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ORIGINAL ARTICLE

Left atrial dimension is related to blood pressure variability in newly diagnosed untreated hypertensive patients

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Variability in daily blood pressure (BPV) recorded 24-h ambulatory blood pressure monitoring (ABPM) is known to be related to left ventricular hypertrophy and an increased incidence of cardiovascular events in hypertensive patients. The aim of this study was to evaluate whether left atrium dimension, which increases early in hypertensive subjects, was related to BPV in a group of 167 drug-naive patients (100M/67F, age: 46 ± 11yr). The patients were chosen among those consecutively sent by their general practitioners to confirm the existence of arterial hypertension and afterwards diagnosed as hypertensive (mean 24-h ABPM ⩾ 130/80 mm Hg). In each patient, the left atrial posteroanterior diameter index for height (LADi) and the left ventricular mass standardized for body surface area (LVMi) were measured using standardized echocardiographic methods. BPV was calculated as the weighted mean of daytime and nighttime systolic and diastolic blood pressure s.d.'s (ws.d.), according to the formula ws.d. = [(daytime s.d. × 10)+nighttime s.d. × 6)]/16. An increase in left atrial dimension (LADi > 24 mm m^{-1}) was present in 36 patients (21.6% of the total population). In a univariate regression, LVMi was significantly related to systolic BPV ($r = 0.24$; $P = 0.02$) only in men, whereas LADi was significantly related to both systolic and diastolic BPV in both genders. After adjusting for sex, age, BMI, heart rate, diastolic function and estimated glomerular filtration rate, both systolic and diastolic BPV remained significantly related to LADi ($P = 0.02$ for both) but not to LVMi. In conclusion, this study suggests that BVP, as measured as BPws.d., is significantly and independently associated with increased LADi in newly diagnosed, treatment-naive hypertensive patients.
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Keywords: blood pressure variability; left atrial dimension; left ventricular mass; newly diagnosed hypertension

INTRODUCTION

Left atrial enlargement (LAE) is a common feature of hypertensive heart disease[1,2] and is present in ~30% of the population with arterial hypertension.[3,4] Most previous studies concerning the relationship between LAE and arterial hypertension, however, have included both treated and untreated patients and did not separate early, newly diagnosed from long-standing hypertension, thus leaving undetermined whether the rise in left atrial size may be considered a specific marker of heart damage, independent of the presence of left ventricular hypertrophy and of the effect of antihypertensive therapy.

Furthermore, the actual trigger of the heart damage in hypertension remains to be fully elucidated, and accordingly, the role played by variability in daily blood pressure (BPV) is still uncertain,[5] although several previous studies have related BPV to left ventricular hypertrophy and increased mortality due to cardiovascular diseases among hypertensive patients.[6–9] To the best of our knowledge, however, no data have been presented relating BVP and left atrium dimension in newly diagnosed non-treated hypertensive subjects.

The present study has been, therefore, conceived to verify the hypothesis that BPV is associated with an increase in atrial dimension as expressed by its diameter, independent from any modification in left ventricular mass, in a population of newly diagnosed and treatment-naive hypertensive patients.

METHODS

Subjects

The population under study was composed of all individuals who consecutively came to the Outpatient Clinic of the Hypertension Unit of S. Jacopo Hospital, Pistoia, Italy, from 2011 to 2013 and were sent by their primary care providers to confirm a diagnosis of arterial hypertension. Subjects were recruited for this study if they: (a) never previously used antihypertensive drugs or any cardioactive medication, (b) were not diabetic, that is, had fasting plasma glucose < 7 mmol l^{-1} and HbA1c < 6.5% (47.5 mmol mol^{-1}), and/or did not use antidiabetic drugs, (c) did not have atrial fibrillation and did not mention previous cardiovascular events or symptoms.

All patients had blood hemoglobin levels > 120 g l^{-1}, and the estimated glomerular filtration rate (eGFR) was measured using the four-variable equation from the Modification of Diet in Renal Disease (MDRD) study.[10]

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Blood pressure and echocardiographic measurements

Twenty-four-hour ambulatory blood pressure monitoring was performed using Spacelabs Healthcare model 90207 (WA, USA), and all patients had their blood pressure measured every 15 min during the daytime (1000 to 2000 hours) and every 20 min during the night (0000 to 0600 hours). Arterial hypertension was diagnosed if the average 24-h systolic BP was $\geqslant$130 mm Hg and/or average 24-h diastolic BP $\geqslant$80 mm Hg, according to current guidelines. Dipping *vs.* non-dipping status was diagnosed if subjects exhibited a nocturnal reduction in mean BP by 10% or more of the average daytime systolic BP.[11]

BPV was calculated as the weighted mean s.d. of both systolic and diastolic daytime and night blood pressure (ws.d.) (that is, as the mean day and night s.d. values corrected for the number of hours included in each of these subperiods, according to the following formula: ws.d. = [(daytime s.d. $\times$10) +nighttime s.d. $\times$6)]/16[12]).

Subjects were studied using both M-mode and two-dimensional echocardiography with an Acuson X 300 (Siemens, Malvern, PA, USA) with a 2–3.5 MHz phased-array transducer. Left ventricular internal diameter and wall thicknesses were measured at end-diastole, according to the recommendations of the American Society of Echocardiography,[13] which have been recently updated.[14]

Left ventricular mass (LVM) was calculated according to the following formula: LVM = 0.8*{1.04[([LVEDD+IVSd+PWTD]^3 − LVEDD^3)]}+0.6 g where IVSd = interventricular septum thickness in diastole; LVEDD = left ventricular end-diastolic diameter; PWTD = posterior wall thickness in diastole.[15] LVM was standardized for body surface area (LVMi) and expressed as g m^{-2}. Left ventricular hypertrophy was diagnosed if LVM indexed for body surface area (LVMI) was $>$115 g m^{-2} in males and $>$95 g m^{-2} in females.[16]

In all patients, the ejection fraction was $>$50% and diastolic function assessment was performed. Transmitral flow from the apical four-chamber window was recorded, placing the sample volume at the level of the mitral valve leaflet tips and obtaining the ratio of early diastolic velocity to atrial velocity (E/A ratio).[17] Clinically relevant diastolic dysfunction was scored as present if the E/A ratio was $<$1 (pattern of abnormal relaxation) or was $>$1.5 (restrictive patterns).[18]

In each patient, left atrial posteroanterior diameter was measured according to a standardized method,[19] indexed for measured height (LADi), and expressed as mm m^{-1}. LAE was defined as a LADi diameter indexed to a level $>$24 mm m^{-1}, as previously described.[3] All measurements were made by the same experienced physician (FC). All patients gave their written informed consent, and the study was approved by the Ethical Committee of our Hospital.

Table 1 Characteristics of the population under study

No.	167
Males (%)	59
Age (years)	46 ± 11
BMI (kg m^{-2})	25.6 ± 4.1
eGFR (ml min^{-1} 1.73 m^{-2})	89.1 ± 14.9
Smoking (%)	31
Heart rate (b.p.m.)	74 ± 11
Day-time 24-h systolic BP (mm Hg)	138.5 ± 9.7
Night-time 24-h systolic BP (mm Hg)	123.3 ± 11.7
Day-time 24-h diastolic BP (mm Hg)	91.2 ± 7.4
Night-time 24-h diastolic BP (mm Hg)	77.4 ± 9.1
Mean 24-h systolic BP (mm Hg)	133.1 ± 9.2
Mean 24-h diastolic BP (mm Hg)	85.9 ± 6.6
S.d. of mean 24-h systolic BP (mm Hg)	12.44 ± 3.02
S.d. of mean 24 h-diastolic BP (mm Hg)	10.68 ± 2.41
Mean 24-h systolic BP variability[a] (mm Hg)	9.13 ± 2.35
Mean 24-h diastolic BP variability[a] (mm Hg)	7.61 ± 1.88
Dippers, systolic BP (%)	43
Dippers, diastolic BP (%)	72
% Nocturnal systolic BP fall	11.2 ± 7.1
% Nocturnal diastolic BP fall	15.5 ± 8.9
Ventricular diastolic dysfunction[b] no. (%)	60 (36)
LVMi (g m^{-2})	95.4 ± 20.1
Left ventricular hypertrophy no. (%)	35 (20.9)
LADi (mm m^{-1})	21.7 ± 2.7
Left atrium enlargement (LaDi $>$ 24 mm m^{-1}) no. (%)	36 (21.6)

Abbreviations: eGFR, estimated glomerular filtration rate (MDRD); LADi, left atrial diameter expressed in millimetres indexed for height expressed in meters; LVMi, left ventricular mass indexed for body surface.
Values are means ± s.d.
[a]Expressed as ws.d. = weight means of mean blood pressure s.d. according to the formula: ws.d. = [(daytime s.d. $\times$10) +nighttime s.d. $\times$ 6)]/16.
[b]E/A ratio $<$1 or $>$1.5.

Statistics

Univariate regression analysis was performed using the least squares method. Multiple regression analysis was performed after adjusting for main confounders. Differences between means were calculated by the Wilcoxon rank-sum test, and differences between frequencies were tested by the chi-square method. All values are presented as means ± s.d., and a *P*-value $\leqslant$0.05 was considered statistically significant. All analyses were performed with SAS software, version 9.3 for Windows (SAS Institute, Cary, NC, USA).

RESULTS

The main characteristics of the population under study are reported in Table 1. In this population of newly diagnosed non-treated hypertensive patients, the prevalence rate of LAE was approximately the same as that of left ventricular hypertrophy (21.6% *vs.* 20.9%).

Diastolic dysfunction was present in 77 of 131 patients with normal atrial size (58%) and in 30 of 36 patients with LAE (83%). Consequently, patients with diastolic dysfunction had an approximate 40% higher risk of having LAE, as compared with those with normal atrial dimension (relative risk, by chi-square method: 1.42 (95% confidence interval: 1.15–1.47; P=0.006)). Compared with patients with normal atrial dimension, LAE was not associated with non-dipping status (chi-square: 0.168; P=NS).

In the univariate analysis, after stratifying by sex, LVMi and LADi were significantly related, and LVMi was significantly related to daytime, night and mean 24-h systolic blood pressure in both men and women, whereas LADi was related to only daytime blood pressure in men (Table 2). In addition, LVMi was significantly related to mean 24-h systolic BPV, as expressed by ws.d, and related inversely to heart rate and nocturnal diastolic BP fall only in men (Table 2). The rate of non-dippers was higher in patients with left ventricular hypertrophy (14 of 35) than in those without hypertrophy (28 of 132) (chi-square: 5.187; P=0.02) and was similar in patients with LAE (10 of 36) compared with those with normal left atrial size (32 of 131) (chi-square: 0.168; P=NS). LADi was, by contrast, related to daytime 24-h systolic BP (in men) and either to mean 24-h systolic or diastolic BPV in both genders (Table 2 and Figure 1). The s.d. of mean 24-h systolic BP was directly associated to LADi in men (Table 2). Both LVMi and LADi were significantly related to aging in both genders. No relation was evident between LADi or LVMi and eGFR, which ranged between 54 and 152 ml min^{-1} 1.73 m^{-2}. Finally, diastolic dysfunction (scored as 1 if present and 0 if absent) was significantly related to LADi (r=0.22; P=0.003) and not to LVMi (r=0.13; P=NS).

Systolic BPV was significantly higher in the group with left atrium enlargement (n=36; 10.21 ± 2.83 mm Hg) compared with the group with normal atrial size (n=131; 8.83 ± 2.32 mm Hg; P=0.001), whereas diastolic BPV, mean systolic BP or their s.d.'s were not significantly different (data not shown). Similarly, systolic BPV was significantly higher in patients with left ventricular hypertrophy than in those with normal ventricular mass (n=35; 10.29 ± 2.57 mm Hg *vs.* n=132; 8.82 ± 2.20 mm Hg; P=0.0009).

The relationship between LADi and diastolic or systolic BPV, as measured by ws.d., was confirmed by a multiple regression analysis

Table 2 Univariate regression analysis (correlation coefficients *r*) relating the variables under study, stratified by sex with

	LVMi [a] *r (P-value)*		*LADi r (P-value)*	
	Males (n = 100)	*Females (n = 67)*	*Males (n = 100)*	*Females (n = 67)*
Age	0.22 (0.03)	0.30 (0.01)	0.42 (0.0001)	0.38 (0.001)
eGFR	0.06 (NS)	0.07 (NS)	−0.14 (NS)	0.13 (NS)
Heart rate	−0.24 (0.02)	−0.11 (NS)	−0.07 (NS)	−0.08 (NS)
LVMi	—	—	0.37 (0.0002)	0.41 (0.0006)
LADi	0.37 (0.0002)	0.41 (0.0006)	—	—
Day-time 24-h systolic BP (mm Hg)	0.22 (0.02)	0.36 (0.002)	0.19 (0.04)	0.12 (NS)
Night-time 24-h systolic BP (mm Hg)	0.29 (0.003)	0.42 (0.0004)	−0.01 (NS)	0.12 (NS)
Mean 24-h systolic BP	0.22 (0.02)	0.47 (0.0001)	0.16 (NS)	0.18 (NS)
Mean 24-h diastolic BP	0.18 (NS)	0.11 (NS)	0.006 (NS)	−0.10 (NS)
Mean 24-h systolic BP variability[a]	0.24 (0.02)	0.19 (NS)	0.40 (0.0001)	0.26 (0.03)
Mean 24-h diastolic BP variability[a]	0.16 (NS)	0.02 (NS)	0.19 (0.05)	0.25 (0.04)
S.d. of 24-h systolic BP variability	0.05 (NS)	−0.05 (NS)	0.35 (0.0004)	0.11 (NS)
S.d. of 24-h diastolic BP variability	−0.09 (NS)	−0.17 (NS)	0.03 (NS)	0.13 (NS)
% Nocturnal systolic BP fall	−0.16 (NS)	−0.17 (NS)	0.17 (NS)	−0.03 (NS)
% Nocturnal diastolic BP fall	−0.21 (0.03)	−0.22 (NS)	0.04 (NS)	−0.15 (NS)

Abbreviations: eGFR, estimated glomerular filtration rate (MDRD); LADi, left atrial diameter indexed for height; LVMi, left ventricular mass indexed for body surface.
[a]Expressed as weight means of s.d. (ws.d.) according to the formula: ws.d. = [(daytime s.d. ×10) +nighttime s.d. ×6)]/16.

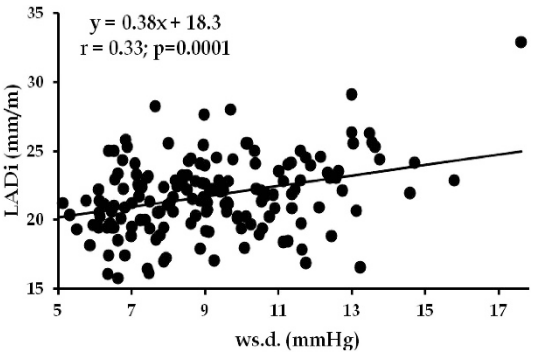

Figure 1 Regression between BPV expressed as weighted s.d. of mean systolic BP (ws.d.) and height-indexed left atrium diameter (LADi).

after adjusting for sex, age, body weight, heart rate, eGFR and presence of diastolic dysfunction. According to this same model, by contrast, LVMi was not independently associated with BPV (Table 3). In addition, it was evident that male sex and heart rate were significant independent predictors of only LVMi. Finally, adding diastolic dysfunction as a covariate into the multiple regression model did not modify the independent association between LADi and BPV.

DISCUSSION

Increase in left atrial dimension is an early event in patients with arterial hypertension[1,2] and, according to the present study, occurs in approximately one of five newly diagnosed patients. Moreover, it is equally prevalent as left ventricular hypertrophy in these subjects. It has been described that LAE, expressed as an increase in left atrial volume index, simply reflects the duration and severity of raised left atrial pressure and is independently associated with the response to exercise in hypertensive patients but not in normotensive control subjects.[20] This evidence further highlights that LAE is specifically due to hypertension. The driving cause, other than the elevation in blood pressure, of the increase in left atrial diameter and whether both ventricular hypertrophy and LAE share the same pathogenesis remains unclear. Among possible pathogenetic candidates, a recent study suggests that each of the clinical correlates of the metabolic syndrome (obesity, hypertension, diabetes, dyslipidemia) may be able to increase left atrial size and impair both left atrial and ventricular function.[21] Furthermore, the present study confirms that LAE is strongly associated with left ventricular diastolic dysfunction.[17,22] In addition, this study introduces novel data supporting the hypothesis that increased 24-h variability may be related to LAE in patients with newly diagnosed arterial hypertension, independent from the presence of left ventricular hypertrophy or function.

Previous studies have indeed shown a direct association linking increased 24-h BPV and incidence of cardiovascular complications in patients with treated hypertension, even after accounting for the elevation of mean BP levels.[6–9,23] Variability in arterial blood pressure rises with hypertension severity[24,25] and may be the culprit of heart and micro-vessel damage through increasing sympathetic activity, which leads to a direct effect on vessel or myocardial walls.[26,27] Nonetheless, whereas the relationship between mean BP levels and LVMi has been consistently found,[26,28] the relationship between 24-h BP variability and LVMi still remains controversial. Some studies have reported such a relationship,[6,7,23] and other studies have not,[29–31] particularly if the confounding effects of age and mean SBP were considered.[30] A recent cross-sectional study of a population of newly diagnosed hypertensive patients showed that 24-h systolic BPV is significantly related to early systolic dysfunction independent of left ventricular mass.[32] Interestingly, this association was found by the various methods used in measuring BP variability, either calculating the s.d. of mean awake systolic BP or, even if at a lesser extent, considering the 24-h weighted SBP variability. The main reason for these discrepancies may be because, in studying the relationship between BPV and the damage of target organs, the confounding effect of many related variables should be considered.[33] In this study's univariate analysis, the 24-h weighted SBP variability seems to be significantly higher in both patients with LAE and those with left ventricular hypertrophy. However, for LVMi, this relationship loses statistical significance after adjusting for other covariates. In addition, the issue of whether BPV and heart damage are related in newly diagnosed hypertension becomes more complex if considering that BPV is largely dependent on blood pressure physiological falls during

Table 3 Multiple regression analysis relating LADi (top) and LVMi (bottom) with both diastolic and systolic BP variability expressed as weight means of blood pressure s.d., after adjusting for heart rate, age, BMI, eGFR, sex and ventricular diastolic function

	β-Coefficient	P-*value*			P-*value*
LADi[a]					
Intercept	1.071	0.0001		1.021	0.0001
Mean 24-h systolic BP variability	0.018	0.02	Mean 24 h-diastolic BP variability	0.022	0.02
Heart rate	−0.0001	NS		−0.00011	NS
eGFR	−0.00007	NS		−0.0001	NS
Age	0.007	<0.0001		0.008	<0.0001
BMI	0.023	<0.0001		0.023	<0.0001
Sex[a]	0.003	NS		0.005	NS
Ventricular diastolic dysfunction[b]	0.012	NS		0.001	NS
LVMi[b]					
Intercept	87.771	NS		87.405	NS
Mean 24-h systolic BP variability	0.798	NS	Mean 24 h-diastolic BP variability	0.543	NS
Heart rate	−0.264	0.05		−0.264	0.05
eGFR	0.134	NS		0.138	NS
Age	0.276	0.04		0.319	0.01
BMI	0.964	0.005		1.012	0.003
Sex[a]	−12.448	<0.0001		−12.194	<0.0001
Ventricular diastolic dysfunction[b]	−0.041	NS		−0.495	NS

Abbreviations: eGFR, estimated glomerular filtration rate (MDRD); LADi, left atrial diameter indexed for height; LVMi, left ventricular mass indexed for body surface.
[a]1 = male; 2 = female.
[b]E/A ratio < 1 or > 1.5 scored as 1 or else 0.

the night. Nighttime falls in blood pressure seem to have a protective role against myocardial hypertrophy or remodeling, so that the absence of nocturnal falls in BP, such as in non-dipping status, has been considered an independent risk of left ventricular hypertrophy as well as of cardiovascular events.[11,34] This factor is slightly evidenced in this study, as only left ventricular hypertrophy appears to be independently associated with non-dipping status. LAE, by contrast, is not related to non-dipping status, and the way BPV has been measured, namely by calculating the weighted 24-h blood pressure variability, is largely independent from the extent of nighttime falls in blood pressure. In summary, both night falls in diastolic BP and heart rate appear inversely related with LVMi, at least in men ($r = -0.21$; $P = 0.03$ and $r = -0.24$; $P = 0.02$, respectively; Table 2), in agreement with previous studies.[35–38] However, there is no significant association with left atrial dimension.

In conclusion, whereas previous studies have related BPV with left ventricular geometry or function in newly diagnosed hypertension, no data exist, to our knowledge, on the independent relationship between BPV and LAE in this condition. We hypothesize that any increase in BPV may be associated more with the early enlargement of the thin atrial wall than with the remodeling of the thicker ventricular myocardium in these patients. In addition, the relationship between BPV and LAE seems to be consistent after controlling for main confounders, such as the direct effect of blood pressure itself, the dipping status and any possible interference of previous or current drug therapy. Moreover, the increase in atrial dimension is a major risk factor for future development of atrial fibrillation,[39] which represents a major concern in patients with hypertension.[40] Moreover, our findings suggest the hypothesis that administration, as early as possible, of anti-hypertensive drugs able to reduce abnormal BPV, such as calcium channel blockers or those acting on the renin–angiotensin system,[41,42] could exert their preventive action against atrial fibrillation incidence[43] through this mechanism other than their proven effect on atrial structural and electrical remodeling.[44]

Limitations and strengths of the study

The main limitation of this study is that we used only a linear measurement of atrial dimensions, and left atrium volume would have been more accurate than LA diameter. However, the simple linear measurement had the advantage of being more convenient in daily clinical practice and possibly less associated with multiple measurement errors. In addition, when atrial diameter is standardized for a linear measure such as height, it seems to be well related to patients' main anthropometric parameters.[45] Furthermore, previous studies that highlighted how switching from linear to volumetric measurements of the left atrium may have led to a greater sensitivity in detecting LAE were based on patients who were relatively older and had more advanced cardiac damage than the newly diagnosed hypertensive subjects enrolled in the present study.[46,47] The main strength of our study is that it considers drug naive patients of both genders at their initial clinical diagnosis of hypertension.

CONCLUSIONS

In conclusion, according to this study, both systolic and diastolic BPV are independent risk factors of LAE in newly diagnosed hypertension. In our opinion, this finding opens new perspectives to better understand the pathophysiology of initial heart damage in patients with arterial hypertension, suggesting possible implications in its prediction, prevention and therapy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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