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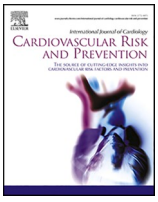

Relationship between plasma aldosterone levels and arterial stiffness parameters in hypertensive patients with subclinical vascular damage

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ABSTRACT

Purpose: Aldosterone plays important role in cardiovascular damage. Aim was to evaluate arterial subclinical damage through arterial stiffness parameters in patients with Essential Hypertension (EH) and Primary Aldosteronism (PA).

Methods: From 2018 to 2019 we consecutively enrolled 82 subjects (37 males and 45 women), distinguished in two groups: 60 EH [systolic blood pressure (SBP) 143.4 ± 16.7 mmHg, diastolic blood pressure (DBP) 89.5 ± 12.1 mmHg] and 22 PA (SBP 149 ± 19.5 mmHg, DBP 92.7 ± 12.4 mmHg) [5 with aldosterone-secreting adrenal adenoma(APA), 17 with idiopathic aldosteronism(IHA)]; 40 matched normotensive subjects (NS) were enrolled (SBP 109.7 ± 6.2 mmHg, DBP 71.3 ± 9.7 mmHg). We used non-invasive applanation tonometer to acquire pressure waveform.

Results: PA patients showed higher μ-Albuminuria (UAE) (65.7 ± 11.0mg/24 h) than EH and NS (21.5 ± 7.0 mg/24 h and 21.5 ± 7.0 mg/24 h, respectively); APA group showed increased levels of arterial stiffness index (11.7 ± 4.8 m/s; $p < 0.02$) compared to EH subjects (8.3 ± 3 m/s) and NS subjects (7.2 ± 1.7 m/s) as well as higher carotid intima-media thickness (c-IMT); APA patients showed significant reduction of subendocardial viability ratio (SEVR) and travel time of the reflected waves (TI) respect EH and NS. PA groups showed high percentage of augmented "worsening age" (60%), compared to EH (38%) and NS (37%). PAC was positively correlated with Arterial Stiffness Index. Performing multiple linear regression analysis (evaluating anthropometric and biochemical parameters), we found UAE as predictor of Augmentation Index, Arterial Stiffness Index and Travel Time of reflected waves in the enrolled population.

Conclusion: PA patients showed higher cardiovascular subclinical damage respect to EH; UAE excretion had significant correlation with aldosterone, resulting best marker of subclinical vascular remodeling.

1. Introduction

Aldosterone, secreted by adrenal gland as component of the renin-angiotensin-aldosterone system (RAAS), physiologically regulates the reabsorption of water and sodium, influencing blood pressure values. In primary aldosteronism (PA) there is an excessive autonomous production of aldosterone, mainly caused by aldosterone-secreting adenoma or mono/bilateral hyperplasia [1]. Beyond hypertensive effects, aldosterone excess shown pleiotropic effects on cardiovascular system through mineralcorticoid receptors (MR) widely localized in the cardiovascular system and heart [2], determining endothelial dysfunction, impairment of vascular elasticity, increased inflammation in myocardium, arterial system, and kidney [3,4].

The 2018 European Guidelines of Hypertension (ESC/ESH) [5] have focused attention on hypertension-mediated organ damage (HMOD), influencing heart, brain, retina, kidney, and arterial system. Recently, in newly diagnosed hypertensive subject the evaluation of subclinical atherosclerotic damage is increasingly seen as pivotal key in the classifying global cardiovascular (CV) risk, especially to discriminate those asymptomatic patients without overt damage, but at very high risk of its

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development, that would be misclassified by traditional score systems.

Large artery stiffening is pathophysiologically responsible of isolated systolic hypertension and age-dependent increase in pulse pressure [6]. Carotid-femoral Pulse Wave Velocity (cf- PWV) is the gold standard for measuring large artery stiffness, strong predictor of cardiovascular morbidity and mortality in hypertensive patients. Thus, recent Guidelines suggest adding PWV in traditional evaluation risks score of asymptomatic subjects [5,7].

We hypothesized that aldosterone excess, leading to myocardial hyperthrophy and interstitial fibrosis, affects arterial stiffness in newly diagnosed PA patients without overt organ damage. Thus, the current study investigated the relationship between plasma aldosterone concentration (PAC) with arterial stiffness, using non-invasive portable tonometer in determining arterial pressure wave and PWV, carotid-intima media thickness (c-IMT), 24-ambulatory monitoring blood pressure (ABPM) and main biochemical surrogated parameters of atherosclerosis (uricaemia and μ-albuminuria), in patients with PA compared to essential hypertensive patients (EH), without clinically evident signs or symptoms of organ damage.

2. Materials and methods

Study protocol was in accordance with ethical guidelines of the Declaration of Helsinki, and all participants signed informed consent before the study. The experimental protocol was approved by our academic Department (Dpt of Translational and Precision Medicine, University of Rome "Sapienza", Italy). The study did not involve the use of invasive methods, but instruments routinely used in clinical practice.

We performed a cross-sectional study, consecutively enrolling 82 subjects (22 PA patients and 60 EH subjects, matched for anthropometric parameters and blood pressure values), who referred to Specialized Centre of Secondary Arterial Hypertension, Department of Translational and Precision Medicine, University "Sapienza'' of Rome, Italy, from January 2018 to May 2019 in order to evaluate the nature of arterial hypertension and the stratification of cardiovascular risk in patients with recent diagnosis of arterial hypertension (less than 1 year). All patients were evaluated during diagnostic path to define primary or secondary hypertension. As regard, we excluded patients whit diagnosis of other forms of secondary hypertension (obstructive sleep apnea, phaeochromocytoma, Cushing's syndrome, thyroid disease, hyperparathyroidism, kidney parenchymal or vascular disease) [5,8]. As control group, we also evaluated 40 healthy subjects (NS) matched for age, sex, and lipid profile.

2.1. Diagnosis of essential hypertension and primary aldosteronism

Hypertension was defined as office systolic blood pressure (SBP) values at least 140 mmHg and/or diastolic blood pressure (DBP) values at least 90 mmHg [5]. In all patients were performed an extended hormonal evaluation [plasma aldosterone concentration (PAC), plasma renin activity (PRA), serum cortisol (PC), and 24-h urine excretion for metanephrines, aldosterone (AUR) and free urinary cortisol]. As suggested by International Guidelines (5,8) all antihypertensive medications were withdrawn at least 3 weeks (up to 2 months for spironolactone) before evaluation. In patients in whom anti-hypertensive treatment could not be completely withdrawn because clinical reasons, calcium-channel blockers (verapamil) or α-receptor blockers (doxazosin) were allowed at the minimal doses required to achieve BP control.

PA diagnosis was carried out following the main international guidelines, using screening and confirmatory test, and imaging study (computed tomography, magnetic resonance, adrenal venous sampling) [1,4,8]. Diagnosis of essential hypertension was made when any other cause of secondary hypertension was excluded [1,4,8].

Patients who fulfilled the following criteria were excluded from the study: arrhythmias; drug or alcohol abuse; end-stage chronic kidney-disease; pregnancy; prior cardio-vascular events; obstructive sleep apnea syndrome (OSAS) [9]. Patients with Metabolic Syndrome, according to ATP III criteria [10] were excluded from design of the study. All patients underwent a complete physical examination, anthropometric and laboratory data were collected. Glomerular filtration-rate was estimated using Chronic Kidney Disease Epidemiology Collaboration (EPI-CKD) formula [11].

2.2. Ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring (ABPM) was performed using the oscillometric technique, which involves a portable lightweight, non-invasive monitor with self-insufflating cuff (Spacelabs Medical, 90207, Issequah, WA, USA). ABPM readings were obtained at 15-min intervals from 6 a.m. to midnight and at 30-min intervals from midnight to 6 a.m. The following ABPM parameters were evaluated: average daytime SBP, average daytime DBP and average daytime heart rate; average nighttime SBP, average nighttime DBP and average nighttime hear rate; average 24-h SBP, average 24-h DBP and average 24-h heart rate. Periods were determined by the subjects' diaries. The definitions "dipper" was established where nighttime SBP and DBP decrease was >10%. Ambulatory hypertension was defined as 24-h BP more than 130/80 mmHg [5].

2.3. Pulse pen and applanation tonometry

The PulsePen (DiaTecne s.r.l., Milan, Italy; www.pulsepen.com) is composed of two units: one tonometer, that serves to non-invasive acquires pressure waveform [12] by principles of applanation tonometry [13], and an integrated electrocardiogram (ECG) unit. A physician has been trained to register arterial carotid and femoral pulse waves. All tests were performed by a single operator (MM). Following parameters were acquired and calculated by software: the peak time of the first, second, and the reflected wave; carotid-femoral pulse wave velocity (cfPWV), expressed as velocity in m/sec; augmentation index (AI, calculated as ratio of the second to the first peak of the central blood pressure wave), and pulse reflection time, as well as ejection duration; Subendocardial Variability Ratio (SEVR), also known as Buckberg index, which is an index of myocardial oxygen supply and demand automatically calculated through pulse wave analysis and defined as diastolic to systolic pressure-time integral ratio, reflecting balance between coronary perfusion and arterial load; travel time of the reflected waves (TI) [14]. Obtaining all these parameters, it was also calculated parameter called "vascular age" by a dedicated computed algorithm and it had been compared to chronological age; the difference between "chronological age" and calculated "vascular age" is defined "age worsening", expressed in years. "Worsening age" parameter can be used in two different ways: as a dichotomic variable (if vascular age is worse than chronological one, expressed as percentage of the samples) or expressed in years between chronological age and vascular age, as a continuous variable.

2.4. Evaluation of carotid-intima media thickness

A Hewlett-Packard Sonor 5500 Ultrasound system (Hewlett- Packard, Andover, MA, USA), equipped with a 3–11 MHz real-time B-mode scanner was used for the evaluation. Imaging of the right common carotid artery (CCA) was performed with the subjects turning their head 45° to the left. Carotid-intima media thickness (c-IMT) was defined as average value of thickness of the vascular intima-media complex obtained in five consecutive regions of the wall of the CCA, every 4–5 mm beginning close to the bifurcation. All examinations were performed by a single operator (FO), to minimize intra-variability measurement bias.

2.5. Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences, software, version 25 (SPSS Inc, Chicago, Illinois, USA). Quantitative variables are expressed as mean ± standard deviation (SD); qualitative variables are described as frequency and percentage (%). Differences between means were assessed by the Student *t*-test or the Mann-Whitney *U* test in non-normally distributed data for two-sample comparison, or by one-way analysis of variance (ANOVA) applying the Fisher least significant difference post hoc test for multiple comparisons. $\chi 2$ statistics were used to assess differences between categorical variables. Relationships between continuous variables were assessed calculating the Pearson correlation coefficient or the Spearman rank correlation coefficient when appropriate. Multiple linear regression analysis was made with Backward Stepwise Regression method. p values < 0.05 were taken as statistically significant.

3. Results

Our study included 82 hypertensive subjects, 37 males and 45 females, distinguished in the following groups: 60 EH patients, 22 PA (5 with diagnosis of APA, 17 with diagnosis of IHA). We enrolled 40 normotensive subjects (NS) as group control (26 males, 14 females). Anthropometric, biochemical and laboratoristic parameters are resumed in Table 1.

No statistically significant differences were observed between groups for anthropometric parameters. APA patients had higher levels of glycaemia (111.4 ± 35.3 mg/dl; $p < 0.05$) compared to EH and NS patients (89.2 ± 18.7 mg/dl and 86.8 ± 12.3 mg/dl, respectively). Furthermore, we observed higher 24-h urinary albumin concentration (μ-albuminuria) in PA patients (65.7 ± 11.0 mg/24 h; $p < 0.02$) compared to EH and NS (respectively, 21.5 ± 7.0 mg/24 h, 9.2 ± 15.0 mg/24 h); as regard, APA patients showed higher μ-albuminuria respect to IHA.

Subjects affected by APA had increased levels of arterial stiffness index (11.7 ± 4.8 m/s; $p < 0.02$) compared to EH subjects (8.3 ± 3 m/s)

Table 1
Anthropometric. biochemical. Pulse Wave Velocity parameters (PWV). Doppler ultrasonography of carotids. blood pressure behaviours evaluated by office and 24-h ambulatory blood pressure monitoring (ABPM) in all groups evaluated (expressed as mean ± standard deviation).

	NS (n. 40)	EH (n. 60)	PA (n. 22)	APA (n. 5)	IHA (n. 17)	p
Age (yrs)	45.6 ± 16.4	47.9 ± 14.6	46.7 ± 10.5	47.2 ± 6.9	46.6 ± 11.5	ns
Gender M (%)	35.3	46.6	31.8	20	35.3	ns
BMI (kg/m^2)	22.9 ± 3.9 *	26.4 ± 3.8	26.9 ± 5.9	28.7 ± 4.3	26.3 ± 6.3	*<0.05 vs EH. PA
WC (cm)	93.8 ± 11.5	94.9 ± 13.5	94.2 ± 20	99.2 ± 8.3	92.5 ± 22.6	ns
Creatinine (mg/dL)	0.9 ± 0.2	0.9 ± 0.3	1.0 ± 0.3	1.2 ± 0.5	0.9 ± 0.2	ns
Glycaemia (mg/dL)	86.8 ± 12.3	89.2 ± 18.7	93.2 ± 21.5	111.4 ± 35.3*	87.9 ± 12.7	*<0.05 vs EH.NS
TC (mg/dL)	184 ± 38	118 ± 34	175 ± 24	176 ± 29	174 ± 23	ns
LDL-C (mg/dL)	108 ± 34	111 ± 28	98 ± 22	105 ± 23	96 ± 22	ns
HDL-C (mg/dL)	55.0 ± 12	54.8 ± 13	54.8 ± 15	45.8 ± 6	58.1 ± 16	ns
TGL (mg/dL)	107 ± 84	107 ± 56	121 ± 117	135 ± 36	117 ± 71	ns
SUA (mg/dL)	5.2 ± 1.3	5.4 ± 1.5	5.7 ± 1.5	5.6 ± 0.4	5.8 ± 1.7	Ns
μ-Albuminuria (mg/24 h)	9.2 ± 15	21.5 ± 7	65.7 ± 11**	111.8 ± 56°	44.8 ± 28	**<0.02 vs EH.NS °<0.001 vs IHA
PAC (pg/ml)	80.5 ± 3.2	110.2 ± 47	325.4 ± 45.2***	355.7 ± 65.2	316.5 ± 41.2	***<0.001 vs EH.NS
PRA (ng/ml/h)	1.2 ± 0.4	0.9 ± 0.3	0.5 ± 0.02***	0.59 ± 0.02	0.47 ± 0.02	***<0.001 vs EH.NS
PAC/PRA ratio	0.9 ± 0.2	10.5 ± 1.5	101.5 ± 17.5***	110.3 ± 21	98 ± 16.7	***<0.001 vs EH.NS
UAR (μg/24h)	15.6 ± 8.8	21.8 ± 9	31.4 ± 9.8*	35.4 ± 11.5	30.2 ± 7.4	*<0.05 vs EH.NS
Vascular Age (yrs)	45.0 ± 15.6	48.6 ± 15.7	51.5 ± 13.8	59.8 ± 20.1	49.0 ± 11	ns
Worsening % [a]	37	38	60*	80*.	53	*<0.05 vs EH.NS <0.02 vs IHA
Augmentation Index %	16.8 ± 11.5	26.4 ± 7.6	28.2 ± 9.4	30.3 ± 16.7	28.2 ± 6.5	ns
Stiffness Index (m/s)	7.2 ± 1.7	8.3 ± 3	9.4 ± 3.2**	11.7 ± 4.8**	8.8 ± 2.3	**<0.02 vs EH.NS <0.02 vs IHA
SEVR (%)	119.8 ± 12	120.5 ± 22.4	112 ± 24*	104.8 ± 25.7	114 ± 23	*<0.05 vs EH.NS
TI (m/s)	131.2 ± 32.1	113.0 ± 38.2	103.1 ± 28.4*	83.8 ± 24.1	109.0 ± 27.5	*<0.05 vs EH.NS
c-IMT (mm)	0.8 ± 0.1	0.8 ± 0.2	1.0 ± 0.3*	1.2 ± 0.2*	0.9 ± 0.3	*<0.05 vs EH.NS
c-IMT>0.9 mm (%) [a]	32	42	66*	80*	60	*<0.05 vs EH.NS
Plaque (%)	18	20	28	20	30	ns
Stenosis (%)	25	29	34	45	30	ns
Office SBP (mmHg)	109.7 ± 6.2	143.4 ± 16.7***	149 ± 19.5***	146.4 ± 13.2***	150.2 ± 21.2***	***<0.001 vs NS
Office DBP (mmHg)	71.3 ± 9.7	89.5 ± 12.1***	92.7 ± 12.4***	90.8 ± 13.5***	92.9 ± 8.1***	***<0.001 vs NS
24-h ABPM						
G-SBP (mmHg)	108.3 ± 11.4	134.0 ± 11.4***	133.4 ± 13.9***	141.4 ± 8.8***	129.9 ± 12.4***	***<0.001 vs NS
G-DBP (mmHg)	58.2 ± 8.8	82.4 ± 9.4***	83.4 ± 9.5***	84.5 ± 7.5***	83.0 ± 10.2***	***<0.001 vs NS
D-SBP (mmHg)	111.6 ± 11.5	136.8 ± 11.7***	135 ± 12.7***	144.6 ± 11.1***	132.2 ± 12.0***	***<0.001 vs NS
D-DBP (mmHg)	61.1 ± 8.7	85.0 ± 9.5***	85.5 ± 9.5***	85.9 ± 7.6***	85.4 ± 10.2***	***<0.001 vs NS
N-SBP (mmHg)	97.8 ± 12	123.2 ± 21.5***	129 ± 19.5***	138.6 ± 11.4***	123.9 ± 16.3***	***<0.001 vs NS
N-DBP (mmHg)	48.2 ± 9.8	73.7 ± 15.6***	77.8 ± 11.9***	80.4 ± 11.4***	76.9 ± 12.3***	***<0.001 vs NS
Non Dipper (%) [a]	19	56*	59*	60*	59*	*<0.05 vs NS

NS: normotensive subjects; EH: essential hypertension; PA: primary aldosteronism; APA: primary aldosteronism with aldosterone producing adenoma; IHA: primary aldosteronism with idiopathic aldosteronism; BMI: body mass Index; WC: Waist circumference; TC: total cholesterol; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein-cholesterol; TGL: triglycerides; SUA: serum uric acid; PAC: plasma aldosterone concentration; UAR: 24-h urine excretion for aldosterone; SEVR: subendocardial viability ratio; TI: travel time of the reflected waves; c-IMT: carotid intima media thickness; plaque: percentage of incidence of plaques; stenosis: percentage of incidence of stenosis.

Office SBP: Office systolic blood pressure; Office DBP: Office diastolic blood pressure; G-SBP: Global average systolic blood pressure; G-DBP: Global average diastolic blood pressure; D-SBP: Daytime average systolic blood pressure; D-DBP: Daytime average diastolic blood pressure; N-SBP: Nighttime average systolic blood pressure; N-DBP: Nighttime average diastolic blood pressure; Non-Dipper: Non- Dipper Pattern.

ANOVA test has been performed to compare parameters between evaluated groups.

[a] Chi-Square statistic has been performed to compare parameters between evaluated groups.

and NS subjects (7.2 ± 1.7 m/s), as well as to IHA patients (8.8 ± 2.3 m/s; $p < 0.03$).

Furthermore, APA patients showed statistically significant reduced levels both of SEVR and TI, compared to EH patients and NS subjects.

Algorithmic analysis of PulsePen Diatecne® software allowed to compare vascular age to the chronological one ("worsening age"). PA groups showed an elevate percentage of patients with augmented "worsening age" (60%), compared to patients with EH (38%) and NS (37%). As regard, APA subjects had a statistically significant increase of percentage of subjects with "worsening age", compared to IHA subjects.

Regarding data obtained by Doppler ultrasonography of carotids, PA patients (especially APA) had higher levels of c-IMT compared to EH and NS subjects. Evaluating prevalence of c-IMT altered (>0.9 mm), higher prevalence has been found in PA patients (66%) and APA group (80%),

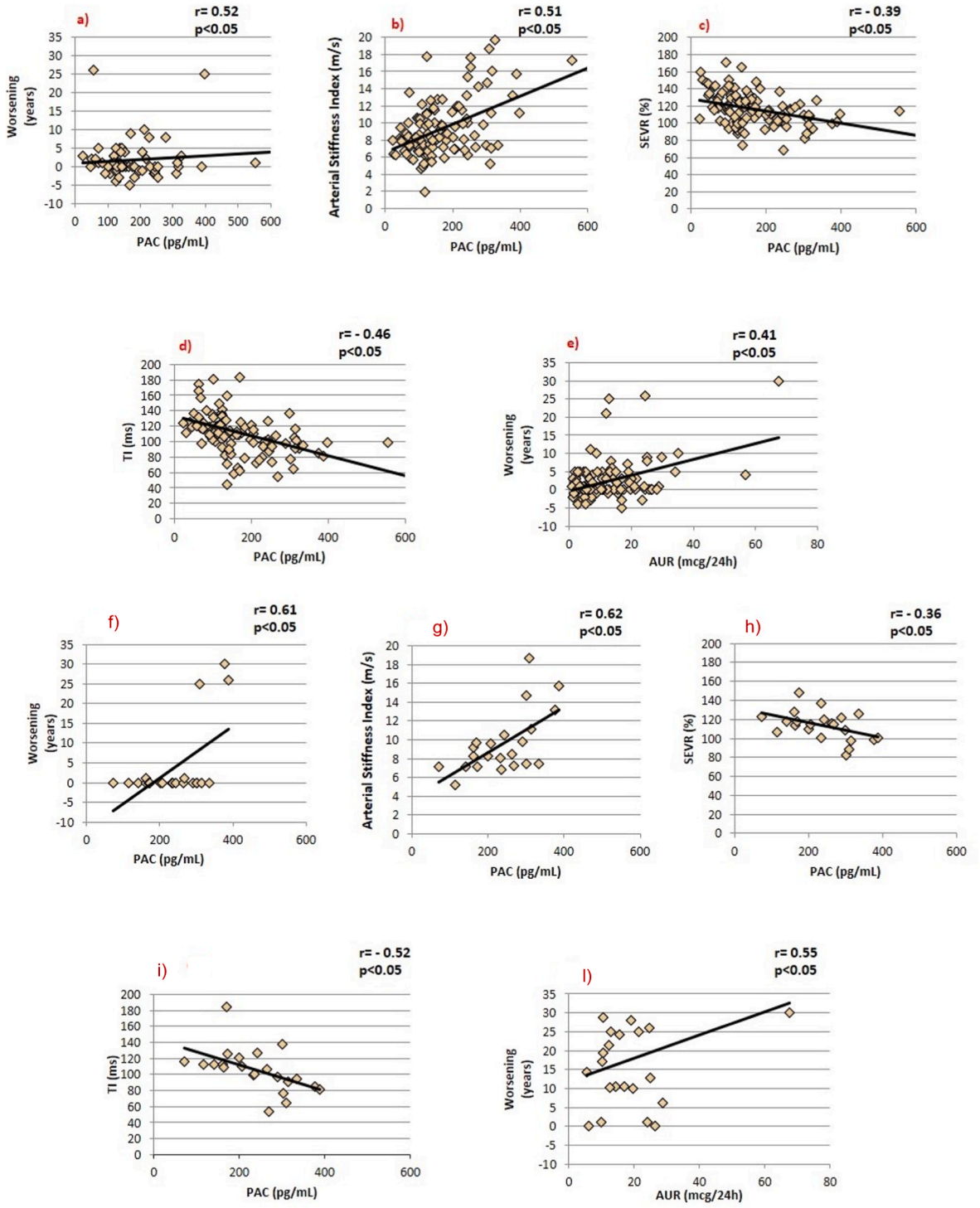

Fig. 1. Study correlation in overall hypertensive subjects (A–E) and primary aldosteronism (F–L): a) vascular age compared to chronological worsening (expressed in years) with PAC; b) arterial stiffness index with PAC; c) subendocardial viability ratio (SEVR) with PAC; d) travel time of the reflected waves (TI) with PAC; e) vascular age compared to chronological worsening (expressed in years) with AUR. f) vascular age compared to chronological worsening (expressed in years) with PAC; g) arterial stiffness index with PAC; h) subendocardial viability ratio (SEVR) with PAC; i) travel time of the reflected waves (TI) with PAC; l) vascular age compared to chronological worsening (expressed in years) with AUR. PAC: plasma aldosterone concentration; AUR: 24-h urinary aldosterone.

compared to patients affected by EH and NS (42% and 32%). Regarding Office BP values and 24-h ABPM values in the overall studied population, nonsignificant differences were observed between EH and PA subjects enrolled.

The correlation study on overall hypertensive patients showed that PAC levels positively correlated with "worsening age" (r = 0.52) and arterial stiffness index (r = 0.51) and inversely correlated with SEVR (r = −0.39) and TI (r = -0.46) (Fig. 1A–D). Moreover, 24-h aldosterone urinary excretion was significantly correlated with "worsening age" (r = 0.41) (Fig. 1E).

In PA patients, PAC levels are strongly correlated to "worsening age" (r = 0.61) and arterial stiffness index (r = 0.62) and inversely correlated to SEVR (r = −0.36) and TI (r = −0.52) (Fig. 1F–I); moreover, 24-h aldosterone urinary levels were significantly correlated to "worsening age" (r = 0.55) (Fig. 1L).

Interestingly, we found that μ-albuminuria was positively correlated with PAC (r = 0.25; p < 0.02) and AUR levels in overall hypertensive population (r = 0.30; p < 0.001) (Fig. 2).

Table 2 illustrates results from multivariate analysis, performed with multiple logistic regression, using backward method. In the analysis we included all clinically relevant variables, such as 24-urinary aldosterone, μ-Albuminuria, plasma aldosterone concentration, LDL-Cholesterol, waist-circumference, serum uric acid, carotid-intima media thickness, heart rate, office diastolic blood pressure, office systolic blood pressure, body mass index, serum uric acid, age, heart rate, glycaemia, global average systolic blood pressure (G-SBP). In the overall hypertensive subjects enrolled, Augmentation Index predictor was μ-Albuminuria value (β = 0.198). Best predictors of arterial stiffness index were μ-Albuminuria (β = 0.426), age (β = 0.362) and G-SBP (β = 0.324).

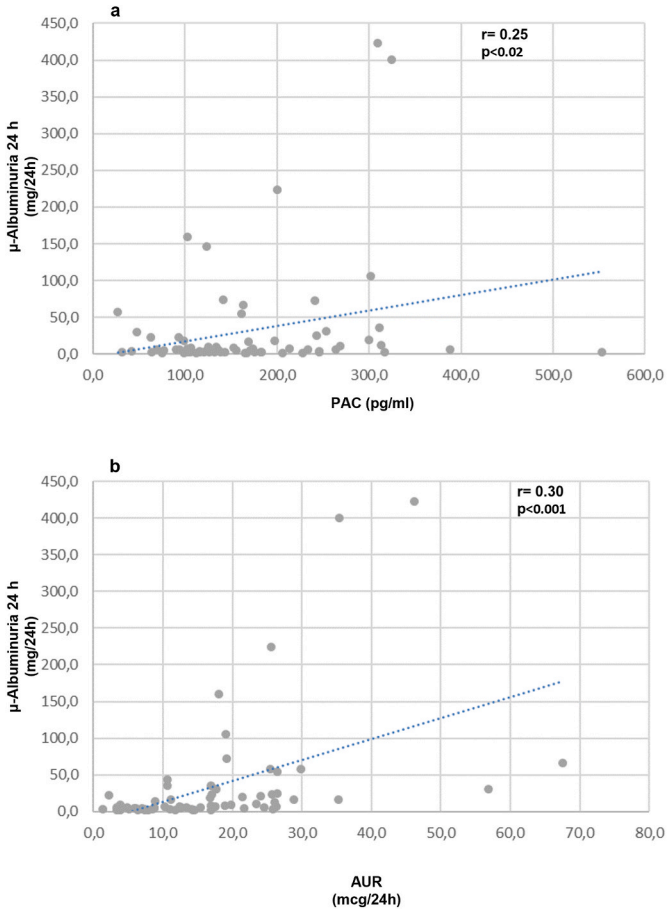

Fig. 2. Study correlation between μ-Albuminuria with PAC (a) and AUR (b). PAC: plasma aldosterone concentration; AUR: 24-h urinary aldosterone.

Finally, most important predictors of TI parameters were age (β = −0.325), G-SBP (β = −0.225), office DBP (β = −0.529), and μ-Albuminuria (β = −0.324).

4. Discussion

In addition to moderate-severe hypertension or resistant hypertension, PA is associated to important target organ damage and several complications, related to pressure overload and to pleiotropic effects of aldosterone on CV system; as regard, PA is characterized by several metabolic changes, as metabolic syndrome [4], cardiac fibrosis [15], myocardial hypertrophy [16], arrhythmias, heart failure and deleterious effects on vascular remodeling, endothelial dysfunction, oxidative stress, perivascular inflammatory lesions, fibrosis, and platelets activation [3,17–20].

European Guidelines of Hypertension have introduced non-invasive measurement of PWV suggesting using applanation tonometry [5]. PWV is the velocity of pulse wave along vascular segment, recently deeply studied as instrument to evaluate subclinical damage in hypertensive subjects with no overt signs of organ damage [21]. Beyond hypertension [22], augmented PWV has been demonstrated to be independently associated with higher incidence of cardiovascular events in patients with diabetes mellitus [23] and end-stage renal disease [24].

Since the well-established data of role of aldosterone excess in heart failure, as far as higher cardiovascular complications in PA, recent efforts were addressed to acknowledge the pivotal act of aldosterone in subclinical damage in the early stages of hypertension.

In our study specifically conducted on asymptomatic patients with brief history of hypertension, we have found significant increase of "worsening age" phenomenon in PA patients respect to EH. This phenomenon characterized by impaired arterial stiffness is due to degenerated elastic fibers, increased collagen deposition, vascular smooth muscles hypertrophy, increased proinflammatory cytokines and subsequent calcium deposition [25,26]. Beyond "worsening age", we have found significant correlations between other main PWV-derived parameters (Augmentation Index, Buckberg Subendocardial Viability Ratio, Travel Time of the reflected waves) with plasma aldosterone and 24-h urinary aldosterone levels in overall hypertensive patients, and strongly in PA.

In an original study of Park S. [27], hormonal parameters and PWV were measured in 438 hypertensive subjects; multiple linear regression revealed that PAC, but not ARR, was significantly associated with central aortic PWV, after controlling for age, systolic blood pressure, BMI, gender, low-density lipoprotein-cholesterol, triglyceride, high-density lipoprotein-cholesterol, blood pressure medication and statins. In analogous study, in PA and EH patients Tsioufis et al. have evaluated the aortic stiffness by carotid-femoral PWV and echocardiographic parameters, not finding statistical significance, even the Authors attributed this lack of significance to the unknown duration of hypertensive disease [28]. As regard, it's well described that data obtained from PWV are particularly useful in asymptomatic patients with a short history of arterial hypertension.

Evaluating data obtained through wave reflection analysis, Hung CS enrolled 67 PA patients and 132 EH subjects, comparing them after 6 months of pharmacological treatment, observing that PA group had backward and forward wave amplitude higher than EH group. Furthermore, presence of PA was significantly associated with increases in backward and forward wave amplitude, independently of age, PWV and BP [29].

Similar results were observed by Rosa J. [30], in 49 PA patients and 49 EH patients matched for age, BP, BMI, lipid profile and fasting glucose. Peripheral and central PWV were significantly higher in PA patients compared to EH patients, while clinical BP were similar, suggesting that PAC was the main predictor of cf-PWV in PA.

In the assessment of arterial remodeling, we have found significative increase of IMT values (expressed either as thickness in millimeter and

Table 2
Multiple linear regression analysis results.

	Unstandardized Coefficients		Standardized β	95% CI		P
	B	Standard error		Lower	Upper	
Augmentation Index as dependent variable						
Age (yrs)	−0.030	0.050	−0.054	−0.129	0.070	0.555
BMI (Kg/m2)	−0.154	0.223	−0.086	−0.597	0.289	0.492
WC (cm)	0.077	0.075	0.130	−0.071	0.225	0.307
HR (bpm)	−0.073	0.074	−0.091	−0.218	0.073	0.324
PAC (pg/ml)	−0.005	0.007	−0.075	−0.019	0.008	0.420
G-SBP (mmHg)	0.102	0.062	0.175	−0.022	0.225	0.105
DBP (mmHg)	0.097	0.063	0.169	−0.026	0.221	0.122
μ-Albuminuria (mg/24h)	0.025	0.012	0.198	−7.975	26.289	**0.036**
$R^2 = 0.361$; adapted $R^2 = 0.130$ (*SBP. Glycaemia and LDL-C were excluded for high collinearity coefficient)*						
Arterial Stiffness Index as dependent variable						
Age (yrs)	0.077	0.017	0.362	0.044	0.110	**<0.001**
BMI (Kg/m2)	−0.128	0.068	−0.185	−0.263	0.007	0.063
WC (cm)	0.028	0.023	0.124	−0.017	0.073	0.217
HR (bpm)	0.004	0.023	0.013	−0.041	0.049	0.856
Glycaemia (mg/dl)	−0.003	0.014	−0.020	−0.031	0.024	0.809
LDL-C (mg/dl)	0.005	0.008	0.053	−0.010	0.021	0.493
PAC (pg/ml)	0.000	0.002	0.010	−0.004	0.004	0.889
G-SBP (mmHg)	0.073	0.021	0.324	0.032	0.115	**0.001**
DBP (mmHg)	−0.005	0.025	−0.025	−0.054	0.043	0.824
μ-Albuminuria (mg/24h)	0.021	0.004	0.426	0.013	0.028	**<0.001**
$R^2 = 0.486$; adapted $R^2 = 0.434$						
Time of the reflected waves (TI) as dependent variable						
Age (yrs)	−0.935	0.272	−0.325	−1.474	−0.396	**0.001**
BMI (Kg/m2)	0.176	1.108	0.019	−2.020	2.372	0.874
WC (cm)	−0.079	0.371	−0.026	−0.814	0.656	0.832
HR (bpm)	0.185	0.369	0.044	−0.546	0.917	0.617
Glycaemia (mg/dl)	−0.105	0.224	−0.047	−0.548	0.338	0.639
LDL-C (mg/dl)	0.058	0.127	0.042	−0.195	0.310	0.652
PAC (pg/ml)	−0.047	0.034	−0.124	−0.116	0.021	0.172
G-SBP (mmHg)	−0.686	0.340	−0.225	−1.359	−0.013	**0.046**
DBP (mmHg)	−1.593	0.402	−0.529	−2.390	−0.796	**<0.001**
μ-Albuminuria (mg/24h)	−0.155	0.062	−0.234	−0.278	−0.031	**0.015**
$R^2 = 0.249$; adapted $R^2 = 0.176$						
Inserted variables: *Age; BMI; WC; HR; glycaemia; LDL-C; PAC; G-SBP; SBP, DBP; AUR; μ-Albuminuria; TGL; c-IMT.*						

BMI: body mass index; WC: waist circumference; HR: heart rate; LDL-C: LDL-cholesterol; PAC: plasma aldosterone concentration; G-SBP: Global average systolic blood pressure; SBP: office systolic blood pressure; DBP: office diastolic blood pressure; AUR: 24-h urinary aldosterone; TGL: triglycerides; c-IMT: carotid-intima media thickness.

as percentage of altered thickness) in PA patients, especially in APA subgroup, respect to EH and NS.

An interesting meta-analysis of Ambrosino [31] had evaluated studies aimed to describe the relationship between PA and c-IMT, flow mediated-dilation, PWV, AI and ABI. When compared to normotensive controls, PA patients showed significantly higher c-IMT, aortic PWV and significantly lower FMD. Meta-regression model showed that male gender, diabetes, and smoking had the strongest impact. According to this review, PA appears significantly associated with markers of subclinical atherosclerosis. As regard, we have shown that different parameters obtained by PWV are altered in PA patients respect EH patients, matched for blood pressure load, using well standardized technique, carried out with dedicated software.

Regarding the effects of the specific treatment of PA, Lin et al. [32] prospectively analyzed APA patients surgically treated (adrenalectomy), and EH patients pharmacologically treated. While APA patients had significantly higher DBP, PAC, c-IMT and heart-ankle PWV compared to EH patients, it was observed a reduction of c-IMT, brachial-ankle PWV and heart-ankle PWV, one year after adrenalectomy. Moreover, Holaj et al. have examined the long-term impact of PAC on c-IMT in a cohort of 42 patients affected by PA, highlighted that both surgical and medical treatment were effective in regression of common carotid IMT, even though the effect was more pronounced after adrenalectomy than after spironolactone therapy [33]. Moreover, Strauch B. and collaborators [34] conducted a study on PA patients, observing that surgical but not conservative treatment of PA led to a significant decrease of BP and arterial stiffness parameters.

PWV is recognized as useful method at the time of diagnosis for cardiovascular risk stratification, there are no indications of its use in follow-up. As regard, Bouhanick has conducted a multicenter study [35] to evaluate arterial stiffness parameters in PA patients who underwent surgery, assessing aortic PWV and ABPM 6 and 12 months after surgery. While there was a decreased trend in 24-h systolic and diastolic BP values, in the multivariable analysis, no statistically significant interaction was found between time and PWV (for any outcomes), suggesting that PWV has low sensitivity and specificity to predict therapeutic response.

Interestingly we have found significant increased 24-h urinary excretion of μ-albuminuria in PA patients compared to EH, strongly correlated to PAC and AUR. In multivariate linear analysis of all hypertensive subjects, 24-h urinary excretion of μ-albuminuria has been seen as stronger predictor for main parameters derived by the evaluation of arterial stiffness parameters (augmentation index, SEVR, arterial stiffness index, travel time of the reflected waves).

Previous study showed substantial increase of μ-albuminuria in PA, suggesting the direct aldosterone-dependent pathophysiological mechanisms into development of kidney injury, including mesangial cell proliferation, sclerotic changes, glomerular tuft expansion, podocyte injury, interstitial inflammation, arteriolar hyalinosis, and fibrosis [36]. Whaley-Connel A. and al [37]. have focused the effects of aldosterone on glomerular podocytes, highlighting that aldosterone induces the loss of glomerular podocytes, leading to decreased slit-pore membrane integrity and proteinuria. As regard, recent review confirmed that PA patients, compared with EH patients, beyond pronounced TOD and altered glomerular filtration rate, are characterized by progression of renal disease, that, after specific treatment can be improved [38].

The specific treatment of PA, through reduction of renal damage and μ-albuminuria, as well as reduction of pleiotropic effects of aldosterone excess on cardiovascular and metabolic systems, could explain reduction of altered arterial stiffness parameters in hypertensive patients with subclinical vascular damage due to aldosterone excess. In Kishimoto's pilot study [39], IHA patients treated with eplerenone for 12 weeks showed an improvement of microvascular endothelial function, including arterial stiffness, brachial-ankle pulse wave velocity and nitroglycerine-induced vasodilatation.

In the present study we consecutively enrolled a large population of patients affected by EH and PA, without overt signs of HMOD and with newly diagnosed arterial hypertension (less than 1 year). We found as relevant and significative data the increased urinary excretion of μ-albuminuria in PA patients compared to EH and NS, and significant relationship between μ-albuminuria with PAC and 24-h urinary aldosterone levels in overall hypertensive patients. Furthermore, we found significative predictive role of μ-albuminuria to influence main PWV-derived parameters, as Augmentation Index, Arterial Stiffness and Time of the reflected waves. These data confirm the strict role of aldosterone excess in development of organ-damage, evaluated as increased urinary excretion of μ-albuminuria and altered parameters obtained by applanation tonometer, respect patients with EH, with similar blood pressure overload (evaluated clinically and by ABPM).

Limits of this study are moderate number of observed cases and the design; it was cross-sectional and observational study, not allowing results in terms of therapeutic intervention and how this could influence arterial stiffness parameters. As regard, it would be interesting to expand our APA and IHA population, comparing surgical or pharmacological treatment, to emphasize correlations between PAC and PWV; moreover, the statistical analysis didn't show relevant results regarding the distribution of sex, probably due to the low number of cases and different distribution in the groups.

Moreover, we suggest to extend observations about PWV and arterial stiffness in other secondary forms of hypertension that were excluded in our casuistry.

In conclusion, our results demonstrate how aldosterone overproduction, in uncomplicated hypertensive patients, with recent diagnosis of arterial hypertension, is associated to augmented asymptomatic HMOD, which is an independent risk factor for major cardiovascular events. Moreover, our study focused the importance of a non-invasive evaluation to establish cardiovascular risk classification in asymptomatic patients. In our experience, at constant systolic and diastolic BP values, patients with aldosterone excess had worse PWV and arterial stiffness index, compared to EH patients, and higher μ-albuminuria, as early sign of renal vascular damage, strictly related to subclinical arterial damage. In clinical practice it is fundamental to reach optimal BP control, but also identify subclinical endothelial changes, to obtain a better definition of the early cardiovascular risk, as well as prevent irreversible arterial damage.

Author contributions

Conceptualization: CL, LP, MM; methodology: AC, MS, FS, MS; software: MM, FS; validation: CL, GI, LP; formal analysis: MM, FS, LP; investigation: AC, FS, MS, MS; resources: CL, GI; data curation: MM, FS, MS, AC; writing-original draft preparation: LP, MM; writing-review and editing: CL, GI, LP; visualization: LP; supervision: CL, GI; project administration: MS, LP. All authors have read and agreed to the published version of the manuscript.

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Declaration of competing interest

The authors declare no conflict of interest.

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