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ENDOCRINE SURGERY

Larger ascending aorta in primary aldosteronism: a 3-year prospective evaluation of adrenalectomy vs. medical treatment

Guido Zavatta[1] · Guido Di Dalmazi[1] · Carmine Pizzi[2] · Giovanni Bracchetti[2] · Cristina Mosconi[3] · Caterina Balacchi[3] · Uberto Pagotto[1] · Valentina Vicennati[1]

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Abstract

Objective Primary aldosteronism is associated with higher cardiovascular morbidity as compared with essential hypertension. Vascular complications encompass myocardial infarction and cerebrovascular events. Aortic damage in primary aldosteronism has never been explored, although a few cases of ascending aorta aneurisms have been reported.

Design and methods We consecutively enrolled patients affected by primary aldosteronism ($n = 45$) and compared them with patients affected by essential hypertension ($n = 47$), on an outpatient setting. Echocardiographic data of patients with primary aldosteronism were collected during a mean follow-up of 3 years, in subjects who underwent adrenal surgery ($n = 12$) and those on mineralocorticoid receptor antagonists ($n = 33$).

Results and conclusion We found that patients with primary aldosteronism had larger ascending aorta diameters than those with essential hypertension before starting any specific treatment. Patients with primary aldosteronism did not show significant changes in the size of ascending aorta during a mean of 3 years of follow-up, irrespective of the type of treatment (medical vs. surgical treatment). A longer follow-up will better clarify if worsening of the aortic damage may be better prevented by surgery rather than by mineralocorticoid receptor antagonists.

Keywords Primary aldosteronism · Ascending aorta · Aortic root · Aortic aneurysm · Aldosterone · Adrenal cortex

Abbreviations

PA	primary aldosteronism
C	hypertensive control patients with nonsecreting adrenal adenoma
BSA	body-surface-area (m^2)
TTE	transthoracic echocardiogram
CT	computed tomography
CCT	captopril-challenge test
ARR	aldosterone-to-renin-ratio
MR	mineralocorticoid receptor
BP	blood pressure
TA	tubular ascending
EH	essential hypertension
LVH	left ventricular hypertrophy

✉ Valentina Vicennati
vicennati@aosp.bo.it

1 Endocrinology Unit, Department of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, Alma Mater Studiorum-University of Bologna, Via Massarenti 9, 40138 Bologna, Italy

2 Institute of Cardiology, S. Orsola-Malpighi Hospital, Via Massarenti 9, 40138 Bologna, Italy

3 Division of Radiology, S. Orsola-Malpighi Hospital, Via Massarenti 9, 40138 Bologna, Italy

Introduction

Primary aldosteronism (PA) is the most frequent cause of endocrine secondary hypertension [1]. Its exact prevalence among hypertensive patients is still on debate, ranging from 5 to 13%, depending on the selected populations [2]. PA has been associated with increased cardiovascular morbidity, as compared with essential hypertension (EH), and higher incidence of left ventricular hypertrophy, atrial fibrillation, myocardial infarction, and cerebrovascular events [3–6]. Also, renal impairment and microalbuminuria have been shown to be more prevalent in patients with PA [7, 8]. The only available retrospective study on mortality in PA published by Reincke et al. [9] in 2012 analyzed the data of the German Conn registry showing an increased cardiovascular mortality among patients affected by PA, as compared with EH controls, with no difference in the overall mortality.

Several studies [10, 11], including the RALES [12] and EPHESUS [13] trials, have focused on the impact of the mineralocorticoid receptor (MR) on myocardium and concluded for a beneficial effect of MR antagonism in terms of cardiac remodeling and cardiovascular mortality. Moreover, several studies have shown that aldosterone induces vascular oxidative stress, inflammation, and fibrosis, resulting in vascular remodeling [14–16] and endothelial damage [17] in the presence of a salt-rich diet.

MR-mediated effects on the aorta have been studied in animal models. Aldosterone has been shown to induce aortic vascular muscle cell apoptosis in a rat PA model, independently of the presence of high blood pressure [18]. In male rats, aorta damage brought about by aldosterone excess seems to be induced via MR, whose activation, in association with high-salt intake, seems to be a key factor in determining the enlargement of the aorta and its rupture [19]. These findings suggest a crucial role for MR antagonists in preventing aldosterone-mediated detrimental effects on the aorta. Likewise, that implies the relative inefficacy of the renin–angiotensin–aldosterone system blockers (angiotensin-converting enzyme inhibitors and angiotensin II receptor type 1 (AT1) blockers) to prevent aortic damage in the presence of autonomous aldosterone hypersecretion. However, the clinical impact of hyperaldosteronism on large vessels remodeling, like thoracic and abdominal aorta, has been poorly investigated up to now and no studies are available about the prevalence of aortic dilatation in PA in humans. Only a few cases of aortic dissection or aortic aneurysm ruptures in patients with PA have been described in previous case reports [20–23].

The evaluation of the ascending aorta can be performed by transthoracic echocardiographic examination [25]. Notably, ascending aorta dimension is highly dependent on age, sex, and body size measurements [26, 27]. The effect of blood pressure on aortic root dimensions appears to be small, with direct associations with diastolic and mean blood pressures and inverse associations with systolic and pulse pressures [25]. Studies performed so far have shown the lack of an independent association between BP and thoracic aortic diameter, and a minor impact of hypertension on proximal thoracic aortic dimensions, when models are adjusted for age and body surface area [27]. Additionally, treatment of hypertension did not show an impact on the natural history of thoracic aortic dilatation, while having a major impact on abdominal aortic dilatation [28].

The prevalence of ascending aorta dilatation/aneurisms increase with age. Aortic enlargement is usually asymptomatic and without abnormalities on physical examination; thus, diagnosis and follow-up depend exclusively on imaging techniques. The risk of aneurism rupture or dissection increases with the size of the aorta as well as depending on intrinsic vessel-properties. A year risk of dissection of 2.2% has been reported for thoracic aortic diameter higher than 35 mm [29].

On the basis of the available data regarding the relationship between aldosterone excess and vascular damage, the present study aims to investigate the ascending aorta diameter in patients with PA as compared with hypertensive controls (C), and to analyze the effect of surgical and pharmacological treatment of PA on the ascending aorta during follow-up.

Subjects and methods

The study was approved by the Independent Ethics Committee of the University Hospital of Bologna S.Orsola-Malpighi. Consent has been obtained from each patient after full explanation of the purpose and nature of all procedures used.

Patients

A total of 45 consecutive patients (24 males and 21 females) attending the Endocrinology Unit of the S. Orsola-Malpighi University Hospital of Bologna, diagnosed with PA were included in the study. The diagnosis of PA had been made according to the current guidelines [30], on the basis of: (i) clinical evaluation; (ii) morphological evaluation of the adrenals by contrast enhanced computed tomography (CT), (iii) biochemical assessment, including electrolyte balance, as well as aldosterone, plasma renin activity and aldosterone-to-plasma renin activity ratio after upright position for 2 h (2 hARR); (iv) the captopril challenge test (CCT). The cut-off ratio for definition of positive 2 hARR and CCT was 30 (ng/dL)/(ng/mL/h). All hormonal tests were performed after the discontinuation of interfering drugs (alpha-blockers or nondihydropyridine calcium channel blockers were the only allowed drugs) and appropriate nutritional counseling for four weeks, as recommended by the current guidelines [30]. Overnight 1-mg dexamethasone suppression test was also performed, as recommended [31, 32]. Cortisol values below 1.8 µg/dL were considered normal. Diagnosis of pheochromocytoma had been ruled out on the basis of clinical assessment, radiological evaluation, and assay of metanephrines on an acidified 24-h urine sample. Patients had also been instructed to abstain from cathecolamine-interfering food or drugs for at least 2 weeks prior to urine collection. Patients with known aortic bicuspid valve or connective tissue disorders, such as Marfan syndrome, were excluded.

Control subjects

Fourty-seven consecutive hypertensive patients (22 males and 25 females) with a benign incidentally discovered adrenal tumor without PA were selected as a control group

(C). The inclusion criteria for control hypertensive patients was the treatment with at least one antihypertensive drug. The determination of the levels of aldosterone and plasma renin activity after upright position for 2 h was made as described above. Patients with hypercortisolism or pheochromocytoma, evaluated by appropriate tests, as reported above [32, 33], known aortic bicuspid valve or connective tissue disorders were excluded.

Study protocol

Anthropometric parameters such as height and body weight were registered. Patients were asked to recall when treatment for hypertension had been initiated and smoking status was recorded. Body surface area was calculated from the formula of DuBois and DuBois: BSA = (weight (kg)$^{0.425}$ × Height (cm)$^{0.725}$) × 0.007184. All subjects underwent echocardiographic assessment performed by two expert cardiologists of the Institute of Cardiology of the S. Orsola-Malpighi Hospital of Bologna. The cardiologists were blinded to the patients' group. The presence of left ventricular hypertrophy (LVH) was reported and diagnosed according to current guidelines [24]. Dimensions of the ascending aorta was investigated by measuring the aortic root and/or tubular ascending aorta, assessed on M-mode images in the para-sternal long-axis view at end-diastole from leading edge to leading edge [25].

Twelve PA patients underwent adrenalectomy due to unilateral disease, whereas the other 33 patients started treatment with aldosterone antagonists (canrenone). We defined unilateral disease in PA on the basis of contrast enhanced CT images showing a single unilateral adrenal adenoma. The histopathological examination confirmed the presence of an adrenal adenoma in all of the patients. The mean dose of aldosterone antagonist was 61.5 ± 31.4 mg die (range: 12.5–100 mg). Echocardiographic parameters were reassessed in patients with PA after a median time period of 1.5 (1–7) years in the surgical group and 3.5 (1–15) years in the medical group. Data were retrospectively analyzed.

Statistical analysis

The results are expressed as means ± SD or frequencies. Data were compared between groups by using the χ^2 tests and Student *t* test, where appropriate. The two-way analysis of covariance (ANCOVA) was applied to compare the aortic diameters between PA and C, by considering the following factors potentially implicated in aortic enlargement as covariates: age, sex, BSA, subclinical hypercortisolism, duration of hypertension, and the number of classes of antihypertensive agents. Baseline and follow-up data within PA group were compared by using paired *t* test.

Table 1 Clinical, biochemical, and echocardiographic characteristics of PA and C groups at baseline

	PA (*n* = 45)	C (*n* = 47)	*P* value
Age (y)	53.7 ± 10.6	59.6 ± 14.3	0.028
Sex (M/F)	24/21	22/25	0.338
BSA (m^2)	1.89 ± 0.23	1.86 ± 0.21	0.490
Duration of hypertension (y)	12.1 ± 12.6	8.1 ± 8.3	0.073
Antihypertensive drugs (*n*)	2.4 ± 1.2	1.5 ± 0.8	0.001
Former/current smokers (no./total no., %)	14/42, 33%	17/44, 38%	0.387
Aortic root diameter (mm)	35.1 ± 4.6	32.2 ± 3.6	0.020[a]
TA aorta diameter (mm)	36.1 ± 3.7	33.4 ± 5.1	0.021[b]
LVH (%)	53%	43%	0.204
Sodium (mmol/L)	142.6 ± 2.4	142.0 ± 2.9	0.274
Potassium (mmol/L)	3.73 ± 0.66	4.28 ± 0.34	<0.001
Creatinine (mg/dl)	0.94 ± 0.21	0.95 ± 0.50	0.197
1 mg-DST cortisol (nmol/L)	41.9 ± 22.6	32.1 ± 8.3	0.024
ACTH (pg/ml)	16 ± 6	19 ± 4	0.264
Cortisol (ng/ml)	132 ± 56	136 ± 43	0.738
Aldosterone (pg/ml)	367 ± 247	211 ± 108	0.001
PRA (ng/ml/h)	0.43 ± 0.77	1.42 ± 1.19	<0.001

BSA body surface area, *TA* tubular ascending, *ACTH*adrenocorticotrophic hormone, *PRA*plasma renin activity, *1mg-DST* 8.00 a.m. cortisol after the administration of oral 1 mg desametasone at 11.00 p.m. of the day before, *LVH* left ventricular hypertrophy.

[a]Univariate analysis adjusted for age ($P = 0.098$), sex ($P = 0.065$), BSA ($P = 0.001$), subclinical hypercortisolism ($P = 0.211$), duration of hypertension ($P = 0.879$), and number of antihypertensive classes ($P = 0.466$).

[b]Univariate analysis adjusted for age ($P = 0.025$), sex ($P = 0.355$), BSA ($P = 0.001$), subclinical hypercortisolism ($P = 0.090$), duration of hypertension ($P = 0.191$), and number of antihypertensive classes ($P = 0.753$).

Statistical analyses were performed by using the IBM-SPSS statistical package (version 23; IBM, Armonk, NY, USA). Two-tailed *P* values less than 0.05 were considered significant.

Results

The baseline clinical data of PA and C are shown in Table 1. Age was different between groups ($P = 0.028$). Male-to-female ratio and prevalence of smokers did not differ between the two groups. Duration of hypertension was slightly longer in patients with PA, although not statistically significant ($P = 0.073$). The number of drugs used to control hypertension was significantly higher in patients with hyperaldosteronism ($P = 0.001$). Among 22 PA patients tested with 1-mg-dexamethasone suppression test, 10 showed cortisol values >1.8 µg/dL. As expected,

Table 2 Comparison between the aortic root and tubular ascending aorta in PA group at baseline and during follow-up

	All PA ($n=45$)			Surgical group ($n=12$)			Medical group ($n=33$)		
	Baseline	Follow-up (3 y)	P value	Baseline	Follow-up (1.5 y)	P value	Baseline	Follow-up (3.5 y)	P value
Aortic root diameter (mm)	35.1 ± 4.6	34.4 ± 4.3	0.286	35.2 ± 5.0*	33.9 ± 4.2°	0.373	35.2 ± 4.6*	34.8 ± 4.3°	0.579
TA aorta diameter (mm)	36.1 ± 3.7	36.0 ± 3.2	0.383	35.9 ± 3.0*	34.3 ± 3.4°	0.334	37.0 ± 3.4*	36.9 ± 4.3°	0.938
LVH (%)	53%	51%	0.660	50%*	42%°	0.339	55%*	55%°	1.000
BSA (m^2)	1.89 ± 0.23	1.88 ± 0.23	0.535	1.85 ± 0.19*	1.84 ± 0.19°	0.764	1.91 ± 0.25*	1.90 ± 0.25°	0.585
Antihypertensive drugs (n)	2.4 ± 1.2	2.1 ± 1.4	0.096	2.6 ± 1.2*	1.8 ± 1.7°	0.034	2.4 ± 1.2*	2.3 ± 1.3°	0.514

BSA body surface area, *LVH* left ventricular hypertrophy.

*$P > 0.05$, between surgical and medical group at baseline. °$P > 0.05$, between surgical and medical group at follow-up.

aldosterone and plasma renin activity levels, as well as serum potassium were different between the two groups.

Baseline echocardiographic characteristics are shown in Table 1. Aortic root and tubular ascending aorta were higher in PA than C ($P = 0.020$ and $P = 0.021$, respectively). The frequency of LVH was not statistically different between PA and C (53% vs. 43%, respectively; $P = 0.204$). As to the aortic root diameter, body surface area was a significant covariate at univariate analysis ($P = 0.001$). Age ($P = 0.098$), sex ($P = 0.065$), subclinical hypercortisolism ($P = 0.211$), duration of hypertension ($P = 0.879$), and the number of antihypertensive drugs ($P = 0.466$), were not determinants of the aortic root at univariate analysis. Regarding tubular ascending aorta, both age ($P = 0.025$) and body surface area ($P = 0.001$) were the two significant covariates at univariate analysis, while sex ($P = 0.355$), subclinical hypercortisolism ($P = 0.090$), duration of hypertension ($P = 0.191$), and the number of antihypertensive classes ($P = 0.753$) were not. Aldosterone, plasma renin activity, and ARR at the time of diagnosis were not determinants of either diameters, on a linear regression analysis.

As shown in Table 2, baseline values of both aortic diameters in PA under medical treatment and surgical treatment undergoing follow-up were not different ($P = 0.992$ and $P = 0.873$, respectively). Follow-up values were similar as well ($P = 0.447$ and $P = 0.717$, respectively). The aortic root and tubular ascending aorta diameters did not show any variations at follow-up either after adrenalectomy and medical treatment. The number of antihypertensive agents was similar between medical and surgical group at baseline ($P = 0.627$) and at follow-up ($P = 0.291$). Within each group, the number of antihypertensive drugs at follow-up decreased in the surgical group, whereas this was not the case for the medical group. Also, no significant variations occurred as far as BSA and LVH are concerned.

Discussion

The present study supports a potential relationship between PA and aortic damage. We compared patients affected by PA to a hypertensive population, in which aldosterone excess had been excluded. Several studies have already been published concerning the detrimental effects of aldosterone on vessels [33, 34]. However, up to now, only animal studies have linked aldosterone excess to alterations of the aorta morphology [18, 19]. LVH is generally investigated in hypertensive subject as one of the clues that induce clinicians to screen for secondary hypertension, if its severity is disproportionate to the grade of hypertension [35]. Aortic dissection or rupture have been described in a few case reports of patients affected by PA [20, 21, 23, 37–39]. Underdiagnosis of PA might explain why only case-reports are described as to thoracic aorta aneurisms.

This study shows a higher prevalence of aortic dilatation in PA as compared with EH. The analysis was adjusted for the main determinants of the aortic diameters: age, sex, and BSA, as described by the guidelines [36]. Also, potential confounders were considered in the analysis: the number of antihypertensive agents, evidence of subclinical hypercortisolism, and the duration of hypertension. Both the aortic root and the tubular ascending aorta, were higher in the PA population, as compared to the control group. This sheds light on the systemic disease of PA, involving the heart, the kidney, and blood vessels. Thoracic aorta enlargement does not necessarily imply the presence of an aneurysm, but it is certainly a detrimental effect seen in PA group that should not be neglected. This alteration should expecially be kept under consideration in the medical group, as they will not ever be cured from PA but treated with a receptor antagonist. The available drug is certainly a valid tool to contrast cardiovascular morbidity, but not fully capable in restoring a physiological setting, for example, normal aldosterone levels. Therefore, for the first time, this study photographs a pathological condition of a large vessel at a preclinical stage.

Follow-up data are more intriguing to interpret. Both the aortic diameters did not vary in spite of the administration of MR blockers or undergoing surgical treatment. In fact, aortic enlargement seems to persist despite the available recommended options for PA. However, it is also true that worsening of either aortic diameter is not observed in our treated PA patients, at least during the period of observation. Similar data about the description of aortic diameters during follow-up of treated PA patients were shown in a previous study, in which, however, the aortic root diameter at baseline was not different between PA and EH subjects [4]. However, no data on tubular ascending aorta were available.

An expected outcome in the surgical group is the reduction in the number of antihypertensive medications.

The results of this study raise several important issues. Answers are still lacking on whether aldosterone-receptor antagonism could have a protective role on thoracic aorta in patients with a diagnosis of PA. In fact, pathogenesis of aortic enlargement is still unclear and may be multifactorial. It is also unknown if a threshold dose of MR antagonist should be kept in order to possibly prevent or ameliorate aortic enlargement. Plasma renin activity was not determined during follow-up of MR-antagonist treated patients, but it might be a useful parameter in addition to electrolyte balance to better evaluate full dose titration. Third, it is not yet sure whether aldosterone acts through a genomic or nongenomic modality on the arterial wall, although animal models support the former hypothesis [18, 19]. If a nongenomic modality were responsible for the arterial wall damage, adrenalectomy could represent a better choice in this regard.

This study has two main limitations. The first is represented by the small sample size of PA group, especially those undergoing surgical treatment. The other drawback is the short duration of follow-up, which may limit the interpretation of the results. In addition to that, follow-up time differs between medically and surgically treated PA patients. Such discrepancy may undermine the interpretation of the results especially in the surgical group, also considering that vascular damage is a slow-developing complication.

In conclusion, ascending aorta dilatation seems to be more prevalent in patients with PA than in those with EH. Regression of the aortic diameters apparently does not occur after treatment, both in patients who undergo adrenalectomy and in patients treated with a MR blocker. A prompt diagnosis might be crucial to prevent the onset of this condition, although no data are available yet. Measurement of aortic root by routine echocardiograms may be helpful in defining the cardiovascular status of patients with PA, even though a longer period of observation might be necessary to detect clinically significant differences.

Eventually, future studies are needed to unravel the potential role of aldosterone hypersecretion in inducing and sustaining aortic dilatation.

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Author contributions The authors equally contributed in writing the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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