Assessment of Short-term Blood Pressure Variability in Patients With Ascending Aortic Dilatation

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ABSTRACT

Background: Blood pressure variability (BPV) is a novel parameter related to adverse cardiovascular findings and events, especially in hypertensive patients. The aim of the present study was to investigate the relationship between short-term BPV and ascending aortic dilatation (AAD).

Hypothesis: Hypertensive patients with AAD may exhibit higher short-term BPV compared to hypertensive patients with normal diameter ascending aorta and BPV may be correlated with aortic sizes.

Methods: Seventy-six hypertensive patients with AAD and 181 hypertensive patients with a normal-diameter ascending aorta were retrospectively enrolled in the study. Clinical data, echocardiographic characteristics, and 24-hour ambulatory blood pressure monitoring characteristics were compared between the 2 groups. Standard deviation (SD) and Δ of BP were used as parameters of BPV.

Results: Although 24-hour mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) were similar between the 2 groups, the SD of SBP and SD of DBP values were significantly higher in AAD patients (17.2 ± 6.8 vs 13.8 ± 3.5 , $P < 0.01$; and 12.1 ± 5.1 vs 10.7 ± 3.1 , $P = 0.02$, respectively). Daytime SD of SBP values were higher in AAD patients, whereas nighttime SD of SBP values did not differ between groups. In multivariate linear regression analysis, 24-hour SD of SBP, 24-hour Δ SBP, daytime SD of SBP, daytime Δ SBP, and left ventricular mass index were independently correlated with aortic size index.

Conclusions: Our study revealed higher levels of short-term BPV in hypertensive patients with AAD. This conclusion warrants further study.

Introduction

Hypertension can lead to serious end-organ damage including coronary artery disease, peripheral artery disease, left ventricular hypertrophy, nephropathy, and retinopathy.¹ Average blood pressure (BP) was considered to be responsible for these complications for a long time. But nowadays, independent of average BP, blood pressure variability (BPV) has emerged as a new risk factor for adverse cardiovascular events in hypertensive patients.² Additionally, BPV is considered to have a role in development and progression of these end-organ injuries,³ so it can be a novel therapeutic target.

Normally, blood pressure exhibits beat-to-beat, minute-to-minute, hour-to-hour, and day-to-night fluctuations (short-term BPV) and diurnal, monthly, or seasonal fluctuations (long-term BPV). Twenty-four-hour ambulatory BP monitoring is a widely used method evaluating short-term BPV.⁴

Hypertension has a well-known association with ascending aortic dilatation (AAD) and dissection.⁵ But there are no data regarding association between BPV and AAD in the literature. The aim of our study is to investigate the relationship between short-term BPV and AAD.

Methods

Study Population

We evaluated 2700 patients who underwent 24-hour ambulatory blood pressure monitoring (ABPM) from July

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2013 to July 2015 at Siyami Ersek Cardiovascular Center in Istanbul, Turkey were excluded. Patients who did not have echocardiographic evaluation, as well as those who were using antihypertensive drugs or who had congenital heart disease (including bicuspid aortic valve), connective tissue disorders, trauma, familial thoracic aortic aneurysm syndromes, genetic diseases, infectious diseases, coronary artery diseases, congestive heart failure, postsurgical state, and normotension. In total, 257 patients with a new diagnosis of hypertension who had not undergone any antihypertensive treatment were included in the study. Medical reports of these patients were investigated and clinical characteristics were recorded.

Measurement of Blood Pressure and Assessment of Blood Pressure Variability

Office BP values were recorded from the outpatient clinic database. Office BP measurements were achieved in accordance with Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure Seventh Report (JNC-7) guidelines in an outpatient clinic using a standard mercury sphygmomanometer. Twenty-four-hour ABPM was performed with a noninvasive portable BP monitor (Oscar 2 system; SunTech Medical, Morrisville, NC). Blood pressure was measured at 30-minute intervals during the day (7 AM to 10 PM) and 60-minute intervals at night (10 PM to 7 AM). Mean BP and SD of BP measurements were obtained from the printed outputs of ABPM tests. Mean BP was reported as mean of 24-hour, daytime (7 AM to 10 PM) and nighttime (10 PM to 7 AM) BP recordings. Standard deviation of BP is the measure of dispersion from the mean of BP value and is reported automatically as 24-hour, daytime, and nighttime results in the test report. The Δ BP was defined as the difference between maximum BP and minimum BP and was reported for 24-hour, daytime, and nighttime recordings. Standard deviation and Δ BP were used as parameters of BPV.² Non-dipper patients were determined as individuals whose mean systolic blood pressure (SBP) decreased $<10\%$ at nighttime; dipper patients have a $\geq 10\%$ decrease in mean SBP at nighttime. Inverted dipper patients have an increase in mean SBP at nighttime compared with daytime.⁶ Dipper, non-dipper, and inverted dipper individuals were recorded.

Transthoracic Echocardiographic Imaging

Transthoracic echocardiography of hypertensive patients who were recently diagnosed using 24-ABPM were retrospectively recruited. The medical database was searched for reports of transthoracic echocardiography tests that were performed during evaluation of hypertension. Transthoracic echocardiographic studies were performed by cardiology specialists using the Vivid 3 system (General Electric, Milwaukee, WI) in accordance with the American Society of Echocardiography guidelines.¹ Interventricular septum diameter (IVSd), left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD) were recorded. Left ventricular (LV) mass was calculated according to the American Society of Echocardiography formula.¹ The ascending aortic

diameter was measured perpendicular to the long axis of the aorta with the use of the leading-edge method in the parasternal long-axis view showing the largest aortic diameters at 3 levels as annulus, sinus of Valsalva, and tubular ascending aorta. Aortic size index was calculated by dividing the ascending aortic diameter (mm) into the body surface area (BSA; m^2).⁷

Patients with tubular ascending aortic size index $>21 mm/m^2$ were considered the aortic dilatation group (Group 1).^{8,9} Individuals whose tubular ascending aortic size index was $<21 mm/m^2$ served as the control group (Group 2). Echocardiographic and ABPM findings were compared between the 2 groups. The study was approved by the local ethics committee.

Definitions

Hypertension was defined as a SBP ≥ 140 mm Hg and/or a DBP ≥ 90 mm Hg at office or a SBP ≥ 130 mm Hg and/or a DBP ≥ 80 mm Hg in ABPM.¹ Diabetes mellitus (DM) was defined as a fasting glucose level >126 mg/dL and/or if the patient was taking antidiabetic medication. Hyperlipidemia was defined as total serum cholesterol levels >240 mg/dL. Individuals who reported smoking at least one cigarette per day during the year before examination were classified as smokers. Body mass index (BMI) was calculated by dividing weight into the square of height, and BSA was calculated using the $[(height(cm) \times weight(kg))/3600]^{1/2}$ formula.^{7,10,11} Left ventricular mass index (LVMI) was calculated by dividing LV mass into the BSA.⁷

Statistical Analysis

All data are presented as a mean $\pm$ SD for variables with normal distribution. Categorical variables are reported as numbers and percentages. Continuous variables were checked for the normal distribution assumption using Kolmogorov-Smirnov statistics. Categorical variables were tested by the Pearson χ^2 test and the Fisher exact test. Differences between patients and control subjects were evaluated using the *t* test. The relation between numerical variables was identified using Pearson or Spearman ρ test. Univariate and multivariate linear regression analyses were performed to investigate the independent correlates of aortic size index in the study population. *P* values were 2-sided and values <0.05 were considered statistically significant. All statistical studies were carried out using SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL).

Results

Demographic, clinical, and echocardiographic characteristics of the study population are summarized in Table 1. Group 1 consisted of 76 consecutive patients with a dilated ascending aorta (mean age, 52.9 ± 8.6 years), and Group 2 consisted of 181 consecutive patients with a normal-size ascending aorta (mean age, 52.4 ± 9.6 years). The 2 groups were similar in terms of age, male sex, BMI, BSA, frequencies of DM and hyperlipidemia, smoking status, office SBP, and office DBP. Left ventricular ejection fraction, LVEDD, and LVESD did not differ between the 2 groups. However, LVMI was higher in Group 1 compared with the control

Table 1. Demographic, Clinical, and Echocardiographic Characteristics of the Study Population

Characteristics	Group 1, n = 76	Group 2, n = 181	P Value
Age, y	52.9 ± 8.6	52.4 ± 9.6	0.64
Male sex, n (%)	42 (55)	78 (43)	0.08
Hyperlipidemia, n (%)	24 (32)	57 (31)	0.98
DM, n (%)	13 (17)	30 (16)	0.91
Smoking, n (%)	17 (22)	39 (21)	0.88
BMI, kg/m ²	23.2 ± 2.7	23.7 ± 2.8	0.21
BSA, m ²	1.95 ± 0.1	1.94 ± 0.11	0.87
Office SBP, mm Hg	147.1 ± 12.2	145 ± 10.8	0.79
Office DBP, mm Hg	81.6 ± 6.8	80.4 ± 6.7	0.82
LVEDD, mm	47.6 ± 5.2	46.7 ± 5.1	0.22
LVESD, mm	28.4 ± 5.9	27.7 ± 5.7	0.45
IVSd, mm	10.8 ± 1.7	10.3 ± 1.4	0.02
LVEF, %	57.4 ± 5.8	58.4 ± 4.28	0.15
LVMI, g/m ²	105 ± 11	98 ± 10	0.01
Annulus diameter, mm	22.1 ± 0.8	21.5 ± 1.1	<0.01
Sinus of Valsalva diameter, mm	34.9 ± 3.9	30.6 ± 3.6	<0.01
Ascending aortic diameter, mm	45.1 ± 4.4	31.9 ± 2.5	<0.01
Aortic size index, mm/m ²	23.4 ± 2.2	16.7 ± 1.6	<0.01

Abbreviations: BMI, body mass index; BSA, body surface area; DM, diabetes mellitus; DBP, diastolic blood pressure; IVSd, interventricular septum thickness at diastole; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVMI, left ventricular mass index; SBP, systolic blood pressure.
Group 1, patients with dilated ascending aorta; Group 2, patients with normal-diameter ascending aorta.

group (105 ± 11 vs 98 ± 10 g/m², respectively; $P = 0.01$). Annulus, sinus of valsalva, tubular ascending aortic diameters, and aortic size index were higher in Group 1 compared with the control group (22.1 ± 0.8 vs 21.5 ± 1.1 mm, 34.9 ± 3.9 vs 30.6 ± 3.6 mm, 45.1 ± 4.4 vs 31.9 ± 2.5 mm, and 23.4 ± 2.2 vs 16.7 ± 1.6 mm/m², respectively; $P < 0.01$ for each comparison).

Comparison of ABPM findings between the 2 groups are summarized in Table 2. Mean systolic and diastolic BPs in the 24-hour period were similar between the 2 groups ($P = 0.84$ and $P = 0.69$, respectively). Standard deviation of SBP and SD of DBP values in the 24-hour period were significantly higher in Group 1 compared with the control group ($P < 0.01$ and $P = 0.02$, respectively). The 24-hour Δ SBP values were also significantly higher in AAD patients. However, 24-hour Δ DBP values were similar. Although mean daytime SBP did not differ between groups, SD of SBP and Δ SBP in the daytime period were significantly higher in AAD patients ($P = 0.94$, $P < 0.01$, and $P < 0.01$, respectively). When the nighttime period was assessed,

Table 2. 24-Hour Ambulatory BP Monitoring Findings of the Study Population

Characteristics	Group 1, n = 76	Group 2, n = 181	P Value
24-hour			
Mean SBP, mm Hg	138.0 ± 15.7	137.1 ± 10.6	0.84
Maximum SBP, mm Hg	167.9 ± 25.7	165.5 ± 22.8	0.46
SD of SBP, mm Hg	17.2 ± 6.8	13.8 ± 3.5	<0.01
Δ SBP, mm Hg	69.4 ± 17.9	57.7 ± 17.8	<0.01
Mean DBP, mm Hg	81.0 ± 10.8	80.2 ± 8.2	0.69
Maximum DBP, mm Hg	102.1 ± 18.7	100.4 ± 17.8	0.72
SD of DBP, mm Hg	12.1 ± 5.1	10.7 ± 3.1	0.02
Δ DBP, mm Hg	49.5 ± 20.4	45.2 ± 16.9	0.08
Daytime			
Mean SBP, mm Hg	142 ± 18.2	142 ± 10.7	0.94
SD of SBP, mm Hg	16.5 ± 7.7	13.1 ± 3.8	<0.01
Δ SBP, mm Hg	63.4 ± 18.5	50.8 ± 16.7	<0.01
Nighttime			
Mean SBP, mm Hg	130 ± 17.6	129 ± 11.9	0.54
SD of SBP, mm Hg	12.1 ± 4.9	12.4 ± 5	0.71
Δ SBP, mm Hg	36.2 ± 14.5	36.7 ± 16.3	0.80
Non-dipper HT, n (%)	46 (61)	97 (54)	0.30
Inverted dipper HT, n (%)	10 (13)	18 (10)	0.45

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; HT, hypertension; SBP, systolic blood pressure; SD, standard deviation.
Group 1, patients with dilated ascending aorta; Group 2, patients with normal-diameter ascending aorta.

mean SBP, SD of SBP, and Δ SBP did not differ between the 2 groups ($P = 0.54$, $P = 0.71$, and $P = 0.80$, respectively). The frequency of non-dipper and inverted dipper hypertensive patients was higher in AAD patients but the difference did not reach statistical significance (61% vs 54%, $P = 0.30$; and 13% vs 10%, $P = 0.45$, respectively).

In univariate correlation analysis, LVMI values were positively correlated with 24-hour mean SBP ($r = 0.14$, $P = 0.02$), 24-hour SD of SBP ($r = 0.18$, $P < 0.01$), 24-hour mean DBP ($r = 0.21$, $P < 0.01$), 24-hour SD of DBP ($r = 0.16$, $P < 0.01$), daytime mean SBP ($r = 0.16$, $P < 0.01$), daytime SD of SBP ($r = 0.15$, $P < 0.01$), daytime Δ SBP ($r = 0.12$, $P = 0.04$), 24-hour maximum SBP ($r = 0.18$, $P < 0.01$), and ascending aortic diameter/BSA ($r = 0.25$, $P < 0.01$). In addition, aortic size index was positively correlated with 24-hour SD of SBP ($r = 0.21$, $P < 0.01$), 24-hour Δ SBP ($r = 0.19$, $P < 0.01$), daytime SD of SBP ($r = 0.22$, $P < 0.01$), daytime Δ SBP ($r = 0.23$, $P < 0.01$), and LVMI ($r = 0.25$, $P < 0.01$; Table 3).

To investigate the independent correlates of aortic size index, we performed a multivariate linear regression analysis using a model adjusted for age, sex, DM,

Table 3. Univariate Correlation Analysis of Aortic Size Index With Study Parameters

Characteristics	Aortic Size Index	
	<i>r</i>	<i>P</i> Value
Age	0.10	0.12
24-h mean SBP	0.03	0.71
24-h SD of SBP	0.21	<0.01
24-h ΔSBP	0.19	<0.01
24-h mean DBP	−0.06	0.32
24-h SD of DBP	0.10	0.11
24-h ΔDBP	0.02	0.76
Daytime mean SBP	0.02	0.74
Daytime SD of SBP	0.22	<0.01
Daytime ΔSBP	0.23	<0.01
Nighttime mean SBP	0.02	0.71
Nighttime SD of SBP	−0.08	0.17
Nighttime ΔSBP	−0.07	0.24
24-h maximum SBP	0.04	0.56
24-h maximum DBP	−0.01	0.86
Office mean SBP	0.04	0.51
Office mean DBP	−0.01	0.96
LVMI	0.25	<0.01

Abbreviations: 24-h, 24-hour; DBP, diastolic blood pressure; LVMI, left ventricular mass index; SBP, systolic blood pressure; SD, standard deviation.

hyperlipidemia, smoking status, and LVMI. The 24-hour SD of SBP, 24-hour ΔSBP, daytime SD of SBP, and daytime ΔSBP were independently correlated with aortic size index (Table 4). In addition, LVMI (unstandardized coefficient $\beta = 0.008$, SE = 0.002, standardized coefficient $\beta = 0.273$, $P < 0.01$) was independently correlated with aortic size index according to the model including age, sex, DM, hyperlipidemia, smoking status, and 24-hour SD of SBP. Other ABPM parameters, age, sex, DM, hyperlipidemia, and smoking status were not correlated with aortic size index.

In receiver operating characteristic (ROC) analysis, 24-hour SD of SBP levels >15.7 mm Hg predicted dilatation of the ascending aorta with a sensitivity of 56.6% and a specificity of 75.7% (area under the curve: 0.701, 95% confidence interval: 0.632–0.770, $P < 0.01$); 24-hour ΔSBP levels >67 mm Hg predicted dilatation of the ascending aorta with sensitivity of 57.9% and a specificity of 74% (area under the curve: 0.693, 95% confidence interval: 0.623–0.762, $P < 0.01$).

Discussion

The main finding of our present study was that hypertensive patients with a dilated ascending aorta exhibited higher

Table 4. Multivariate Linear Regression Analyses for the Independent Correlates of the Study Parameters With Aortic Size Index^a

Characteristics	Unstandardized Coefficients β	SE	Standardized Coefficients β	<i>P</i> Value
24-h SD SBP ^b	0.011	0.004	0.158	<0.01
24-h Δ SBP ^b	0.003	0.001	0.158	<0.01
Daytime SD SBP ^b	0.011	0.004	0.169	<0.01
Daytime Δ SBP ^b	0.004	0.001	0.197	<0.01

Abbreviations: 24-h, 24-hour; DM, diabetes mellitus; LVMI, left ventricular mass index; SBP, systolic blood pressure; SD, standard deviation; SE, standard error.

^aMultivariable model was adjusted for age, sex, history of DM, hyperlipidemia, smoking status, and LVMI. ^bThese parameters were entered into the multivariable model separately to prevent multicollinearity.

short-term BPV compared with hypertensive patients with ascending aorta of normal diameter. In multivariate regression analysis, 24-hour SD of SBP, 24-hour ΔSBP, daytime SD of SBP, daytime ΔSBP, and LVMI were established as the independent correlates of aortic size index.

Hypertension is a common cardiovascular disease, and related end-organ injuries are known as the leading causes of cardiovascular morbidity and mortality.¹ To date, average BP obtained from clinical visits has been accepted as the most important sign and therapeutic target of hypertension. Significant relation of adverse cardiovascular events with BPV and the non-dipper phenomenon, in addition to average BP, have recently been reported in hypertensive patients.^{3,12}

Non-dipper hypertension is a clinical situation with blunted decrease in BP at nighttime. Increased cardiovascular morbidity and mortality have been demonstrated in non-dipper patients when compared with the dipper patients in previous studies.¹² Blood pressure variability reflects the fluctuations of BP over short-term (beat-to-beat, hour-to-hour, day-to-night) and long-term (days, weeks, months) periods. Twenty-four-hour ABPM is the widely used method for evaluation of short-term BPV.⁶ In recent studies, short-term BPV was found to be associated with target-organ damage and cardiovascular adverse events in normal and hypertensive individuals.¹³ Consistent with our results, prior studies have shown that increased BPV is associated with increased LVMI.¹⁴ Also, Milan et al reported association of LV mass with dilatation of the ascending aorta in hypertensive patients.¹⁵ Likewise, we found that LVMI was independently correlated with aortic size index.

Palatini et al indicated that daytime BPV, evaluated as SD of SBP, was associated with increased vascular injury in hypertensive patients.¹⁶ Moreover, nighttime BPV was found to be related to adverse cardiovascular events.¹⁷ However, Tatasciore et al reported that nighttime systolic BPV was not correlated with target-organ damage in patients with untreated and recently diagnosed hypertension.¹⁸ Similarly, in our study, nighttime BPV was not correlated with aortic size index, but 24-hour and daytime systolic BPV were found to be positively correlated with aortic size index in recently diagnosed hypertensive patients.

This difference between nighttime and daytime may be explained by the insufficiency of the 60-minute nocturnal measurement interval to enable an accurate quantification of short-term BPV.

Besides the SD of BP, the Δ BP value has been used to determine BPV.¹⁹ Similarly, we have used delta SBP and found significant correlation of Δ SBP with aortic size index. Also in our study, 24-hour Δ SBP values >67 mm Hg independently predicted dilatation of the ascending aorta.

In the literature, studies related with BPV usually indicate significance of systolic BPV. However, the relationship between diastolic BPV and cardiovascular events is controversial. Diastolic BPV was not found to be associated with target-organ damage and cardiovascular events in most of the studies.¹⁹ Conversely, a few studies do demonstrate the positive correlation of diastolic BPV with adverse cardiovascular events in the literature.^{17,20} In our study, 24-hour diastolic BPV was significantly higher in AAD patients. However, we did not find a positive correlation between diastolic BPV and ascending aorta diameter.

Several clinical and laboratory parameters contribute to aortic dilatation. Particularly, increased mean arterial BP is the leading predisposing factor for dilatation of the aorta.⁹ In addition to connective tissue disorders, bicuspid aortic valve, trauma, familial syndromes, infectious diseases, and postsurgical state may cause dilatation of the aorta.⁹ In a recent study, thoracic aortic diameters were found to be significantly higher in non-dipping hypertensive metabolic syndrome patients.⁶ But this was a study with a small sample size, and univariate and multivariate analyses of study parameters were not carried out. Also, the authors did not mention inverted dipper patients. We found that non-dippers and the inverted dipper pattern were more frequent in AAD patients. Nevertheless, the differences between the 2 groups were not statistically significant.

Milan et al reported that AAD was prevalent in hypertensive patients and that this dilatation was associated with increased aortic stiffness.¹⁵ Another study, conducted by Kotsis et al, revealed that increased BPV is related to increased aortic stiffness.²¹ Blood pressure variability may cause dilatation via increased aortic stiffness. Also it is known that hypertension exerts a destructive effect on the vasa vasorum of the aorta through 2 different mechanisms: one is direct compression on the vessel wall and hypoperfusion of the vasa vasorum, and the other is microangiopathic complications of hypertension on the vasa vasorum.²² In addition, BPV is related to microangiopathic complications at end organs, such as hypertension.²³ Hence, BPV may yield disruption of the vasa vasorum that supplies blood for fibroblasts. This situation can result in reduction of elastin and dilatation of the aorta. Also, the direct physical pressure effect of sudden alterations in BP may contribute to dilatation. These hypotheses may help to provide a link between BPV and aortic dilatation.

A meta-analysis investigating echocardiographic root dilatation in hypertensive patients revealed that office BP values were not directly associated with aortic root diameters.²³ Similarly, in our study, we did not find a relationship between office BP values and ascending aortic dimensions. However, short-term BPV and LVMI were found to be independently correlated with aortic diameters

in hypertensive patients. Therefore, BPV may be a more important determinant of aortic dilatation in hypertensive patients.

Effects of several antihypertensive drugs (amlodipine, telmisartan, losartan, atenolol, nebivolol, thiazides) on BPV have been investigated in preclinical and clinical studies. Among these drugs, calcium channel blockers have demonstrated greater attenuation in short-term BPV assessed with SD of SBP in 24-hour ABPM.^{14,24} The results of the studies investigating the effect of β -blockers on BPV are controversial. Rotwell et al found that atenolol increased BPV in hypertensive patients. Conversely, Cahan et al indicated that β -blocker therapy is not associated with increased BPV after heart-rate adjustment.²⁵ Consistent with this study, a recent review showed that increase in BPV is the result with nonselective β -blockers, but not with selective β -blockers.²⁶ Thus, to prevent the effect of antihypertensive drugs on BPV, we performed our study in hypertensive patients who did not receive treatment.

Study Limitations

A few limitations of our study deserve mention. This is a single-center retrospective study with a relatively small sample size. Our findings do not implicate an exact pathophysiological mechanism between higher BPV and AAD, and we could not report the correlation of the study parameters with long-term outcome in the study population. As the echocardiography reports were retrospectively recruited, echocardiographic images were obtained by different cardiology specialists. Although we included patients with a new diagnosis of hypertension, we could not investigate the effect of BP elevation on aortic diameters before the diagnosis of hypertension. Hence, we couldn't evaluate the relationship between duration of the disease, BPV, and ascending aortic diameters.

Conclusion

Although we could not draw a causal relationship, for the first time in the literature we have observed higher levels of short-term BPV in hypertensive patients with AAD. Further studies are needed to confirm our results and the importance of these findings in the long-term outcome and prognosis of patients with AAD.

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