

## **IN essential hypertension, a change in the renal resistive index is associated with a change in the ratio of 24-hour diastolic to systolic blood pressure**

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Short title: Change of renal resistive index in essential hypertension

## Summary

**Background:** An increase in the renal resistive index (RRI) in patients with essential hypertension (EH) predicts deterioration in renal function. In patients with EH, changes in hemodynamic parameters significantly affect the RRI. This study aimed to define changes in Ambulatory Blood Pressure Monitoring (ABPM) parameters that are significantly associated with a change in RRI in patients with EH.

**Methods:** We evaluated ABPM and the RRI in 96 patients with EH without organ extrarenal changes at baseline and after two years of follow-up. The relationships between changes in ABPM parameters and the RRI over the period were evaluated.

**Results:** After two years of follow-up, the increase in RRI was consequential. Simultaneously, 24-h systolic blood pressure increased significantly and 24-h diastolic blood pressure decreased. In the whole group and in the group with calculated cystatin C clearance ( $eGFR_{cyst} \geq 90 \text{ mL/min/1.73m}^2$ ), the change in RRI significantly negatively correlated with the change in the ratio of 24-h diastolic to systolic blood pressure (D/S ratio), but also with the change in 24-h pulse blood pressure. However, in patients with  $eGFR_{cyst} < 90 \text{ mL/min/1.73m}^2$ , only the change in the 24-h D/S ratio significantly correlated with the change in RRI. Based on the backward stepwise regression analysis, the change in RRI was significantly dependent only on the change in 24-h D/S ratio and not on the change in 24-h pulse pressure.

**Conclusion:** A change in the ratio of diastolic to systolic pressure better reflects a change in RRI than a change in pulse pressure

**Key words:** renal resistive index, 24-hour blood pressure monitoring, diastolic pressure, pulse pressure, ratio of diastolic to systolic blood pressure

## **Introduction**

The renal resistive index (RRI) is examined at the level of the renal interlobar arteries. In the intrarenal arteries, the Doppler waveform produces a steep systolic upstroke followed by diastolic decline. The RRI is calculated using the following formula:  $\text{peak systolic velocity} - \text{end diastolic velocity} / \text{peak systolic velocity}$  [1-3]. The RRI has been considered a valid tool for the study of changes in renal microcirculation in response to pathological conditions [1-3]. In the evaluation of RRI, it is necessary to consider the hemodynamic factors involved, which could be extrarenal or renal. The renal factors include the renal capillary wedge pressure, interstitial pressure, and venous pressure. The extrarenal factors include arterial blood pressure parameters, systemic vascular compliance, and cardiac function [1-3].

Essential hypertension (EH) is one of the cardiovascular risk factors [4-9]. Concurrently, it leads to gradual renal function impairment [10-14]. Stable renal blood flow is dependent on the interaction between systemic blood pressure and renal vascular resistance. The RRI is a non-invasive parameter that is significantly associated with renal vascular resistance, provided that the presence of other pathological conditions that affect RRI can be ruled out [3].

During EH, an increase in the RRI is associated with a faster renal function decline, even when glomerular filtration rates are still within normal limits [3]. In patients with EH and mild renal impairment, the RRI significantly predicts disease progression [14]. Moreover, in patients with EH, the RRI is also associated with the presence of extrarenal organ changes such as left ventricular hypertrophy or carotid artery intima-media thickness [12, 13]. Monitoring the RRI dynamics is therefore important for assessing the risk of subsequent complications during EH.

According to previous studies, the RRI correlates with pulse pressure in patients with EH [16, 17]. However, according to a recent study, the RRI is more significantly associated with the ratio of diastolic to systolic blood pressure (D/S ratio) [18]. This study aimed therefore to compare the relationship between the change in pulse pressure and the D/S ratio with the change in the RRI using its 24-h monitoring during the two-year follow-up.

## **Methods**

The study included patients with EH, who were followed-up and treated for at least one year, without a history of cardiovascular complications, signs of systolic dysfunction and regional contractility disorders according to initial echocardiography, presence of diabetes mellitus, other renal or urological diseases other than hypertensive nephropathy, and without pathological signs of kidney and urinary system or other associated diseases that significantly affect prognosis and co-operation. This study was performed between 2017 and 2020.

The local ethics committee (Masaryk Hospital, Ústí nad Labem, Czech Republic) approved this study and each participant was acquainted in detail with the study protocol and signed an informed consent before getting into the study.

Consequently, all considered patients underwent 24-h blood pressure monitoring, RRI measurement, transthoracic echocardiography, and blood tests for laboratory examination including the value of plasma cystatin on the basis of which calculated cystin clearance (eGFR<sub>cyst</sub>) was determined. For each individual patient, all examinations were performed within 24 h.

In our study uncomplicated patients with EH were treated to achieve a target systolic blood pressure 130 mmHg. In this group, according to a previous cross-sectional study, the value of glomerular filtration was dependent on the value of 24-hour diastolic blood pressure [19]. 24-hour blood pressure below 75 mmHg was associated with a significant decrease in glomerular filtration, often below 60 ml/min/1.73 m<sup>2</sup>. If the 24-hour systolic blood pressure in these patients was below 120 mmHg, subsequent treatment of hypertension was reduced. In the other group of patients, treatment of EH was not modified. After two years of follow-up, the effect of this approach on blood pressure, non-invasive cardiovascular parameters, RRI and glomerular filtration rate was assessed. The changes in the systolic, diastolic, mean arterial, pulse pressure, and the D/S ratio were compared, as well as noninvasive cardiovascular and renal parameters including RRI.

Performed examinations: ABPM was performed on a BTL CardiPointABPM monitor (BTL Industries Ltd., Newcastle, UK). Twenty-four-hour examinations were divided into two periods:- measurements from 7 to 22 h in the evening were considered as daily measurements; and from 22 to 7 h in the morning were considered as night measurements. Intervals between individual measurements were 30 min. Examinations, where at least 70% of measurements were successful, were considered valid. The following parameters were evaluated: 24-h systolic, diastolic, mean, pulse pressure and heart rate; daytime systolic, diastolic, mean, pulse pressure; and nocturnal systolic, diastolic, mean, and pulse pressure.

Transthoracic echocardiography (Affinity, C50, Philips, Bothell, USA) examined left ventricular size, intraventricular septal strength and left ventricular posterior wall, left ventricular mass according to the Devereux equation, and left ventricular mass based on body surface area (mass index left ventricle) [20]. The left ventricular ejection fraction was calculated according to the Teichholz method [21]. The mitral valve flow in diastole E was measured by Doppler examination and the speed of mitral valve movement in diastole E' was measured by tissue Doppler echocardiography. The E/E' ratio was determined.

The RRI was evaluated via ultrasound imaging (Aixplorer, SuperSonicImagine, Aix-en-Provence, France) using the XC6-1 convex probe, which measured peak systolic velocity (PSV) and end-diastolic

velocity (EDV) in the interlobar renal arteries. The RRI was calculated as the average of measurements in both kidneys in the upper, middle, and lower segments based on the following formula:

$$\text{RRI} = (\text{PSV}-\text{EDV}) : \text{PSV}$$

One experienced specialist performed all examinations in stable supine position. His intraobservational variability was 4%.

Glomerular filtration was evaluated on the basis of eGFR<sub>cyst</sub> according to the Grubber formula. Based on the value of eGFR<sub>cyst</sub>, patients were divided according to KDIGO - values above 90 mL/min were considered normal values (G1), values between 60–90 mL/min were considered G2, below 60 mL/min were considered G3. Concurrently, urine was examined for the presence of albumin using the ratio of urine albumin/creatinine (ACR; g/mol) - in its absence it was A1 (ACR <3), in microalbuminuria A2 (ACR 3 - 30) and at ACR values >30 A3. According to the G and A values, the patients were divided into two groups for further follow-up; the first group consisted of patients with a G1A1 finding, and the second group was all the others.

Statistical evaluation: SW STATISTICA version 11 was used for descriptive and for analytical purposes. The normality of the data was checked using the Shapiro-Wilk test. Based on its result a parametric or nonparametric pairwise test was used to detect significant changes when comparing the initial data with the data after two years (i.e. pairwise t-test or Wilcoxon test). Pearson coefficient of correlation was calculated to assess the relationship between numeric variables, when necessary. The multiple regression model was constructed to assess the common influence of all the suspected predictors (sex, age, the change of body mass index (BMI) and of the parameters of 24-h ABPM, of 24-h D/S ratio, 24-h pulse pressure and 24-h heart rate) to the change of the RRI. The backward stepwise regression was applied to detect the subset of the significant predictors. The standard 5% level of significance was assumed.

## Results

The study involved 96 patients; 33 men and 63 women. The follow-up period was 24 months. Prior to study entry, patients were treated for hypertension for an average of 11.48 years (standard deviation [SD] +/- 7.91). Fifty-one percent of patients took angiotensin converting enzyme (ACEi) inhibitors, 42% took calcium receptor blockers, 31% took angiotensin-receptor blockers (ARBs), 29% took beta-

blockers, 31% took diuretics, 4% took centrally acting antihypertensives, and 1% took alpha-blockers. 60% of patients were using combination antihypertensive therapy.

After the initial examination, the treatment was changed in 32 patients in the following period, while in another 64, the prescribed medication was continued unchanged for a period of 2 years.

Based on the KDIGO classification there were 47 patients (49%) in the G1A1 group, 49 patients had a different classification, namely G2A1 - 37 patients (39%), G3A1 - 8 patients (8%), G1A2 - 2 patients (2%), 1 patient G2A2 (1%) and 1 patient G3A2 (1%).

Clinical characteristics, including echocardiographic examination and their comparison at initial examination and after 24 months are presented in Table 1.

By ACR assessment, grade2 albuminuria was initially detected in 4 patients/subjects (4%), which did not change during the 2-year follow-up. In other patients, albuminuria was grade 1.

The results of the 24-h blood pressure monitoring at the initial examination and after the two-year follow-up are presented in Table 2. As the table shows, there were notable changes in all examined blood pressure parameters.

The change in the RRI after two years of follow-up in the whole group significantly correlated with the change in 24-h pulse pressure, but even more significantly with the change in 24-h ratio of diastolic to systolic pressure, while no significant correlation was found with the change in 24-h systolic, diastolic or mean blood pressure. These results are shown in Table 3.

When assessing the change in the RRI in patients with  $eGFR_{cyst} \geq 90$  mL/min, a significant correlation was found with the change in 24-h pulse pressure and the RRI, however the correlation was more significant with the change in the ratio of 24-h diastolic to systolic blood pressure. In the group with  $eGFR_{cyst} < 90$  mL/min, the change in the resistive index correlated exclusively with the change in the ratio of 24-h diastolic to systolic blood pressure, Table 4.

Correlations between the RRI and other variables in the patients with and without change in hypertension treatment are shown in Table 5.

In the multiple regression model for the RRI change as the dependent variable, which included age, sex, the change of BMI, the changes of the parameters of 24-h ABPM (systolic and diastolic blood pressure), the change of the heart rate, of 24-h D/S ratio and of 24-h pulse pressure, only the change of heart rate seemed to be the significant predictor ( $p=0.010$ , the overall  $p=0.002$  for the whole model). Nevertheless, taking into account the correlations among the variables and applying the backward stepwise regression analysis, this approach resulted in the simple regression model with only the change of 24-h D/S ratio ( $R = -0.405$ ;  $p < 0.001$ ) as a unique significant statistical predictor in the whole group, not the change in 24-h pulse pressure (Figure 1).

## Discussion

In the treatment of EH, based on recent studies, it is recommended to adjust systolic blood pressure below a target value of 130 mmHg which is associated with a significantly improved cardiovascular prognosis [13].

In contrast, excessive reduction in blood pressure can lead to deterioration of renal function [22].

Changes in cardiac and renal parameters over a longer period reflect changes in blood pressure throughout the study period. For this reason, the method of ABPM monitoring at the beginning and after a two-year period was chosen [23,24].

The eGFR<sub>cyst</sub> for monitoring changes in glomerular filtration was chosen because serum cystatin levels are not associated with age, gender or muscle mass and therefore are a better marker than serum creatinine, especially in long-term follow-up [25, 26].

There was a small but significant increase in 24-hour systolic blood pressure, which may be explained by a reduction in hypertensive treatment in patients with 24-hour blood pressure below 120/75 mmHg after the initial examination. On the other hand, there was a significant reduction in 24-hour diastolic blood pressure, an increase in 24-hour pulse pressure and a decrease in the ratio of 24-hour diastolic to systolic blood pressure. Despite the observed changes in blood pressure values, no significant changes in non-invasive cardiovascular parameters were found. When evaluating the effect of these changes on renal parameters, no significant change in glomerular filtration rate was detected, but there was a significant increase in RRI.

An increase in renal vascular resistance precedes a decrease in glomerular filtration rate (3, 15). RRI is a non-invasive parameter that is affected by renal vascular resistance, provided that other factors involved are excluded, which was a prerequisite for inclusion in our study [3, 15].

The change in renal vascular resistance and RRI depends on the change in pulse blood pressure according to previous studies [16, 17]. However, recently it was suggested that the ratio of diastolic to systolic blood pressure is associated significantly better with the RRI than pulse pressure [18]. In our study, this conclusion was confirmed and, in addition, it was found that a change in the ratio of diastolic to systolic blood pressure corresponds to changes in the RRI better than a change in pulse blood pressure in patients with EH.

In the ratio of diastolic to systolic pressure, there is a value of diastolic pressure in the numerator and thus mathematically the change in diastolic pressure will affect the change in this ratio more than the change in systolic pressure. This fact supports the importance of monitoring diastolic blood pressure in patients with EH for the long-term prevention of renal damage.

The fact that the treatment of EH has impact on the RRI as well as on blood pressure parameters, it is crucial that the relationship between the change in the RRI and 24-h ratio of diastolic to systolic

pressure was also significant both in the group of patients in whom the treatment of hypertension was modified and for those without change of treatment [6-8].

Our results support the idea that in order to maintain renal hemodynamics at the desired level, it is necessary to evaluate changes in systolic and diastolic blood pressure simultaneously.

## **Conclusion**

Both changes in the ratio of 24-h D/S and 24-h pulse pressure correlate with change in the RRI in hypertensive patients with normal renal function.

However change in ratio of 24-h D/S but not change in 24-h pulse pressure correlates with change in RRI in hypertensive patients with mild or moderate chronic renal dysfunction.

This result suggests that a change in the ratio of diastolic to systolic pressure better reflects a change in the RRI than a change in pulse pressure, which indicates the importance of both diastolic and systolic blood pressure monitoring.

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## **Conflict of interest**

All the authors have approved and accepted responsibility for content of the manuscript. All the authors declare that no author has any potential conflicts of Interest or any financial and personal relationships with other people or organizations that could inappropriately influence our work.

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Table 1. Clinical characteristics and echocardiography results of the 96 patients with essential hypertension.

n=96	Initial examination	After 24 months	p
Age (years)	58.8±10.9	60.8±10.9	
BMI (kg/m <sup>2</sup> )	29.4±4.7	29.7±4.9	0.007
Serum cystatin (mg/L)	0.98±0.19	0.98±0.20	NS
Serum creatinine (umol/L)	76.7±15.6	76.7±15.5	NS
eGFR <sub>cyst</sub> (ml/min/1.73m <sup>2</sup> )	93.9±26.6	94.3±28.5	NS
RRI (units)	0.65±0.05	0.67±0.06	<0.001
PSV (cm/s)	39.7±13.8	37.3±8.3	NS
EDV (cm/s)	13.7±4.4	12.2±3.1	0.006
ACR (g/mol)	2.1±3.3*	2.5±6.4**	NS
LV-EF (%)	75.3±6.9	74.7±5.5	NS
LVMI g/m <sup>2</sup>	100.9±19.7	103.8±20.0	NS
E/E'	9.2±2.8	8.9±2.5	NS

BMI: body mass index; eGFR<sub>cyst</sub>: glomerular filtration rate estimated by cystatin C; RRI: renal resistive index; PSV: peak systolic velocity; EDV: end-diastolic velocity; ACR: urine albumin to creatinine ratio; LV-EF: left ventricular ejection fraction; LVMI: left ventricular mass index; E/E': ratio between early mitral inflow velocity and mitral annular early diastolic velocity; NS: not significant.

Data are presented as mean ± standard deviation (range).

\*n= 29, patients with measurable ACR during initial examination.

\*\*n=26, patients with measurable ACR after 24 months

Table 2. Ambulatory blood pressure measurement results

n=96	Initial examination	After 24 months	p
24-hour systolic BP (mmHg)	126.6±10.7	130.3±12.2	0.009
24-hour diastolic BP (mmHg)	78.8±8.1	75.5±7.3	<0.001
24 hour mean BP (mmHg)	98.3±9.8	94.0±7.8	<0.001
Daytimesystolic BP (mmHg)	129.4±11.3	133.9±13.1	0.001
Daytime diastolic BP (mmHg)	81.3±8.5	78.6±9.5	<0.001
Mean daytime BP (mmHg)	101.0±10.2	97.4±9.0	<0.001
Night-time systolic BP (mmHg)	118.3±12.5	122.7±14.6	0.009
Night-time diastolic BP (mmHg)	71.8±8.1	69.0±7.9	0.005
Mean night-time BP (mmHg)	90.9±10.3	87.0±9.0	0.002
24-hour pulse pressure (mmHg)	47.8±8.3	54.8±10.4	<0.001
Daytime pulse pressure (mmHg)	48.1±8.4	55.4±11.0	<0.001
Night-time pulse pressure (mmHg)	46.5±9.3	53.7±11.6	<0.001
24-hour diastolic/systolic BP	0.62±0.05	0.58±0.05	<0.001
Daytime diastolic/systolic BP	0.63±0.05	0.59±0.06	<0.001
24-hour heart rate (beats/min)	71.5±9.1	70.7±8.5	NS

Data are presented as mean ± standard deviation (range); NS: not significant.

BP: blood pressure.

Table 3. Correlations between RRI and given variable

	CC	p
24-hour systolic BP change	0.116	NS
24-hour diastolic BP change	-0.137	NS
24 hour mean BP change	-0.153	NS
Daytime systolic BP change	0.134	NS
Daytime diastolic BP change	-0.106	NS
Mean daytime BP change	-0.131	NS
24-hour pulse pressure change	0.292	0.004
Daytime pulse pressure change	0.275	0.007
24-hour diastolic/systolic BP change	-0.403	<0.001
Daytime diastolic/systolic BP change	-0.293	0.004
24-hour heart rate change	0.128	NS

CC: coefficient of correlation between RRI change and given variable.

NS: not significant.

BP: blood pressure.

Table 4. Correlations between RRI and given variable in two subsets of patients

	eGFRcyst $\geq$ 90		eGFRcyst $<$ 90	
	ml/min	(n=46)	ml/min	(n=50)
	CC	P	CC	p
24-hour systolic BP change	0.18	NS	0.035	NS
24-hour diastolic BP change	-0.078	NS	-0.221	NS
24-hour mean BP change	-0.099	NS	-0.215	NS
Daytime systolic BP change	0.209	NS	0.045	NS
Daytime diastolic BP change	-0.101	NS	-0.141	NS
Mean daytime BP change	-0.114	NS	-0.173	NS
24-hour pulse pressure change	0.328	0.026	0.241	NS
Daytime pulse pressure change	0.367	0.012	0.189	NS
24-hour diastolic/systolic BP change	-0.385	0.008	-0.405	0.003
Daytime diastolic/systolic BP change	-0.412	0.004	-0.218	NS
24-hour heart rate change	0.086	NS	0.129	NS

CC: coefficient of correlation between RRI change and given variable.

NS: not significant.

BP: blood pressure.

Table 5. Correlations between RRI and given variable in two subsets of patients

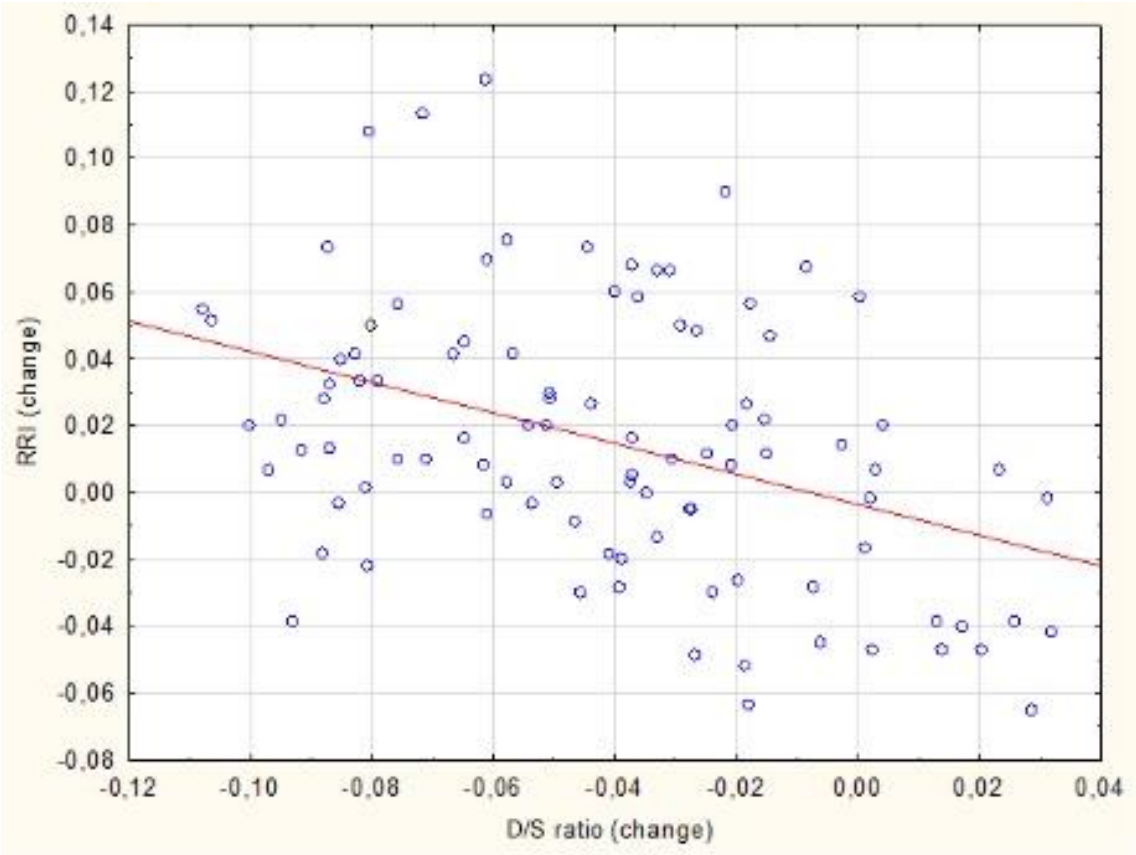
	With change of treatment (n=32)		Without change of treatment (n=64)	
	CC	P	CC	p
24-hour systolic BP change	0.194	NS	0.154	NS
24-hour diastolic BP change	-0.181	NS	-0.088	NS
24-hour mean BP change	-0.123	NS	-0.123	NS
Daytime systolic BP change	0.125	NS	0.125	NS
Daytime diastolic BP change	-0.083	NS	-0.083	NS
Mean daytime BP change	-0.136	NS	-0.136	NS
24-hour pulse pressure change	0.415	0.020	0.284	0.024
Daytime pulse pressure change	0.431	0.014	0.238	NS
24-hour diastolic/systolic BP change	-0.557	0.001	-0.312	0.013
Daytime diastolic/systolic BP change	-0.410	0.02	-0.241	0.05
24-hour heart rate change	0.119	NS	0.080	NS

CC: coefficient of correlation between RRI change and given variable.

NS: not significant.

BP: blood pressure.

Figure 1: The relation of 24-hour D/S ratio change to RRI change



Legend – Figure 1

RRI: renal resistive index

D/S ratio: ratio of diastolic to systolic blood pressure