Lack of Association between Dialysis Modality and Outcomes in Atheroembolic Renal Disease

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Background and objectives: Atheroembolic renal disease (AERD) can require dialytic support. Because anticoagulation may trigger atheroembolization, peritoneal dialysis may be preferred to hemodialysis. However, the effect of dialysis modality on renal and patient outcomes in AERD is unknown.

Design, settings, participants, & measurements: A subcohort of 111 subjects who developed acute/subacute renal failure requiring dialysis was identified from a larger longitudinal study of AERD. The main exposure of interest was dialysis modality (peritoneal *versus* extracorporeal therapies). Logistic regression was used to study the probability of renal function recovery. Times from dialysis initiation to death were studied using Cox's regression.

Results: Eighty-six patients received hemodialysis and 25 received peritoneal dialysis. The probability of renal function recovery was similar by dialysis modality (25% among hemodialysis patients and 24% among peritoneal dialysis patients; $P = 0.873$). During follow-up, 58 patients died, 14 among peritoneal patients and 44 among hemodialysis patients ($P = 0.705$). In multivariable analysis, gastrointestinal tract involvement and use of statins maintained an independent effect on the risk of patient death.

Conclusions: This study does not support the notion that one dialysis modality is superior to the other. However, the observational nature of the data precludes any firm conclusions.

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Atheroembolic renal disease (AERD) is due to the occlusion of small renal arteries and glomerular capillaries by cholesterol crystals derived from atherosclerotic aortic plaques (1). The severity of renal dysfunction depends on the amount and frequency of embolic showers and inflammatory reactions. Although chronic "spontaneous" AERD may represent an underdiagnosed, slowly progressive cause of ESRD mimicking nephrosclerosis, in patients developing acute or subacute renal failure AERD is usually "iatrogenic" and dialysis may be required in 25% to 60% of the patients. In one third of these patients renal function may recover. Recovery may be related to reversal of inflammation, resolution of acute tubular necrosis in ischemic areas, hypertrophy in surviving nephrons, and reduction in intensity of embolic showers (2–6).

Invasive aortic manipulation, including angiography and vascular surgery, is the leading cause of AERD. However, the disease may be rarely precipitated by anticoagulation; by preventing the formation of a protective thrombus overlying the ulcerated plaques; or even disrupting the fibrin cap of atherosclerotic plaques and exposing their soft, cholesterol-laden core to the arterial circulation (1–3,7–12). The requirement for systemic anticoagulation makes extracorporeal dialysis treatments less attractive for patients with AERD who need dialysis. Although systemic anticoagulation can be avoided or at least minimized initially, this can be more difficult in the long run. On the other hand, peritoneal dialysis may not be available in all facilities to treat acute kidney injury and can be contraindicated in patients with AERD for gut ischemia or protein losses.

Current data on benefits and harms of extracorporeal and peritoneal dialysis therapies are scant and come from small cohorts or case series (2,3,13–16). Although evidence from clinical trials of interventions is ideally necessary to inform practice, for rare disorders cohort studies may provide relevant information. In this study, we sought to determine whether peritoneal dialysis is superior to extracorporeal therapies in

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terms of renal and patient outcomes of acute/subacute AERD using data from a large longitudinal study (12).

Materials and Methods

Study Design, Patient Selection, and Follow-Up

For the purpose of the study presented here, a subcohort of 116 subjects who developed renal failure requiring dialysis treatment was selected from a larger cohort of 354 incident cases of AERD (15). Patients were referred to the nephrologist for kidney function impairment and clinical suspicion of AERD at 12 tertiary care centers between June 1987 and January 2006. Patients were followed from diagnosis until death as described elsewhere (12).

Diagnostic Criteria and Prognosis Indicators

Per protocol, AERD was considered iatrogenic in the contemporary presence of (*1*) renal function deterioration in atherosclerotic patients, (*2*) simultaneous ischemic changes to the lower abdomen and/or extremities, (*3*) and one or more precipitating factors (arterial angiography with or without angioplasty, vascular abdominal or cardiac surgery, and fibrinolytic/anticoagulant therapy). A diagnosis of spontaneous AERD was made only in the presence of (*1*) clinical suspicion; and (*2*) a biopsy-proven deposition of cholesterol clefts in the skin, gastrointestinal, or renal tissue or, alternatively, the disclosure of retinal emboli upon funduscopic examination. Signs of extrarenal involvement, eosinophil count, and the rate of renal function deterioration were considered to evaluate the severity of the disease (12).

Kidney Function, Clinical Presentation, and Eligibility

Serum creatinine concentration was available shortly before the precipitating event for all iatrogenic forms of AERD and in the year before the onset of symptoms for spontaneous forms. Information on renal function was updated at the time of AERD diagnosis, during the course of the acute/subacute phase of renal disease, and reassessed at each follow-up visit for those with milder forms. GFR was estimated using the abbreviated Modification of Diet in Renal Disease formula (17). With respect to the clinical presentation of AERD, renal failure was defined as "acute" if a sudden 50% reduction of GFR was evident within 1 week after the precipitating event, "subacute" if the same deterioration occurred over 2 to 6 weeks, and "chronic" if the patient had a stable chronic renal impairment mimicking nephrosclerosis. Patients with chronic AERD who required dialysis (two peritoneal and three hemodialysis) were excluded.

Exposure of Interest and Outcomes

The main exposure of interest (type of dialysis) was only categorized into two levels: peritoneal *versus* extracorporeal dialysis treatment. The choice of the dialysis modality was made according to local policies, clinical indication, and patient preferences. Peritoneal dialysis included intermitted cycler fluid exchange by means of a dialysis machine and continuous treatment with 4 to 5 exchanges per day. Peritoneal dialysis was started with a cuffed permanent catheter in all patients assigned to this modality. Extracorporeal dialysis included standard bicarbonate schedule and mixed methods with more biocompatible membranes. In all extracorporeal treatment schedules heparin was used as an anticoagulant starting with a boost of 1000 IU followed by 500 to 800 IU/h. Anticoagulation was not part of the peritoneal dialysis prescriptions. The effect of dialysis type was studied using probabilities of renal function recovery, defined as dialysis withdrawal, and patient survival as outcomes.

Data Collection and Risk Factors

In addition to kidney function, demographic, clinical, and pathologic data as well as exposure to precipitating maneuvers were recorded at the time of AERD diagnosis. Considered vascular comorbidities were (12): coronary artery disease (documented angina or infarction), cerebrovascular disease (clinical signs or radiologic confirmation of a transient ischemic attack or stroke), and peripheral artery disease (symptoms of "claudicatio intermittens," previous surgery for lower-limb arterial insufficiency, and/or angiographic evidence of significant stenosis in one or more peripheral vessels). The diagnosis of congestive heart failure was based on symptoms of pump failure (New York Heart Association classification class II or greater). Angiography or magnetic resonance angiography were used to confirm abdominal aortic aneurysm or renal artery stenosis (>50% in one or both renal arteries) when these lesions where suspected. Patients were considered diabetic if they had been given either oral antidiabetic drugs or insulin and smokers in case of current or previous smoking habit (at least 10 cigarettes per day and for >10 years). Hypercholesterolemia was defined by total cholesterol levels >220 mg/dl or if cholesterol-lowering treatment was prescribed. Hypertension was defined as systolic or diastolic pressure of >140 or >90 mmHg, respectively, or if antihypertensive drugs had been given.

Statistical Analyses

Logistic regression was used to model the probability of renal function recovery as a function of dialysis modality. Given the limited event number and to adhere to the "rule of ten" (ten events per each estimated parameter), potential confounders and their interactions were assessed in reduced models after screening for co-linearity. These models were built on dialysis type using either (*1*) baseline characteristics, traditional cardiovascular risk factors, and comorbidity; (*2*) precipitating factors (radiodiagnostic, interventional, or surgical procedures); (*3*) markers of clinical severity of the AERD (time course of kidney function deterioration, involvement of extrarenal organ systems, eosinophil count); (*4*) or treatments initiated after diagnosis to improve peripheral oxygenation or reduce inflammation (pentoxifylline, statins, or steroids). Progressive models were built on those covariates for which the effects were significant at the level of 0.1 or modified the parameter estimate of the exposure (dialysis modality). Times from dialysis initiation to death or censoring (last follow-up visit day) were described with the Kaplan–Meier method. Cox's regression was used for multivariate analysis using stratification to control for variables for which the effect was not of interest or violating the proportionality assumption. The model building approach was the same as for logistic regression. Center effects were studied as random effects in both outcome analyses. Model specification and overall fit were checked by re-estimation and formal and graphical tests based on residuals. Calculations were made using R (18).

Results

Baseline Characteristics, Risk Factors, and Clinical Findings

Demographic and clinical characteristics of the 111 patients who received dialysis for acute/subacute renal failure during the AERD study (12) are summarized in Tables 1 and 2 (40% of the acute/subacute cases in the original cohort). Eighty-six patients received extracorporeal treatment and 25 received peritoneal dialysis. Of these, five patients received peritoneal dialysis after 3 to 5 runs of hemodialysis and were still on dialysis at the study end date.

Overall, patients tended to be male and elderly with a high

Table 1. Baseline patient characteristics and risk factors[a]

	All (n = 111)	Peritoneal Dialysis (n = 25)	Extracorporeal Dialysis (n = 86)	P Value[b]
Age (years)	72.0 (6.9)	71.8 (6.0)	72.1 (7.2)	0.841
Male gender	94 (84.7)	21 (84.0)	73 (84.8)	0.914
History of hypertension	93 (83.7)	17 (68.0)	76 (88.3)	0.015
Current or previous smoking habit	80 (72.0)	17 (68.0)	63 (73.2)	0.606
Diabetes	22 (19.8)	3 (12.0)	19 (22.0)	0.265
Total cholesterol >220 mg/dl	33 (29.7)	8 (32.0)	25 (29.0)	0.778
Statin use	28 (25.2)	8 (32.0)	20 (23.2)	0.376
CAD	76 (68.4)	14 (56.0)	62 (72.0)	0.127
Peripheral artery disease	66 (59.4)	15 (60.0)	51 (59.3)	0.950
Cerebrovascular disease	39 (35.2)	6 (24.0)	33 (38.3)	0.185
Heart failure	52 (46.8)	10 (40.0)	42 (48.8)	0.436
Cardiovascular disease[c]	103 (92.7)	23 (92.0)	80 (93.0)	0.862
GFR	38.0 (16.4)	38.5 (15.6)	37.9 (16.8)	0.929
Chronic kidney disease[d]				
stage 1 to 2	11 (9.9)	2 (8.00)	9 (10.4)	0.636
stage 3	60 (54.0)	12 (48.0)	48 (55.8)	
stage 4 to 5	40 (36.0)	11 (44.0)	29 (33.7)	

[a]Values expressed as mean (SD) or number (%) as appropriate.
[b]Two-sided significance level.
[c]Excluding hypertension.
[d]Defined as absent/mild GFR >60 ml/min (1 ml/s, stage 1 to 2), moderate GFR 30 to 60 ml/min (0.5 to 1 ml/s, stage 3), and severe/advanced GFR <30 ml/min (0.5 ml/s, stage 4 to 5).

prevalence of traditional cardiovascular risk factors and diseases. Average (± SD) total cholesterol levels were 196 ± 47 mg/dl. The estimated GFR at baseline was 38.0 ± 16.4 ml/min/1.73 m^2. Urinalysis showed bland urine with minimal proteinuria. The legs represented the most common extrarenal site involved. Most patients had an iatrogenic form of AERD (86%), with half of them experiencing two or more precipitating factors. How the diagnosis was confirmed and the distribution of case characteristics did not change over the study period, except the use of statins, which increased from 40% in the initial 5 years to 65% in the last 5 years. Measured characteristics did not vary substantially by treatment modality. As expected, extracorporeal dialysis was more likely in hypertensive subjects and peritoneal treatment was less likely after surgical procedures.

Renal Outcome

Patients were followed for 2.9 years on average. Within 6 months of dialysis start, 28 subjects recovered sufficient kidney function to stop dialysis therapy. Of these, four patients restarted hemodialysis, one restarted peritoneal dialysis, and seven died (five hemodialysis and two peritoneal dialysis) during the study period. The probability of renal function recovery tended to increase over time (from 11% in the first 5 years to 30% in the last 5 years) but was similar by dialysis modality (25% among HD patients and 24% among PD patients; P = 0.873). The odds of dialysis withdrawal did not change in multivariate analysis. None of the measured clinical characteristics and risk factors predicted renal function recovery at the level of significance of ≤0.1. Results were the same excluding the five patients who received hemodialysis before peritoneal dialysis.

Patient Survival

During the follow-up, 58 patients died—14 among peritoneal patients and 44 among hemodialysis patients (Figure 1). The yearly risk for death tended to decline over time from 0.35 in the initial 10 years to 0.25 in the last 10 years. The relative risk for death was similar in hemodialysis and peritoneal dialysis. Adjustment for potential confounders did not change the result (Figure 2). In the multivariate model only gastrointestinal tract involvement (hazard ratio 2.6, from 1.4 to 4.9) and use of statins (hazard ratio 0.48, from 0.28 to 0.84) maintained an independent effect on the risk of patient death. Results did not change excluding the five patients who received hemodialysis before peritoneal dialysis.

Discussion

AERD arise from atherosclerotic plaques in the aorta, when the soft, lipid-laden core of the plaques is exposed to the arterial circulation. Catheter angiographic procedures and vascular surgery are the most common factors identified as precipitants of AERD. In a subgroup of patients, AERD may be caused by anticoagulation (1–4).

As opposed to chronic AERD, in the acute and subacute forms of AERD, dialysis support may be required in some patients soon after an identifiable onset and a less challenging diagnosis (2,3,5,12). In such patients, the choice of type of renal

Table 2. Clinical findings[a,b]

	All (n = 111)	Peritoneal Dialysis (n = 25)			Extracorporeal Dialysis (n = 86)			P Value[c]
		AC	SA	All	AC	SA	All	
Precipitating factors								
angiography	74 (66.6)	4	10	14 (56.0)	21	39	60 (69.7)	0.199
PCTA[d]	26 (23.4)	2	2	4 (16.0)	8	14	22 (25.6)	0.319
any surgery[e]	29 (26.1)	0	1	1 (4)	11	17	28 (32.5)	0.004
AC/FB[f]	36 (32.4)	3	7	10 (40.0)	7	19	26 (30.2)	0.358
No PF (spontaneous)	15 (13.5)	1	5	6 (24.0)	2	7	9 (10.4)	0.080
1 precipitating factor	46 (41.4)	3	9	12 (48.0)	11	23	34 (39.5)	
≥2 precipitating factors	50 (45.0)	3	4	7 (28.0)	16	27	43 (50.0)	
Presentation								
acute (*versus* subacute) onset	36 (32.4)	–	–	7 (28.0)	–	–	29 (33.7)	0.591
skin manifestations[g]	91 (81.9)	7	13	20 (80.0)	24	47	71 (82.5)	0.770
central nervous system[h]	25 (22.5)	1	3	4 (16.0)	8	13	21 (24.4)	0.375
gastrointestinal involvement[i]	22 (19.8)	1	2	3 (12.0)	11	8	19 (22.0)	0.265
eosinophilia[j]	75 (67.5)	7	12	19 (76.0)	16	40	56 (65.1)	0.306
Diagnosis and confirmation								
clinical only	53 (47.7)	3	6	9 (36.0)	17	27	44 (51.1)	0.182
plus biopsy	55 (49.5)	4	12	16 (64.0)	12	27	39 (45.3)	0.101
plus autopsy	6 (5.4)	0	1	1 (4.0)	3	2	5 (5.8)	0.724
plus ophthalmoscopy	7 (6.3)	0	1	1 (4.0)	1	5	6 (6.9)	0.590
Treatments								
statins initiated	57 (51.3)	4	10	14 (56.0)	14	29	43 (50.0)	0.597
steroids	51 (45.9)	4	6	10 (40.1)	15	26	41 (47.6)	0.498
pentoxifillyn	23 (20.7)	1	6	7 (28.0)	5	11	16 (18.0)	0.308

[a]Variable values expressed as n (%).
[b]AC, acute absolute cases; SA, subacute absolute cases.
[c]Two-sided significant level (χ^2/exact or t test as appropriate).
[d]PCTA, percutaneous angioplasty.
[e]Cardiovascular surgery.
[f]AC/FB, anticoagulant/fibrinolytic therapy.
[g]Purple toes/livedo reticularis on the feet/lower abdomen.
[h]Transient ischemic attack, amaurosis fugax, confusional states, and gradual deterioration of neurological functions.
[i]Abdominal pain, diarrhea, bleeding, intestinal infarction.
[j]Eosinophil count >500 cells/μl.

replacement therapy is influenced by facility policies and local expertise. However, in the subset of patients with AERD and renal failure requiring dialysis, the precipitating role of anticoagulation raises the question of the ideal dialysis modality (3,5,13–16). To avoid clotting within the extracorporeal circuit, hemodialysis treatment requires systemic anticoagulation, which may trigger new bouts of atheroemboli, reducing the likelihood of recovery of renal function. For this reason, peritoneal dialysis may be preferred in these patients to avoid heparin administration. On the other hand, AERD patients may have contraindications to peritoneal dialysis, including mesenteric ischemia and protein losses in a malnourished patient.

Few studies, most retrospective, have addressed the potential for renal functional recovery in patients with AERD and renal failure requiring dialysis (13–16). Little is known about the effect of the dialysis modality on the probability of renal functional recovery. In one study 52 of 129 patients (40%) required dialysis. Peritoneal dialysis and hemodialysis were used, and 11 of 52 (21%) patients recovered sufficient renal function to allow dialysis cessation. However, the effect of dialysis modality on the probability of renal function recovery was not studied (2). In 1999, Belenfant *et al.* described 67 patients admitted to a renal intensive care unit for acute AERD (3). Forty-one of them (61%) were treated by hemodialysis, and 13 (32%) regained sufficient renal function to obviate the need for dialysis. No patient was treated with peritoneal dialysis, which was deemed inappropriate. Hemodialysis was conducted without systemic anticoagulation or with a very low dose of heparin (1000 IU/session). In another study 43 patients with AERD and renal failure severe enough to require dialysis were described; 10 received peritoneal dialysis and 33 received hemodialysis. The rate of renal functional recovery sufficient to discontinue dialysis was 27.9%, and the chances of renal recovery appeared higher for the subgroup on peritoneal dialysis (14). In a more

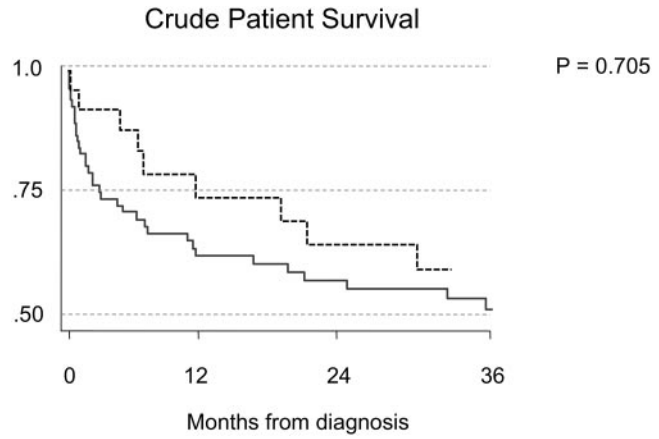

Figure 1. Kaplan–Meier survival curve of time to patient death from dialysis initiation (Log-rank $P = 0.705$). Effect estimation with Cox's regression: unadjusted hazard ratio 0.88, 95% confidence interval 0.48 to 1.62.

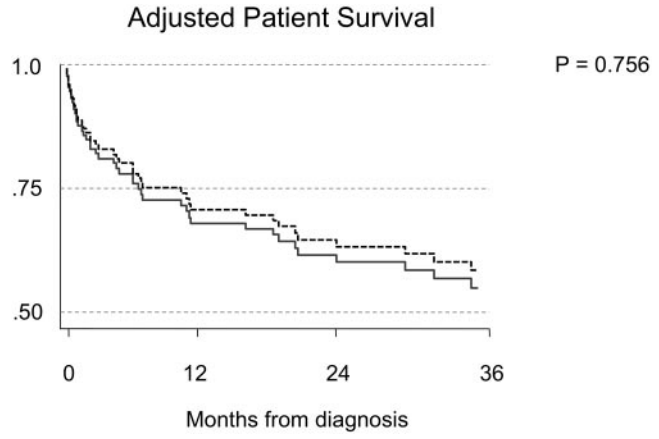

Figure 2. Predicted patient survival probabilities by dialysis type from frailty Cox's regression (observations $n = 111$, death $n = 58$). Model adjusted for age, gastrointestinal tract involvement, center effect, and use of statins. Effect estimation: adjusted hazard ratio 0.90, 95% confidence interval 0.48 to 1.70 (Wald test $P = 0.756$).

recent study 35 of 95 patients with AERD (37%) received dialysis therapy (23 hemodialysis and 12 peritoneal dialysis), and 14 patients (40%) recovered sufficient renal function to stop dialysis (5). Despite the limitations, mainly due to sample size and study design, these studies suggest that renal functional recovery can be observed in one third of the patients and may occur after peritoneal dialysis or hemodialysis therapy.

To our knowledge, our study is the largest study evaluating the effect of dialysis modality on renal functional recovery and patient survival in the subgroup of patients with AERD requiring dialytic support. Of 354 patients (32.7%) enrolled in a multicenter study (12), 116 received dialysis. After exclusion of those with chronic AERD ($n = 5$), 111 subjects with acute/subacute forms (40%) required dialysis. Of these, 25 patients were treated with peritoneal dialysis and 86 with hemodialysis. Dialysis was temporary in 28 patients (25%). However, the probability of renal function recovery at 6 months was similar by dialysis modality. In addition, dialysis modality did not seem to affect the high risk for death of these patients (0.3 per year). These data suggest that in patients with AERD and renal failure requiring dialysis the potential for renal function recovery and patient survival may not be influenced by dialysis modality.

The findings of our study should be interpreted with caution. First, the observational nature of the data does not allow any firm conclusion on benefits and harms deriving from the choice of peritoneal dialysis over hemodialysis. In fact, the results of our study may not represent the true effects of the exposure but may be confounded by indication. If patients with worse prognoses received a superior treatment, results would be leveled off toward the null hypothesis. The opposite would have occurred if an inferior dialysis method were assigned to those with worse prognoses. Only randomized trials would provide reliable information to guide clinical decision-making. However, given the relatively rare occurrence of the disorder, only a very large, multicenter trial would be adequately powered to answer the question. Second, the effect of dialysis modality may be affected by local factors such as infrastructures, human resources, preferences, and experience. For example, some degree of variability in the anticoagulation schedule, dialysis duration, and intensity may have, to some extent, affected the outcome. It is possible that peritoneal and extracorporeal dialysis modalities have similar performances when these local factors are accounted for. To enhance external validity (generalization) a multicenter clinical trial should account for these clustering effects as we did in the analysis of the observational data presented here using random effects modeling. Finally, although our study is the largest longitudinal study reported so far, it remains relatively small and unbalanced because most patients received hemodialysis. This has implications on the likelihood to detect an effect if this effect existed. In fact, a sample of 110 individuals has a power of 80% to detect as significant at the two-sided P level of 0.05, only large effects (risk ratios <0.5 or >1.5) when baseline risks are high (0.5). Unfortunately, the wide confidence intervals around the hazard ratio for death in our study are consistent with this range of possible effects of peritoneal *versus* hemodialysis. On the other hand, the estimated effect most compatible with our study data ("point estimate" or "best guess") is close to the point of "zero effect," whereas more extreme values are progressively less likely. To detect as significant such small and possibly clinically irrelevant effects (*e.g.*, a hazard ratio of 0.9), several thousand patients would be necessary.

In conclusion, acute/subacute atheroembolism may require dialysis treatment in 40% of the patients. These patients carry a high risk of mortality. One quarter of them may recover sufficient kidney function to stop dialysis. Data from the study presented here, although observational in nature, do not support the notion that one dialysis modality is superior to the other in such patients in terms of renal or patient outcomes.

Disclosures

None.

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