International Journal of Cardiology Hypertension 2 (2019) 100015

Contents lists available at ScienceDirect

International Journal of Cardiology Hypertension

journal homepage: www.journals.elsevier.com/international-journal-of-cardiology-hypertension/

Research Paper

Association between elevated plasma aldosterone concentration and left atrial conduit function in hypertension

Shenglin Zhang [a], Xin Gao [b], Dongxia Wang [b], Yinong Jiang [b], Yan Liu [b,*]

[a] Department of General Surgery, The 1st Affiliated Hospital of Dalian Medical University, Zhongshan Road No. 222, Xigang District, Dalian, Liaoning, China
[b] Department of Cardiology, The 1st Affiliated Hospital of Dalian Medical University, Lianhe Road, No. 193, Shahekou District, Dalian, Liaoning, China

ARTICLE INFO

Keywords:
PAC
Atrial function
Hypertension

ABSTRACT

Aldosterone affects myocardial fibrosis and remodeling. The aim was to investigate the relationship between plasma aldosterone concentration (PAC) and left atrial (LA) function in hypertension. 148 hypertensive patients were studied. LA phasic function was evaluated by strain and strain rate imaging. Patients were divided into two groups based on PAC. LA early diastolic strain and strain rate (LA_{S-E} and LA_{SR-E}) were lower in group II compared with group I ($P < 0.05$). Multivariate regression analysis showed that LA_{S-E} was independently related to PAC ($\beta = -0.581$, $P < 0.001$). In conclusion, PAC is associated with LA conduit function in hypertension.

1. Introduction

Aldosterone, which is secreted by the adrenal cortex, is an important component of the rennin-angiotensin-aldosterone system (RAAS). Aldosterone not only influences the reabsorption of water and sodium but also affects myocardial fibrosis and remodeling. The relationship between plasma aldosterone concentration (PAC) and left ventricular (LV) mass in essential hypertension has been reported [1–4]. Researchers have also shown that PAC is related to arterial stiffness [5,6]. However, the association between PAC and atrial function in essential hypertension has not been clarified.

Aldosterone, binding to Mineralocorticoid receptor (MR), has genomic and non-genomic mechanism for cardiovascular remodeling, and in the heart, MR distributes widely in cardiomyocytes, fibroblasts, and inflammatory cells [7–11]. The action of aldosterone and MR should affect the whole heart, both ventricle and atrium. Furthermore, left atrial function is closely interconnected with LV diastolic function and compliance. We hypothesize that aldosterone, leading to myocardial hypertrophy and interstitial fibrosis, also affects atrial structural and functional remodeling. Thus, the current study investigated the relationship between PAC and left atrial structure and function in essential hypertension.

2. Methods

2.1. Study population

The current study included 148 patients with uncomplicated essential hypertension who were recruited from the Cardiac Department of the First Affiliated Hospital of Dalian Medical University from January 2017 to December 2017. Antihypertension medication included only calcium channel blockers or alpha blockers. Patients were divided into two groups according to whether PAC was above or below the median value (138 pg/mL) as follows: group I (n = 75), PAC ≤ 138 pg/mL; group II (n = 73), PAC > 138 pg/mL. Exclusion criteria were as follows: systolic heart failure (including a history of dyspnea and left ventricular ejection fraction < 50% as well as end-diastolic left ventricular diameter ≥ 55 mm); coronary heart disease (including a history of angina pectoris, acute coronary syndrome, or coronary revascularization; segmental wall motion abnormalities on echocardiography; or > 50% narrowing in one of the epicardial coronary arteries on coronary computed tomography angiography), a history of sustained atrial arrhythmias, any grade of valvular stenosis, or more than mild valvular regurgitation. The study complied with the Declaration of Helsinki. All patients provided informed consent to participate in this study. The Ethics Committee of the First Affiliated Hospital of Dalian Medical University approved this study.

* Corresponding author.
E-mail address: liuyanjulie@outlook.com (Y. Liu).

https://doi.org/10.1016/j.ijchy.2019.100015
Received 12 December 2018; Received in revised form 11 June 2019; Accepted 16 June 2019
Available online 2 July 2019

2.2. Measurement of plasma angiotensin I, angiotensin II, and aldosterone levels

The plasma angiotensin II (Ang II) concentration and the plasma angiotensin I (Ang I) generation rate were measured with a radioimmunoassay (Iodine [^{125}I] Angiotensin I/II Radioimmunoassay Kit, Beijing North Institute of Biological Technology, Beijing, China). PAC was measured with ACTIVE Aldosterone RIA (DSL8600, Beckman Coulter, Prague, Czech Republic). Blood samples were collected in the morning using tubes with an inhibitor cocktail (edetate disodium, dimercaprol, and 8-hydroxyquinoline sulfate) and centrifuged at 2500 rpm for 10 min. Plasma was frozen and stored at −20 °C.

2.3. Standard echocardiography

We used a Vivid 7 ultrasound system (GE Vingmed Ultrasound, Horten, Norway), with a 3S phased-array transducer (1.5–3.8 MHz). When we obtained the electrocardiographic recording, the patients were asked to hold their breath during end-expiration. All of the images and measurements were acquired from standard views according to the guidelines of the American Society of Echocardiography [12]. The images were stored digitally and analyzed offline.

From the left ventricular parasternal long-axis view, we measured the left ventricular chamber dimension (LVD), left atrial chamber dimension, septum thickness (IVST), and left ventricular posterior wall thickness (LVPWT) at left ventricular end diastole. Left ventricular mass (LVM) was determined by the formula: $LVM = 0.8 \times 1.04[(LVD + IVST + LVPWT)^3 - LVD^3] + 0.6$, and LVM index (LVMI) (g/m^2) was determined by being normalized according to body surface area.

Pulsed-wave Doppler-derived transmitral inflow velocities were obtained by placing the sample volume between the tips of the mitral leaflets in the apical four-chamber view. Early diastolic (E) and late atrial (A) transmitral flow velocities were measured, and the E/A ratio was calculated.

From the apical four-chamber view, myocardial early (e') diastolic velocity was obtained by pulsed-tissue Doppler, with the sample volume placed at the lateral mitral annulus. The E/e' ratio was calculated as an index of the left ventricular filling pressure.

2.4. Assessment of left atrial phasic function using two-dimensional speckle tracking and volumetric parameters

Standard two-dimensional grayscale images of apical four- and two-chamber views were obtained. Left atrial volume was measured with the biplane modified Simpson's rule. Maximum left atrial volume (LAV) was measured immediately before mitral valve opening. The left atrial volume index (LAVI) was the LAV indexed according to body surface area. For the two-dimensional speckle tracking echocardiography (2DSTE)-derived strain and strain rate analyses, three successive heart cycles were recorded digitally for offline analysis with EchoPAC software (Vivid 7, GE). The specific methods and detailed parameters are described elsewhere [13].

2.5. Statistical analysis

All statistical analyses were performed with SPSS software, version 19.0 (SPSS Inc., Chicago, IL). All continuous variables were expressed as mean ± standard deviation. Differences between two groups were evaluated with the independent samples *t* test. Categorical variables were expressed as frequencies and then analyzed with a chi-square test or Fisher's exact test if appropriate. The correlation between two PAC and clinical or echocardiographic parameters was assessed with Pearson or Spearman coefficients based on the distribution of the data. Multivariate stepwise regression was used to assess the independent factors for PAC, and parameters with a *P* value of <0.05 in correlation analyses were entered into multivariate regression. Statistical significance was set at $P < 0.05$.

Table 1
Clinical and Echocardiographic characteristics of the study population.

	Group I (n = 75)	Group II (n = 73)	*P*
Male (%)	53.33	47.95	0.512
Age (years)	49 ± 12	51 ± 12	0.999
BMI (kg/m^2)	26.0 ± 3.0	26.6 ± 3.6	0.453
SBP (mmHg)	150.0 ± 19.6	159.4 ± 23.4	0.499
DBP (mmHg)	90.5 ± 13.1	92.4 ± 16.5	0.908
DM (%)	38.67	42.47	0.638
Ang I (ng/mL/h)	1.37 ± 1.51	2.36 ± 1.78	0.034
Ang II (pg/mL)	29.57 ± 8.32	37.45 ± 13.03	0.022
BNP (pg/mL)	32.62 ± 25.23 (n = 68)	43.87 ± 44.16 (n = 68)	0.001
LAVI (mL/m2)	24.81 ± 6.45	28.26 ± 7.73	0.187
LVEF (%)	64.57 ± 6.41	63.95 ± 6.25	0.049
LVMI (g/m2)	89.59 ± 21.70	103.03 ± 24.51	0.360
E/A ratio	1.03 ± 0.31	0.90 ± 0.24	0.005
E/e' ratio	7.08 ± 1.84	8.27 ± 3.05	0.008
LATEF (%)	65.05 ± 6.98	61.71 ± 9.13	0.179
LAPEF (%)	36.39 ± 8.68	32.74 ± 10.78	0.159
LAAEF (%)	52.44 ± 8.89	50.12 ± 10.78	0.094

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; Ang I, angiotensin I; Ang II, angiotensin II; Ald, aldosterone; LAVI, the maximum left atrial volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LATEF, left atrial total emptying fraction; LAPEF, left atrial passive emptying fraction; LAAEF, left atrial active emptying fraction.

3. Results

3.1. Clinical characteristics of the study population

Table 1 shows the clinical and echocardiographic characteristics of the study patients. The plasma concentration of Ang II, the plasma Ang I generation rate, and brain natriuretic peptide (BNP) level were significantly increased in group II compared with group I ($P < 0.05$). No significant difference was found in patient sex, age, body mass index (BMI), systolic blood pressure (SBP) or diastolic blood pressure (DBP), or morbidity because of diabetes mellitus (DM) between the two groups ($P > 0.05$).

3.2. Traditional echocardiographic parameters

Compared with group I, the E/e'ratio was significantly higher in group II ($P < 0.05$), and the LVEF and E/A ratio were significantly lower in group II ($P < 0.05$). The LAVI and LVMI were not significantly different between the two groups ($P > 0.05$). Among left atrial volumetric parameters, left atrial total emptying fraction (LATEF), left atrial passive emptying fraction (LAPEF), and left atrial active emptying fraction (LAAEF) were not significantly different between the two groups ($P > 0.05$) (Table 1).

Table 2
Left atrial measurements with two-dimensional speckle-tracking echocardiography.

Variable	Group I (n = 67)	Group II (n = 69)	*P*
LA_{S-S} (%)	31.25 ± 7.71	24.60 ± 6.48	0.660
LA_{S-E} (%)	19.92 ± 4.71	10.66 ± 3.68	0.008
LA_{S-A} (%)	14.78 ± 4.00	13.77 ± 3.83	0.775
LA_{SR-S} (s^{-1})	1.38 ± 0.34	1.10 ± 0.26	0.027
LA_{SR-E} (s^{-1})	−1.37 ± 0.39	−0.84 ± 0.30	0.019
LA_{SR-A} (s^{-1})	−1.56 ± 0.42	−1.32 ± 0.47	0.297

LA_{S-S}, peak left atrial longitudinal strain; LA_{S-E}, left atrial longitudinal strain during early diastole; LA_{S-A}, left atrial longitudinal strain during late diastole; LA_{SR-S}, left atrial longitudinal strain rate during ventricular systole; LA_{SR-E}, left atrial longitudinal strain rate during early diastole; LA_{SR-A}, left atrial longitudinal strain rate during late diastole.

Table 3
Relationships between plasma aldosterone concentration and echocardiographic and clinical parameters.

Variable	PAC (ng/dL)		Variables	PAC (ng/dL)	
	r	*P*		r	*P*
Age (y)	0.040	0.628	LATEF (%)	−0.102	0.215
DM (%)	0.038	0.651	LAPEF (%)	−0.191	0.020
SBP (mmHg)	0.223	0.006	LAAEF (%)	−0.029	0.725
DBP (mmHg)	0.139	0.092	LA_{S-S} (%)	−0.412	<0.001
BMI (kg/m^2)	0.115	0.165	LA_{S-E} (%)	−0.636	<0.001
LVMI (g/m^2)	0.296	<0.001	LA_{S-A} (%)	−0.052	0.548
LAVI (mL/m^2)	0.233	0.004	LA_{SR-S} (s^{-1})	−0.298	<0.001
LVEF (%)	−0.108	0.192	LA_{SR-E} (s^{-1})	0.502	<0.001
E/A ratio	−0.215	0.009	LA_{SR-A} (s^{-1})	0.132	0.126
E/e' ratio	0.168	0.041			
Ang I (ng/mL/h)	0.325	<0.001			
Ang II (pg/mL)	0.344	<0.001			
BNP (pg/mL)	0.045	0.603			

DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; LVMI, left ventricular mass index; LAVI, the maximum left atrial volume index; LVEF, left ventricular ejection fraction; Ang I, angiotensin I; Ang II, angiotensin II; LATEF, left atrial total emptying fraction; LAPEF, left atrial passive emptying fraction; LAAEF, left atrial active emptying fraction; LA_{S-S}, peak left atrial longitudinal strain; LA_{S-E}, left atrial longitudinal strain during early diastole; LA_{S-A}, left atrial longitudinal strain during late diastole; LA_{SR-S}, left atrial longitudinal strain rate during ventricular systole; LA_{SR-E}, left atrial longitudinal strain rate during early diastole; LA_{SR-A}, left atrial longitudinal strain rate during late diastole.

3.3. Left atrial strain and strain rate

In the overall study population (148 subjects), 12 subjects (8 in group I and 4 in group II) had no strain or strain rate parameters measured because these images were not clear enough to allow tracking for more than three left atrial segments.

LA_{S-E} was lower in group II compared with group I (10.66 ± 3.68% vs. 19.92 ± 4.71%) ($P < 0.05$). LA_{S-S} and LA_{S-A} did not differ significantly between the two groups ($P > 0.05$ for both). LA_{SR-S} and LA_{SR-E} were lower in group II (1.10 ± 0.26 s^{-1} and −0.84 ± 0.30 s^{-1}, respectively) than in group I (1.38 ± 0.34 s^{-1} and −1.37 ± 0.39 s^{-1}, respectively) ($P < 0.05$ for both). The LA_{SR-A} did not differ significantly between the two groups ($P > 0.05$) (Table 2).

3.4. Regression analysis

We evaluated the relationship between PAC and clinical characteristics as well as echocardiographic parameters in hypertension. Systolic blood pressure (SBP) (r = 0.223, $P = 0.006$), LVMI (r = 0.296, $P < 0.001$), LAVI (r = 0.233, $P = 0.004$), E/e' ratio (r = 0.168, $P = 0.041$), Ang I (r = 0.325, $P < 0.001$), Ang II (r = 0.344, $P < 0.001$), and LA_{SR-E} (r = 0.502, $P < 0.001$) correlated positively with PAC. The E/A ratio (r = −0.215, $P = 0.009$), LAPEF (r = −0.191, $P = 0.020$), LA_{S-S} (r = −0.412, $P < 0.001$), LA_{S-E} (r = −0.636, $P < 0.001$), and LA_{SR-S} (r = −0.298, $P < 0.001$) correlated negatively with PAC (Table 3). Further, multivariate regression analysis showed that LA_{S-E}, the plasma Ang I generation rate, and plasma Ang II concentration were independent factors related to PAC (Figure 1).

4. Discussion

The current study showed that left atrial conduit function, evaluated by 2DSTE-based strain and strain rate, decreased in higher PAC group in hypertension. PAC was related to SBP, LVMI, E/A ratio, E/e' ratio, Ang I, Ang II, and left atrial structural and functional remodeling (LAVI, LAPEF, LA_{S-S}, LA_{S-E}, LA_{SR-S}, LA_{SR-E}). Further, the plasma Ang I generation rate, plasma Ang II concentration, and LA_{S-E} were independently related to PAC.

Recently, several studies suggested a crucial role of aldosterone in LV remodeling of hypertension. Many clinical studies of essential hypertension have reported that plasma aldosterone is related to LV mass [1–4, 14]. Aldosterone has been reported to affect the increase in LV mass and deposition of myocardial collagen in patients with hypertension [15,16]. Clinical trials and animal experiments have confirmed that the contribution of aldosterone to LV remodeling is independent of its effect on blood pressure [17–19]. Further, patients with primary aldosteronism have greater LV mass and more myocardial collagen deposition than patients with essential hypertension, when matched for age, duration of hypertension, and blood pressure [18,20]. This study found that PAC is related not only to LV geometric remodeling (LVMI) but also to LV diastolic function (E/A ratio and E/e' ratio).

Aldosterone is also responsible for the electrical and structural remodeling of the atria [21,22]. Aldosterone can stimulate signaling pathway and trigger oxidative stress, inflammatory response, and necrosis of atrial myocytes [18,23,24]. Moreover, Tsai et al. [25] found that expression of the atrial MR in patients with atrial fibrillation increased significantly compared with patients with sinus rhythm, so the role of aldosterone in atrial remodeling may include increasing the expression of atrial MR. MR activation by excess of aldosterone leads to either genomic or nongenomic complex mechanisms of action [26], which regulates pro-inflammatory and pro-hypertrophic genes in the heart and contributes to cardiac hypertrophy and fibrosis [27–29]. Left atrial conduit function is mainly influenced by left atrial and ventricular compliance, both commonly reduced in presence of extensive myocardial fibrosis.

The left atrial myocardial fibers show a different arrangement in the subendocardial and subepicardial layers. The subendocardial layer is mainly composed of longitudinal fibers, and the subepicardial layer is composed of circumferential fibers [13,30]. Both 2DSTE-based strain and strain rate are reliable, angle-independent methods to evaluate left atrial longitudinal myocardial deformation and left atrial function. The current study showed that LA_{S-E}, which indicates left atrial conduit function, is an independent factor of PAC. Left atrial function assessed by 2DSTE, especially for an atrial conduit, may become a useful parameter to predict atrial fibrillation. This association should be further explored, and the role of aldosterone receptor antagonists in blocking atrial remodeling and preventing atrial fibrillation should be determined.

4.1. Clinical implications

As an important factor of RAAS, aldosterone is associated with both chronic heart failure and atrial fibrillation. Aldesterone can lead to cardiomyocyte apoptosis [31,32], myocardial fibrosis [28,29] and participate in ventricular and atrial remodeling [33,34]. The aldosterone

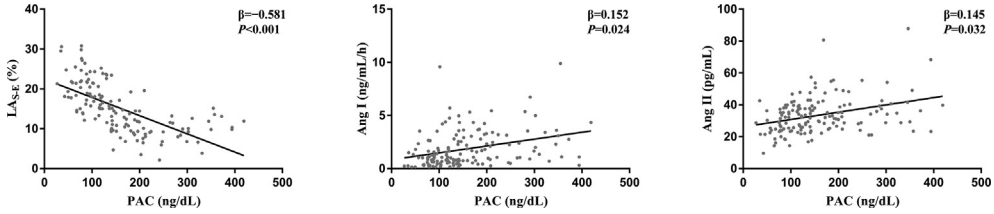

Figure 1. PAC was negatively correlated with LA_{S-E} and positively correlated with Ang I and Ang II. PAC, plasma aldosterone concentration; LA_{S-E}, left atrial longitudinal strain during early diastole; Ang I, angiotensin I; Ang II, angiotensin II.

receptor antagonist has been proven to play a crucial role in cardioprotection in patients with systolic heart failure, and it is a component of guideline-directed management and therapy for systolic heart failure [35]. PAC is a promising evaluative indicator for left atrial remodeling in hypertension. The aldosterone receptor antagonist also has potential use in relieving atrial remodeling and preventing atrial fibrillation.

5. Conclusion

Plasma aldosterone concentration is associated with left atrial structural and functional remodeling, particularly with left atrial conduit function, in patients with hypertension.

Funding

This study was supported by the National Natural Science Foundation of China (grant no. 81500304).

Conflicts of interest

None.

References

[1] T. Nakahara, Y. Takata, Y. Hirayama, K. Asano, H. Adachi, G. Shiokawa, et al., Left ventricular hypertrophy and geometry in untreated essential hypertension is associated with blood levels of aldosterone and procollagen type III amino-terminal peptide, Circ. J. 71 (2007) 716–721.
[2] R.S. Velagaleti, P. Gona, D. Levy, J. Aragam, M.G. Larson, G.H. Tofler, et al., Relations of biomarkers representing distinct biological pathways to left ventricular geometry, Circulation 118 (2008) 2252–2258.
[3] A.D. Stewart, S.C. Millasseau, M. Dawes, P.A. Kyd, J.B. Chambers, J.M. Ritter, et al., Aldosterone and left ventricular hypertrophy in Afro-Caribbean subjects with low renin hypertension, Am. J. Hypertens. 19 (2006) 19–24.
[4] G. Mule, E. Nardi, P. Cusimano, S. Cottone, G. Seddio, C. Geraci, et al., Plasma aldosterone and its relationships with left ventricular mass in essential hypertensive patients with the metabolic syndrome, Am. J. Hypertens. 21 (2008) 1055–1061.
[5] P. Lacolley, C. Labat, A. Pujol, C. Delcayre, A. Benetos, M. Safar, Increased carotid wall elastic modulus and fibronectin in aldosterone-salt-treated rats: effects of eplerenone, Circulation 106 (2002) 2848–2853.
[6] J.A. Nehme, P. Lacolley, C. Labat, P. Challande, E. Robidel, C. Perret, et al., Spironolactone improves carotid artery fibrosis and distensibility in rat post-ischaemic heart failure, J. Mol. Cell. Cardiol. 39 (2005) 511–519.
[7] M.J. Young, A.J. Rickard, Mineralocorticoid receptors in the heart: lessons from cell-selective transgenic animals, J. Endocrinol. 224 (2015) R1–R13.
[8] J. Bauersachs, F. Jaisser, R. Toto, Mineralocorticoid receptor activation and mineralocorticoid receptor antagonist treatment in cardiac and renal diseases, Hypertension 65 (2015) 257–263.
[9] A. McCurley, P.W. Pires, S.B. Bender, M. Aronovitz, M.J. Zhao, D. Metzger, et al., Direct regulation of blood pressure by smooth muscle cell mineralocorticoid receptors, Nat. Med. 18 (2012) 1429–1433.
[10] D. Fraccarollo, S. Berger, P. Galuppo, S. Kneitz, L. Hein, G. Schutz, et al., Deletion of cardiomyocyte mineralocorticoid receptor ameliorates adverse remodeling after myocardial infarction, Circulation 123 (2011) 400–408.
[11] L.A. Bienvenu, J. Morgan, A.J. Rickard, G.H. Tesch, G.A. Cranston, E.K. Fletcher, et al., Macrophage mineralocorticoid receptor signaling plays a key role in aldosterone-independent cardiac fibrosis, Endocrinology 153 (2012) 3416–3425.
[12] R.M. Lang, M. Bierig, R.B. Devereux, F.A. Flachskampf, E. Foster, P.A. Pellikka, et al., Recommendations for chamber quantification: a report from the American society of echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the european association of echocardiography, a branch of the european society of cardiology, J. Am. Soc. Echocardiogr. 18 (2005) 1440–1463.
[13] Y. Liu, K. Wang, D. Su, T. Cong, Y. Cheng, Y. Zhang, et al., Noninvasive assessment of left atrial phasic function in patients with hypertension and diabetes using two-dimensional speckle tracking and volumetric parameters, Echocardiography 31 (2014) 727–735.
[14] C. Yoshida, A. Goda, Y. Naito, A. Nakaboh, M. Matsumoto, M. Otsuka, et al., Role of plasma aldosterone concentration in regression of left-ventricular mass following antihypertensive medication, J. Hypertens. 29 (2011) 357–363.
[15] G.P. Rossi, V. Di Bello, C. Ganzaroli, A. Sacchetto, M. Cesari, A. Bertini, et al., Excess aldosterone is associated with alterations of myocardial texture in primary aldosteronism, Hypertension 40 (2002) 23–27.
[16] M. Kozakova, S. Buralli, C. Palombo, G. Bernini, A. Moretti, S. Favilla, et al., Myocardial ultrasonic backscatter in hypertension: relation to aldosterone and endothelin, Hypertension 41 (2003) 230–236.
[17] C.S. Hung, C.H. Chou, X.M. Wu, Y.Y. Chang, V.C. Wu, Y.H. Chen, et al., Circulating tissue inhibitor of matrix metalloproteinase-1 is associated with aldosterone-induced diastolic dysfunction, J. Hypertens. 33 (2015) 1922–1930.
[18] B.M. Schmidt, R.E. Schmieder, Aldosterone-induced cardiac damage: focus on blood pressure independent effects, Am. J. Hypertens. 16 (2003) 80–86.
[19] C. Adolf, A. Kohler, A. Franke, K. Lang, A. Riester, A. Low, et al., Cortisol excess in patients with primary aldosteronism impacts on left ventricular hypertrophy, J. Clin. Endocrinol. Metab. 103 (12) (2018 Dec 1) 4543–4552.
[20] G.P. Rossi, A. Sacchetto, E. Pavan, P. Palatini, G.R. Graniero, C. Canali, et al., Remodeling of the left ventricle in primary aldosteronism due to Conn's adenoma, Circulation 95 (1997) 1471–1478.
[21] H. Nakashima, K. Kumagai, H. Urata, N. Gondo, M. Ideishi, K. Arakawa, Angiotensin II antagonist prevents electrical remodeling in atrial fibrillation, Circulation 101 (2000) 2612–2617.
[22] A. Goette, T. Staack, C. Rocken, M. Arndt, J.C. Geller, C. Huth, et al., Increased expression of extracellular signal-regulated kinase and angiotensin-converting enzyme in human atria during atrial fibrillation, J. Am. Coll. Cardiol. 35 (2000) 1669–1677.
[23] A.D. Struthers, Aldosterone: cardiovascular assault, Am. Heart J. 144 (2002) S2–S7.
[24] B.J. He, M.L. Joiner, M.V. Singh, E.D. Luczak, P.D. Swaminathan, O.M. Koval, et al., Oxidation of CaMKII determines the cardiotoxic effects of aldosterone, Nat. Med. 17 (2011) 1610–1618.
[25] C.T. Tsai, F.T. Chiang, C.D. Tseng, J.J. Hwang, K.T. Kuo, C.K. Wu, et al., Increased expression of mineralocorticoid receptor in human atrial fibrillation and a cellular model of atrial fibrillation, J. Am. Coll. Cardiol. 55 (2010) 758–770.
[26] B.J. He, M.E. Anderson, Aldosterone and cardiovascular disease: the heart of the matter, Trends Endocrinol. Metabol. 24 (2013) 21–30.
[27] N. Tsybouleva, L. Zhang, S. Chen, R. Patel, S. Lutucuta, S. Nemoto, et al., Aldosterone, through novel signaling proteins, is a fundamental molecular bridge between the genetic defect and the cardiac phenotype of hypertrophic cardiomyopathy, Circulation 109 (2004) 1284–1291.
[28] E. Gomez-Sanchez, C.E. Gomez-Sanchez, The multifaceted mineralocorticoid receptor, Comp. Physiol. 4 (2014) 965–994.
[29] E.E. Essick, F. Sam, Cardiac hypertrophy and fibrosis in the metabolic syndrome: a role for aldosterone and the mineralocorticoid receptor, Int. J. Hypertens. 2011 (2011), 346985.
[30] S.Y. Ho, D. Sanchez-Quintana, J.A. Cabrera, R.H. Anderson, Anatomy of the left atrium: implications for radiofrequency ablation of atrial fibrillation, J. Cardiovasc. Electrophysiol. 10 (1999) 1525–1533.
[31] J.G. Burniston, A. Saini, L.B. Tan, D.F. Goldspink, Aldosterone induces myocyte apoptosis in the heart and skeletal muscles of rats in vivo, J. Mol. Cell. Cardiol. 39 (2005) 395–399.
[32] T. Xiao, Y. Zhang, Y. Wang, Y. Xu, Z. Yu, X. Shen, Activation of an apoptotic signal transduction pathway involved in the upregulation of calpain and apoptosis-inducing factor in aldosterone-induced primary cultured cardiomyocytes, Food Chem. Toxicol. 53 (2013) 364–370.
[33] C. Catena, G. Colussi, G. Brosolo, M. Novello, L.A. Sechi, Aldosterone and left ventricular remodeling, Horm. Metab. Res. 47 (2015) 981–986.
[34] J.E. Udelson, A.M. Feldman, B. Greenberg, B. Pitt, R. Mukherjee, H.A. Solomon, et al., Randomized, double-blind, multicenter, placebo-controlled study evaluating the effect of aldosterone antagonism with eplerenone on ventricular remodeling in patients with mild-to-moderate heart failure and left ventricular systolic dysfunction, Circ Heart Fail 3 (2010) 347–353.
[35] C.W. Yancy, M. Jessup, B. Bozkurt, J. Butler, D.E. Casey Jr., M.M. Colvin, et al., Acc/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American college of cardiology/American heart association task force on clinical practice guidelines and the heart failure society of America, J. Am. Coll. Cardiol. 70 (2017) 776–803.