High-efficiency on-line haemodiafiltration improves conduit artery endothelial function compared with high-flux haemodialysis in end-stage renal disease patients

Jérémy Bellien1,2,3,4, Caroline Fréguin-Bouilland2,3,5, Robinson Joannidès1,2,3,4, Mélanie Hanoy5, Isabelle Rémy-Jouet2,3, Christelle Monteil3,6, Michèle Iacob1, Laurent Martin4, Sylvanie Renet2,3, Cathy Vendeville3,6, Michel Godin2,3,5, Christian Thuillez1,2,3 and Frank Le Roy5

1Department of Pharmacology, Rouen University Hospital, Rouen, France, 2Institut National de la Sante et de la Recherche Médicale (INSERM) U1096, Rouen, France, 3University of Rouen, Institute for Research and Innovation in Biomedicine, Rouen, France, 4Centre d’Investigation Clinique (CIC)-INSERM 0204, Rouen, France, 5Department of Nephrology, Rouen University Hospital, Rouen, France and 6Equipe d’Accueil (EA) 4651, Rouen, France

Correspondence and offprint requests to: Jeremy Bellien; E-mail: jeremy.bellien@chu-rouen.fr

ABSTRACT.

Background. Middle molecular weight uraemic toxins are considered to play an important role in vascular dysfunction and cardiovascular outcomes in end-stage renal disease (ESRD) patients. Recent dialysis techniques based on convection, specifically high-efficiency on-line haemodiafiltration (HDF), enhance the removal of middle molecular weight toxins and reduce all-cause mortality in haemodialysis (HD) patients. However, the mechanisms of these improved outcomes remain to be established.

Methods. This prospective study randomly assigned 42 ESRD patients to switch from high-flux HD to high-efficiency on-line HDF (n = 22) or to continue HD (n = 20). Brachial artery endothelium-dependent flow-mediated dilatation, central pulse pressure, carotid artery intima-media thickness (IMT), internal diastolic diameter and distensibility and circulating markers of uraemia, inflammation and oxidative stress were blindly assessed before and after a 4-month follow-up.

Results. Brachial flow-mediated dilatation and carotid artery distensibility increased significantly in the HDF group compared with HD, while carotid IMT and diameter remained similar. HDF decreased predialysis levels of the uraemic toxins β2-microglobulin, phosphate and blood TNFα mRNA expression. Oxidative stress markers were not different between the HD and HDF groups. Blood mRNA expression of protein kinase C β2, an endothelial NO-synthase (eNOS) inhibitor, decreased significantly with HDF.

Conclusions. High-efficiency on-line HDF prevents the endothelial dysfunction and stiffening of the conduit arteries in ESRD patients compared with high-flux HD. HDF decreases uraemic toxins, vascular inflammation, and is associated with subsequent improvement in eNOS functionality. These results suggest that reduced endothelial dysfunction may be an intermediate mechanism explaining the beneficial outcomes associated with HDF.

Keywords: arterial stiffness, endothelium, end-stage renal disease, haemodiafiltration, haemodialysis

INTRODUCTION

The number of patients with end-stage renal disease (ESRD) requiring chronic dialysis therapy has increased dramatically worldwide, with a current prevalence of 1000 per million in Europe [1, 2]. Dialysis is far from perfect, and ESRD is associated with high mortality, mainly due to a 9-fold increased risk of cardiovascular death compared with the general population [1, 2]. Specific measures to reduce cardiovascular disease,
especially by improving dialysis techniques, are therefore a major healthcare challenge in this population.

ESRD patients develop hypertrophy, fibrosis and calcifications of the conduit arteries, leading to increased stiffness and accelerated atherosclerosis [3–5]. One common mechanism for these vascular abnormalities is endothelial dysfunction, characterized by altered nitric oxide (NO) availability and resulting in a reduced flow-mediated dilatation of the conduit arteries [3–6]. In chronic haemodialysis (HD) patients, increased levels of pro-inflammatory and pro-oxidant uraemic toxins, in particular, of middle molecular weight, are thought to be the main cause of endothelial dysfunction. Among them, β2-microglobulin, homocystein, asymmetric dimethylarginine (ADMA), a competitive inhibitor of endothelial NO synthase (eNOS) and phosphate that may directly affect endothelial function, are well-recognized as non-traditional cardiovascular risk factors [3–7]. These uraemic toxins are poorly removed by HD techniques based on diffusion [3–6].

New dialysis modalities improving the clearance of uraemic toxins have therefore been developed. The use of high-flux rather than low-flux dialysis membranes, allowing for the removal of larger solutes, is associated with lower inflammation and oxidative stress [8–11], and reduced cardiovascular mortality, in particular in high-risk ESRD patients [11, 12]. More recently, haemodiafiltration (HDF), which combines diffusive and convective transports, has been proposed to further reduce uraemic toxins, in particular of middle molecular weight, and protein-bound solutes [12, 13]. Convection requires a fluid movement caused by a transmembrane pressure gradient. In this case, ultrafiltration exceeds the desired fluid loss in the patient, and an on-line generated replacement fluid is administered to achieve the target fluid balance [12, 13]. On-line HDF, performed using high-flux biocompatible membrane and high-quality ultrapure dialysate, is suggested to provide superior reduction in inflammation and oxidative stress than in high-flux HD [12–15]. However, this technique may also have negative effects, including the loss of water-soluble antioxidant vitamins and l-arginine, the substrate of eNOS, which are not replaced by the dialysate reinfusion [16, 17].

Three recent prospective randomized studies compared the survival of patients treated by on-line HDF or conventional, low-flux or high-flux HD [18–21]. Post hoc analysis of the first two trials suggested the possibility of a survival benefit among patients who receive high-volume HDF [18, 19], and the reduction in all-cause mortality using high-efficiency on-line HDF was confirmed by the last trial [20]. In addition, although this study was not adequately powered for this analysis, a lower risk of cardiovascular mortality and/or cardiovascular events was suggested in the on-line HDF treated group [20].

Importantly, the mechanistic link between the increased removal of uraemic toxins and improved clinical outcomes related to HDF remains uncertain. We hypothesized that HDF may improve endothelial dysfunction, a well-recognized surrogate marker of cardiovascular disease in chronic kidney disease (CKD) patients [22, 23]. We therefore designed a prospective randomized controlled trial in ESRD patients to investigate the effects of high-efficiency on-line HDF and high-flux HD on the endothelial function of the conduit arteries, evaluated by measuring flow-mediated dilatation, as well as on arterial stiffness, and assessed the associated changes in uraemic toxins, inflammation and oxidative stress.

**Subjects and Methods**

**Study design**

This is a prospective parallel randomized controlled trial comparing the effects of high-efficiency on-line HDF and high-flux HD on vascular endothelial function. The study was approved by the local Ethics Committee (Committee for the Protection of Persons Nord-Ouest I), and all participants gave written informed consent. The study was conducted according to the Principles of Good Clinical Practice and the Declaration of Helsinki, and registered at https://eudract.ema.europa.eu under the unique identifier RCB2008-A01335-50.

**Participants and dialysis modalities**

Forty-two ESRD patients were recruited and followed in the Department of Nephrology and Haemodialysis of Rouen University Hospital (C.F.-B., M.H., M.G., F.L.). ESRD patients were selected on the basis of the following inclusion and exclusion criteria: age between 35 and 80 years, arteriovenous fistula as vascular access, haemoglobin level ranging between 10 and 13 g/dL in the previous 3 months and absence of cancer, unstable heart failure, severe hypertension (SBP > 180 or DBP > 110 mmHg) or severe malnutrition (albumin < 20 g/L). At inclusion, all subjects were treated for at least 3 months, three times per week with 240-min ultrapure bicarbonate-based dialysate, using high-flux polysulfone membranes (Helexone 2.2 m², FX1000, ultrafiltration coefficient: 75 mL/h/ mmHg) and 5008 monitor (Fresenius Medical Care, Germany). A first exploration visit was performed in the Department of Pharmacology of Rouen University Hospital (J.B., R.J., M.I., L.M.), and patients were randomized to continue high-flux HD or to switch from high-flux HD to high-efficiency on-line HDF. High-efficiency HDF was performed using the same high-flux polysulfone membranes and 5008 monitor, and dialysis modalities (blood flow rate of 400 mL/min and flow rate of 800 mL/min of dialysate flux) similar to high-flux HD, plus the on-line production of ultrapure bicarbonate-buffered substitution volume in post-dilution mode with a target convective volume of ≥22 L. In addition, both HD and HDF were performed with an ultrapure dialysate, defined as bacterial counts <0.1/mL colony-forming unit endotoxin levels and <0.025 endotoxins units/mL. The use of the similar apparatus in HD and HDF allowed the patients to be blinded for the dialysis group. After a 4-month follow-up, a second exploration visit was performed.

**General procedure**

Conventional biological parameters and uraemic toxin removal (single-pool Kt/V, β2-microglobulin level) were measured during the day of dialysis preceding the exploration visits. The two exploration visits were performed during the half-week interdialytic day at a similar time of day. All the
biological and functional measurements were performed by investigators blinded to the technique of dialysis (J.B., R.J., I. R.-J., C.M., M.I., S.R., C.V.).

Conduit artery endothelial function
Brachial blood pressures were measured over the brachial artery of the arm without fistula using an oscillometric device (Omron HEM-705CP, Colson, Rosny-sous-Bois, France). Brachial artery diameter and blood flow were measured on the arm without fistula with multiarray high-resolution echotracking and Doppler (ArtLab system, Esaote Pie Medical, Maastricht, the Netherlands) [24, 25]. An arterial occlusion cuff placed on the forearm 2 cm below the elbow was inflated for 5 min 50 mmHg above systolic blood pressure and was deflated to allow reactive hyperaemia with the continuous measurements of all parameters [6, 24, 25]. Flow-mediated dilatation was calculated as the percent change in brachial artery diameter in response to reactive hyperaemia, with the peak diameter after cuff deflation and the basal diameter before cuff inflation [6, 26, 27]. After return to the baseline value, brachial artery endothelium-independent dilatation to glyceryl trinitrate (spray: 0.3 mg) was measured [6].

Carotid artery geometry and function
Intima-media thickness (IMT), internal diastolic diameter and stroke change in diameter were measured on the right common carotid artery, 1 cm beneath the bifurcation, by high-resolution echotracking (ArtLab System). The cross-sectional distensibility coefficient was estimated from the variations in arterial cross-sectional area (AA) and blood pressure (AP), assuming the lumen to be circular, as DC = ΔA/AA · ΔP, where A is the diastolic lumen area, ΔA is the stroke change in lumen area and ΔP is the central pulse pressure obtained with applanation tonometry [25, 28].

Markers of oxidative stress, inflammation and NO pathway
A 4-F catheter was inserted into the fistula allowing blood sampling for the quantification of high-sensitivity C-reactive protein (hs-CRP), plasma level of thiobarbituric acid reactive substances (TBARS), an index of systemic lipid peroxidation, total antioxidant status (TAS) and the l-arginine/ADMA ratio after 4-month follow-up [29–31]. In addition, 600-μL blood was drawn on prechilled 1-mL syringes containing 10-μL of the spin probe 1-hydroxy-3-methoxycarbonyl-2,2,5,5-tetramethylpyrrolidine (CMH, Noxygen Science Transfer & Diagnostics GmbH, Elzach, Germany), allowing the quantification of whole blood reactive oxygen species (ROS) by electron paramagnetic resonance spectroscopy (Miniscope MS-200, MagNetTech, Berlin, Germany) [32]. Further blood samples were drawn on PAXgene blood RNA tubes (PreAnalytix GmbH, Hombrechtikon, Switzerland), allowing whole blood mRNA extraction [33]. Quantification of the mRNA expression of the pro-inflammatory cytokine tumour necrosis factor-alpha (TNFα), the protein kinase C β2 (PKCβ2), an eNOS inhibitor previously shown to be increased by hyperphosphataemia [34], and the regulatory subunit P85β of the eNOS activator phosphatidyl inositol-3 kinase (PI3K) was performed by quantitative reverse transcriptase-polymerase chain reaction [35, 36]. The results are normalized to 18S rRNA expression to correct for loading differences.

Statistical analysis
The primary endpoint of the study was the difference in the variation of flow-mediated dilatation between the high-flux HD and on-line HDF groups. Using the reproducibility of the measurement of flow-mediated dilatation, calculated in eight subjects explored at a 48-h interval (mean difference: 57 μm, SD: 22 μm), a target sample size of 23 participants in each group was calculated to demonstrate significant between-group differences for the primary endpoint of 22 μm with 90% power and a 5% significance level. Values are mean ± SD or median (interquartile range) if non-normally distributed.

Fisher’s test was used to compare categorical variables and the unpaired two-sample t-test or Wilcoxon’s rank-sum test in case of non-normality were used to compare baseline continuous variables. Between-group differences in the change from baseline of all measured parameters were analysed using generalized linear models with the group as a factor and baseline value as a covariate. Robust multiple regression analysis was performed to assess, in the whole study population, the relations between the variations in flow-mediated dilatation and relevant clinical and biological variables, i.e. age, sex, smoking habit, the presence of diabetes, hypertension and dyslipidaemia (no = 0, yes = 1), time on dialysis as well as changes in body weight, LDL, HDL, triglycerides levels, glycaemia, phosphate, β2-microglobulin, Kt/V, hs-CRP, ROS levels, blood pressure and peak flow during reactive hyperaemia. Analyses were performed using NCSS software (version 07.1.14, Kaysville, Utah). A two-sided P ≤ 0.05 was considered statistically significant.

RESULTS
Baseline characteristics
Forty-two ESRD patients were included during the recruitment period. All patients completed the 4-month follow-up in accordance with the treatment protocol and were thus included in the analysis. There was no difference between the HD and HDF groups for age, gender proportion, body mass index, smoking habit, blood pressure and heart rate (Table 1). The frequencies for major comorbidities were similar, except for the number of hypertensive patients which was higher in HDF compared with HD (P < 0.05). In addition, there was no significant difference between groups for the causes of ESRD as well as for the time on dialysis at inclusion. The mean convection volume in patients on HDF, defined by the sum of ultrafiltration plus substitution volumes, was 26.6 ± 2.9 L per session, with a value of ≥22 L reached in 91% of the patients.

Pharmacological treatments
At baseline, there was no significant difference between the HD and HDF groups for the use of erythropoietin, folic acid and vitamin supplementation, phosphate binders, lipid-lowering agents, insulin and anti-hypertensive therapies, and all
these parameters remained similar during the 4-month follow-up (Table 2).

### Conventional clinical and biological parameters and uraemic toxins

At baseline, there was no significant difference between groups for weight, haemoglobin, albumin, glucose, LDL and HDL cholesterol, triglyceride, creatinine, uric acid, calcium, parathyroid hormone and homocysteine levels, and all these parameters remained similar during the 4-month follow-up (Table 3).

At baseline, there was no significant difference between groups for phosphataemia, K\textsubscript{d}/V urea, percent reduction in β2-microglobulin during the dialysis procedure (Table 3) and for the predialysis level of β2-microglobulin (Figure 1). After 4 months, there was a trend for a decrease in phosphataemia (adjusted mean difference between groups: −1.2 mg/L, 95% confidence interval (CI): −2.3 to 0 mg/L, P = 0.06) and a significant increase in K\textsubscript{d}/V urea (adjusted mean difference between groups: 0.30, 95% CI: 0.02 to 0.58, P = 0.04) in HDF compared with HD. In addition, the percent reduction in β2-microglobulin significantly increased in HDF compared with HD (adjusted mean difference between groups: 12%, 95% CI: 8–17%, P < 0.001), resulting in a decrease in the predialysis level of β2-microglobulin (Figure 1; adjusted mean difference between groups: −3.8 mg/dL, 95% CI: −7.3 to −0.3 mg/dL, P = 0.04). Moreover, after 4 months, the mean L-arginine/ADMA ratio was higher in HDF compared with HD (HDF: 139 ± 33, HD: 103 ± 31, mean difference: 36, 95% CI: 2–71, P = 0.04).

**Markers of oxidative stress, inflammation and NO pathway**

At baseline, the markers of oxidative stress (plasma level of TBARS, whole blood ROS and TAS), inflammation (hs-CRP and TNFα blood mRNA expression) and NO pathway (mRNA expressions of PKCβ\textsubscript{2} and P85β), were similar between groups (Table 4).

After 4 months, the mRNA expression of TNFα decreased in HDF compared with HD (adjusted mean difference between groups: −0.68, 95% CI: −0.98 to −0.38, P < 0.001), suggesting an improved inflammatory status. TBARS, ROS, TAS and hs-CRP were not different between HD and HDF groups. Regarding the NO pathway, PKCβ\textsubscript{2} expression decreased in HDF compared with HD (adjusted mean difference between groups: −0.36, 95% CI: −0.52 to −0.19, P < 0.001), without a significant difference in P85β expression.

Multiple regression analysis revealed that the variations in flow-mediated dilatation in the whole population of ESRD patients were significantly associated with changes in glycemia (β = −37.7 ± 15.9, P = 0.037), Kt/V (β = 28.4 ± 12.1, P = 0.032), predialysis β2-microglobulin levels (β = −1.5 ± 0.7, P = 0.018), systolic blood pressure (β = −0.4 ± 0.2, P = 0.015) and post-ischaemic peak flow (β = 0.04 ± 0.02, P = 0.045) in our model (R² = 0.83, F ratio = 4.46, P < 0.01).

**Conduit artery endothelial function**

At baseline, there was no significant difference between groups for systemic haemodynamics, resting brachial artery diameter and blood flow, post-ischaemic peak flow and endothelium-independent dilatation, and all these parameters remained similar during the 4-month follow-up (Table 5). Brachial flow-mediated dilatation was similar between groups at baseline but increased after 4 months in HDF compared with HD (Figure 2; adjusted mean difference between groups: −27 μm, 95% CI: −38 to −15 μm, P < 0.001), demonstrating an improved conduit artery endothelial function.

**Carotid artery geometry and function**

At baseline, there was no significant difference between groups for central pulse pressure, carotid artery IMT and diastolic internal diameter, and all these parameters remained similar during the 4-month follow-up (Table 5). Carotid artery distensibility was similar between groups at baseline but increased in HDF compared with HD (Figure 3; adjusted mean difference between groups: −6.7 kPa⁻¹.10⁻³, 95% CI: −9.9 to −3.5 kPa⁻¹.10⁻³, P = 0.048), showing improved arterial stiffness.

**DISCUSSION**

The main findings of the present study are that patients switched from high-flux HD to high-efficiency on-line HDF have an improvement in the endothelial function and stiffness...
of the conduit arteries compared with patients maintained on high-flux HD.

To eliminate confounding factors in comparing high-efficiency on-line HDF with the reference method of high-flux HD, all other dialysis modalities were strictly similar, including the use of high-flux polysulfone membranes and ultrapure dialysate. According to the randomized study design, baseline characteristics were similar between arms. Moreover, pharmacological treatments remained stable during follow-up and may therefore not account for differences between groups.

In this context, we observed an increase in the flow-mediated dilatation of the brachial artery in patients switched to on-line HDF compared with patients maintained on high-flux HD. This result was obtained in the absence of modification in the hyperaemic stimulus and endothelium-independent dilatation, demonstrating for the first time an improvement in conduit artery endothelial function with high-efficiency on-line HDF. Additionally, a decreased arterial stiffness was obtained in patients switched to high-efficiency on-line HDF, assessed by measuring carotid artery distensibility. A longer time on HDF may be necessary to obtain a significant modification in central pulse pressure, and subsequently in conduit artery geometry, in particular carotid IMT, which is closely influenced by the local distending pressure [37].

As suggested by the results of the multiple regression analysis, showing in the whole population of ESRD patients an

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<tr>
<th>Table 2. Pharmacological treatments</th>
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<td><strong>Supplementation (%)</strong></td>
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<tr>
<td>Erythropoietin (%)</td>
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<td>Darbepoetin alfa (μg/week) Median</td>
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<td>Phosphate binders (%)</td>
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<td>Calcium acetate/carbonate (g/week)</td>
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<td>Sevelamer/lanthanum (number of tablets/day) Median</td>
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<td>Lipid-lowering agents (%)</td>
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<td>Statins</td>
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<tr>
<td>Others</td>
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<tr>
<td>Insulin</td>
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<tr>
<td>Anti-hypertensive agents (%)</td>
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<tr>
<td>ACEI or ARB</td>
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<tr>
<td>β-blockers</td>
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<td>Calcium antagonists</td>
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<th>Table 3. Conventional clinical and biological parameters and uraemic toxins</th>
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<td><strong>Weight (kg)</strong></td>
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<tr>
<td><strong>Haemoglobin (g/dL)</strong></td>
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<td><strong>Albumin (g/L)</strong></td>
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<td><strong>Glycaemia (mg/dL) Median (IQR)</strong></td>
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<td><strong>LDL cholesterol (mg/dL)</strong></td>
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<td><strong>HDL cholesterol (mg/dL) Median (IQR)</strong></td>
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<td><strong>Triglycerides (mg/dL) Median (IQR)</strong></td>
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<td><strong>Creatinine (mg/dL)</strong></td>
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<td><strong>Uric acid (mg/dL) Median (IQR)</strong></td>
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<td><strong>Calcium (mg/dL)</strong></td>
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<tr>
<td><strong>Parathyroid hormone (pg/mL) Median (IQR)</strong></td>
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<tr>
<td><strong>Homocysteine (μmol/L) Median (IQR)</strong></td>
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<td><strong>Phosphate, mg/L Median (IQR)</strong></td>
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<tr>
<td><strong>Single-pool Kt/V urea</strong></td>
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<td><strong>β2-microglobulin removal (%) Median (IQR)</strong></td>
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**HD**, high-flux haemodialysis; **HDF**, high-efficiency on-line haemodiafiltration; **IQR**, interquartile range; **ACEI**: angiotensin-converting enzyme inhibitors; **ARB**: angiotensin II type 1 receptor blockers.

Values are expressed as mean ± SD, if not specified.
association between the variations in flow-mediated dilatation and changes in \( Kt/V \) and \( \beta_2 \)-microglobulin levels, a reduction in uraemic toxins presumably plays a major role in the improved arterial function with HDF. Indeed, convective transport with on-line HDF provided superior removal of large molecules than high-flux HD, as shown by the reduction in \( \beta_2 \)-microglobulin level, with slight effects on small solutes such as urea and creatinine, as previously shown [38, 39]. This decreased predialysis level of \( \beta_2 \)-microglobulin in HDF may notably have facilitated the regeneration of injured endothelium by increasing endothelial progenitor cell mobilization [5, 40]. Furthermore, the ratio between the natural substrate of eNOS, L-arginine, and its competitive endogenous inhibitor, ADMA, was higher in HDF compared with HD. This effect, which was not observed in studies based on a single HD session [17], may have contributed to ameliorating endothelial function. One other mechanism may be the decrease in phosphate level in HDF, probably related to the higher epuration of protein-bound phosphate and phosphate complexes by convection [41, 42]. Indeed, in addition to promoting vascular calcifications, hyperphosphataemia may directly affect eNOS activity by altering the expression of kinases involved in the regulation of eNOS functionality [34]. In particular, hyperphosphataemia increased PKC\( \beta_2 \), which decreased eNOS activity by increasing its phosphorylation at the inhibitory site Thr495 and by inhibiting the PI3 K/Akt signalling pathway [34, 43]. According to their near significant decrease in phosphataemia, patients on HDF had a lesser blood mRNA expression of PKC\( \beta_2 \), and this was observed in the absence of difference in P85\( \beta \) expression, suggesting a shift towards the activation of endothelial NO-synthase with HDF.

Furthermore, although hs-CRP was similar between groups, probably due to its high variability in dialysis patients, TNF\( \alpha \) mRNA expression was decreased in HDF, showing a reduced inflammatory stress status. This decrease in inflammation has been reported in previous studies comparing high-flux HD and HDF, and may be related to an increased removal of cytokines by convection regimens, and decreased production through the reduction in pro-inflammatory uraemic toxins [14, 44]. In contrast, our results demonstrated no significant modification in the oxidative stress status with HDF, as shown by the absence of a difference between groups for oxidative stress, inflammation and NO pathway.

### Table 4. Markers of oxidative stress, inflammation and NO pathway

<table>
<thead>
<tr>
<th>Oxidative stress</th>
<th>Baseline</th>
<th>Change after 4 months</th>
<th>( P ) value</th>
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<tbody>
<tr>
<td>TBArs (( \mu )mol/L) Median (IQR)</td>
<td>0.24 (0.19–0.32)</td>
<td>0.22 (0.16–0.45)</td>
<td>0.02 (−0.1 to 0.2)</td>
</tr>
<tr>
<td>ROS (( \mu )mol/L) Median (IQR)</td>
<td>34.7 (29.5–50.0)</td>
<td>38.3 (30.0–49.5)</td>
<td>−3 (−11 to 2)</td>
</tr>
<tr>
<td>TAS (( \mu )mol/L) Median (IQR)</td>
<td>1.55 ± 0.22</td>
<td>1.58 ± 0.26</td>
<td>−0.16 ± 0.29</td>
</tr>
<tr>
<td>Inflammation</td>
<td></td>
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<tr>
<td>hs-CRP (( \mu )g/L)</td>
<td>4.4 (1.8–16)</td>
<td>4.7 (2.1–13.5)</td>
<td>1 (−2 to 4)</td>
</tr>
<tr>
<td>TNF( \alpha ) mRNA to 18S rRNA ratio</td>
<td>0.61 (0.56–0.88)</td>
<td>0.51 (0.42–1.12)</td>
<td>0.37 (0.30 to 1.02)</td>
</tr>
<tr>
<td>NO pathway</td>
<td></td>
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<tr>
<td>PKC( \beta ) mRNA to 18S rRNA ratio</td>
<td>0.59 (0.56–0.70)</td>
<td>0.48 (0.36–0.59)</td>
<td>0.12 (0.03 to 0.31)</td>
</tr>
<tr>
<td>P85( \beta ) mRNA to 18S rRNA ratio</td>
<td>0.80 (0.58–1.12)</td>
<td>0.77 (0.60–1.00)</td>
<td>−0.04 (−0.27 to −0.03)</td>
</tr>
</tbody>
</table>

HD, high-flux haemodialysis; HDF, high-efficiency on-line haemodiafiltration; TBArs, thiobarbituric acid reactive substances; ROS, reactive oxygen species; TAS, total antioxidant status; hs-CRP, high-sensitivity C-reactive protein; PKC, protein kinase C; IQR, interquartile range.

Values are expressed as mean ± SD, if not specified.

**FIGURE 1**: Individual (white circles) and summary data (black square, mean ± SD) of \( \beta_2 \)-microglobulin predialysis level at baseline and after 4-month follow-up in patients maintained on high-flux HD or switched to high-efficiency on-line HDF. *\( P < 0.05 \) versus high-flux HD (between-group differences for the mean change from baseline).
TAS, TBARS and ROS level. Whether this result is due to a neutral effect of HDF or to the fact that the majority of our patients received folic acid, antioxidant vitamins and statins warrants further investigations. In favour of the latter hypothesis, the levels of oxidative stress markers were close to physiological values since the beginning of the study, and
homocysteine remained within the normal range during follow-up [4, 29, 32]. However, we cannot exclude that a beneficial effect of HDF on oxidative stress may be observed for ESRD patients dialysed for a longer period of time.

In conclusion, this study demonstrates that high-efficiency on-line HDF improves endothelial function and reduces the stiffness of the conduit arteries in ESRD patients, comparatively with high-flux HD. This beneficial impact on arterial function may be related to the decrease in uraemic toxins, the reduction in vascular inflammation and subsequent improvement in eNOS functionality. Although these effects were observed in a limited number of participants, this study supports the growing interest of developing and optimizing on-line HDF modalities to prevent the development of cardiovascular diseases and contribute to prolonging lifespan in dialysis patients [18–21].

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CONFLICT OF INTEREST STATEMENT

None declared.

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Variation in centre-specific survival in patients starting renal replacement therapy in England is explained by enhanced comorbidity information from hospitalization data

James Fotheringham1,2, Richard M. Jacques1, Damian Fogarty3, Charles R.V. Tomson3, Meguid El Nahas4 and Michael J. Campbell1

1School for Health and Related Research, University of Sheffield, Sheffield, UK, 2Sheffield Kidney Institute, Sheffield, UK, 3UK Renal Registry, Southmead Hospital, Bristol, UK and 4Global Kidney Academy, Sheffield, UK

Correspondence and offprint requests to: James Fotheringham; E-mail: james.fotheringham@nhs.net

ABSTRACT

Background. Unadjusted survival on renal replacement therapy (RRT) varies widely from centre to centre in England. Until now, missing data on case mix have made it impossible to determine whether this variation reflects genuine differences in the quality of care. Data linkage has the capacity to reduce missing data.

Methods. Modelling of survival using Cox proportional hazards of data returned to the UK Renal Registry on patients starting RRT for established renal failure in England. Data on ethnicity, socioeconomic status and comorbidity were obtained by linkage to the Hospital Episode Statistics database, using data from hospitalizations prior to starting RRT.

Results. Patients with missing data were reduced from 61 to 4%. The prevalence of comorbid conditions was remarkably similar across centres. When centre-specific survival was compared after adjustment solely for age, survival was below the 95% limit for 6 of 46 centres. The addition of variables into the multivariable model altered the number of centres that appeared to be ‘outliers’ with worse than expected survival as follows: ethnic origin four outliers, socioeconomic status eight outliers and year of the start of RRT four outliers. The addition of a combination of 16 comorbid conditions present at the