Myocardial and Aortic Stiffening in the Early Course of Primary Aldosteronism

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ABSTRACT

Background: Primary aldosteronism (PA) has been experimentally and clinically linked to myocardial and vascular fibrosis, and it has been further associated with left ventricular (LV) structural adaptations.

Hypothesis: Functional cardiovascular adaptations in hypertensive patients with PA precede structural alterations in the early stages of the disease.

Methods: We studied 17 hypertensive subjects with a recent diagnosis of PA (10 male patients, aged approximately 55 y, with office blood pressure [BP] of 137/88 mm Hg), and 30 essential hypertensives matched for age, sex, office BP levels, treatment status, and LV mass index (LVMI). Apart from standard 2-Dimensional (2-D) and conventional Doppler parameters, tissue Doppler imaging (TDI) methodology was used to assess LV diastolic function; averaging early and late diastolic mitral annular peak velocities (Em_{av} , Am_{av} , Em_{av}/Am_{av} ratio) from 4 separate sites of measurement (septal, lateral, anterior, and inferior walls). Aortic stiffness was evaluated by means of carotid-femoral pulse wave velocity (cf-PWV) measurements.

Results: Although transmitral E/A ratio was similar in both groups (0.95 ± 0.26 versus 0.98 ± 0.24 , $p = 0.66$), hypertensive subjects with PA compared with essential hypertensives are characterized by significantly higher relative wall thickness (0.50 ± 0.07 versus 0.41 ± 0.06 , $p < 0.001$), decreased values of Em_{av} (7.1 ± 1.7 versus 8.1 ± 1.8 cm/s, $p = 0.048$), and Em_{av}/Am_{av} ratio (0.63 ± 0.16 versus 0.77 ± 0.17 , $p = 0.015$). The higher PWV in the PA population failed to reach statistical significance (8.5 ± 1.6 versus 7.9 ± 0.9 msec, $p = 0.19$).

Conclusion: Our study demonstrates altered LV geometry and TDI-revealed diastolic dysfunction in hypertensives with PA compared with demographically- and LVMI-matched essential hypertensives. Furthermore, the increased aortic stiffening in PA patients failed to reach statistical significance.

Key words: primary aldosteronism, essential hypertension, diastolic function, tissue Doppler imaging, arterial stiffness, pulse wave velocity

Introduction

Primary aldosteronism (PA) is one of the few potentially curable forms of secondary hypertension, and its prevalence in unselected hypertensive patients, although still a matter of conflict, appears to be rather high.^{1,2} The rate of cardiovascular events in patients suffering from PA increases independently of blood pressure (BP) levels,³ and aldosterone excess may play a key role in differentiating the progression of target organ damage.⁴ Focusing on the heart, hypertensive patients with PA have greater left ventricular (LV) mass compared with essential hypertensive patients, even after making adjustments for confounders.^{5–7} Moreover, myocardial texture has been shown to be altered in PA, suggesting increased collagen deposition.⁸

In addition to structural adaptations, functional abnormalities, such as diastolic dysfunction and arterial stiffening, represent 2 major interrelated components of hypertensive heart disease.^{9,10} Tissue Doppler imaging (TDI) is superior to conventional Doppler in evaluating diastolic function in a preload-independent manner,¹¹ while pulse wave velocity (PWV) provides a reliable clinical measure of aortic stiffness

in various clinical settings.¹² However, data regarding TDI-assessed diastolic properties and PWV-estimated arterial stiffening are limited in normotensive individuals with familial hyperaldosteronism.¹³ Therefore, in the present study, we sought to assess the functional cardiovascular adaptations in the early course of hypertensive PA by using both conventional and novel techniques.

Methods

Study Patients

From our pool of recently diagnosed hypertensive patients with clinical suspicion of PA and laboratory findings compatible to the disease (plasma aldosterone >15 ng/dL, plasma renin activity ratio [PRA] <1 ng/mL/h, aldosterone/plasma renin activity ratio [ARR] >50 ng/dL/ng/mL/h and post captopril test¹⁴ with a cut-off value of ARR >35 in all cases), we selected 17 subjects (10 male patients\ aged 55 y $\pm$ 10 y) with absence of adrenal adenoma or hyperplasia (neither unilateral nor bilateral) on computed tomography (CT) imaging.

Subjects with a history of atherosclerotic cardiovascular disease, heart failure, diabetes mellitus, and renal

insufficiency were primarily excluded from the study. Also excluded were patients with absent or abnormal sinus rhythm in order to obtain reliable TDI and PWV measurements. The control group consisted of 30 subjects with uncomplicated essential hypertension, matched for age, sex, office systolic and diastolic BP, LV mass index (LVMI), and treatment status. In particular, none of the participants was under previous treatment with aldosterone antagonists, nor had they received angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin II-receptor blockers (ARBs) in the last year. No difference was exhibited between the 2 groups regarding the baseline antihypertensive medication (Table 1). All patients in the study discontinued their usual antihypertensive therapy and were switched to amlodipine 5–10 mg±prazosin for at least 7 d before the investigation in order to eliminate the interference of other antihypertensive drugs with the renin-angiotensin-aldosterone system and to secure control of their BP. The study protocol, that included assessment of LV diastolic function and aortic stiffness, was approved by the ethics committee of our institution and all subjects had given their written informed consent.

Procedures

Office BP measurements were obtained by a mercury sphygmomanometer according to the current guidelines of the Joint National Committee (JNC) 7. Hypertension was defined as an average office BP $\geq 140/90$ mm Hg on at least 3 consecutive visits at a 1-w interval. The duration of hypertension was based on the cross-checking of patients' history and from the records of general practitioners.

Cardiac Ultrasonography

Standard transthoracic echocardiographic examination was carried out by an experienced senior operator, who was blinded to the clinical status of the examined subject, using a Vivid 3 ultrasound imager equipped with a 2.2/4.4 MHz (harmonics) phased-array transducer (General Electric, Waukesha, Wis., USA), according to established guidelines.¹⁵ The LV mass was calculated by the Devereux formula, normalized for body surface area to obtain LVMI, while the relative wall thickness was estimated as per the following equation: (interventricular septum thickness + posterior wall thickness)/(LV end-diastolic diameter). Left atrial volume was also indexed for body surface area to estimate the left atrial volume index (LAVI), as previously described.¹⁶

Left ventricular diastolic function was determined using both conventional Doppler parameters (peak velocities of E and A waves of the transmitral flow, E/A ratio, isovolumic relaxation time, and the deceleration time of the E wave) and TDI-derived indices of the basal site of lateral, septal, anterior, and inferior walls (peak early diastolic velocity [Em], peak atrial systolic velocity [Am]). All of the above measurements were obtained in 5 consecutive cardiac cycles and the mean values were used for analysis, along with the

PR interval estimation on simultaneous electrocardiogram (ECG) recording (MAC 1200ST, General Electric, Waukesha, Wis., USA). In order to evaluate the global LV diastolic function, we averaged the mean Em and Am values from the 4 aforementioned sites (Em_{av} and Am_{av}). Furthermore, special care was taken for TDI measurements to align the cursor as parallel as possible through the annulus to adjust the sample volume size proportionally to the annular motion, and to obtain recordings at end-expiratory apnea.

Evaluation of Aortic Stiffness

Aortic stiffness was evaluated by means of the carotid-femoral (cf)-PWV measurements using a validated noninvasive device (Complior SP, Artech Medical, Pantin, France). Measurements of the PWV were performed by 2 clinicians who were familiar with the technique and unaware of the patients' clinical data. Evaluation was performed while the patient was in the supine position, with a slight extension of the head, and with the right lower limb in external rotation. Two different pulse wave tracings were recorded simultaneously: one at the base of the neck for the common carotid artery, and 1 over the right femoral artery with 2 transducers. Five consecutive measurements were performed in each patient and the mean PWV value was obtained.¹⁰ The intraobserver and interobserver variability for the measurement was 4.9% and 6.0%, respectively.

Statistical Analysis

The SPSS statistical package 12.0 (SPSS Inc., Chicago, Ill., USA) was used for all statistical analysis. Differences between groups were evaluated using the independent-samples Student *t* test for continuous variables (given as mean±standard deviation [SD]) and the chi-square for categorical variables. Associations between variables were determined using the Pearson's correlation coefficient. Analysis of covariance (ANCOVA) was performed in order to eliminate any influence of LVMI on detected differences of TDI-derived indices between hypertensives with PA and essential hypertensives. All tests were considered to be significant at the level of $p < 0.05$.

Results

Regarding demographic characteristics, apart from the selection criteria, hypertensives with PA compared with essential hypertensives did not differ with respect to the known duration of hypertension, body mass index (BMI), and smoking status. No differences existed concerning heart rate and PR interval (164 ± 28 versus 159 ± 23 msec, $p = 0.84$). Hypertensives with PA had significantly lower serum potassium levels by 0.7 meq/L ($p < 0.001$), while the renal function indices and metabolic profile were similar for both groups (Table 2).

Although LVMI was within the rather normal values in both groups, hypertensives with PA compared

TABLE 1: Demographic parameters in essential hypertensives and hypertensives with primary aldosteronism

Parameter	Hypertensives with PA (n = 17)	Essential hypertensives (n = 30)	p-value
Age (y)	55±10	58±8	0.28
Males (%)	10 (59%)	17 (57%)	1
Body mass index (kg/m ²)	30.3±3.9	28.3±5	0.12
Smoking, currently (%)	31%	33%	0.9
Duration of hypertension (y)	2±0.6	2.2±0.5	0.88
Office systolic BP (mm Hg)	137±11	135±10	0.64
Office diastolic BP (mm Hg)	88±9	87±7	0.88
Office pulse pressure (mm Hg)	50±7	48±6	0.74
Heart rate (bpm)	73±6	72±10	0.81
Treatment with ACEIs/ARBs	0	0	1
Treatment with diuretics	8 (47%)	8 (27%)	0.20
Treatment with CCBs	7 (41%)	11 (37%)	0.76
Treatment with BBs	4 (23%)	9 (30%)	0.74

Abbreviations: ACEIs = angiotensin-converting-enzyme inhibitors; ARBs = angiotensin II-receptor blockers; BBs = β -blockers; BP = blood pressure; CCBs = calcium channel blockers; PA = primary aldosteronism.

TABLE 2: Laboratory parameters in essential hypertensives and hypertensives with primary aldosteronism

Parameter	Hypertensives with PA (n = 17)	Essential hypertensives (n = 30)	p-value
Glucose (mg/dl)	105±19	105±18	0.96
High density lipoprotein (mg/dl)	50±10	52±10	0.64
Low density lipoprotein (mg/dl)	128±30	130±27	0.82
Triglycerides (mg/dl)	127±55	116±48	0.44
Creatinine (mg/dl)	1.00±0.3	0.92±0.15	0.22
Serum K (meq/L)	3.5±0.3	4.2±0.45	<0.001
ALDO (ng/dL)	24±8	10.2±4	<0.001
PRA (ng/mL/h)	0.32±0.22	1.1±0.42	<0.001
ALDO, post captopril (ng/dL)	22±7	7.5±4	<0.001
PRA, post captopril (ng/mL/h)	0.35±0.28	1.5±0.66	<0.001

Abbreviations: ALDO = plasma aldosterone; PA = primary aldosteronism; PRA = plasma renin activity.

with essential hypertensives exhibited significantly higher relative wall thickness by 0.09 ($p<0.001$). This difference in the pattern of LV geometry was attributed to the significantly thickened LV posterior and interventricular septum walls by 1.4 and 1.2 mm, respectively ($p<0.05$ for both cases). Systolic function measured as fractional shortening at the endocardial surface, left

atrium diameter, and LAVI were similar in both groups (Table 3).

Regarding the conventional Doppler parameters (E wave, A wave, E/A ratio, isovolumic relaxation, and deceleration time), there were no significant differences between groups. In contrast, hypertensives with PA compared with essential hypertensives exhibited significantly lower Em_{av}

TABLE 3: Standard 2-D and transmitral flow echocardiographic measurements in essential hypertensives and hypertensives with primary aldosteronism

Parameter	Hypertensives with PA (n = 17)	Essential hypertensives (n = 30)	p-value
LV end-diastolic diameter (mm)	46.2±4.6	49.4±3.4	0.009
LV end-systolic diameter (mm)	31.8±7.4	31.6±3	NS
Posterior wall (mm)	11.6±1.6	10.2±1	0.005
Interventricular septum (mm)	11.4±1.9	10.2±1.1	0.013
LVMI (gr/m ²)	117.2±34.5	114.7±12.4	0.66
Relative wall thickness	0.50±0.07	0.41±0.06	<0.001
Ejection fraction (%)	63.5±5	63.3±6	0.92
Left atrial diameter (mm)	41.3±3.5	40.2±3.2	0.28
Left atrial volume index (ml/m ²)	25.5±7.5	23±7	0.30
E/A	0.95±0.26	0.98±0.24	0.66
Isovolumic relaxation time (ms)	94±28	96±16	0.75
Deceleration time (ms)	250±76	241±43	0.59

Abbreviations: 2-D = 2-Dimensional; E/A = peak velocity of E and A waves; LV = left ventricular; LVMI = left ventricular mass index; NS = not significant; PA = primary aldosteronism.

and Em_{av}/Am_{av} by 1.1 cm/sec and 0.14, respectively, even after adjustment for LVMI ($p < 0.05$ for both cases). In particular, the PA group had significantly decreased values of the Em/Am ratios for the septal, lateral, and inferior walls by 0.12, 0.24, and 0.12, respectively ($p < 0.05$ for all) (Table 4). When ANCOVA was performed for each case separately, only the difference concerning Em/Am ratio of the inferior wall lost statistical significance after adjusting for LVMI (adjusted $p = 0.087$).

As far as evaluation of aortic stiffness is concerned, the greater values of PWV in hypertensives with PA compared with controls failed to reach statistical significance (8.5 ± 1.6 m/sec versus 7.9 ± 0.9 m/sec, $p = 0.19$).

Assessing correlations with indices of LV diastolic function, Em_{av}/Am_{av} was negatively correlated with age in both groups of PA ($r = -0.748$, $p = 0.001$) and essential hypertension ($r = -0.698$, $p < 0.001$), while a negative correlation with systolic BP ($r = -0.390$, $p = 0.033$) was demonstrated only in the latter population. No correlation was observed between diastolic function indices and the LVMI. Regarding the index of aortic stiffness, PWV was positively correlated with systolic BP ($r = 0.452$, $p = 0.014$) and age ($r = 0.383$, $p = 0.040$) only in essential hypertensives, while such correlations in PA population were not observed ($p =$ not significant [NS] for both cases). Additionally, PWV was negatively correlated with Em_{av}/Am_{av} in both essential hypertensives ($r = -0.490$, $p = 0.007$) and hypertensives with PA ($r = -0.530$, $p = 0.029$).

Discussion

The main finding of the present study was that hypertensives with PA compared with demographically- and LVMI-matched essential hypertensives are characterized by LV concentric remodeling and a state of pronounced diastolic dysfunction detected by preload-independent TDI methods. Moreover, the increased aortic stiffening failing to reach statistical significance does not seem to accompany these adaptations in the early course of the disease.

Left ventricular hypertrophy represents an important independent risk factor for cardiovascular events, and classification into patterns of LV geometry provides an additional prognostic significance. In contrast to previous studies by Rossi et al.,⁶⁻⁸ our hypertensive patients with PA exhibited neither overt LV hypertrophy (according to the high normal values of LVMI) nor a significant impairment of LV diastolic filling and a prolonged PR interval (probably due to the early stage of the disease). The existing differentiation of LV geometry between the 2 hypertensive groups, based on the significantly higher value of myocardial relative wall thickness in the PA population, could be mainly attributed to the aldosterone excess because our study groups were matched for major confounders.

Left ventricular diastolic dysfunction represents an early sign of hypertensive heart disease, and is responsible for half of the patients with symptomatic heart failure and preserved systolic function.¹⁷ Although there is a close association between diastolic dysfunction and LV remodeling, controversy still exists regarding their causality

TABLE 4: Tissue Doppler imaging measurements in essential hypertensives and hypertensives with primary aldosteronism

Parameter	Hypertensives with PA (n=17)	Essential hypertensives (n=30)	p-value
Em septal	5.9±2	6.6±1.2	0.13
Em/Am septal	0.54±0.18	0.66±0.15	0.026
Em lateral	7.5±2.1	9.9±2.7	0.007
Em/Am lateral	0.68±0.24	0.92±0.33	0.021
Em anterior	7±2.6	8.3±2.5	0.11
Em/Am anterior	0.69±0.30	0.82±0.27	0.17
Em inferior	6.8±1.4	7.5±2	0.24
Em/Am inferior	0.59±0.12	0.71±0.22	0.041
Em _{av} (cm/s)	7±1.7	8.1±1.8	0.048
Am _{av} (cm/s)	11.2±1.7	10.6±1.5	0.29
Em _{av} /Am _{av}	0.63±0.16	0.77±0.17	0.015

Em and Am = early and late diastolic mitral annular peak velocities from 4 separate LV sites. PA = Primary aldosteronism.

and temporal order in the progress of hypertension. Indeed, impairment of diastolic properties may be attributed more to the adverse quality caused by a disproportionate involvement of nonmyocytic elements rather than the increased quantity of myocardial tissue.¹⁸ Accordingly, in states of aldosterone excess, such as our PA population, and the absence of LV hypertrophy, the TDI-derived lower average Em and Em/Am ratio, apart from reflecting prolonged ventricular relaxation,¹⁹ suggests a mechanistic link with early LV structural changes.

Regarding aortic stiffness, we found that it is related to TDI-revealed diastolic dysfunction, in accordance with our previous findings from a cross-sectional study of untreated essential hypertensives.¹⁰ Although others have suggested pronounced arterial stiffening in hypertensives with PA, we failed to confirm this in our study.²⁰ This could be due to the smaller known duration of hypertensive disease in our case given that the latter is a major determinant of stiffening.

Regarding the pathophysiological perspectives of our findings, one could support that hypertensive changes in the cardiac and aortic walls may occur concurrently; thus, arterial stiffening and LV diastolic dysfunction could represent epiphenomena of the myocardial and aortic lesions observed even in the absence of LV hypertrophy, as typically demonstrated in normotensive individuals with familial hyperaldosteronism.^{10,13} In our PA population, characterized by aldosterone excess, the quality of myocardium may be altered and increased collagen deposition might constitute a potent determinant of this process. From a clinical point of view, TDI-derived indices could reveal mild and unfavorable LV diastolic function alterations even before the state of aortic vascular remodeling, prolongation of PR

interval, and dependence of LV filling on atrial kick. The lack of correlation between BP levels and indices of cardiovascular stiffening in PA subjects, but not in essential hypertensives, indicates that current management should not only focus on reduction of BP but also target the adverse structural myocardial remodeling. This may be achieved through a more integrated therapeutic approach by a complete blockade of the renin-angiotensin-aldosterone system using ACEIs, ARBs, and aldosterone antagonists.

Our study has several potential limitations. First, the findings are applicable only to the fraction of PA patients with an absence of adrenal adenoma or hyperplasia (neither unilateral nor bilateral). Second, the rarity of this specific entity and the early course of the disease limit the ability to recruit large numbers of participants, rendering it difficult to reveal existing difference in aortic stiffness. Third, the fact that our data were not corrected for multiple comparisons is attributed to the multiple matching of both active and control groups for all the major confounders of the compared parameters; thus strengthening in this sense our study findings.

In conclusion, our study demonstrates altered LV geometry and TDI-revealed diastolic dysfunction in hypertensives with PA compared with demographically- and LVMI-matched essential hypertensives. Moreover, the increased aortic stiffening failing to reach statistical significance does not seem to accompany these adaptations in the early course of the disease.

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