นิพนธ์ต้นฉบับ

Differentiation between acute renal allograft rejection and acute tubular necrosis by renal vascular transit time

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Background : *Renal biopsy has been the investigation of choice for differentiating renal allograft rejection (AR) from acute tubular necrosis (ATN) during acute renal allograft dysfunction. However, the procedure is invasive and not suitable for repeated measurements. It has been demonstrated that renal microcirculation was more impaired in AR than in ATN. Renal vascular transit time (RVTT), calculated by deconvolution analysis, has been shown to represent the renal microcirculation.*

Objective : *We compared RVTT in AR and in ATN groups during the first month post-transplantation.*

Setting : *Division of Nephrology, Department of Medicine and Division of Nuclear Medicine, Department of Radiology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.*

Design : *Retrospective study*

Patients : *Thirteen transplanted patients with acute renal allogroft dysfunction (AAD) during the first month postoperation*

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Methods : *The studied population was divided into two groups, AR and ATN, based on clinical and/or pathological criteria. ^{99m}Technetium-labeled diethylenetriamine-pentaacetic acid (^{99m}Tc-DTPA) renal scintigraphy and RVTT determination were performed on the first and seventh postoperative days and at any time when there was clinical indication of AR.*

Results : *There were 5 patients in the AR group and 8 patients in the ATN group. The values (mean ± SEM) of RVTT in the AR group were significantly higher than in the ATN group (21.7 ± 6.70 sec. vs. 7.3 ± 1.27 sec. ; $p < 0.05$). Patients in the AR group, when compared with the ATN group, also had a higher increment of RVTT from the baseline levels (16.3 ± 6.44 vs. 1.6 ± 1.34 sec.; $p < 0.05$).*

Conclusion : *RVTT is a very useful noninvasive tool for diagnosing AAD secondary to AR.*

Key words : *Renal scintigraphy, Renal vascular transit time, Acute renal allograft dysfunction, Acute rejection, Acute tubular necrosis.*

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ธวัชชัย ชัยวัฒนรัตน์, ยิ่งยศ อวิหิงสานนท์, ศศิธร ศิริสาลิโภชน์, สมชาย เอี่ยมอ่อง, สุพจน์ บุญวิสุทธิ์, เสาวลักษณ์ ชูศิลป์, เกรียง ตั้งสง่า. การวินิจฉัยแยกโรคระหว่างภาวะสลัดกราฟท์กับ acute tubular necrosis **ในผู้ป่วยปลูกถ่ายไต โดยใช้** renal vascular transit time. **จุฬาลงกรณ์เวชสาร** 2542 ธ.ค; 43 (12): 873-83

เหตุผลของการทำวิจัย : *การวินิจฉัยแยกโรคระหว่างภาวะสลัดกราฟท์กับภาวะ acute tubular necrosis (ATN) ในผู้ป่วยที่มีภาวะไตวายภายหลังการปลูกถ่ายไต ต้องใช้การเจาะเนื้อไตเป็นวิธีหลัก อย่างไรก็ตามการเจาะเนื้อไตเป็นวิธีที่มีความเสี่ยงและไม่เหมาะกับการตรวจหลาย ๆ ครั้ง ได้มีการหา Renal vascular transit time (RVTT) เพื่อใช้ทำนายระยะเวลาของการไหลเวียนของเลือดภายในไต โดยพบว่าในภาวะสลัดกราฟท์จะมีการไหลเวียนของเลือดในไตเลวลงมากเมื่อเปรียบเทียบกับใน ATN*

วัตถุประสงค์ : *เพื่อเปรียบเทียบ RVTT ในภาวะสลัดกราฟท์กับภาวะ ATN ในผู้ป่วยหลังผ่าตัดปลูกถ่ายไต 1 เดือนแรก*

สถานที่ที่ทำการศึกษา : *ภาควิชาอายุรศาสตร์ และภาควิชารังสีวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย*

รูปแบบการวิจัย : *การศึกษาย้อนหลัง*

ประชากรที่ศึกษา : *ผู้ป่วยที่มีภาวะไตวายภายหลังการปลูกถ่ายไต 1 เดือนแรก จำนวน 13 ราย*

วิธีการศึกษา-วัดผล : *แบ่งผู้ป่วยเป็น 2 กลุ่ม ได้แก่ กลุ่มที่เกิดภาวะสลัดกราฟท์กับกลุ่ม ATN โดยใช้เกณฑ์ทางพยาธิวิทยาร่วมกับอาการทางคลินิก ได้ส่งตรวจ ^{99m}Techneciumlabeled diethylenetriampentaacetic acid (^{99m}Tc-DTPA) renal scintigraphy และหาค่า RVTT ในวันที่ 1 และ 7 หลังผ่าตัด และส่งตรวจเพิ่มทุกครั้งที่อาการเข้าได้กับภาวะสลัดกราฟท์*

ผลการศึกษา : *ผู้ป่วยที่มีภาวะสลัดกราฟท์ (กลุ่มที่ 1) มี 5 ราย และผู้ป่วยที่มี ATN (กลุ่มที่ 2) มี 8 ราย ค่าเฉลี่ย (mean $\pm$ SEM) RVTT ของกลุ่มที่ 1 ยาวกว่ากลุ่มที่ 2 อย่างมีนัยสำคัญ (21.7$\pm$ 6.70 และ 7.3$\pm$1.27 วินาที; P< 0.05) การเพิ่มขึ้นของ RVTT เทียบกับค่าตั้งต้นในกลุ่มที่ 1 มีค่ามากกว่ากลุ่มที่ 2 อย่างมีนัยสำคัญ (16.3 $\pm$ 6.44 vs 1.6 $\pm$1.34 วินาที; P < 0.05)*

วิจารณ์และสรุปผล : *สามารถใช้ RVTT ในการวินิจฉัยแยกโรคระหว่างภาวะสลัดกราฟท์กับภาวะ ATN ในผู้ป่วยหลังผ่าตัดปลูกถ่ายไตได้*

Acute renal allograft dysfunction (AAD: defined as persistent azotemia and/or oliguria for more than 2 weeks) is common during the first month post-transplantation. The major pathophysiologic mechanisms of this event are acute rejection (AR), acute tubular necrosis (ATN), vascular thrombosis and ureteric obstruction.[1] Doppler ultrasonogram examination of the transplanted kidneys are useful for detection of vascular thrombosis and ureteric obstruction. However, clinical criteria and ultrasonograms are not always helpful for differentiating AR from ATN.[2,3] Kidney allograft biopsy is still the definite diagnosis of AR despite its invasive procedure. In AR, vascular endothelial injury is a consistent finding. This can activate endothelin release,[4] coagulation pathway and platelet deposition along the allograft blood vessels.[5,6] Histopathological changes in AR are endothelial hyperplasia, fibrinoid necrosis, and polymorphonuclear cell infiltration of the intima and media of vascular walls.[7] It has been shown that in AR, impairment of renal microcirculation can occur even before the decrease in urine output.[8] This is in contrast to the changes in ATN in which luminal obstruction with necrotic tubular cells is predominant but renal microcirculation is relatively spared.[9,10]

Several scintigraphic methods have been used to assess renal microcirculation. These are ^{99m}Tc-DTPA study of vascular blood flow index[11,12] or aorto-renal transit time.[13,14] However, these methods require a rapid bolus injection of the radioisotopes and are subject to inaccuracy of the result if the injection rate is suboptimal.[15] To eliminate the need for rapid bolus injection, deconvolution analysis of renogram data has been introduced for calculation of renal vascular transit time (RVTT).[16,17] This technique has also been applied to analyzing renal,[18,19] cardiac, and pulmonary blood flow data. Recently, we studied RVTT in post-renal transplant patients who developed renal dysfunction of various etiologies and found that RVTT can be used to differentiate AR from ATN.[20] Nevertheless, we did not pay attention to the first postoperative month in which both entities commonly occur.

We speculate that RVTT is helpful, especially in the first month post - transplantation, for distinguishing AR from ATN. It might be used as a noninvasive test and substitute for invasive renal allograft biopsy for the diagnosis of AR.

Patients and Methods

Eighty case records of renal transplantation performed at Chulalongkorn University Hospital during 1994 –1999 were reviewed. Thirteen cases (16%) developed acute allograft dysfunction during the first postoperative month and were enrolled into the study. Exclusion criteria were :1. presence of cyclosporin levels above 500 ng/mL[21] during the graft dysfunction period, 2. vascular or urological complications as shown by renal scintigrams or ultrasonograms. ^{99m}Tc-DTPA and ^{131}I-hippuran renal scintigrams were performed on the first and seventh postoperative days and whenever AR was suspected clinically. Renal biopsies were performed during the graft dysfunction period if there was clinical evidence suggestive of AR. The studied population was divided into 2 groups. Group 1 had biopsy-proven AR and had all of the following diagnostic criteria for AR as described in the "Cooperative Clinical Trial in Transplantation" (CCTT) system[22]: 1) Peak serum creatinine (Scr) during the first 14 days after onset of suspected AR was higher than 120 percent of baseline. 2) Clinical

improvement developed after antirejection therapy (0.5 g of methylprednisolone, antilymphocyte globulin, or OKT3). 3) Patients had one or both of the following: a) serum creatinine returned to within 20 percent of baseline within 14 days. b) serum creatinine on day 14 was lower than the highest levels during the first 3 days of rejection and was below 5 mg/dL. Group 2 had all of the following diagnostic criteria for ATN:[23] 1. Kidney donors had required high-dose vasopressor ($\geq$ 10 μg/kg/min) and had shown urine output below 30 mL/h during the braindead period. 2. Total ischemic time of renal allograft exceeded 12 h. 3. Kidney recipients must have two or more of the following characteristics: a) postoperative urine output below 60 mL/h, b) postoperative serum creatinine above 2 mg/dL for more than 1 week and decreased to 2 mg/dL or less within 4 weeks, c) dialysis therapy was required to correct complications from renal dysfunction.

Histopathologic criteria for grading the severity of AR

The CCTT histopathologic criteria[22] consist of 3 grades. Grade I: presence of interstitial mononuclear infiltration in the renal cortical tissues. In addition, there are at least two of the following three features: tubular interstitial edema, tubular degeneration/injury, or tubulitis. Grade II: presence of mononuclear cell infiltration at the endothelial layer of arteries or arterioles (endothelialitis or endarteritis). Grade III: presence of mononuclear cells and edema at all layers, or of fibrinoid necrosis of arterial or arteriolar walls. This may be accompanied by thrombosis, parenchymal necrosis, or hemorrhage.

Imaging technique

The details of the imaging technique have previously been described[20]. Briefly, the gamma camera (starcam 400AC, General Electric, USA) was positioned anterior to the patient over the renal allograft in the pelvic cavity, and over the distal part of the abdominal aorta. The image acquisition was started immediately after intravenous (IV.) injection of 10 mCi of ^{99m}Tc-DTPA through an anti-cubital vein. RVTT was calculated by one of our co-investigators (S.S.) who had no knowledge as to the population studied. Deconvolution analysis of the renal blood flow curve was employed for RVTT calculation.[20]

Statistical analysis

Comparison between the two groups was made using the Mann-Whitney test with the SPSS program for Windows 95. The RVTT and RVTTdiff (defined as difference between RVTT during allograft dysfunction and RVTT at baseline) were calculated. Data were expressed as mean $\pm$ SEM.

Results

Group 1 (AR) comprised 5 patients (Table 1). aged 45 $\pm$ 4.1 years. There were three males and two females. Four cases were transplanted with cadaveric kidneys and one with a living-related kidney. There were two cases of grade 1, two of grade 2 and one of grade 3 of the CCTT pathologic gradings.[22] The patient with (pathologic) grade 3 rejection had a markedly prolonged RVTT (38.6 sec.) and did not respond to antirejection therapy and finally died from sepsis. One of the AR grade 1 patients developed biopsy-proven AR after recovery from postoperative ATN.

Group 2 (ATN) consisted of 8 patients (Table 1), aged 34 ± 2.8 years. Five were male and three were female. All had cadaveric kidney transplantations and their allografts effectively functioned at the fourth week. The mean total ischemic time of group 2 was longer than that of group 1 but not statistically significant (17.5 ± 1.65 vs 10.0 ± 3.27 hours; $p > 0.05$). Peak serum creatinine and urine output were not different between both groups (9.6 ± 0.8 vs 9.4 ± 2.2 mg/dL and 1.3 ± 0.4 vs 1.2 ± 0.8 L/day; $p > 0.05$). Whole blood cyclosporin A trough levels were comparable (298 ± 14 vs 267 ± 23 ng/mL; $p > 0.05$).

Table 1. Demographic characteristics in 13 cases of acute allograft dysfunction according to study groups.

	Acute rejection (N = 5)	Acute tubular necrosis (N = 8)	
CKT : LKT	4:1	8:0	
Age – yr			
Mean	45 ± 4.1	34 ± 2.8	P <0.05
Range	31 – 53	30 – 51	
Sex-M : F	3:2	5:3	
No. of cases with symptom & sign of AR*	3	None	
Total ischemic time (h)			
Mean ± SEM	10 ± 3.27	17.5 ± 1.65	P = NS
Range	0.5 –14.5	13.0 – 21.5	
Peak serum creatinine (mg/dL)			
Mean ± SEM	9.4 ± 2.2	9.6 ± 0.8	P = NS
Range	3.0 – 12.5	7.2 – 12.6	
Urine volume during 1st day of AAD (L/ day)			
Mean ± SEM	1.2 ± 0.8	1.3 ± 0.4	P = NS
Range	0.1 – 2.6	0.2 – 1.8	
Number of hemodialysis during AAD (sessions performed)	2.6 ± 2	2 ± 0.5	P = NS
CsA levels (ng/mL)	267 ± 23	298 ± 14	P = NS

CKT = cadaveric kidney transplant, LKT = living-related kidney transplant
CsA = cyclosporin A, AAD = acute renal allograft dysfunction

* Fever, graft tender, abnormal urine sediment

The mean RVTT in group 1 (21.7 ± 6.70 sec) was significantly longer than in group 2 (7.3 ± 1.27 sec), $p < 0.05$ (Fig.1). The RVTTdiff was also greater in group 1 (16.3 ± 6.44 sec) than in group 2 (1.6 ± 1.34 sec), $p < 0.05$ (Fig. 2). In the patient who had AR after ATN, the RVTT was markedly increased during AR (Fig. 3) and declined to normal after antirejection therapy. No patient in group 2 had an RVTTdiff of more than 4 seconds.

Using the previously reported cut-off value of RVTT at 12.8 seconds as the upper limit of controls,[20] AR was diagnosed with a 60 percent sensitivity and a 100 percent specificity. The positive predictive value was 100 percent and the negative predictive value was 77 percent. In addition, using the RVTTdiff of more than 4 seconds, AR was diagnosed with an 80 percent sensitivity and a 100 percent specificity. The positive predictive value was 100 percent and the negative predictive value was 86 percent.

Discussion

In this study, about 16 % of the renal transplant patients developed AAD within the first postoperative month; five cases (38%) were in group 1 (AR) and eight cases (62%) were in group 2 (ATN). The total ischemic time of allograft, peak serum creatinine during the AAD period, urine output of recipients during the first postoperative day, and cyclosporin levels were not useful for distinguishing AR from ATN (Table 1). In group 1, only three out of five cases (60%) had the clinical characteristics of AR including fever, graft tenderness, and abnormal urine sediment.

Interestingly, our results demonstrated that renal circulating time is longer in AR than in ATN. We also found that an RVTTdiff exceeding 4 seconds was exclusively found in group 1. Thus, RVTT diff provides a more sensitive tool than RVTT for diagnosing AR. This could imply that in order to diagnose AR, RVTT during AAD relative to RVTT at baseline is more

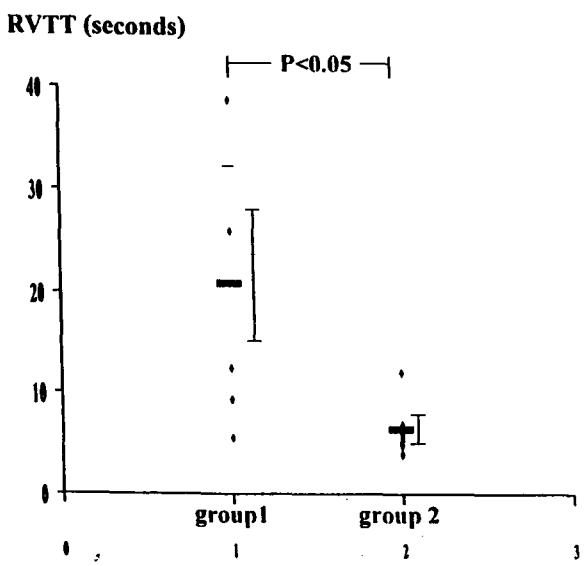

Figure 1. Individual values of RVTT in group (AR) and group 2 (ATN) the horizontal bars represent mean values of each group. The "vertical" bars represent mean ± SEM

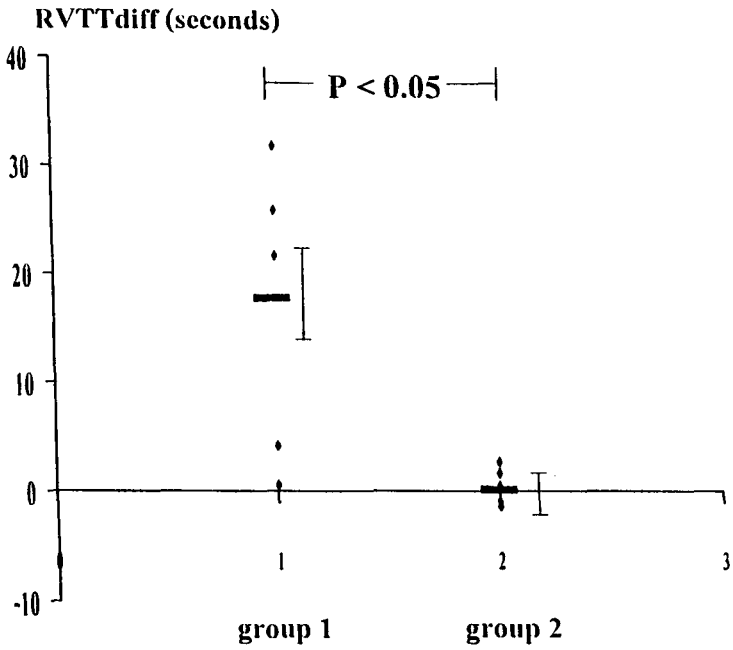

Figure 2. Individual values of RVTTdiff* in group 1 (AR) and group 2 (ATN) the horizontal bars represent mean values of each group.
*defined by RVTT during allograft dysfunction - RVTT baseline.
The "vertical" bars represent mean ± SEM

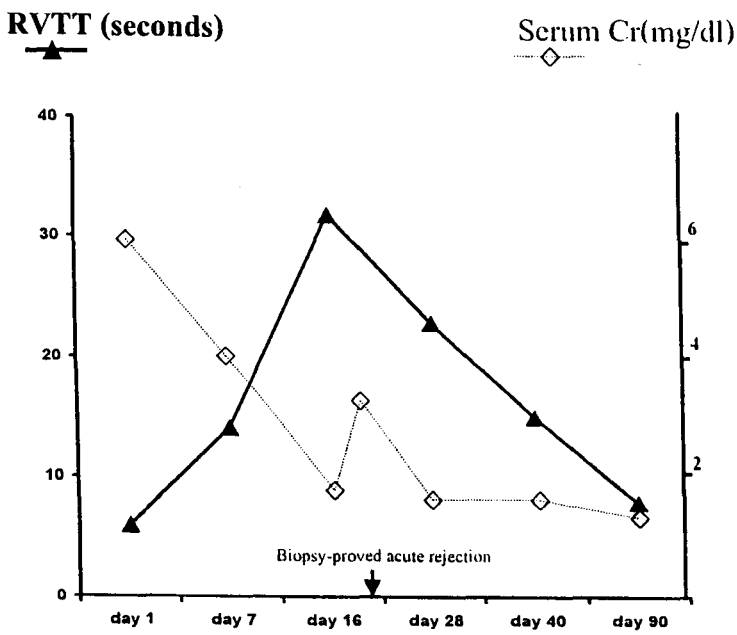

Figure 3. RVTT values of a patient who had acute rejection after postoperative ATN. The RVTT correlates very well with the course of the disease.

helpful than a single value. Our data supported the previous observation that RVTT is a good indicator of renal circulatory change and a time value above 12.8 seconds is characteristic of AR.[20]

The RVTT could be prolonged even in renal allografts of patients having ATN preceding AR. As shown in the Results, one patient in group 1 had ATN prior to the development of AR. RVTT was below the upper normal limit during ATN. Thereafter, when she developed AR, RVTT became prolonged. The RVTT exceeding 12.8 seconds which coincides with histologically-proved AR and the second increment in serum creatinine (Fig. 3). Therefore, RVTT might be useful for diagnosing AR even in cases with ATN. RVTT might also correlate with the severity of the AR. The one case of grade III AR had a markedly prolonged RVTT. Unfortunately, our data was too limited to illustrate the correlation between RVTT and the renal histopathologic change of AR.

The increment of RVTT during AR may represent the prolongation of intrarenal circulating time due to endothelial injury and endothelin release in the allograft. On the contrary, a normal level of RVTT in ATN may imply the preserved renal microcirculation.

The RVTT provides many advantages. It is noninvasive, reliable, and reproducible. The test can be repeated as often as required, particularly during the AAD period. Fig.4 shows our proposed algorithm for investigation of postoperative AAD. Clinical evaluation, ^{99m}Tc-DTPA renal scintigraphy and doppler ultrasonograms are helpful for diagnosis of ureteral obstruction, or vascular thrombosis of the renal

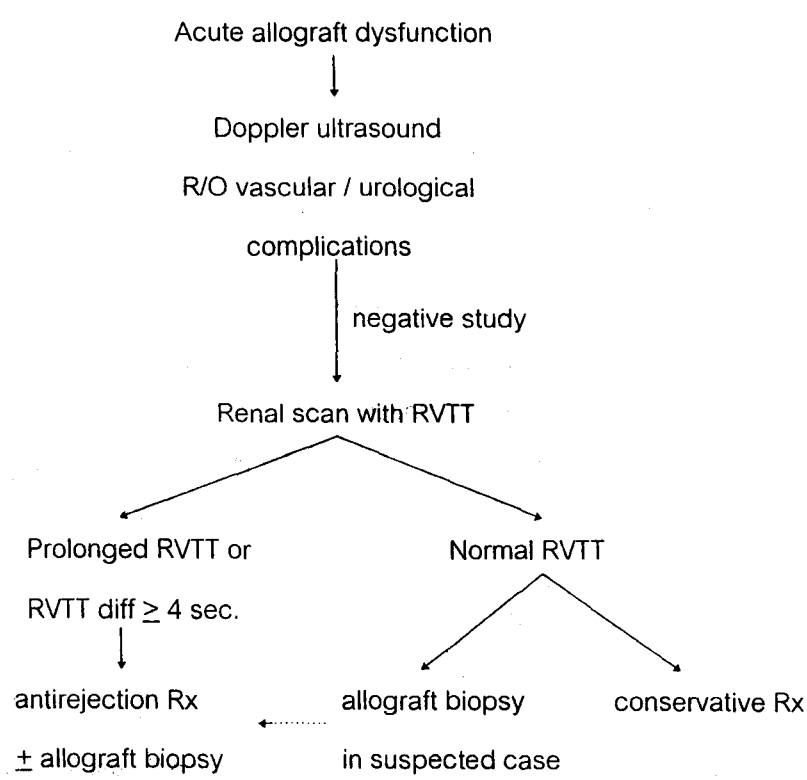

Figure 4. Diagnostic algorithm for the differential diagnosis of acute allograft dysfunction.

RVTT study should be performed routinely. If RVTT is prolonged, especially exceeding 12.8 seconds and/or increases by more than 4 seconds from the baseline values, AR is suspected and antirejection therapy should be administered immediately. If RVTT is normal, a diagnosis of AR is less likely but can not be completely ruled out. In the latter situation, a renal biopsy should be considered.

In conclusion, we have shown that the RVTT is a very useful and noninvasive tool for diagnosing acute rejection during acute allograft dysfunction.

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