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Dialysis modality and the risk of allograft thrombosis in adult renal transplant recipients

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Background. Renal vascular thrombosis (RVT) is a rare but catastrophic complication of renal transplantation. Although a plethora of risk factors has been identified, a large proportion of cases of RVT is unexplained. Uremic coagulopathy and dialysis modality may predispose to RVT. We investigated the impact of the pretransplant dialysis modality on the risk of RVT in adult renal transplant recipients.

Methods. Renal transplant recipients (age 18 years or more) who were enrolled in the national registry between 1990 and 1996 ($N = 84{,}513$) were evaluated for RVT occurring within 30 days of transplantation. Each case was matched with two controls from the same transplant center and with the year of transplantation. The association between RVT and 18 factors was studied with multivariate conditional logistic regression.

Results. Forty-nine percent of all cases of RVT (365 out of 743) occurred in repeat transplant recipients with an adjusted odds ratio (OR) of 5.72 compared with first transplants ($P < 0.001$). There were a significantly higher odds of RVT in peritoneal dialysis (PD)-compared with hemodialysis (HD)-treated patients (OR = 1.87, $P = 0.001$). Change in dialysis modality was an independent predictor of RVT: switching from HD to PD (OR = 3.59, $P < 0.001$) and from PD to HD (OR = 1.62, $P = 0.047$). Compared with primary transplant recipients on HD (OR = 1.00), the highest odds of RVT were in repeat transplant recipients treated with PD (OR = 12.95, $P < 0.001$) and HD (OR = 4.50, $P < 0.001$). Other independent predictors of RVT were preemptive transplantation, relatively young and old donor age, diabetes mellitus and systemic lupus erythematosus as causes of end-stage renal disease, recipient gender, and lower panel reactive antibody levels (PRAs).

Conclusions. The strongest risk factors for RVT were retransplantation and prior PD treatment. Prevention of RVT with perioperative anticoagulation should be studied in patients who have a constellation of the identified risk factors.

Key words: kidney transplantation, renal graft, uremic coagulopathy, hemodialysis, perioperative anticoagulation, vascular thrombosis.

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Allograft vascular thrombosis is a catastrophic complication of kidney transplantation. Graft thrombosis is the most common in the early postoperative period, often presenting as primary nonfunction or oligoanuric graft dysfunction. Renal angiography or surgical exploration of the allograft bed [1, 2] establishes a definite diagnosis. There is no effective treatment, and in most cases, transplant nephrectomy is required [2–5]. Graft loss caused by primary renal vascular thrombosis (RVT) affects 0.4 to 7.0% of renal transplants, accounting for a significant proportion of early graft losses [2, 6–11].

In addition to the well-established systemic hypercoagulable states, other risk factors for RVT include technical problems during organ procurement and vascular anastomosis, acute rejection, extremes of donor age, perioperative hemodynamics, multiple donor renal arteries, primary cause of end-stage renal disease (ESRD), pretransplant thrombocytosis, high hematocrit and use of erythropoietin, and a history of prior renal transplantation [2, 8, 11–18]. Several investigators have reported a threefold to fourfold increase in the incidence of RVT in renal transplant recipients treated with cyclosporine (CsA) when compared with recipients who received only azathioprine and prednisone [2, 9, 12, 19]. More recently, attention has been drawn to antiphospholipid antibody syndromes, factor V Leiden mutation, and hyperhomocysteinemia as possible causes of RVT [4, 6, 20–24].

Despite the plethora of risk factors, a significant proportion of RVT occurs in the absence of any established risk factors, suggesting the possibility of unidentified predisposing factors. Peritoneal dialysis (PD) has been implicated as an etiological factor for RVT [25]. PD may be a predisposing factor to RVT by causing diffuse elevation of the activities of plasma procoagulant factors [26]. In addition, patients receiving PD demonstrate increased hemostatic tendency because of hemoconcentration resulting from efficient control of extracellular volume

(ECV) [27]. However, any role of pretransplant PD has remained controversial because several studies have found no association between the mode of pretransplant dialysis and RVT [7, 28, 29].

The purpose of this study was to investigate the risk factors associated with RVT in adult renal transplant recipients who were registered in the national transplant and dialysis database. We specifically address the question of whether pretransplant PD is associated with an increased risk of RVT compared with hemodialysis (HD).

METHODS

The study was based on transplant data collected by the United Network for Organ Sharing (UNOS) and the dialysis treatment data in the U.S. Renal Data System (USRDS). We identified all cases of early (30 days or less) graft failure in renal transplants performed between 1990 and 1996. Case definition was based on the individual transplant center report to the UNOS on the kidney transplant recipient registration and follow-up forms, which were completed at the time of kidney transplantation, after discharge from the transplant hospitalization, and during follow-up. A study case was defined as graft loss occurring within 30 days of renal transplantation, with the primary cause of graft loss coded as "renal vascular thrombosis." Each case was matched with two controls (1:2 matching). The controls chosen for each case were renal transplants performed at the same transplant center and in the same year. The pretransplant dialysis modality, sequence, and duration of dialysis modality for each case and its controls were identified in the ESRD modality sequence database. Multiorgan transplant recipients and those younger than 18 years at the time of transplantation were excluded from the study. From a total of 751 index cases, we excluded eight patients who were missing essential data, leaving 743 eligible cases for whom 1486 appropriate controls were selected. A matching ratio of one case to two controls was successfully accomplished in all cases. Six controls were excluded because of missing data. The final study sample ($N = 2223$) consisted of 743 cases and 1480 controls.

Univariate analysis of baseline characteristics was performed with the chi-square (categorical variables) and the *t*-test (continuous variables). In order to obtain a clear measure of the association between pretransplant dialysis mode and RVT, we used a noninteractive multivariate model in which the study subjects were divided into seven groups according to their pretransplant modality history and sequence (Table 1). The seven study groups were primary transplant recipients who had been treated with HD only (group I) or with PD only (group II), had switched from HD to PD (group III) or from PD to HD (group IV), repeat renal transplant recipients on HD (group V) or PD (group VI), and preemptive renal transplantation without preceding dialysis (group VII).

The multivariate analysis was based on the conditional logistic regression for matched case-control data in which the log odds of RVT were the dependent variables. The independent variables ($N = 18$) were pretransplant dialysis modality and duration; donor age, gender, race and cause of death; donor type (living vs. cadaveric); recipient age, race, gender, and cause of ESRD; HLA matching; cold and warm ischemia time; historical peak panel reactive antibody level (PRA); donor/recipient cytomegalovirus antibody (CMV) match; recipient body mass index; history of prior renal transplant; and history of preemptive transplantation.

The odds ratio (OR) of RVT and the corresponding 95% confidence intervals were obtained from the conditional logistic regression model according to the following derivation: Odds $= 1/\{1 + \exp[-(\beta_0 + \beta_1\chi_1 + \ldots \ldots + \beta_j\chi_j)]\}$ and the log (OR) for RVT $= \beta_1(\chi^C_1 - \chi^N_1) + \beta_2(\chi^C_2 - \chi^N_2)$ for case (C) versus control (N). The notation χ_j is the value of the predictor variable of interest "j," and β_j is its coefficient in the logistic model. The value χ_j was either the original value of the characteristic "j" or an indicator of the level of its classification. Several variables were classified according to ranges. For example, donor age was classified as 0 to 6, 7 to 12, 13 to 44, 45 to 54, and 55 years or more. The choice of the reference group was based on natural order of the variable or the largest category; for example, for cold ischemia time, 0 to 12 hours was used as the reference with an assigned OR of 1.00. An OR greater than 1.00 indicates increased risk for RVT, and an OR less than 1.00 suggests a protective effect against RVT relative to the reference group.

RESULTS

Between 1990 and 1996, a total of 84,513 solitary renal transplants were performed in recipients aged 18 years or more. The study sample (total $N = 2223$) consisted of 743 cases of RVT and 1480 controls from 171 transplant programs. At the time of transplantation, 67.0% of study subjects ($N = 1489$) were receiving maintenance HD; 22.6% ($N = 502$) were on PD, and 10.4% ($N = 231$) received preemptive renal transplantation. The incidence of RVT in the first 30 days after transplantation was 0.89% ($N = 751$). RVT accounted for 17.4% of all graft failures in that period. Sixteen percent of the cases of RVT ($N = 107$) occurred within the first 24 hours of the transplant procedure, with the cumulating frequency rising to 62 and 89% by postoperative day 10 and 20, respectively. The median time from transplantation to RVT was eight days.

Table 2 shows the distribution of baseline characteris-

Table 1. Classification of study subjects according to pretransplant dialysis modality and prior renal transplant status

Study group	Subjects	Prior renal transplant	Cases	Controls	Mean duration of dialysis *months*
			N (%)		
I	HD	No	161 (7.2)	690 (31.0)	27.4 (±31.6)
II	PD	No	63 (2.8)	142 (6.4)	17 (±15.6)
III	Switched from HD to PD	No	60 (2.7)	75 (3.4)	30.1 (±27.3)
IV	Switched from PD to HD	No	32 (1.4)	85 (3.8)	25.2 (±29.8)
V	HD	Yes	249 (11.2)	272 (12.2)	30.1 (±23.7)
VI	PD	Yes	116 (5.2)	46 (2.1)	32.0 (±30.5)
VII	No prior dialysis	No	62 (2.8)	170 (7.7)	
	All		743 (33.4)	1,480 (66.6)	27.9 (±29.9)

tics between cases and controls. The study groups were unbalanced with respect to several baseline characteristics, including the pretransplant mode of dialysis, duration of dialysis, recipient age, the number of HLA DR mismatches, and cold ischemia time. The cases were more likely to be on PD, had longer periods of pretransplant dialysis, were slightly younger at transplantation, had longer cold ischemia times, and had a statistically greater number of HLA DR mismatches.

There were substantial differences among the study groups with respect to the mode and the duration of dialysis prior to transplantation (Table 1). Among primary transplant recipients, PD-treated patients tended to have spent less time on dialysis prior to transplantation (17.0 ± 15.6 months) compared with 27.4 ± 31.6 months for HD-treated patients ($P < 0.001$). There was little difference in the duration of dialysis treatment between HD and PD among repeat transplant recipients.

The results of the multivariate analysis of the risk of RVT are shown in Table 3. Using patients receiving pretransplant HD as the reference group (OR = 1.00), primary transplant recipients on PD at the time of transplantation had a significantly higher risk of RVT (OR = 1.87, $P = 0.001$). A change of dialysis modality was also an independent predictor of RVT. Among primary renal transplant recipients, switching from HD to PD was the strongest predictor of RVT. When the pretransplant dialysis modality switch was from HD to PD, the odds of RVT was more than threefold higher than that of HD patients who never switched (OR = 3.59, $P < 0.001$). Primary renal transplant recipients who switched from PD to HD had an odds ratio of RVT that was 62% higher than that of HD patients, who never switched dialysis modality (OR = 1.62, $P = 0.047$).

Allograft thrombosis is most likely to occur in the first few days after transplantation; therefore, the certainty of diagnosis is greatest for the early cases. Because we could not confirm that all reporting transplant centers verified their diagnosis of RVT with renal angiography or surgical exploration, we performed a subanalysis of subjects who were most likely to be true cases of RVT, that is, those in which the diagnosis was made in the first 96-hours post-transplantation. In this series of early cases ($N = 289$, 39% of all cases) and their controls, the excess risk of RVT with PD relative to HD was also evident (RR = 2.60, $P = 0.004$).

Forty-nine percent of all cases of RVT occurred in repeat transplant recipients. The risk of RVT among repeat transplant patients varies by dialysis modality. Using primary transplant recipients on HD as the reference group (OR = 1.00), repeat transplant recipients on HD had an OR of 4.50 ($P < 0.001$), and those on PD had an OR of 12.95 ($P < 0.001$). Thus, the joint effect of PD and retransplantation appears to be synergistic (multiplicative) on the risk of RVT.

Patients who underwent kidney transplantation with no prior dialysis history (preemptive transplantation, study group VII) had a higher likelihood of RVT (OR = 1.66, $P = 0.008$) compared with primary transplant recipients treated with only HD before transplantation.

Donor age was associated with RVT in a nonlinear fashion. The donor age effect was highest at the youngest and oldest ages. Compared with donor ages 13 to 44 years (OR = 1.00), organs from the youngest donors (age 0 to 6 years) were more than twofold as likely to have RVT (OR = 2.48, $P < 0.001$). The likelihood of RVT in other donor age groups was 7 to 12 years (OR = 1.57, $P = 0.052$), 45 to 54 years (1.40, $P = 0.028$), and more than 55 years (OR = 1.95, $P < 0.001$).

The primary cause of ESRD may predispose to hypercoagulability. In this study, patients with ESRD caused by systemic lupus erythematosus (SLE) and diabetes mellitus were more likely to suffer RVT. Compared with patients whose ESRD was due to hypertension, the adjusted OR for SLE was 1.75 ($P = 0.050$) and 1.58 for diabetes mellitus ($P = 0.007$). There was no significant association between RVT and other causes of ESRD, including glomerulonephritis not caused by SLE, polycystic kidney disease, and obstructive uropathy.

Other factors found to be associated with RVT were peak PRAs and recipient gender. Compared with a PRA of 0%, recipients with PRA levels greater than 10% had a significantly lower likelihood of allograft thrombosis.

Table 2. Baseline characteristics of cases and controls

Characteristic	Cases (% or SD) $N = 743$	Controls (% or SD) $N = 1,480$	P-value
Pretransplant dialysis modality			
Hemodialysis	442 (59.5)	1,047 (70.7)	0.001
Peritoneal dialysis	239 (32.2)	263 (17.8)	0.001
Preemptive transplantation	62 (8.3)	170 (11.5)	0.681
Duration of dialysis *months*	28.2 (±31.1)	23.6 (±29.4)	0.011
Mean recipient age *years*	41.1 (±12.9)	42.7 (±12.6)	0.010
Male recipient	389 (52.4)	817 (59.9)	0.001
Recipient race			
White	575 (77.4)	1,068 (72.1)	0.008
African American	145 (19.5)	330 (22.3)	0.131
Other race	23 (3.1)	82 (5.5)	0.010
Primary cause of ESRD			
Glomerulonephritis	211 (28.4)	405 (27.4)	0.740
Hypertension	86 (11.6)	222 (15.0)	0.027
Diabetes mellitus	194 (26.1)	311 (21.0)	0.007
Other	252 (33.9)	542 (36.6)	0.209
Peak PRA	16.4 (±27.0)	17.4 (±27.8)	0.907
Mean donor age	32.6 (±18.0)	33.5 (±15.5)	0.750
% Male donors	410 (55.2)	879 (59.3)	0.058
Living donors	120 (16.2)	304 (20.5)	0.013
Donor race			
White	637 (85.7)	1,283 (86.7)	0.536
African American	87 (11.7)	147 (9.9)	0.198
Other race	14 (1.9)	36 (2.43)	0.411
Donor cause of death			
Anoxia	48 (6.5)	78 (5.3)	0.252
Cerebrovascular accident	218 (29.3)	387 (26.2)	0.111
Head trauma	200 (26.9)	392 (26.5)	0.828
Other causes	152 (20.5)	309 (20.9)	0.817
HLA matching			
A,B			
0	33	36	0.174
1–2	53	51	0.350
3–4	14	13	0.605
DR			
0	51	56	0.036
1	33	31	0.339
2	16	13	0.092
Cold ischemia time *hours*	20.3 (±12.5)	18.7 (±12.8)	0.021
Warm ischemia time *minutes*	28.0 (±22.2)	28.7 (±23.3)	0.200
Antibody induction therapy	262 (35.3)	514 (34.7)	0.804

Percentages were rounded to the nearest 0.1. Percentages may not add up to 100% for each variable because of rounding and missing values. Values in parentheses indicate one standard deviation (SD) for continuous variables and percentages for categorical variables.

Female recipients had a 46% higher likelihood of RVT (OR = 1.46, $P < 0.001$).

The multivariate analysis showed no significant association between renal allograft thrombosis and any of the following factors: recipient's age, race, or body mass index; donor cause of death, race, or gender; donor source (cadaveric versus living); HLA matching; cold ischemia time; warm ischemia time; donor/recipient CMV match status; and organ preservation technique.

DISCUSSION

This case-control study is the largest series of renal allograft vascular thrombosis in adult transplant recipients. Because of its low incidence in individual programs, RVT is most suited for a case-control investigation of registry data [30]. The objective of matching on the basis of transplant center and year of transplantation was to reduce bias from comparisons across centers and between transplants performed at different time periods.

This study found a combined incidence of renal allograft arterial and venous thrombosis of 0.9%, which is at the lower end of the incidence rates in studies in which the diagnosis of vascular thrombosis was confirmed by angiography or surgical exploration. These studies have reported incidence rates ranging from 1.0 to 7.3% (Table 4). The wide variance in the reported incidence of RVT reflects large differences in both the risk periods covered by various studies and the number of subjects studied. In general, larger series tended to report lower incidence rates (Table 4). In addition, several investigators have reported a twofold to threefold higher incidence of RVT in the pediatric population. Hence, different estimates are reported depending on the pediatric mix of the series

Table 3. Factors associated with early renal allograft thrombosis in adult kidney transplant recipients[a]

Variable	Odds ratio	95% C.I.[b]	*P* value
Primary transplant			
HD	1.00	—	ref[c]
PD	1.87	1.28–2.72	0.001
Switched from HD to PD	3.59	2.36–5.46	<0.001
Switched from PD to HD	1.62	1.00–2.61	0.047
Repeat transplant (overall)	5.72	4.40–7.45	<0.001
HD	4.50	3.41–5.93	<0.001
PD	12.95	8.31–20.19	<0.001
Preemptive transplantation	1.66	1.14–2.43	0.008
Female recipient	1.46	1.18–1.81	<0.001
Primary cause of ESRD			
Hypertension	1.00	—	ref
Diabetes mellitus	1.58	1.13–2.22	0.007
Systemic lupus erythematosus	1.75	1.01–3.05	0.050
Donor age *years*			
0–6	2.48	1.49–4.14	0.001
7–12	1.57	1.00–2.48	0.052
13–44	1.00	—	ref
45–54	1.40	1.04–1.89	0.028
55+	1.95	1.35–2.80	<0.001
Peak panel reactive antibodies %			
0	1.00	—	ref
1–10	1.01	0.77–1.34	0.933
11–50	0.69	0.49–0.94	0.020
51–100	0.65	0.45–0.95	0.026

[a] Odds ratio was calculated with the conditional logistic regression for matched case-control. Covariates adjusted for in the logit model include those listed above in addition to recipient age and race; donor race, gender and cause of death; recipient body mass index at transplantation; donor type (living vs. cadaveric); donor/recipient CMV match status; cold and warm ischemia times; organ preservation technique and HLA matching

[b] Indicates confidence interval

[c] Indicates reference group

studied [7–9, 11, 17, 19, 31–33]. Allowing for the exclusion of pediatric cases, the incidence of 0.9% found in this study compares favorably with the rates found in larger series in which the diagnosis was confirmed by angiography and/or surgical exploration (Table 4).

We found that recipients with RVT were significantly more likely to have received pretransplant PD than HD. The excess risk associated with PD was further accentuated after controlling for other confounding variables. This finding is consistent with the report by Murphy et al [25]. In a retrospective study of 202 renal transplants, all nine cases of RVT were found in patients on PD at the time of transplantation. In a corroborating report from the European Dialysis and Transplantation Registry (EDTA) data, the incidence of renovascular graft thrombosis in PD patients was 7.1% compared with 1.8% in HD patients [25].

The higher risk of RVT in PD-treated patients is consistent with an acquired thrombophilic state. The mechanism by which PD may predispose to increased systemic thrombophilia has not been fully elucidated. However, a number of studies have identified several hemostatic abnormalities favoring increased thrombogenesis in PD patients.

Peritoneal dialysis patients have significantly higher concentration of apolipoprotein(a) [Apo(a)], which is the thrombogenic plasminogen-like moiety of lipoprotein(a) [34]. Apo(a) has sequence homology with plasminogen, and although it has the ability to bind fibrin and plasminogen receptors, it lacks significant fibrinolytic properties [35, 36]. In addition, significantly higher procoagulant activities of factors II, VII, VIII, IX, X, XI, and XII without a concomitant alteration of endogenous anticoagulants such as antithrombin III and protein C have been found in PD-treated patients [26]. The diffuse elevation of plasma procoagulant factor activities unopposed by any increase in endogenous fibrinolytic or anticoagulant activity places PD patients at an increased risk of thrombosis [26].

Some of the thrombotic traits described in PD patients may also be present in HD patients [37, 38]. In fact, some investigators have found a greater thrombotic tendency in HD compared with PD patients [39]. However, the preponderance of evidence suggests that the HD procedure is attended by several antithrombotic events, including exogenous heparin administration during dialysis sessions and the use of antiplatelet drugs to prevent vascular access occlusion. Furthermore, endogenous tissue-type plasminogen activator (tPA) is released in measurable quantities during the HD session, which then results in a demonstrable acceleration of fibrinolytic activity [38, 40].

Hemoconcentration is a risk factor for vascular thrombosis [33]. A higher hematocrit level resulting from reduction in ECV is more likely in PD compared with HD patients [41]. Elegant physiological studies using molecular markers of the hydration state have also found significantly lower ECV in PD compared with HD patients [42]. In ESRD patients, blood pressure control is a correlate of the degree of ECV expansion because hypertension in this setting is partly dependent on volume status [43, 44]. Several lines of evidence suggest that PD patients were at greater risk of hemoconcentration. First, in contrast to the wide swings in ECV associated with intermittent HD, ECV is more stable and easily adjusted with PD treatment [45]. Second, more effective ECV reduction in PD has been associated with a concomitant reduction in blood pressure and the number of antihypertensive medications compared with HD [27, 45–47]. Third, HD patients have been found to have lower blood pressures after switching to PD [48]. The effective reduction of ECV in PD patients may be achieved at the expense of reduced plasma volume with an increased propensity to hemoconcentration. Although a number of investigators have reported lower systolic and diastolic blood pressure loads and therefore lower ECV in HD patients, the confounding effect of undertreatment of PD patients and consequent volume

Table 4. Reported incidence of early macrovascular renal allograft thrombosis[a]

Author, year [reference number]	Number (*N*) of renal transplants	Arterial thrombosis	Venous thrombosis	Overall incidence of graft thrombosis	Maximum post-transplant days to diagnosis of RVT[b,c]
		N (%)			
Bakir, 1996 [10]	558	11 (1.9)	19 (3.4)	34 (6.0)	15
Benoit, 1994 [23]	200	4 (2.0)	1 (0.5)	5 (2.5)	—
Dodhia, 1991 [3]	136	6 (4.4)	—	—	33
Gruber, 1989 [61]	224	0 (0.0)	3 (1.3)	3 (1.3)	11
Jones, 1988 [9]	110	2 (1.8)	6 (5.5)	8 (7.3)	—
Ismail, 1997[d] [7]	176	3 (1.7)	4 (2.3)	7 (4.0)	14
Laupacis, 1983 [19]	291	4 (1.4)	—	—	—
Louridas, 1987 [4]	909	3 (0.3)	6 (0.7)	9 (1.0)	—
Merion, 1984 [56]	108	2 (1.9)	4 (3.7)	6 (5.7)	30
Merion, 1985 [2]	168	—	7 (4.2)	—	8
Murphy, 1994 [25]	202	2 (1.0)	7 (3.5)	9 (4.5)	—
Nerstrøm, 1973 [5]	155	3 (1.9)	5 (3.2)	8 (5.2)	—
Palleschi, 1980 [32]	600	5	2	7 (1.2)	16
Penny, 1994 [55]	6,153	70 (1.1)	64 (1.0)	134 (2.2)	30
Rijksen, 1982 [1]	400	7 (1.8)	2 (0.5)	9 (2.3)	28
Rigotti, 1986 [12]	622	6 (1.0)	—	—	12
van Lieburg, 1995[d] [33]	100	4 (4.5)	7 (7.5)	12 (12.0)	6
van Roye, 1993 [13]	1,300	11 (0.9)	17 (1.3)	—	—
Vidne, 1976 [31]	202	4 (2.0)	1 (0.5)	5 (2.5)	42

[a] Diagnosis of RVT was established by angiography and/or surgical exploration in all the series
[b] Longest time to event from postoperative day in each series
[c] The overall incidence may be higher than the sum of arterial and venous thromboses because of cases with both renal and arterial thromboses
[d] Pediatric cases only

overload was not taken into account in these studies [49–51].

Peritoneal dialysis patients may also be at an increased risk of renal allograft vascular thrombosis because the choice of PD as a modality of treatment may not be independent of other thrombotic risk factors. Studies have shown that patients with prothrombotic comorbid conditions such as low output cardiac failure, atherosclerotic heart disease, and vascular access problems may have been preferentially selected to PD either at the onset of ESRD or after technique failure on HD [52–54]. Indeed, we found that switching from HD to PD, which in itself may be an indicator of vascular access problem or atherosclerotic disease, is the strongest risk factor for RVT in primary renal transplant recipients.

End-stage renal disease (ESRD) due to systemic lupus erythrematosus (SLE) and diabetes mellitus was predictive of RVT. The association with SLE is mostly likely due to antiphospholipid antibody syndrome, which has been implicated as a cause of allograft thrombosis in SLE patients undergoing renal transplantation [6, 22]. The diffuse atherosclerotic process in large blood vessels may explain the disposition to RVT in patients who developed ESRD secondary to diabetes mellitus.

The finding of an increased likelihood of graft thrombosis among recipients undergoing preemptive renal transplantation is consistent with the observation in pediatric recipients [11, 33]. Analysis of data from the North American Pediatric Renal Transplant Cooperative Study showed a graft thrombosis incidence of 12.5% in pediatric recipients without prior dialysis compared with 2.8% in recipients who had been on pretransplant maintenance dialysis. Preemptive transplant recipients may have an increased risk of RVT as a result of perioperative intravascular volume depletion secondary to high urine output from the native kidneys [33].

The strong association between the history of prior renal transplantation and RVT has been shown in previous studies [8, 11]. It is not clear whether immunological mechanisms underlie the predisposition to RVT in repeat kidney transplant recipients.

Transplant recipients who developed RVT were more likely than controls to have received kidneys from donors in the extremes of age. This is in agreement with the findings by others [8, 9, 11, 55]. In one series, 33% of cases of renal vein thrombosis occurred in kidneys from very young donors (≤6 years old) [9]. In pediatric recipients, donor age was shown to have a linear inverse relationship to RVT [8, 11], but we observed a nonlinear relationship with highest risks in donors age 0 to 6 years and 55 years or more. The donor age effect may be mediated by technical difficulties associated with the procurement and implantation of kidneys from young donors and progressive atheromatous lesions in older donors.

Several investigators have reported a dramatic increase in the incidence of RVT among CsA-treated renal transplant recipients when compared with recipients treated with prednisone and azathioprine only [12, 19, 56]. CsA is the mainstay of maintenance immunosup-

pression in more than 90% of renal transplant recipients. Thus, a small elevation of risk could have a large impact on the incidence of RVT. CsA has numerous procoagulant properties, including the inhibition of prostacyclin production by the vascular endothelium, increased adenosine diphosphate-induced platelet aggregation, release of thromboxane A_2, generation of thromboplastin, and increased factor VIII activity [57–60]. Notwithstanding these prothrombotic properties, some large studies have not found an elevated risk of RVT in CsA-treated transplant recipients [4, 10, 14, 33, 61]. Moreover, delayed graft function/primary nonfunction, which is usually the classic presentation of RVT, often leads to a management decision to delay the introduction CsA or belated initiation of antibody-induction therapy. In concert, we found that 37% of cases of RVT were treated with CsA compared with 79% among the controls ($P = 0.001$). In this setting, the use of CsA may be a consequence rather than a cause of RVT, thereby making it methodologically erroneous to include it as an independent predictor of RVT.

There are several bases for caution in interpreting these findings. First, an investigation that is based on registry data cannot capture detailed clinical information that might provide alternative explanations for the observed associations. For example, the case definition was based on the report to the registry from the individual transplant centers. Therefore, it was not possible to ascertain the diagnosis or the method used by the transplant center to establish the diagnosis or to distinguish between cases of arterial and venous graft vascular thromboses. Second, we could not evaluate the role of vascular abnormalities, for example, multiple donor arteries and intraoperative technical problems, which are likely factors associated with RVT [62]. Third, we were not able to control for the major clotting disorders such as antiphospholipid syndrome and Factor V Leiden mutation that may predispose to RVT. More detailed clinical information would have enabled us to determine whether the excess risk of RVT in patients who switched from HD to PD was due to the possibility that ESRD patients with underlying clotting disorders made a modality switch because of thrombotic vascular access complications. Although this potential treatment selection bias is etiologically relevant, it does not impugn the validity of the observed association between PD and RVT.

In summary, renal allograft thrombosis occurred in 0.9% of solitary renal transplants in adults and accounted for 17.4% of all graft failures in the first 30 days after transplantation. Retransplantation and PD treatment are codominant risk factors for RVT. These two risk factors have a joint multiplicative effect in predisposing to RVT. Other covariates independently predictive of RVT are donor age, female recipient, preemptive transplantation, and ESRD caused by SLE and diabetes mellitus. In the absence of an effective treatment for RVT, preventive strategies are of paramount importance. Attention to intravascular volume status may be critical in preventing RVT in patients undergoing preemptive renal transplantation. Additional studies are needed to consider future screening for thrombotic risks in patients on PD at the time of renal transplantation. A randomized clinical trial of perioperative anticoagulation therapy with an 85% power to detect a 20% reduction in risk of RVT would require 3700 high-risk patients. The initiation of preventive anticoagulation therapy must await the results of a prospective clinical investigation to test whether a combination of the identified risk factors in prospective renal transplant recipients constitutes an appropriate indication for perioperative anticoagulation therapy.

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