

Does Residual Renal Function Decline More Rapidly in Hemodialysis than in Peritoneal Dialysis? How Good Is the Evidence?

Anthony Horinek, Madhukar Misra

Residual renal function (RRF) is an important determinant of survival on dialysis. Preservation of RRF is also important for lowering comorbidity and improving quality of life. Initiation of dialysis is associated with gradual loss of RRF over time. As compared with hemodialysis, peritoneal dialysis is reported to be associated with a slower decline of RRF. Also, RRF depends on several factors that may affect its decline independent of dialysis. The analysis of RRF decline on dialysis is therefore complex. The present article examines the issues in detail and provides evidence if one form of dialysis is superior to the other in preserving RRF.

Key words

Residual renal function, hemodialysis

Introduction

The importance of residual renal function (RRF) during dialysis is increasingly being recognized. In dialysis patients, RRF is an independent predictor of actuarial patient survival. Each 1 mL/min of RRF [measured as the glomerular filtration rate (GFR)] is associated with a nearly 50% reduction in the rate of mortality (1). Preservation of RRF then becomes an important goal in light of evidence that RRF, unlike peritoneal clearance, determines survival in patients on dialysis. In the CANUSA study, a 12% reduction in the relative risk of death was observed for a weekly 5 L/1.73 m² increment in GFR. No such association was found with peritoneal clearance (2).

Discussion

RRF during dialysis

An increasing realization of the importance of RRF has made preservation of RRF an important but often neglected goal during dialysis. Preservation of RRF has gained further significance because of reports (3–5) of a faster decline of GFR on hemodialysis (HD) than on peritoneal dialysis (PD). However, comparing the loss of RRF across dialysis modalities is an issue fraught with difficulties. The literature is replete with studies in which follow-up is relatively short or flaws in methodology complicate the analysis. Those flaws include a small study population (*n*), retrospective design, incident–prevalent bias, and use of surrogate markers (such as urinary volume) for RRF to evaluate RRF. Lack of adjustment for comorbid disease, hemodynamic instability, infection, administration of nephrotoxins, and use of bioincompatible membranes, among others, also thwarts proper analysis.

Predictors of RRF during dialysis

In studying a random sample from a national data base [Dialysis Morbidity and Mortality Study (DMMS), wave 2], Moist *et al.* (6) demonstrated that demographic factors such as diabetes mellitus, congestive heart failure, female sex, and non white race predicted a faster rate of RRF decline in a group of patients starting dialysis. The study highlighted the fact that sicker patients may lose GFR faster, for reasons that are entirely unrelated to the type of dialysis. In the same study, the use of PD, of angiotensin converting enzyme inhibitors, and of calcium channel blockers were associated with a slower rate of RRF decline. In a prospective cohort study of 242 incident patients on PD,

Singhal *et al.* (7) reported that the faster loss of RRF (measured as slope of decline of residual GFR) during dialysis is predicted by the use of a larger dialysate volume, use of aminoglycosides, presence of diabetes mellitus, larger body mass index, and higher peritonitis rate. More recently, an Australian group reported that a high baseline RRF (measured as slope of decline of GFR) and a high dialysate-to-plasma (D/P) creatinine ratio may be risk factors for rapid loss of RRF in a group of patients starting PD (8).

Effect of inflammation and infection on RRF

Circulating levels of cytokines and other inflammatory markers are markedly elevated in patients with chronic renal failure. A low GFR is associated with an inflammatory state, suggesting impaired renal elimination of proinflammatory cytokines, increased generation of cytokines in uremia, or an adverse effect of inflammation on renal function (9). Furthermore, elevated levels of inflammatory markers such as C-reactive protein and interleukin-6 are reported to be inversely related to serum creatinine in predialysis patients (10). In patients on PD, enhanced peritoneal transport has been reported to be linked to loss of RRF as well as to inflammatory load (11). In keeping with the observations linking RRF to inflammatory load, Shin *et al.* (12) found, in a study of 102 stable PD patients, that the peritonitis rate was linked to a faster rate of decline of GFR. Similarly, the inflammatory milieu generated by bioincompatible membranes in HD has been the subject of much study. Biocompatible membranes such as polysulfone (as compared with bioincompatible cuprophane) have been reported to be associated with a slower rate of decline of RRF (13–15), although not always (16).

Effect of mode of PD on RRF

The rate of RRF decline has also been studied in continuous and intermittent PD (17,18). Initially, patients were thought to experience a more rapid rate of RRF loss with nightly intermittent PD and continuous cycling PD than with continuous ambulatory PD (CAPD). However, other studies have failed to find such a difference in the rate of RRF decline (6,8,19,20).

Informative censoring and its impact on comparative analysis of RRF decline on dialysis

Another methodologic factor that might affect comparisons of RRF decline between HD and PD is in-

formative censoring. The effect is seen when patients on PD with a very low GFR, or a more rapid rate of GFR decline, drop out of a study (die, are transplanted, or are transferred to another facility), with their data being excluded from the final analysis. That exclusion skews the analysis by creating a selection bias that may affect the final analysis of unadjusted data. Such an effect was first reported in the CANUSA study (21). A subsequent analysis by same workers reported that, even when data are adjusted for censoring, PD is associated with a slower rate of GFR decline (22).

Studies of the decline of RRF on dialysis

In one of the earlier studies that looked at the issue of RRF decline between PD and HD, Rottembourg (4) studied two matched groups of HD and PD patients over an 18-month period (Figure 1). Both groups demonstrated loss of RRF, but the HD group demonstrated a much greater loss over the first 18 months. During that time, 8% of PD patients became anuric, as compared with 56% of HD patients.

In a retrospective study of CAPD and HD patients, Lysaght *et al.* (5) studied RRF decline by using non linear regression to plot “best fit” lines of residual creatinine clearance over time. Those authors reported that the rate of decline in HD was double that in PD (fractional monthly decline: 58% in HD, 29% in PD).

To complicate such analyses further, a more recent report (23) found no difference in the rate of RRF decline between CAPD and HD. In this study of 475 incident dialysis patients, no difference in the rate of decline was observed. The HD patients in the study were dialyzed using high-flux, biocompatible mem-

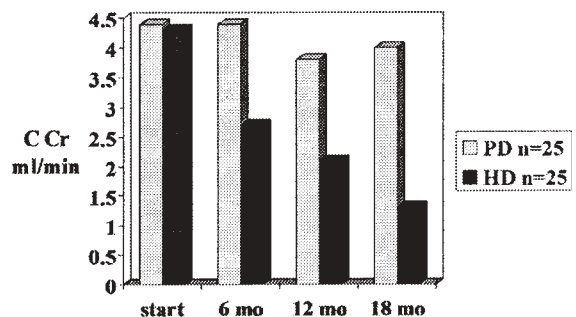


Figure 1 Residual renal function is preserved longer in peritoneal dialysis (PD). ^aC Cr = creatinine clearance; HD = hemodialysis. ^aBased on data from (4).

branes and ultra-pure dialysate. The data were adjusted for censoring, although the patients were not matched for age or comorbidity and were studied in a non-randomized fashion.

Table I summarizes some important studies in this area. In the most comprehensive analysis of decline of RRF on dialysis, Jansen *et al.* (25) prospectively studied 522 incident HD and PD patients and found that the decline of GFR was slower in PD patients than in HD patients. However, the difference in the rate of decline was less than that reported in other studies (Table I). That finding was thought to be attributable to the more widespread use of biocompatible membranes and adjustment for most of the baseline determinants of GFR decline. Higher diastolic blood pressure and higher urinary protein losses were found to be negatively associated with RRF at 1 year. Intradialytic hypotension in HD and dehydration in PD were associated with accelerated loss of RRF (25).

Does PD have a protective effect on RRF?

Several possible beneficial effects of PD on RRF have been postulated. As compared with HD patients, patients on PD are in a slightly volume-expanded state. Their osmotic drive is preserved, and they have a lower protein intake. HD patients, on the other hand, are prone to episodes of intradialytic hypotension and volume fluctuations with dialysis. Also, HD is complicated by the use of bioincompatible membranes that activate inflammatory mediators.

Conclusions

The question of which dialysis modality best preserves RRF is difficult to answer. As outlined earlier, the confounders are many, and the inter-patient variability is large. Moreover, many factors other than the dialysis modality may influence GFR. Informative censoring must also be taken into account in any analysis.

Evidence so far points to a slower rate of RRF decline on PD. However, none of the studies conducted thus far conclusively answer the question. A well-designed, prospective, longitudinal study should be performed to settle the issue; however, randomization will be extremely difficult to achieve. Such a study should adjust for comorbidities and should be large enough to obtain equivalent baseline groups. Patients on HD should be dialyzed using biocompatible membranes and ultra-pure bicarbonate-based dialysate. Long-term, systemic follow-up for GFR and patient outcome, adjusted for informative censoring, will be required.

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TABLE I Decline of residual renal function is faster on hemodialysis (HD) than on peritoneal dialysis (PD)^a

<i>Study</i>	<i>Type</i>	<i>HD/PD patients (n)</i>	<i>Difference in rate of decline</i>
Rottembourg (4)	Prospective	25/25	80%
Lysaght <i>et al.</i> (5)	Retrospective	57/58	50%
Misra <i>et al.</i> (22)	Retrospective	40/103	69%
Lang (24)	Prospective	30/15	69%
Jansen <i>et al.</i> (25)	Prospective	279/243	24%

^a Adapted from (25).

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- Corresponding author:*
 Madhukar Misra, MD MRCP (UK), Division of Nephrology, University of Missouri School of Medicine, Columbia, Missouri 65212 U.S.A.
E-mail:
 misram@health.missouri.edu

Dialysis Dose and Nutrition in Japanese Peritoneal Dialysis Patients

Makoto Ishizaki,¹ Akihiro C. Yamashita,² Hideki Kawanishi,³ Masahiko Nakamoto,⁴ Hiroyuki Hamada⁵

In the present study, we tried to determine the relationship between dialysis dose and nutrition in PD patients. We enrolled 100 Japanese outpatients, including 11 diabetic patients, who were on continuous ambulatory peritoneal dialysis [CAPD (n = 74)] and automated peritoneal dialysis [APD (n = 26)] at 49 local hospitals. In all patients, a peritoneal function test (PET) was performed using the PD NAVI software (JMS, Hiroshima, Japan). The PD NAVI software measured parameters of nutrition and dialysis dose; percentage creatinine generation rate (%CGR); percentage lean body mass normalized to body weight (%LBM); normalized protein nitrogen appearance (nPNA); total fluid removal (TFR), including urine; weekly total Kt/V; and creatinine clearance (CCr).

The %CGR correlated linearly with %LBM and nPNA, parameters of the nutrition status of the patients. The %CGR also showed a significant linear correlation with Kt/V, CCr, and TFR. Patients with a %CGR below 100% (the "low group") numbered 37 (32 men, 5 women). The CCr and TFR values in that group were lower than the CCr and TFR values in the other patients (the "high group"). Conclusively, the dialysis dose did not reach the solute clearance values proposed by the National Kidney Foundation Dialysis Outcomes Quality Initiative. That finding may be the result of prescribing and monitoring dialysis therapy based on the PET. The %CGR by PD NAVI may become an important index for clinical evaluation of PD dose and optimal dialysis prescription.

Key words

Weekly creatinine clearance, Kt/V, total fluid removal, percentage creatinine generation rate, nPNA, nutrition

Introduction

To improve the clinical effects of long-term peritoneal dialysis (PD), nephrologists must evaluate peritoneal function precisely and prescribe an optimal dialysis dose based on peritoneal transport characteristics. In 2003, Yamashita *et al.* (1) demonstrated and verified that the PD NAVI software (JMS, Hiroshima, Japan) simulated clinical PD trials and provided highly reliable information for better prescription. In the present study, we used the PD NAVI software to evaluate targets for optimal dialysis dose in Japanese patients.

Patients and methods

For the present study, we enrolled 100 Japanese outpatients (77 men, 23 women) on continuous ambulatory peritoneal dialysis [CAPD ($n = 74$)] and automated peritoneal dialysis [APD ($n = 26$)] at 49 local hospitals. We used the PD NAVI software (2) to perform a peritoneal function test (PET) in each patient. We also measured daily total fluid removal (TFR), including urine. The PD NAVI software calculated the weekly total Kt/V for urea, the weekly creatinine clearance (CCr), the percentage creatinine generation rate normalized to age and sex [%CGR (3)], the percentage lean body mass normalized to body weight (%LBM), and the normalized protein nitrogen appearance (nPNA). We used the %CGR as a parameter of nutrition.

Results and discussion

The 100 study patients included 11 patients with diabetes. Mean age of the group was 57.0 ± 11.0 years, mean height was 163.5 ± 8.4 cm, and mean weight was 61.7 ± 10.0 kg.

Based on the PET results, 17 patients were considered high transporters; 45 were considered high average; 36 were considered low average; and 2 were considered low transporters. Weekly Kt/V and CCr, and daily TFR were 1.99 ± 0.35 , 59.12 ± 12.06 L/1.73 m², and 1035.4 ± 617.3 mL respectively.

From: ¹Eijinkai Hospital, Miyagi; ²Department of Materials Science and Engineering, Shonan Institute of Technology, Kanagawa; ³Akane-Foundation Tsuchiya General Hospital, Hiroshima; ⁴Saiseikai Yahata Hospital, Kita-Kyushu; and ⁵Kyushu University, Fukuoka, Japan.

The %CGR correlated strongly with %LBM ($r = 0.721$, data not shown), nPNA ($r = 0.568$), Kt/V ($r = 0.537$), CCr ($r = 0.456$), and TFR ($r = 0.257$, Figure 1).

We divided patients into 2 groups by %CGR value: a “low group” at $<100\%$, and a “high group” at $\geq 100\%$. The low group contained 37 patients (32 men, 5 women). The Kt/V, CCr, and TFR in the low group were statistically lower than the respective values in the high group. Values of CCr and TFR in the low group were lower than the respective values in the high group (Figure 2).

Conclusively, the dialysis dose in the low group did not reach the solute clearance values proposed by the National Kidney Foundation Dialysis Outcomes Quality Initiative (4). That finding may be the result

of prescribing and monitoring dialysis therapy based on the PET (5,6).

The %CGR was strongly influenced by CCr, Kt/V, and TFR. Furthermore, the nPNA, which reflects dietary protein intake, was lower in the low group than in the high group [Figure 1(D)]. Based on those data, PD regimens aiming to increase CCr and maintain appropriate TFR may play an important role in improving the nutrition status of PD patients.

Conclusions

The PD NAVI software, which bases its results on a 24-hour dialysate collection, is useful not only for estimating peritoneal transport characteristics, but also for evaluating the nutrition status of patients.

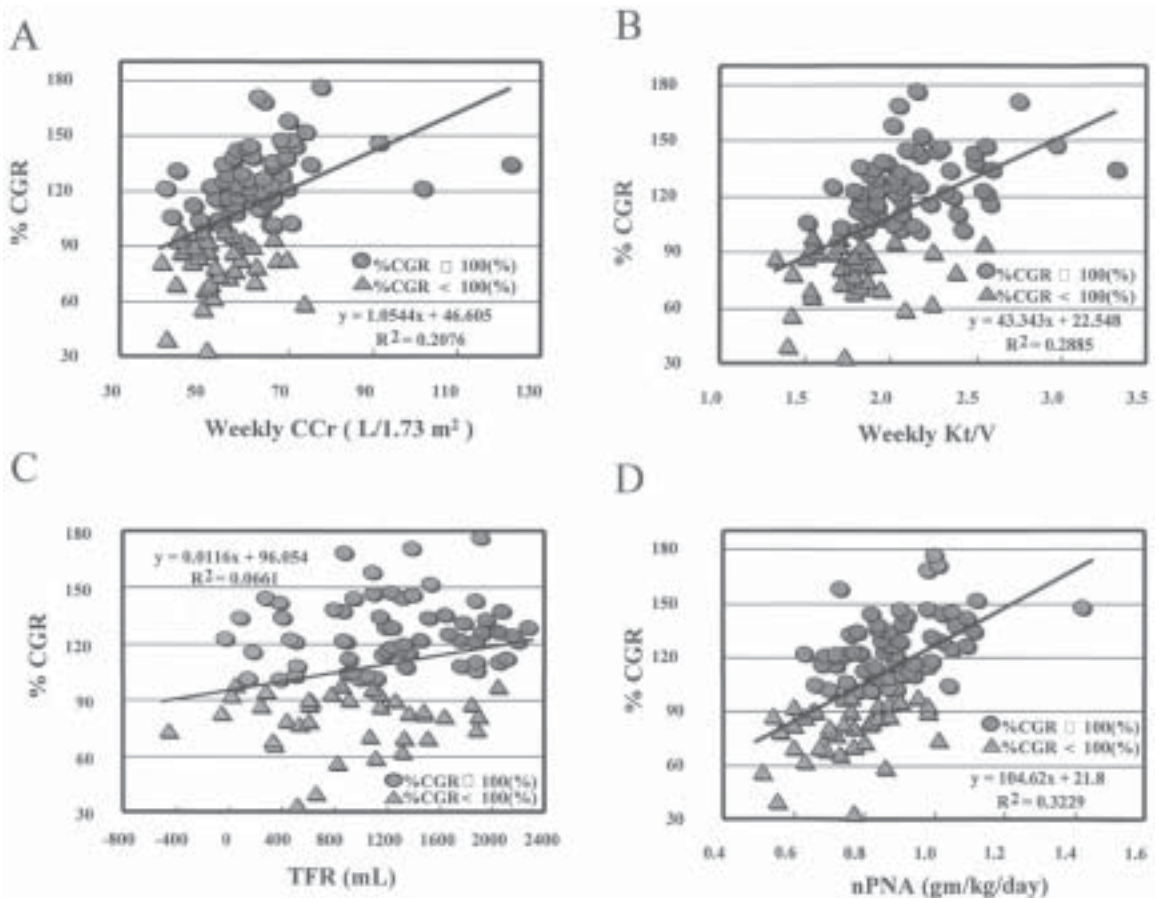


FIGURE 1 Relationships between percentage creatinine generation rate (%CGR) and (A) weekly total creatinine clearance (CCr), (B) weekly Kt/V urea, (C) daily total fluid removal (TFR), and (D) normalized protein nitrogen appearance (nPNA).

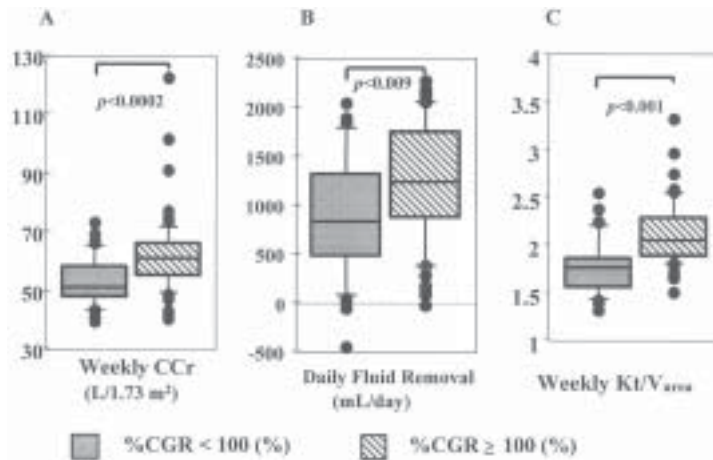


FIGURE 2 Comparison of (A) weekly creatinine clearance (CCr), (B) daily fluid removal, and (C) weekly Kt/V urea between the “low” (<100%) and “high” ($\geq 100\%$) percentage creatinine generation rate (%CGR) groups.

The %CGR is an important index for the clinical evaluation of PD dose and optimal dialysis prescription.

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Corresponding author:

Makoto Ishizaki, MD, Eijinkai Hospital, 2-5-1 Asahi, Furukawa, Miyagi 989–6117 Japan.

E-mail:

naganokc@coral.ocn.ne.jp