The impact of residual renal function on survival

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Dialysis patients have 10–20 higher mortality rates compared to controls. Factors discussed to influence mortality in dialysis patients are hypertension, left ventricular hypertrophy (LVH), increased pulse pressure, phosphorus, calcification, inflammation, malnutrition, fluid and sodium balance, interdialytic weight gain, removal of middle molecule uraemic toxins and residual renal function (RRF) [1]. LVH and hypertension are frequent findings in dialysis patients.
and the presence of LVH has been confirmed to be an important independent determinant of survival in dialysis patients [2]. One main goal is therefore to prevent LVH and control hypertension. Whereas the role of RRF for survival is well recognized in the peritoneal dialysis population, RRF is not currently emphasized in haemodialysis (HD) patients [3,4]. At the moment there exist two strategies for HD patients: (1) control of hypertension mainly by volume control with no or few antihypertensives at the expense of early loss of RRF and (2) preservation of RRF and control of hypertension with antihypertensive drugs.

The aim of this editorial should be to discuss the role of RRF for survival of dialysis patients with a special focus on the way of controlling hypertension in dialysis patients.

Residual renal function and uraemic toxicity profile

Several years ago, Cheung [5] already demonstrated that renal clearance is superior to dialysate clearance in eliminating toxins > 10 000 Da. This was confirmed by many other studies showing an overriding importance of RRF in beta2-M clearance and plasma levels [6,7]. RRF is also associated with better removal of protein-bound uraemic toxins like p-Cresol and phosphate [6]. Preservation of RRF is associated with lower plasma levels of AGE compounds in PD patients [8]. Another study also found an association of RRF and plasma levels of inflammation mediators, such as IL-6, CRP, hyaluron and nepterin [9].

Besides the overriding effect of RRF on middle molecule clearance, RRF is also of great importance in fluid and sodium removal. Cheng et al. [10] found a significant higher sodium removal in PD patients with RRF compared to anuric patients.

Residual renal function in relation to volume state/hypertension and cardiac hypertrophy

There has been an intriguing concern as to whether preservation of RRF in dialysis patients is actually at the expense of chronic volume overload. Gural et al. [11] in a prospective study of 19 incident HD patients subjected these patients for 3 months to antihypertensive therapy initially followed by 3 months of strict volume control with salt restriction. There was a 6% reduction in the LVH after antihypertensive therapy, compared with a 36% reduction after strict volume control. A dramatic fall of urine output after strict volume control was noted. The authors concluded that volume control had more significant effects when compared with blood pressure control alone with antihypertensives in inducing regression of LVH and that loss of RRF is the price to be paid. Limitations of this study should be a very small study population, better blood pressure control under volume control as opposed to antihypertensives and a short follow-up period.

This study is in direct contrast to the retrospective study by Wang et al. [15] where loss of RRF was associated with more severe LVH. Similar results as found by Wang are described by Menon et al. [13] showing that blood pressure control worsened with time on peritoneal dialysis as RRF declines. Wang [12] argues that loss of RRF is associated with more severe anaemia, greater degree of hypoalbuminaemia and higher arterial pressure, all well-known risk factors for cardiac hypertrophy. Other factors besides volume control like uraemic toxins and inflammation might play a role in LVH.

Lower extracellular fluid was observed in PD patients with a GFR > 2 ml/min compared to patients with GFR <2 ml/min despite higher peritoneal ultrafiltration [14]. Cheng et al. [10] in contrast to Könings et al. [14] found no difference in extracellular fluid and even higher mean blood pressure in patients with preserved RRF compared to anuric patients despite higher fluid and sodium removal in patients with RRF. The authors argued that the patients with RRF had possibly a higher intake of sodium than the anuric group since serum sodium was higher in this group. A study by Ates et al. confirmed the importance of total sodium and fluid removal in predicting survival of peritoneal dialysis patients. Total sodium and fluid removal was negatively correlated to blood pressure and significantly influenced hospitalization [15]. The importance of sodium balance was supported by Gunal et al. [16] showing that simple dietary restriction of salt intake was able to restore normal volume status in PD patients. Sodium balance achieved by low-sodium diet seems to be the key for volume control. The importance of low-sodium diet in HD has also been pointed out by Tuccillo et al. [17]. It has been proven that the normalization of blood pressure and volume overload with a low-salt diet is associated with LVH regression and diastolic dysfunction improvement. Ahmad [18] and Kooman et al. [19] also suggest that the effective management of hypertension requires normalization of the sodium balance. Use of diuretics was shown to increase urine volume and sodium, but not urea or creatinine excretion in PD patients [20,21]. Bragg-Gresham et al. [22] showed that HD patients administered diuretics had a 7% lower all-cause mortality risk and 14% lower cardiac-specific mortality risk. The authors argued that the positive effect of diuretic may simply reflect the known survival benefit conferred by RRF.

Residual renal function and survival

Several recent publications confirm that RRF and not the dose of peritoneal dialysis clearance was a powerful predictor of survival in PD patients [3]. RRF of 1 ml/min or 0.5 ml/min was associated with a 12% reduction of mortality in the NECOSAC study [23] and CANUSA study [24]. Reanalysis of the CANUSA study [24] showed that every 250 ml urine output was associated with a 36% reduction in overall mortality. There exist only few studies on the effect of RRF on survival in HD patients. Shemin et al. [25] reported that RRF was associated with a lower mortality risk in 114 prevalent HD patients in a prospective cross-sectional observational study. Termorshuizen et al. [26] analysed 740 HD patients and showed that each increase of 1/week in renal Kt/V was associated with an RR of death of 0.44. In contrast to these studies, Ozkalhaya et al. [27] found in their HD patient population a better long-term survival treated with strict volume control compared to US, EDTA and Turkish dialysis registries. Since Ozkalhaya et al. also applied to their dialysis population a strict sodium
restriction of 5 g per day, this alone might be the cause for the better survival compared to the registries. Such a strict sodium restriction is usually not applied to the general dialysis population in Europe and the United States. Charra [28] blames in his review that sodium restriction has been forgotten over the years and a very liberal diet of 10–15 g sodium per day is used in Europe.

**How to control hypertension in dialysis patients**

The key for blood pressure control in dialysis patients seems to be sodium restriction. Progressively, as renal failure worsens, the capacity of the kidney to excrete sodium decreases, and salt sensitivity and the incidence for hypertension increase. About 90% of end-stage renal failure patients are hypertensive and excess sodium is the dominant factor [28]. A sodium load essentially acts by expanding the ECV. Therefore, patients have to be educated to restrict sodium intake already in predialysis state and also by dialysis patient with preserved RRF to avoid volume overload.

Balancing sodium intake and removal is easier with RRF since sodium removal can be increased by diuretics. Furthermore, patients with RRF have less problems with potassium. Since potassium restriction in the diet is often contradictory to sodium restriction, it should be easier for patients with RRF to realize sodium restriction.

An independent protective effect of antihypertensive drugs on mortality was reported by Agarwal [2]. He postulated that ACE inhibitors and beta blockers appear to be attractive agents due to their independent cardiovascular benefits. Drugs that block the sympathetic nervous system are uniformly protective in dialysis patients [29]. A novel flavin adenine dinucleotide-dependent amine oxidase, called renalase, was recently discovered. It is secreted by the kidney and metabolizes catecholamines. The plasma concentration of renalase is markedly reduced in patients with end-stage renal disease. Renalase reduces sympathetic activity, decreases cardiac contractility and blood pressure and prevents increase in peripheral vascular tone. Low levels of renalase might be an explanation for the increased sympathetic activity found in dialysis patients [30].

**Conclusion**

Preservation of RRF improves survival both in peritoneal and HD patients. RRF is important for clearances of middle molecules and sodium removal. Up to now, there exists no prospective controlled study to answer the question about the right strategy especially in HD. We need prospective studies comparing blood pressure control via aggressive ultrafiltration control and sodium restriction at the expense of RRF or with drugs, sodium restriction and preservation of RRF. Preservation of RRF makes it necessary to control volume status of the patients. Sodium restriction in patients with and without RRF seems to be the prerequisite to avoid overhydration.

**Conflict of interest statement.** None declared.

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**Short- and long-term survival after acute kidney injury**

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**Introduction**

Acute kidney injury (AKI) is a heterogeneous syndrome encompassing a broad spectrum of insults and changes in function that occur acutely to the kidneys [1]. This syndrome is increasingly encountered in sick hospitalized patients, in particular those admitted to intensive care [2–4]. This recent increase in the occurrence of AKI probably reflects not only changes in the characteristics of hospitalized patients (i.e. aging population, greater burden comorbid disease, severity of illness) but also perhaps a corollary of achievements made by modern medicine (i.e. more complex interventions, capability of advanced and prolonged life support) [5].

The development of AKI undoubtedly has important implications on both short- and long-term morbidity and mortality [6]. Observational data consistently indicate that 4–5% of all critically ill patients develop severe AKI and require initiation of renal replacement therapy (RRT) [7–9]. This cohort generally has a poor prognosis with mortality rates often exceeding 60% [7–9]. Moreover, survivors often have protracted stays in ICU and hospital, mild declines in health-related quality of life, impairments in functional status and their care consumes enormous health resources [8,10–12]. Despite this, the available literature provides surprisingly little insight into the long-term kidney prognosis for these patients.

The risk of developing AKI associated with critical illness is likely modified by the presence of pre-morbid chronic kidney disease (CKD) [13]. Similarly, the development of AKI in those with CKD may modify the natural history of their illness and accelerate progression towards end-stage kidney disease (ESKD) and dialysis dependence [14]. Overall, an estimated 8–22% of critically ill patients suffering an episode of severe AKI fail to recover kidney function during hospitalization and need to be discharged on chronic dialysis [8,9,15]. Yet, there is a paucity of data exploring the impact of only partial or incomplete recovery of function in those surviving critical illness.

In the last few years, a consensus definition and classification scheme for AKI, the RIFLE criteria, has been developed, validated and shown to have predictive ability, robustness and clinical relevance across a range of settings [16–20]. This has been a key advance for both clinical care and research activities in a field that was previously beleaguered by the lack of a standardized definition [21]. The RIFLE criteria also share some commonality with the recently developed staging criteria for CKD proposed by the Kidney Disease Outcomes Quality Initiative (K/DOQI) [22]. While the RIFLE criteria incorporate two outcome stages associated with AKI (i.e. loss, ESKD), these are likely insufficient over the long term for those patients with incomplete...