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Original Article

Comparison between Doppler Ultrasound and Biopsy Findings in Patients with Suspected Kidney Transplant Rejection

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Abstract

Introduction: The role of Doppler ultrasound in diagnosing kidney allograft rejections is controversial. Our goal in this study was to investigate the utility of Doppler-measured resistive index (RI) as a screening tool for kidney transplant rejection.

Methods: We retrospectively studied a random sample of 188 kidney transplanted patients who had Doppler-ultrasound examination followed within two weeks by transplant biopsy. We evaluated the specificity and sensitivity of Doppler ultrasound in diagnosing rejection at different RI thresholds, using the reported biopsy findings as the gold standard.

Results: The RI values of the study population had a mean value of 0.7 ± 0.11 (mean ± SD) and a range of 0.4-1.0. There was no significant difference in the mean RI between patients with biopsy proven rejection and patients without rejection (0.68±0.09 versus 0.71±0.12, P = 0.16). The sensitivity and specificity of Doppler-measured RI in diagnosing rejection was highly variable depending on the chosen cut-off value, ranging between 4.1-98.6% and 2.6-92.2% respectively. Acceptable specificity was only achieved at the expense of very low sensitivity. Acute tubular necrosis (ATN) and interstitial edema (IE) were associated with higher RI values than other pathological entities, while very low RI values had high specificity and low sensitivity for transplanted renal artery stenosis (TRAS).

Conclusion: Doppler-measured RI lacks accuracy in diagnosing transplanted kidney rejection, resulting in poor utility of this test as a screening tool for rejection.

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Keywords: Doppler Ultrasound; Rejection; Resistive Index (RI); Transplant kidney

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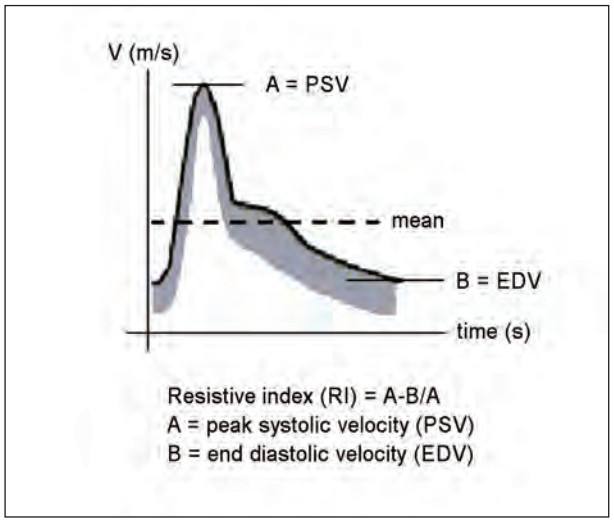
Introduction

The first renal transplantation was performed in 1954 and since then the kidney tops the list of organs transplanted. However, despite of all the advances in kidney transplantation, clinicians still deal with relatively frequent dilemmas of allograft dysfunction and usually resort to ultrasound as a first line investigative tool. The role of gray-scale ultrasonography in the management of renal dysfunction is still limited despite the dramatic improvement in the image quality that occurred over the last 20 years [1]. The information obtained from gray-scale ultrasonography remains largely anatomic. Other parameters like the increased cortical echogenicity seen in gray-scale ultrasonography have a poor sensitivity (62%) and specificity (58%) in detecting kidney diseases [2, 3].

The introduction of Doppler-ultrasound promised to improve the clinical utility of ultrasound in patients with renal dysfunction. Many publications support the utility of Doppler-ultrasound in the management of both native and transplanted kidney dysfunction [4-11]. On the other hand, opinions and data arguing against the utility of Doppler-ultrasound in differentiating various kidney diseases also exist [12-14]. Tublin *et al* argued that Doppler ultrasound's ability to detect different renal pathologies is based on the assumption that changes in the intrarenal arterial waveforms accurately reflect the subtle changes in renal vascular resistances (RVR) that occur with renal disease [1]. These changes are generally quantified using the so called Doppler ultrasounds resistive index (RI), which is equal to the difference between the peak systolic velocity and end diastolic velocity divided by the peak systolic velocity (figures 1-3).

Figure 1: Calculation of RI from the spectral waveform



Krumme *et al* studied the RI of 110 stable renal allografts, and found a mean value of 0.70 ± 0.07 (mean ± SD), with a range of 0.53-0.88 [15].

During rejection, the changes that lead to an increase in RVR and RI probably occur as a direct result of the impedance of blood flow caused by external pressure exerted on blood vessels by expanding interstitium, infiltration by inflammatory cells, edema or the process of fibrosis. Changes that occur in the vascular wall itself as a response to the injury e.g. intimal thickening or lumen narrowing by thrombus might also lead to direct change in the RVR. In acute cellular rejection there is marked interstitial infiltration with mononuclear cells and occasionally eosinophils, and disruption of the tubular basement membranes (tubulitis) by the infiltrating cells [16]. This infiltration together with the associated edema is speculated to be behind the change in the RVR that leads to elevated RI. While, and due to its direct effect on the kidney vasculature, vascular rejection might have a direct effect on RVR and RI.

Data from models of chronic kidney diseases may be extrapolated for a better understanding of the situation in chronic rejection and chronic allograft nephropathy. Professor El Nahas reported that when the endothelial cell is injured, it loses its mature anticoagulant, anti-inflammatory and anti-proliferative phenotype and acquires new pro-coagulant, pro-inflammatory and mitogenic characteristics [17]. This marks the initiation of the chronic inflammatory process. The chronicity of the process aids the overlapping of inflammation and scaring. This dual pathological process, ongoing inflammation and scaring, is speculated to be behind the increase in the renal vascular resistance that leads to elevated RI. However, unlike the acute rejection process, RI may or may not be elevated in chronic rejection. Kelcz *et al* noted that patients with chronic rejection (as well as cyclosporine toxicity) were unlikely to have RI higher than 0.80 [18].

It is generally agreed that RI is the single most reliable Doppler ultrasound parameter in detecting kidney allograft rejection [19]. However, the variability of data concerning the reliability of Doppler-calculated RI in detecting transplanted kidney rejection represents the main motivation behind conducting our study. Meyer *et al* concluded that Duplex Doppler ultrasound, although less invasive, is neither sufficiently sensitive nor specific in the diagnosis of acute rejection [12]. While Hollenbeck *et al* reported that an elevated RI has a sensitivity of 90% in detecting rejection [20]; Allen *et al* reported a lower sensitivity of 76 %, using a cut point of 0.75 [21]. Furthermore, Dupont *et al* reported that at RI cut-point of 0.9, the test had specificity for acute rejection of 89%, but a sensitivity of just 6% [14].

Figure 2: Spectral Doppler waveform obtained at the level of the interlobar artery of a stable kidney transplant with a calculated RI of 0.60

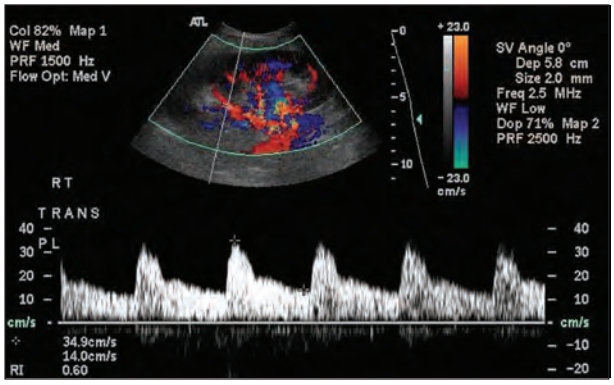


Figure 3: Spectral Doppler waveform of a transplanted kidney affected by acute tubular necrosis (ATN) and interstitial edema, with a calculated RI of 1.0

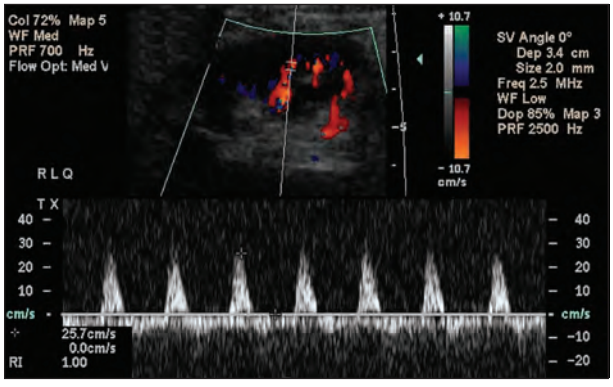


Table 1: Clinical, Doppler ultrasound and biopsy findings of the study population (N=188)

Characteristic	Details	Number (%)
Gender	Male	122 (64.9%)
	Female	66 (35.1%)
Ethnicity	White	89 (47.3%)
	Black	67 (35.7%)
	Other minorities	32 (17%)
Source of graft	Living donor	75 (40%)
	Deceased donor	133 (60%)
Immunosuppressant used	Tacrolimus	142 (75.5%)
	Cyclosporine	40 (21.3%)
	Sirolimus	6 (3.2%)
Findings suggestive of TRAS	Reported	19 (10.1%)
	Not reported	169 (89.9%)
Peri-transplant fluid collection	Present	14 (7.4%)
	Absent	174 (92.6)
Biopsy findings	Biopsy proven rejection	72 (38.3%)
	CAN	43 (22.9%)
	Interstitial fibrosis	34 (18.1%)
	Drug toxicity	14 (7.4%)
	Acute tubular necrosis	10 (5.3%)
	Interstitial nephritis	6 (3.2%)
	Interstitial edema	3 (1.6%)
	No biopsy findings	17 (9%)
BANFF classification	No rejection	116 (61.7%)
	IA	34 (18.1%)
	IB	19 (10.1%)
	IIA	7 (3.7%)
	IIB	1 (0.5%)
	Borderline rejection	11 (5.9%)

TRAS: transplanted renal artery stenosis; CAN: chronic allograft nephropathy

In this study, we compared ultrasound and biopsy findings in patients with suspected transplanted kidney rejection at INOVA Fairfax Hospital, Virginia USA, aiming to evaluate the utility of Doppler ultrasound in detecting kidney allograft rejection.

Methods

The main objective of this study was to determine the sensitivity and specificity of the Doppler-measured RI in detecting transplanted kidney rejection. Only patients who had kidney transplant biopsy within two weeks of a Doppler ultrasound study were included in the study. Out of our kidney-transplant patients' pool at Fairfax Hospital Virginia who fulfilled the inclusion criteria, we randomly selected a sample of 188 patients and retrospectively compared the reported Doppler ultrasound findings and kidney allograft biopsy findings. All the Doppler ultrasound studies were done using HDI 5000 or iU22, Phillips-ATL® Ultrasound, Bothell, Washington (USA), ultrasound systems equipped with multi-Hertz Curvilinear, 3-5 MHz and 4-7 MHz, ultrasound transducers. SPSS version 16.0 for Windows was used for the statistical analysis. We evaluated different cut-off values for the RI (0.5, 0.6, 0.7, 0.8 and 0.9) by dichotomizing patients into two groups around each cut-off value; those with RI > the cut-off value, were considered to be the test positive and those with RI ≤ the cut-off value were considered the test negative. The reported biopsy finding was considered the gold standard test. Sensitivity was calculated as the test true positive cases divided by the sum of the test true positive and the test false negative cases. Specificity was calculated as the test true negative cases divided by the sum of the test true negative and false positive cases. Accuracy was calculated as the sum of the test true positive and the test true negative cases divided by the total number of patients.

Continuous data are presented as mean ± SD and compared using t-test or one-way ANVOVA as appropriate. Categorical data are presented as frequencies and percentages and compared using X^2 and Fisher exact test.

Results

The study included 188 patients. The overall characteristics of the study population are shown (Table 1).

The RI values of the study population had a normal distribution, with a mean value of 0.7 ± 0.11 (mean ± SD) and a range of 0.4 – 1.0. There was no significant difference in the mean RI between patients taking tacrolimus, cyclosporine and sirolimus (0.69±0.12, 0.71±0.01 and 0.7±0.05 respectively, P = 0.8). There was no significant difference in the mean RI between patients reported to have peri-transplant fluid collection and patients without fluid collection (0.74±0.12 versus 0.69±0.11, P=0.9). There was no significant difference in the mean RI between patients with findings suggestive of transplanted renal artery stenosis (TRAS) and patients without such findings (0.7±0.17 versus 0.7±0.11, P = 0.97). However, we found that patients who have very low RI are more likely to have TRAS with a specificity of 99%, a sensitivity of 16%, and an accuracy of 91% at an RI cut-off value of 0.5. There was no significant difference in the mean RI between patients with and without biopsy proven rejection (0.68±0.09 versus 0.71±0.12, P = 0.16). However, the RI was found to be significantly different between different categories of graft biopsy findings other than rejection, with acute tubular necrosis (ATN)

Table 2: Mean RI values for different categories of graft biopsy findings other than rejection (P = 0.001)

	Number	Mean RI	SD
Rejection	72	0.68	0.09
Acute tubular necrosis	10	0.79	0.15
Interstitial fibrosis	34	0.69	0.10
Interstitial nephritis	6	0.75	0.20
Interstitial edema	3	0.91	0.15
Drug toxicity	14	0.66	0.10
Chronic allograft nephropathy	43	0.69	0.09
No biopsy findings	17	0.66	0.12

Table 3: sensitivity, specificity and accuracy of RI in diagnosing kidney transplant rejection at different RI thresholds

Cut-off value for RI	Sensitivity (%)	Specificity (%)	Accuracy (%)
0.5	98.6	2.6	39.4
0.6	80.6	19.0	42.6
0.7	31.9	57.8	47.9
0.8	6.9	85.3	55.3
0.9	4.1	92.2	58.5

and interstitial edema (IE) having higher RI values than other categories (Table 2).

The sensitivity of RI in diagnosing rejection decreased and its specificity increased with increasing RI thresholds (Table 3). Using an RI threshold of 0.5 resulted in high sensitivity (98.6%) at the cost of very low specificity (2.6%), while using an RI threshold of 0.9 resulted in high specificity (92.2%) at the cost of very low sensitivity (4.1%).

Discussion

The mean RI value in our study was found to be similar to what has been reported by Krumme *et al* [15], although they did their study on patients with stable renal function while our sample was comprised mainly of patients with worsening graft function.

The lack of difference in the mean RI between patients with and without biopsy proven rejection correlates with the data reported by Dupont *et al* who stated that the average RI in the rejection group was not higher than in controls [14].

When we considered histopathological findings other than allograft rejection, we observed that ATN and IE had a relatively higher mean RI (>0.8) compared to other categories. However, these findings should be considered with caution due to the reported overlapping between these pathological entities, as some patients were reported to have IE with ATN and some reported to have ATN with interstitial nephritis.

Many different values were reported in literature for the sensitivity of Doppler ultrasound in diagnosing transplanted kidney rejection. It is apparent from this study that the Doppler sensitivity is greatly affected by the chosen RI threshold. Sensitivity was found to be 98% at an RI threshold of 0.5; as this threshold was increased, sensitivity dropped sharply reaching a value of 4.1% at an RI threshold of 0.9. The same findings were reported by Dupont *et al* [14], which would explain the variability found in the literature.

Despite the high sensitivity achieved with a low RI threshold of 0.5, the value of Doppler ultrasound as a screening tool for rejection remains poor. This is due to the fact that at such a low RI threshold, test specificity is very low (2.6%), with a high false positive rate of 97.5%. The poor utility of Doppler ultrasound as a screening tool for rejection is reflected by a test accuracy of only 39.4-58.5%.

The low accuracy of Doppler-measured RI in detecting rejection may be attributed to many factors. Overlapping of pathological processes often exists. The observed RI can be the net resultant effect of this overlap rather than the absolute effect of any single process. Thus the effect

of one pathological process can be masked or altered by the effect of another.

Also, blood flow through the kidneys forms a closed circuit that starts at the renal artery and ends at the renal vein. Any pathological process acting at any point of this continuum will affect the hemodynamics of the blood flowing through the entire circuit. By convention and for standardization, Doppler sampling for RI measurement is taken at the level of the interlobar and arcuate arteries. Proximally acting pathologies like renal artery stenosis tends to increase resistance to blood flow. If the Doppler sampling is taken immediately before or at the stenotic segment, high blood-flow velocities can be detected. The energy loss at the point of stenosis will lead to a decrease in the blood pressure and thus dampen down the blood flow in the distal vessel past the point of stenosis. This dampening will result in very weak upstroke leading to the formation of the so-called Tardus Parvus waveform and a very low RI. Pathological processes that affect the renal parenchyma distal to the arcuate artery tend to increase the pressure at the sampling point leading to a high RI. When rejection (acts distally and tends to increase the RI) occurs concomitantly with renal artery stenosis (acts proximally and tends to decrease the RI) the net result is often a falsely low RI thus masking the effect of rejection on the RI. As a matter of fact, we found that a very low RI (<0.5) can be considered a strong clue pointing towards the presence of TRAS with a specificity of 99% and an accuracy of 90%, but very low sensitivity at 16 %.

In addition, the variations in RI cannot be solely due to the pathological processes involving the transplanted kidney. While deprived of neuronal control, the renal vascular bed remains under hormonal control mechanisms besides its autoregulation. The effect of humeral or pharmacological factors on renal RI during episodes of rejection cannot be ruled out. In addition, the state of the circulation, the presence of fever and variability in heart rate are all factors that might affect the amount of blood flowing through the transplanted kidney and accordingly alter the RI value. Mostbeck *et al* stated that an increase in heart rate decreases the RI [22]. In addition, Pozniak *et al* stated that bradycardia and general hypotension also affect the RI value [23]. Many transplant patients are under antihypertensive medications that can lower blood pressure and heart rate, at least from the pathological hypertensive range to the normal range. This pharmacological effect may be equivalent to hypotension, and may lead to variations in RI values.

Inter-patient variation may also lead to alterations in the RI value. Recipient age, donor age and graft age all lead to significant variations in the baseline value of RI. Krumme *et al* reported a statistically significant correlation between RI value and recipient age [15]. In this study, other factors that might contribute to variability include ethnicity, gender and the source of the graft.

In addition, the Doppler-measured RI values in this study have been measured by different sonographist, due the retrospective nature of the study. Hence, the chance for inter-observer error is high.

Conclusion

There was no significant difference in the mean RI value between patients with and without biopsy proven rejection. The sensitivity and specificity of Doppler-measured RI in diagnosing rejection is highly variable depending on the chosen cut-off value. Acceptable specificity is only achieved at the expense of very low sensitivity, resulting in poor utility of this test as a screening tool for rejection. Very high RI values were found to be associated with edematous allograft conditions such as IE and ATN, while very low RI values had high specificity and low sensitivity for TRAS.

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