

Renal Doppler Sonography – Update in Clinical Nephrology

Bernd Krumme

Deutsche Klinik für Diagnostik, Fachbereich Nephrologie und Hypertensiologie, Wiesbaden, Germany

Key Words

Doppler sonography · Ultrasound · Renovascular disease · Kidney transplantation

Abstract



Introduction

B-mode ultrasound of the kidneys is still performed as one of the first diagnostic steps in the evaluation of both native and transplant renal dysfunction. Cortical thickness and echogenicity, renal length as well as grade of collecting duct dilatation are assessed. Although cortical echogenicity and renal size correlate well with histopathology [1], these parameters may only help in evaluating disease chronicity rather than to make final histopathologic diagnosis, where renal biopsy is essential.

Since the middle of the 1980s, when renal Doppler sonography was primarily introduced for the screening of renovascular disease [2], a series of articles that were published indicated the potential of Doppler sonography for improving the sonographic assessment of native and transplant renal dysfunction. However, the results of these studies were discrepant and did not lead to any final conclusive recommendations. Why is it so?

In most of the studies the Doppler resistive index (RI) ($[\text{peak systolic velocity} - \text{end-diastolic velocity}] / \text{peak systolic velocity}$) was used to evaluate renal blood flow for the diagnosis of kidney disease. This was often performed with only rudimentary understanding of non-renal factors affecting arterial Doppler waveform in the kidney. The clarification of these different factors, which have a main impact on renal Doppler waveform, is one of the motivations of this review. Another is to give detailed information from recent papers about the value of

Copyright © 2006 S. Karger AG, Basel

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2006 S. Karger AG, Basel
1660–2110/06/1032–0024\$23.50/0

Accessible online at:
www.karger.com/nec

Prof. Dr. med. Bernd Krumme
Deutsche Klinik für Diagnostik (DKD)
Fachbereich Nephrologie und Hypertensiologie
Von-Leydenstrasse 23, DE-65191 Wiesbaden (Germany)
Tel. +49 611 577 210, Fax +49 611 9568 330, E-Mail krumme@nephrologie-wiesbaden.de

Doppler sonography for the diagnosis of renal and renovascular diseases. The RI will be in the focus of discussion, because this parameter was evaluated in the majority of the papers in the current literature [3].

Factors Affecting Renal Doppler Waveform

In the detailed view one has to discriminate between factors that have only impact on the Doppler flow pattern without any changes of the vascular system and between those which affect the Doppler waveform by changes of elasticity and compliance of the pre-renal and renal arteries.

The heart rate, for example, does really affect the flow pattern in the intrarenal arteries without any differences of renal vascular resistance. The higher the heart rate, the higher the end-diastolic velocity is measured before the next heart beat follows and vice versa, the lower the heart rate the lower the end-diastolic velocity is registered. This relationship between heart rate and end-diastolic velocity is important, because the RI is calculated from the ratio of peak systolic and end-diastolic velocity (see the equation above). That means, the higher the heart frequency the lower the RI in the renal vessels is measured. More than a decade ago, Mostbeck et al. [4] calculated a regression equation for a standardized RI to overcome this source of variance when estimating the renal RI. However, the use of this standardized RI corrected for heart frequency did not improve diagnostic accuracy for the early diagnosis of acute rejection after renal transplantation [5].

Another way to diminish the end-diastolic velocity (or to increase the RI), especially in the segmental renal arteries of transplanted kidneys, is simply to compress the kidney with the transducer. This potential pitfall may lead to a higher interobserver variability, when Doppler signals are assessed in transplanted kidneys by different operators. Last but not least, the so-called 'Valsalva's maneuver' through the breath-hold during Doppler examination of the kidney decreases the diastolic flow velocity and therefore increases the RI without changes of the renovascular bed or of the real vascular resistance [6].

The vascular resistance and especially the vascular compliance are main predictors of the renal RI. Compliance is the rate of change of volume of a vessel as a function of pressure. From a series of in vitro experiments we know that the RI of the kidney is dependent on the pre-renal vascular compliance and renal resistance, becoming less and less dependent on resistance as compliance de-

creases, and being completely independent of renal resistance when vascular compliance is zero [3, 7]. The knowledge of these relationships between RI and different vascular conditions may protect nephrologists from too much enthusiasm to interpret RI as a marker of renal damage. Renal transplantation is an excellent 'in vivo model' to explain the dependency of RI from different vascular systems, the transplanted kidney on the one side and the arteries of the recipient on the other side. Several years ago we showed that the RI of the transplanted kidney significantly correlates with the age of the recipient, however it does not correlate with the age of the kidney [8]. This means that the stiffness of the pre-renal vessels, e.g. the aorta and iliac artery, has a main impact on the renal Doppler indices.

For the practical use it means that an excellent functioning kidney without severe damage transplanted in a patient with extensive atherosclerosis will give higher renal Doppler indices than the same kidney transplanted in a young patient with elastic vessels. For a long time these data were disregarded in many Doppler studies dealing with RI and diagnosis of renal parenchymal damage. However, recently they came into the focus of interest again. Radermacher et al. [9] published a high predictive value of renal RI in patients after renal transplantation for allograft survival as well as for patient survival. The authors conclude that renal RI is non-specific for the kidney and is influenced by many cardiovascular factors [9]. As a consequence of these previous results, Heine et al. [10] recently investigated the relationship between Doppler resistance indices of transplanted kidneys and parameters of cardiovascular disease, such as carotid intima media thickness (IMT) and ankle-brachial blood pressure index (ABI) of these patients. Interestingly, the authors found a significant correlation of renal RI with IMT and ABI; however, glomerular filtration rate of the grafts did not correlate with Doppler indices [10]. Similarly, we found in our own transplanted patients a significant correlation of renal RI with pulse pressure, carotid-femoral pulse wave velocity and IMT without any correlation of creatinine clearance of the graft [11].

It has to be concluded that intrarenal resistance indices are a complex integration of arterial compliance, pulsatility and peripheral resistance and therefore should not be used as specific markers of renal damage [10, 11]. Further studies in this field have to show whether RI may be used as a marker of progression of renal disease rather than as a marker of renal damage [12].

Doppler Sonography for the Diagnosis of Renal Failure

For the above-mentioned reasons it seems to be ineffective to perform renal Doppler sonography for diagnosing chronic parenchymal damage of the kidney. This has already been confirmed in several older studies which showed normal Doppler indices in patients with severe glomerular disease with little correlation between the degree of renal dysfunction and the RI [13, 14].

However, there is one exception to this rule, such as the acute renal failure. With B-mode ultrasound, ureteral obstruction can be diagnosed in most of the cases when hydronephrosis is present. However, limitations of this technique for potential acute and chronic obstruction have been recognized. The purely anatomic information of the B-scan may be incomplete or misleading: collecting systems dilatation can be caused by conditions that are not obstructive. Also, in the acute setting, obstruction may be present for several hours before collecting system dilatation occurs. In this issue, renal Doppler sonography can help to discriminate acute from chronic obstruction by measuring the changes of RI detecting the vasoconstriction response of the obstructed kidney. The increase of RI with a difference >0.10 between the kidneys was seen to be a reliable parameter for diagnosing acute ureteral obstruction [15]. These initially encouraging results were confirmed by several studies so that many clinicians use Doppler sonography routinely in the evaluation of obstructive renal disease [16, 17].

In patients with non-obstructive acute renal failure the RI is also markedly increased, however, in both kidneys and the underlying disease of acute renal failure it cannot be further differentiated – although it may be interesting to study patients with acute renal failure during the follow-up of the disease. For example in patients with hemolytic uremic syndrome, renal Doppler indices may fall before clinical parameters, such as creatinine or lactate dehydrogenase, show improvement of the disease [18]. Moreover, in patients with hepatorenal syndrome, renal Doppler sonography enables the early detection of renal hemodynamic disturbances in patients with liver cirrhosis even before renal dysfunction becomes clinically evident [19].

Doppler Sonography for the Diagnosis of Renovascular Disease

The presence of hemodynamically relevant renal artery stenosis has an impact on the Doppler flow pattern in the segmental and interlobar arteries of the kidney. This phenomenon makes it impossible to detect renal damage in a stenotic kidney by this technique. The higher the stenotic gradient in the renal artery, the slower and smoother the systolic upstream with identical diastolic velocity in the kidney is measured [20]. This so-called ‘parvus-tardus flow’ results in a decrease of the RI, so that this index can be compared with that of the contralateral kidney. In patients with significant unilateral renal artery stenosis, the side-to-side difference of RI of >0.05 seems to be a reliable parameter to detect stenosis [21, 22]. It is of note that this RI is based on 3–6 measurements in the kidney, because single values show high variance. Gottlieb et al. [23] investigated different Doppler parameters for the screening of renal artery stenosis; however, RI was the most reliable. Others, such as acceleration time or acceleration index, were more operator-dependent and therefore less reliable. These data were recently confirmed by Demirpolat et al. [24].

Atherosclerotic renal artery stenosis occurs bilaterally in 20–30% of the patients. In these patients, side-to-side comparison of RI fails to detect stenosis. Therefore it is useful to measure additionally the blood flow velocity at the ostium and in the course of the renal artery. The thresholds range from 1.8 to 2.0 m/s with sensitivity and specificity of 70 to 90%, respectively [21, 22]. However, it is unwise to rely exclusively on the direct imaging of the renal arteries. This is often technically difficult, time-consuming and in 20% of the patients, meteorism and bowel movement lead to insufficient visualizing of the course of the renal arteries.

Recently, Radermacher et al. [22] have shown that renal Doppler sonography is not only useful for detecting stenosis but also for giving a prognosis of interventional treatment of renal artery stenosis. They found that patients with intrarenal RI ≥ 0.80 obtained in segmental renal arteries neither respond with improvement of blood pressure nor with increase of renal function after dilation of renal artery stenosis. Unfortunately, the authors did not exactly describe which RI (the stenotic or non-stenotic RI) was calculated for the multivariate regression analysis. As mentioned above, the RI obtained in the stenotic kidney cannot be used to get any information of renal damage. As a consequence of this inconsistency, other papers could not confirm this highly predictive val-

ue of RI in patients with renal artery stenosis [25, 26]. Zeller et al. [26] did the follow-up of 241 patients who underwent percutaneous ■■■■ with atherosclerotic renal artery stenosis. However, in the subgroup of 39 patients with a pre-interventional RI >0.80, mean arterial blood pressure as well as mean serum creatinine significantly decreased 1 year after angioplasty or stenting. Further prospective studies have to show whether measurement of intrarenal RI can help in the decision of interventional treatment of renal artery stenosis.

Other renovascular diseases such as arteriovenous fistulae after kidney biopsy or renal artery aneurysms in female patients with fibromuscular dysplasia [27] may also be detectable with Doppler sonography; however, in most of these patients a further imaging technique is needed for the planning of therapeutic procedures.

Doppler Sonography after Renal Transplantation

All vascular problems, mentioned above for native kidneys, can be diagnosed often more easily in transplanted kidneys. However, it has to be additionally considered that significant iliac artery stenosis proximal to the anastomosis may also induce the same stenotic flow pattern as in the renal artery itself [28]. As a consequence, all clinical symptoms of transplant renal artery stenosis, such as renovascular hypertension and renal dysfunction, may also occur in patients with proximal iliac artery stenosis. Therefore, the common iliac artery and transplant renal artery should always be examined in the same session [28].

It is much more difficult, if not impossible, to further characterize the parenchymal cause of transplant dysfunction by Doppler sonography than renovascular diseases. After initial enthusiasm in the late 1980s, when several authors found an increase of Doppler indices in patients with acute rejection, later on more and more skepticism came up over the specificity of these results [3, 5, 29]. Acute tubular necrosis as well as cyclosporine toxicity or chronic vascular rejection may also lead to high resistance indices so that final diagnosis is made exclusively with biopsy [3]. Additionally, one has to keep in mind that vessel compliance of the recipient also has a main impact on the renal resistance indices of the graft, as mentioned earlier [10, 11]. Doppler sonography seems to be more suitable for giving a prognosis of the graft rather than giving an exact diagnosis of transplant dysfunction. During the early period after transplantation this technique is often used to monitor antirejection treatment. The missing decrease of Doppler indices is correlated with a bad prognosis of the graft [30]. In the later period, RI >0.80 predicts graft as well as patient survival. Therefore, many clinicians perform routinely Doppler sonography during the long-term follow-up to identify the high-risk patients without diagnosing the exact cause of transplant dysfunction [9].

In summary, renal Doppler sonography is well established for the nephrological workup of kidney diseases and should not be outsourced to other faculties. Only in the context with the clinical and pathophysiological understanding of the kidney can the results be correctly interpreted. However, one has to be aware of the several pitfalls to avoid overinterpretation of the Doppler signals.

References

- Moghazi S, Jones E, Schroepple J, Arya K, McClellan W, Hennigar R, O'Neill WC: Correlation of renal histopathology with sonographic findings. *Kidney Int* 2005;67:1515–1520.
- Avasthi PS, Voyles WF, Greene ER: Noninvasive diagnosis of renal artery stenosis by echo-Doppler velocimetry. *Kidney Int* 1984;25:824–829.
- Tublin ME, Bude RO, Platt JF: The resistive index in renal Doppler sonography: where do we stand? *AJR Am J Roentgenol* 2003;180:885–892.
- Mostbeck GH, Gossinger HD, Mallek R, Siostrzonek P, Schneider B, Tscholakoff D: Effect of heart rate on Doppler measurements of resistive index in renal arteries. *Radiology* 1990;175:511–513.
- Wollenberg K, Waibel B, Pisarski P, Rump LC, Kirste G, Krumme B: Careful clinical monitoring in comparison to sequential Doppler sonography for the detection of acute rejection in the early phase after renal transplantation. *Transpl Int* 2000;13(suppl 1):S45–S51.
- Takano R, Ando Y, Taniguchi N, Itoh K, Asano Y: Power Doppler sonography of the kidney: effect of Valsalva's maneuver. *J Clin Ultrasound* 2001;29:384–388.
- Bude RO, Rubin JM: Relationship between the resistive index and vascular compliance and resistance. *Radiology* 1999;211:411–417.
- Krumme B, Grotz W, Kirste G, Schollmeyer P, Rump LC: Determinants of intrarenal Doppler indices in stable allografts. *J Am Soc Nephrol* 1997;8:813–816.
- Radermacher J, Mengel M, Ellis S, Stucht S, Hiss M, Schwarz A, Eisenberger U, Burg M, Luft F, Gwinner W, Haller H: The renal arterial resistance index and renal allograft survival. *N Engl J Med* 2003;349:115–124.
- Heine GH, Gerhart MK, Ulrich C, Kohler H, Girndt M: Renal Doppler resistance indices are associated with systemic atherosclerosis in kidney transplant recipients. *Kidney Int* 2005;68:878–885.
- Krumme B, Keller T, Bohler J, Mettang T, Schwenger V: Intrarenal resistance index and pulsatility index of transplanted kidneys depend on the vascular stiffness of the transplant recipients (abstract). *Nephrol Dial Transplant* 2005;20:193–194.

- 12 Radermacher J, Ellis S, Haller H: Renal resistance index and progression of renal disease. *Hypertension* 2002;39:699–703.
- 13 Mostbeck G, Kain R, Mallek R, Derfler K, Walter R, Havelec L, Tschokaloff D: Duplex Doppler sonography in renal parenchymal disease. *J Ultrasound Med* 1991;10:189–194.
- 14 McDermott R, Teeffe S, Middleton W: The resistive index in renal parenchymal disease: no correlation with histopathologic findings (abstract). *Radiology* 2001;217:560.
- 15 Platt J, Rubin J, Ellis J: Distinction between obstructive and nonobstructive pyelocaliectasis with duplex Doppler sonography. *AJR Am J Roentgenol* 1989;153:997–1000.
- 16 Shokeir AA, Abdulmaaboud M: Resistive index in renal colic: a prospective study. *BJU Int* 1999;83:378–382.
- 17 Opdenakker L, Oyen R, Vervloessem I: Acute obstruction of the renal collecting system: the intrarenal resistive index is a useful yet time-dependent parameter for diagnosis. *Eur Radiol* 1998;8:1429–1432.
- 18 Patriquin H, O'Regan S, Robitaille P, Paltiel H: Hemolytic-uremic syndrome: intrarenal arterial Doppler patterns as a useful guide to therapy. *Radiology* 1989;172:625–628.
- 19 Kastelan S, Ljubicic N, Kastelan Z, Ostojic R, Uravic M: The role of duplex-Doppler ultrasonography in the diagnosis of renal dysfunction and hepatorenal syndrome in patients with liver cirrhosis. *Hepatogastroenterology* 2004;51:1408–1412.
- 20 Schwertfeger E, Donauer J, Krumme B: Doppler sonography for the grading of renal artery stenosis (abstract). *J Am Soc Nephrol* 1999;10:A1871.
- 21 Krumme B, Blum U, Schwertfeger E, Flügel P, Hölstin F, Schollmeyer P, Rump LC: Diagnosis of renovascular disease by intra- and extra-renal Doppler scanning. *Kidney Int* 1996;50:1288–1292.
- 22 Radermacher J, Chavan A, Bleck J, Vitzthum A, Stoess B, Gebel MJ, Galanski M, Koch KM, Haller H: Use of Doppler ultrasonography to predict the outcome of therapy for the renal artery stenosis. *N Engl J Med* 2001;344:410–417.
- 23 Gottlieb RH, Snitzer EL, Hartley DF, Fultz PJ, Rubens DJ: Interobserver and intraobserver variation in determining intrarenal parameters by Doppler sonography. *AJR Am J Roentgenol* 1997;168:627–631.
- 24 Demirpolat G, Ozbek SS, Parildar M, Oran I, Memis A: Reliability of intrarenal Doppler sonographic parameters of renal artery stenosis. *J Clin Ultrasound* 2003;31:346–351.
- 25 Frauchiger B, Zierler R, Bergelin RO, Isaacson JA, Strandness: Prognostic significance of intrarenal resistance indices in patients with renal artery interventions: a preliminary duplex sonographic study. *Cardiovascular Surg* 1996;4:324–330.
- 26 Zeller T, Muller C, Frank U, Burgelin K, Horn B, Schwarzwaldner U, Cook-Brunns N, Neumann FJ: Stent angioplasty of severe atherosclerotic ostial renal artery stenosis in patients with diabetes mellitus nephrosclerosis. *Catheter Cardiovasc Interv* 2003;58:510–515.
- 27 Krumme B, Blum U: Renal artery aneurysm and fibromuscular dysplasia. *Nephrol Dial Transplant* 1997;12:1067–1069.
- 28 Voiculescu A, Hollenbeck M, Plum J, Hetzel GR, Mödder U, Sandmann W, Grabensee B: Iliac artery stenosis proximal to a kidney transplant: clinical findings, duplex-sonographic criteria, treatment, and outcome. *Transplantation* 2003;76:332–339.
- 29 Dupont PJ, Dooldeniya M, Cook T, Warrens AN: Role of duplex Doppler sonography in diagnosis of acute allograft dysfunction-time to stop measuring the resistive index? *Transplant Int* 2003;16:648–652.
- 30 Hollenbeck M, Hetzel GR, Hilbert N, Meusel F, Willers R, Grabensee B: Doppler sonographic evaluation of the effectiveness of an antirejection treatment after kidney transplantation. *Dtsch Med Wochenschr* 1995;120:277–282.

5. Vasbinder GB, Nelemans PJ, Kessels AG *et al.* Accuracy of computed tomographic angiography and magnetic resonance angiography for diagnosing renal artery stenosis. *Ann Intern Med* 2004; 141: 674–682; discussion 682
6. Kuroda S, Nishida N, Uzu T *et al.* Prevalence of renal artery stenosis in autopsy patients with stroke. *Stroke* 2000; 31: 61–65
7. Hansen KJ, Edwards MS, Craven TE *et al.* Prevalence of renovascular disease in the elderly: a population-based study. *J Vasc Surg* 2002; 36: 443–451
8. Krijnen P, Van Jaarsveld BC, Steyerberg EW, Man in't Veld AJM, Schalekamp MADH, Habbema JDF. A clinical prediction rule for renal artery stenosis. *Ann Intern Med* 1998; 129: 705–711
9. Krijnen P, Steyerberg EW, Postma CT, Flobbe K, de Leeuw PW, Hunink MG. Validation of a prediction rule for renal artery stenosis. *J Hypertens* 2005; 23: 1583–1588
10. Rihal CS, Textor SC, Breen JF *et al.* Incidental renal artery stenosis among a prospective cohort of hypertensive patients undergoing coronary angiography. *Mayo Clin Proc* 2002; 77: 309–316
11. Vasbinder GBC, Nelemans PJ, Kessels AGH, Kroon AA, De Leeuw PW, Van Engelshoven JMA. Diagnostic tests for renal artery stenosis in patients suspected of having renovascular hypertension: a meta-analysis. *Ann Intern Med* 2001; 135: 401–411
12. Van Onna M, Houben AJ, Kroon AA *et al.* Asymmetry of renal blood flow in patients with moderate to severe hypertension. *Hypertension* 2003; 41: 108–113
13. Wierema TK, Houben AJ, Kroon AA *et al.* Nitric oxide dependence of renal blood flow in patients with renal artery stenosis. *J Am Soc Nephrol* 2001; 12: 1836–1843
14. Finke R, Gross R, Hackenthal E, Huber J, Kirchheim HR. Threshold pressure for the pressure-dependent renin release in the autoregulating kidney of conscious dogs. *Pflugers Arch* 1983; 399: 102–110
15. Wright JR, Shurrab AE, Cheung C *et al.* A prospective study of the determinants of renal functional outcome and mortality in atherosclerotic renovascular disease. *Am J Kidney Dis* 2002; 39: 1153–1161
16. Caps MT, Perissinotto C, Zierler RE *et al.* Prospective study of atherosclerotic disease progression in the renal artery. *Circulation* 1998; 98: 2866–2872
17. Caps MT, Zierler RE, Polissar NL *et al.* Risk of atrophy in kidneys with atherosclerotic renal artery stenosis. *Kidney Int* 1998; 53: 735–742
18. Schreij G, de Haan MW, Oei TK, Koster D, de Leeuw PW. Interpretation of renal angiography by radiologists. *J Hypertens* 1999; 17: 1737–1741
19. Schoenberg SO, Bock M, Kallinowski F, Just A. Correlation of hemodynamic impact and morphologic degree of renal artery stenosis in a canine model. *J Am Soc Nephrol* 2000; 11: 2190–2198
20. Schreij G, Ritsema GH, Vreugdenhil G, de Leeuw PW. Stenosis and renographic characteristics in renovascular disease. *J Nucl Med* 1996; 37: 594–597
21. Gross CM, Kramer J, Weingartner O *et al.* Determination of renal arterial stenosis severity: comparison of pressure gradient and vessel diameter. *Radiology* 2001; 220: 751–756
22. Dworkin LD. Controversial treatment of atherosclerotic renal vascular disease: the cardiovascular outcomes in renal atherosclerotic lesions trial. *Hypertension* 2006; 48: 350–356

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?

Bernd Krumme¹ and Markus Hollenbeck²

¹Deutsche Klinik für Diagnostik, Division of Nephrology and Hypertension, Wiesbaden and ²Knappschafts Krankenhaus Bottrop, Division of Nephrology and Rheumatology, Bottrop, Germany

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%,

Correspondence and offprint requests to: Prof. Dr Bernd Krumme, Division of Nephrology and Hypertension, Deutsche Klinik für Diagnostik, Von Leyden-Str. 23, D-65191 Wiesbaden, Germany. Email: Krumme@nephrologie-wiesbaden.de

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, Schwark *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

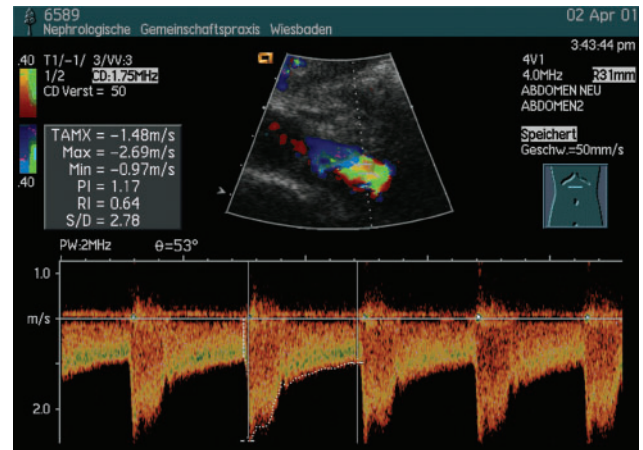


Fig. 1. The green colour indicates high blood flow velocities and turbulences near the ostium of the left renal artery scanned with the patient in a supine position. Peak systolic velocity of 269 cm/s detected with an angle of 53° indicates moderate renal artery stenosis.

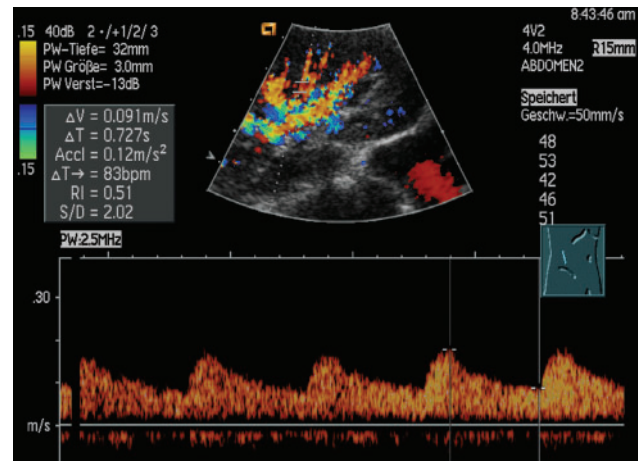


Fig. 2. Intrarenal RI is derived from the formula of Pourcelot [16]. RI of 51 is determined in the Doppler flow pattern of a kidney with proximal RAS. The ‘tardus-parvus’-flow pattern reveals low peak systolic and high end diastolic velocity resulting in low RI-values from 42 to 53.

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 arteriosclerosis, 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 end-diastolic 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 ≥ 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 ≥ 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 ≥ 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. Similarly, 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.

References

1. Geyskes GG, de Bruyn AJ. Captopril renography and the effect of percutaneous transluminal angioplasty on blood pressure in 94 patients with renal artery stenosis. *Am J Hypertens* 1991; 4: 685S–689S
2. Van Jaarsfeld BC, Krijnen P, Derckx FHM, Oei HY, Postma CT, Schalekamp MADH. The place of renal scintigraphy in the diagnosis of renal artery stenosis. *Arch Intern Med* 1997; 157: 1226–1234
3. Schoenberg SO, Knopp MV, Londy F *et al.* Morphologic and functional magnetic resonance imaging of renal artery stenosis: a multireader tricenter study. *J Am Soc Nephrol* 2002; 13: 158–169
4. Hoffmann U, Edwards JM, Carter S *et al.* Role of duplex scanning for the detection of atherosclerotic renal artery disease. *Kidney Int* 1991; 39: 1232–1239
5. Krumme B, Blum U, Schwertfeger E *et al.* Diagnosis of renovascular disease by intra- and extrarenal Doppler scanning. *Kidney Int* 1996; 50: 1288–1292
6. Radermacher J, Chavan A, Schaffer J *et al.* Detection of significant renal artery stenosis with color Doppler sonography: combining extrarenal and intrarenal approaches to minimize technical failure. *Clin Nephrol* 2000; 53: 333–343
7. Bardelli M, Veglio F, Arosio E *et al.* New intrarenal echo-Doppler velocimetric indices for the diagnosis of renal artery stenosis. *Kidney Int* 2006; 69: 580–587
8. Malatino LS, Polizzi G, Garozzo M *et al.* Diagnosis of renovascular disease by extra- and intrarenal Doppler parameters. *Angiology* 1998; 49: 707–721
9. Schwerk WB, Restrepo IK, Stellwaag M *et al.* Renal artery stenosis: grading with image-directed Doppler US evaluation of renal resistive index. *Radiology* 1994; 190: 785–790
10. Krumme B. Renal Doppler sonography – update in clinical nephrology. *Nephron Clin Pract* 2006; 103: c24–c28
11. Pearce JD, Edwards MS, Craven TE *et al.* Renal duplex parameters, blood pressure, and renal function in elderly people. *Am J Kidney Dis* 2005; 45: 842–850
12. Radermacher J, Chavan A, Bleck J *et al.* Use of Doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. *N Engl J Med* 2001; 344: 410–417
13. Zeller T, Muller C, Frank U *et al.* Stent angioplasty of severe atherosclerotic ostial renal artery stenosis in patients with diabetes mellitus and nephrosclerosis. *Catheter Cardiovasc Intervent* 2003; 58: 510–515
14. Garcia-Criado A, Gilabert R, Nicolau C *et al.* Value of Doppler sonography for predicting clinical outcome after renal artery revascularization in atherosclerotic renal artery stenosis. *J Ultrasound Med* 2005; 24: 1641–1647
15. Soulez G, Therasse E, Qanadli SD *et al.* Prediction of clinical response after renal angioplasty: respective value of renal Doppler sonography and scintigraphy. *Am J Radiology* 2003; 181: 1029–1035

16. Pourcelot L. Applications cliniques de l'examen Doppler examinations transcutane. In: Peronneau P, ed. *Velocimetrie Ultrasonore Doppler*, Inserm, Paris: 1971; 213–217
17. Halpern EJ, Deane CR, Needleman L, Merton DA, East SA. Normal renal artery spectral Doppler waveform: a closer look. *Radiology* 1995; 196: 667–673
18. Bude RO, Rubin JM, Platt JF, Fechner KP, Adler RS. Pulsus tardus: its cause and potential limitations in detection of arterial stenosis. *Radiology* 1994; 190: 779–784
19. Heine GH, Gerhardt MK, Ulrich C, Köhler H, Girndt M. Renal Doppler resistance indices are associated with systemic atherosclerosis in kidney transplant recipients. *Kidney Int* 2005; 68: 878–885
20. Schwenger V, Keller T, Hofmann N *et al.* Intrarenal color Doppler indices of renal allografts depend on vascular stiffness of the transplant recipients. *Am J Transplant* 2006; 6: 2721–2724
21. Ikee R, Kobayashi S, Hemmi N *et al.* Correlation between the Resistive Index by Doppler ultrasound and kidney function and histology. *Am J Kid Dis* 2005; 46: 603–609
22. Opendakker L, Oyen R, Vervloessem I. Acute obstruction of the renal collecting system: the intrarenal resistive index is a useful yet time-dependent parameter for diagnosis. *Eur Radiol* 1998; 8: 1429–1432
23. Patriquin H, O'Regan S, Robitaille P, Paltiel H. Hemolytic-uremic syndrome: intrarenal arterial Doppler patterns as a useful guide to therapy. *Radiology* 1989; 172: 625–628
24. Hollenbeck M, Hilbert N, Meusel F, Willers R, Grabensee B. Increasing sensitivity and specificity of Doppler sonographic detection of renal transplant rejection with serial investigation technique. *Clin Investig* 1994; 72: 609–615
25. Rundback JH, Sacks D, Kent C *et al.* Guidelines for the reporting of renal artery revascularization in clinical trials. *J Vasc Interv Radiol* 2002; 13: 959–974
26. Chonchol M, Linas S. Diagnosis and management of ischaemic nephropathy. *Clin J Am Soc Nephrol* 2006; 1: 172–181
27. Voiculescu A, Schmitz M, Plum J *et al.* Duplex ultrasound and renin ratio predict treatment failure after revascularization for renal artery stenosis. *Am J Hypertens* 2006; 19: 756–763
28. Frauchiger B, Zierler R, Bergelin RO, Isaacson JA, Strandness DE, Jr. Prognostic significance of intrarenal resistance indices in patients with renal artery interventions: a preliminary duplex sonographic study. *Cardiovascular Surg* 1996; 4: 324–330

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

Friedhelm Raue and Karin Frank-Raue

Endocrine practice, Heidelberg, Germany

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

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.

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

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

Correspondence and offprint requests to: Prof. Dr Med. Friedhelm Raue, Endokrinologische Gemeinschaftspraxis, Brückenstr.21, 69120 Heidelberg, Germany.
Email: friedhelm.raue@raue-endokrinologie.de