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Utility of serial Doppler ultrasound scans for the diagnosis of acute rejection in renal allografts

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Abstract This study aims to explore the utility of serial duplex scanning and to compare its results with those of single time-point scans of renal allografts in the diagnosis of acute rejection (AR). A retrospective analysis of 6017 serial duplex scans (mean: 9.8 scans per patient, 5.7 of which were done during the first 10 days) was performed in 614 patients with 462 episodes of AR from 1992–2000. Even in the absence of AR ($n=278$), there were day-to-day fluctuations in pulsatility index (PI) and resistive index (RI). An increase of >10% in intra-renal indices was noted 0.95 days (mean) before the commencement of treatment for AR (SD 1.3, range 1–6 days). In patients with acute tubular necrosis (ATN), who have high base line indices, sensitivity of single value of PI and RI was 58% (cut-off level 1.8) and 68% (cut-off level 0.8), with specificity of 66% and 56%, respectively. By contrast, a >10% increase over the previous 'best' in PI and RI had a sensitivity of 78% and 60% respectively, and a specificity of 78% and 90%, respectively. Reversal of flow during diastole ($n=50$) was found to be associated with 22% graft loss within 3 months of transplantation. We can conclude that a considerable overlap between the indices of patients with AR and those with ATN greatly limits the diagnostic yield of duplex scanning. Nonetheless, serial scanning of renal allografts is more likely to herald the need for biopsy in the diagnosis of AR than one-time scanning.

Keywords Duplex scan · Intra-renal indices · Renal allografts · Acute rejection

Introduction

Early and accurate diagnosis of renal graft dysfunction soon after transplantation is the key to prompt institution of appropriate treatment. Therefore, there is a great need for a reliable, prompt and non-invasive diagnostic modality. The diagnosis of acute rejection (AR) on the basis of morphological changes (such as increase in size and cortical thickness, prominence of pyramids, reduced cortico-medullary differentiation and decreased amplitude of renal sinus echoes) demonstrable by grey scale ultra-sonography has not been found to be satisfactory due to its limited reproducibility, low sensitivity and poor positive predictive value [1, 2, 3, 4, 5]. The interpretation of studies reporting Doppler ultra-sonography has certain limitations, such as small sample size, subjectivity of observations, inter-observer variations and lack of quantification. Another key factor is the lack of data on day-to-day variations during the critical first 2 weeks [3, 5]. With the advent of the duplex scan, it has become possible to study the pattern of flow in intra-renal arteries, such as inter-segmental flow, which reflects intra-renal pressure and vascular impedance. Resistive index (RI) is measured as a ratio of the dif-

ference between peak and minimum velocity divided by peak velocity. Pulsatility index (PI) is dependent on the pattern of blood flow and is calculated as a ratio of the difference between peak and minimum velocity divided by mean velocity [2]. Since these two parameters are ratio values, they are less likely to be affected by variations in heart rate and cardiac output [1]. The Doppler indices measured at a single time-point are of limited value for patients whose baseline indices are either too low or too high. This study was performed to assess the utility of serial duplex scanning and to compare it with single time-point scans of renal grafts in the diagnosis of AR in a large series of serial duplex scans.

Patients and methods

Serial duplex imaging

In our regional transplant unit, duplex scans of renal allografts were performed routinely during the immediate post-transplant period with a ward based scanner (18XP/10 Acuson) using a 3.5–4 mHz (multi-frequency) probe (vector array transducer) operated by two in-house trained ultrasonographers. Serial scanning was commenced on the first post-transplant day to determine base-line values of intra-renal Doppler indices and thereafter every 48 h. The process of duplex scanning was standardised to minimise intra- and inter-individual variations. The wave-form 'frozen' on the screen was manually traced, and PI and RI were calculated using built-in software. Measurements for each artery (inter-segmental, inter-lobar and the renal artery) were performed on two occasions to ensure uniformity in tracing and calculation. If there was discrepancy in two consecutively performed indices for an artery, a third measurement was performed to ascertain which of the two discrepant value was to be taken as correct. A cut-off point of 1.4 for PI and 0.7 for RI is based on reported literature [6, 7] and on the basis of distribution pattern of this data.

The database comprised the details of 6017 duplex scans performed in 614 patients between 1992 amd 2000 (mean of 5.7 scans during the first 10 days, and a total of 9.8 scans per patient). Only serial duplex scanning data of the first 14 days was consistently available. Data of serial ultrasound scanning used in the diagnosis of 462 episodes of AR in patients with primary function ($n=366$) or with acute tubular necrosis i.e., ATN ($n=96$). The data includes multiple AR episodes in 97 patients (two episodes of AR in 97 patients and three episodes in 16 patients). The response to anti-rejection treatment were used as a gold standard for confirmation of AR. Patients ($n=278$) who did not develop AR during this time were used as controls (194 patients with primary function; 84 patients with ATN). For the purpose of defining specificity and positive predictability of serial duplex scanning, false positive cases and true negative cases were identified from the serial scanning data of these patients. In order to calculate sensitivity and positive predictability, 265 patients (206 with primary function and 59 with ATN) developing AR within the first 14 days of transplantation were included for comparative analysis.

Immunosuppressive protocol

Cyclosporine monotherapy was used as the primary mode of immunosuppression. Oral prednisolone, azathioprine (mycophenolate mofetil since 1996) were added later for recurrent/severe AR. Conversion from cyclosporine to tacrolimus-based immunosuppression was carried out in cases of cyclosporine failure or toxicity. AR episodes were treated with methyl prednisolone (0.5–1 g, intravenously for 3 days). Anti-thymocyte globulin (Merieux) was administered in cases of steroid-resistant rejection, however infrequently.

Interpretation of duplex findings

The indices of inter-segmental and f interlobular arteries were measured. However, we found that indices of inter-lobular arteries were less reliable; we therefore based our interpretation on inter-segmental parameters. Renal artery indices were recorded but excluded from the analysis of this study. The increase of intra-renal Doppler indices in percent was calculated by analysing the difference in indices on 'day 0' (the day of commencement of treatment for AR) over the indices recorded on 'day minus 2' (2 days before 'day 0') and the 'best indices' (the lowest indices recorded until day '0'). This difference was divided by the indices on 'day minus 2' and the 'best indices', respectively. These parameters were referred to as ΔPIday-2 & ΔRIday-2 and ΔPIbest and ΔRIbest, respectively. Absolute values and percentages of the increases (or drops) in indices over a period of 2 consecutive recordings in control patients in the first 14 days were used to define true negatives and false positives. This information was used to calculate the specificity and positive predictability of ΔPIday-2, ΔRIday-2, ΔPIbest and ΔRIbest in the diagnosis of AR.

The diagnosis of AR

In the patients with primary function, the clinical diagnosis of AR was based on clinical features (i.e., fever, tender and swollen graft), and at least 20% deterioration of serum creatinine and creatinine clearance) having ruled out high 12-h trough cyclosporine levels, and absence of infection on urine microscopy and culture. The data of only those patients was included who showed improvement to steroid pulse therapy. Since the patients with ATN could not be monitored by a change in serum creatinine or creatinine clearance, the diagnosis of AR was made much less often on clinical grounds only, as shown in Fig. 1.

Histopathological grading was performed according to Banff criteria. Primary function was defined as a urine output sufficient to avoid dialysis (for any reason except hyperkalemia) in post transplant period. ATN was diagnosed when there was initial anuria/oliguria, lack of improvement in serum creatinine despite good urine output, or subsequent biopsies showing ATN without AR. Patients with infection, urine outflow obstruction or cyclosporine toxicity as a possible (solely or in addition to AR) cause of graft dysfunction were excluded from this analysis, in order to define the corelation of duplex findings with AR. Data analysis was performed using the Microstat statistical programme. The comparison of indices in two different groups was performed by hypothesis test. $P < 0.05$ was considered as statistically significant.

Results

The mean age of patients suffering from AR was 42.1 years (S.D. 14.6), and 46.5 years (S.D. 14.3) for controls ($P > 0.05$). The ratio between male and female was 1.8 to 1; it was similar in both groups. Of all transplant patients with AR, 81.2% had undergone their first transplantation, and of the controls, 84.6% ($P > 0.05$); 86.7% patients had received cadaveric grafts, the rest were living-related.

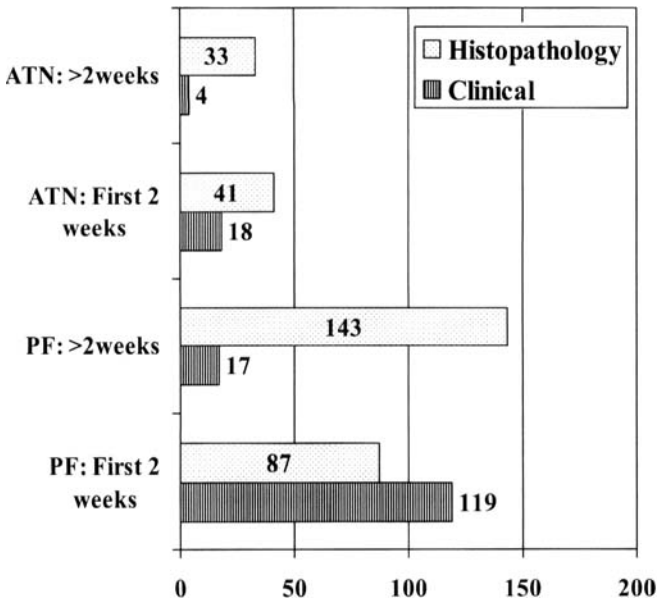

Fig. 1 Proportion of acute rejections ($n=462$) diagnosed by histopathology at various stages of transplant follow-up. *PF* primary function, *ATN* acute tubular necrosis, $P<0.05$

Diagnosis of AR

Of 462, 304 (65.8%) episodes of AR were biopsy proven, while 158 of 462 (34.2%) the diagnosis of AR was made on clinical grounds and biochemical parameters (Fig. 1).

Fluctuations in intra-renal indices in patients without AR (controls, $n=278$)

Table 1 shows that the patients with ATN display many more variations (as is reflected in a higher standard deviation) than those with primary function. Patients with ATN tended to have higher PI and RI on days 5 and 7 of transplantation, than on day 1; though significant difference was noted in changes in RI (not in PI).

Comparative promptness of Doppler scanning

On serial Doppler scanning, a >10% change in ΔPIbest and ΔRIbest was observed well before day '0', ranging from 1 – 6 days with a mean of 0.95 days (SD 1.3) in advance.

Changes in intra-renal arterial indices in renal grafts

Intra-renal indices in the patients with developing AR were significantly higher on 'day 0' than those on 'day minus 2', 'day minus 1' and the 'best indices'; Table 2 and Figs. 2 and 3. The indices in patients with AR on 'day 0' with grade III ($n=45$, PI 1.92+0.87, and RI 0.80+0.12) tended to be higher than in patients with grade I ($n=180$, PI 1.81+0.94, and RI 0.79+0.15) and grade II ($n=79$, PI 1.68+0.87, and RI 0.77+0.13), but the difference did not reach significant levels. Vascular components of AR did not have a significant effect on intra-renal indices.

Table 1 Changes in intra-renal indices in inter-segmental arteries of renal grafts in patients without acute rejection (controls) in the first 10 days of renal transplantation. The figures are mean values and those in brackets are standard deviations. *ATN*=Acute tubular necrosis; *PI*=pulsatility index; *RI*=resistive index; Comparisons were made between the indices on day 1 versus indices in other columns. * $P<0.05$; ** $P<0.001$, all other comparison are not significant

	Day 1	Day 3	Day 5	Day 7	Day 10
Patients with primary function					
PI	1.26 (0.38) (0.35)	1.24 (0.34)	1.28 (0.34)	1.27 (0.30)	1.27
RI	0.68 (0.09)	0.69 (0.09)	0.69 (0.09)	0.69 (0.09)	0.70 (0.08)
Patients with ATN					
PI	1.77 (0.97)	1.89 (0.99)	1.93 (0.81)	1.93 (0.83)	1.75 (0.71)
RI	0.77 (0.14)	0.81* (0.13)	0.83** (0.11)	0.83** (0.15)	0.81 (0.15)

Table 2 Sensitivity of Doppler indices in the patients with low base-line intra-renal indices (RI>0.7 in inter-segmental arteries, $n=111$). *PI* Pulsatility; *RI* Resistive index. ΔPIday-2 (or ΔRIday-2) and ΔPIbest (or ΔRIbest), mean increase of percentage on 'day 0' over the figure 'day minus 2' and over previous 'best figures' in percentages. 'Day 0' is the day of commencement of treatment for acute rejection. Cut-off point for the calculation of sensitivity PI is 1.4, and 0.7 for RI. Cut-off point for the calculation of sensitivity of the increase of indices in percentages (RI or PI) is 10%

	Absolute Value	ΔPIday-2	ΔPIbest
PI	2/111 (1.8%)	24/72 (33.3%)	59/107 (55.1%)
RI	0/111 (0.0 %)	8/67 (31.3%)	54/98 (55.1%)

Reliability of serial Doppler scanning compared with single scanning within the first 2 weeks after renal transplantation

Tables 3 and 4 show the comparative reliability of single value PI & RI versus an increment in values. In patients with primary graft function, an RI value of at least 0.7 in the inter-segmental artery was most sensitive (90.2%) for detecting acute rejection. Specificity and positive predictive value of the increase of PI and RI in percentages were much higher when a cut-off figure of >20%

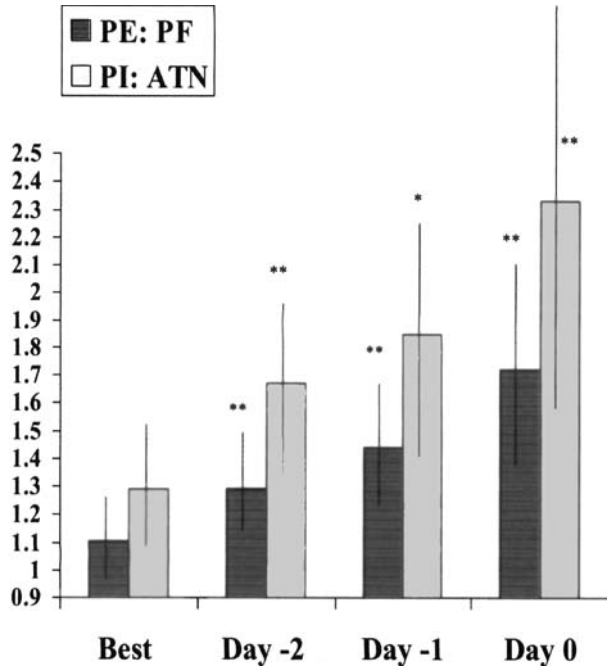

Fig. 2 Sequential changes in pulsatility index (*PIseg*) in inter-segmental arteries of renal allografts. *PF* primary function, *ATN* acute tubular necrosis, *Day 0* commencement of anti-rejection treatment, *Best* lowest index value of a particular patient. Figures given are mean values. *Vertical line* standard deviation. Comparisons were made between the indices on day 0 versus others. $*P < 0.05$, $**P < 0.001$

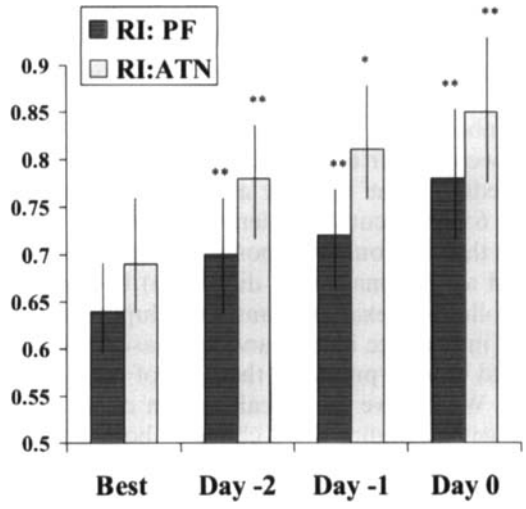

Fig. 3 Sequential changes in resistive index (*RIseg*) in inter-segmental arteries of renal allografts. *PF* primary function, *ATN* acute tubular necrosis, *Day 0* commencement of anti-rejection treatment, *Best* lowest index value of a particular patient. Figures given are mean values. *Vertical line* standard deviation. Comparisons were made between the indices on day 0 versus others. $*P < 0.05$, $**P < 0.001$

rise was used, rather than one of > 10%, however at the cost of sensitivity. Similarly, when the cut-off point of PI and RI were elevated to 1.8 and 0.8 respectively, the specificity and positive predictability improved, but it did so at the cost of sensitivity. In patients with ATN, base-line PI and RI were much higher, therefore, the specificity and positive predictability of single absolute value of PI and RI were unreliable (Table 4). In these patients, the finding of a > 10% increase over the previous best PI and RI offered much better combination of good sensitivity and reliable specificity.

Table 3 Sensitivity, specificity and positive predictability of a single value of *PI* Pulsatility index and *RI* Resistive index of inter-segmental arteries compared to the increase (ΔPIbest and ΔRIbest) in indices in detection of acute rejection in patients with primary function ($n = 206$). Values are expressed in percentages. ΔPIbest and ΔRIbest, mean increase of intra-renal indices in percentages on 'day 0' over previous the 'best figures'

		Sensitivity	Specificity	Positive Predictability
PI	≥1.4	70.6	77.6	34.5
PI	≥1.8	43.6	94.1	55.9
ΔPIbest	≥10% rise	85.6	73.5	44.6
ΔPIbest	≥20% rise	74.7	85.7	55.9
RI	≥0.7	90.2	59.4	26.5
RI	≥0.8	52.7	89	49.3
ΔRIbest	≥10% rise	73.8	86.1	56.2
ΔRIbest	≥20% rise	52.3	97.1	81.6

Table 4 Sensitivity, specificity and positive predictability of a single value of *PI* Pulsatility index and *RI* Resistive index of inter-segmental arteries in comparison to increase (ΔPIbest and ΔRIbest) in indices in detection of acute rejection in patients with acute tubular necrosis ($n = 59$). Values are expressed in percentages. ΔPIbest and ΔRIbest, mean percentage of increase in intra-renal indices on 'day 0' over previous the 'best figures'

		Sensitivity	Specificity	Positive Predictability
PI	≥1.4	81.7	42.9	14.7
PI	≥1.8	58.3	66.2	17.8
ΔPIbest	≥10% rise	78.2	70.5	29.4
ΔPIbest	≥20% rise	67.3	78.7	33.3
RI	≥0.7	93.3	26.5	13.5
RI	≥0.8	68.3	6.4	16.7
ΔRIbest	≥10% rise	60	79.4	33.3
ΔRIbest	≥20% rise	47.3	92.2	50.9

Reliability of Doppler indices in the diagnosis of AR at any time after transplantation

Since the patients without AR (controls) were discharged from in-patient care within 2 weeks of transplantation, the value of serial intra-renal indices of true negative cases (of AR) and false positive cases (of AR), required for the calculation of specificity and positive predictability, only sensitivity was calculated for the patients who developed AR after this period. Nevertheless, PI at a cut-off figure of (one-time scan report)

1.4 in all the patients was 87.8% and 77.1%, respectively in those with primary function and with ATN, whilst the sensitivity of serial scanning showing a >10% increase in PI over the previous best PI was 79.8% and 84.3%, respectively in patients with primary function and those with ATN. Similarly, the sensitivity of RI at a cut-off figure of 0.7 in inter-segmental arteries in all the patients (whether or not within 2 weeks of transplantation) was 79.1% and 84.4%, respectively, in those with primary function and those with ATN. While the sensitivity of a >10% increase over the previous best RI was 70.4% and 63.7%, respectively, in those with primary function and those with ATN.

Reliability of Doppler scan in detection of AR in patients with low intra-renal indices

The sensitivity of Doppler scans in the detection of AR in the patients with low intra-renal indices (RI of <0.7 as base line in inter-segmental arteries) was very low (0–3%) if a single value of PI or RI was taken into consideration. When the increase of intra-renal indices in percentages over the previous 'best' was calculated, the sensitivity of >10% increase in intra-renal indices approached 38–55%.

Reversal of flow during diastole (RFD)

RFD was noted in 50 patients with either AR ($n=33$) or ATN ($n=17$). In these patients, renal vein thrombosis was excluded by the demonstration of blood-flow in the renal vein by duplex scan or contrast venography, if duplex was inconclusive. Within 3 months, 11 (22%) of these grafts were lost, 12 (24%) within 1 year, and 21 (42%) within 5 years. Of those, 9 (18%) required graft nephrectomy within 3 months of transplantation. All these 9 patients lost cortico-medullary differentiation on the grey scale within 48 h of graft nephrectomy. Among 33 patients with AR who developed RFD, there were 73 episodes of AR, before and after RFD, (2.2 per patient). However, the mean number of ARs after the episode of RFD was 0.6 per patient (S.D. 0.7). 21/32 (75.4%) grafts with RFD due to AR had more than grade 1 rejection. RI, at a mean of 1.2 (S.D. 0.2), was significantly higher in patients with RFD due to AR with vascular changes, versus that of patients with RFD due to AR without vascular component, at a mean of 1.1 (S.D. 0.9), $P<0.05$. Of 33 patients, 16 (48.5%) with AR and RFD episodes had SRR and therefore required rescue therapy with ATG ($n=12$) and Tacrolimus ($n=4$).

Among 17 patients with ATN developing RFD, there were 31 episodes of AR (1.8 acute rejections per patient).The mean number of ARs in patients with ATN after the episode of RFD was 0.5 per patient (S.D. 0.7). Two patients were managed by ATG. There was no significant difference in peak PI and peak RI of patients with RFD due to acute rejection, versus those with RFD due to ATN. Overall graft survival in patients with RFD, either due to AR or ATN at 1 and 5 years, respectively, was 38/50 (76.0%) and 16/36 (44.4%).This is in contrast to overall 1 and 5-year graft survival of 89% and 79%, respectively, at this unit.

Discussion

Since there is a considerable overlap in the indices of patients with 'normal' function, ATN and patients with acute rejection, a single PI and RI value is of limited utility in the diagnosis [3, 8, 9]. Trilaud et al. [9] reported that one-time Doppler sonongraphy ($n=31$ patients) is insensitive in differentiating the causes of graft dysfunction. A number of patients in our series who developed AR were noted to have relatively lower indices (PI of <1.4 and RI of <0.7), contrary to that observed by Rifkin et al. who reported that an RI of 0.70 was unlikely to be associated with AR [6]. We noted that even in the absence of AR, some grafts have high intra-renal indices. This is more common in cases of ATN than in those with primary function. Table 1 highlights this important observation, based on a large cohort of 278 patients. This explains low specificity and positive predictability of a single value of PI (cut-off point of 1.8) and RI (cut-off point of 0.8) in diagnosing AR in patients with ATN; Table 4. However, ΔPIbest and ΔRIbest improved the specificity and positive predictability.

Hollenbeck et al. [10] reported that primary rejections ($n=41$) were better identified by an increase in PI over the preceding value than by an absolute PI value (330 scans in 65 consecutive patients). Jensen et al. [2] emphasised that it is only it is possible to detect alterations (reported as maximal index difference) by means of repeated follow-up examinations with duplex ultrasonography in impedance indices and emphasized that PI and RI should be interpreted in the light of intra-individual changes. We believe that a calculation of the change in percentages quantifies these changes, both normal day-to-day changes and such due to AR) more reliably than just a measurement of the difference from the previous value. For example, a maximal index difference, as suggested by Jensen et al. [2] of 0.10 in a patient with basal RI of 0.55 amounts to a much higher percentage change than a similar change over a baseline RI of 0.75 as in someone with ATN.

Mercus et al. reported that Doppler spectrum analysis enables the detection of AR as early as 5 days after transplantation [5]. Using serial Doppler ultrasonography, we observed that it is possible to detect an increase in intra-renal indices well in advance (0.95 days before

the commencement of anti-rejection treatment). Hollenbeck et al. reported that PI commenced to increase at an average of 3.3 days before the diagnosis of AR [10]. On the basis of a study on AR in experimental canine models, Takahashi et al. noted that an increase in intra-renal indices preceded deterioration in serum creatinine by 1–3.5 days and, therefore, underlined the role of sequential duplex scanning [11].

Higher impedance has been reported in grafts with elements of vascular rejection than in such with interstitial rejection, [2, 10] however we did not note any such difference. Tranquart et al. [7] observed that RI at 30 min after transplantation was significantly higher in patients who developed ATN ($n=8$, mean RI $0.80+0.09$) than in those who did not develop ATN ($n=9$, mean RI $0.66+0.12$). Needleman and Kurtz [5] reported that duplex ultrasonography could not distinguish between ATN and AR and concluded that biopsy remained the procedure of choice. By raising the cut-off line from of PI from 1.4 to 1.8 and that of RI from 0.7 to 0.8, a marked improvement was noted in specificity and positive predictability reciprocal to, and thereby at the cost of, reduced sensitivity, Tables 3 and 4. This finding is not unexpected [6, 12] because of a tremendous degree of overlap in the intra-renal indices of AR and ATN.

In a number of conditions such as hypertension, diabetes, chronic graft rejection and most appreciably in AR, PI and RI have been observed to be higher than normal than in AR, ATN and 'normal' [13, 14, 15]. Therefore there is need for clinico-pathological corelation in interpreting PI and RI report. Krumme et al. studied the Doppler indices of patients with stable grafts and suggested that intra-individual comparison of the Doppler indices may be useful to detect potential changes of graft resistance during long-term follow-up, justifying the need for serial scanning [12]. Wollenberg et al. stressed that duplex ultrasonongraphy should be performed within the first 24 h after transplantation to evaluate graft perfusion and baseline values, so that it can be used for interpretation of further duplex scannings in corelation with clinical signs of AR, asserting the decision for renal biopsy even in borderline cases [16].

RFD was noted in 33/462 (7.1%) grafts with AR. This apparently high frequency of RFD is possibly due to regular serial scanning by a ward based scanner enabling detection even in such patients in whom it is a temporary phenomenon of a few days of duration. It indicates a marked increase in impedance, reflecting a tension higher than the diastolic pressure in the renal tissue. It is non-specific and may occur in AR, ATN or renal vein thrombosis and is reported to be associated with poor prognosis [17, 18]. The interpretation of previously reported studies is limited due to the short period of observation. Our observations, in contrast, are based on the long term follow up of a large cohort of patients with RFD. RFD in the setting of AR or ATN is an indicator of poorer graft outcome. It is a marker of more severe and more frequent episodes of acute rejections and is associated with high incidence of early and late graft loss.

Day-to-day fluctuations are common in renal grafts, even in absence of AR, and a cut-off figure of 10% increase in intra-renal indices helps to exclude the majority of patients without AR. Since there is a considerable overlap between the indices of patients with AR and those with ATN, the measurement of the increase in intra-renal indices using serial duplex scanning was more valuable than that of a single time observation. With the help of serial duplex scanning, it has become possible to detect changes in intra-renal indices well before the treatment for AR. In heralding the need for renal graft biopsy, serial duplex scanning is of great value in patients who have either a high base-line (such as those who have ATN) or low base-line indices.

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