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DOI 10.1055/s-0035-1565124
Horm Metab Res

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Georg Thieme Verlag KG
Rüdigerstraße 14
70469 Stuttgart
ISSN 0018-5043

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Cardiovascular Risk in Primary Hyperaldosteronism

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Key words
- aldosterone
- cardiovascular event
- target organ damage
- blood pressure

Abstract

After the first cases of primary aldosteronism were described and characterized by Conn, a substantial body of experimental and clinical evidence about the long-term effects of excess aldosterone on the cardiovascular system was gathered over the last 5 decades. The prevalence of primary aldosteronism varies considerably between different studies among hypertensive patients, depending on patient selection, the used diagnostic methods, and the severity of hypertension. Prevalence rates vary from 4.6 to 16.6% in those studies in which confirmatory tests to diagnose primary aldosteronism were used. There is also growing evidence indicating that prolonged exposure to elevated aldosterone concentrations is associated with target organ damage in the heart, kidney, and arterial wall, and high cardiovascular risk in patients with primary aldosteronism. Therefore, the aim of treatment should not be confined to BP normalization and hypokalemia correction, but rather should focus on restoring the deleterious effects of excess aldosterone on the cardiovascular system. Current evidence convincingly demonstrates that both surgical and medical treatment strategies beneficially affect cardiovascular outcomes and mortality in the long term. Further studies can be expected to provide better insight into the relationship between cardiovascular risk and complications and the genetic background of primary aldosteronism.

Introduction

After the first cases of primary aldosteronism (PA) were described and characterized by Conn, a substantial body of experimental and clinical evidence about the long-term effects of excess aldosterone on the cardiovascular system was gathered over the decades [1–4].

Elevated aldosterone levels promote excessive renal sodium retention, impair endothelial function, increase oxidative stress, and reduce vascular compliance. Experimental studies in animal models have demonstrated that inappropriate aldosterone levels for sodium status can produce extensive renal damage [5]. Evidence was obtained in uninephrectomized and stroke-prone spontaneously hypertensive rats, in which aldosterone produced intrarenal vascular damage, glomerular injury and tubulointerstitial fibrosis [5–7].

Several experimental investigations in salt-fed animals documented profibrotic and pro-hypertrophic effects of aldosterone independent from the arterial BP level and the circulating plasma volume [3,4]. It has been documented that absolute aldosterone excess in patients with PA has been associated with a higher risk of heart, vascular, and kidney damage regardless of the blood pressure (BP) and results in increased total cardiovascular risk (**Fig. 1**) [5]. Like in patients with essential hypertension (EH), in patients with PA total cardiovascular risk can be stratified into various categories, based on the BP level, cardiovascular risk factors, asymptomatic organ damage, and presence of metabolic diseases and symptomatic cardiovascular disease [8].

Prevalence of PA

The prevalence of PA varies considerably between different studies among hypertensive patients, depending on patient selection, used diagnostic methods, and severity of hypertension [9–13]. Several cross-sectional and prospective studies in unselected hypertensive populations have shown that the prevalence of PA is much higher

received 20.08.2015
accepted 12.10.2015

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DOI http://dx.doi.org/10.1055/s-0035-1565124
Published online: 2015
Horm Metab Res

ISSN 0018-5043

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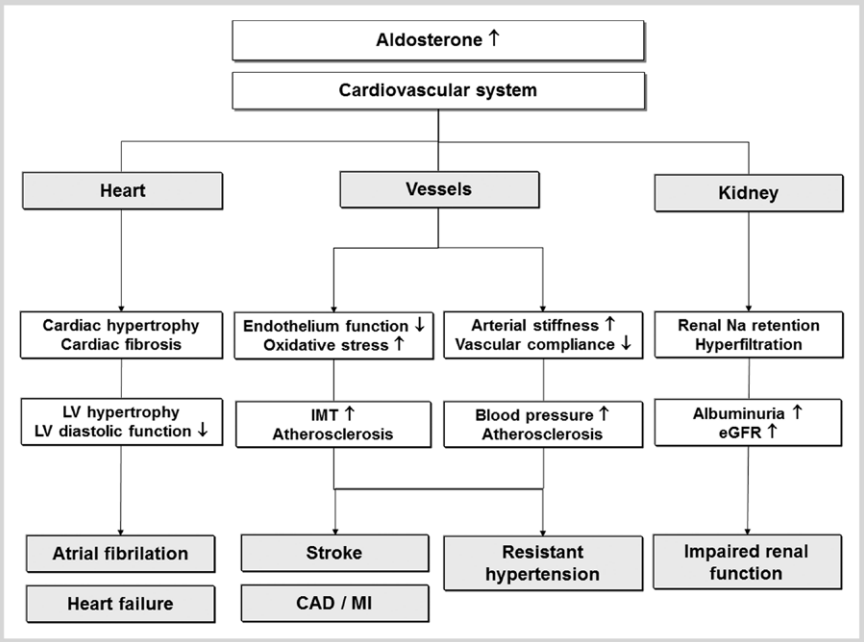

Fig. 1 Cardiovascular burden of primary aldosteronism. Selected and proposed mechanisms of impact of high aldosterone levels. Clinical presentations of the high cardiovascular risk related to primary aldosteronism. CAD: Coronary artery disease; eGFR: Estimated glomerular filtration ratio; IMT: Intima media thickness; LV: Left ventricular; MI: Myocardial infarction.

than previously believed and varies significantly between studies, ranging from 4.6 to 16.6% when confirmatory tests to diagnose PA were used [9].

The prevalence of PA has been shown to be similar in normotensive subjects and patients with stage 1 hypertension (1.99%), but was significantly higher in stages 2 (8.55%) and 3 (13.5%) of the disease [14]. This was confirmed by the PAPY study showing an increase in PA patients with grade 1 (7.2%) to grade 3 (19.5%) hypertension [15].

Although there is still debate, it has been commonly agreed that resistant hypertension is the condition with the highest probability of PA detection. In a large group of patients with resistant hypertension, the diagnosis of PA was established in 11.3% in the total study population when a confirmatory test was used [16]. This suggests that the prevalence of PA in patients with resistant hypertension is lower than that reported in the previous smaller studies [16]. In the RESIST-Pol study, the diagnosis of PA in patients with resistant hypertension was made in 15.7% of subjects [17].

Taken together, many methodological factors may be responsible for the wide variation in the prevalence of PA in patients with hypertension, because the prevalence data depend on patient selection, assays used and on drugs that interfere with renin and/or aldosterone measurements, affecting the diagnostic accuracy of both screening and diagnostic tests [9–13, 18–20].

Blood Pressure Profile

Large community-based studies have shown that serum aldosterone and renin levels, as well as the aldosterone/renin ratio (ARR), may influence BP and may predispose to hypertension in the general population [21, 22].

Available data evaluating circadian BP profile in patients with PA are inconsistent. Mansoor et al. found no differences in ambulatory daytime, night-time, and nocturnal decline between hypertensive patients with PA and control hypertensive patients without PA on ambulatory blood pressure measurement (ABPM) [23]. In contrast, Zelinka et al. documented a significantly smaller night-time decline in systolic BP in all forms of PA compared to the control group while only the night-time fall in diastolic BP was significantly lower only in the patients with bilateral hyperplasia, compared to control group. There was no difference in the BP profile between aldosterone producing adenoma (APA) and bilateral adrenal hyperplasia (BAH) [24]. In a recent study, Ceruti et al. evaluated ABPM patterns in patients with secondary hypertension due to adrenal disease and the prevalence of nondipping in patients with PA, EH, and normotensive controls was 51.5, 34.2, and 15% respectively. The results of the study revealed that the BAH group showed a greater and significantly higher prevalence of nondippers (58%), compared to the APA group (38%) [25]. More recent studies also found that daytime, night-time and 24-h systolic and diastolic BP were significantly higher in resistant hypertensive patients with PA, compared to those without PA. So it has to be concluded that ABPM is necessary to identify aldosterone effects on cardiovascular outcomes [26].

The nondipping pattern of the BP during the night has been reported as a feature of patients with PA and resistant hypertension in the RESIST-Pol study. Patients with PA were characterized by higher systolic clinic, systolic daytime, and both systolic and diastolic night-time BP levels, as well as by a less pronounced nocturnal fall of systolic and diastolic BP and a higher frequency of nondipping diastolic BP (54.8 vs. 33.3%), compared to those without PA (**Fig. 2**) [17].

The studies evaluating the effects of surgical and medical treatment of PA on BP level and BP profile are unequivocal. It has been reported that both surgical and medical treatment of PA resulted in marked BP decline and a normalized previously attenuated nocturnal BP fall. A systematic review of retrospective and prospective studies, comparing the long term effect of surgery and medical treatment on the outcomes in patients with PA disclosed more pronounced effects on BP in surgically treated patients [27, 28]. Also another recent analysis showed that the percentage of patients with normalization of blood pressure ranged from 16 to 72% in the 19 series after adrenalectomy, with a pooled cure rate of 41% [28].

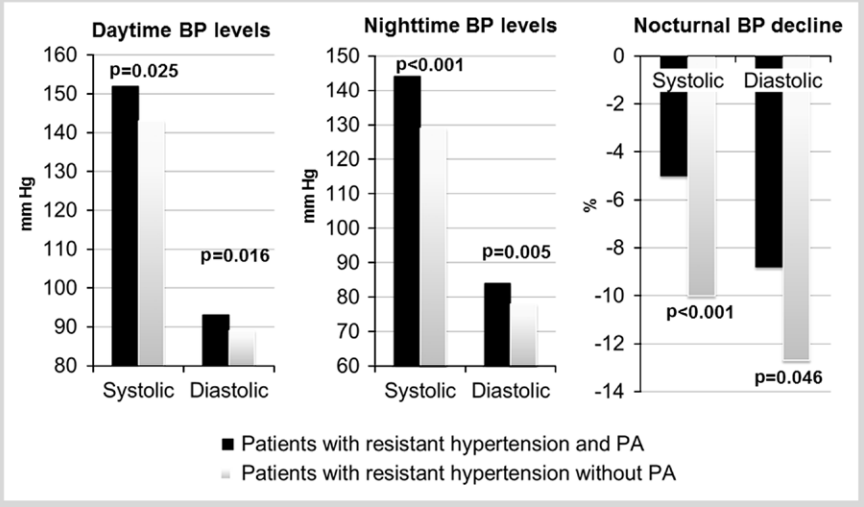

Fig. 2 Daytime and nighttime blood pressure levels and nighttime blood pressure decline in patients with resistant hypertension with and without primary aldosteronism in the RESIST-Pol study. Adapted from [17]. BP: Blood pressure; PA: Primary aldosteronism.

Target Organ Damage

There is growing evidence to suggest that prolonged exposure to elevated aldosterone concentrations has a deleterious effect on the cardiovascular system and is associated with target organ damage independently from the BP (**Fig. 1**). Therefore, the aim of treatment should not be confined to BP normalization and hypokalemia correction, but rather should focus on restoring the deleterious effects of excess aldosterone on the cardiovascular system.

Heart

Experimental studies demonstrated the presence of mineralocorticoid receptors (MR) in cardiomyocytes and their activation by high aldosterone levels might contribute to myocardial hypertrophy in PA, via mechanisms that include accelerated fibrosis and modulation of ionic movements [29–31]. The detrimental effect of high aldosterone levels may also result from interactions of aldosterone with other hormones including angiotensin II, endothelin, bradykinin, activation of inflammatory cells and stimulation of fibroblast proliferation, and collagen synthesis [29–31].

Structural and functional changes of the heart have been documented in patients with PA (**Fig. 3**). Several cross-sectional echocardiographic studies have reported an increase in the left ventricular (LV) mass in patients with PA as compared to other forms of hypertensive disease, being related to both increased LV dimension and increased LV wall thickness [32–34]. Muiesan et al. have reported that the frequency of inappropriate LV mass is increased in patients with PA, even in the absence of LV hypertrophy, as defined by the current criteria. This observation strongly suggests that elevated aldosterone contributes to an increase in LV mass beyond the level needed to compensate for the BP-related hemodynamic load [33]. Recent studies have shown the importance of dietary sodium in determining the degree of cardiac damage in patients with PA, indicating that a high-salt diet is associated with greater LV mass [35].

Lately, Rossi et al. reported that KCNJ5 gene somatic mutation affects cardiac remodeling in patients with PA and that patients with APA carrying this mutation develop more pronounced LV hypertrophy, compared to those with wild-type APA. Patients

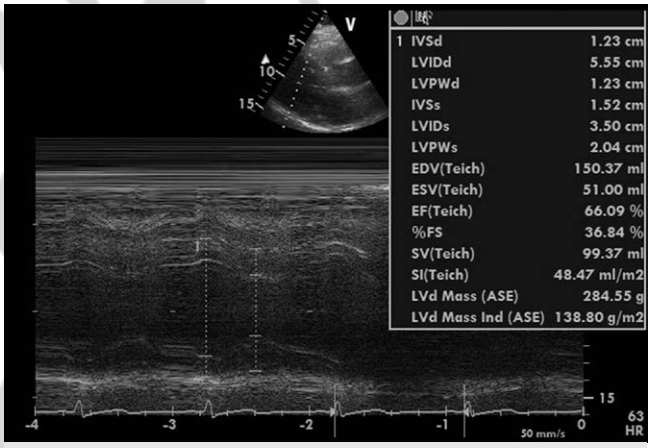

Fig. 3 M-mode echocardiography in a male patient with primary aldosteronism – increased left ventricular posterior wall and intraventricular septum diastolic dimensions, left ventricular mass and left ventricular mass index as well as relative wall thickness (0.44) – concentric left ventricular hypertrophy. By courtesy of Dr P. Dobrowolski. ASE: American Society of Echocardiography; EDV: End-diastolic volume; ESF: End-systolic volume; EF: Ejection fraction; FS: Fractional shortening; Ind: Index; IVSd: Intraventricular septum diastolic; IVSs: Intraventricular septum systolic; LVd: Left ventricular diastolic; LVIDs: Left ventricular dimension systolic; LVIDd: Left ventricular dimension diastolic; LVPWd: Left ventricular posterior wall diastolic; LVPWs: Left ventricular posterior wall systolic; SI: Stroke index; SV: Stroke volume.

with such mutation also exhibit a lower chance of cure after adrenalectomy [36].

In patients with PA, LV hypertrophy occurs in association with an abnormal pattern of LV filling indicating the presence of diastolic dysfunction, whereas systolic function is generally found to be comparable with that of patients with EH [32].

All of these aldosterone-related cardiac abnormalities could contribute to the increased cardiovascular risk observed in patients with PA and could account for a greater incidence of arrhythmia, CAD, and heart failure [5].

Most echocardiographic observations of cardiac changes after treatment of PA are confined to short-term follow-up studies, mostly after removal of adrenal adenoma. Initial observations showed that, in patients with APA treated by adrenalectomy, both LV mass and LV filling patterns were normalized one year after surgery, whereas patients who were treated for a year with

spironolactone showed no comparable LV hypertrophy regression [37–41]. A recent study has provided data on long term echocardiographic follow-up, in a cohort of patients with PA after either surgical or medical treatment. This 7 year lasting study has demonstrated that patients treated either with adrenalectomy or spironolactone undergo a significant and comparable decrease of LV mass, although the decrease is significant only within the first year after surgery. In both treatment groups, baseline LV mass was correlated with plasma aldosterone concentration, which was an independent predictor of changes of LV mass after treatment [42]. These studies demonstrated that the decrease in the LV mass obtained by treatment of PA is only partially explained by blood pressure reduction, clearly supporting a role of aldosterone that is independent from the hemodynamic overload.

Vessels

In patients with PA, the mechanisms that mediate the deleterious effects of aldosterone excess on functional and/or structural abnormalities of the blood vessel wall are more pronounced than in patients with EH. Studies performed so far have documented that patients with PA suffer from increased oxidative stress and showed that PA is associated with endothelial dysfunction and that circulating aldosterone levels significantly correlated with endothelial function [43,44]. Recently Matsumoto et al. reported that in patients with PA, endothelial function was impaired in subjects with APA, compared with patients with BAH and control EH subjects, and surgical treatment resulted in the improvement of endothelial function in this subtype of PA [45].

Recent studies demonstrated the deficiency of endothelial progenitor cells in PA, which may contribute to increased arterial stiffness and vascular damage [46]. Excessive amounts of aldosterone in patients with PA may also lead to perivascular leukocyte infiltration and fibrinoid remodeling of vascular smooth muscle cells [43]. Rizzoni et al. reported a pronounced fibrosis in small resistance arteries being more evident than in BP-matched patients with EH [47]. Total collagen and Type III vascular collagen were significantly higher in PA, compared with EH, despite the BP levels being comparable. Tunica media to internal lumen ratio was significantly increased in PA and EH compared with normotensive controls and was significantly greater in patients with concentric LV hypertrophy [48]. It has been also reported that in patients with PA, retinal arterioles assessed for the first time in vivo by means of by scanning laser Dopller flowmetry, were characterized by hypertrophic remodeling as compared with patients with essential hypertension [49].

The intima media-thickness (IMT) was also found to be increased in carotid arteries and in comparison with subjects with EH carotid artery lesions were more frequent in patients with PA [43]. Holaj et al. documented that these differences between patients with PA and EH groups remained statistically significant after adjustment for age and 24-h systolic BP. In the long-term, spironolactone therapy in patients with PA exerted significant effect on regression of IMT, which was comparable to surgical treatment in patients with APA [50,51]. In addition, Lin et al. reported higher IMT in APA patients with PA than in control subjects with EH and, after a 12 month follow-up, significant regression in IMT was observed [52]. Pulse wave velocity (PWV) is regarded to be a reliable marker of arterial stiffness. Several studies showed increased PWV values as compared to EH patients and this difference was independent from BP levels on office and ABPM [53,54]. It is of interest that, in contrast to surgical treatment, medical treatment with spironolactone had no effect on aortic stiffness indices, including PWV. One possible explanation for this is that medical treatment was not sufficient to decrease BP properly because the dose of spironolactone was too low [43,54].

Kidney

Clinical studies indicate that PA is associated with renal complications that reflect the capability of elevated aldosterone levels to induce kidney dysfunction beyond what could be expected from BP elevation. Involvement of the kidney in PA deserves attention, because structural renal damage may be associated with unfavorable outcomes, such as progressive renal failure. Also prolonged hyperfiltration observed in patients with PA might have detrimental effect on kidneys. However, early involvement of the kidney in PA is characterized by functional changes that are largely reversible with treatment [5,55,56].

Previous studies reported a large variability in the prevalence of overt renal damage in patients with PA. Renal failure and proteinuria have been found to occur in 8–24% of subjects with PA [5,55]. In the large multicenter cross sectional PAPY study, 24-h microalbuminuria was significantly greater in patients with both APA and BAH, compared to control patients with EH [57]. Important information has been obtained from 2 prospective studies with short-term and long-term follow-up after treatment. Ribstein et al. documented a significant decrease in urinary albumin excretion after adrenalectomy in 25 patients with adrenal adenoma who were followed up for 6 months. The authors concluded that PA was associated with relative hyperfiltration, unmasked after the elimination of excess aldosterone, resulting in the decrease in albumin secretion [58]. Sechi et al. reported in a long-term study that in 50 patients with PA, albuminuria was higher at baseline in patients with PA than in those with EH. In the follow-up lasting on average 6.4 years, microalbuminuria was more likely to subside to normal levels after treatment than to progress to overt proteinuria [59]. In addition, the restoration of normal albumin excretion was more frequent in patients with PA than in those with EH and this effect was independent of BP. These 2 prospective studies have consistently indicated that PA is characterized by partially reversible renal dysfunction. In The German Conn's Registry lower GFR levels in untreated patients with PA, compared with age, BMI and gender-matched hypertensives, were found. Although the absolute difference was small (3 ml/min), it proved to be highly significant because of the large number of subjects studied. Regression analysis showed that age, male gender, low potassium and high aldosterone concentrations were independent predictors of lower GFR [60].

This finding contrasts with those of studies showing no difference in GFR or the presence of increased GFR in patients with PA compared with EH matched for age, gender, severity and duration of hypertension. The main reason for this difference is probably related to the differences in the retrospective control cohorts [58–60].

Several studies have investigated the effect of the surgical and medical treatment of PA on GFR. Ribstein et al. documented that the increased GFR was reversed after the surgical and medical

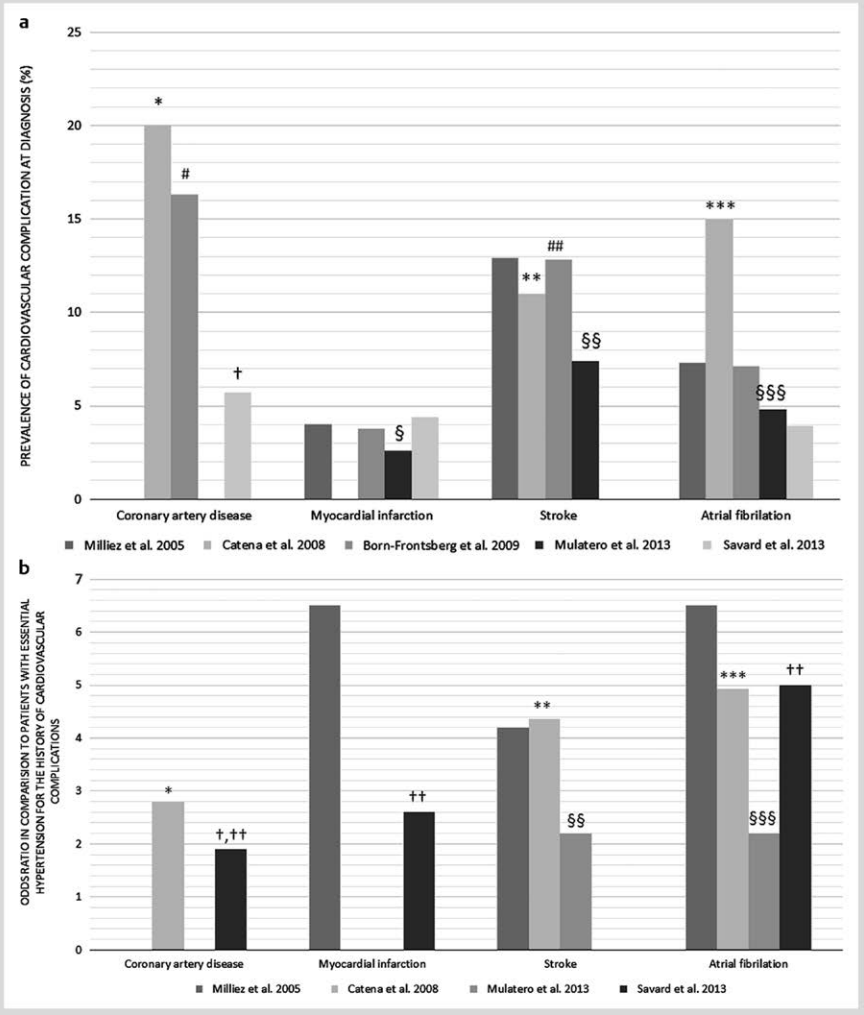

Fig. 4 Cardiovascular complications in patients with primary aldosteronism at the diagnosis – prevalence **a** and odds ratio for the history of cardiovascular complication in comparison to patients with essential hypertension **b**. All odds ratio depicted were of statistical significance. Adapted from [62–65, 67]. * Myocardial infarction or reversible ischemia; ** Stroke or transient ischemic attack; *** Sustained arrhythmias; # Cardiovascular events (angina pectoris, myocardial infarction, chronic cardiac insufficiency, coronary angioplasty); ## Cerebrovascular events (stroke, cerebrovascular stenosis, transient ischemic attack, and prolonged reversible ischemic neurological deficit). § Myocardial infarction and unstable angina requiring angioplasty; §§ Stroke or transient ischemic attack; §§§ Sustained arrhythmias (atrial fibrillation, atrial flutter, sustained ventricular tachycardia and ventricular fibrillation); † Myocardial infarction or angina with objectively recorded ischemia; †† Adjusted for hypertension duration.

treatment of PA, a finding that has been subsequently confirmed in larger cohorts of patients with PA and recent meta-analysis [58, 61]. In the study by Sechi et al. during the 6 months after intervention, the mean GFR decreased by −13.6 ml/min in patients with PA, but only −2.1 ml/min in patients with EH. However, subsequent declines in GFR were similar in this study in patients with PA and EH during a 9 year follow-up [59]. The data from the German Conn's Registry confirm this observation and showed that GFR declined soon after treatment of PA and remained relatively stable thereafter. Analysis of renal outcomes in patients with PA who were treated by adrenalectomy or spironolactone did not reveal a significant difference [60].

Taken together, these data suggest that effective treatment of mineralocorticoid excess removes renal hyperfiltration, and may uncover the real extent of renal damage associated with PA.

Other Cardiovascular Complications

An increasing body of information coming from longitudinal, retrospective studies convincingly supports the presence of greater prevalence of cardiovascular complications in patients with PA, compared with those with EH (**Fig. 4**) [5]. Milliez et al. for the first time examined a large cohort of patients with APA and BAH reporting a significantly higher rate of myocardial infarction (4.0 vs. 0.6%), atrial fibrillation (7.3 vs. 0.6%) and stroke (12.9 vs. 3.4%), in comparison with patients with EH [62]. More recent evidence obtained in a French cohort of 459 patients with PA has indicated that patients with PA had significantly higher prevalence of CAD (adjusted odds ratio 1.9), nonfatal myocardial infarction (adjusted odds ratio 2.6) and atrial fibrillation (adjusted odds ratio 5.0). The risk associated with PA was similar across different levels of serum potassium and plasma aldosterone [63].

Also Catena et al. have documented that, at baseline, the prevalence of cardiovascular events was higher in PA than in EH (35 vs. 11%) with odds ratios of 4.93, 4.36, and 2.80 for sustained arrhythmias, cerebrovascular events, and coronary heart disease, respectively. In addition, the prevalence of cardiovascular complications was comparable in patients with APA and idiopathic disease, indicating that those with both subtypes are at increased risk [64]. Likewise, in the retrospective study by Mulatero et al., a significantly higher number of PA patients at baseline experienced cardiovascular events, compared with matched patients with EH [65].

The study by Turchi et al. evaluated global cardiovascular risk in patients with PA and the results indicated that 53% of PA patients were at high CV risk, 33% were at very high CV risk and only a small percentage of subjects was at low-intermediate risk. It has been also documented that patients with PA presented a higher global CV risk at the time of diagnosis, compared to control subjects with EH [66].

Data from the German Conn's Registry, representing the largest cohort ever reported in literature, indicate that in patients with

PA the prevalence of cardiovascular events (including angina pectoris, myocardial infarction, chronic cardiac insufficiency and coronary angioplasty) was 16.3%. Atrial fibrillation and other atrial or ventricular arrhythmias occurred in 7.1 and 5.2% respectively. Interestingly, a significant positive correlation was evident between the serum aldosterone levels and the prevalence of comorbidities in all PA patients [67]. Although the German study lacked a matched control group, the prevalence of cardiovascular complications in PA patients was higher than that reported in the literature for patients with EH of comparable cardiovascular risk profile. A significant difference in the prevalence of cardiovascular comorbidities between normokalemic and hypokalemic PA was demonstrated in this study also. The hypokalemic variant was associated with higher morbidity than the normokalemic variant regarding some cardiovascular (particularly angina pectoris and chronic cardiac insufficiency) but not cerebrovascular events, which can be explained by the higher aldosterone levels in the first group [67].

It should be noted that studies evaluating the impact of medical and surgical treatment on morbidity and mortality in patients with PA in the long term follow-up are equivocal. In the above mentioned study by Catena et al., the authors also evaluated long-term cardiovascular outcomes in patients with PA after surgical or medical treatment and the primary end point included MI, stroke, any type of revascularization procedure, and sustained arrhythmias. During the follow-up, whose mean duration was 7.4 years, cardiovascular outcome was not different between patients with PA and EH and was comparable in PA between patients with AHA and BAH. Further analysis indicated that older age and longer duration of hypertension were independently associated with a higher risk of a cardiovascular event [64].

However in the study by Mulatero et al., patients treated for PA, during median follow-up of 12 years, had a higher rate of events (8.5 vs. 4.3% EH patients) and, in particular, arrhythmias and stroke were more frequent in patients with PA. Age, the duration of the hypertension and systolic BP were independently associated with the occurrence of all events [65].

Recent data from the German Conn's Registry and a German control cohort of subjects from a population-based survey allowed the mortality of patients treated for PA to be assessed, as well as enabling risk factors for the adverse outcomes to be identified. The study showed that cardiovascular mortality is increased in patients treated for PA (50 vs. 34% in hypertensive controls). However, after matching for age, gender, BMI, or BP, the data showed that all-cause mortality in patients with PA were not significantly different from matched hypertensive controls [68].

In summary, current evidence convincingly demonstrates that patients with PA are at a higher risk of cardiovascular events than those with EH (**Fig. 4**). Surgical and medical treatments have a beneficial impact on the cardiovascular outcomes and mortality in the long term follow-up.

Conclusion

There is growing evidence indicating that prolonged exposure to elevated aldosterone concentrations in patients with PA is associated with target organ damage in the heart, kidney and arterial wall, as well as with high cardiovascular risk, independently from the BP level.

Therefore a low threshold to initiate workup of PA should be taken since early diagnosis and treatment have a substantial impact on the cardiovascular outcomes and mortality in the long term. Further studies may provide better insight into the relationship between cardiovascular risk and complications and the genetic background of PA.

Acknowledgements

AP and AJ received the research project founded by the National Science Centre, Poland (Project's decision NCN DEC-2011/03/B/NZ5/05325).

Conflict of Interest

The authors declare no conflict of interest.

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