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Estimation of residual renal function using beta-trace protein: Impact of dialysis procedures

Anne-Sophie Bargnoux¹ | Delphine Buthiau² | Marion Morena¹ | Annie Rodriguez^{2,3} | Maria-Eugenia Noguera-Gonzalez⁴ | Olivia Gilbert³ | Moglie Le Quintrec⁴ | Nils Kuster¹ | Jean-Paul Cristol¹

¹Département de Biochimie et Hormonologie, PhyMedExp, INSERM, CNRS, Université de Montpellier, CHU de Montpellier, Montpellier Cedex 5, France

²Département de Biochimie et Hormonologie, Université de Montpellier, CHU de Montpellier, Montpellier Cedex 5, France

³AIDER, Montpellier, France

⁴Département de Néphrologie, Dialyse et Transplantation, CHU de Montpellier, Université de Montpellier, Montpellier Cedex 5, France

Correspondence

Jean-Paul Cristol, Laboratoire de Biochimie, PhyMedExp, Université de Montpellier, INSERM, CNRS, CHU de Montpellier, 191 Avenue du Doyen Gaston Giraud, 34295 Montpellier Cedex 5, France. Email: jp-cristol@chu-montpellier.fr

Abstract

Beta-trace protein (BTP), a low molecular weight protein of 23-29 kDa, has been proposed as a promising biomarker to estimate residual renal function (RRF) in patients on maintenance hemodialysis (HD). Indeed, BTP is cleared by native kidney but not during conventional HD session. By contrast, the removal rate of BTP using convective processes (mainly hemodiafiltration [HDF]) and peritoneal dialysis (PD) has been little or not investigated. Therefore, an aim of this study was to evaluate the impact of dialysis procedures (high-flux HD, on-line post-dilution HDF and PD) on BTP removal in comparison with beta-2 microglobulin (B2M) and cystatin C (CYSC) removals after a single session. In addition, the ability of BTP to predict RRF in PD was assessed. This observational cross-sectional study included a total of 82 stable chronic kidney disease patients, 53 patients were on maintenance dialysis (with $n = 26$ in HD and $n = 27$ in HDF) and 29 were on PD. Serum concentrations of BTP, B2M, and CYSC were measured (a) before and after a single dialysis session in HD and HDF anuric patients to calculate reduction percentages, (b) in serum, 24-hour-dialysate and 24-hour-urine in PD patients to compute total, peritoneal, and urinary clearance. RRF was estimated using four equations developed for dialysis patients without urine collection and compared to the mean of the urea and creatinine clearances in PD. The concentrations of the three studied molecules were significantly reduced ($P < .001$) after dialysis session with significantly higher reduction ratio using HDF compared to HD modality ($P < .001$): BTP 49.3% vs 17.5%; B2M 82.3% vs 69.7%; CYSC 77.4% vs 66% in HDF and HD, respectively. In non-anuric PD patients, B2M and CYSC were partly removed by peritoneal clearance (72.3% and 57.6% for B2M and CYSC, respectively). By contrast, BTP removal by the peritoneum was negligible and a low bias for the BTP-based equation to estimate RRF ($-1.4 \text{ mL/min/1.73 m}^2$) was calculated. BTP is significantly removed by high-flux HD or HDF, thereby compromising its use to estimate RRF. By contrast, BTP appears as a promising biomarker to estimate RRF in PD patients since it is not affected by peritoneal clearance, unlike B2M and CYSC, and it is well correlated to RRF.

KEYWORDS

beta-2 microglobulin, beta-trace protein, conventional hemodialysis, cystatin C, hemodiafiltration, peritoneal dialysis, residual renal function

1 | INTRODUCTION

Residual renal function (RRF) has been associated with improved survival and quality of life in hemodialysis (HD)¹ and peritoneal dialysis (PD).^{2,3} RRF can be measured using clearance of exogenous markers but such methods are complex to implement.⁴ In routine clinical practice, equations based on the mean of urinary urea and creatinine clearance^{5,6} or on urea clearance^{7,8} to estimate RRF are widely used. However, urinary collections for 24 hours in PD or over the interdialytic period in HD are required which may represent another source of error. In this context, low molecular weight proteins (LMWP) that can be filtered by the native kidney but not (or poorly) removed by the dialysis process have been proposed as endogenous glomerular filtration markers in dialysis patients.

In particular, dialysis-specific equations based on beta-2 microglobulin (B2M), cystatin C (CYSC) and beta-trace protein (BTP) or a combination of two of these markers have been developed to estimate RRF without urine collection.^{9,10} However, clearance of these LMWP is more or less affected by dialysis methods depending on their size and the specificities of the dialysis membrane used. B2M and CYSC are proteins of 12 and 13 kDa, respectively, and are freely filtered by the glomerulus following by tubular reabsorption and metabolization.⁴ Previous studies have shown that B2M and CYSC are both removed by high-flux HD, hemodiafiltration (HDF),¹¹⁻¹³ and PD.¹⁴⁻¹⁶ Their concentrations in blood are not in the steady state during the interdialytic period. BTP is a heterogeneous monomeric glycoprotein with multiple isoforms which are the result of posttranslational N-glycosylation leading to molecular weight between 23 and 29 kDa.¹⁷ Conflicting data have been reported regarding removal of BTP during HD or HDF.^{12,13,18,19} In addition, to the best of our knowledge, to date no data on BTP removal with PD have been published.

The aim of this study was, therefore, to evaluate the impact of dialysis procedures on BTP elimination in comparison with B2M and CYSC. First, we compared the acute effect of a high-flux HD and an on-line post-dilution HDF session on the removal of these parameters in patients with no RRF. Second, we assessed BTP removal in PD patients and its ability to predict RRF.

2 | PATIENTS AND METHODS

2.1 | Study design and patients

This observational cross-sectional study included a total of 82 stable chronic kidney disease patients (n = 53 on maintenance dialysis and n = 29 on PD) who originated from one of the two dialysis facilities of Montpellier, France

(a hospital-based facility [Lapeyronie University Hospital] and a public nonprofit association [Aide pour l'Installation à Domicile de l'Épuration extra Rénale]). Dialysis efficiency was estimated using single pool Kt/V ratio.²⁰ Patients with symptoms or signs of acute inflammatory or infectious diseases were excluded from the study.

All maintenance dialysis patients were on regular dialysis treatment for at least 6 months, had no residual kidney function and received either high-flux HD (n = 26) or on-line post-dilution HDF (n = 27) treatments with ultrapure bicarbonate-buffered dialysate three times a week (12-15 hours per week). Fifteen high-flux dialyzers were used during the study: *polysulfone membranes*: APS-21H (surface 2.1 m², Asahi Kasei Medical; HD n = 3, HDF n = 1), Diacap HIPS 20 (surface 2 m², B.Braun; HD n = 2), Xevonta HI 20 (surface 2 m², B.Braun; HD n = 4, HDF n = 3); VIE 21 (2.1 m² coated in vitamin E, Asahi Kasei Medical; HD n = 2); *helixone membranes* : FX 100 (surface 2.2 m², Fresenius Medical Care; HD n = 1, HDF n = 2), FX 800 (surface 1.8 m², Fresenius Medical Care; HDF n = 8), FX 1000 (surface 2.2 m², Fresenius Medical Care; HDF n = 9); *polyethersulfone membranes*: Vitapes 150HF (surface 1.5 m², Membrana; HD n = 3, HDF n = 1); Vitapes 190HF (surface 1.9 m², Membrana; HD n = 1); *polyester polymer alloy membranes*: PEPA FDX 210 GW (surface 2.1 m², Nikkiso; HD n = 4); *polyacrylonitrile membranes*: Evodial 2.2 (surface 2.15 m², Gambro; HD n = 2, HDF n = 1); *polymethylmethacrylate membranes*: BK 2-1F (surface 2.1 m², Toray; HD n = 1, HDF n = 1); *polyphenylene membranes*: PHYLTER HF20 G (surface 2 m², Bellco; HD n = 2) and *polynephron membranes*: ELISIO 21H (surface 2.1 m², Nipro; HD n = 1), ELISIO 250H (surface 2.5 m², Nipro; HDF n = 1).

PD patients were on automated PD (APD, n = 27) or continuous PD (CAPD, n = 2) and eight patients had no residual kidney function. Regular treatment of all patients was according to an individualized dialysis scheme. Patients were treated with glucose (1.36% and/or 3.86%; 1.5% and/or 4.25%); amino acids solutions (n = 6) and icodextrin 7.5% (n = 20) as clinically needed. APD was done on a Baxter HomeChoice PRO cyclor (n = 21) or a Fresenius Sleep Safe cyclor (n = 6). As part of patient follow-up, an evaluation of peritoneal membrane characteristics is routinely performed using the modified peritoneal equilibrium test (PET) with 3.86% glucose.²¹ Patients were then categorized into fast, fast average, slow, and slow average transport type according to creatinine dialysate/blood ratio (D/Pcreat).

The study was conducted according to the principles of the Declaration of Helsinki and in compliance with International Conference on Harmonization/Good Clinical Practice regulations. According to the French Law, the study was registered at the Ministère de l'Enseignement Supérieur et de la Recherche after approval by our institution's ethical committee with the number DC-2008-417.

2.2 | Sample collection and assays

All samples were collected and centrifuged (1500 g for 15 minutes) for routine parameters measurements and the remaining supernatant was stored at -80°C for processing B2M, CYSC, and BTP. Blood samples were drawn before and after the mid-week session for maintenance dialysis patients. Blood sample, 24-hour-dialysate and 24-hour-urine were taken for maintenance PD patients. Creatinine and urea were measured by enzymatic method on a c701/cobas 8000 analyzer (Roche Diagnostics, Mannheim, Germany). B2M, CYSC, and BTP were determined by particle-enhanced immunonephelometry (PENIA) using Siemens reagents on the

BN Prospec (Siemens Healthcare Diagnostics, Marburg, Germany). Sensitivity of each assay was established by the lower limit of the reference curve and depended therefore on the concentration of the protein in the N Protein Standard. In this study, detection limit was 0.219, 0.06 and 0.235 mg/L for B2M, CYSC, and BTP, respectively.

2.3 | Clearance and eRRF calculations

The reduction percentages during HD and HDF sessions were calculated using the following equation:

$$100 \times C_{\text{pre}} - \left(C_{\text{post}} / \left(1 + \left(\text{weight}_{\text{pre}} - \text{weight}_{\text{post}} \right) / 0.2 \times \text{weight}_{\text{post}} \right) \right) / C_{\text{pre}}$$

where C_{pre} and C_{post} are concentrations of the molecules pre- and post-treatment, respectively; $\text{weight}_{\text{pre}}$ and $\text{weight}_{\text{post}}$ are pre- and post-treatment body weights.

Here, C_{post} was corrected for hemoconcentration using Bergström's formula.²²

In PD patients, weekly solute clearances provided by PD and RRF were calculated and normalized to body surface area (BSA) as follows:

$$\text{peritoneal clearance (L/week/1.73 m}^2\text{)} = 7 \times (C_{\text{D}} \times V_{\text{D}}/C) \times (1.73/\text{BSA})$$

$$\text{renal clearance (L/week/1.73 m}^2\text{)} = 7 \times (C_{\text{U}} \times V_{\text{U}}/C) \times (1.73/\text{BSA})$$

where C is the concentration in the serum; C_{D} and C_{U} are the concentrations of the molecules in the 24-hour-dialysate and the 24-hour-urine; V_{D} and V_{U} are the volumes of the 24-hour-dialysate and the 24-hour-urine.

Total clearance was the sum of the peritoneal and the renal clearance.

Residual renal glomerular filtration rate (GFR) was assessed as the mean of the urea and creatinine clearances.^{5,23,24}

In addition, residual kidney function was estimated using four equations developed for dialysis patients without urine collection by Shafi et al⁹:

$$\begin{aligned} \text{BTP - based eRRF (mL/min/1.73 m}^2\text{)} \\ = 95 \times \text{BTP}^{-2.16} \times \text{gender factor} \end{aligned}$$

where for gender, male = 1.652, female = 1

$$\begin{aligned} \text{B2M - based eRRF (mL/min/1.73 m}^2\text{)} \\ = 2852 \times \text{B2M} - 2.417 \times \text{gender factor} \end{aligned}$$

where for gender, male = 1.592, female = 1

$$\text{CYSC - based eRRF (mL/min/1.73 m}^2\text{)} = 123 \times \text{CYSC}^{-2.468}$$

$$\text{BTP and B2M based RRF (mL/min/1.73 m}^2\text{)} = 673 \times \text{BTP}^{-1.406} \times \text{B2M}^{-1.096}$$

where for gender, male = 1.670, female = 1.

2.4 | Statistical analysis

Statistical analysis was performed with the XLSTAT software for Windows, version 2016.06.35661 (Long Island City, NY, USA). Normality assumption was tested using Shapiro-Wilk test and this assumption was not satisfied for several variables. Thus descriptive statistics are presented as medians with interquartile ranges (IQR) for quantitative variables and proportions for categorical variables. The

comparisons of variables between two groups of patients were performed using the Mann-Whitney and the Chi-square tests for quantitative and qualitative variables, respectively. To compare measures on the same subjects, pairwise comparisons were carried out with the Wilcoxon signed rank. Values were considered statically significant at $P < .05$.

In patients with maintained RRF, BTP was plotted against measured RRF based on the mean of the urea and creatinine clearances. Both linear and nonlinear regression analyses were then achieved to model the link between measured RRF (explanatory variable) and BTP (dependent variable). In addition, Passing-Bablok regression and Bland and Altman analyses were performed to compare data from the different equations used for RRF estimation.

3 | RESULTS

3.1 | Removal of BTP in maintenance dialysis patients

The group consisted of 19 women and 34 men with a median age of 71.9 years (IQR, 59.1-81.5). The median time spent on dialysis was 2.8 years (IQR, 1.5-4.9); and their median single pool (sp) Kt/V was 1.8 (IQR, 1.6-2.0). Age, time spent on dialysis, body weight, length of dialysis session, and dialysate flow rate were not different between HD and HDF groups (Table 1). Both B2M and BTP levels were significantly different between HD and HDF groups, before and after the session. By contrast, CYSC levels between the two groups were significantly different after but not before the session (Table 1). The concentrations of the three studied molecules were significantly reduced ($P < .001$) by renal replacement therapy, whichever dialysis modality was used. The reduction ratio of the three molecules were significantly higher in HDF than in HD ($P < .001$) (Table 1). Within each group (HD, HDF), the reduction ratio of BTP (17.5% and 49.3% in HD and HDF, respectively) was weaker than that of B2M (69.7% and 82.3% in HD and HDF, respectively, $P < .001$) and

the CYSC (66% and 77.4% in HD and HDF, respectively, $P < .001$).

3.2 | Removal of BTP in PD patients

Participants were 13 women and 16 men with a median age of 69.7 years (IQR, 59.-1-81.5). The median time spent on dialysis was 1.3 years (IQR, 0.6-5.0); and their median Kt/V was 1.9 (IQR, 1.7-2.2). Median RRF, defined as the mean of the urea and creatinine clearances, in the 21 non-anuric patients was 4.4 (IQR, 2.5-9) mL/min/1.73 m². According to the modified PET, median D/Pcreat was 0.7 (IQR, 0.61-0.77) with 6 fast, 13 fast average and 10 slow average transporter peritoneal membranes. Serum, renal, and peritoneal concentrations as well as total solute clearance of the three LMWP are depicted in Table 2. Median BTP level in dialysate was <0.234 [$<0.234-0.28$] and 0.34 [0.30-0.56] mg/L in patients with RRF and anuric patients, respectively. BTP content in dialysate was undetectable in 14 out of 21 patients with RRF. Peritoneal clearance was set at 0 mL/min/1.73 m² in these patients. The highest and maximal proportion of renal clearance was observed with BTP (100%) followed by B2M (72.3%) and CYSC (57.6%).

	All patients	HD group (n = 26)	HDF group (n = 27)	P
Gender (men/women)	34/19	15/11	19/8	.34
Age (years)	68.9 [56.3-80.7]	65.2 [38.8-76.6]	72.8 [64.1-81.7]	.06
Duration of dialysis (years)	2.8 [1.5-4.9]	4.1 [1.8-10.5]	2.6 [1.4-4.0]	.17
Body weight (kg)	67.9 [57.9-75.8]	66.1 [55.6-70.0]	72.6 [59.3-78.7]	.09
Dialysis time (hours)	4.0 [3.5-4.0]	3.6 [3.5-4]	4.0 [3.5-4.0]	.57
Blood flow rate (mL/min)	350 [350-400]	350 [350-400]	400 [350-400]	.009
Dialysate flow rate (mL/min)	500 [500-500]	500 [500-500]	500 [500-500]	.92
Total convective volume (L)	15.1 [2.2-24.5]	2.2 [1.2-3.3]	24.6 [22.3-27.0]	<.001
sp Kt/V	1.8 [1.6-2.0]	1.7 [1.5-1.8]	1.9 [1.8-2.0]	.002
B2M (mg/L)				
<i>Cpre</i>	27.0 [21.2-31.1]	30.1 [24.8-32.3]	22.9 [19.4-30.0]	.006
<i>Cpost</i>	6.3 [3.7-8.9]	8.7 [6.5-10.6]	3.7 [3.3-5.9]	<.001
CYSC (mg/L)				
<i>Cpre</i>	5.8 [5.1-7.2]	5.9 [5.4-7.2]	5.8 [5.1-6.6]	.37
<i>Cpost</i>	1.5 [1.2-2.1]	2.1 [1.6-2.6]	1.2 [1.1-1.6]	<.001
BTP (mg/L)				
<i>Cpre</i>	9.2 [6.9-11]	10.5 [9.1-11.3]	7.6 [5.9-9.8]	.003
<i>Cpost</i>	5.9 [3.6-8.2]	8.1 [6.2-10.0]	3.6 [2.8-5.2]	<.001
Reduction ratio (%)				
<i>B2M</i>		69.7 [63.3-74.7]	82.3 [79.0-84.2]	<.001
<i>CYSC</i>		66.0 [59.7-70.8]	77.4 [75.1-80.5]	<.001
<i>BTP</i>		17.5 [12.9-28.2]	49.3 [43.6-58.5]	<.001

TABLE 1 Main characteristics and serum concentrations of β -trace protein (BTP), β 2-microglobulin (B2M), and cystatin C (CYSC) before (*Cpre*) and after (*Cpost*) the dialysis session. Data are expressed as medians and interquartile ranges for quantitative variables

TABLE 2 Solutes' concentrations and clearances in peritoneal dialysis patients. Data are expressed as medians and interquartile ranges

	Urea (mmol/L)	Creatinine ($\mu\text{mol/L}$)	B2M (mg/L)	CYSC (mg/L)	BTP (mg/L)
All patients (n = 29)					
Serum concentration	18.2 [14.8-20.9]	573 [442-865]	25.2 [15.3-37.4]	5.9 [4.6-7.3]	9.1 [4.2-12.5]
Dialysate concentration	11.2 [8.4-12.4]	241 [168-288]	1.5 [1.1-2.6]	0.3 [0.2-0.6]	<0.234 [<0.234-0.51]
Urine concentration	81.1 [53.5-86.0]	5100 [3465-6252]	22.2 [10.7-47.6]	2.7 [1.5-7.6]	10.8 [7.0-18.6]
	Urea (60 Da)	Creatinine (113 Da)	B2M (11.8 kDa)	CYSC (13 kDa)	BTP (23-29 kDa)
Patients with RRF (n = 21)					
Total clearance (L/week/1.73 m ²)	80.7 [66.2-107.5]	92.9 [62.3-164.1]	19.1 [10.3-28.1]	10.6 [6.6-13.6]	15.4 [9.8-27.4]
Peritoneal clearance (L/week/1.73 m ²)	44.1 [38.4-61.8]	24.8 [19.8-47.1]	4.6 [2.8-9.6]	3.2 [2.1-7.5]	0 [0-4.3]
% of total clearance	55.5 [45.0-85.8]	24.8 [16.7-53.0]	27.7 [15.5-84.6]	42.4 [26.6-84.1]	0 [0-4.3]
Renal clearance (L/week/1.73 m ²)	29.2 [10.7-49.2]	69.1 [36.8-143.6]	11.6 [0.9-18.9]	3.8 [1.9-9.5]	15.3 [5.5-27.4]
% of total clearance	44.5 [14.2-55]	75.2 [47.0-83.3]	72.3 [15.4-84.5]	57.6 [15.9-73.4]	100 [70.5-100]
Anuric patients (n = 8)					
Peritoneal clearance (L/week/1.73 m ²)	59.7 [56.2-69.4]	43.5 [29.5-50.1]	7.7 [4.2-10.6]	5.8 [3.4-10.4]	2.8 [2.3-5.3]

TABLE 3 Results of the Passing-Bablok regression analysis for the four tested equations to estimate RRF (Y) vs measured RRF (X) using the mean of urea and creatinine clearance (n = 21)

	Slope (95% CI)	Intercept (95% CI)	Determination coefficient (R ²)
BTP-based eRRF	0.77 (0.53 to 1.20)	-0.11 (-2.37 to 0.26)	.62
B2M-based eRRF	0.72 (0.49 to 1.19)	-0.51 (-2.11 to 0.64)	.56
CYSC-based eRRF	0.29 (0.21 to 0.37)	0.69 (0.20 to 0.95)	.59
BTP and B2M-based eRRF	0.82 (0.63 to 1.29)	0.53 (-3.36 to 0.30)	.63

3.3 | Estimation of RRF with BTP in PD patients

The clinical relevance of LMWP was assessed by comparison of estimated RRF using Shafi's formula⁹ with measurement of RRF as mean of urea and creatinine clearance. Results of Passing-Bablok regression and Bland-Altman bias analyses are shown in Table 3 and Figure 1, respectively. All tested equations underestimated the mRRF. Bias for BTP and/or B2M-based eRRF was low (around 1 mL/min/1.73 m²). Using CYSC-based eRRF, bias was higher and proportional to RRF. As shown in Figure 2; a nonlinear regression line (exponential relationship) between the concentrations of BTP and the measured RRF could be drawn. In our study, 78.1% of the variability of the BTP is explained by the RRF.

4 | DISCUSSION

Renal handling of BTP is not yet fully understood but appears to be similar to those of B2M and CYSC. Recently,

BTP has been proposed as a promising marker to estimate RRF in dialysis patients^{9,10} since it seems to be not or less affected by dialysis procedure.^{12,18} In the present work, we first investigated the effect of high-flux HD, HDF, and PD on serum BTP levels in comparison with two other middle molecules B2M and CYSC; and then we considered the potential role of BTP to assess RRF.

Dialysis process differently interacts on the LMWP clearance according to their molecular weight, the membrane permeability, the dialysis fluid, the ultrafiltration profile, or the convective components used. BTP with a molecular weight between 23 and 29 kDa has a reduction ratio lower than that of B2M (11.8 kDa) and CYSC (13.2 kDa) measured in the same conditions.^{12,13} Furthermore, high-efficiency convective therapies, such as HDF, are claimed to be superior to conventional diffusive HD in improving the dialysis efficacy by enlarging the molecular weight spectrum of uremic toxins up to middle and large solutes.²⁵ In our study, the acute effect of a high-flux HD or HDF session on serum LMWP was associated with good removal of both B2M (69.7% and 82.3% for high-flux HD and HDF, respectively) and CYSC (66.0% and

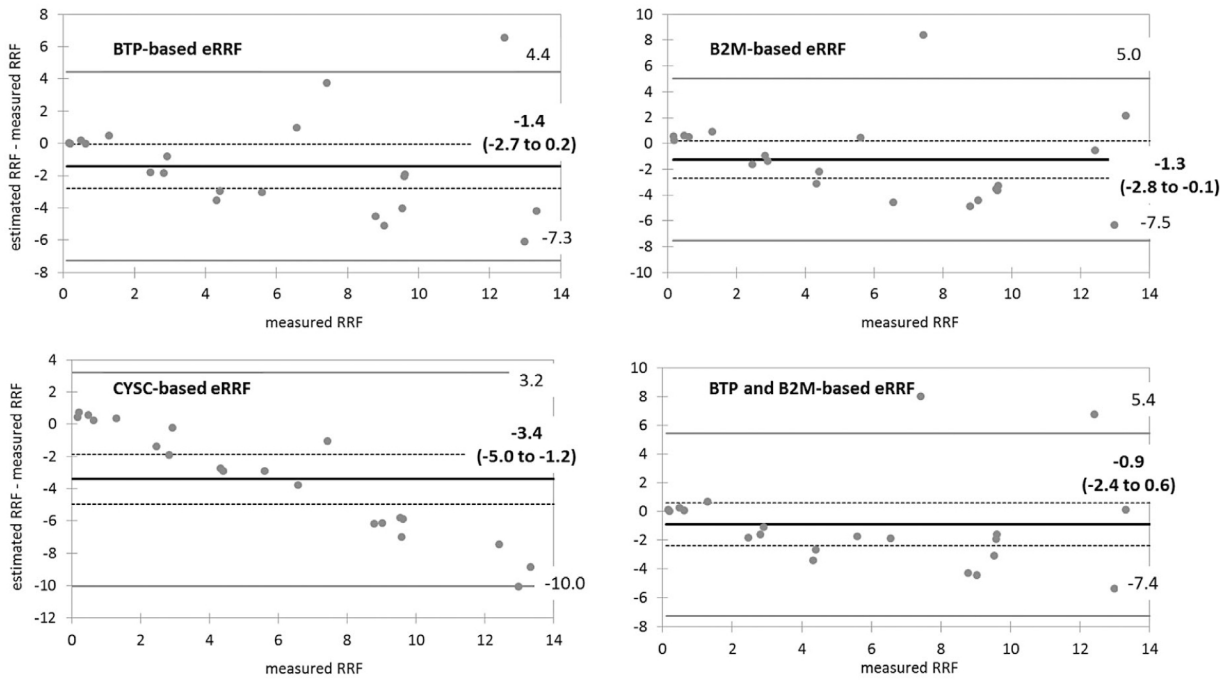


FIGURE 1 Differences between measured and estimated residual renal function (RRF) for four estimating equations, according to the level of measured RRF. Solid and broken black lines represent the mean difference and the 95% confidence interval. Solid grey lines represent lower and upper limits of agreement (mean of difference \pm 1.96 standard deviation). All values are expressed in mL/min/1.73 m² [Color figure can be viewed at [wileyonlinelibrary.com](#)]

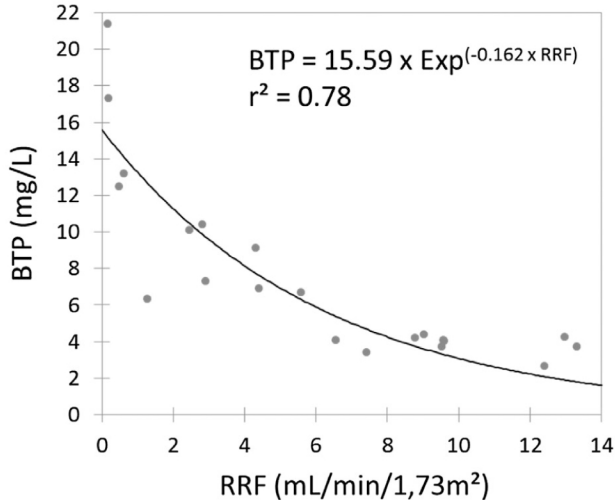


FIGURE 2 The relationships between residual renal function (RRF) (mean of urea and creatinine clearance) and serum concentrations of BTP in PD patients with maintained RRF ($n = 21$) [Color figure can be viewed at [wileyonlinelibrary.com](#)]

77.4% for HF-HD and HDF, respectively) comparable to previous studies,^{12,13} with a greater removal of BTP (17.5% and 49.3% for high-flux HD and HDF, respectively). Conflicting results have been published regarding BTP removal by HD.^{12,13,18,19,26} The removal pattern of the three molecules studied here is comparable to that described by Donadio et al in high-flux HD¹³ and by Lindström et al in HDF.¹² The discrepancies observed between the studies can be attributed

to the characteristics of the dialysis membranes, the presence or absence of a RRF, and the correction of post-dialysis concentration by hemoconcentration. In PD patients, total, renal, and peritoneal clearances found in this study were similar to those observed in previous studies for B2M and CYSC.^{14–16} In addition, we reported herein for the first time the lack of BTP removal by PD. While B2M and CYSC were partly removed by peritoneal clearance (72.3% and 57.6% for B2M and CYSC, respectively), elimination of BTP by the peritoneum was negligible in PD patients. The zero BTP removal in dialysate observed in our study could be associated with the short-time changes of APD since long-time changes favor middle molecular weight protein removal. Indeed, Kim et al²⁷ demonstrated that, in contrast to peritoneal clearance of small molecules, peritoneal clearance of middle molecules, such as B2M, depended mainly on the total dwell hours of PD and not on the number of exchanges of peritoneal dialysate in PD. Thus, B2M clearance was noted to be 5.4 ± 2.7 L/week with two exchanges over 12 hours per day but 9.5 ± 4.4 L/week with the same two exchanges over 24 hours. However, it is not possible within the limits of this study (there are only 2 CAPD patients) to address such differences.

RRF is generally assessed by the method used to estimate GFR with creatinine as a widely available and reliable marker of renal function when integrated in GFR predictive formula. However, the tubular secretion of creatinine increases with chronic kidney disease leading to an unpredictable overestimation of GFR and limiting its use in patients with advanced

renal failure.²⁸ The method based on mean of urea and creatinine clearance for calculating the RRF has the drawbacks of urine collections, timing of blood sampling and duration of collection.⁴ In maintenance HD patients, a minimum of two blood samples are required, the first when the urine collection is initiated, generally at the end of a dialysis session, and the second when the urine collection is achieved, generally at the start of the next dialysis session or another blood draw. This could lead to an interdialytic period of 48 hours in maintenance dialysis patients. In PD patients, a 24-hour urine collection is usually performed with a single blood sample at the end of the collection. As a result, the use of an endogenous filtration marker like BTP could provide reliable assessment of RRF without urine collection and thus improve the dialysis prescription dose. Several LMWP with only a weak removal by conventional HD, already tested outside the context of end stage renal disease,^{29,30} have been tested to estimate RRF in patients on dialysis.⁹ Previous studies were performed on dialysis patients, mainly incident patients with RRF, and primarily on conventional HD techniques^{9,18,31} and clearly suggested that BTP is correlated with RRF. Our results, showing that BTP is poorly removed by high-flux HD (20%), support the hypothesis that BTP may be helpful in estimating RRF in conventional HD process. However, BTP is significantly removed in HDF (up to 50%) suggesting that BTP could not be used as a RRF biomarker in this condition. Interestingly, in our study, probably due to the higher molecular size, BTP is not significantly affected by PD and equations based on BTP gave the smallest bias to estimate RRF in comparison to the average of urea and creatinine clearance. Accuracy of the predictive equations to estimate GFR is generally expressed as proportion of estimates within 30% (P30) of the measured GFR using a reference method. However, since the level of GFR has a great impact on the performances of the equation, P30 seems not appropriate in end stage renal disease. According to KDOQI guidelines,⁸ in maintenance dialysis patients with residual urea clearance greater than or equal to 2 mL/min/1.73 m², the minimum session spKt/V can be reduced. Therefore the value of 2 mL/min/1.73 m² has been proposed to evaluate the accuracy of eRRF by some authors.^{9,10} The accuracy appeared to be better for equations using BTP compared with equations using urea and creatinine.⁹ Accuracy of BTP based equation in the NECOSAD cohort, expressed as percentage of estimates within ± 2 mL/min/1.73 m² of mean of the urea and creatinine clearances, was 71%.⁹ The BTP based equations have demonstrated low sensitivity but high specificity for identifying measured urea clearance > 2 mL/min/1.73 m².^{4,9,10}

5 | CONCLUSION

Our results showed that BTP is significantly removed by HDF and to a lesser extent by high-flux HD, thereby compromising

its use to estimate RRF. By contrast, BTP, unlike B2M and CYSC, is not affected by peritoneal clearance and is well correlated to RRF in PD patients. As a result, BTP seems to be a promising biomarker to estimate RRF in this PD population.

6 | COMPETING INTEREST

The authors declare that they have no competing interest. JPC received honorarium from Siemens for invited lectures.

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AUTHOR CONTRIBUTIONS

Study design: Bargnoux, Cristol

Data collection and analysis: Bargnoux, Buthiau, Morena, Rodriguez, Noguera-Gonzalez, Gilbert, Kuster

Manuscript writing: Bargnoux, Cristol, Le Quintrec, Morena, Kuster

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