

Vascular Disturbances in Primary Aldosteronism: Clinical Evidence

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Key Words

Primary aldosteronism • Blood vessels • Abnormalities

Abstract

Primary aldosteronism (PA) is a common form of arterial hypertension with a high prevalence of cardiovascular complications. In patients with PA, complex mechanisms may lead to functional and/or structural abnormalities of the blood vessel wall. Clinical evidence indicates that patients with PA may have immune cell activation, increased oxidative stress, impaired endothelial function and vascular remodeling. Activation of fibroproliferation has been found in resistant arteries of patients with PA. Subjects with PA compared to essential hypertensives with similar blood pressure levels have increased intima-media thickness and arterial stiffness as measured by pulse wave velocity. These functional and morphological changes can be modified by an increased sodium intake. Vascular remodeling in PA may indicate a poor response to specific therapy with lower probability of cure and/or normalization of blood pressure. Early diagnosis of PA before blood vessel wall disturbances develop is of utmost importance.

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Introduction

Primary aldosteronism (PA) is an endocrine/secondary form of hypertension defined by an autonomous aldosterone overproduction usually caused by adrenocortical adenoma or bilateral adrenal hyperplasia. PA is of relatively high prevalence in populations of hypertensive patients [1–3]. The likelihood of a diagnosis of PA in clinical practice, however, may differ depending on the studied population and/or severity of hypertension [4]. While in mild hypertension PA may be relatively rare [4], it has been reported to be common in patients with severe/resistant hypertension with a prevalence of 11–20% [5–7]. Increased frequency of PA may be attributed to the detection of normokalemic cases of PA due to the use of the aldosterone-to-renin ratio (ARR) as a screening tool [1, 3, 4, 8].

A retrospective study by Milliez et al. [9] showed that subjects with PA are at higher cardiovascular risk than patients with essential hypertension (EH). Patients with PA exhibited a higher occurrence of stroke, myocardial infarction, left ventricular hypertrophy and atrial fibrillation [9]. A prospective Italian study with follow-up at 7.4 years demonstrated that cardiovascular complications (myocardial infarction or reversible ischemia, stroke or transient ischemic attack, sustained arrhythmias) are more prevalent in patients with PA than in EH

Table 1. Major clinical evidence of vascular disturbances in PA

Increased oxidative stress
Endothelial dysfunction
Increased vascular collagen (total and type III) in small resistance arteries
Increased tunica media to lumen ratio in small resistant arteries
Increased intima-media thickness of carotid arteries
Increased arterial stiffness

[10]. The difference in the rate of cardiovascular events was reversed in this study by specific treatment in the form of either adrenalectomy or mineralocorticoid receptor antagonists [10]. Data from the large German Conn's registry indicated a high rate of comorbidities in patients with PA [11], with higher prevalence of cardiovascular events in the hypokalemic than normokalemic cases [11]. High rates of cardiovascular complications in PA were also noted in other studies [12, 13]. An increasing body of evidence has been gathered about long-term effects of aldosterone overproduction on the cardiovascular [14–17] and renal systems [18].

This short review focuses on clinical evidence of alteration in vascular function and/or morphology in patients with PA and their possible reversal by specific treatment.

Clinical Evidence for Vascular Damage in PA

Major clinical evidence of vascular disturbances in PA is summarized in table 1

Patients with PA have increased oxidative stress, as reflected by the elevation of malondialdehyde levels, compared to essential hypertensives matched by age and blood pressure [19]. Progressive endothelial inflammation appears to be closely related to increased oxidative stress [19] with potential endothelial dysfunction. In fact, a previous study by Taddei et al. [20] showed impaired endothelial-dependent vasodilatation in patients with PA and renovascular hypertension. A recent study found the deficiency of endothelial progenitor cells in PA, which may contribute to increased arterial stiffness and vascular damage [21]. Activation of aldosterone in PA may also lead to perivascular leukocyte infiltration and fibrinoid remodeling of vascular smooth muscle cells. These vascular inflammatory effects seem to be independent on blood pressure elevation [22].

Patients with PA, in comparison to patients with EH of comparable blood pressure levels and age, have in-

creased levels of aminoterminal propeptide type I procollagen as a marker of collagen synthesis and turnover [19]. These results suggest the activation of fibroproliferation in PA. This notion was confirmed in study by Rizzoni et al. [23], who focused on the measurement of collagen content and tunica media thickness of small subcutaneous resistance arteries from biopsies in patients with PA, EH and normotensive controls. Small resistance arteries from gluteal subcutaneous fat tissue were dissected and mounted on an isometric myograph, and the tunica media-to-internal lumen ratio was measured. Total collagen and type III vascular collagen were significantly higher in PA than EH despite comparable blood pressure levels, age and BMI [23]. The tunica media-to-internal lumen ratio was significantly increased in PA and EH compared with normotensive controls [23]. Based on these results, it seems that marked fibrosis is present in small resistance arteries of patients with PA.

A previous study by Holaj et al. [24] focused on the evaluation of potential differences in carotid intima-media thickness (IMT) between PA and EH patients matched for age and blood pressure. Normotensive patients served as controls. IMT was measured by a high-resolution B-mode ultrasound probe at the level of common carotid artery and carotid bifurcation. The patients with PA had significantly higher IMT in the common carotid artery than EH patients and controls [24]. The differences between both hypertensive groups remained statistically significant after adjustment for age and 24-hour systolic blood pressure. The differences of the IMT in the carotid bifurcation were, however, significant only between PA and controls and not between PA and EH subjects. This discrepancy is not clear and may reflect the differences in the density/affinity of aldosterone receptors in different regions of carotid arteries and/or differences in local physical forces [24]. Higher carotid IMT in PA was also found by Bernini et al. [25], who examined carotid IMT diameter in patients with PA, EH and controls [25] and in addition measured the corrected integrated backscatter signal in the carotid arteries as a marker of fibrous tissue content. IMT of patients with PA was greater than in EH and controls [25]. Similar results were found for the corrected integrated backscatter signal in the carotid arteries, which was significantly higher in PA than EH and controls [25].

Rossi et al. [26] evaluated the small artery structure of resistance arteries isolated from periadrenal or subcutaneous adipose tissue of patients with PA treated by laparoscopic adrenalectomy. Subjects with a higher media/lumen ratio and higher media thickness had a poor re-

sponse to surgery. Media/lumen ratio of resistance arteries and duration of hypertension were significant predictors of the outcome of adrenalectomy in patients with PA [26].

Pulse wave velocity (PWV) is considered to be a reliable marker of arterial stiffness. A study by Strauch et al. [27] aimed at comparing arterial stiffness between patients with PA, EH and normotensive controls using applanation tonometry with SphygmoCor®. Carotid-femoral PWV and central aortic augmentation index (AI) derived from the radial artery pulse wave were determined. PA patients had significantly higher PWV as a marker of arterial stiffness than EH or controls, and this difference was independent of all clinical characteristics, including office blood pressure and 24-hour ambulatory blood pressure [27]. Surprisingly, no differences in AI were noted between the two hypertensive groups. AI is a complex index describing mainly wave reflections occurring at the branching of the arterioles. Therefore, AI seems to be more influenced by different confounding factors than PWV. PWV may predominantly reflect changes in the central parts of the arterial tree [27]. Higher arterial stiffness in PA was found also by Bernini et al. [25], who investigated femoral and radial PWV in patients with PA, EH and controls. PA subjects exhibited significantly higher femoral and radial PWV and AI than EH or controls. Tsioufis et al. [28] also noted higher mean value for PWV in patients with a recent diagnosis of PA than in EH. The differences did not reach statistical significance, perhaps due to the smaller group of subjects and/or early stage of the disease. Increased central aortic stiffness measured by PWV was also noted in a general population of hypertensive patients with higher aldosterone-to-renin ratio [29]. Patients with an aldosterone-to-renin ratio of at least 20 (ng/dl per ng/(ml·h) and plasma aldosterone ≥ 12 ng/dl had a significantly higher PWV than subjects with lower aldosterone-to-renin ratio and plasma aldosterone [29]. These results indicate that PA/hypertension with inappropriate aldosterone activation is associated with higher arterial stiffness. High sodium intake in PA patients may also contribute to increased arterial stiffness [30]. In addition, sodium intake seems to modulate the effect of aldosterone synthase polymorphism (CYP11B2 C-344T) on arterial stiffness [30]. Contrary to sodium, potassium might exert vascular protective effects. Despite expected differences in plasma potassium concentrations, no convincing impact of this variable on PWV was found in the study by Strauch et al. [27].

Vascular damage in PA patients may be also exaggerated by very high blood pressure levels. In fact, a previous

study with 24-hour blood pressure monitoring showed that patients with PA had more severe hypertension and impaired diurnal variation compared with EH [31].

Aldosterone concentrations are higher in obese subjects and patients with metabolic syndrome [32]. Fat tissue produces a lipid soluble factor that can stimulate aldosterone production from zona glomerulosa [33]. It has been shown that PA patients have a higher prevalence of metabolic syndrome compared to essential hypertensives of comparable age [34]. Although these results were not confirmed by all authors [35], potential metabolic disturbances in lipid and glucose control may mediate or contribute to vascular damage in PA.

There are only limited data on the potential differences in the occurrence and/or severity of (cardio)vascular damage between the two main types of PA, e.g. aldosterone-producing adenoma and idiopathic aldosteronism. A previous study by Somlóová et al. [36] suggested metabolic differences between aldosterone-producing adenoma and idiopathic aldosteronism. It is impossible, however, from the available data to evaluate the impact of differences in the severity of aldosterone production in PA on vascular changes.

Vascular remodeling and damage in PA subjects thus potentially translates into the higher rate of clinical cardiovascular complications. This notion was confirmed by the retrospective study of Milliez et al. [9]. Catena et al. [10] also found a higher prevalence of cardiovascular events in PA compared to EH. Patients with PA exhibited a higher rate of myocardial infarction/reversible ischemia and stroke/transient ischemic attack. Prevalence of peripheral arterial disease was, however, not different between PA and EH, perhaps reflecting the very low frequency of this disease in the population studied [10]. Data from the large German Conn's registry showed a very high rate of peripheral vascular disease and of cerebrovascular and cardiac complications in PA patients [11].

Can Specific Therapy of PA Reverse Vascular Changes?

Specific treatment of PA with mineralocorticoid receptor antagonists resulted in normalization of oxidative stress as reflected by reduction of malondialdehyde levels [19].

Therapy of PA in the form of unilateral laparoscopic adrenalectomy or administration of mineralocorticoid receptor antagonists (spironolactone or eplerenone) is well established [4, 37]. Cure of the disease with normal-

ization of blood pressure after adrenalectomy is seen in only approximately one third of subjects [38, 39]. Normalization of hypertension following spironolactone monotherapy is even more rare and has been described in only a quarter of the patients [40]. Additional antihypertensive therapy in PA patients is usually needed [4, 38–40], which may further complicate the interpretation of the benefit of specific therapy in PA.

There is little data available on the effect of specific therapy in PA on vascular changes and/or cardiovascular complications.

A previous study by Strauch et al. [41] was aimed at evaluating the effect of specific therapy of PA on arterial stiffness. Patients with confirmed PA were investigated by SphygmoCor applanation tonometry at the time of the diagnosis and then approximately 1 year after treatment [41]. Office blood pressure as well as 24-hour blood pressure decreased significantly after adrenalectomy, and medical treatment was inferior to surgery in terms of blood pressure decrease. The PWV significantly decreased after surgery. We, however, found no changes in arterial stiffness (PWV, AI) indices in patients treated with spironolactone. A possible explanation of this discrepancy is that conservative treatment strategy was not sufficient to decrease blood pressure properly. It may be caused by the relatively low dose of spironolactone used due to frequent dose-dependent side effects [41].

The less pronounced effect of conservative treatment with spironolactone on PWV may be also potentially related to incomplete blockade of aldosterone actions by available mineralocorticoid receptor antagonists. Conservative treatment of PA by spironolactone/eplerenone, however, is considered a valid alternative to surgical therapy in prevention of cardiovascular and renal complications in patients with PA [10, 37]. The duration of hypertension before the diagnosis of PA was comparable in surgically and conservatively treated subjects [27, 41], and thus should not play any major role in observed differences in arterial stiffness. Therefore, It seems that surgi-

cal but not conservative treatment of PA leads to the decrease of arterial stiffness.

A prospective study by Catena et al. [10] found no differences in the occurrence of myocardial infarction, stroke or revascularization procedures between EH and PA during 7.4 years of follow-up [10]. In the course of this study, patients with PA were treated by adrenalectomy (25 cases) or a spironolactone-based regimen (25 subjects). No differences were noted in the frequency of combined cardiovascular endpoints between the two therapeutic modalities in PA [10].

Conclusions

PA is a frequent form of arterial hypertension with a high prevalence of cardiovascular complications. Complex mechanisms including endothelial damage, increased oxidative stress, activation of inflammation and fibroproliferation may lead to functional and/or structural blood vessel wall abnormalities in PA. The occurrence of these vascular changes seems to be higher in patients with PA than in EH, independent of blood pressure levels. Aldosterone may thus act as an independent risk factor for vascular damage. Clinical evidence indicates that patients with PA have higher vascular collagen concentrations in resistance arteries than in EH. Increased IMT and arterial stiffness has been repeatedly observed in PA subjects, especially in large arteries. Specific therapy of PA may lead to partial reversal of blood vessel wall abnormalities. Early detection of PA in clinical practice with evaluation of vascular structure abnormalities and specific treatment is needed to prevent target organ damage in PA.

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