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*Received for publication: 7.2.06*
*Accepted in revised form: 18.10.06*

Nephrol Dial Transplant (2007) 22: 692–696
doi:10.1093/ndt/gfl686
Advance Access publication 27 December 2006

# Doppler sonography in renal artery stenosis—does the Resistive Index predict the success of intervention?

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**Keywords:** colour Doppler ultrasound; Doppler sonography; ischaemic nephropathy; renal artery stenosis; renal ultrasound; renovascular disease

## Introduction

Renal artery stenosis (RAS) may induce renovascular hypertension and ischaemic nephropathy. For decades, research has been focused on non-invasive diagnostic techniques, which might reliably predict the outcome of blood pressure and renal function after revascularization of RAS. In 1991, Geyskes and de Bruyn [1] found that captopril renography predicted the outcome of blood pressure in 94 patients with significant RAS with sensitivity and specificity of 91 and 62%,

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respectively. However, this technique shows less diagnostic accuracy in patients with renal failure [2]. Schoenberg *et al.* [3] have shown that magnetic resonance angiography is a reliable tool for the non-invasive grading of RAS, if phase-contrast flow measurement is achieved [3]. This technique offers important information on functional consequences of stenoses with potential impact on the glomerular filtration rate. Nevertheless, a correlation with the clinical outcome after intervention in patients with significant RAS is still not available.

Doppler sonography has been steadily improved over the last years and is now frequently used as first-line screening test for patients with suspected RAS [4–7]. In addition, arguments have been presented to indicate that it may also be useful to predict outcome after revascularization. The combined approach to the main renal artery, as well as to the intrarenal arteries, seems to be the ideal technique to overcome the limitations of this tool, such as impaired visualization due to bowel movement and obesity [5,6,8].

The 'extra-renal' parameters of choice are the peak systolic velocity, obtained in the main renal artery, as well as the renal aortic ratio of the maximum blood flow velocities, determined in the aorta and in the main renal artery. Significant RAS is present, if peak systolic velocity >1.8–2.0 m/s or renal aortic ratio >3.5 are obtained [4–8] (Figure 1).

Additional intrarenal scanning permits the diagnosis of RAS without direct imaging of the main renal artery. In 1994, Schwerk *et al.* [9] introduced the Resistive Index (RI) obtained in the interlobar arteries as a reliable indirect parameter for detecting RAS. The authors calculated the side-to-side difference of intrarenal RI >5% with the lower RI in the post-stenotic kidney. Sensitivity and specificity were 100 and 94%, respectively, for moderate and severe RAS [9]. In the meantime, intrarenal RI has been frequently evaluated for different nephrological issues [10,11]. In a single prospective study [12] a high intrarenal RI was found to be negatively correlated with the outcome of intervention in patients with atherosclerotic RAS. A high RI (RI $\geq$ 80) was felt to reflect advanced renal damage, which would explain the interventional treatment failure. However, these amazing results were not uniformly confirmed in different studies [13–15].

The aim of this review is to comment on the contradictory findings of recent papers and to shed some light on the mystification of intrarenal RI, with special attention paid to its use as a predictive parameter for the outcome of intervention in patients with RAS.

## Intrarenal Resistive Index and its affecting factors

The RI is a ratio of peak systolic and end diastolic velocity, derived from the Doppler spectrum of any vessel (Figure 2). Initially this index was introduced

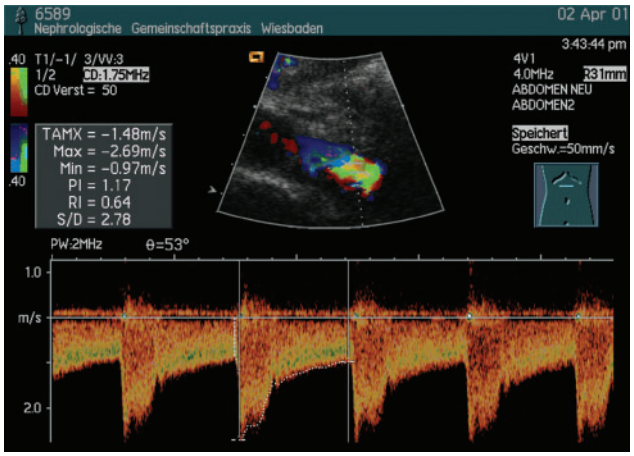


**Fig. 1.** The green colour indicates high blood flow velocities and turbulences near the ostium of the left renal artery scanned with the patient in a supine position. Peak systolic velocity of 269 cm/s detected with an angle of 53° indicates moderate renal artery stenosis.

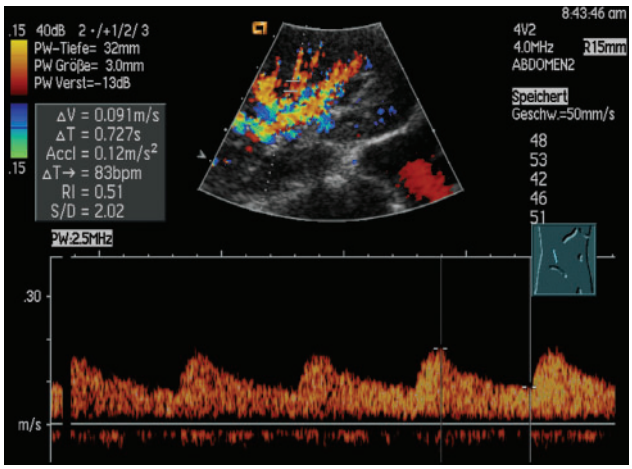


**Fig. 2.** Intrarenal RI is derived from the formula of Pourcelot [16]. RI of 51 is determined in the Doppler flow pattern of a kidney with proximal RAS. The 'tardus-parvus'-flow pattern reveals low peak systolic and high end diastolic velocity resulting in low RI-values from 42 to 53.

by Pourcelot [16] for the grading of stenoses of the carotid artery. There is some evidence that several factors influence intrarenal RI: (i) the extent of stenosis; (ii) the distensibility/stiffness of the vascular system; (iii) non-renal factors and (iv) the location of intrarenal Doppler measurement.

### *Extent of stenosis*

Significant narrowing of the vessel induces a reduction of the peak systolic flow velocity, including a loss of the so-called 'early systolic peak'. While end diastolic velocity increases in stenoses, RI decreases, because PSV is calculated in the nominator of the ratio (Figure 2). The more severe the RAS, the lower the RI is determined [5].

*Distensibility/stiffness of the arteries*

*In vitro* experiments have shown that the degree of distensibility of the vessel has an important impact on the post-stenotic Doppler waveform. The loss of the early systolic peak is normal in an artery with high compliance; however, this is a sign of significant stenosis in an artery with low compliance. Therefore, a higher RI is measured in vessels with low compliance than in those with excellent compliance [17,18].

The interaction between distensibility and Doppler waveform of the vessel may explain the data of intrarenal RI, recently evaluated in patients with renal allografts [19,20]. Heine *et al*. [19] found a significant correlation between intrarenal RI, derived in 105 stable renal allografts, with parameters of atherosclerosis of the recipients, e.g. intima media thickness, Ankle Brachial Index and the Framingham risk score. Very recently we found corresponding data. Intrarenal RI of 76 renal allografts with stable renal function significantly correlated with the pulse wave velocity of the recipients, obtained from the carotid to the femoral artery [20].

In summary, the stiffness of the supplying arteries, e.g. the aorta or the iliac artery, have a significant impact on the RI derived in renal allografts. Both the *in vitro* data as well as those of transplanted grafts must be borne in mind when interpreting the RI of native kidneys. The Doppler signal of the kidney appears to be a mirror of the vascular system of the patient independently from the degree of renal damage. Consequently, there was no correlation found between RI and the glomerular filtration rate of the grafts in both trials [19,20]. In another study, correlation of RI with renal histopathological parameters revealed a relationship exclusively with the degree of renal arteriolosclerosis, measured as percentage of vessels showing wall thickening or hyaline change [21].

*Non-renal factors*

Further non-renal factors have an impact on the intrarenal RI of the kidneys. For example, tachycardia induces low values of RI, simply because the systolic peak begins earlier than in the case of normal heart rate. Similarly, bradycardia (heart rate <60 beats/min) induces high values of RI due to later beginning of the next systolic peak with less endiastolic velocity. Needless to say, the vascular resistance of kidney does not change with the heart rate. It is worth mentioning that in case of arrhythmias, RI does not give any information on renal perfusion. Especially in patients with atrial fibrillation, RI should not be used for the diagnosis of RAS.

In patients with insufficient aortic valve, high intrarenal RI is calculated due to the high amplitude of blood pressure. Vice versa, in patients with significant stenosis of the aortic valve, low RI is registered in the kidneys.

Acute swelling of the kidney leads to an increase in vascular resistance. Therefore, high RI is registered in patients with significant renal obstruction [22], with haemolytic uraemic syndrome [23], as well as in those with acute transplant rejection [24]. In these cases, renal Doppler sonography may be useful for therapeutic monitoring, rather than for making the final diagnosis.

*The location of intrarenal Doppler measurement*

Intrarenal RI decreases from the hilum of the kidney towards the renal cortex [18]. While the 'early systolic peak' frequently appears in the normal Doppler flow pattern of an hilar artery, this phenomenon is rarely detected in the interlobular renal arteries. Therefore, if intrarenal RI is calculated from the flow pattern of the hilar artery, higher values of RI are expected. This might be one reason for the discrepancy in current published data. However, it is common sense to calculate intrarenal RI without the 'early systolic peak' obtained from the spectra of the interlobar or segmental arteries.

Bearing all non-renal factors in mind, it might be valid to question whether high intrarenal RI is really an indicator of advanced morphological damage and thus helpful in predicting interventional outcome in patients with RAS?

## Is the intrarenal Resistive Index predictive for patients with RAS?

Radermacher *et al*. [12] found that intrarenal RI $\geq 80$ obtained in segmental renal arteries was highly predictive of treatment failure in patients with atherosclerotic RAS. In this single-centre prospective trial, 90 of 91 patients with RI $< 80$ showed improvement of blood pressure after angioplasty or stenting of RAS. Multivariate odds ratio of RI $\geq 80$ for worsening of renal function was 100-fold higher than the odds ratio of other diagnostic tests or established predictive clinical parameters [12]. Due to this clear superiority in a single study, the Doppler parameter was implemented in several guidelines and reviews on the approach to patients with RAS [25,26]. However, there are essential limitations to the study. The authors did not clearly affirm whether they used the RI of the stenotic kidney or the RI of the contralateral side for statistical evaluation. This detail is important, due to the impact of stenotic grading on intrarenal RI. The lower the post-stenotic RI, the higher the percentage of luminal reduction of the renal artery [5]. Therefore it is useless to use post-stenotic RI to identify advanced renal damage. Because 47 patients with bilateral RAS were included in the study, post-stenotic RI was used for statistical evaluation in 36% of the patients [12]. It is likely that several of these patients with RI $\geq 80$, who were treated with angioplasty, did not have severe RAS. In addition,

it is notable that patients with a reduction in the diameter of renal arteries of at least 50%, which might be not significant, were included in the study [12]. This may explain the high rate of treatment failure in the group of patients with RI $\geq$ 80.

Recently, Voiculescu *et al*. [27] evaluated post-stenotic RI separately from contralateral RI in patients with unilateral RAS. The univariate odds ratio for contralateral RI $\geq$ 80 was not significant for the prediction of blood pressure outcome in this study. However, post-stenotic RI of <55, in combination with renin ratio of selective renal vein sampling, showed best sensitivity and specificity of 88 and 67%, respectively, for predicting blood pressure outcome after intervention [27]. It seems plausible that severe RAS detected by low post-stenotic RI (RI < 55) responds more frequently to intervention than moderate RAS with higher post-stenotic RI.

Although several recent studies did not explicitly calculate the predictive value of RI for the outcome of RAS after intervention, there are some important data worthy of mention.

In a huge group of 241 patients uniformly treated with stent angioplasty for severe RAS ($\geq$70%), Zeller *et al*. [13] found, in 39 patients with RI > 80, significant improvement of blood pressure as well as improvement of renal function. Similarily, in a small study of 36 patients with successful revascularization of atherosclerotic renal artery stenosis, Garcia-Criado *et al*. [14] found no difference of renal function outcome between patients with intrarenal RI > 80 and those with RI < 80.

Soulez *et al*. [15] calculated the bilateral RI representing an average of RI measurements of both kidneys. A threshold of RI <75, together with a kidney length of >90 mm, predicted a favourable outcome after angioplasty with sensitivity and specificity of 81 and 50%, respectively. This low specificity does not really help the physician to decide for or against angioplasty for the patient.

Finally, the latter results confirm the early data of Frauchiger *et al*. [28], who studied the predictive value of the ratio of diastolic and systolic intrarenal flow in 32 patients with 35 interventions for RAS. They found that the ratio <0.30, corresponding to RI > 70, weakly correlated with clinical failure of subsequent renal artery intervention. However, in the majority of patients, a ratio >0.30, corresponding to normal RI, had no prognostic significance.

## Conclusions

Many 'non-renal' factors affect the RI obtained in the intrarenal arteries of the kidney. These factors must be considered, if intrarenal RI is used as parameter to predict interventional success. The haemodynamic impact of the post-stenotic flow pattern in RAS prohibits the use of RI for the diagnosis of advanced renal damage in patients with severe RAS. The predictive value of RI in non-stenotic contralateral kidneys is contradictory in the recent literature. An RI $\geq$ 80 cannot be recommended as the predictive parameter of choice for the outcome of intervention in patients with significant unilateral RAS. However, low intrarenal post-stenotic RI indicates more severe stenosis, which is more likely to respond to intervention than low grade or moderate RAS. The current controversy must be solved by further studies.

*Conflict of interest statement*. None declared.

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*Received for publication: 4.9.06*
*Accepted in revised form: 24.10.06*

Nephrol Dial Transplant (2007) 22: 696–699
doi:10.1093/ndt/gfl728
Advance Access publication 30 November 2006

# Primary hyperparathyroidism—what the nephrologist should know—an update

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**Keywords:** calcium sensing receptor; familial hypocalciuric hypercalcaemia; HRPT-2 gene; MEN-1 gene; primary hyperparathyroidism; RET-gene

## Introduction

In the first 40 years, after its recognition as a clinical entity, primary hyperparathyroidism (HPT) presented as a disorder with kidney stones and bone disease. Now, HPT is often recognized as a result of biochemical screening, or as part of an evaluation for decreased bone mass [1,2]. The diagnosis of HPT is usually made by finding an inappropriately elevated serum parathyroid hormone (PTH) concentration associated with hypercalcaemia. The current understanding of molecular mechanisms of calcium regulation by calcium-sensing receptor (CaSR) and proliferation of parathyroid cells by oncogenes (RET) and tumour suppressor genes (MEN1 gene, HRPT2 gene) has in part changed the management of HPT.

## Calcium-sensing receptor

Serum ionized calcium concentrations are normally maintained within the very narrow range achieved through a tightly regulated calcium-PTH homeostatic system [3]. PTH is secreted almost instantaneously in response to very slight reductions in serum ionized calcium, which are sensed by the CaSR. The CaSR which is responsible for calcium-sensing by the parathyroid gland is a seven transmembrane-domain GTP-binding protein. There is a steep inverse sigmoidal relationship between the serum ionized calcium and PTH concentrations, with a mid-point or set-point of this function, i.e. the calcium concentration at which

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