Decline in Residual Renal Function in Automated Compared with Continuous Ambulatory Peritoneal Dialysis

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Summary
Background and objectives We compared the decline of RRF in patients starting dialysis on APD with those starting on CAPD, because a faster decline on APD has been suggested.

Design, setting, participants, & measurements NECOSAD patients starting dialysis on APD or CAPD with RRF at baseline were included and followed for 3 years. Residual GFR (rGFR) was the mean of urea and creatinine clearances. Differences in yearly decline of rGFR were estimated in analyses with linear repeated measures models, whereas the risk of complete loss of RRF was estimated by calculating hazard ratios (HRs) for APD compared with CAPD. As-treated (AT) and intention-to-treat (ITT) designs were used. All of the analyses were adjusted for age, gender, comorbidity, and primary kidney disease and stratified according to follow-up and mean baseline GFR.

Results The 505 CAPD and 78 APD patients had no major baseline differences. No differences were found in the analyses on yearly decline of rGFR. APD patients did have a higher risk of losing RRF in the first year (ITT crude HR 2.43 [confidence interval 95%, 1.48 to 4.00], adjusted 2.66 [1.60 to 4.44]; AT crude 1.89 [1.04 to 3.45], adjusted 2.15 [1.16 to 3.98]). The higher risk of losing all RRF was most pronounced in patients with the highest rGFR at baseline (ITT; crude 3.91 [1.54 to 9.94], adjusted 1.85 to 14.17).

Conclusions The risk of losing RRF is higher for patients starting dialysis on APD compared with those starting on CAPD, especially in the first year.


Introduction
Up to now, dialysis cannot replace real kidney function completely, because native kidneys have additional properties that cannot be taken over by dialysis. These properties include a better removal of small solutes, middle and larger molecular weight toxins and organic acids, the maintenance of fluid balance, phosphorus control, and also endocrine functions. They result in a better overall health, well being (1), and survival in dialysis patients with residual renal function (RRF) (2,3). Therefore, preservation of RRF in dialysis patients is one of the main challenges nephrologists face when starting a patient on dialysis.

It has previously been shown that starting a dialysis career on peritoneal dialysis (PD) instead of hemodialysis gives a better preservation of RRF (4–6). Within PD two modalities can be chosen: automated peritoneal dialysis (APD) and continuous ambulatory peritoneal dialysis (CAPD). Whether one of these has an advantage over the other in preservation of RRF is not clear yet (2,7). A faster decline on APD has been suggested in four small studies (8–11) but could not be confirmed in two small randomized controlled trials (12,13), two letters to the editor (14,15), and a few studies designed to analyze factors influencing RRF (5,14,16–19).

APD has become more popular over the last years, making determination of the possible drawbacks of APD increasingly important. This means that if patients who start dialysis on APD lose their RRF more rapidly than those starting on CAPD, this should be taken into account when choosing between modalities.

Thus, a large study with a considerable follow-up is needed to clarify the question of whether patients who start dialysis on APD have a faster decline of RRF than those who start on CAPD. We studied this question in the prospective Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) cohort and followed the patients for 3 years.
Materials and Methods

Patients

All adult patients starting dialysis in one of the participating 38 Dutch dialysis centers between 1997 and 2006 were asked to participate in the NECOSAD. The committees of all participating centers approved the study, and all patients who decided to take part in NECOSAD gave informed consent before inclusion. The patients were monitored at the start of dialysis, 3 months later, and every 6 months thereafter until kidney transplantation or death. For these analyses, patients treated with APD or CAPD at 3 months after the start were included for a maximum of 3 years if a GFR measurement was available at the start of dialysis or at the 3-month time point. Because only incident dialysis patients were included, patients could not have failed at another modality yet. Furthermore, because peritoneal transport status was not known at the time the modality choice was made, the patient’s preference was the only determinant for the choice between APD and CAPD. No indication was found that the APD modality during the training period was determined by the drained dialysate volume, causing an overrepresentation of patients with immediate low net ultrafiltration volumes in the APD group.

Data Collection

Demographics, data on primary kidney disease, and comorbidity were obtained 0 to 4 weeks before the start of dialysis. Primary kidney disease was classified according to the codes of the European Renal Association-European Dialysis and Transplant Association Registry (20). Comorbidity was scored on the basis of the number of comorbid conditions according to the comorbidity index described by Davies et al. (21). The patients were classified as having no, intermediate, or severe comorbidity.

Data on biochemistry and dialysis parameters were collected from the 3-month visit onwards. Residual renal function was measured at all visits using 24-hour urine collection. It was expressed as the residual GFR (rGFR), calculated as the mean of creatinine and urea clearance (22), and adjusted for body surface area (ml/min per 1.73 m²). The rGFR was set to 0 when urine production was <200 ml/24 h. When a patient had an rGFR value of 0 at two successive time points, the first time point where the rGFR was 0 was chosen as the moment the patient has lost all RRF.

Statistical Analyses

Baseline was set at the 3-month visit to avoid analytical problems caused by early modality switching. Differences between APD and CAPD patients at baseline were tested with the t test and χ² or Fisher’s exact test, whatever was appropriate. A P value of <0.05 was considered statistically significant. The numbers are presented as the means with SD for continuous variables or as numbers with percentages for categorical variables. The statistical analyses were performed in SPSS for windows version 17.0 (SPSS Inc., Chicago, IL).

A linear repeated measures model was applied to estimate the differences in decline of rGFR between both modalities. An unstructured covariance structure was chosen on the basis of the Akaikes Information Criterion. Time was included in the model as a linear covariate. An interaction term between time and modality was entered to allow for differences in the decline of rGFR over time between groups. The estimate of this interaction term reflects the difference in decline between APD and CAPD.

To analyze the time until the complete loss of RRF, the proportional hazards model was used. Differences between groups were expressed as hazard ratios (HRs) for APD compared with CAPD. Because rGFR was often not recorded if a patient was anuric, a missing rGFR at two subsequent time points was considered an event at the first time point. If patients dropped out for any other reason, the time of loss of RRF was censored at the time of dropout. Life table methods were used to estimate the percentage of patients losing all RRF over time on both modalities.

Intention-to-treat and stay-on-treatment analyses were performed. In both analyses, groups were defined on the basis of the treatment with APD or CAPD at baseline. In the intention-to-treat analysis, the data of patients were used until a complete loss of RRF or the end of follow-up. In the stay-on-treatment analysis, the measurements were used until the complete loss of rGFR, a switch to any other dialysis modality, including the switch from CAPD to APD or vice versa, or the end of follow-up.

To allow for different effects on short- and long-term follow-up, all of the analyses were separately performed for the first year and for the second and third years. To be included in the analyses in the second and third years, patients must have survived the first year without complete loss of RRF. Because age, gender, comorbidity, and primary kidney disease were considered possible confounders in the relation between PD modality and loss of GFR, all of the analyses were adjusted for these variables. Because the decline in RRF might be different for patients starting dialysis with a high and low rGFR, all of the analyses were also performed after stratification, using two strata on the basis of the mean GFR at baseline for the complete group. A relation between the use of icodextrin and the decline of RRF has been suggested in previous studies (23,24). Therefore, a sensitivity analysis restricted to nonusers at baseline was performed.

Results

At baseline, 647 patients were treated with APD or CAPD. Of these, 505 CAPD and 78 APD patients had data available on GFR. Their baseline characteristics are presented in Table 1. Compared with the APD patients, more CAPD patients were on either angiotensin-converting enzyme inhibitors (ACEI) or AII receptor blockers (42 versus 30%, P = 0.04) at baseline. APD patients used icodextrin more frequently (28 versus 10%, P < 0.01), but CAPD patients used higher amounts of icodextrin (2.0 versus 1.6 L/24h, P < 0.01).

Decline of rGFR

The repeated measures model showed that the yearly decline of rGFR was not different for APD patients compared with CAPD patients (Table 2). Exclusion of patients who used icodextrin (n = 74) at the start of dialysis did not change the results.
Time until Complete Loss of Residual Renal Function

Figure 1 presents the number of patients who lost all of their RRF over time. In the intention-to-treat analysis, 221 (44%) of the CAPD and 41 (53%) of the APD patients lost their complete RRF during the complete follow-up. In the stay-on-treatment analysis, 123 (24%) of the patients on CAPD and 25 (32%) of the patients on APD lost all RRF. Patients who started their dialysis career on APD had a two times higher risk of losing all RRF in the first year compared with those starting on CAPD (Table 3). Exclusion of icodextrin users at the start of dialysis did not change the results.

Stratification on mean rGFR at baseline showed that the increased risk of losing all RRF on APD in the first year was most pronounced in the patients starting with a high rGFR. In the second and third years on dialysis, patients with a low rGFR at baseline had a higher risk of losing all RRF compared with CAPD (Table 3).

Discussion

This study comparing the decline of RRF on APD and CAPD in incident dialysis patients shows that patients who start their dialysis career on APD have a higher risk of losing all RRF in the first year after the start. The increased risk in the first year was more pronounced in patients with a high rGFR at baseline. In patients with a low rGFR at baseline, the higher risk of losing their rGFR on APD remained present in the second and third years.
The slopes of the yearly decline of rGFR were not significantly different between the groups. The estimates of the repeated measure analyses are in the same direction as those of the survival analyses, although the fact that we found a significant difference between APD and CAPD only in the survival analyses might be due to a lack of power in the repeated measure analyses. The difference between the groups had to be very large to be able to detect a statistically significant difference, because the variation in rGFR at the start of dialysis was large. Furthermore, the repeated measure analyses were on the basis of a limited number of measurements, because patients were included in the analysis until the first time they reached a GFR of 0.

Our finding that APD patients lose their RRF more rapidly than CAPD patients is in line with four previous studies (8–11). However, not all studies support this conclusion (5,12–19). This difference can be explained by the fact that most of these studies included a very small number of patients (12–15). Our study had a limited number of patients as well; however, our APD group was at least twice as large as the largest APD group in these studies (12–15,17,19). One study included 114 APD patients (18), but in this study all of the patients using a cycler at any time were recorded as APD patients. This could have resulted in misclassification in modality, causing an underestimation of the difference in the decline of rGFR between patients who start dialysis on APD and those who start on CAPD (18).

In this study, patients starting dialysis with a high GFR had the highest risk of losing all RRF in the first year when starting on APD. This difference could be the result of a higher comorbidity burden in this group, which could have been a reason to start dialysis with a higher GFR. However, a higher comorbidity burden is not the only reason to start earlier with dialysis; also complaints of uremia or fluid overload combined with the patient’s preference can be a reason. Furthermore, adjustment of our analysis for some identifiable comorbidities did not result in lower HRs. From our analysis, we can conclude that patients starting dialysis on APD with a high GFR seem to be more vulnerable for this risk than those starting on CAPD. We did not compare the risk of losing RRF in patients starting with a high GFR with those starting with a low GFR, because the aim of the study was to investigate the risk of losing RRF in patients starting dialysis on APD compared with those starting on CAPD.

Survival bias could account for the finding that patients with a high GFR at baseline had a lower risk of losing all RRF in the second and third years on dialysis. In these patients the risk of losing all RRF in the first year was high. Thus, once they survived the first year without losing all RRF on APD, modality was no obvious risk factor anymore in losing their RRF for the two subsequent years. In line with this reasoning, it is not surprising that most studies including prevalent patients were not able to find an effect of PD modality on the decline of RRF (12,15,16). The study by Moïst et al. (5) was...
performed in incident patients. However, only patients who survived the first 18 months on dialysis on their initial modality were included, which also might have led to survival bias (5).

Previous studies showed a possible beneficial effect of ACEi or angiotensin receptor blockers (ARB) on the decline of RRF in dialysis patients (5,25,26). Therefore, we additionally adjusted our analyses for the use of ACEi of ARB at baseline. This adjustment did not change the higher risk to lose all RRF for patients starting dialysis on APD compared with those starting on CAPD in the first year (HR; intention-to-treat analysis, 2.60 [confidence interval 1.55 to 4.34]; stay-on-treatment, 2.11 [1.14 to 3.91]). This finding that the risk of losing all RRF was not influenced by the use of ACEi and ARBs at baseline was in line with two other observational studies (19,27), which were also performed in representative patient populations. It is, however, not in line with earlier publications. This is can be explained by the exclusion of most patients with comorbidities in the randomized controlled trials (25,26). The study by Moist et al. (5) was also observational but studied all kinds of factors influencing the risk of losing RRF, not this one in particular.

It has been suggested that the use of biocompatible PD solutions or icodextrin can give a better preservation of RRF (23,24,28,29). Whether this preservation was due to a better fluid balance or by the fluids themselves is, however, not clear yet (30–33). Our results cannot be explained by a different use of icodextrin at baseline, because restriction of the analyses to nonusers did not change the results. The data on the use of biocompatible dialysis fluids were not collected in NECOSAD, making it impossible to perform a similar sensitivity analysis for the use of those fluids. Because the use of either fluid over time could well be influenced by the modality itself, we did not study the use of icodextrin over time.

Why patients on APD lose their RRF faster than those starting on CAPD is not completely understood yet. It is known that changes in the patients' fluid status are related to a faster decline of RRF in dialysis (3,4,30–32,34–36). APD provides a less stable fluid status in patients, which might cause a faster decline of RRF. Another hypothesis is that in APD the bulk of ultrafiltration is performed during an 8-hour period at night, when blood pressure is already lowest. This could jeopardize the decline of RRF.

A drawback of this study is the observational design, because the ideal study design comparing therapeutic strategies would be a randomized controlled trial. Previous studies have shown that randomization for dialysis is very difficult (37), which is also reflected in the limited number of patients in the only three studies ever randomizing for APD and CAPD (12,13,38). The exact reason for choosing either therapy in NECOSAD is unknown. However, because the choice is made at the start of dialysis, it is conceivable that it was on the basis of the patient’s preference. Furthermore, the prospective design of the NECOSAD study generated abundant additional information, making it possible to adjust for the most important possible confounders. Residual confounding can, however, never be resolved completely.

Compared with the number of CAPD patients, a relatively low number of APD patients was included. This was mainly due to the inclusion of only incident patients, because most Dutch peritoneal dialysis patients start their dialysis career on CAPD rather than on APD. Furthermore, NECOSAD included patients between 1997 and 2006; in this time frame fewer patients started on APD than nowadays.

In this study with a long follow-up, we have shown that the risk of losing RRF is higher for patients starting dialysis on APD compared with those starting on CAPD, especially in the first year. In the intention-to-treat design, this risk is largest in patients starting dialysis with a high rGFR during the first year. Despite all problems inherent in such an analysis, the results of this study should be considered by patients and physicians when deciding on the initial PD modality.

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