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Renal resistive index—a valid tool to assess renal endothelial function in humans?

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Abstract

Background. In humans, renal endothelial function is assessed by the vasoconstrictive response to L-NG-monomethyl arginine (L-NMMA). We hypothesized that Doppler sonographic measurements of the renal resistive index in response to inhibition of nitric oxide synthase offer a new methodological approach for testing renal endothelial function.

Methods. Forty-one patients without nephropathy were included. Para-aminohippurate and inulin clearance were per-

formed under basal conditions and during L-NMMA infusion. In parallel, renal resistive index was assessed by Doppler sonography, and central blood pressure was determined.
Results. Following nitric oxide synthase inhibition, renal resistive index increased significantly, and 29% of our patients developed Doppler sonographic diastolic zero flow. Renal plasma flow decreased in response to L-NMMA, and conversely, renal vascular resistance increased. There was no correlation of renal vascular resistance and renal resistive index at baseline and during nitric oxide synthase inhibition. Changes in renal resistive index were not related to changes in renal perfusion or renal vascular resistance. Renal resistive index correlated with central pulse pressure at baseline and during L-NMMA infusion, whereas renal vascular resistance did not correlate with central pulse pressure.
Conclusion. Our data do not support the hypothesis that renal resistive index is a tool to test renal endothelial function in humans and should not be used interchangeably with renal vascular resistance.

Keywords: endothelial function; nitric oxide synthase; renal resistive index; renal vascular resistance

Introduction

Impaired renal endothelial function is the precursor of atherosclerosis and a shared feature of different diseases affecting the kidneys such as diabetes or hypertension. For evaluation of renal endothelial function, the invasive clearance technique with inhibition of nitric oxide synthase is currently applied [1–3]. Renal vascular resistance (RVR) and renal plasma flow (RPF) in response to nitric oxide synthase (NOS) inhibition provide information about basal NO activity and have been suggested to be used for early risk stratification [4]. However, since this method is time consuming, invasive and not easily applicable, there is ongoing research for alternative methods that allow evaluation of the renal vasculature in routine clinical diagnostic workup.

In recent years, assessment of the easily applicable and widely accessible Doppler sonographic renal resistive index (RRI) has been examined in multiple studies and different renal conditions [5–7]. The RRI has been established as predictive parameter for progression of hypertensive nephropathy [8] and for renal allograft survival and patient survival [9].

With respect to these promising data and in the face of previous studies, where RRI (or the Doppler sonographic pulsatility index, respectively) and RVR have been used interchangeably [10–12], and a direct relationship between these two parameters has been suggested [13–15], we aimed to establish a new and easily applicable method for evaluation of renal endothelial function by Doppler sonographic assessment of RRI in response to NOS inhibition.

Subjects and methods

Forty-one participants were recruited by our clinical research competence unit in Erlangen–Nürnberg (www.crc-erlangen.de). Inclusion criteria were male or female participants between the age of 18 and 75 years. Exclusion criteria were severe or resistant hypertension or any form of secondary hypertension, history of cerebrovascular, cardiovascular or peripheral vascular disorders, impaired renal function as shown by estimated glomerular filtration rate (GFR) <60 ml/min/1.73m^2 and/or albuminuria >30 mg/day, impaired liver function, any chronic or acute inflammatory disease and any malignant disease. Baseline characteristics are listed in Table 1. Thirty patients had arterial hypertension as defined by casual blood pressure (BP) ≥140/90 mmHg or treatment for hypertension. Antihypertensive treatment consisted of calcium channel blockers, beta-blockers, thiazid diuretics, angiotensin-converting enzymes inhibitors or angiotensin receptor blockers or a combination treatment of these agents. None of the patients was on treatment with a vasodilating agent. If there was any uncertainty as to whether secondary hypertension could be present, the patient was not included in the study. Eighteen patients had type 2 diabetes mellitus and were on oral treatment with biguanides, glitazones, sulfonylureas or glinides or a combination therapy. Eleven patients were without any known disease and did not take any medication. Before enrolment in the study, written informed consent was obtained from each participant. The study protocol was approved by the Clinical Investigations Ethics committee of the University of Erlangen–Nürnberg, Germany. The study was performed in adherence to the principles of the Declaration of Helsinki and according to Good Clinical Practice standards.

Table 1. Clinical characteristics of the study population

	Patients (n = 41)
Age (years)	56.6 ± 13.5
Male gender (n)	32 (78%)
BMI (kg/m^2)	27.4 ± 4.1
Casual systolic BP (mmHg)	132.2 ±13.8
Casual diastolic BP (mmHg)	78.9 ± 10.0
Casual heart rate (bpm)	73 ± 12
Total cholesterol (mg/dl)	202.0 ± 38.0
HDL-cholesterol (mg/dl)	50.4 ± 12.0
LDL-cholesterol (mg/dl)	132.7 ± 30.3
Triglyceride (mg/dl)	196.1 ± 150.9
Urinary albumine excretion (mg/g creatinine)	14.4 ± 18.2
Glomerular filtration rate (ml/min/1.73m^2)	103.4 ± 19.0

Constant infusion input clearance

Constant infusion input clearance technique with inulin (Inutest®, Fresenius, Linz, Austria) and sodium para-aminohippurate (Clinalfa, Basel, Switzerland) was used to determine GFR and RPF, respectively, under baseline conditions and at the end of a 30-min L-NG-monomethyl arginine (L-NMMA) infusion (Clinalfa AG, Läufelingen, Switzerland) as described previously in detail [1,2]. Thereby, L-NMMA was administered intravenously as a bolus infusion (3 mg/kg body weight) over 5 minutes followed by constant infusion (1.25 mg/kg body weight) over 25 min. The total dose of L-NMMA was 4.25 mg/kg body weight.

In parallel, systemic haemodynamic parameters (peripheral systolic, mean and diastolic blood pressure, pulse pressure and heart rate) were monitored by an oscillometric device (Dinamap 1846 SX, Criticon, Norderstedt, Germany).

Doppler sonographic assessment of RRI

The B-Mode measurements and the Doppler measurements of the RRI were performed at the same time using a Hitachi CS 192 Integral/PQ ultrasound machine with a 3.5-MHz sector transducer. Patients were placed in a supine position, and right and left kidneys were evaluated for morphologic criteria in order to exclude patients with any difference in size or morphology between kidneys or suspicion for renal artery stenosis. At baseline, an interlobar artery was located using colour flow imaging. Three measurements of maximum systolic velocity and minimal diastolic velocity were recorded after 120 min of resting as baseline values and at specific time points (0–2 min, 7–10 min, 17–20 min, 27–30 min) during

Table 2. RPF, GFR, RVR and RRI at baseline and in response to L-NMMA

	RVR (mmHg*min*ml^{-1})	GFR (ml/min/1.73m^2)	RPF (ml/min/1.73m^2)	RRI (arbitrary units)
Baseline	85.8 ± 20.8	125.0 ± 21.6	702.6 ± 129.3	62.8 ± 7.4
L-NMMA	104.4 ± 25.7*	128 ± 21.6	621.9 ± 117.8*	76.9 ± 15.3*
% of change	22.4 ± 18.1	3.0 ± 7.3	−11.3 ± 7.5	22.5 ± 15.7

*P-value <0.05 of change between baseline and L-NMMA.

Table 3. Central SBP, central DBP and central PP at baseline and in response to L-NMMA

	Central SBP (mmHg)	Central DBP (mmHg)	Central PP (mmHg)
Baseline	123.5 ± 20.2	77.8 ± 12.2	45.7 ± 13.0
L-NMMA	140.6 ± 28.1	85.1 ± 14.3	55.6 ± 19.7
% of change	14.0 ± 12.9*	9.9 ± 11.2*	21.0 ± 22.2*

*P-value <0.05 of change between baseline and L-NMMA.

Table 4. Correlation coefficients and P-value of RVR and RRI at baseline and in response to L-NMMA with central systolic and diastolic blood pressure, heart rate and pulse pressure at baseline and in response to L-NMMA

	RVR baseline	RRI baseline
A		
Systolic BP at baseline (mmHg)		
r	0.359	0.267
P-value	0.03*	0.10
Diastolic BP at baseline (mmHg)		
r	0.497	−0.167
P-value	0.002*	0.31
Heart rate at baseline (bpm)		
r	0.253	0.168
P-value	0.13	0.31
Pulse pressure at baseline (mmHg)		
r	0.087	0.569
P-value	0.60	<0.001*
	RVR L-NMMA	**RRI L-NMMA**
B		
Systolic BP with L-NMMA (mmHg)		
r	0.470	0.158
P-value	0.004*	0.34
Diastolic BP with L-NMMA (mmHg)		
r	0.539	−0.224
P-value	0.001*	0.17
Heart rate with L-NMMA (bpm)		
r	0.351	0.194
P-value	0.04*	0.24
Pulse pressure with L-NMMA (mmHg)		
r	0.249	0.442
P-value	0.14	0.005*

r = correlation coefficient. *$P < 0.05$.

infusion of L-NMMA using the power Doppler function. The dimensionless RRI was calculated using the formula:

$$\text{RRI} = [(\text{maximal systolic velocity} - \text{minimal diastolic velocity}) / \text{maximal systolic velocity}) \times 100].$$

All measurements were performed by the same investigator.

Pulse wave analysis

To derive the central arterial waveform, a validated system (Sphygmocor™; AtCor Medical, Sydney, Australia) was used that employs high-fidelity applanation tonometry (Millar) for non-invasive registration of peripheral arterial pressure waves and appropriate computer software for pressure wave analysis (Sphygmocor™). Pressure calibration was accomplished through automatically, non-invasively obtained supine BP of the brachial artery of the dominant arm after a 30-min rest (Dinamap Compact T; Johnson & Johnson Medical Ltd, Newport, UK). BP was measured five times over 10 min, and the mean of the last three measurements was taken for calibration after rest.

Pressure wave recording was then performed at the radial artery of the same arm with the wrist gently hyperextended. The pressure wave was averaged from single pressure waves recorded sequentially for 8 s. Averaged pressure waves were accepted only if variation of peak and bottom pressures of single pressure waves were <5%. The central pressure wave was then automatically synthesized from the radial pressures by a built-in generalized transfer function. Prior to analysis, a visual check for correct detection of inflection points was performed in each wave by an independent blinded investigator. From the derived central waveforms, data are given on central systolic and diastolic BP and pulse pressure.

Statistical analyses

All statistical analyses were carried out using SPSS software (release 16.0, SPSS Inc., Chicago, Illinois, USA). Results are given as mean ± SD and as mean ± SEM in figures. Comparison of paired samples was performed using Student's t-test. Comparisons between groups were performed using one-way ANOVA and Bonferroni *post hoc* test. Correlation analyses were performed using Pearson's test for parametric data and Spearman rho for non-parametric data. Two-tailed values of $P < 0.05$ were considered statistically significant. Since, to our knowledge, this study analysing the effect of NOS inhibition on renal perfusion by ultrasonographic methods was carried out for the first time, no corresponding data have been available, and no sample size calculation has been carried out.

Results

Inhibition of NOS leads to a significant increase in RRI from baseline throughout the 30-min L-NMMA infusion. A significant increase of RRI occurred 7–10 min after starting infusion of L-NMMA (23% ± 16, $P < 0.001$) and revealed its maximum after 17–20 min (27% ± 19, $P < 0.001$).

Data of RPF, GFR and RVR at baseline and after L-NMMA infusion are shown in Table 2. Inhibition of

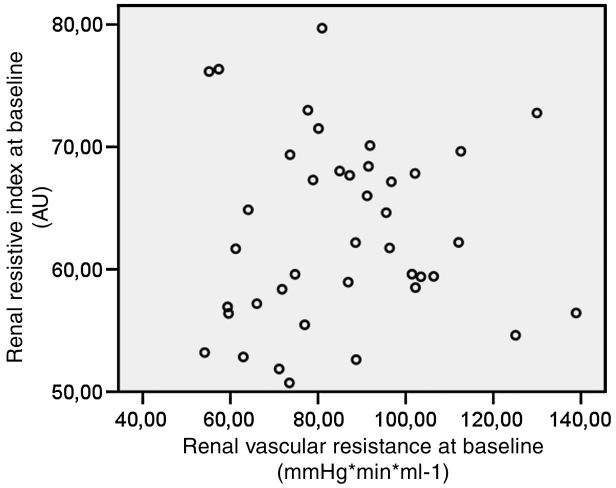

Fig. 1. Scatter plot of Doppler sonographic renal resistive index and renal vascular resistance—assessed by invasive clearance technique—under baseline conditions. Correlation coefficient is 0.032 with $P = 0.84$.

NOS with L-NMMA lead to a significant decrease in RPF ($P = 0.001$). GFR remained stable during infusion of L-NMMA. RVR increased significantly with NOS inhibition ($P < 0.001$).

L-NMMA infusion led to a significant increase of central systolic BP by 14.0% ± 12.9 from baseline ($P < 0.001$). Central diastolic BP increased by 9.9% ± 11.2 from baseline ($P < 0.001$). Central pulse pressure (PP) increased by 21.0% ± 22.2% ($P < 0.001$). Heart rate decreased by 8.9% ± 8.8 ($P < 0.001$) in response to L-NMMA after 17–20 min (Table 3).

RRI at baseline and in response to L-NMMA infusion (mean value of RRI after 7–10 min and 17–20 min) was correlated with central PP but not with central systolic, mean and diastolic BP (Table 4A and B). In contrast, RVR was correlated with central systolic and diastolic BP at baseline and during L-NMMA infusion but not with central PP.

No correlations between the absolute values of RVR and the RRI at baseline ($r = 0.032$, $P = 0.844$) (Figure 1) and during L-NMMA infusion (7–10 min $r = 0.008$, $P = 0.96$; 17–20 min $r = 0.265$ $r = 0.10$; 27–30 min $r = 0.176$ $r = 0.29$) were observed. In accordance, we found no relationship between the changes of RRI and RVR following NOS inhibition ($r = 0.265$, $P = 0.10$).

Subgroup analysis

In an exploratory analysis, we evaluated diabetic patients ($n = 18$) on oral antidiabetic medication, hypertensive patients ($n = 12$) and control subjects. Our control subjects had no history of diabetes or hypertension ($n = 11$) and were younger than the diabetic and hypertensive patients. GFR was within the normal range in all subjects, and no microalbuminuria was present.

There was no correlation between RRI and RVR at baseline (diabetics $r = -0.168$, $P = 0.51$; hypertensives $r = 0.056$, $P = 0.86$; controls $r = 0.333$, $P = 0.35$) and during L-NMMA infusion (diabetics $r = -0.045$, $P = 0.86$; hypertensives $r = -0.027$, $P = 0.94$; controls $r = -0.006$, $P = 0.99$), and the change of RRI and RVR in response to L-NMMA also did not correlate in any of the groups (date not shown). The RRI in diabetics was greater at baseline and during L-NMMA infusion than in hypertensive and control subjects (Figure 2). In diabetic patients, maximum increase of RRI was 32 ± 3.8% over baseline after 7–10 min of L-NMMA infusion whereas maximum increase of RRI was 32 ± 6.6% in hypertensive patients after 17–20 min. In controls, the maximum increase of RRI occurred after 7–10 min and was 17 ± 4.5%.

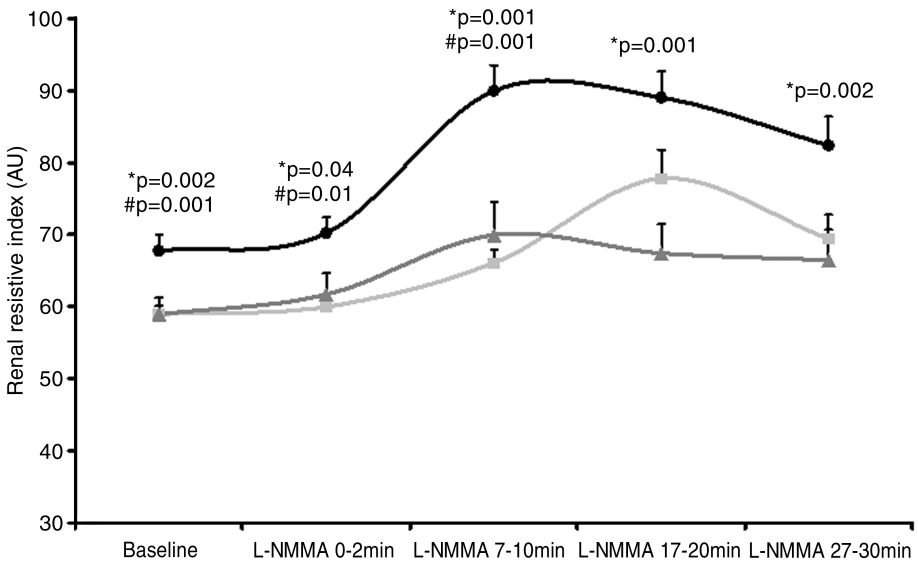

Fig. 2. Changes in renal resistive index over time in response to L-NMMA in diabetic patients (circles), hypertensive patients (squares) and controls who had no history of diabetes or hypertension (triangles). Shown is the average (± SEM) at baseline and at each time point of the ultrasonographic Doppler measurements during L-NMMA infusion. Asterisks indicate significant differences between diabetic patients and controls. Number signs indicate significant differences between diabetic and hypertensive patients.

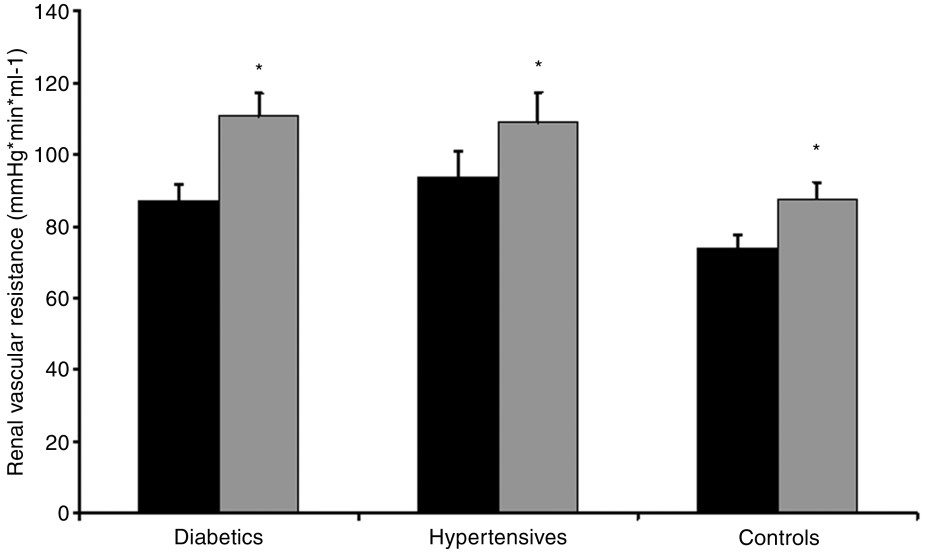

Fig. 3. Renal vascular resistance assessed by invasive clearance technique at baseline (black squares) and in response to inhibition of nitric oxide synthase with L-NMMA (gray squares) in diabetic patients, hypertensive patients and controls who had no history of diabetes or hypertension. Shown is the mean (± SEM) *$P < 0.05$ between baseline values and values in response to nitric oxide synthase inhibition

RVR increased in all groups (diabetics 28.4 ± 21.4%; hypertensives 15.9 ± 17.5%; controls 18.9 ± 7.0%) but there were no significant differences in the increase of RVR between the groups (diabetics *vs.* hypertensives $P = 0.22$; diabetics *vs.* controls $P = 0.54$; hypertensives *vs.* controls $P = 1.0$) (Figure 3).

Discussion

Diabetes and hypertension directly damage the renal vasculature. One early feature of this vascular damage is endothelial dysfunction. To date, only invasive clearance techniques with determination of renal perfusion and RVR in response to NOS inhibition have been applied for evaluation of endothelial function in the renal vasculature. In numerous studies, RRI assessed by Doppler sonography has been used interchangeably with the RVR suggesting a close relationship of these two parameters [10–12]. Hence, in order to evaluate a new and easily applicable non-invasive approach to test renal endothelial function, we measured RVR by invasive clearance technique at baseline and during inhibition of NOS and—in parallel—conducted Doppler sonographic measurements for assessment of RRI. In accordance with previous studies, RPF decreased and RVR increased with inhibition of NOS. Doppler sonographic RRI increased with a maximum of 27% over baseline in response to NOS inhibition. Despite a numerically similar increase of RVR and RRI in response to NOS inhibition, we found no correlation of these two parameters—neither at baseline nor during L-NMMA infusion. In accordance, the percentage of change of RRI and RVR did not correlate. In an *ex vivo* model of perfused rabbit kidneys, Bude *et al.* demonstrated that RRI is dependent on vascular compliance and vascular resistance of the renal circulation, and that RRI becomes less and less dependent on vascular resistance with decreasing compliance [16]. Since some of our patients suffered from diabetes and/or hypertension which may impair vascular compliance of the large arteries, we performed a subgroup analysis but again found no correlation of RRI and RVR in any group not even in the control group at younger age.

Inhibition of NOS resulted in an increase of central blood pressure and pulse pressure. RVR was associated with central systolic and diastolic blood pressure whereas RRI correlated with central pulse pressure at baseline and during L-NMMA inhibition. This disparate pattern of correlations suggests diverse underlying physiological mechanisms of RRI and RVR.

A similar association of RRI with pulse pressure has been previously described by Heine *et al.* [17]. In addition, they demonstrated an association of RRI with systemic atherosclerosis in kidney transplant recipients [18]. In an *ex vivo* pulsatile perfusion model in rabbit kidneys, RRI and pulse pressure were strongly correlated, whereas RRI and RVR were not. In this model, only marked and non-physiologic increases of RVR—induced by infusion of phenylephrine—elevated RRI [19]. In contrary, in our study, we found similar increases of RRI and RVR in response to NOS inhibition. However, an association of these increases was also not found. The discrepant results regarding the increase of RRI and RVR in the *ex vivo* model and our study group might be related to the different mechanism of action of the used vasoconstrictors: Phenylephrine exerts its vasoconstrictive effect on vascular smooth muscle cells, and its vasoconstrictive response can partially be compensated by nitric oxide, the most potent vasodilator. L-NMMA directly inhibits nitric oxide released from the endothelium and might thus induce an exaggerated vasoconstriction of the renal vasculature—both of small and large vessels—without compensatory mechanisms.

In a model of isolated perfused rabbit kidneys, Bude *et al.* found that an increase of the cross-sectional area of the distal arterial bed resulted in a decrease of RRI—independent of vascular compliance and vascular resistance [20]. This might explain the higher baseline RRI observed in the elderly or in patients with diabetes or hypertension, and has been also found in our study population for the diabetic subjects [10,21,22]. In these patients, cross-sectional area might be decreased by remodelling and damage to the small renal arteries and arterioles.

In our subgroup analysis, RVR increase in response to NOS inhibition was not different between the groups, but RRI increase showed a trend towards lower values in the healthy controls compared to diabetic patients ($P = 0.07$; data not shown) underscoring the above results.

Taken together, our *in vivo* results are in context with results from *ex vivo* models and weaken the assumption that RVR is the main determinator of RRI. In fact, RRI is a complex integral of different influences such as vascular resistance vessels, compliance of large arteries (aorta and renal arteries) and pulse pressure, and is not yet fully understood. RRI measurements during inhibition of NOS are not a valid approach for analysing renal endothelial function, since we could not find a close correlation between RRI assessed by Doppler sonography and the RVR determined by invasive clearance technique. Thus, we recommend that RRI and RVR are not to be used interchangeably as long as the RRI is still a miscellaneous parameter of unknown composites.

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Conflict of interest statement. None declared.

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