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## Residual Renal Function in Hemodialysis Patients

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### 1. Introduction

The role of residual renal function (RRF) in the health and quality of life of both pre-dialysis and dialysis patients is equally important and now well established (Termorshuizen, Korevaar et al, 2003).

RRF plays an important role in maintaining fluid balance, phosphorus control, and removal of uremic toxins in dialysis patients. The importance of RRF in hemodialysis (HD) patients is less well appreciated and it is believed that RRF declined rapidly in HD patients (Morduchowicz, Winkler et al, 1994; Wang, Woo, et al, 2005). Decline of RRF also contributed significantly to anemia, inflammation, and malnutrition in end-stage renal disease (ESRD) patients (Wang, Sea et al, 2001; Pecoits-Filho, Heimbürger et al, 2003; Pecoits-Filho, Heimbürger et al, 2002; Wang, Wang et al, 2004). More importantly, RRF has also been shown to be a powerful predictor of mortality, especially in patients on peritoneal dialysis (PD) (Bargman, Thorpe et al, 2001; Brenner, Thijssen et al, 2011; Maiorca, Brunori et al, 1995).

Glomerular filtration rate (GFR) measured by isotope clearance is considered to be the standard measure of renal function. Other tests, such as serum creatinine, creatinine clearance, urea clearance, an average of the creatinine and urea clearances, and urine volume have been used to assess RRF in chronic kidney disease (Levey, 1990). Despite its limitations, urine volume, the simplest measure of RRF, has been correlated to GFR in studies and most authors defined loss of RRF as urine volume < 200 ml/24 hours (Moist, Port et al, 2000). Urine collections (24 hours for PD, interdialytic for HD) to measure urea and/or creatinine clearance usually done at beginning of chronic dialysis and every 1-3 months in patients with RRF.

In this chapter, we will review available data that have shown a positive impact of RRF on the survival and quality of life of dialysis patients, and outline the current strategies to preserve RRF in PD and HD patients.

## 2. The benefits of preserved RRF (Table 1)

- Improving patients survival
- Maintaining fluid balance
- Blood pressure control
- Decrease left ventricular hypertrophy
- Anemia control
- Phosphorus control
- Potassium control
- Uric acid control
- Improving nutritional status
- Decreasing inflammatory response

Table 1. Benefits of preserved RRF

### 2.1 RRF and patient survival (Table 2)

In 1995, Maiorca et al noted an independent relationship between the presence of RRF and survival in dialysis patients (Maiorca, Brunori et al, 2011). In their multivariate survival analysis of 102 PD and HD dialysis patients, each 1-ml/min increase in GFR was associated with a 40% reduced risk of death in the entire cohort and a 50% reduced risk of death in PD patients. Multicenter prospective cohort Canada-USA (CANUSA) Study of 680 incident PD patients clearly demonstrated that the predictive power for mortality in PD patients was attributed to RRF and not to the dose of PD (Bargman, Thorpe et al, 2001). The impact of RRF on outcome has not been examined in large cohorts of HD patients, likely due to the more rapid rate of decrease in RRF and its smaller relative contribution to total small-molecule clearance in HD compared with PD patients. In our retrospective study of 118 incident HD patients survival time was significantly lower in patients without RRF (48 vs 55 months) (Brenner, Thijssen et al, 2011). Crude mortality was 19.4% in anuric patients and 7.8% in patients with RRF, and cardiovascular disease was a leading cause of death for both groups. The presence of RRF was also associated with a strong trend toward fewer hospital days per patient-year. Shemin et al (Shemin, Bostom et al, 2001) reported that in the prospective observational study of 114 incident and prevalent HD patients, the presence of RRF was independently associated with a 65% decrease in risk of death, even after adjustment for duration of dialysis treatment, age, presence of diabetes, cardiovascular disease and serum albumin level. Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) (Termorshuizen, Dekker et al, 2004) has prospectively evaluated the contribution of treatment adequacy and RRF to patients survival after 3 and 6 months of treatment in a large incident HD population (740 patients). It showed the important

- RRF is a powerful predictor of mortality
- Each 1-ml/min increase in GFR was associated with a 40% reduced risk of death
- Each 1-unit increase in renal Kt/V resulted in 66% decrease in relative risk of death
- Independent relationship between the presence of RRF and survival in dialysis patients
- Preservation of RRF is important in the survival of dialysis patients

Table 2. RRF and dialysis patient survival

contribution of RRF to the overall survival of HD patients: each 1-unit increase in renal Kt/V resulted in 66% decrease in relative risk of death. Moreover, in patients with preserved RRF, increasing dialysis dose did not result in improved patient outcomes. The international prospective observational DOPPS study has also recently reported the diuretic use and presence of RRF was associated with a better survival in prevalent HD patients (Bragg-Gresham, Fissell et al, 2007). Diuretic use declined after the start of dialysis (9.2% in Europe versus 21.3% in the United States). Patients with RRF on diuretics had almost twice the chances of retaining RRF after 1 year with 7% lower all-cause and mortality and 14% lower cardiac-specific mortality compared to patients not receiving diuretics. All these and other observational studies suggest that preservation of RRF has an important role in the survival of both HD and PD patients.

## **2.2 RRF, volume control and cardiac hypertrophy**

RRF has been found to be important in maintaining fluid balance of dialysis patients, especially in patients on PD. Suboptimal fluid removal in PD patients is associated with greater rates of all-cause hospitalization and mortality (Ates, Nergizoglu et al, 2001). In the CANUSA Study, urine volume was a strong independent predictor of survival. Every 250 ml/imin urine output was associated with a 36% reduction in overall mortality ((Bargman, Thorpe et al, 2001). RRF may reduce or avoid the need for fluid restriction. Loss of RRF is independently associated with suboptimal blood pressure control, likely a result of chronic volume expansion (Ates, Nergizoglu et al, 2001; Konings, Kooman et al, 2003). The severity of left ventricular hypertrophy (LVH), a strong independent predictor of mortality in dialysis patients, inversely correlates with the presence of RRF (Pecoits-Filho, Heimbürger et al, 2002; Wang, Wang et al, 2004). In addition, loss of RRF is associated with more severe anemia, hypoalbuminemia, and higher arterial pressure (Pecoits-Filho, Heimbürger et al, 2003), all of which are important risk factors for cardiac hypertrophy in dialysis patients. Extracellular fluid (ECF) volume has been also reported to be associated with hypertension and left ventricular hypertrophy in HD patients (Fagugli, Pasini et al, 2003).

## **2.3 RRF and metabolic control**

Middle molecule clearance is one of the most widely recognized benefits of RRF. Patients with significant RRF are shown to have lower  $\beta_2$ -microglobulin ( $\beta_2$ M) levels (McCarthy, Williams et al, 1994; Montenegro, Martinez et al, 1992; Amici G, Virga et al, 1993) and thus are less prone to dialysis-associated amyloidosis (Copley JB, Lindberg et al, 2001). Preserved RRF is also associated with lower blood levels of uric acid, potassium (Morduchowicz, Winkler et al, 1994), and aluminium (Altmann, Butter et al, 1987), and higher levels of hemoglobin (Pecoits-Filho, Heimbürger et al, 2002), presumably due to increased levels of endogenous erythropoietin.

Hyperphosphatemia is prevalent in dialysis patients (Yavuz, Ersoy et al, 2008; Wang, Woo et al, 2004) and has been linked to vascular calcification and increased cardiovascular mortality in both HD and PD patients (Block, Hulbert-Shearon et al, 1998; Wang AY, Lai et al, 2006). RRF plays a major role in improving phosphate balance in both PD and HD patients ((Morduchowicz, Winkler et al, 1994).

## **2.4 RRF and inflammation**

Inflammation is highly prevalent in dialysis patients (Arici M, Walls et al, 2001) and established to be a strong predictor of mortality in dialysis patients. Loss of RRF was

associated with an increased inflammatory response with elevated solute vascular cell adhesion molecules (VCAM-1) and C-reactive protein (CRP) levels in PD patients (Wang AY, Lam et al, 2005), possibly as a result of impaired renal elimination of proinflammatory cytokines and increased cytokine generation (Witko-Sarsat, Descamps-Latscha et al, 1997). Conversely, the presence of inflammation also accelerated the decline of RRF (Shin, Noh et al, 1999).

### 2.5 RRF and nutritional status

Malnutrition is a common serious problem in dialysis patients, may be result of multiple factors including impairments in protein and energy metabolism, hormonal imbalances and poor food intake because of anorexia (Ikizler, Hakim et al, 1996). Dialysis dose may affect nutritional status and low dialysis efficacy is associated with higher rates of morbidity and mortality (Gotch, Sargent, 1985; Bergstrom, Lindholm, 1993). RRF contributes significantly to the appetite and total caloric intake (Wang, Sea et al, 2001; Wang, Sea et al, 2005), and overall nutritional status assessed using subjective global assessment, handgrip strength, or lean body mass in both HD and PD patients. Nutritional status is closely related to inflammation. In our study (Brener, Thijssen et al, 2008) anuric HD patients were older with lower baseline serum albumin and showed a trend toward greater length of stay for all causes, and all cause mortality including infectious mortality. Analysis of albumin kinetics performed in HEMO Study showed that a decrease in serum albumin in adequately dialysed patients was mostly due to an increase in the level of inflammation, rather than a decrease in protein intake (Kaysen, Dubin et al, 2000).

## 3. Preservation of RRF (Table 3)

- PD modality
- Avoidance of ECF volume depletion
- Avoidance of nephrotoxic insults (NSAIDs, radiocontrast agents, aminoglycosides)
- Antihypertensive medications (ACE-inhibitors and calcium channel blockers)

Table 3. Preservation of RRF

### 3.1 Patient-related factors

Decline of RRF is an unavoidable phenomenon caused by the degenerative and fibrosis process of chronic kidney disease (CKD). However, the rate of RRF loss is different among patients and may be affected by other factors such as patient-related factors, treatment modalities and practice patterns (Jansen, Hart et al, 2002). Patient-related factors include age, causal nephropathy and comorbid conditions. Decline of RRF has been shown to be age dependent (Hung, Young, 2003). Intercurrent events such as recurrent blood pressure drop during HD, cardiac events and sepsis may precipitate loss of RRF. Diabetics on PD have been shown to have a more rapid decline in RRF than nondiabetics (Singhal, Bhaskaran et al, 2000). Comorbid conditions, including congestive heart failure, poorly controlled hypertension, and coronary artery disease, also are associated with faster rates of RRF decrease (Shin, Noh et al, 1999). Patients with CKD secondary to glomerular disease lose RRF more rapidly than those with tubulointerstitial disease (Iest, Vanholder et al, 1989). In a large multicenter study, the majority of patients with adult polycystic kidney disease were

found to maintain a GFR greater than 2 ml/min for more than 4 years (Van Stone, 1995). Patients returning to dialysis therapy after kidney transplant failure have a more rapid decline in RRF than those initiating dialysis therapy with native kidney disease (Davies, 2001).

### **3.2 Impact of dialysis modality**

Observational studies showed the advantage of PD compared to HD in preserving RRF (Moist, Port et al, 2000; Rottembourg, Issad et al, 1983; Misra, Vonesh et al, 2001) but data from prospective randomized trials are lacking. PD is associated with better hemodynamic stability that may minimize ischemic renal insults and avoidance of the extracorporeal circulation of HD that promotes systemic inflammation, oxidative stress, and subsequent kidney injury (Rottembourg, Issad et al, 1983). Treatment with ultrapure dialysate and biocompatible membranes has been shown to slow the loss of RRF in incident HD patients (Schiffl, Lang et al, 2002). It has been suggested use of PD as an initial dialysis modality in patients with RRF to maximize RRF conservation and thus survival for patients on dialysis.

### **3.3 Avoidance of ECF volume depletion**

Observational data from NECOSAD Study suggest that episodes of volume depletion were an independent risk factor for the loss of RRF (Termorshuizen, Korevaar et al, 2003).<sup>1</sup> In a study by Gunal et al (Gunal AI, Duman et al, 2001) strict volume control in 47 PD patients led to 6% decrease in left ventricular hypertrophy and 28% decrease in mean urine volume in the 19 patients with RRF. Subclinical hypovolemia, even in presence of normal blood pressure, can lead to a decrease in RRF as a result of overzealous ECF volume depletion. Diuretics have been shown to increase urine volume and sodium removal, but do not affect the solute clearance (Moist, Port et al, 2000; van Olden, Guchelaar et al, 2003), and can be used, where appropriate, to provide better control of volume balance. As mentioned above, the extended use of loop diuretics may help to prolong diuresis and preserve RRF. Correction of fluid volume excess by combining dietary salt restriction and gentle ultrafiltration is a simple and effective approach to control hypertension and to reverse LVH (Konings, Kooman et al, 2003).

### **3.4 Avoidance of nephrotoxic insults**

Avoiding the use of radiocontrast agents or nephrotoxic drugs such as non-steroidal anti-inflammatory drugs or aminoglycosides is an important approach in protecting RRF. Aminoglycoside nephrotoxicity can be decreased by once-daily dosing, avoidance of concomitant nephrotoxins, monitoring of drug levels, and choice of the least nephrotoxic aminoglycoside used (Baker, Senior et al, 2003). Recent trials that used either adequate hydration, low-osmolar radiocontrast agents (Dittrich, Puttinger et al, 2006) as well as prophylactic acetylcysteine (Tepel, van der Giet et al, 2000) did not show long-term decline after contrast exposure despite a temporary decline in GFR immediately after contrast exposure.

### **3.5 Antihypertensive medications**

ACE-inhibitors and calcium channel blockers were associated with preservation of RRF in both PD and HD patients (Tepel, van der Giet et al, 2000). In a prospective study by Li PK et al (Li PK, Chow et al, 2003), PD patients treated with ramipril had a slower rate of RRF loss

compared to the control group. Investigation of the role of combination therapy with ACE inhibitors and ARBs and direct aldosterone blockade on RRF represent promising future strategies in slowing the rate of RRF decline in dialysis patients.

#### 4. Conclusion

RRF contributes to the clearance of both small and medium-sized solutes. It serves important metabolic and hemodynamic functions, and plays a crucial role in maintaining the cardiovascular health, nutritional status, and well-being of dialysis patients. RRF has also been shown to have a significant impact on the survival of dialysis patients, especially in PD dialysis. Health care providers need to realize that RRF is a very valuable asset to dialysis patients. Efforts to preserve RRF should continue even after patients are started on dialysis treatment, irrespective of the modality used

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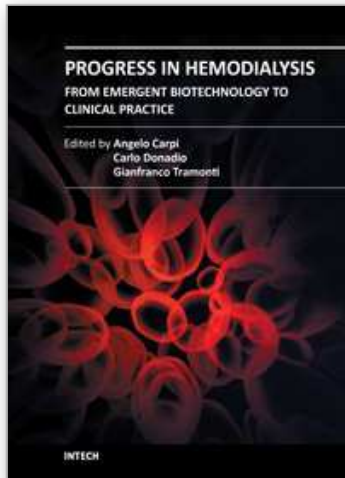
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