Intrarenal Arterial Doppler Sonography in Patients with Nonobstructive Renal Disease: Correlation of Resistive Index with Biopsy Findings

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The resistive index (RI), calculated from the duplex Doppler waveform, was compared with clinical and laboratory findings and the results of renal biopsy in 41 patients with nonobstructive (medical) renal disease. Kidneys with active disease in the tubulointerstitial compartment had a mean RI of 0.75 ± 0.07. This was statistically significantly different ($p < .01$) from the RI in kidneys with disease limited to the glomeruli (mean RI of 0.58 ± 0.05). Acute tubular necrosis resulted in an elevated RI (mean RI = 0.78 ± 0.03) as did vasculitis/vasculopathy (mean RI = 0.82 ± 0.05). Patients with hypertension, proteinuria, or hematuria did not have kidneys with a significantly higher RI than did patients without these clinical factors. Kidneys found to be abnormally echogenic did not have an RI significantly different from kidneys of normal echogenicity. There was a weak correlation between creatinine level and RI value, reflected by a linear correlation coefficient of 0.34. In patients with normal renal RIs, the mean creatinine level was 1.7 ± 1.7, whereas in those with abnormal RI values (≥0.70), the mean creatinine level was 3.7 ± 3.6.

We conclude that some forms of nonobstructive renal disease can produce changes in the Doppler waveform detectable by RI measurement. The production of Doppler waveform changes is strongly influenced by the site of the main disease within the kidneys. Active disease within the tubulointerstitial compartment (acute tubular necrosis, interstitial nephritis) or vasculitis/vasculopathy generally resulted in an elevated RI, whereas disease limited to the glomeruli, no matter how severe, did not significantly elevate the RI. Degree of renal dysfunction as indicated by serum creatinine level probably affects the Doppler waveform to some degree, but the relationship is weak.

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Sonography is often used as the initial imaging procedure in the examination of patients with renal failure. Aside from excluding hydronephrosis, sonography is generally not helpful in characterizing the type of renal disease, especially if the renal failure is acute [1–3]. Investigators have attempted to apply traditional sonographic parameters such as kidney size and relative echogenicity to the identification and characterization of renal disease [4–6]. In the vast majority of cases of renal failure (especially acute or subacute), the real-time sonographic examination is normal [1–3, 7, 8].

We recently reported the use of duplex Doppler sonography to assist in differentiating obstructive from nonobstructive pyelocaliectasis [9, 10]. As part of that study, we examined 50 patients with nonobstructive renal disease (renal medical disease) and found abnormal intrarenal arterial Doppler signals (resistive index [RI] ≥ 0.70) in just over half [10]. The other half had normal Doppler tracings despite often significant renal disease. It appeared clear that certain renal diseases produced states of increased renal vascular resistance (resulting in RI elevation), whereas other renal diseases produced no significant Doppler changes.

Recently two studies have demonstrated Doppler changes in small groups of children with renal failure [11, 12]. However, detailed pathologic correlation was

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not possible in these series because renal biopsies were not uniformly obtained. The purpose of this study is to determine if specific nonobstructive renal diseases alter the Doppler signal. We did this by correlating Doppler data with renal biopsy findings. The results may provide a basis for the use of duplex Doppler sonography in patients with renal failure.

Subjects and Methods

Between January 1989 and September 1989, bilateral duplex Doppler and standard gray-scale real-time sonography was performed prospectively on 86 kidneys in 43 patients (age range, 6–80 years) before renal biopsy. In two of the patients, the renal biopsy specimens were deemed inadequate for characterization of the renal disease and were therefore excluded from our study. Patients with hydronephrosis also would have been excluded, if any had been encountered. The study is therefore based on findings in 41 patients (82 kidneys) in whom unilateral kidney biopsy was adequate for diagnosis.

Real-time sonographic examination with a 3.5-MHz transducer (Acuson 128, Mountain View, CA) or a 3-MHz transducer (Advanced Technology Laboratories, Bothell, WA) and a pulsed Doppler examination of intrarenal arteries were performed on both kidneys before biopsy. For the Doppler study, the wall filter was set to the minimum (50 Hz for ATL and 125 Hz for Acuson) and the sample volume was set at 2–5 mm. Doppler signals were in general obtained from arcuate arteries at the corticomedullary junction and/or interlobar arteries along the border of medullary pyramids. At least two, and in most cases three, different renal vessels were studied with duplex Doppler imaging for each kidney.

Multiple Doppler tracings and a standard gray-scale examination of the kidney were recorded on film. From the hard copy, the RI (defined as [peak systolic frequency shift − minimum diastolic frequency shift]/peak systolic frequency shift) was determined from hand measurements made with a caliper. The RI for each vessel was calculated as an average value obtained from three to five waveforms. Mean RI measurements and standard deviations also were calculated for each kidney and each patient (averaging both kidneys). For purposes of RI correlation with other data, we considered an RI of 0.70 or higher as elevated. This value for a discriminatory RI level is based on our and others' experience with obstructed, medically diseased, and normal native kidneys [9–11, 13].

In addition to a detailed Doppler study, a real-time examination of each kidney was performed. This included longitudinal images of the right kidney and liver to allow assessment of relative renal cortical echogenicity. Kidneys were considered abnormally echogenic if the echo intensity of the cortex of the right kidney was greater than that of adjacent liver. Kidneys with echogenicity equal to that of the adjacent liver were not included as abnormal because our earlier work has shown that this criteria of abnormality includes too many normal kidneys [7].

Renal biopsies were performed with a Tru-Cut biopsy needle (Baxter Health Care Corp., Deerfield, IL) by using sonographic localization of the lower pole of the kidney. The paraffin-embedded sections of the biopsy specimens were reviewed by light microscopy, immunofluorescence, and electron microscopy to determine the diagnosis and the primary site of pathologic changes for each biopsy specimen. An attempt was made to determine if the dominant process was within the nephron (glomeruli), was in the tubulointerstitial compartment, or was vascular. In some biopsy specimens, more than one significant process was evident. The degree of activity and/or chronicity also was assessed if possible for each biopsy specimen. The most common renal diseases in our study were lupus nephritis (12 patients), IgA/IgM nephropathy (four patients), membranoproliferative glomerulonephritis (four patients), and acute tubular necrosis (five patients).

The sonographic and pathologic data were analyzed separately and blindly and correlated with the clinical history and laboratory studies. In all cases, creatinine values from within 24 hr of the biopsy were available for correlation. Creatinine values exceeding 1.3 mg/dl in adults and exceeding age-corrected levels in pediatric patients were considered abnormal. In addition, the presence or absence of proteinuria, hematuria, and hypertension was determined for each patient. The two-tailed Student's t test was used to determine significance of any difference between groups. Statistically, p values less than .05 were considered significant. Linear correlation analysis was performed for the data on RI and creatinine.

Results

The mean RI for the 41 patients (82 kidneys) in our study was 0.68 ± 0.10. Using a discriminatory RI value of 0.70, we found 35 abnormal kidneys and 47 normal kidneys.

As more than one vessel was studied within a particular kidney, we were able to determine any significant variation in mean RI measurements between different sites in the kidney. In general, the amount of variation in RI for different sites within a particular kidney was not great, averaging 4.0%. In addition, we compared the mean RI values between both kidneys in a given patient. The mean difference between the RIs was 0.02, with a range of 0.00 to 0.06. In only one case was the RI of one kidney below the discriminatory level of 0.70 and that of the other kidney above this level (RI values of 0.68 and 0.71).

Renal biopsy findings were analyzed and an attempt was made to classify the location of the primary abnormality as within the nephron (glomeruli), the tubulointerstitial compartment, or within the vascular compartment. However, in some cases more than one significant form of renal disease was present. In all, there were 16 patients (including one of the five patients with evidence for acute tubular necrosis) who had acute/active interstitial nephritis, often accompanied by chronic interstitial changes. In this group, the mean RI was 0.73 ± 0.07, and 24 of the 32 kidneys had an elevated RI (≥0.70). In addition, there were four patients with acute tubular abnormality without significant interstitial nephritis. Therefore, a total of 20 patients had acute/active pathologic findings in the tubulointerstitial compartment of the kidney. In this patient group, the mean RI value was 0.75 ± 0.07, and 31 of these 40 kidneys had an abnormal RI (Fig. 1).

Two patients had a significant vasculitis/vasculopathy without associated glomerular or tubulointerstitial disease. The mean RI in these patients was 0.87 ± 0.04, with both patients' kidneys having abnormal RIs (Fig. 2).

The remaining 19 patients had renal disease essentially limited to the glomeruli with no active abnormalities in the tubulointerstitial region and no vasculitis. In these patients, the mean RI was 0.58 ± 0.05 (Fig. 3). This RI was statistically significantly different ($p < .01$) from the RI of patients with active tubulointerstitial disease. In fact, despite many kidneys having severe or acute glomerular disease, no kidney with disease essentially limited to the glomeruli had an abnormal Doppler waveform.

When all kidneys are considered, the renal biopsy revealed evidence for acute tubular necrosis in five patients with a mean RI of 0.78 ± 0.03 in this group. Nine of these 10 kidneys had an elevated RI. Five patients in this series had evidence for a significant vasculitis/vasculopathy with or without other pathologic findings. In these patients, the mean RI was 0.82 ± 0.05, with all kidneys having an elevated RI.

When the real-time sonographic data are analysed, 15 patients had echogenic kidneys and 26 patients had normal renal echogenicity. The abnormally echogenic kidneys had a mean RI of 0.71 ± 0.11, whereas normally echogenic kidneys had an RI of 0.66 ± 0.09; this difference was not statistically significant ($p > .05$).

Fourteen patients had hypertension with a mean RI of 0.70 ± 0.10, and 27 patients had no history of hypertension with a mean RI of 0.67 ± 0.09; this difference was not statistically significant. No statistically significant difference was found between mean RI values on the basis of the presence or absence of hematuria and proteinuria.

For purposes of correlating the Doppler data with creatinine level, a mean RI value was obtained for each patient by averaging the two kidneys' mean RI values. Table 1 details our data comparing RI values with creatinine levels. The linear correlation coefficient between creatinine and RI values in each patient was 0.34. In patients with a normal creatinine level, the mean RI was 0.61 ± 0.05. When all patients with an elevated creatinine level are considered, the mean RI was 0.71 ± 0.09; this was significantly different from the value for patients with a normal creatinine level ($p < .05$). For the 35 kidneys with an elevated RI (≥0.70), the mean creatinine value was 3.7 ± 3.6 (range, 1.2–16.1), whereas in the 47 kidneys with a normal RI, the patients' mean creatinine level was 1.7 ± 1.7 (range, 0.4–8.7). This difference was not statistically significant. In our series of 41 patients, two patients had an abnormal Doppler examination and a normal creatinine level, and 10 patients had a normal RI value despite an elevated creatinine level.

Discussion

Some investigators have found traditional renal sonography to be of limited value in most cases of renal failure after hydronephrosis has been excluded [1–3]. It has been our and others' experience that the sonogram is unremarkable in the majority of cases of nonobstructive renal disease [1–3]. A few investigators have attempted to use real-time sonographic parameters such as relative echogenicity and renal size to identify and characterize renal medical disease [4–6]. In our prospective study, we have found renal Doppler analysis with RI measurements to be promising in differentiating major types of renal medical disease.

Our results show the RI in kidneys with active/acute tubulointerstitial disease is significantly increased compared with the RI in kidneys that have disease essentially limited to the glomeruli ($p < .01$). This was true no matter how severe or acute the glomerular disease; without accompanying tubulointerstitial disease or vasculitis, all the RIs were normal (Fig. 3). Conversely, 31 of 40 kidneys with active tubulointerstitial disease had elevated RI measurements. The main diseases within this group were acute tubular necrosis (ATN) and interstitial nephritis (either primary or associated with other renal diseases such as lupus nephritis, cryoglobulinemia, or Wegener granulomatosis). In addition, five patients had significant vasculopathy/vasculitis in our series, and these kidneys all had abnormal Doppler waveform (mean RI, 0.82 ± 0.05) (Fig. 2). Similar changes in the Doppler waveform were recently observed with the renal microangiopathy associated with the hemolytic-uremic syndrome in children [11].

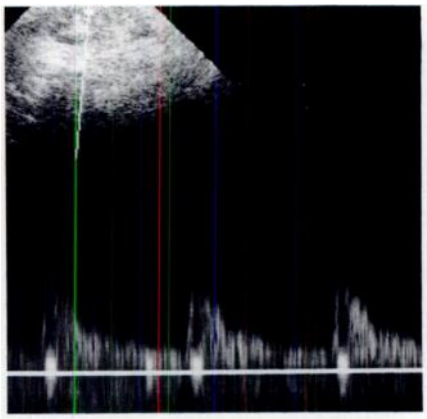

Fig. 1.—Renal Doppler sonogram of patient with acute tubular necrosis. Patient had a rapid rise in creatinine level from 1.4 to 3.1 mg/dl in 2 weeks. Standard real-time sonography of kidneys was normal. Doppler signal from intrarenal artery shows reduced end diastolic flow resulting in an elevated resistive index of 0.78. Renal biopsy was consistent with acute tubular necrosis.

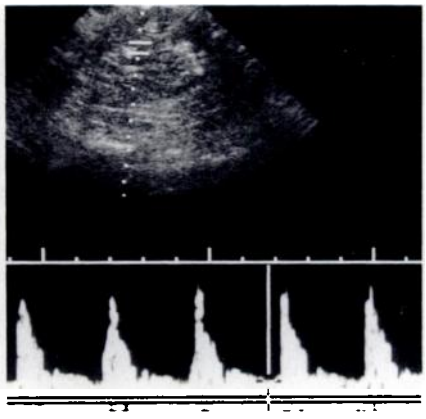

Fig. 2.—Renal Doppler sonogram of patient with vasculopathy. Creatinine level became elevated after a cardiac transplant. Standard real-time sonography was normal. Doppler signal obtained from intrarenal artery shows a significant reduction in end diastolic flow compared with peak systolic flow, resulting in an elevated resistive index of 0.83. Biopsy revealed changes consistent with cyclosporine vasculopathy.

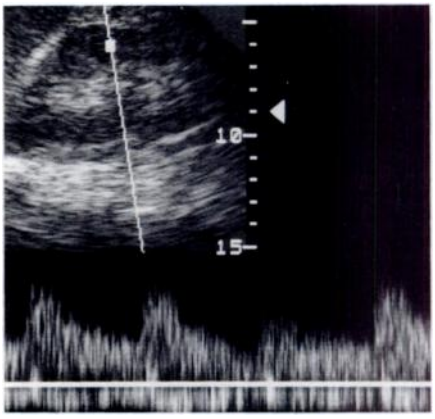

Fig. 3.—Renal Doppler sonogram of patient with glomerular disease. Patient had lupus nephritis and renal biopsy results were consistent with an active proliferative-type glomerulonephritis. Doppler signal from intrarenal artery in this patient with pure glomerular disease shows good diastolic flow, resulting in a normal resistive index of 0.55.

TABLE 1: Relationship of Creatinine Level to Resistive Index in 41 Patients

Resistive Index	No. of Patients per Creatinine Level (mg/dl)			
	Normal	1.4–1.9	2.0–3.9	≥4.0
≤0.54	2	1	0	0
0.55–0.59	4	3	1	1
0.60–0.64	6	0	0	0
0.65–0.69	2	1	1	2
0.70–0.74	1	1	1	0
0.75–0.79	0	2	1	2
≥0.80	1	2	4	2
Total no. of patients	16	10	8	7
Mean resistive index (± one standard deviation)	0.61 ± 0.05	0.69 ± 0.10	0.74 ± 0.08	0.73 ± 0.08

Acute tubular necrosis, the most common cause of acute renal failure, is an instructive example. Prior studies have shown that early in the course of the disease renal vascular resistance is elevated and renal blood flow is reduced [14, 15]. As in other instances of increased resistance, this should result in changes in the Doppler waveform with a more marked reduction in diastolic flow than in systolic flow and a resultant elevation in RI. In our study, the five patients with ATN had a mean RI of 0.78, most likely reflecting the high vascular resistance state (Fig. 1).

Previously, the major sonographic parameter used to characterize renal medical disease was relative renal cortical echogenicity. In one study, echogenic kidneys were positively correlated with pathologic changes such as global sclerosis, focal tubular atrophy, and focal leukocytic infiltration [5]. In our study, no significant difference was seen between the RI of abnormally echogenic kidneys (0.71) and the RI of normally echogenic kidneys (0.66). This suggests that factors affecting relative renal echogenicity are not identical to the processes that alter the Doppler signal. In our study, 37% (15/41) of patients with renal medical disease had echogenic kidneys, again reflecting the well-known finding that renal medical disease may result in increased renal echogenicity. However, echogenicity did not discriminate between major forms of renal disease as renal Doppler imaging did.

In addition to sonographic-pathologic correlation, we compared the RI values with clinical findings of the presence or absence of hypertension, hematuria, and proteinuria. For each clinical parameter, no statistically significant difference was found in the mean RI values when the parameter was present or absent.

For purposes of this study, serum creatinine level was used as an approximation of the degree of renal dysfunction. There did seem to be a trend toward more abnormal waveforms with higher creatinine levels, reflected by a mean creatinine level of 3.7 ± 3.6 in patients with an elevated RI and 1.7 ± 1.7 in patients with normal Doppler waveforms. However, this difference was not statistically significant, probably because of large standard deviations and possibly because of the relatively small population of patients. Dubbins [16] also has suggested that a coarse correlation exists between progressive uremia and increasing index values in his preliminary experience. We agree that the relationship is best categorized as weak, as reflected by the linear correlation coefficient of 0.34 between creatinine level and RI. Although a significant difference in mean RI was seen when comparing patients who had normal creatinine levels (0.61 ± 0.05) with patients who had elevated creatinine levels (0.71 ± 0.09), it would be a mistake to consider RI values as merely reflecting the creatinine level. Over a quarter of the patients in our series had discrepant Doppler-laboratory findings; two patients had abnormal RI values despite a normal creatinine level, and 10 patients had normal Doppler studies despite an elevated creatinine level. Our data therefore suggest that the site of disease within the kidney and its activity affect the Doppler signal more than the degree of renal dysfunction, although severe uremia most likely will have at least some effect on the RI.

Despite studying patients with a wide range of renal disease and pathologic findings that varied from very diffuse to more focal, we did not note a great difference between Doppler studies of the right and left kidneys within a given patient (mean RI difference, 0.02; range, 0.00–0.06). This agrees with the findings of Wong et al. [12], who found no significant difference between right and left kidney Doppler measurements in children. However, as it is still possible some specific forms of renal disease may produce discrepant or unilateral Doppler changes, we still recommend Doppler examination of both kidneys. Although use of a discriminatory RI level of 0.70 reflects our and others' current experience, it is certainly possible that in some instances or diseases a different value may be more appropriate; such determinations are beyond the scope of this study. The availability of a baseline Doppler study for comparison may in fact be even more useful than a single RI determination.

Another limitation that needs to be noted is that our findings may not apply to the infant's or younger child's kidney. This concern is well stressed in a recent editorial by Keller [17], which points out the existence of a high-resistance state (elevated RI) in the normal infant kidney. Although children were included in our series, none were younger than 6 years old. Prior renal functional maturation studies and a prior sonographic report suggest that normally high RI values should be observed in children less than 1 or 2 years old [12]. Hence, we believe inclusion of children 6 years old or older with the adults in our study is appropriate. However,

we do not believe that our renal Doppler data based on observations in the essentially mature kidney should be blindly applied to the infant's kidney.

We conclude that duplex Doppler sonography detects a state of increased arterial vascular resistance (elevated RI) in some forms of renal medical disease but not in others. The main factor determining whether the RI is elevated appears to be the primary site of renal disease. Active or acute disease within the tubulointerstitial compartment and vasculitis generally elevated the RI, whereas disease limited primarily to the glomerulus did not. There appears to be a weak relationship between degree of renal dysfunction and RI; however, this seems less important than the type of renal medical disease present. Our data suggest that certain forms of renal medical disease such as interstitial nephritis and acute tubular necrosis, in which the traditional sonogram is generally unremarkable, should generally be expected to have abnormalities detected on Doppler study. The precise role that duplex Doppler sonography could play in the diagnosis, treatment, and follow-up of such patients requires further study.

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