Ambulatory Blood Pressure Monitoring–Derived Short-Term Blood Pressure Variability in Primary Aldosteronism

Andrea Grillo, MD;[1] Stella Bernardi, MD;[1] Andrea Rebellato, MD;[2] Bruno Fabris, MD;[1] Moreno Bardelli, MD;[1] Jacopo Burrello, MD;[3] Franco Rabbia, MD;[3] Franco Veglio, MD;[3] Francesco Fallo, MD;[2] Renzo Carretta, MD[1]

From the Department of Medical, Surgical and Healthy Science, University of Trieste, Trieste, Italy;[1] Department of Medicine-DIMED, University of Padova, Padova, Italy;[2] and Division of Internal Medicine and Hypertension Unit, Department of Medical Sciences, University of Torino, Torino, Italy[3]

The aim of this study was to investigate the short-term blood pressure (BP) variability (BPV) derived from ambulatory blood pressure monitoring (ABPM) in patients with primary aldosteronism (PA), either idiopathic hyperaldosteronism (IHA) or aldosterone-producing adenoma (APA), in comparison with patients with essential hypertension (EH) and normotensive (NT) controls. Thirty patients with PA (16 with IHA and 14 with APA), 30 patients with EH, and 30 NT controls, matched for sex, age, body mass index, and antihypertensive therapy, were studied. The standard deviation (SD) of 24-hour, daytime, and nighttime BP; 24-hour weighted SD of BP; and 24-hour BP average real variability were not different between patients with PA and those with EH (*P*=not significant). All BPV indices were higher in patients with PA, either IHA or APA subtypes, and patients with EH, compared with NT controls (*P*<.001 to *P*<.05). ABPM-derived short-term BPV is increased in patients with PA, and it may represent an additional cardiovascular risk factor in this disease. The role of aldosterone excess in BPV has to be clarified. *J Clin Hypertens (Greenwich).* 2015;17:603–608. © 2015 Wiley Periodicals, Inc.

Primary aldosteronism (PA) represents the most frequent form of secondary arterial hypertension.[1] Several clinical studies indicate that primary aldosterone excess may lead to higher prevalence of cardiovascular complications than in essential hypertension (EH).[2,3] A number of mechanisms independent from blood pressure (BP) elevation, including enhanced oxidative stress, sympathetic nervous dysfunction, and/or increased prevalence of multiple metabolic abnormalities, have been hypothesized to explain the pathogenesis of this finding.[2,4] The degree of increased short-term (ie, within a 24-hour period) BP variability (BPV) and newer ambulatory BP monitoring (ABPM)–derived BPV indices have been recognized as independent predictors of cardiovascular risk, above the contribution provided by average BP values, in hypertensive populations.[5–10]

The aim of our study was to investigate the ABPM-derived short-term BPV indices in a cohort of patients with PA, in comparison to patients with EH and normotensive (NT) controls.

METHODS

Study Population

In this cross-sectional study, we examined 30 patients with PA (17 men and 13 women; mean age, 54.1±11.8 years; age range, 32–66 years) and 30 patients with EH (17 men and 13 women; mean age, 54.5±12.8 years; age range, 40–68 years). The two hypertensive subgroups were recruited from a much larger patient population (about 1000 patients) consecutively referred to our three hospital-based specialized hypertension outpatient clinics during the past 5 years, and were matched for sex, age, body mass index (BMI), and antihypertensive therapy. The reasons for patient referral were onset of high BP at a young age, hypertension resistant to conventional antihypertensive treatment, hypertension with unexplained spontaneous or diuretic-induced hypokalemia, elevated plasma aldosterone, low plasma renin activity (PRA), and an adrenal incidentaloma.[11] Thirty healthy patients matched for sex, age, and BMI were used as NT controls and were recruited among hospital staff using the same exclusion criteria as hypertensive patients.

Patients with clinical and/or laboratory evidence of associated clinical conditions such as diabetes (ie, those with fasting glucose levels >126 mg/dL on two separate occasions), obesity (BMI ≥30 kg/m^2); cerebrovascular, coronary, or peripheral artery disease; cardiac insufficiency; renal and/or hepatic disease; obstructive sleep disorder; and history of cardiovascular and cerebrovascular events were excluded. The definition of associated clinical conditions was in accordance with that reported by the European Society of Hypertension/European Society of Cardiology guidelines.[12] Other forms of secondary hypertension were excluded on the basis of standard biochemical, hormonal, and radiological tests. Renal disease was defined by the presence of serum creatinine >1.5 mg/dL in men and >0.135 mg/dL in women. Glomerular filtration rate was estimated by calculating creatinine clearance with the formula of Cockroft-Gault.[13] Patients and NT controls with an

Address for correspondence: Francesco Fallo, MD, Department of Medicine-DIMED, University of Padova, Clinica Medica 3, Via Giustiniani 2, Padova 35128, Italy
E-mail: francesco.fallo@unipd.it

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alcohol intake >40 g/d for men or >20 g/d for women in the past year were considered current drinkers. Smoking habit was defined as at least one cigarette daily for 1 year in the past 5 years.

After the first office visit at our clinics, all patients underwent diagnostic procedures as outpatients. During evaluation, they consumed a normal sodium and potassium diet (100–200 mEq/d sodium and 50–70 mEq/d potassium). All patients followed the diet under the control of the hospital staff. After at least a 7-day diet, the relationship between sodium and potassium intake with sodium and potassium urinary excretion was randomly checked in 24-hour urine specimens collected from the majority of patients. Each PA and EH patient group who underwent ABPM included the same number of newly diagnosed and never-treated patients (n=12). Among the remaining patients in either the PA or EH groups, only those receiving calcium channel blockers at the minimal doses required to achieve BP control (n=18) were selected. In these patients, any other antihypertensive medications were withdrawn for 3 weeks (up to 6 weeks for spironolactone) before diagnosis. This allowed to avoid the interference of diverse antihypertensive drugs on ABPM profile. Calcium channel blockers are known to have a neutral effect on renin and aldosterone levels and not to impair glucose and lipid parameters.[14–16] These agents have been also found to slightly reduce BPV.[17,18] All BP measurements were performed according to the European Society of Hypertension/European Society of Cardiology guidelines.[12]

Differential diagnosis criteria for the different forms of PA were in accordance with the Endocrine Society guidelines, as previously described.[19,20] Briefly, for the diagnosis of PA, all patients with an upright plasma aldosterone to PRA ratio >40 (aldosterone in ng/dL and PRA in ng/mL/h), in the presence of aldosterone >15 ng/dL and suppressed PRA, underwent saline infusion (0.9% NaCl 500 mL/h for 4 hours) as a confirmatory test.[21] Patients with plasma aldosterone levels that did not fall below 5 ng/dL after the saline infusion were diagnosed as having PA. In all of these patients, a computed tomography scan with fine cuts (2.5–3 mm) of the adrenal and/or an adrenal venous sampling were performed to differentiate between aldosterone-producing adenoma (APA) and idiopathic hyperaldosteronism (IHA). Sampling was considered successful if the adrenal vein/inferior vena cava cortisol gradient was at least 3; lateralization was considered when the aldosterone to cortisol ratio from one adrenal was at least four times the ratio from the contralateral gland. The presence of the syndrome of glucocorticoid-remediable aldosteronism was excluded by the long polymerase chain reaction test.[22] Sixteen patients were classified as having IHA and 14 as having APA. AVS was performed in 18 of 30 patients. In all patients who underwent unilateral adrenalectomy, an adrenal adenoma was confirmed at surgery and histological examination.

Each patient provided informed consent for the study, which was approved by the local ethical committee. Within the assessed entire PA population from our three outpatient clinics, a total of 84 patients did not meet inclusion criteria for the study, mainly because of the presence of comorbidity and/or different antihypertensive treatment. There was no difference between included and excluded PA patients for sex, age, BMI, clinical BP values, and serum potassium and aldosterone/PRA levels. Among the assessed entire EH population, the majority of patients (more than 500) did not meet inclusion criteria for the same reasons reported above for PA patients; a random selection among the remaining patients, based on similar sex distribution, age, BMI, and antihypertensive therapy, was performed.

Ambulatory BP Monitoring

All patients underwent 24-hour ABPM (Takeda TM2430, Asahi, Japan), which was carried out as a part of the procedures before diagnosis, in a day separate from the first office visit. Recording started between 8:30 AM and 9 AM. Patients were instructed to closely report daily activities during the recordings. Recording was programmed for every 15 minutes during a 24-hour period. Measured values of systolic BP (SBP), diastolic BP (DBP), and heart rate were stored in a digital memory. The readings of the automatic recorder were checked against those obtained with a mercury sphygmomanometer at the beginning and at the end of each 24-hour monitoring session; a difference within ±5 mm Hg was considered an adequate agreement between the two methods. Measured values of SBP, DBP, and heart rate were downloaded from the monitor to an IBM PC (IBM Co, New York, NY) using custom software. BP and heart rate measurements were excluded from the analysis when they were missing or labeled as technically erroneous by the monitor software. If a BP recording had less than 70% successful readings, it was rejected and repeated. During the monitoring period, a written diary of physical and mental activities as well as sleep duration was kept. BP readings of patients were discarded in case of a lack of sleep during the night (patients not included in the study). Daytime and nighttime periods used for ABPM were from 8 AM to 10 PM and from midnight to 6 AM, respectively.

Short-Term BPV Measures

Short-term BPV was derived from ABPM and calculated as the following: (1) standard deviation (SD) of 24-hour, daytime, and nighttime BP;[7] (2) the average of daytime and nighttime SD, each weighted for the duration of the day and night periods (24-hour "weighted" SD of BP), which allows to remove the mathematical interference from nighttime BP fall;[7] and (3) average real variability (ARV), ie, the average of the absolute differences between consecutive BP measurements over 24 hours.[6]

Clinical and Laboratory Methods

In all individuals, clinical parameters and blood samples for biochemical parameters were obtained in the morning after overnight fasting at the time of ABPM study.

PRA and aldosterone were determined by radioimmunoassay kits from Sorin Biomedical Diagnostics, Saluggia, Italy.[21] The normal range for upright PRA is 1.5 ng/mL/h to 5.2 ng/mL/h and the normal range for upright plasma aldosterone is 5 ng/dL to 35 ng/dL. For hormone measurements, intra-assay and interassay coefficients of variation were <10%. All other biochemical variables were assayed in plasma or serum using standard methods.

Statistical Analysis

Statistical analysis was performed using the SPSS, PC version 20.0 (SPSS Inc, Chicago, IL). All results are expressed as mean±SD for continuous variables and as proportion for categorical variables. Continuous data were subjected to the Kolmogorov-Smirnov test to determine their distribution. Differences between means were assessed by Student *t* test or by Mann-Whitney *U* test in non-normally distributed data for two-sample comparison or by one-way analysis of variance applying Fisher's least-significant difference post-hoc test for multiple comparisons. Chi-square statistics test was used to assess differences between categorical variables. Relationships between continuous variables were assessed calculating the Pearson's correlation coefficient or the Spearman's rank correlation coefficient when appropriate. *P* values <.05 were considered statistically significant.

RESULTS

Table I summarizes clinical and biochemical parameters in PA and EH patients and in NT controls. Age, sex, and BMI were similar (*P*=not significant [NS]) in the PA, EH, and NT control groups. Serum potassium levels were lower in patients with PA compared with those with EH, while the aldosterone/PRA ratio in patients with PA was significantly higher than that in EH patients. No differences in the other biochemical parameters between the PA and EH groups were observed.

Table II summarizes 24-hour ABPM values and ABPM-derived short-term BPV parameters in the different subgroups. Twenty-four–hour as well as daytime and nighttime SBP/DBP did not differ between PA and EH patients, while both were higher than in the NT group. In comparison with NT controls, patients with PA and EH had higher SD of 24-hour, daytime, and nighttime SBP/DBP as well as higher weighted SD and ARV of 24-hour SBP/DBP (*P*<.001 to *P*<.05). The difference in BPV parameters between hypertensive patients and NT controls was maintained in spite of reduced BPV parameters, as expected in patients receiving calcium channel blockers as antihypertensive treatment. No difference for 24-hour, daytime, and nighttime SD of SBP/DBP between patients in the PA and EH groups was observed. Within the PA group, no difference for all BPV indices was seen between IHA and APA subtypes, and all levels of statistical significance for short-term BPV parameters were maintained when either APA or IHA subtypes were compared with NT controls. Systolic/diastolic day-night BP fall was not different in the PA and EH groups (−14.3±18.2/−18.4±17.7 mm Hg vs −12.4±7.7/−16.0±8.6 mm Hg, *P*=ns). No correlation was observed between PRA and/or aldosterone levels and the different BPV indices in hypertensive patients overall, and in either PA or EH group, separately (*P*=ns).

DISCUSSION

ABPM has enabled a noninvasive estimate of BPV to be obtained. Several studies suggest that ABPM-derived short-term BPV can have prognostic relevance, predicting organ damage and cardiovascular events over and above the contribution provided by average BP values in different hypertensive populations.[8,10,23] To our knowledge, this is the first study designed to evaluate the ABPM-derived short-term BPV in patients with PA.

Generally, the mechanisms hypothesized to explain increased BPV in the short term involve:[10,21] (1) central and reflex autonomic modulation (ie, an increased central sympathetic drive and impaired baroreflex sensitivity); (2) elastic properties of arteries (ie, a reduced arterial compliance); (3) dysfunction of rheological (ie, increased blood viscosity) and humoral (insulin, angiotensin II, bradykinin, endothelin-1, nitric oxide) factors; and (4) emotional (ie, psychological stress) and behavioral factors. Indeed, all these aspects should be discussed to explain the increased BP variability in our PA patients, similar to that of EH patients.

Several studies refer to the importance of sympathetic activity and arterial baroreflexes in regulating cardiovascular variability, and report other factors, including the vascular response to sympathetic stimuli, which play a role in determining the strength of BP oscillations.[24,25] The pathogenesis of mineralocorticoid hypertension is complicated. In humans it results from a series of dynamic alterations including early expansion of intravascular blood volume, increased or normal cardiac output, and increased peripheral vascular resistance.[26] Early studies have suggested that hypertension might not be related to a hypervolemic state, except possibly in the early phase.[27] A general disturbance of autonomic cardiovascular function has been postulated as a possible mechanism for hypertension in PA.[28] In contrast with early data,[29] there is evidence of an increased peripheral sympathetic overactivity in PA, as measured by muscle sympathetic nerve activity with intraneuronal microelectrodes.[30] Furthermore, an enhanced peripheral vascular responsiveness to a normal sympathetic outflow and an impaired baroreflex gain have been suggested as pathogenic mechanisms of hypertension in PA.[31] At variance, there are other reports in PA showing

TABLE I. Demographic and Biochemical Features of the Study Patients and Normotensive Controls

	PA (n=30)	Essential Hypertension (n=30)	Normotensive Controls (n=30)
Age, y	54.1±11.8	54.5±12.8	56.2±10.7
Male/female, No.	17/13	17/13	15/15
Body mass index, kg/m^2	25.0±6.5	25.8±3.6	25.2±3.4
Smokers, %	23	25	22
Alcohol drinkers, %	18	20	16
Glucose, mg/dL	92.3±15.2	97.6±15.3	NA
Total cholesterol, mg/dL	217.7±52.2	211.2±50.6	NA
LDL cholesterol mg/dL	142.1±44.5	134.7±44.5	NA
HDL cholesterol, mg/dL	53.4±14.7	56.4±17.6	NA
Tryglicerides, mg/dL	115.3±67.2	134.7±44.5	NA
Serum potassium, mEq/L	3.2±0.5	4.1±0.4[a]	NA
Serum creatinine, mg/dL	0.74±0.1	0.78±0.2	NA
Creatinine clearance, mL/min	105.1±10.3	103.2±11.5	NA
Aldosterone, ng/dL	47.2±40	21.5±8.7[a]	NA
PRA, ng/mL/h	0.3±0.2	3.3±0.9[a]	NA
Aldosterone/PRA ratio	200.5±176.4	6.6±3.7[a]	NA

Abbreviation: HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not available. Values are expressed as mean ±standard deviation. Primary aldosteronism (PA) vs essential hypertensive patients, [a]$P<.001$.

TABLE II. ABPM Values and ABPM-Derived Short-Term BP Variability Indices of the Study Patients and Normotensive Controls

	PA (n=30)	Essential Hypertension (n=30)	Normotensive Controls (n=30)
24-h systolic BP, mm Hg	136.3±14.9[a]	137.2±10.1[b]	116.5±6.5
24-h diastolic BP, mm Hg	84.0±8.5[a]	84.4±8.9[b]	71.7±7.3
24-h heart rate, beats per min	71.1±11.1	69.2±10.4	70.8±10.3
24-h SD of systolic BP, mm Hg	15.5±4.3[a]	15.2±4.1[b]	11.3±2.9
Daytime SD of systolic BP, mm Hg	13.1±4.4[c]	12.4±3.2[b]	9.7±2.9
Nighttime SD of systolic BP, mm Hg	11.1±4.1[c]	10.5±4.4[d]	8.7±2.2
24-h SD of diastolic BP, mm Hg	12.3±3.6[a]	11.8±2.9[b]	9.2±2.0
Daytime SD of diastolic BP, mm Hg	10.2±4.0[c]	9.6±2.7[e]	7.9±1.8
Nighttime SD of diastolic BP, mm Hg	8.3±3.3[f]	8.2±2.7[d]	7.1±1.3
24-h weighted SD of systolic BP, mm Hg	12.5±3.9[c]	11.8±3.0[e]	9.4±2.2
24-h weighted SD of diastolic BP, mm Hg	9.7±3.4[a]	9.2±2.3[b]	7.6±1.4
24-h ARV of systolic BP, mm Hg	9.9±2.7[a]	8.9±2.2[b]	7.7±1.4
24-h ARV of diastolic BP, mm Hg	8.0±3.1[c]	7.2±1.3[e]	6.4±0.9

Abbreviations: ABPM, ambulatory blood pressure monitoring; ARV, average real variability; BP, blood pressure. Values are expressed as mean±standard deviation [SD]. Patients with primary aldosteronism (PA) vs normotensive controls: [a]$P<.001$, [c]$P<.01$, [f]$P<.05$ and patients with essential hypertension vs normotensive controls: [b]$P<.001$, [d]$P<.05$, [e]$P<.01$.

reduced muscle sympathetic nerve activity[32] and decreased BP variability, compared with EH patients, as a result of the preservation of baroreflex function.[33] All these studies were obtained when patients were examined for a short time and/or during acute exercise, and therefore may not reflect the overall daily activity of the autonomic system. Our findings that ABPM-derived BPV (which comprises different time intervals, ie 24-hour, daytime, and nighttime) is higher in PA patients than in NT controls seem to support the hypothesis of a persistent circadian link between aldosterone excess and sympathetic overactivity. Rapid fluctuations of multiple circulating factors with direct central or peripheral action, including aldosterone, might in part explain the similar day-night profile of BPV in EH patients. The lack of differences between PA and EH patients also included the weighted 24-hour SD of BP, an index that has been recently shown to correlate better with end-organ damage than conventional 24-hour SD of BP and is not influenced by nocturnal BP fall.[7] This is in accordance with similar circadian BP variation in PA and EH patients generally reported in the literature[34] and confirmed by our present study.

Regarding reduced arterial compliance, 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 BP levels, and aldosterone may thus act as an independent risk factor for vascular damage.[35] We cannot exclude that the lack of difference in BPV parameters between PA and EH in our study was the result of the different stage of hypertensive disease or duration of hypertension. To our knowledge, among rheological factors, the effect of PA on the coagulation system has not been systematically investigated.[36] An insulin-resistant state and/or diabetes have been found to be associated with high ABPM-derived short-term BPV.[37,38] In this respect, we purposely excluded PA or EH patients presenting with diabetes mellitus in order to avoid interference of altered glucose metabolism on BPV parameters. In a large unselected population, PA patients show BPV indices greater than that seen in EH patients, likely because of their frequent association with diabetes and/or glucose intolerance.[4] Patients with obesity, either PA or EH, were also excluded, since this disease may also have an impact per se on cardiovascular autonomic dysfunction.[38,39] We were unable to have comprehensive urinary sodium data in our hypertensive groups. Based on the random control of a normal sodium diet in several patients in both the PA and EH groups, it seems unlikely that the lack of difference in BPV parameters between the two populations could have been caused by interdependence between aldosterone and different salt intakes, as suggested for other BP-related target organ effects.[40] Moreover, potassium levels seem not to have an impact on short-term BPV indices, since they were similar in the two hypertensive groups in spite of significantly lower potassium levels in PA patients. Finally, it is known that PA is associated with a high prevalence of psychopathology aspects, including mood and anxiety disorders.[41] However, the potential impact of a higher level of persistent emotional distress on BP has never been systematically explored in this disease.

Study Limitations

Potential limitations of the present study should be considered. First, the study used a retrospective design and included patients either never treated or receiving antihypertensive monotherapy, introducing selection bias and serendipitous findings. Second, the relatively small size of the patient groups could have led to a type 2 statistical error.

CONCLUSIONS

ABPM-derived short-term BPV is increased in patients with PA, either IHA or APA, and it may represent an additional cardiovascular risk factor in this disease. The role of aldosterone excess in BPV, ie, as the result of an amplified pulsatile secretion,[42] has to be further clarified.

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