Factors Associated With Diastolic Dysfunction in Patients With Resistant Hypertension: Resist-POL Study

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BACKGROUND
Diastolic dysfunction has been shown to be an independent factor of cardiovascular diseases in patients with hypertension. Very often, obstructive sleep apnea (OSA) and metabolic syndrome (MS) coexist with resistant hypertension (RHTN) and may lead to diastolic dysfunction. Thus, the purpose of this study was to investigate whether OSA and MS are associated with diastolic dysfunction in patients with RHTN independently from other factors, including age, left ventricular mass index (LVMI), and blood pressure (BP).

METHODS
Data from 155 patients (n = 92 men and 63 women) were analyzed. All patients underwent thorough examination, including biochemical evaluations, ambulatory blood pressure monitoring, polysomnography with assessment of apnea/hypopnea index (AHI), and echocardiography. LVMI and diastolic function parameters were obtained.

RESULTS
Patients were divided into 2 groups based on the presence or absence of diastolic dysfunction: group 1 (E’ < 10 cm/second; n=87) and group 2 (E’ > 10 cm/second; n = 68). AHI, LVMI, and 24-hour systolic BP/diastolic BP values were higher in group 1. E’ correlated with AHI (r = −0.25; P < 0.001), LVMI (r = −0.36; P < 0.0001), 24-h systolic BP/24-h diastolic BP (r = −0.28, P < 0.001; r = −0.30, P < 0.001, respectively), glucose level (r = −0.26; P < 0.01), and abdominal obesity (r = −0.28; P < 0.0001). In multivariable models decreased E’ was independently related to the presence of MS or abdominal obesity when separate components of MS were included in the model. Age and 24-hour systolic BP were independently associated with decreased E’. However, the relationship of decreased E’ with 24-hour systolic BP was nonsignificant if LVMI was included in the multivariable model.

CONCLUSIONS
MS and abdominal obesity were independently associated with diastolic dysfunction in patients with RHTN. OSA was not confirmed to be an independent factor of diastolic dysfunction.

Keywords: blood pressure; diastolic function; echocardiography; hypertension; metabolic syndrome; obstructive sleep apnea; resistant hypertension.

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Resistant hypertension (RHTN) is of major clinical importance because it has been associated with higher cardiovascular risk. It is postulated that the risk is related not only to high blood pressure levels but also to the development of organ damage, including left ventricular (LV) hypertrophy. Lately, emphasis has been placed on LV diastolic dysfunction, which appears to be a significant and independent predictor of mortality and cardiovascular events.

The most common and frequently coexisting conditions found in patients with RHTN are obstructive sleep apnea (OSA) and metabolic syndrome (MS). OSA and MS are also associated with increased cardiovascular mortality and morbidity. OSA and MS have also been linked to a progressive development of diastolic left ventricular dysfunction.

In the latest European Society of Hypertension/European Society of Cardiology guidelines for the management of arterial hypertension, emphasis was placed on diastolic dysfunction. Until now, little attention has been given to diastolic dysfunction in patients with RHTN. We hypothesized that OSA and MS, which frequently coexist with RHTN, may be independently associated with diastolic dysfunction. Thus, the purpose of this study was to investigate whether OSA and MS are associated with diastolic dysfunction in patients with RHTN independently from other factors, including age, LV mass index (LVMI) and blood pressure (BP).

METHODS
Patients
Patients were enrolled in the Resist-POL study at the Department of Hypertension, Institute of Cardiology, in Warsaw, Poland, between 2009 and 2011. Patients included in this study were free from diabetes, severe cardiovascular diseases, and severe heart failure.

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disorders, chronic kidney disease, and secondary causes of hypertension, which limit the influence of other factors on cardiac structure and function.

The description of the population recruitment has been presented in Supplementary Figure S1. The inclusion criteria were aged 20–65 years and RHTN confirmed by 24-hour BP monitoring (mean daytime BP >135/85 mm Hg while on 3 antihypertensive drugs in optimal doses, including diuretic agent). The exclusion criteria included a history of other cardiovascular diseases (ischemic heart disease, heart failure, transient ischemic attacks, and previous stroke), decreased estimated glomerular filtration rate <60 ml/min/1.73 m², previous diagnosis of diabetes mellitus and other conditions. For the purpose of this analysis, 49 patients were excluded because of secondary causes of hypertension, which may independently influence the LV function. Primary aldosteronism (PA) was found in 32 patients, renal artery stenosis in 11, Cushing syndrome in 2 patients, and other causes in 4 subjects. Written informed consent was also obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. It was approved by the local Research Ethics Committee.

Office and ambulatory BP measurements

BP was measured by a trained nurse with a patient in the sitting position after a 5-minute rest using an automated device (Omron 705IT; Omron, Kyoto, Japan). Based on the upper arm circumference, an appropriately sized cuff was placed on the arm with the lower edge of the cuff located 2 cm above the antecubital fossa. Three consecutive readings were taken. In all patients the ambulatory BP measurements were recorded using SpaceLabs 90207 or 90217 (SpaceLabs, Redmond, WA). Readings were obtained every 15 minutes during the day (6:00 AM to 11:00 PM) and every 30 minutes during the night (11:00 PM to 6:00 AM). Average 24-hour systolic BP (SBP), diastolic BP (DBP), and heart rate (HR) were analyzed.

Polysomnography

The diagnosis of OSA was made by standard attended polysomnography with an Alice 5 device (Respironics, Murrysville, PA). The polysomnographic recordings were scored manually using 30-second epochs, following Rechtschaffen and Kales’ criteria for sleep and wake determination and sleep staging. Abnormal respiratory events were evaluated according to the standard criteria of the American Academy of Sleep Medicine Task Force. The apnea/hypopnea index (AHI), which indicates the number of apneic and hypopneic episodes per hour of sleep, was calculated. OSA was diagnosed when the AHI was >5 events/hour.

Metabolic syndrome

MS was diagnosed if 3 of 5 of the following criteria were met: (i) BP ≥130/85 mm Hg (this criterion was met by all patients); (ii) abdominal obesity (waist circumference >102 cm for men and >88 cm for women); (iii) high-density lipoprotein cholesterol <40 mg/dl for men and <46 mg/dl for women; (iv) triglycerides >150 mg/dl; and (v) fasting plasma glucose ≥100 mg/dl.

Screening for secondary causes of hypertension

To screen for PA, the plasma aldosterone-to-renin ratio was evaluated in all patients. To confirm the diagnosis of PA, further testing was performed in patients with increased aldosterone-to-renin ratio (>30) and serum aldosterone concentration (>15 ng/dl). Given that current guidelines suggest that the saline infusion test should not be performed in patients with severe uncontrolled hypertension, the captopril challenge test was conducted to confirm the diagnosis of PA, which was made in patients showing failure of aldosterone to suppress >30%. Medication treatment was tailored (after other examinations were performed) according to current guidelines, including withdrawing spironolactone, diuretics, and other drugs when appropriate before evaluations. A diagnosis of pheochromocytoma was based on metanephrine excretion in the urine, and diagnosis of Cushing syndrome was based on the 1-mg overnight dexamethasone suppression test, which was performed in all patients. Screening for hyperthyroidism was conducted using TSH levels; in patients with abnormal TSH, further diagnosis included evaluation of free T4 and free T3 levels. Computed tomography (CT) examinations of renal arteries, kidneys, and adrenal glands were performed with a 64-detector CT scanner (Somatom DEFINITION; Siemens, Erlangen, Germany) in all patients. The angio-CT examination of renal arteries was performed after the intravenous injection of a 100-ml bolus 350–370 mg/ml of non-ionic iodinated contrast medium administered at a rate of 5 ml/second. Image acquisition was initiated after 4–5 seconds when the threshold enhancement of 100 HU was reached within the region of interest placed on the descending aorta. Significant renal artery stenosis was defined as a narrowing of the artery diameter of at least 60% in comparison with the diameter of intact arteries (excluding poststenosis dilation) in multplanar reconstructions.

Echocardiography

All patients underwent a complete transthoracic echocardiographic evaluation, using a GE Medical System Vivid 7, GE Vingmed Ultrasound, Horten, Norway with a 2.5 MHz transducer. M-mode, 2-D, tissue Doppler imaging (TDI) was used. The echocardiographic evaluation was performed by 1 experienced researcher. The values for all echocardiographic parameters were obtained as the average of 3 consecutive cardiac cycles. LV mass (LVM) was measured according to the American Society of Echocardiography recommendations, using the formula proposed by Devereux.11 LVMi was obtained by normalizing LVM to body surface area. LV diastolic function was evaluated by mitral inflow values and TDI velocities. Mitral inflow velocities were measured from the apical 4-chamber view, with the sample volume placed at the mitral valve leaflet tips. The transmural early diastolic (E-wave) and atrial (A-wave) velocities
were measured, and the E/A ratio was calculated. Isovolumic relaxation time and deceleration time of the E velocity were obtained. TDI examination was performed from the apical 4-chamber view, with the sample volume placed along the myocardial lateral wall 1 cm above the mitral annulus. Furthermore, the early diastolic velocity (E') was measured, and E/E' ratio was calculated.

**Statistical methods**

Collected data are presented as mean ± SD, and frequency is presented as a percentage. The values of variables between groups were compared; continuous and discrete variables were compared using Student t test or Mann–Whitney test, and categorical variables were compared using χ² test or Fisher exact test. Pearson’s correlation was used to investigate the correlation of variables. Parameters identified as statistically significant based on univariate analysis (P < 0.05) were included in the multivariable logistic and linear regression models to determine the combined effect of several variables on the prevalence of the characteristics. P < 0.05 was considered statistically significant. Intraobserver agreement of the E’measurements was assessed by intraclass correlation coefficient based on the 2-way mixed analysis of variance model. The intraclass correlation coefficient (for E’) was 0.98 (95% confidence interval = 0.96–0.99). All statistical analyses were performed using the commercially available computer software PASW Statistics 18 (SPSS, Chicago, IL).

**RESULTS**

One hundred fifty-five patients (92 men, 63 women; mean age = 47.5 ± 10.5 years) with true RHTN and without secondary causes of hypertension were analyzed. Patients were divided into 2 groups based on the E’ wave velocity value: group 1 (E’ < 10 cm/second; n = 87) and group 2 (E’ > 10 cm/second; n = 68).

MS was found in 68.6% of group 1 and in 31.4% of group 2 (P < 0.0001). OSA (AHI > 5 events/hour) was diagnosed in 62.7% of group 1 and in 37.7% of group 2 (P < 0.01).

Patients in group 1, as compared with group 2, were older (51.33 ± 7.71 vs. 42.94 ± 11.82 years; P < 0.001) and had higher body mass index (31.33 ± 4.62 vs. 28.53 ± 4.73 kg/m²; P < 0.001). AHI was significantly higher in group 1 than in group 2 (25.84 ± 25.10 vs. 14.96 ± 17.89 events/hour; P < 0.001). Considering the metabolic parameters, total cholesterol, low-density lipoprotein cholesterol, and triglycerides were similar in both analyzed groups. Abdominal obesity was found more frequently in group 1 vs. group 2 (84.4% vs. 57.4%; P < 0.0001). There were no differences in the number and classes of antihypertensive drugs between the analyzed groups. Patients in group 1 had higher 24-h SBP and DBP values (142.0 ± 18.6 vs. 133.9 ± 15.1 mm Hg; P < 0.001; 87.6 ± 12.9 vs. 82.6 ± 12.1 mm Hg; P < 0.01, respectively). There were no differences in creatinine levels and glomerular filtration rate between the analyzed groups. Demographic and clinical characteristics are shown in Supplementary Table S1. Echocardiographic parameters of diastolic function and LVMI are presented in Supplementary Table S2. E’ wave velocity correlated significantly with AHI (r = −0.25; P < 0.001), 24-hour SBP (r = −0.28; P < 0.001), 24-hour DBP (r = −0.30; P < 0.001), LVMI (r = −0.36; P < 0.0001), glucose level (r = −0.26; P < 0.01), and abdominal obesity (r = −0.28; P < 0.0001). In multivariable models (Table 1) decreased E’ was independently related to the presence of MS or abdominal obesity when separate components of MS were included in the model. Age and 24-hour SBP were independently associated with decreased E’. However, the relationship of decreased E’ with 24-hour SBP was nonsignificant if LVMI was included in the multivariable model. Additional analysis showed that E/E’ also correlated independently with...
abdominal obesity (beta = 0.21; P = 0.006) and with MS (beta = 0.19; P = 0.02).

DISCUSSION

Diastolic dysfunction has been shown to be an independent risk factor of cardiovascular diseases in patients with hypertension. In this study, mitral inflow parameters and tissue Doppler velocities were obtained from 155 patients with true RHTN. In our studied group 44% of RHTN patients had diastolic dysfunction, as assessed by early diastolic velocity (E’), a parameter that is not dependent on preload. Age, LVMi, and abdominal obesity or MS were independently associated with diastolic dysfunction. The results of this study are consistent with those of the prior studies that identified age and LVM as independent predictors of impaired LV diastolic function. However, a few studies have evaluated the influence of RHTN and concurring MS and OSA on diastolic dysfunction. The vast majority of published papers were based on selected study groups: either MS or OSA. The influence of OSA on diastolic function parameters is not fully elucidated and is still being discussed. 13,14

Niroound and et al. 13 did not prove significant differences in E/A ratio among patients with OSA, compared with those in the non-OSA group. On the other hand, Fung et al. 14 demonstrated an association between the severity of OSA and diastolic dysfunction.

MS represents a clustering of cardiovascular risk factors, such as abdominal obesity and high BP values. The data describing the influence of MS on the diastolic function is unclear. Čuspidi et al. 15 did not prove the effects of MS on diastolic function assessed by E/A ratio. Other authors have described a well-pronounced influence of MS on diastolic function, which was evaluated by mitral E wave deceleration to peak E velocity ratio16 or measured by mitral E/A ratio. 17

In the previous studies, various parameters were used to evaluate the diastolic function. In most studies, diastolic dysfunction was assessed by mitral inflow parameters, which depend on age, sex, heart rate, and, most important, on the intravascular volume status. This study was designed to evaluate the association of these conditions with LV diastolic function assessed by E’ velocity. This parameter is less dependent on preload.

The prevalence of MS and OSA was higher in the group with diastolic dysfunction. Usui et al. 18 found that only coexisting MS and OSA had an impact on diastolic dysfunction. However, our study did not show that AHJ was an independent factor of diastolic dysfunction. In our study, LV diastolic function was independently related with abdominal obesity. This relationship was also independent from hemodynamic factors, such as 24-hour BP and LV hypertrophy.

It could be hypothesized that, apart from hypertrophy, other structural changes in the myocardium may affect its relaxation in obese patients. Previous studies have shown that abdominal obesity leads to abnormalities in myocardial perfusion and impaired ventricular–vascular interaction, which is secondary to endothelial dysfunction, inflammation, oxidative stress, and interstitial fibrosis. 19,20 The results of this study support the necessity of the implementation of lifestyle changes, including weight reduction, in patients with RHTN.

In this study, only middle aged or younger subjects with preserved renal function and without a history of diabetes were included, thus mitigating the potential confounding effects of advanced age and comorbidities on the study results. Therefore, the results may not be applicable to a wider population of patients with RHTN.

This study showed that MS and abdominal obesity are independently associated with diastolic dysfunction of the left ventricle in patients with RHTN. The independent relationship between the severity of OSA and diastolic dysfunction in patients with RHTN was not proven in our study.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at American Journal of Hypertension (http://ajh.oxfordjournals.org).

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DISCLOSURE

The authors declared no conflict of interest.

REFERENCES

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