulsed Doppler recordings were obtained at the level of the mitral valve tips at late expiration. Early (E) and late-wave (A) trans-mitral diastolic peak velocities, the E/A ratio, E wave deceleration time, and isovolumic relaxation time were measured. LV diastolic dysfunction was defined by trans-mitral inflow pattern according to consensus statements by detection of E/A ratio lower than normal for the age of the patient [8,9]. TDI assesses the high-amplitude, low-velocity signals of myocardial tissue motion that identify the early diastolic relaxation rate representing the relaxation velocity during the early active phases of diastole and is significantly more sensitive than conventional echocardiographic technique for detection of early LV diastolic changes [10,11]. A 3.5-mm sample volume was used and the Doppler beam was directed parallel to the myocardial walls. Early-diastolic and late-diastolic velocities of septal and lateral myocardial portions were measured at the level of mitral valve annulus, and the mean values (*e'* and *a'*, respectively) were calculated on 3 consecutive cardiac cycles at end-expiration, together with the average *e'/a'* and E/*e'* ratios. Diastolic dysfunction was defined on the basis of velocities lower than the age-specific cut-off values (*e'* <10 cm/sec in patients younger than 55 years, <9 cm/sec in patients from 55 to 65 years, <8 cm/sec in patients older than 65 years) [4]. Intra-observer coefficient of variation for *e'* velocity was 7.8%.

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S1

Table. Multivariate analysis with the e' velocity measured by tissue-Doppler as the dependent variable

Variables	β	P
Age	-0.504	<0.001
Male sex	-0.115	0.151
Body mass index	0.004	0.968
Systolic blood pressure	-0.078	0.337
Creatinine clearance	-0.128	0.157
LV mass index	-0.160	0.109
Aldosterone	0.095	0.220

LV, left ventricle.