Role of Residual Renal Function in Phosphate Control and Anemia Management in Chronic Hemodialysis Patients

E. Lars Penne,† Neelke C. van der Weerd,*† Muriel P.C. Grooteman,†‡ Albert H.A. Mazairac,* Marinus A. van den Dorpel,§ Menso J. Nubé,†‡ Michiel L. Bots,‖ Renée Lévesque,¶ Piet M. ter Wee,†‡ and Peter J. Blankestijn,* on behalf of the CONTRAST investigators*

*Department of Nephrology, University Medical Center Utrecht, Utrecht, The Netherlands; †Department of Nephrology, VU Medical Center, Amsterdam, The Netherlands; ‡Institute for Cardiovascular Research, VU Medical Center, Amsterdam, The Netherlands; §Department of Internal Medicine, Maasstad Hospital, Rotterdam, The Netherlands; ‖Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; and ¶Department of Nephrology, Centre Hospitalier de l'Université de Montréal, Québec, Canada

Correspondence: Dr. Peter J. Blankestijn, Department of Nephrology, Room F03.223, University Medical Center–Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands. Phone: +31-88-7557336; Fax: +31-30-2543492; E-mail: p.j.blankestijn@umcutrecht.nl

Summary

Background and objectives There is increasing awareness that residual renal function (RRF) has beneficial effects in hemodialysis (HD) patients. The aim of this study was to investigate the role of RRF, expressed as GFR, in phosphate and anemia management in chronic HD patients.

Design, setting, participants, & measurements Baseline data of 552 consecutive patients from the Convective Transport Study (CONTRAST) were analyzed. Patients with a urinary output ≥100 ml/24 h ($n = 295$) were categorized in tertiles on the basis of degree of GFR and compared with anuric patients (*i.e.*, urinary output <100 ml/24 h, $n = 274$). Relations between GFR and serum phosphate and erythropoiesis-stimulating agent (ESA) index (weekly ESA dose per kg body weight divided by hematocrit) were analyzed with multivariable regression models.

Results Phosphate levels were between 3.5 and 5.5 mg/dl in 68% of patients in the upper tertile (GFR > 4.13 ml/min per 1.73 m^2), as compared with 46% in anuric patients despite lower prescription of phosphate-binding agents. Mean hemoglobin levels were 11.9 ± 1.2 g/dl with no differences between the GFR categories. The ESA index was 31% lower in patients in the upper tertile as compared with anuric patients. After adjustments for patient characteristics, patients in the upper tertile had significantly lower serum phosphate levels and ESA index as compared with anuric patients.

Conclusions This study suggests a strong relation between RRF and improved phosphate and anemia control in HD patients. Efforts to preserve RRF in HD patients could improve outcomes and should be encouraged.

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Introduction

The presence of residual renal function (RRF) in chronic dialysis patients contributes to improved clearance of uremic toxins, in particular the clearance of middle molecules and protein-bound solutes (1,2). Concentrations of uremic substances such as uric acid, β_2-microglobulin (β2M), and *p*-cresol are substantially lower in patients with RRF as compared with anuric patients (2–7). In addition, the need for dietary and fluid restriction is reduced, which may partly explain their better nutritional state (8) and quality of life (9). In terms of clinical outcomes, the degree of RRF has been inversely associated with left ventricular hypertrophy, independent of blood pressure or anemia level (10). Moreover RRF has been associated with improved survival in hemodialysis (HD) and peritoneal dialysis (PD) patients (11–16).

Most of the above mentioned studies have been performed in PD patients and not in HD patients. The importance of RRF seems often underappreciated in HD patients, possibly because of the general belief that renal function rapidly declines after initiation of HD treatment. However, renal function can be preserved for several years after the start of HD in many patients, especially when ultrapure dialysis fluids and biocompatible dialyzers are used (17,18).

The effect of RRF on phosphate control and anemia management has been reported for PD patients but has thus far not been well studied in HD patients (1). In a cohort consisting of HD and PD patients, a relation between phosphate levels and RRF was found, but phosphate-binding agents were not accounted for in that study (19). Furthermore, erythropoiesis-stimulating agent (ESA) requirements were lower in HD patients with RRF in a single-center retrospective study, possibly because of decreased ESA resistance, but these observations were not adjusted for potential confounders (15). In a recent study, erythropoietin dose requirements were significantly lower in patients with urinary output 1 year after initiation of HD as compared with those without (16). The aim of the study presented here was to investigate the relation

between RRF and phosphate control and anemia management in a large cohort of stable chronic HD patients.

Materials and Methods

Patients

For the study presented here, baseline data of 569 consecutive HD patients recruited from 25 Dutch and 2 Canadian dialysis centers and participating in the Convective Transport Study (CONTRAST; NCT00205556) were analyzed (20). Seventeen patients were excluded from the analyses because data on RRF, serum phosphate, hemoglobin level, and prescription of phosphate binders or ESAs were missing. The 552 remaining patients (≥18 years) were treated 2 or 3 times per week with a single-pool Kt/V > 1.2 using low-flux synthetic dialyzers and ultrapure dialysis fluids. Exclusion criteria included treatment with hemo(dia)filtration or high-flux HD in the preceding 6 months, a life expectancy <3 months, and severe incompliance, as described previously (20). The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Boards of the participating centers. Written informed consent was obtained from all patients before enrollment.

Data Collection

Data on demographics and medical history (history of cardiovascular disease, diabetic state, and dialysis vintage) were prospectively collected, in addition to clinical parameters (predialysis blood pressure, dry weight, and body mass index), dialysis treatment parameters (dialysis vintage, frequency, session length, intradialytic weight loss [pre- − postweight], and type of vascular access) and prescribed medication (phosphate-binding agents, ESAs, angiotensin converting enzyme inhibitors [ACEIs], and angiotensin II receptor antagonists [ARBs]). Blood samples were generally drawn on the first session of the week before dialysis, for routine laboratory assessments, and for β2M. An additional blood sample was drawn after dialysis for determination of postdialysis urea and creatinine concentration. All laboratory samples were analyzed in the local hospitals by standard laboratory techniques. Albumin was measured with bromcresol green (BCG) and bromcresol purple (BCP) assays. Values obtained with BCP were converted to BCG using the formula: $albumin_{BCG} = 0.55 + albumin_{BCP}$ (in g/dl) (21). Calcium concentrations were corrected for albumin (22). Twenty-four-hour urinary samples were collected in patients with a urinary output of ≥100 ml/d. GFR was calculated as the mean of creatinine and urea clearance and adjusted for body surface area (ml/min per 1.73 m^2) using the geometric mean of post- and predialysis plasma samples to estimate the mean creatinine and urea concentrations during the collection period (23). RRF was expressed as GFR and was considered zero in patients with a urinary output <100 ml/d. The second-generation Daugirdas formula was used to calculate single-pool Kt/V for urea (24). The normalized protein equivalent of total nitrogen appearance (nPNA; g/kg per day) (25) and albumin were considered as surrogates for nutritional state. Prescribed dosages of phosphate-binding agents and ESAs were converted to daily defined doses (DDD) using conversion factors as provided by the World Health Organization (WHO) Drug Classification (http://www.whocc.no/atcddd/). Phosphate-lowering agents included calcium carbonate (DDD 3 g), calcium acetate (DDD 2 g), calcium carbonate/calcium lactogluconate (DDD 0.5 g), sevelamer (DDD 6.4 g), and lanthanum carbonate (DDD 2.25 g). ESA included darbepoetin (DDD 4.5 μg) and epoetin α and β (DDD 1000 IU). Phosphate and anemia treatment targets were defined as a serum phosphate concentration between 3.5 and 5.5 mg/dl and a hemoglobin concentration between 11 and 13 g/dl, respectively (22,26). ESA resistance was expressed as an ESA index (*i.e.*, weekly ESA dose [in DDD] divided by body weight [kg] and hematocrit [%]).

Statistical Analyses

All variables were reported as mean ± SD or SEM, median with interquartile range, or as proportion when appropriate. Patients were subdivided into four groups. The first group consisted of all anuric patients (urinary output < 100/ml per 24 hours). The second, third, and fourth groups comprised patients with residual urinary output ≥100 ml/24 h categorized in tertiles according to GFR (first tertile: <1.65 ml/min per 1.73 m^2; second tertile: 1.66 to 4.13 ml/min per 1.73 m^2; third tertile >4.13 ml/min per 1.73 m^2). Comparisons between these groups were analyzed with ANOVA, Kruskal–Wallace, and χ^2 tests, respectively. To test whether patients with RRF more frequently reached phosphate and anemia treatment targets, we used logistic regression. The relation between GFR and predialysis phosphate level was analyzed with a multivariable linear regression model. Predefined variables (*i.e.*, sex, age, diabetes, dialysis vintage, body mass index, albumin, nPNA, Kt/V, and phosphate-binder dose) were selected for this model if they showed a univariate relation with serum using a cutoff value of $P < 0.15$. A similar model was developed to investigate the relation between GFR and ESA index. Because of non-normality, ESA index was log transformed (logESA index) and the analysis was restricted to ESA users. For this model sex, age, diabetes, dialysis vintage, Kt/V, ACEI or ARB use, albumin, transferrin saturation (TSAT), and intact parathyroid hormone (iPTH) were selected. Finally, the multivariable regression analyses were repeated after replacing the GFR tertiles by tertiles of 24-hour urinary output (first tertile: <430 ml/24 h; second tertile: 431 to 999 ml/24 h; third tertile: >999 ml/24 h). Two-tailed $P < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS software (version 16.0.1; SPSS, Inc., Chicago, IL).

Results

Patient Characteristics

The primary renal diagnoses of the 552 patients are shown in Table 1. The mean age of the patients was 63.8 ± 14 (±SD) years and 62% were men (Table 2). Ninety-four percent of the patients were treated 3 times per week. An arteriovenous fistula was the predominant type of vascular access (79%). Dialysis vintage, treatment times, and dialysis Kt/V were higher in anuric patients as compared with patients with GFR, but the total weekly Kt/V was lower in anuric patients (Table 2). Predialysis serum β2M levels (Table 3) were more than 2 times higher in anuric patients (38.9 ± 13.3 g/L) as compared with patients with an GFR > 4.18 ml/min per 1.73 m^2 (17.7 ± 6.1 g/L, $P < 0.001$). GFR was positively related to urinary output ($r_s = 0.79$, $P < 0.001$) and inversely related to intradialytic weight loss.

Phosphate Control

Patients in the upper tertile (GFR > 4.13 ml/min per 1.73 m^2) were more likely to have a phosphate level between 3.5 and 5.5 mg/dl than anuric patients (68% *versus* 46%, respectively, odds ratio = 2.4 ± 0.3). This could mainly be explained by the observation that patients with RRF less often had phosphate levels above 5.5 mg/dl (Figure 1). Overall, 51% of the patients had a phosphate level between 3.5 and 5.5 mg/dl. Eighty-four percent of the patients were taking at least one phosphate-binding agent. Anuric patients used on average six tablets (3 to 9.5) of phosphate-binding agents per day, as compared with 3 (1 to 6.3) in patients in the upper tertile ($P = 0.001$). The dose of phosphate-binding agents, expressed as DDD, was lower in patients within the higher GFR tertiles (Figure 2; P value for univariable linear trend = 0.008). In the multivariable regression model (Table 4), the predialysis phosphate concentration was significantly lower in patients in the upper tertile ($B = -0.7$ mg/dl 95% confidence interval [CI] −1.1 to −0.3, $P < 0.001$). Apart from GFR, age ($P < 0.001$) and dialysis vintage ($P = 0.001$) were inversely related to the predialysis phosphate concentration, whereas nPNA ($P < 0.001$) and albumin ($P < 0.001$) were positively related. Excluding patients on a 2-times weekly dialysis schedule did not materially change these results. When GFR tertiles were replaced by tertiles of urinary output, patients in the upper tertile (≥1000 ml/24 h) had significantly lower predialysis serum phosphate than anuric patients ($B = -0.4$ mg/dl 95% CI −0.8 to −0.1, $P = 0.03$); the relation between urinary output and serum phosphate level did not reach significance for the other two tertiles.

Table 1. Primary renal diagnosis

Category	Percent
Renal vascular disease	28
Diabetes mellitus	18
Primary glomerulopathy	13
Interstitial nephropathy	9
Cystic kidney disease	8
Multisystem disease	4
Other	12
Unknown	8

Anemia Management

Hemoglobin levels were >11 g/dl in 77% of the patients and >13 g/dl in 19%. Mean hemoglobin levels (11.9 ± 1.2 g/dl, Table 2) were not different for anuric patients and for patients with RRF. Ninety percent of the patients ($n = 499$) were using ESAs. Of these patients, 71% used darbepoetin alpha ($n = 356$, median dose 0.58 μg/kg per week, interquartile range 0.33 to 1.03), 5% used epoetin alpha ($n = 36$, 68 U/kg per week, interquartile range 53 to 163), and 23% used epoetin beta ($n = 117$, 83 U/kg per week, interquartile range 54 to 132). The ESA index was inversely related to GFR (Figure 3, P value for univariable linear trend = 0.001). The mean ESA index was 31% lower in the patients with GFR >4.13 ml/min per 1.73 m^2 as compared with the anuric patients (0.42 *versus* 0.29 DDD/wk per kg per hematocrit, $P = 0.003$). Among ESA users (Table 5), logESA index was inversely related to male sex ($P = 0.001$), dialysis vintage ($P < 0.001$), GFR >4.13 ml/min per 1.73 m^2 ($P < 0.001$), albumin ($P < 0.001$), and TSAT ($P < 0.001$, Table 5). ACEIs and/or ARB use and iPTH did not show a relation with logESA index. Excluding patients on a 2-times weekly dialysis schedule did not materially change these results. Similar results were obtained with tertiles of urinary output instead of GFR; that is, logESA index was lowest in patients with urinary output ≥1000 ml/24 h ($B = -0.42$ DDD/wk per kg per hematocrit, 95% CI −0.61 to −0.22, $P < 0.001$).

Discussion

The study presented here showed a relation between RRF and phosphate and anemia management in a large cohort of stable and adequately dialyzed HD patients. Phosphate treatment targets were reached much more often in patients with high GFR, although these patients used less phosphate-binding agents. Moreover, less ESAs were required to reach target hemoglobin levels independent of other risk factors, suggesting less ESA resistance in patients with high GFR because hemoglobin levels were similar. Dialysis dose and treatment time tended to be lower in the patients with RRF.

Hyperphosphatemia is a well known risk factor for all-cause and cardiovascular mortality in HD patients (27–29). It has been associated with secondary hyperparathyroidism, renal osteodystrophy, and with the development of vascular calcifications (30). Conversely, low phosphate levels have also been associated with increased mortality, partly reflecting low nutritional state (29). Despite dietary counseling and treatment with phosphate-binding agents, adequate phosphate control is not achieved in many HD patients. In the study presented here, only half of the

Table 2. Patient and dialysis characteristics

	GFR = 0 (ml/min per 1.73 m^2)	GFR 0 to 1.65 (ml/min per 1.73 m^2)	GFR 1.66 to 4.13 (ml/min per 1.73 m^2)	GFR > 4.13 (ml/min per 1.73 m^2)	All Patients	P^a
n	270	94	94	94	552	
Gender (% male)	61	63	67	56	62	0.51
Age (years)	62.3 ± 14	64.4 ± 16	64.8 ± 13	66.2 ± 12	63.8 ± 14	0.08
History of cardiovascular disease (%)	42	39	45	51	43	0.34
Diabetes mellitus (%)	19	28	27	27	23	0.17
Body mass index (kg/m^2)	24.9 ± 4.2	25.7 ± 5.4	24.7 ± 4.1	26.4 ± 5.1	25.2 ± 4.9	0.02
Dialysis vintage (years)	3.1 (1.5 to 5.4)	1.8 (0.8 to 3.1)	1.5 (0.83 to 2.5)	1.0 (0.7 to 2.1)	2.0 (1.0 to 4.0)	<0.001
Treatment time (h/wk)	12 (10.5 to 12)	12 (10.5 to 12)	10.9 (10.5 to 12)	10.5 (9 to 12)	12 (10.5 to 12)	<0.001
Kt/V–dialysis (per week)	4.23 ± 0.66	4.07 ± 0.54	4.07 ± 0.82	3.64 ± 0.62	4.08 ± 0.69	<0.001
Kt/V–renal (per week)	–	0.21 ± 0.10	0.64 ± 0.23	1.56 ± 0.68	0.40 ± 0.64	<0.001
Kt/V–total (per week)	4.23 ± 0.66	4.28 ± 0.53	4.70 ± 0.83	5.21 ± 0.84	4.48 ± 0.80	<0.001
Intradialytic weight loss (L)	2.13 ± 0.79	2.15 ± 0.90	1.69 ± 0.89	0.99 ± 0.93	1.87 ± 0.95	<0.001
GFR (ml/min per 1.73 m^2)	–	0.87 (0.56 to 1.17)	2.64 (2.13 to 3.46)	6.19 (4.71 to 7.95)	0.24 (0.0 to 2.69)	<0.001
Urinary output (L per day)	–	241 (158 to 400)	745 (488 to 1000)	1245 (916 to 1800)	700 (350 to 1150)	<0.001
nPNA	1.07 ± 0.24	1.12 ± 0.23	1.25 ± 0.56	1.25 ± 0.29	1.14 ± 0.34	<0.001
Phosphate-binding agents (%)	85	88	83	77	84	0.14
ESA (%)	90	92	92	89	90	0.94
ACEI or ARB (%)	40	64	49	61	49	<0.001

A urinary output <100 ml/24 h was defined as GFR = 0 ml/min per 1.73 m^2. Patients with a urinary output >100 ml/24 h were divided in tertiles based on GFR. Values expressed as mean ± SD or median (interquartile range) or as percentages.

[a]Between groups ANOVA.

Table 3. Hematologic and biochemical laboratory parameters

	GFR = 0 (ml/min per 1.73 m^2)	GFR 0 to 1.65 (ml/min per 1.73 m^2)	GFR 1.66 to 4.13 (ml/min per 1.73 m^2)	GFR > 4.13 (ml/min per 1.73 m^2)	All Patients	P[a]
n	270	94	94	94	552	
Hemoglobin (g/dl)	11.8 ± 1.3	12.0 ± 1.2	11.8 ± 1.1	12.0 ± 1.2	11.9 ± 1.2	0.39
Hematocrit (%)	36.0 ± 4.0	36.4 ± 3.7	35.8 ± 3.5	36.3 ± 4.1	36.1 ± 3.9	0.60
β2M (g/L)	38.9 ± 13.3	30.4 ± 10.4	28.7 ± 9.9	17.7 ± 6.1	32.1 ± 13.8	<0.001
Phosphate (mg/dl)	5.15 ± 1.62	5.51 ± 1.57	5.01 ± 1.42	4.77 ± 1.17	5.12 ± 1.53	0.008
Calcium (mg/dl)	9.3 ± 0.7	9.2 ± 0.8	9.3 ± 0.7	9.3 ± 0.6	9.3 ± 0.7	0.41
iPTH (pg/ml)	21.0 (10.0 to 38.3)	28.0 (14.4 to 40.5)	16.7 (7.9 to 30.8)	16.1 (8.1 to 30.1)	20.3 (10.0 to 35.8)	0.005
Albumin (g/dl)	4.0 ± 0.4	4.0 ± 0.4	4.0 ± 0.4	4.1 ± 0.4	4.0 ± 0.4	0.26
Ferritin (ng/ml)	330 (182 to 601)	386 (224 to 683)	329 (210 to 546)	292 (152 to 554)	331 (190 to 581)	0.09
TSAT (%)	23 ± 11	24 ± 11	26 ± 12	24 ± 11	24 ± 11	0.29

Values expressed as mean ± SD or median (interquartile range). To convert hemoglobin in g/dl to mmol/L, multiply by 0.62; albumin in g/dl to g/L, multiply by 10; phosphate in mg/dl to mmol/L, multiply by 0.323; calcium in mg/dl to mmol/L, multiply by 0.25; ferritin from ng/ml to μg/L, multiply by 1.

[a]Between-group ANOVA.

Figure 1. | Percentage of patients below, within, or above phosphate treatment targets by GFR category.

Figure 2. | Relationship between RRF and use of phosphate-binding agents. Each box shows the distribution of phosphate-binding agent use in DDD for the range of RRF as indicated on the horizontal axis. The mean dose is shown by the black circle, the median by the middle horizontal line, and the 25th and 75th percentiles by the bottom and top of the box, respectively. P for univariable linear trend = 0.008.

patients had phosphate levels within the range from 3.5 to 5.5 mg/dl, similar to previous reports (29,31). However, HD patients with GFR >4.13 ml/min per 1.73 m^2 were much more likely to have a phosphate level within this range as compared with anuric patients, although less phosphate-binding agents were required. Previously it has been shown that phosphorus excretion strongly correlates with creatinine clearance in chronic HD patients (3), suggesting that a beneficial role of RRF on phosphate control may to a certain extent be explained by increased urinary removal. At the same time, a serum phosphate level below 3.5 mg/dl was more prevalent in the anuric patients and may reflect a worse nutritional state. Less use of phosphate-binding agents in patients with RRF may contribute to improved quality of life and

Table 4. Univariable and multivariable analyses into factors that relate to predialysis serum phosphate level

Determinant	Univariable Model		Multivariable Model	
	B	95% CI	*B*	95% CI
Gender (male)	−0.12	−0.38 to 0.14		
Age (10 years)	−0.26	−0.35 to −0.17[a]	−0.22	−0.31 to −0.12[a]
Diabetes	−0.09	−0.39 to 0.22		
Dialysis vintage (years)	−0.04	−0.09 to 0.00[a]	−0.08	−0.12 to −0.03[a]
Body mass index (kg/m^2)	0.01	−0.01 to 0.04		
GFR 0 to 1.65 (ml/min per 1.73 m^2)[b]	0.45	0.12 to 0.79	0.19	−0.17 to 0.54
GFR 1.66 to 4.13 (ml/min per 1.73 m^2)[b]	−0.11	−0.45 to 0.22	−0.32	−0.67 to 0.03
GFR > 4.13 (ml/min per 1.73 m^2)[b]	−0.45	−0.79 to −0.10	−0.69	−1.1 to −0.31[a]
Serum albumin (g/dl)	0.74	0.41 to 1.08[a]	0.46	0.12 to 0.79[a]
nPNA (g/kg per day)	1.04	0.56 to 1.51[a]	1.09	0.60 to 1.57[a]
Weekly dialysis Kt/V	−0.01	−0.19 to 0.18		
Phosphate binders (DDD)	0.18	0.06 to 0.30[a]	0.09	−0.03 to 0.21

B, regression coefficient (*i.e.*, the change in serum phosphate level per unit increment in the determinant.
[a]$P < 0.05$.
[b]Anuric patient group is reference.

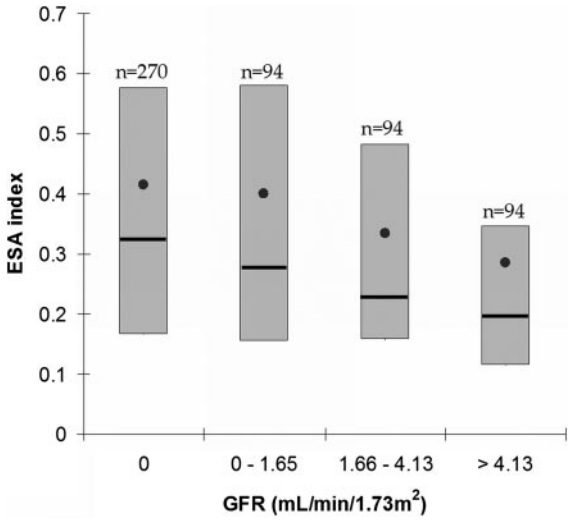

Figure 3. | Relationship between residual renal function and ESA index. Each box shows the distribution of ESA index, defined as the ESA dose per week (in DDD) per kilogram of body weight per percent hematocrit, for the range of RRF as indicated on the horizontal axis. The mean dose for each group is shown by the black circles, the median by the middle horizontal line, and the 25th and 75th percentiles by the bottom and top of the box, respectively. *P* for univariable linear trend = 0.001.

reduced treatment costs. However, it should be mentioned that the phosphate treatment targets as defined in this study (22), as well as the more recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines on bone and mineral disorders, are mainly based on level B and C evidence because data from large randomized controlled trials on optimal phosphate target levels are lacking (32).

The present analyses clearly identified GFR as an important determinant of the ESA resistance, especially in patients with an GFR >4.13 ml/min per 1.73 m^2. A relation between decline of RRF and more severe anemia and increased ESA resistance has been recognized previously in PD patients (1,10), but data in HD patients have been limited. Recently, it was shown that the mean ESA resistance index over time was 10% to 30% lower in patients with residual urea clearance ≥1 ml/min as compared with patients with residual urea clearance <1 ml/min (15). In the latter study, C-reactive protein levels were not statistically different between the low and high RRF groups. Our data showed that in anuric patients ESA resistance was almost 40% higher than in patients with a GFR > 4.13 ml/min per 1.73 m^2. Notably, a high ESA index has been associated with increased mortality in some (33,34) but not all studies (35). As expected and in agreement with previous observations, low TSAT and low albumin were significantly related to the ESA resistance, reflecting low available iron for erythropoiesis and inflammation, respectively (36–38). Dialysis Kt/V was not associated with ESA index in our study, likely because only patients with an adequate dialysis Kt/V were included (39). ACEIs and ARBs are associated with slight reductions in hemoglobin levels in patients with chronic kidney disease, which can possibly be explained by the stimulatory effects of angiotensin II on erythopoiesis in the bone marrow (40,41). In agreement with other (42,43) but not all (44) studies, we found no relation with the use of ARBs or ACEIs and ESA index in our study. It is not evident how the large effect of RRF on ESA resistance can be explained. Patients with RRF may have lower serum concentrations of substances with inhibitory activity on erythropoiesis such as polyamines, parathyroid hormone, or certain cytokines (45). However, in con-

Table 5. Univariable and multivariable analyses into factors that relate to ESA index in patients using ESA

Determinant	Univariable Model		Multivariable Model	
	B	95% CI	*B*	95% CI
Gender (male)	−0.21	−0.35 to −0.07[b]	−0.23	−0.37 to −0.09[b]
Age (10 years)	−0.04	−0.09 to 0.01	−0.04	−0.09 to 0.01
Diabetes mellitus	0.07	−0.10 to 0.23		
Dialysis vintage (years)	−0.02	−0.04 to 0.01	−0.04	−0.07 to −0.02[b]
Weekly dialysis Kt/V	0.07	−0.03 to 0.17		
ACEI or ARB	0.05	−0.09 to 0.19		
GFR 0 to 1.65 (ml/min per 1.73 m^2)[a]	0.04	−0.14 to −0.22	−0.14	−0.33 to 0.05
GFR 1.66 to 4.13 (ml/min per 1.73 m^2)[a]	−0.08	−0.26 to 0.10	−0.19	−0.37 to 0.00
GFR > 4.13 (ml/min per 1.73 m^2)[a]	−0.34	−0.53 to −0.16[b]	−0.49	−0.69 to −0.29[b]
Serum albumin (g/dl)	−0.38	−0.56 to −0.21[b]	−0.33	−0.51 to −0.16[b]
TSAT (%)	−0.02	−0.02 to −0.01[b]	−0.02	−0.02 to −0.01[b]
iPTH (pg/ml)	0.00	0.00 to 0.003		

The dependent variable is the logarithm of ESA index. *B*, regression coefficient (*i.e.*, the change in serum phosphate level per unit increment in the determinant).
[a]Anuric patient group is reference.
[b]$P < 0.05$.

trast to previous observations (37,46), we found no relation between iPTH levels and ESA resistance. In addition, inflammation has been associated with ESA resistance (37) as well as with GFR and GFR decline (47,48). Apparent clinical effects of preserved RRF on ESA resistance may therefore partly be explained by less inflammation in patients with RRF.

Apart from phosphate and anemia control, our data showed a strong relation between RRF and β2M level, as previously reported (6,7,49), and suggested that even a GFR <1.65 ml/min contributes to β2M removal. Notably, we have recently shown that RRF appears to be more important for β2M removal than intensifying dialysis treatment with online hemodiafiltration (50). Not surprising, but of potential clinical interest, is the finding that intradialytic weight loss was much lower in patients with urinary output as compared with anuric patients. This may translate to better volume control, less necessity for stringent fluid and salt restriction, and generally fewer intradialytic symptoms in patients with RRF. In view of the potential important role of RRF on multiple biochemical and clinical outcomes, controlling for RRF in observational studies should be considered (15), even if the GFR is very low.

Because of the cross-sectional design of this study, causality of the relationships cannot be established. For instance, the beneficial effects of RRF may partly be explained by reduced inflammation. Unfortunately, a specific marker for inflammation such as high-sensitivity C-reactive protein was not available. Although we did adjust for serum albumin in the multivariable analyses, the value of albumin as a marker for inflammation is questionable. Furthermore, only a single time-point GFR was available for the analyses, and rate of decline of RRF could therefore not be evaluated. Additional GFR measurements would potentially strengthen the relationships as found in this study by reducing measurement errors. The study population consisted exclusively of trial participants, which may theoretically limit generalizability of the study results. In these baseline data from the CONTRAST study, all patients were considered clinically stable and had a Kt/V of 1.2 or higher. The effects of RRF in less stable patients (*e.g.*, those with inadequate dialysis) may even be more pronounced. The strengths of this study are the large sample size and the prospective data collection. Thus far, only a few studies have evaluated medication use in large groups of HD patients.

In conclusion, the study presented here clearly demonstrates that RRF has a considerable effect on phosphate and anemia management, especially in patients with a GFR >4.13 ml/min per 1.73 m^2. Higher GFR levels are associated with a greater likelihood that treatment targets are reached, despite lesser medication use. RRF is often not assessed in observational clinical studies in HD patients. However, our data and other data show that RRF, even in a very low range as commonly found in HD patients, should be considered and adjusted for in clinical research. Efforts to preserve kidney function may improve clinical outcomes and be highly cost-effective, but this needs further evaluation in prospective interventional studies.

Appendix

Members of the CONTRAST executive committee: P.M. ter Wee (chair), VU Medical Center, Amsterdam, The Netherlands; P.J. Blankestijn (chair), University Medical Center (UMC)–Utrecht, Utrecht, The Netherlands; M.L. Bots, Julius Center for Health Sciences and Primary Care, UMC–Utrecht, Utrecht, The Netherlands; M.A. van den Dorpel, Maasstad Hospital,

Rotterdam, The Netherlands; M.P.C. Grooteman, VU Medical Center, Amsterdam, The Netherlands; M.J. Nubé, VU Medical Center, Amsterdam, The Netherlands.

CONTRAST collaborators: M. Dorval, Dr. Georges-L Dumont Regional Hospital, Moncton, New Brunswick, Canada; R. Lévesque, St. Luc Hospital, Montreal, Quebec, Canada; M.G. Koopman, Academic Medical Center, Amsterdam, The Netherlands; C.J. Konings, Catharina Hospital, Eindhoven, The Netherlands; W.P. Haanstra, Dialysis Clinic Noord, Beilen, The Netherlands; P. Vos, Dianet Dialysis Centers, Utrecht, The Netherlands; T. Noordzij, Fransiscus Hospital, Roosendaal, The Netherlands; G.W. Feith, Gelderse Vallei Hospital, Ede, The Netherlands; M. van Buren, Haga Hospital, The Hague, The Netherlands; J.J. Offerman, Isala Clinics, Zwolle, The Netherlands; E.K. Hoogeveen, Jeroen Bosch Hospital, 's-Hertogenbosch, The Netherlands; F. de Heer, Maasland Hospital, Sittard, The Netherlands; P.J. van de Ven, Maasstad Hospital, Rotterdam, The Netherlands; T.K. Kremer Hovinga, Martini Hospital, Groningen, The Netherlands; W. Bax, Medical Center Alkmaar, Alkmaar, The Netherlands; J.O. Groeneveld, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands; A.T. Lavrijssen, Oosterschelde Hospital, Goes, The Netherlands; A.M. Schrander-Van der Meer, Rijnland Hospital, Leiderdorp, The Netherlands; L.J. Reichert, Rijnstate Hospital, Arnhem, The Netherlands; G.J. Bruinings, Slingeland Hospital, Doetinchem, The Netherlands; P.L. Rensma, St. Elisabeth Hospital, Tilburg, The Netherlands; Y. Schrama, St. Fransiscus Gasthuis, Rotterdam, The Netherlands; H.W. van Hamersvelt, University Medical Center St. Radboud, Nijmegen, The Netherlands; W.H. Boer, UMC–Utrecht, Utrecht, The Netherlands; W.H. van Kuijk, VieCuri Medical Center, Venlo, The Netherlands; M.G. Vervloet, VU Medical Center, Amsterdam, The Netherlands; I.M. Wauters, Zeeuws-Vlaanderen Hospital, Terneuzen, The Netherlands; I. Sekse, Haukeland University Hospital, Bergen, Norway.

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Disclosures

None.

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