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Association between 24-hour diastolic blood pressure and renal function in patients receiving treatment for essential hypertension

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Abstract

Objectives: To evaluate the association between diastolic blood pressure (BP), measured by 24-hour ambulatory blood pressure monitoring (ABPM) and renal function in patients receiving treatment for essential hypertension.

Methods: In this cross-sectional study, ABPM, transthoracic echocardiography, estimated glomerular filtration rate (eGFR) on the basis of serum cystatin C (eGFRcyst) and the renal resistive index (RRI) were measured in patients with essential hypertension.

Results: The cohort consisted of 105 patients (39 men, 66 women), with a mean ± SD age of 58 ± 12 years who had been receiving treatment for 11 ± 8 years. 24-hour diastolic BP significantly positively correlated with eGFRcyst and negatively correlated with RRI. No correlation was observed with 24-hour systolic BP values. 24-hour diastolic BP values ≤70 mmHg were associated with eGFRcyst ≤60 ml/min/1.73 m^2 (i.e., decreased GFR).

Conclusion: 24-hour diastolic BP values were significantly associated with markers of kidney function in patients receiving treatment for essential hypertension and values ≤70 mmHg may be associated with subnormal eGFRcyst.

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Introduction

Lowering systolic blood pressure (BP) to less than 130 mmHg during treatment of hypertension is associated with a significant improvement of cardiovascular morbidity, mortality and lower risk of stroke.[1–7] According to some studies, an association exists between intensive antihypertensive therapy and attenuation of kidney disease progression.[8–10] In contrast, other studies have shown a negative impact of intensive antihypertensive therapy on the glomerular filtration rate (GFR).[11,12] Most of these studies have used systolic BP to assess the efficacy of antihypertensive therapy because cardiovascular prognosis has been shown to be associated more significantly with this parameter than diastolic BP.[3]

Blood levels of the small protein, cystatin C, have been reported to be a stronger predictor of renal outcome and risk of cardiovascular events than blood levels of creatinine.[13] In addition, serum levels of cystatin C were found to be closely related to the left ventricle mass index in hypertensive patients.[14] Moreover, it has been reported that serum cystatin C is an independent biomarker associated with the renal resistive index (RRI) in patients with chronic kidney disease (CKD).[13] The RRI provides a non-invasive and reproducible measure of arterial resistance and in essential hypertension is associated with subclinical markers of target organ damage and has been reported to reflect renal disease progression.[15]

The aim of this present study was to evaluate the relationship between 24-hour systolic BP, diastolic BP with GFR estimated by serum Cystatin C (eGFRcyst) and RRI in patients receiving treatment for essential hypertension.

Methods

Patients with essential hypertension who attended our clinic from February 2016 to June 2017 for treatment were included in this cross-sectional study. The goal of their therapy was to reduce their BP to less than 130/85 mm Hg. Patients with a history of stroke or cardiac disease and those with diabetes mellitus, secondary hypertension, echocardiographic signs of systolic or diastolic dysfunction, regional alteration of cardiac contractility or valve dysfunction, pre-existing chronic renal disease apart from hypertensive nephropathy, ultrasound abnormalities of the kidneys and urinary tract were excluded from the study.

Patients were assessed over a 7–10 day period. Baseline blood pressure was recorded prior to ambulatory BP measurements (ABPM) which were taken over one day (24 hours) using a BTL CardiPoint-ABPM monitor (BTL Industries Ltd., Newcastle, UK), the cuff being placed on the patient's non-dominant arm. Measurements were recorded every 30 minutes; the day measurements were taken from 07.00 to 22.00 and the night measurements taken from 22.00 until

07.00 the next day. Daytime, night-time, 24 hour and overall mean systolic and diastolic BP were measured together with pulse pressure and heart rate. If the mean systolic and diastolic BP decreased by <10% or did not fall during the night, the patient was considered a 'non-dipper', and if it decreased by >10%, the patient was considered a 'dipper'.[16]

Glomerular filtration rate (GFR) estimated by serum Cystatin C (eGFRcyst) was calculated according to the Grubb formula.[17] Decreased GFR was defined as estimated GFR (eGFR) <60 ml/min/1.73 m^2. The RRI was derived from intrarenal Doppler arterial waveforms (i.e., peak systolic velocity – end-diastolic velocity)/peak systolic velocity as assessed by an ultrasound system (Aixplorer, SuperSonic Imagine, Aix-en-Provence, France) using XC6-1 convex probe with a working frequency 1-6 MHz.[18] The RRI was measured in both kidneys in the upper, medium and lower segments and a mean derived from the six measurements.[19]

Assessment of cardiac structural changes and cardiac functions was undertaken by transthoracic echocardiographic examination (Affinity, C 50, Philips, Bothell, USA).[20] Dimensions of the left ventricle, septum and posterior wall thickness were recorded.[21] The weight of the left ventricle was assessed according to the Devereux equation.[22] The mass of the left ventricle was corrected for body surface area (g/m^2) and left ventricular ejection fraction was calculated from M - mode applying the method of Teichholz.[23] Both assessors (one for echocardiography and another for RRI assessments) were blinded to the outcomes.

All patients provided written informed consent. The study was carried out in accordance with the ethical principles of the Helsinki Declaration and was approved by the Ethics Committee of the regional hospital (Masaryk Hospital, Usti nad Labem, Czech Republic).

Statistical analyses

The data were analysed using SW STATISTICA™ software version 11 (Dell Software) and a *P*-value <0.05 was considered to indicate statistical significance.

The relationship between variables was analysed using linear regression analysis and adjusting for age. Analyses were performed in a stepwise method (forward or backward) which facilitated detection of the best predictive variables.[24] The following variables were used in the analyses: 24-hour systolic BP, 24-hour diastolic BP, 24-hour heart rate, LVMI, LV-EF. Multicollinearity was assessed using variance inflation factor (VIF) for each variable,[25] VIF values >10 a high risk of multicollinearity.

A receiver operating characteristic (ROC) curve was constructed to quantify the relationship between eGFRcyst <60 ml/min/1.73 m^2 (i.e., decreased GFR) and mean 24-hour diastolic BP.

Results

One hundred and five patients (39 men and 66 women) with a mean ± SD age of 58 ± 12 years who had been treated for hypertension for 11 ± 8 years, participated in study. Their clinical characteristics are shown in Table 1. At baseline, systolic BP for the group was 128 ± 11 mmHg and diastolic BP was 82 ± 7 mmHg.

Patients were graded according to the severity of their CKD;[26] 51 (47%) had G1A1, 40 (38%) had G2A1, 7 (7%) had G3aA1, 2 (2%) had G3bA1, 3 patients (3%) had G1A2, 1 (1%) had G2A2 and 1 (1%) had G3aA2. Most of the patients had eGFRcyst values >60 ml/min/1.73 m.^{2} In terms of treatment, 52% patients received angiotensin converting enzyme

(ACE) inhibitors, 39% calcium receptor blockers, 30% angiotensin-receptor blockers, 30% beta-blockers, 29% diuretics, 4% centrally acting antihypertensive drugs and 1% alpha-receptor blockers (some patients received more than one antihypertensive drug).

Table 1. Clinical characteristics of the 105 patients with essential hypertension.

Characteristic	Study population n=105
Age, years	57.9 ± 12.0 (18.0, 75.0)
Duration of hypertension, years	11.0 ± 8.0 (0.0, 43.0)
BMI, kg/m^2	29.4 ± 4.9 (19.9, 42.6)
Serum creatinine, umol/l	77.1 ± 15.3 (47.0, 128.0)
eGFRcyst, ml/min/1.73m^2	94.5 ± 26.6 (32.4, 157.8)
RRI, units	0.65 ± 0.05 (0.55, 0.77)
LVMI, g/m^2	101.0 ± 19.4 (61.8, 148.6)
LV-EF, %	75.4 ± 6.9 (58.5, 89.8)
ACR, g/mol*	2.1 ± 3.4 (0.21, 13.8)

Data are presented as mean ± standard deviation (range);
*n = 29, patients with measurable ACR;
BMI, body mass index; eGFRcyst: glomerular filtration rate estimated by cystatin C; RRI, renal resistive index; LVMI, left ventricular mass index; LV-EF, left ventricular ejection fraction; ACR, urine albumin to creatinine ratio.

The patients' ABPM and echocardiography results are summarized in Table 2. According to ABPM, 49 (47%) patients were dippers (i.e., blood pressure fell during the night) and 56 (53%) were non-dippers.[16]

Bivariate (Pearson's correlation) correlations are summarized in Table 3. A statistically significant positive correlation was found between eGFRcyst and 24-hour diastolic BP (r = 0.33, P= 0.001; Figure 1) but the relationship between eGFRcyst and 24-hour systolic BP was not significant (Table 3). According to 24-hour diastolic BP, 57 (54%) patients had values <80 mm Hg, 35 (33%) patients had values <75 mmHg and 22 (21%) of patients had values <70 mmHg.

Statistically significant positive correlations were also found between eGFRcyst and 24-hour mean BP, daytime systolic BP, daytime diastolic BP, daytime BP, and 24-hour heart rate. Statistically significant negative correlation was found between

Table 2. Patients' ambulatory blood pressure measurements and echocardiography results.

Parameters	Study population n=105
24-hour systolic BP, mmHg	127.1 ± 11.0 (106.0, 159.0)
24-hour diastolic BP, mmHg	78.9 ± 8.2 (62.0, 98.0)
24-hour mean BP, mmHg	98.5 ± 10.1 (75.0, 120.0)
Daytime systolic BP, mmHg	129.8 ± 11.6 (107.0, 164.0)
Daytime diastolic BP, mmHg	81.4 ± 8.7 (63.0, 104.0)
Mean daytime BP, mmHg	101.2 ± 10.5 (77.0, 130.0)
Night-time systolic BP, mmHg	118.6 ± 12.8 (91.0, 168.0)
Night-time diastolic BP, mmHg	71.7 ± 8.6 (53.0, 94.0)
Mean night-time BP, mmHg	90.9 ± 10.8 (66.0, 122.0)
24-hour pulse pressure, mmHg	48.2 ± 8.3 (33.0, 72.0)
Daytime pulse pressure, mmHg	48.5 ± 8.4 (33.0, 73.0)
Night-time pulse pressure, mmHg	46.9 ± 9.2 (29.0, 85.0)
24-hour heart rate, beats/min	71.6 ± 8.8 (55.0, 96.0)

Data are presented as mean ± standard deviation (range);
BP, blood pressure.

Table 3. Relationship between variables using Pearson's correlation analysis.

	eGFRcyst ($n = 105$)		RRI ($n = 105$)	
	Correlation coefficient	Statistical significance	Correlation coefficient	Statistical significance
Age, years	−0.55	$P<0.001$	0.44	$P < 0.001$
24-hour systolic BP, mmHg	0.19	ns	−0.15	ns
24-hour diastolic BP, mmHg	0.33	$P = 0.001$	−0.54	$P < 0.001$
24-hour mean BP, mmHg	0.22	$P = 0.023$	−0.40	$P < 0.001$
Daytime systolic BP, mmHg	0.22	$P = 0.024$	−0.15	ns
Daytime diastolic BP, mmHg	0.36	$P < 0.001$	−0.52	$P < 0.001$
Mean daytime BP, mmHg	0.26	$P = 0.008$	−0.40	$P < 0.001$
Night-time systolic BP, mmHg	0.06	ns	−0.07	ns
Night-time diastolic BP, mmHg	0.184	ns	−0.39	$P < 0.001$
Mean night-time BP, mmHg	0.09	ns	−0.28	$P = 0.004$
24-hour pulse pressure, mmHg	−0.08	ns	0.34	$P < 0.001$
Daytime pulse pressure, mmHg	−0.07	ns	0.34	$P < 0.001$
Night-time pulse pressure, mmHg	−0.10	ns	0.26	$P = 0.007$
24-hour heart rate, beats/min	0.20	$P = 0.043$	−0.33	$P = 0.001$

eGFRcyst: glomerular filtration rate estimated by cystatin C; RRI, renal resistive index; ns, not significant.

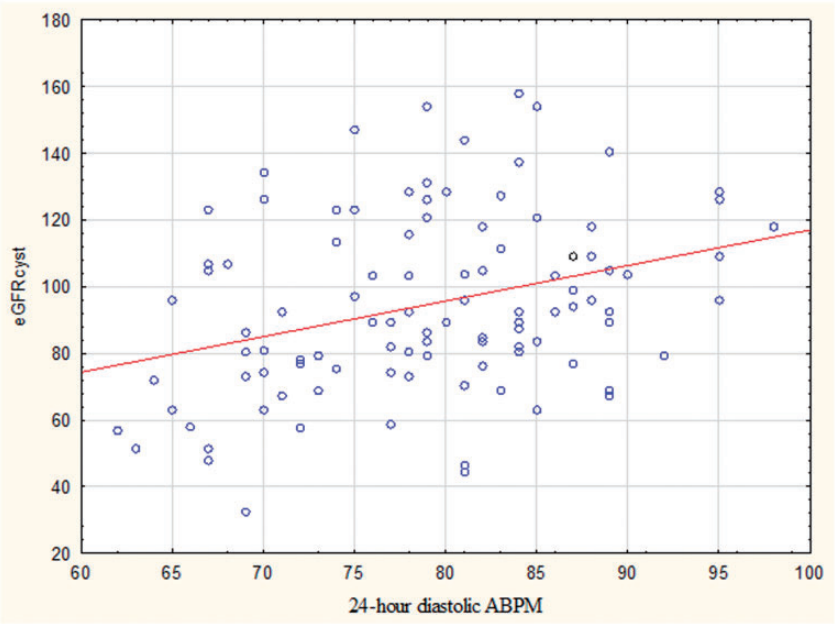

Figure 1. Relationship between 24-hour diastolic blood pressure and glomerular filtration rate estimated by Cystatin C (eGFRcyst) ($n = 105$) ($r = 0.33$, $P = 0.001$).

eGFRcyst and the age of the patients (Table 3).

Statistically significant negative correlations were found between RRI and 24-hour diastolic BP ($r = -0.541$, $P < 0.001$; Table 3, Figure 2). Significant negative correlations were also found between RRI and 24-hour mean BP, daytime diastolic BP, daytime BP, night-time diastolic BP night-time BP and 24-hour heart rate (Table 3). In addition, significant positive correlations were found between RRI and age, 24-hour pulse pressure, daytime and night-time pulse pressures. Interestingly, although pulse pressure was not correlated with eGFRcyst, it was correlated with RRI values (Table 3).

Stepwise regression was applied to the model for eGFRcyst using the following variables: age, 24-hour systolic BP, 24-hour diastolic BP, 24-hour heart rate, LVMI, LV-EF and RRI. Forward stepwise regression showed a significant dependency of eGFRcyst on age ($\beta = -1.088$ [95% CI: -1.464, -0.711]; $P < 0.001$) and on 24-hour diastolic blood pressure ($\beta = 0.567$ [95% CI: 0.017, 1.116]; $P = 0.043$). There was no risk of multicollinearity; VIF values were ≤ 3.

Table 4 shows the results of the multivariate analysis of RRI. The backward stepwise regression was applied to the model using the following variables: age, 24-hour systolic BP, 24-hour diastolic BP, 24-hour heart rate, LVMI, LV-EF and eGFRcyst. RRI was negatively correlated with 24-hour diastolic BP and positively correlated with age and 24-hour systolic blood pressure. Again, VIF values did not exceed 3.

The ROC curve analysis showed that a 24-hour diastolic BP of 70 mmHg had a sensitivity of 60% and specificity of 88% for detecting patients with eGFRcyst below 60 ml/min/1.73 m^2 (i.e., decreased GFR) (Figure 3).

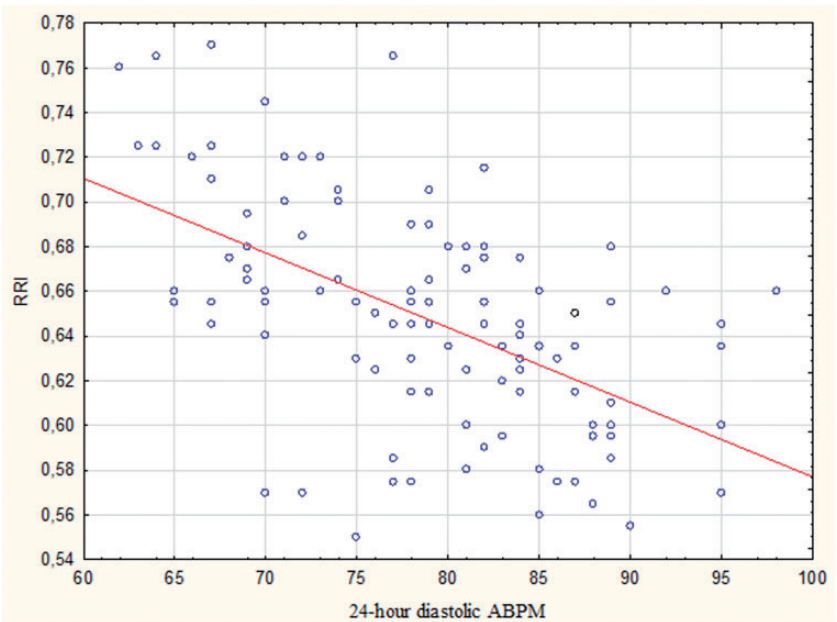

Figure 2. Relationship between 24-hour diastolic blood pressure and renal resistive index (RRI) ($n = 105$) ($r = -0.54$, $P < 0.001$).

Table 4. Multivariate analysis of variables associated with renal resistive index among patients with essential hypertension.

Variable	β (95% CI)	Statistical significance
Age	0.001 (0.001, 0.002)	$P < 0.001$
24-hour diastolic blood pressure	−0.004 (−0.006, −0.003)	$P < 0.001$
24-hour systolic blood pressure	0.002 (0.001, 0.003)	$P = 0.001$

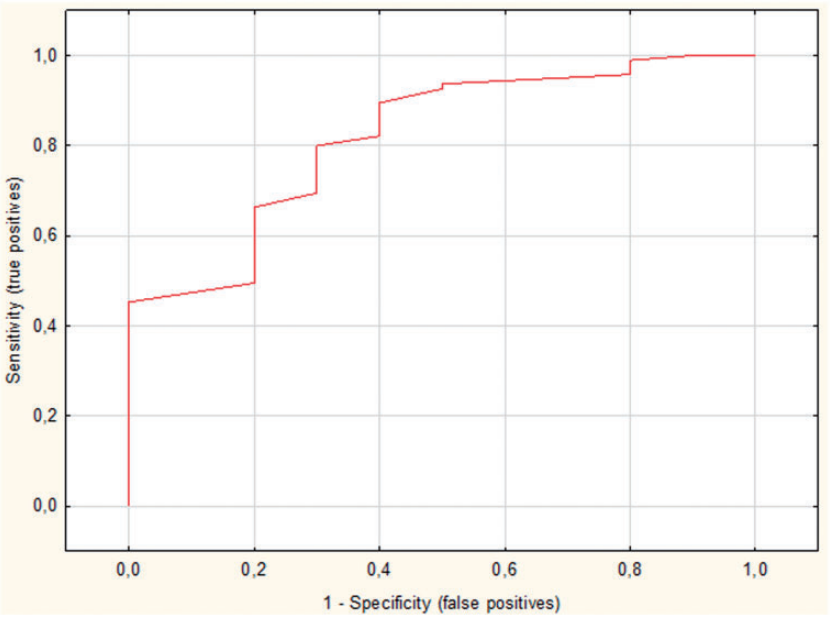

Figure 3. Receiver operating characteristic (ROC) curve showing 24-hour diastolic blood pressure 70 mmHg and glomerular filtration rate estimated by Cystatin C (eGFRcyst) below 60 ml/min/1.73 m^2.

Discussion

In this cross-sectional study of 105 patients receiving various treatments for essential hypertension for an average of 11 years, we investigated the relationship between 24-hour diastolic BP and the renal parameters of eGFRcyst and RRI. The assessment of GFR is important because it can point to a significant decrease in renal function and thus prevent the possibility of iatrogenic-induced renal failure in patients treated for essential hypertension.[11,12] Endogenous creatinine concentration has been used as an estimate of GFR (eGFR) in medical and clinical research settings because of its ease of measurement. Nevertheless, it has limitations as a renal biomarker because it is subject to high analytic variability and is affected by large biological variability associated with sex, age, ethnicity, and muscle mass.[27] Several eGFR formulae (i.e., Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) were developed to correct for these

confounding factors and improve accuracy.[27] However, limitations surrounding their sensitivities and specificities still remain.[28] Serum cystatin C has no association with age, sex, and/or muscle mass and so it has been suggested that this protein is a superior marker of GRF compared with serum creatinine.[13] Indeed, one study showed that serum cystatin C was better correlated with gold-standard direct measures of GFR than serum creatinine or MDRD and was more sensitive to early changes in kidney function than the other two measures.[28] Therefore, for this current study we chose eGFRcyst as a measure of kidney function. We also used RRI to help support the non-invasive assessment of renal haemodynamics. RRI is the result of a complex interaction of many variables. It is influenced by changes in renal interstitial pressure, renal vascular resistance and compliance and systemic haemodynamic changes.[29,30]

Our results showed that eGFRcyst values were significantly positively corelated with 24-hour diastolic BP but not 24-hour systolic BP. Moreover, the 24-hour diastolic BP threshold value of 70 mmHg was associated with eGFRcyst $\leq$60 ml/min/1,73 m^2 with a sensitivity of 60% and specificity of 88%. We found a significant negative correlation between 24-hour diastolic BP and RRI values but no correlation between 24-hour systolic BP and RRI. We observed that low diastolic BP values were associated with high RRI values and a reduction in eGFRcyst. However, there was no correlation between RRI and eGFRcyst values. Our findings support the significance of 24-hour diastolic BP in the evaluation of blood pressure effects on renal function. The significant correlations we found between age and kidney function were not surprising. GFR is known to decline with age and progressive loss of nephron mass, global glomerulosclerosis, arteriolo-nephrosclerosis, and an increase in interstitial volume are common and expected findings in normal ageing.[31]

The relationship between ABPM parameters and renal function in patients treated for essential hypertension has been investigated previously.[32] Results showed that a deterioration in renal function was associated with increased 24-hour pulse pressure, high night-time systolic BP and a large number of non-dippers. Another study found that 24-hour pulse pressure predicted mortality better than 24-hour systolic BP and that pulse pressure and systolic BP rather than diastolic BP predicted mortality in older treated hypertensives.[33] By contrast, we observed that 24-hour diastolic BP correlated with eGFRcyst more than systolic BP or pulse pressure. Nevertheless, the significant positive correlation we found between RRI and pulse pressure confirms the significance of 24-hour pulse pressure in renal haemodynamics.

The study had several limitations. For example, the sample size was small, there were no controls and it was cross sectional performed at one point without sequential measurements. In addition, concomitant medications were not recorded or considered which may also have influenced renal function,[34] and most patients had good renal function. While the change in serum cystatin C has been reported to be a more sensitive marker of GFR the change in serum creatinine,[35] perhaps the correlation of other estimations of GFR with 24-hour diastolic BP should have been investigated. Further, prospective studies involving large numbers of patients are required to confirm our results.

In summary, we found significant correlations between 24-hour diastolic BP and eGFRcyst and RRI in patients receiving treatment for essential hypertension. Values of 24-hour diastolic BP $\leq$70 mmHg in patient receiving antihypertensive

treatment may possibly be associated with decreased renal function.

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Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

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