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ORIGINAL ARTICLE

Renal resistive index and cardiovascular organ damage in a large population of hypertensive patients

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We evaluated the relationship between renal resistive index (RRI) of the intrarenal vasculature and cardiovascular (CV) organ damage such as left ventricular hypertrophy (LVH), diastolic dysfunction and carotid atherosclerosis in a large sample of hypertensive patients. 566 hypertensive patients underwent echocardiography with conventional Doppler and Doppler tissue imaging (DTI), carotid and renal ultrasonography. In addition, lipids profile, creatinine in serum, and urinary albumin concentrations were determined. The patients were divided according to their RRI values in 2 groups: <70 and $\geqslant 70$. Subjects with high RRI were older, had higher systolic and pulse pressure (PP) and more years of hypertension, compared to those with low RRI ($P<0.0001$). Patients with the higher RRI showed an increased left ventricular mass index (LVMI) and carotid intima–media thickness (IMT) with a higher prevalence of LVH, carotid plaques and microalbuminuria ($P<0.001$). There were differences in overall diastolic parameters, in particular when evaluated by DTI ($P<0.001$). A positive correlation was found between RRI and age, PP, carotid IMT, LVMI, SBP and a negative correlation was found with DTI diastolic parameters ($P<0.001$). Age, PP, carotid IMT and LVMI were independently related to RRI. While, RRI was independently related to IMT and IVRT. RRI, especially the higher values, are positively correlated with target organ damage in hypertensive patients, indicating that renal vascular resistance is related to morphologic and hemodynamic alteration of the CV system. The evaluation of RRI could predict the presence of early CV damage and provide an accurate estimate of overall risk.
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Introduction

Epidemiologic and clinical studies have emphasized the close relationship between the rise of blood pressure (BP) and the incidence of cardiovascular (CV) disease.[1,2] It has been recognized that increased BP is a typical finding in patients with end-stage renal disease, and more recently increased pulse pressure and arterial stiffness have been linked to plasma creatinine and microalbuminuria in subjects with mild and moderate renal insufficiency.[3–5] In addition, given the insidious nature of most CV risk factors and the atherosclerotic processes, early recognition of arterial functional and/or structural alterations may help us identify individuals with high risk of clinical complications.[6,7] Increased renal vascular resistance has recently been associated with the severity and duration of essential hypertension and with declining renal function in renal parenchymal disease.[8] Previous studies have shown that the renal resistive index (RRI) is an indicator of renal vascular resistance in essential hypertension.[9] Determining RRI is inexpensive (the same probe is used for the heart), fast (it takes a minute to perform) and requires little training (less than 1 month). In addition, RRI has been shown to be highly reproducible and independent of mean arterial BP.[10,11] Predicting future decline in renal function is important for subsequent therapeutic decision making.[12] Here, we describe a study carried out to investigate which value of RRI, based on ultrasonic duplex scanning, is associated with the classic primary risk factors and the worst CV organ damage from hypertension. We studied the relationship between RRI of the intrarenal vasculature and CV organ damage such as left ventricular hypertrophy (LVH), diastolic dysfunction and carotid atherosclerosis in a large sample of hypertensive patients. We also investigated whether hypertensives with high levels of RRI have an adverse metabolic risk profile.

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Methods

Study population

We studied 566 consecutive patients (324 men, mean age 55 ± 11 years, range 29–90) with stage I or II essential hypertension who were referred to our outpatient clinic. All subjects received a full history and a complete physical examination. The diagnosis of hypertension was considered when SBP was ⩾140 mm Hg and/or DBP ⩾90 mm Hg on at least three visits and when antihypertensive therapy was present. BP was measured by mercury sphygmomanometer with an appropriate size rubber cuff applied around the nondominant arm. Readings were based on Korotkoff first and fifth phase sounds. During each visit, three consecutive BP readings were obtained with the subject in the sitting position after a rest of at least 10 min. The average of the three readings was used for the analyses, recorded to the nearest 2 mm on the scale. Measurements were performed early in the morning and carried out by a trained investigator. We also determined lipid profile and creatinine in serum by standard laboratory methods. Moreover, a spot urine sample was investigated by measuring urinary albumin concentrations using albumin-specific dipstick test. Patients with renal failure (creatinine ⩾1.5 mg/dl in men and ⩾1.4 mg/dl in women), diabetes mellitus, congestive heart failure, atrial fibrillation and severe valvular heart disease were excluded from the study. Additional exclusions were severe obesity, defined as a body mass index (BMI) ⩾40 kg/m^2, and peripheral vascular disease. None had any evidence or history of myocardial infarction or stroke. Each patient provided informed consent for the study and the Institutional Review Board at the participating clinical site approved the study. Of the 566 patients, 38% were previously treated for hypertension. The most frequent classes of antihypertensive drugs used were ACE inhibitors, calcium antagonists and diuretics. None received concomitant medications such as statins and antiplatelet drugs. Before the investigation, all drugs were discontinued, under medical supervision, for at least 1 week. All patients underwent the following instrumental procedures.

Renal colour-Doppler ultrasonography

Based on the mean and distribution of RRI in 40 normal volunteers (mean value 62 ± 03, mean age 54 ± 10 years), the normal upper limit was found to be 70. Thus, the patients were divided according to their arcuate artery resistance index values in two groups: <70 and ⩾70. RRI examinations were performed with 3.5 MHz transducer while the subject was in the supine position. The transducer was placed on the lumbar region, and the kidney was displayed by tomographic echography. Blood flow was visualized with colour-Doppler sonography superimposed on tomographic image. Thereafter, the Doppler signal was obtained from the arcuate arteries at the corticomedullary junction. RRI was calculated by the following equation: peak systolic velocity−peak end diastolic velocity/peak systolic velocity. RRI was determined at least three times for one kidney and then averaged. The mean RRI of the right and left kidneys was used for the subsequent analyses.

Carotid ultrasonography

Ultrasound examination of the carotid was performed with a 7.5-MHz linear-array transducer. Measurements involved a primary transverse and longitudinal scanning of common carotid artery, bifurcation and internal carotid. The end-diastolic intima-media thickness (IMT) of the far wall of the middle segment of both common carotid arteries, defined by a simultaneous electrocardiographic recording, was measured 1 cm caudal to the bulb, as the distance between the lumen–intima interface and the media–adventitia interface.[13,14] Each measurement was calculated by taking the average of three readings. Intima-media thickening of the common carotid arteries was defined as an average IMT ⩾0.9 mm. All measurements were made at a site without plaque. The near and far walls of the carotid were scanned longitudinally and transversally to assess the presence of plaques. The presence of plaques was defined as localized echo structures encroaching into the vessel lumen for which the distance between the media adventitia interface and internal side of the lesion was ⩾1.3 mm, or as the presence of calcification.

Echocardiography

The M-mode echocardiogram was performed with 3.5 MHz phased array placed on the III–IV left intercostal space along the parasternal line, with patients supine, in left lateral decubitus and the head of the bed kept at 30°. The end-diastolic measurements of left ventricular internal dimension, left interventricular septum and posterior wall thickness at the QRS peak using the Penn convention were measured. The left ventricular mass was calculated according to the Devereux formula. Patients with a left ventricular mass index (LVMI) >125 g/m^2 in men and >110 g/m^2 in women were classified as having LVH.[15] Complete two-dimensional echocardiograms were obtained during normal respiration.

Diastolic function assessment

The pulsed Doppler sample volume was placed at the mitral valve tips and 5–10 cardiac cycles were recorded from the apical window on super-VHS videotape at a velocity of 100 mm/s. The following measurements of left ventricular diastolic function were determined: E and A peak velocities (m/s) and their ratio and E-wave deceleration time (ms) by

placing a continuous-wave Doppler sample volume between left ventricular outflow tract and the mitral valve. Pulsed Doppler recordings from left ventricular outflow tract were used to measure isovolumic relaxation time (IVRT) from the closure spike of the aortic valve to onset of mitral flow.

Moreover, the Doppler tissue imaging (DTI) program was set to the pulsed-wave Doppler mode. Filters were set to exclude high-frequency signals, and the Nyquist limit was adjusted to a velocity range of 15–20 cm/s, gains were minimized to allow for a clear tissue signal with minimal background noise. All DTI recordings were obtained during normal respiration. A 5-mm sample volume was placed at the apical four-chamber view on the lateral corner of the mitral annulus. The resulting velocities were recorded for 5–10 cardiac cycles at a sweep speed of 100 mm/s and stored on a 1/2-inch VHS videotape for later playback and analysis. The following measurements were determined as diastolic indexes: myocardial early (Em) and atrial (Am) peak velocities (m/s) and their ratios. We used DTI because the technique is better than conventional Doppler at detecting hypertension-associated dysfunction, in particular when LVH is present.[16]

All echocardiographic and ultrasonographic examinations, were recorded on videotape and performed by the same experienced physician. For all ultrasonographic examinations, we used the Aloka ProSound 5500 (Aloka CO, Ltd, Tokyo, Japan) equipped with a variable-frequency phased-array transducer and DTI capabilities.

Analysis of urine

Urinary albumin concentration was performed using Micral test strips (Roche Diagnostics GmBH, Mannheim, Germany) by an experienced physician. Micral test is an immunoassay test. After immersing the strip in the urine sample for 5 s, a colour reaction takes place and the colour is proportional to the albumin concentration in the urine. The Micral test yields a range of semiquantitative results, which are determined by comparing the strip colour with four colour blocks on the vial label corresponding to concentrations approximating 0, 20, 50, 100 mg of albumin/l.[17,18] Following the manufacturer's instructions, albumin concentration readings $\geqslant$20 mg/l were classified as positive for microalbuminuria. All patients positive at the first test underwent a second test to confirm the previous value. Patients had confirmed microalbuminuria when both tests were positive.

Data analysis

Statistical analysis was carried out by GB-STAT version 6.50 (Dynamic Microsystems, Inc., Silver Spring, MD, USA). Comparison between groups was performed using the Student's *t*-test for unpaired data. Comparisons of categorical data were made using Fisher's exact test. Pearson correlation coefficient was calculated to investigate the linear relationship between RRI and other variables. Stepwise forward regression analysis was performed to assess which factors independently influence RRI and whether RRI is an independent predictor of CV damage. Variables selected for inclusion in the models were those significant at univariate analysis. Significance was defined as $P<0.05$. The results are expressed as means $\pm$ s.d. Kappa statistic was used to assess inter and intrareader variability for echocardiographic and ultrasonographic parameters.

Table 1 Clinical characteristics of study patients according to renal resistive index

Data	*<70 (64±4)* n = *318*	*⩾70 (75±4)* n = *208*	P
Age (years)	51±10	62±8	<0.001
Male (%)	60	55	NS
Body mass index (kg/m^2)	29±4	29±4	NS
Smokers (%)	25	23	NS
Systolic blood pressure (mm Hg)	146±10	154±14	<0.001
Diastolic blood pressure (mm Hg)	95±7	93±7	<0.002
Pulse pressure (mm Hg)	50±10	60±14	<0.001
Heart rate (beats/min)	73±11	72±11	NS
Duration of hypertension (years)	6±5	9±7	<0.001
Carotid intima-media thickness (mm)	0.70±0.16	0.84±0.17	<0.001
Left ventricular mass index (g/m^2)	107±21	120±25	<0.001
E-wave deceleration time (ms)	222±37	232±35	<0.003
E/A ratio	1.04±0.37	0.87±0.26	<0.001
Em/Am ratio	0.94±0.44	0.73±0.29	<0.001
Isovolumic relaxation time (ms)	99±11	108±14	<0.001
Serum creatinine (ímol/l)	84±16	82±19	NS
Total cholesterol (mmol/l)	5.24±0.9	5.32±0.9	NS
Triglycerides (mmol/l)	1.49±0.6	1.45±0.6	NS
HDL cholesterol (mmol/l)	1.26±0.3	1.29±0.3	NS

Abbreviation: HDL, high-density lipoprotein.
Values are means ± s.d.

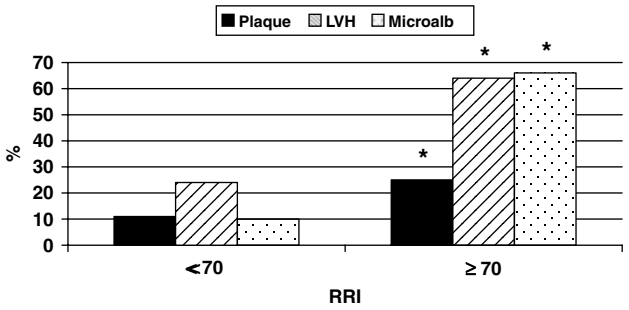

Figure 1 Prevalence of LVH, carotid plaques and microalbuminuria according to RRI (*$P<0.001$).

Table 2 Independent predictors for renal resistive index by stepwise forward regression analysis

	β-*coefficient*	*Standard error (β)*	t-*value*	P
Age	0.002435	0.000326	7.4806	<0.0001
Pulse pressure	0.00181	0.000404	4.4809	<0.0001
Carotid IMT	0.051606	0.015938	3.238	0.0013
LVMI	0.000273	0.000111	2.4525	0.0145

Abbreviations: IMT, intima-media thickness; LVMI, left ventricular mass index.
Other tested variables (see Data analysis) did not achieve statistical significance.
Multiple $R=0.66$.

Results

Table 1 shows the demographic and clinical characteristics distinguishing the 338 patients with RRI <70 from the 228 patients with an index $\geqslant 70$. Subjects with high RRI were older, had higher systolic and pulse pressure and more years of hypertension, compared to those with low resistance index ($P<0.0001$). There were no significant differences in total cholesterol, HDL cholesterol, triglycerides and serum creatinine. BMI and smoking habit did not differ significantly between groups. Patients with the higher RRI showed a significantly increased LVMI and carotid IMT ($P<0.001$). Moreover, there were significant differences in overall diastolic parameters, in particular when evaluated by DTI ($P<0.001$). These showed a left ventricular diastolic dysfunction in patients with high RRI. Furthermore, patients with the higher value of RRI also showed a significant higher prevalence of LVH, carotid plaques and microalbuminuria ($P<0.001$) (Figure 1). A high positive correlation was found between RRI and age ($r=0.59$, $P<0.001$), pulse pressure ($r=0.47$, $P<0.001$), carotid IMT ($r=0.44$, $P<0.001$), LVMI ($r=0.37$, $P<0.001$), SBP ($r=0.35$, $P<0.001$), duration of hypertension ($r=0.31$, $P<0.001$). Furthermore, RRI was negatively correlated with DTI diastolic parameters ($r=-0.34$, $P<0.001$). A low positive correlation was found between RRI and E/A ($r=-0.24$, $P<0.001$), E-wave deceleration time ($r=0.23$, $P<0.001$), BMI ($r=0.16$, $P<0.01$), total cholesterol ($r=0.14$, $P<0.01$) and HDL cholesterol ($r=0.11$, $P<0.05$). There was no correlation between RRI and DBP ($r=0.08$, $P=0.079$), triglycerides ($r=0.009$, $P=0.82$) and serum creatinine ($r=-0.02$, $P=0.60$). Stepwise forward regression analysis was performed with RRI as a dependant variable and with age, SBP, DBP, PP, carotid IMT, LVMI, E-wave deceleration time, E/A and Em/Am ratios and IVRT as independent variables. As shown in Table 2, age, PP, carotid IMT and LVMI were independently related to RRI, while RRI was independently related only to IMT (β-coefficient: 0.571; Standard error (β): 0.147; t-value: 3.873; $P=0.0001$) and IVRT (β-coefficient: 134.917; Standard error (β): 7.999; t value: 16.868; $P=0.0001$). The inter and intrareader variability was good ($K>0.75$).

Discussion

This is the largest study, using all non-invasive CV procedures, confirming that high RRI is a strong, independent predictor of CV target organ damage and renal dysfunction. Hypertensive patients with RRI $\geqslant 70$ had increased carotid IMT and LVMI with preclinical impairment of left ventricular diastolic function and exhibited a higher percentage of LVH, plaques and microalbuminuria compared with low RRI. A high resistive index is associated with a great difference in velocity between the systolic and the diastolic phase that, in part, depends on the degree of peripheral arterial stiffness.[19] Hypertension may cause nephrosclerosis or glomerulosclerosis, reducing the intrarenal vascular surface area and increasing vascular resistance even in the unaffected kidney.[20] The evaluation of RRI in hypertensive patients reveals significantly higher values than normotensive subjects, even without overt nephropathy.[21] Nevertheless, lower RRI values were associated with low renal and CV target organ damage.[22] This finding is not surprising because patients with hypertension in an early phase maintain stable function even over long periods. This is especially true when a good control of BP is achieved using antihypertensive agents that might convey additional specific CV protection beyond BP control.[23] In this condition, the alteration in renal vascular resistance is probably functional and reversible, partly caused by vascular changes such as vasoconstriction mediated by circulating angiotensin II or other neuroendocrine agents. While in an advanced phase, the alteration is structural and irreversible. Although RRI may not be useful in the differential diagnosis of intrinsic renal disease because it does not differ in the various types of renal parenchymal diseases.[24] It is also well known that high RRI values are associated with poor renal prognosis; recently, Radermacher *et al.*,[8] showed that a very high RRI of at least 80 or higher reliably identifies hypertensive patients, without renal artery stenosis, at risk for

progressive renal disease.[8] It is unclear whether this indicates irreversible renal scarring or whether a therapeutic strategy could favourably influence the prognosis.[8] Other studies reported that RRI was positively correlated with IMT, albumin-to-creatinine ratio, macroangiopathy and carotid arteriosclerosis.[22,25] Furthermore, when the resistive index is measured in the internal carotid artery, it shows a high correlation with increased IMT and with the severity of atherosclerosis as well as the ability to distinguish between low- and high-risk patients.[26] A direct correlation between IMT, LVMI and the risk of myocardial infarction and stroke in a population of patients without a prior history of CV disease has been shown.[27–28] We report that the highest RRI levels are associated with other forms of CV organ damage. Our results suggest that the RI of intrarenal arteries could be a useful marker for early organ damage and might be a predictor of future CV complications in hypertensive patients. Furthermore, the present findings show that there is a significant relation between left ventricular diastolic function, renal Doppler parameters and microalbuminuria in hypertensive patients, suggesting that cardiac damage progresses in parallel with renal involvement from the early stage. Microalbuminuria is an early sign of nephropathy, but is also an established marker of increased risk for end-stage renal disease, atherosclerotic risk, CV morbidity and mortality, and is a marker of generalized vascular dysfunction in hypertensive patients.[6,29] Our findings pointed out that RRI could be a good indicator of renal function and early intravascular and cardiac dysfunction such as microalbuminuria. To measure microalbuminuria, we used the semiquantitative Micral test for our large cohort. This is a simple and valuable method, with a negative predictive value of 92%, to identify hypertensive patients with microalbuminuria in a primary care setting and is a screening rather than a diagnostic test.[17–18]

In conclusion, we have shown that RRI, especially the high values, are positively correlated with target organ damage in hypertensive patients, indicating that renal vascular resistance is related to morphologic and hemodynamic alteration of the CV system. The evaluation of RRI may predict early CV damage and provide an accurate estimate of overall risk. Assessment of global CV risk is one of the main elements of most current hypertension management guidelines. Changes in renal haemodynamics and cardiac geometry already occur in subjects with high-normal BP and CV events are consistently increased when compared to people with optimal BP.[12,30] The 2003 European guidelines for management of hypertension suggest that high normal BP includes values considered high in high-risk subjects for whom antihypertensive treatment is recommended.[15] As an extensive diagnostic workup may be too expensive, the use of integrated, low-cost and easy-to-detect parameters may be helpful in clinical practise to discover high-risk subjects. The ability to stratify patients according to their CV risk is important for subsequent therapeutic decisions and could help to identify hypertensive patients for whom more aggressive, preventive therapy is advisable. Furthermore, longitudinal studies are needed to assess the predictive role of increased RRI in hypertensive patients and whether this could be prevented by optimal BP or by specific agents is still unclear. Evidence is emerging on the beneficial effect of blocking renin–angiotensin system activation that may reverse subclinical target organ damage and prevent CV events.[23,31–32]

What is known about this topic

- Several studies in recent years have shown the potential use of Doppler sonography to improve the assessment of renal dysfunction.
- The Doppler renal resistive index (RRI) was proposed as a useful parameter for quantifying the alterations in renal blood flow that may occur with renal disease.
- Over the last years some studies have investigated, in small samples of hypertensive patients, the relationship between RRI and subclinical cardiovascular target organ damage, namely, LVH and/or carotid atherosclerosis, and/or renal function.

What this study adds

- The merit of our study is that we used, in the largest sample of hypertensive patients, all the most sensitive and reliable non-invasive techniques (for the first time DTI) to detect cardiovascular target organ damage (LVH, diastolic dysfunction, carotid atherosclerosis, microalbuminuria), and evaluate some metabolic parameters.
- Clinical implications can be drawn from our findings because the relationship between RRI and CV TOD is largely confirmed.
- The impact of vascular compliance on the RRI may help to assess the end-organ damage in patients with hypertension and arteriosclerosis and could help to identify hypertensive patients for whom more aggressive, preventive therapy is advisable.

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