Benefits of preserving residual renal function in peritoneal dialysis

B Marrón[1], C Remón[2], M Pérez-Fontán[3], P Quirós[4] and A Ortíz[5]

[1]Renal Division, Baxter Healthcare, Madrid, Spain; [2]Peritoneal Dialysis Unit, Division of Nephrology, Hospital Universitario de Puerto Real, Cádiz, Spain; [3]Peritoneal Dialysis Unit, Division of Nephrology, Hospital Juan Canalejo, A Coruña, Spain; [4]Peritoneal Dialysis Unit, Division of Nephrology, Hospital Universitario de Puerto Real, Cádiz, Spain and [5]Peritoneal Dialysis Unit, Division of Nephrology, Fundación Jiménez Díaz, Madrid, Spain

Residual renal function (RRF) is of paramount importance in patients with end-stage renal disease, with benefits that go beyond contributing to achievement of adequacy targets. Several studies have found that RRF rather than overall adequacy (as estimated from total small solute removal rates) is an essential marker of patient and, to a lesser extent, technique survival during chronic peritoneal dialysis (PD) therapy. In addition, RRF is associated with a reduction in blood pressure and left ventricular hypertrophy, increased sodium removal and improved fluid status, lower serum β_2-microglobulin, phosphate and uric acid levels, higher serum hemoglobin and bicarbonate levels, better nutritional status, a more favorable lipid profile, decreased circulating inflammatory markers, and lower risk for peritonitis in PD. As compared with conventional hemodialysis, PD is associated with a slower decrease in RRF. This highlights the usefulness of strategies oriented to preserve both RRF and the long-term viability of the peritoneal membrane. Several factors contributing to the loss of RRF have been identified and should be avoided. Renoprotective drugs and new glucose-sparing, more biocompatible PD regimes may prove useful tools to preserve RRF and peritoneal membrane function in the near future.

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Correspondence: *B Marrón, Medical Affairs, Renal Division, Baxter Healthcare, P. Emp. San Fernando, Edificio Londres, 28830 Madrid, Spain. E-mail: belen_marron@baxter.com*

THE CONCEPT OF RESIDUAL RENAL FUNCTION AND A HISTORICAL REVIEW

Residual renal function (RRF) is in general defined as the residual glomerular filtration rate (GFR) in patients with end-stage renal disease. A progressive decrease in RRF is commonly observed in incident chronic kidney disease (CKD) stage 5 dialyzed patients as functional renal parenchyma is lost. The rate of decrease depends on several factors such as etiology of end-stage renal disease, treatment modalities, and exposure to nephrotoxic agents. It is important to remark that a residual GFR of $1\,ml\,min^{-1}$ is equivalent to a weekly peritoneal clearance of about 10 l. GFR is, however, not easy to measure in the common clinical setting, especially in patients receiving renal replacement therapy. The best clearance measure is still uncertain and different approaches have been used. Renal creatinine clearance is most frequently used, but it overestimates GFR and has errors of accuracy related to urine collection. Alternatively, the average of renal creatinine and urea clearances balances the overestimation of GFR by creatinine clearance with the underestimation by urea clearance. The presence of residual diuresis is required for RRF to exist. However, there may be discrepancies between the amount of residual diuresis and the residual GFR.

RRF has been a concept in evolution since the first reference to its importance in hemodialysis (HD) patients by Ahmad *et al.*[1] who studied the effect of RRF on the development of dialysis neuropathy and found that RRF played a major determinant role in dialysis requirements. More recently, Suda *et al.*[2] described the important contribution of RRF to overall nutritional status even in chronic HD patients. Despite this, the well-established importance of RRF is still ignored by many nephrologists, particularly in the HD field. Since the initial observation by Rottembourg *et al.*[3] that RRF is better preserved in patients treated with standard peritoneal dialysis (PD) than in those treated with conventional thrice-weekly HD, several other reports have confirmed this original finding.[4–9] In the pre-dialysis setting, maximal efforts are made by most physicians to preserve RRF to retard the need for renal replacement therapy.[10]

GENERAL BENEFITS OF RRF PRESERVATION

RRF has been associated with multiple beneficial effects. Preservation of RRF is associated with better long-term survival (lower relative risk of death) in dialysis patients,[11–17] a reduction in blood pressure (BP)[18] and left ventricular hypertrophy (LVH),[17,19–20] increased sodium removal,[21–22] improved fluid status,[22,23] increased serum β_2-microglobulin clearance and lower serum β_2-microglobulin levels,[24–27] higher serum hemoglobin levels,[17,19] better nutritional status,[17,26,28–29] and decreased circulating inflammatory markers.[30] Preservation of RRF contributes to achievement of adequacy targets,[11–17,31] better control of serum phosphate and uric acid levels,[17,21,32] higher serum bicarbonate levels,[26] a more favorable lipid profile,[33] and lower risk for peritonitis in PD.[28,34–36] We will now discuss in detail the relationship between RRF and PD adequacy, patient survival, cardiovascular disease, nutritional status, incidence of peritonitis, and quality of life.

THE IMPACT OF RRF ON PD ADEQUACY AND SURVIVAL

The relative contribution of endogenous (RRF) and exogenous (delivered dose of PD) clearance to the well-being and clinical outcome of PD patients has been a recurrent matter of interest during the last decade. In 1995, Maiorca *et al.*[37] provided evidence suggesting that total removal of small-size molecules could predict the outcome of PD patients. Their findings were basically confirmed 1 year later by the landmark CANUSA study.[38] Both studies disclosed a specific impact of RRF on survival. Unfortunately, the notion prevailed that the total dose of small solute clearance delivered was the essential point and that the removal rates provided by RRF and dialysis therapy were basically equivalent and interchangeable. This misinterpretation brought changes in the clinical guidelines for PD adequacy, which contributed significantly to hamper the progression of PD therapy during the following years. Ample quality evidence has now accumulated indicating that RRF and the delivered dose of dialysis have a well-differentiated influence on the global results of PD therapy. In 1999, two retrospective studies[11,28] suggested an association of RRF, but not of the dose of PD, with patient and technique survival. One year later, a cohort study of 1446 PD patients[12] showed a survival benefit of 40% for each 10 l per week per 1.73 m^2 increase in GFR, whereas PD removal rates had no apparent impact on outcome. Szeto *et al.*[39] reported similar findings the same year. The following year, an in-depth reanalysis of the CANUSA data showed that RRF and fluid removal, but not the amount of delivered PD, were strongly associated with survival.[14] For each 5 l per week per 1.73 m^2 increment in GFR, a 12% decrease in the risk of death was observed. Interestingly, diuresis (but not ultrafiltration (UF) or total fluid removal) was a stronger predictor of outcome than GFR itself. Also in 2001, another prospective study disclosed a risk reduction of 47% for each 10 l per week per 1.73 m^2 increase in GFR at the start of follow-up; in this case, total fluid and sodium removal did carry an independent effect on survival.[22] In 2003, a comprehensive report from the Netherlands Cooperative Study on the Adequacy of Dialysis, phase 2 (NECOSAD) group[16] confirmed previous findings showing a death risk reduction of 12% and a combined death-technique failure risk reduction of 10% per 10 l per week per 1.73 m^2 of GFR. Once again, the delivered dose of PD showed no apparent effect on clinical outcomes.

The ADEMEX study[40] was the first to provide hard evidence that, above certain limits, total small solute removal does not show an association with survival. Remarkably, RRF was, again, an independent marker of survival (risk reduction 11% for each 10 l per week per 1.73 m^2 increment in creatinine clearance). In summary, the main studies have very consistently shown that RRF rather than the delivered dose of PD is an essential marker of patient survival, whereas the relative effect of both factors on technique survival is less clear.[11,16,28,39]

We have reviewed the experience of the Andalusian Registry (Spain) (Remon C *et al.*, personal communication). All Andalusian incident PD patients from 1999 to 2005 with at least one complete measure of peritoneal kinetics and RRF (mean of urea and creatinine clearance) within the first year of therapy were included (402 patients). The population was divided in two groups of 201 patients each, according to whether the earliest value of RRF following initiation of PD was higher or lower than the median of the sample (4.33 ml min^{-1}). Renal and total small solute clearances and normalized protein catabolism rate were higher in the high

Table 1 | Andalusian registry—kinetic data

	RRF < 4.33	RRF > 4.33	*P*-value
RRF (ml min^{-1})	1.87 ± 1.4	7.48 ± 2.97	< 0.001
Renal Kt/*V*	0.39 ± 0.35	1.46 ± 0.64	< 0.001
Renal ClCr (l per week)	18.66 ± 16.33	72 ± 33.27	< 0.001
Peritoneal Kt/V	1.72 ± 0.43	1.41 ± 0.44	< 0.001
Peritoneal ClCr (l per week)	45.91 ± 13.65	38.65 ± 13.63	< 0.001
Total Kt/V	2.10 ± 0.54	2.82 ± 0.74	< 0.001
Total ClCr (l per week)	65.88 ± 20.03	109.22 ± 32.78	< 0.001
UF (ml)	238 ± 307	256 ± 336	NS
D/P creatinine	0.66 ± 0.13	0.67 ± 0.12	NS
nPCR (g per kg per 24 h)	0.90 ± 0.25	1.04 ± 0.26	< 0.001
Months on PD	22.09 ± 14.53	21.07 ± 15.65	NS

D/P, creatinine dialysate/plasma rate; nPCR, normalized protein catabolic rate; PD, peritoneal dialysis; RRF, residual renal function; UF, ultrafiltration.
Parameters of peritoneal kinetics in patients with RRF higher or lower than the median (median=4.33 ml min^{-1}). Mean 4.67 ± 3.64 ml min^{-1}.