Doppler US of Renal Allografts: Causes of Elevated Resitive Index

The authors retrospectively investigated the utility of the resistive index (RI) in evaluating the major causes of renal allograft dysfunction. Three hundred fourteen duplex US studies in 162 patients with 150 episodes of renal allograft dysfunction within a 17-month period were reviewed. Histologic findings were available in 69 cases. Three patients had hyperacute rejection with a mean RI of 0.85 ± 0.049. There were 37 episodes of acute rejection (mean RI, 0.76 ± 0.054) and 22 instances of chronic rejection (mean RI, 0.71 ± 0.065). Ureteral obstruction (nine cases; mean RI, 0.72 ± 0.026) was the only cause of allograft dysfunction other than rejection with a mean RI greater than 0.70. Mean RI values associated with rejection were significantly elevated above those in the 88 cases of dysfunction without rejection (mean, 0.64 ± 0.064) and in baseline examinations (mean, 0.63 ± 0.066). The results identified two causes of increased RI values in addition to acute rejection: chronic rejection and ureteral obstruction.

PATIENTS AND METHODS

This study retrospectively evaluated the records of all recipients of renal allografts in whom duplex US was performed between January 1, 1987, and April 28, 1988. The study included 314 consecutive duplex US images in 162 patients. The time from transplantation to the examination ranged from 1 day to 20 years. Two patients who underwent four duplex US examinations were not included in the study because complete clinical follow-up could not be obtained.

All studies were performed with an Acuson 128 3.5-MHz real-time sector scanner (Mountain View, Calif). The RI was calculated from the equation RI = 1 − (end diastolic velocity/peak systolic velocity).

A cursor on the US unit was used to manually choose the (relative) velocities on the Doppler spectrum, and the RI was calculated by the unit's computer. The RI was measured in the renal cortex with a wide Doppler gate, probably including signals from the interlobar arteries. The RIs in at least three separate locations were measured, and the mean values were recorded. Hydronephrosis and abnormal fluid collections were also noted.

The images were separated into baseline studies and studies of "events." Eighty-four baseline examinations included those in patients with stable renal function either in the early postoperative period (between 4 and 10 days after surgery [66 patients]) and those in patients who underwent abdominal US for reasons not related to disease of the genitourinary system (18 patients). The images of these 84 patients served as a normal control group. Thirty-six patients underwent baseline examinations only. An event was defined as symptoms (complaints of decreased urine output, graft or abdominal pain), signs (graft tenderness or swelling, fever), or laboratory evidence of worsening renal function (increase in serum creatinine or urinary protein levels, decreased creatinine clearance). There were 150 such events in the 226 nonbaseline examinations. If more than one duplex US examination was performed per event, the examination at the time of biopsy or before the initiation of therapy was chosen, whichever was first. The number of events per patient ranged from one to four, with a mode of one.

Events were classified as rejections or dysfunctions without rejection on the basis of clinical findings, laboratory and pathologic investigation, therapy, and response to therapy. Sixty-nine events were supported by pathologic findings, 64 with findings at biopsy, and five with findings at nephrectomy. The classification described by Sanfilippo et al (11) and modified by the treatment protocol at our institution was used to separate rejection into three major categories: hyperacute, acute, and chronic (Table 1).

When the accuracy of detecting each type of rejection was calculated, the remaining forms of rejection were eliminat-

Abbreviations: ATN = acute tubular necrosis, RI = resistive index.
RESULTS

As expected from the classification of rejection, the time after transplantation can be helpful in predicting the type of rejection (Table 2). The three cases of hyperacute rejection occurred within 24 hours of transplantation. Two resulted in nephrectomy, and the other was successfully managed with plasmapheresis. These were the only cases in which duplex US was performed within 24 hours of transplantation; therefore, no statements can be made about the RI in normal allografts in this time period.

Eighth-six percent of acute rejections occurred within 6 months of transplantation, and 73% of chronic rejections occurred after 6 months.

Perioperative baseline examinations of living (n = 32) and cadaveric (n = 34) donors were separated into two groups. The mean RI values, 0.60 ± 0.061 and 0.65 ± 0.071, respectively, were calculated and found to be significantly different (P < .02).

The mean RI values of hyperacute (0.85), acute (0.76), and chronic rejection (0.71) were significantly elevated (P < .02, P < .0001, and P < .0001, respectively) above those in the baseline studies and studies of dysfunction other than rejection (Table 3).

The accuracy in detecting acute (Table 4) and chronic rejection (Table 5) was calculated. The sensitivity for detecting acute rejection with an RI of 0.70 or greater was 92%, with a specificity of 75%, not including the other types of rejections. As expected with the lower mean RI, detection of chronic rejection was less sensitive (59% at RI ≥ 0.70). An analysis of the false-positive diagnoses of rejection (RI ≥ 0.70) revealed that eight of nine cases of ureteral obstruction constituted over one-third of this group. The other causes included five cases of cyclosporine toxicity, two cases of bacterial infection, two cases of renal artery stenosis, one case of viral infection, one case of ATN, and three cases of idiopathic dysfunction.

To evaluate the effects of time on vascular impedance, the RI values in cases of dysfunction without rejection were evaluated as a function of time from transplantation. There was no correlation between RI and time after transplantation; therefore, the elevation in RI seen in chronic rejection was not due to the time after transplantation.

Cases of dysfunction without rejection were divided by causes (Table 3). Ureteral obstruction, with a mean RI of 0.72—in the same range as that for rejection—was statistically elevated above that in other cases of dysfunction without rejection and the baseline group (P < .0005). Cyclosporine toxicity caused a smaller but significant rise in RI (P < .02). Bacterial nephritis or sepsis, viral infection, and renal artery stenosis did not show an elevated mean RI. The other causes included idiopathic worsening of renal function (35 patients). This group of patients had transient worsening.

Table 1
General Criteria for Classification of Kidney Rejection

<table>
<thead>
<tr>
<th>Rejection</th>
<th>Time of Onset</th>
<th>Immunologic/Pathologic Findings</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute</td>
<td>Within 24 h</td>
<td>Humoral/granulocytic infiltrates with vascular damage</td>
<td>Plasmapheresis</td>
</tr>
<tr>
<td>Acute</td>
<td>Rapid, usually early</td>
<td>Humoral, cellular/vascular damage; mononuclear infiltrates</td>
<td>Pulsed steroid and/or antilymphocytic serum administration</td>
</tr>
<tr>
<td>Chronic</td>
<td>Indolent, usually late</td>
<td>Cellular /mononuclear infiltrates, fibrosis</td>
<td>Maintenance of immunosuppressive regimen</td>
</tr>
</tbody>
</table>

Table 2
Type of Rejection versus Time from Kidney Transplantation

<table>
<thead>
<tr>
<th>Time after Transplantation (mo)</th>
<th>Type of Rejection</th>
<th>Dysfunction without Rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hyperacute</td>
<td>Acute</td>
</tr>
<tr>
<td>0-6</td>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td>&gt;6</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>37</td>
</tr>
</tbody>
</table>

Note.—Baseline images were obtained in 84 patients (mean RI = 0.63 ± 0.066). * SD = standard deviation.

Table 3
Final Diagnosis versus Mean RI in Duplex US

<table>
<thead>
<tr>
<th>Final Diagnosis</th>
<th>No. of Cases</th>
<th>Mean RI</th>
<th>SD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute rejection</td>
<td>3</td>
<td>0.85</td>
<td>0.049</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>37</td>
<td>0.76</td>
<td>0.054</td>
</tr>
<tr>
<td>Chronic rejection</td>
<td>22</td>
<td>0.71</td>
<td>0.065</td>
</tr>
<tr>
<td>Dysfunction without rejection</td>
<td>88</td>
<td>0.64</td>
<td>0.064</td>
</tr>
<tr>
<td>Ureteral obstruction</td>
<td>9</td>
<td>0.72</td>
<td>0.026</td>
</tr>
<tr>
<td>Cyclosporine toxicity</td>
<td>12</td>
<td>0.67</td>
<td>0.045</td>
</tr>
<tr>
<td>Bacterial nephritis/sepsis</td>
<td>11</td>
<td>0.64</td>
<td>0.070</td>
</tr>
<tr>
<td>Viral infection</td>
<td>7</td>
<td>0.63</td>
<td>0.078</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>5</td>
<td>0.64</td>
<td>0.098</td>
</tr>
<tr>
<td>Other dysfunction</td>
<td>44</td>
<td>0.63</td>
<td>0.057</td>
</tr>
</tbody>
</table>

Table 4
Accuracy in the Detection of Acute Kidney Rejection with Duplex US

<table>
<thead>
<tr>
<th>RI</th>
<th>Sensitivity* (%)</th>
<th>Specificity† (%)</th>
<th>PPV‡ (%)</th>
<th>NPV§ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.60</td>
<td>97</td>
<td>34</td>
<td>38</td>
<td>98</td>
</tr>
<tr>
<td>≥0.65</td>
<td>97</td>
<td>55</td>
<td>47</td>
<td>98</td>
</tr>
<tr>
<td>≥0.70</td>
<td>92</td>
<td>75</td>
<td>60</td>
<td>96</td>
</tr>
<tr>
<td>≥0.75</td>
<td>65</td>
<td>93</td>
<td>80</td>
<td>86</td>
</tr>
</tbody>
</table>

Note.—PPV = positive predictive value, NPV = negative predictive value.

* Sensitivity = true positive/(true positive + false negative) × 100.
† Specificity = true negative/(true negative + false positive) × 100.
‡ PPV = true positive/(true positive + false positive) × 100.
§ NPV = true negative/(false positive + false negative) × 100.

Note.—RI elevation as a function of time of onset from transplantation.
of renal function, which returned to baseline values without specific treatment. Additional other causes of renal dysfunction included four cases of hypovolemia, one case of ATN, two cases of worsening renal function secondary to chronic oral antibiotic administration, and two cases of recurrent glomerulonephritis. The only case of ATN showed an elevated RI of 0.78. In cases of dysfunction without rejection, the same mean RI was seen in the baseline studies.

Eighteen patients had dilatation of the collecting system (hydronephrosis). Nine patients proved to have obstruction and showed a higher mean RI (0.72) than the nine patients with dilatation without obstruction (mean RI = 0.62, P < .0005). In patients with obstruction, the causes included ureterovesical anastomotic obstruction (n = 5), lymphoceles causing ureteral compression (n = 3), and bladder cancer involving the ureteral orifice (n = 1). Renal function improved in all patients who underwent intervention to relieve obstruction. Follow-up duplex sonograms in two patients after lymphoceles drainage revealed decreased RI. The other patients did not undergo repeated duplex US.

**DISCUSSION**

Clinical, immunologic, and histologic methods are used in the classification of rejection. Previous reports on duplex US have focused on the histologic differences between acute vascular and acute interstitial rejection and the relationship of these findings to increased vascular impedance (3,4,6). This separation is based on a pathologic rather than clinical classification of rejection. We chose to classify rejection into three major clinical groups—hyperacute, acute, and chronic—because they form the basis of rejection therapy at our institution (Table 1) (11).

One criticism of the Doppler technique is poor reproducibility of quantitative information. For each kidney, we measured the RI in at least three different locations and recorded the mean value. Significant variations in values were observed within the same kidney. This may have been due to differences in the manual pressure applied to the kidney with the transducer (12), the size and orientation of the arteries interrogated, the placement of the measuring cursors on the spectra, the width of the Doppler gate, the depth of the artery from the skin, or the regional cortical blood flow (focal disease). These variables could not be completely controlled in this study, which may explain why the standard deviations of the RI measurements were relatively large.

We found, as did others, increased vascular impedance in acute rejection (Fig 1). With an RI of 0.70 or greater, the sensitivity was 92% and the specificity was 75% in the diagnosis of acute rejection. As a screening test to exclude acute rejection, the negative predictive value at an RI of 0.70 or greater was 96%, a finding indicating that RI values below this level were rarely associated with acute rejection. At an RI of 0.75 or greater, the sensitivity decreased to 65% and the specificity was 93%, findings similar to those in the study by Rifkin et al (5), who used RI values of 0.80 or greater to diagnose rejection.

Previous studies have paid little attention to chronic rejection. Other investigators studying chronic rejection found normal Doppler spectra (4,6). We found elevated RI in chronic rejection. With an RI of 0.70 or greater, the sensitivity was 59% and the specificity was 75% in the diagnosis of chronic rejection. In this disease, angiography demonstrates a reduction in the numbers of arteries and narrowing of the existing arteries (13). Narrowing of the vessel lumen is seen at histologic evaluation and is due to intimal fibrosis (14,15). It seems reasonable that these changes would increase vascular impedance.

Since hyperacute rejection causes severe vasculitis resulting in throm-
bosis and occlusion of vessels, as may be seen in vascular forms of acute rejection, it follows that vascular impedance is increased. While hyperacute rejection, vascular and interstitial forms of acute rejection, and chronic rejection have different immunologic and histologic features, the result is narrowing or occlusion of the vessel lumen (11,13-15), which was reflected by the elevation of RI in our study.

In animals, acute ureteral ligation causes decreased renal blood flow, presumably because edema and back pressure cause compression of the renal vessels (16). Elevated RI values in patients with ureteral obstruction in our study are consistent with these laboratory data. We conclude that obstruction should be considered in a renal allograft with hydrenephrosis if the RI is 0.70 or greater, in agreement with the findings of Platt et al (17) in native kidneys.

Buckley et al (6) found normal renal blood flow in cyclosporine toxicity. In our study, the mean RI for cyclosporine toxicity (0.67) was slightly elevated above that in cases of dysfunction without rejection (RI = 0.64, P < .02). This difference is less than one standard deviation for the mean RI values of both groups, a fact indicating significant overlap. Pathologic studies of cyclosporine toxicity show dystrophic microcalcification and vacuoles within the tubular cells. Vasculopathy is also present and may explain the slight elevation in mean RI (18).

A recent article addressed two cases of severe bacterial nephritis causing increased vascular impedance (9). In focal, severe nephritis, it is plausible that edema may cause compression of the vascular bed and hence increase impedance. In the 11 patients in our study with bacterial nephritis or sepsis, only two showed an RI of 0.70 or greater. The mean RI values in the sonograms of patients with viral and bacterial infections were not significantly elevated above baseline values.

Taylor et al (19) showed that the diagnosis of renal artery stenosis can be suggested by the Doppler frequency shift in the region of the anastomosis and by the turbulence distally. The abnormalities in the waveform at the level of the renal sinus were minimal (19). In our study, we did not evaluate the waveform at the anastomotic site. The mean RI, measured in the cortex, was normal (0.64), which agreed with the experience of Taylor et al.

Only one episode of documented renal failure due to ATN was seen in our study and it had an RI of 0.78. Other reports indicate that ATN is associated with increased vascular impedance (5,8,9). The frequency of ATN was low in our study because the diagnosis was usually made on the basis of clinical findings and sonography was not performed. This frequency may also be low because we use cold pulsatile perfusion for storage of cadaver allografts rather than ice storage, which is used at many institutions. The frequency of ATN could also appear low because subclinical disease may have been overlooked. Evidence for this was found in the analysis of postoperative baseline studies, which showed a significantly higher mean RI in cadaveric (0.65) versus living, related donor (0.60) kidneys.

Our study demonstrated that evaluation of the RI is a fairly sensitive, although nonspecific, indicator of allograft dysfunction. We found that urinary obstruction and hyperacute, acute, and chronic rejection caused elevation of the RI. We found no elevation of the RI in infection; however, the patient population in our study was small. Others have shown elevated vascular resistance in some allografts with ATN (5,8,9), renal vein thrombosis (8-10), and infection (9). The finding of an elevated RI alone in the setting of renal allograft dysfunction is insufficient data to suggest a specific cause.

References