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Role of duplex Doppler sonography in diagnosis of acute allograft dysfunction—time to stop measuring the resistive index?

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Abstract Measurement of vascular resistive index (RI) by duplex Doppler sonography (DDS) has been proposed as a non-invasive technique to detect the presence of acute rejection in renal allograft recipients. Our aim was to evaluate the clinical utility of this technique. From 107 patients we reviewed 159 biopsies that were performed from 1993 to 2001 for the investigation of acute allograft dysfunction. Histological findings were correlated with RI measurements by contemporaneously performed DDS. The majority of biopsies were carried out within the first 3 months post-transplantation (111/159). Sixty-eight biopsies showed acute rejection, 91 biopsies had findings other than rejection (acute tubular necrosis, CyA toxicity, recurrent GN). Using a threshold mean RI value of 0.9, the test had a specificity for acute rejection of 89%, but a sensitivity of just 6%. If the threshold was lowered the sensitivity rose, but specificity declined sharply. Average RI in the rejection group was not higher than in controls (0.73 ± 0.11 vs 0.74 ± 0.11, respectively). We conclude that measurement of RI by DDS does not contribute to the diagnosis of acute allograft dysfunction.

Keywords Renal transplantation · Rejection · Resistive index · Duplex Doppler sonography

Introduction

A non-invasive technique to detect the presence of acute rejection in renal allograft recipients has long been sought. Measurement of the vascular resistive index (RI) by duplex Doppler sonography (DDS) has been proposed as one such method [7, 16, 17], but there are conflicting reports in the literature as to the clinical utility of the technique [1, 8, 9, 10, 11, 13]. It has been suggested that acute rejection leads to a rise in vascular resistance that might be detectable by duplex Doppler ultrasound. The purpose of our study was to evaluate retrospectively the degree of correlation between changes in renal arterial flow pattern (RI) on DDS and histological findings at allograft biopsy.

Patients and methods

We identified all renal allograft biopsies performed at Hammersmith Hospitals NHS Trust from 1993 to 2001 and examined the correlation, if any, between histological findings and the results of the contemporaneously performed duplex Doppler ultrasound study (median interval between ultrasound and biopsy, 1 day; range 0–7 days). Doppler tracings were taken of the interlobar arteries at the upper, middle and lower poles of the graft, and the RI was calculated at each site (peak systolic velocity minus lowest diastolic velocity divided by the peak systolic velocity, Fig. 1). The mean RI value was used for all calculations. The utility of RI

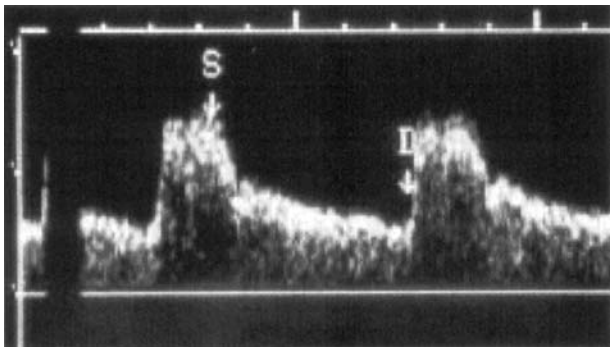

Fig. 1 Measurement of RI by duplex Doppler sonography (*S* peak systolic flow velocity, *D* minimum diastolic flow velocity)

measurement as a method of diagnosing acute rejection was evaluated by calculation of receiver operating characteristic (ROC) curves.

Results

A total of 388 biopsies were performed from June 1993 to January 2001 in 186 patients for the investigation of acute allograft dysfunction. All biopsies were reported by one of us (T.C.), and the histological findings classified and coded. Contemporaneous sonographic data were available for 159 of the biopsies (from 107 patients). These 159 cases were sub-divided into two groups:

a Acute rejection: 68 biopsies (43%)—see Table 1.
b Controls: 91 biopsies (57%)—see Table 2.

The mean number of diagnoses per biopsy was 1.4.

The majority of biopsies were performed in the first 3 months following transplantation (55/68 in the acute rejection group, 56/91 in the control group).

Overall, there was no significant difference in RI values between the control and acute rejection groups (Fig. 2). If anything, RI values were slightly higher in the control group (mean RI in controls 0.74 ± 0.11 vs 0.73 ± 0.11 in the acute rejection group). At any given RI threshold value, many patients with acute rejection will have normal RI values and will, therefore, not be detected by the use of DDS as a screening tool.

We evaluated the utility of RI measurement as a diagnostic test for the presence of acute rejection by means of ROC-curve analysis. This is done by plotting the true-positive rate for the test against the false-positive rate. The graphing of the results in this way allows easy visualisation of the trade-off between sensitivity and specificity. Any increase in sensitivity will be accompanied by a decrease in specificity. For an accurate diagnostic test, the curve will be seen to follow the left-hand border closely and then the top border of the ROC space. Where a diagnostic test is of poor discriminatory value, the curve aligns with the 45-degree diagonal of the ROC space.

Table 1 Diagnoses in acute rejection group ($n=68$). All biopsies showed evidence of acute rejection, but many also showed additional pathology

Diagnosis	No. of patients
Acute rejection	$n=68$
Acute cellular rejection alone	53
Acute vascular rejection alone	6
Acute cellular + vascular rejection	9
Secondary diagnoses	
Glomerulopathy (acute/chronic)	7
Thrombosis	4
Acute tubular necrosis	3
Thrombotic micro-angiopathy	3
Pyelonephritis	2
Cyclosporin-A toxicity	1
Ischaemia	1
Cytomegalovirus infection	1
Recurrence of primary disease	1

Table 2 Diagnoses in control group ($n=91$). Many biopsies showed evidence of more than one pathological category

Diagnosis	No. of patients
Acute tubular necrosis	35
Acute graft dysfunction of unknown cause[a]	19
Chronic graft dysfunction of unknown cause	13
Cyclosporin-A toxicity	11
Ischaemia	8
Recurrence of primary disease	6
Normal	5
Pyelonephritis	2
Graft thrombosis	2
Glomerulopathy (acute/chronic)	2
De novo glomerulonephritis	1
Granulomatous interstitial nephritis	1
Thrombotic micro-angiopathy	1

[a]Biopsy size was adequate for us to exclude rejection in all cases

The ROC curve plotted in Fig. 3a suggests that RI measurement as a diagnostic tool is of little value, having poor sensitivity and specificity. The curve almost exactly follows the 45-degree diagonal. The significance of this becomes clear when individual cut-off points are examined. At a threshold mean RI value of 0.9, an elevated RI is relatively specific for a diagnosis of acute rejection, 89%, but the sensitivity is poor, at just 6%. If the cut-off is lowered, there are small improvements in sensitivity, but with the result that a positive test is entirely non-specific for the presence of rejection. Sub-group analysis screening for the presence of vascular rejection yielded similar results (data not shown).

Being mindful that the causes of allograft dysfunction are different in the early post-transplant period compared with long-term patients, we also performed a subgroup analysis of those patients with acute allograft dysfunction in the early post-transplant phase (< 3

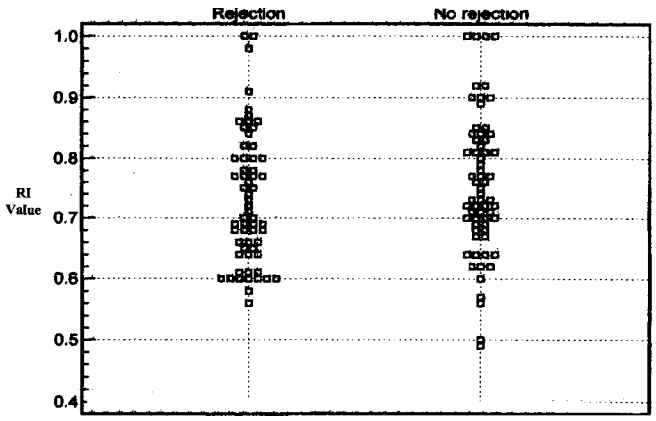

Fig. 2 Dot plot showing distribution of RI values in the control and acute rejection groups (early post-transplant data, $n = 111$)

months post-transplantation, $n = 111$). Again, similar results were obtained (Fig. 3b).

We were somewhat concerned at the inclusion in the control group of those patients with acute graft dysfunction of unknown cause. Although the biopsy size was adequate for us to exclude acute rejection in each case, this group lacked a firm histological diagnosis. To ensure that this cohort was not skewing the results, we repeated the statistical analysis, censoring for the data from this group. This made no significant difference to the results (data not shown).

Discussion

Ultrasonography has proved to be an invaluable asset in the assessment of patients with renal allograft dysfunction. As an inexpensive, non-invasive technique it gives useful information on graft arterial blood supply and venous patency and is useful to screen for evidence of outflow obstruction or peri-graft collection.

In addition to this, measurement of RI by DDS is commonly performed. In the normal renal allograft, arterial Doppler signals show continuous antegrade diastolic blood flow, reflecting the normal, low renovascular impedance [2]. Several studies have shown that during episodes of acute rejection, diastolic flow velocity is reduced in all branches of the renal arterial vasculature, reflecting a rise in vascular impedance [3, 19, 21]. It is postulated that this change may be due to endovasculitis (as occurs in acute vascular rejection) or due to the presence of interstitial oedema or alterations in vasomotor tone. This change in renal arterial flow may be detected by means of DDS.

The earliest application of a Doppler sonographic technique as a screening tool for renal allograft rejection was reported by Rigsby et al. [17] in 1987. In a study of 55 patients they correlated DDS findings with histology

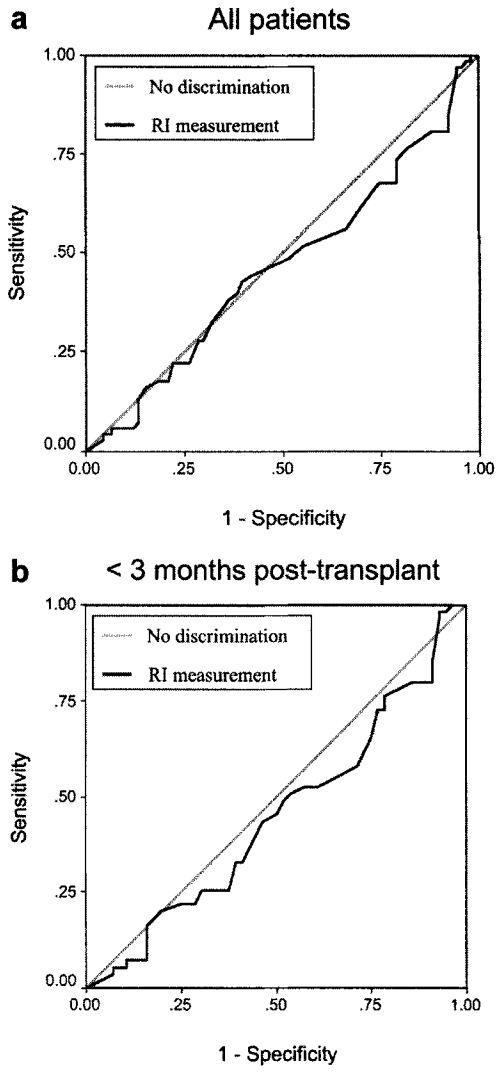

Fig. 3a, b ROC-curve analysis for (**a**) all patients ($n = 159$) and (**b**) early post-transplant patients (< 3 months) ($n = 111$). RI is of limited value as a screening tool

results obtained at percutaneous biopsy or nephrectomy. An increase in vascular impedance, as measured by pulsatility index (PI = peak systolic velocity–minimum diastolic velocity/mean flow velocity), was associated with episodes of acute rejection. With a threshold PI value of 1.5, the sensitivity for the detection of all forms of acute rejection was 75%, with a specificity of 90%. Raising the threshold to 1.8, they achieved a specificity of 100%, but with reduced sensitivity. However, only three of their patients had acute tubular necrosis (ATN), which may have artificially improved specificity for acute rejection at the higher PI threshold.

Rifkin et al. [16], in 1987, were the first to employ RI measurement as a screening test for the presence of acute rejection. Using a threshold of 0.9 they achieved a positive predictive value of 100% for the diagnosis of acute

Table 3 Summary of principal studies evaluating RI measurement by DDS as a screening technique for the detection of the presence of acute renal allograft rejection. Figures in parentheses are biopsy-proven. *CyA* Cyclosporin A

Reference	No. of patients	No. of DDS examinations	No. of biopsies	Acute rejection	CyA toxicity	ATN	Sensitivity	Specificity	Positive predictive value	Threshold RI
This study	107	159	159	69 (69)	11 (11)	35 (35)	6%	89%	29%	0.9
Mallek et al. 1992 [11]	98	137	137	83 (83)	42 (42)	19 (19)	–	62%	–	>0.9
Renowden et al. 1992 [15]	66	71	71	50 (50)	0	14 (14)	60%	40%	–	>0.7
Perchik et al. 1991 [12]	75	234	67	176 (66)	11 (–)	24 (–)	52%	82%	–	>0.7
Saarinen et al. 1992 [18]	150	150	0	31%	?	34 (0)	45%	85%	–	0.93
Don et al. 1990 [6]	71	84	49	32 (–)	5 (–)	0	90%	76%	47%	>0.7
Kelcz et al. 1990 [10]	89	96	96	46 (46)	10 (10)	1 (1)	10%	90%	–	>0.8
Perrella et al. 1990 [13]	33	46	46	28 (28)	1 (1)	9 (9)	43%	67%	67%	>0.9
Genkins et al. 1989 [8]	77	77	48	23 (21)	8 (8)	6 (6)	9%	91%	–	>0.9
Evans et al. 1989 [7]	42	61	?	?	?	?	94%	96.5%	82%	>0.8
Allen et al. 1988 [1]	56	96	28	38 (24)	5 (–)	24 (1)	76%	83%	–	>0.75
Rifkin et al. 1987 [16]	81	145	34	54 (–)	9 (–)	33 (–)	13%	100%	100%	>0.9
Rigsby et al. 1987 [17]	81	60	54	54 (54)	0	3 (–)	75%	90%	–	PI>1.5

rejection. Values less than 0.7 had a negative predictive value of 94%. In contrast to later studies, the population they screened had a very low incidence of high RI associated with ATN. This will have helped improve positive predictive value of the test when high cut-off thresholds were used. In this study, biopsies, the gold standard for establishing the cause of renal allograft dysfunction, were performed in only 42% of cases.

Subsequent studies have cast doubt on the value of RI measurement in discriminating different causes of acute allograft dysfunction and are summarised in Table 3 [1, 8, 11, 13]. Di Palo et al. [5] have suggested that an increase in RI values might simply be an index of glomerular hyperfiltration. Further support for this concept has recently been provided by Splendiani et al. [20], who demonstrated that, in patients with chronic renal disease, an elevated RI was predictive of subsequent decline in renal function.

It has been demonstrated that RI values may be influenced by many extraneous factors [14] such as compression of the graft due to peri-nephric fluid collections, sub-capsular haematoma, or even excessive pressure transmitted via the transducer by a heavy-handed sonographer. Inaccurate scanning can also yield a falsely low RI, as can experimentally induced hypotension.

To our knowledge, this is the largest study in the literature to correlate DDS findings with definitive histological diagnoses. Our study suggests that the use of RI measurement as a screening tool for the presence of acute rejection has two inherent flaws that limit its utility. Firstly, it seems clear, from this and other studies, that acute rejection episodes can be associated with normal RI values [8, 10, 11, 13]. Secondly, our study confirms the finding that ATN is frequently associated with an elevation in RI (49% of those with ATN (17/35) had RI values >0.8), thus making it impossible for the two to be distinguished on the basis of RI measurement alone. Several earlier studies were undoubtedly confounded by having a low proportion of [6, 17], or excluding [4], patients with ATN. Accordingly, we conclude that it seems unlikely that DDS will ever be a sufficiently sensitive and specific test for acute rejection to obviate the need for allograft biopsy.

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