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A reliable method to assess the water permeability of a dialysis system: the global ultrafiltration coefficient^{*}

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ABSTRACT

Background: Recent randomized controlled trials suggest that sufficiently high convection post-dilutional haemodiafiltration (HC-HDF) improves survival in dialysis patients, consequently this technique is increasingly being adopted. However, when performing HC-HDF, rigorous control systems of the ultrafiltration setting are required. Assessing the global ultrafiltration coefficient of the dialysis system [$G_{K_{D-UF}}$; defined as ultrafiltration rate (Q_{UF})/transmembrane pressure] or water permeability may be adapted to the present dialysis settings and be of value in clinics.

Methods: $G_{K_{D-UF}}$ was determined and its reproducibility, variability and influencing factors were specifically assessed in 15 stable patients routinely treated by high-flux haemodialysis or HC-HDF in a single unit.

Results: $G_{K_{D-UF}}$ invariably followed a parabolic function with increasing Q_{UF} in dialysis and both pre- and post-dilution HC-HDF (R^2 constantly >0.96). The vertex of the parabola, $G_{K_{D-UF-max}}$ and related Q_{UF} were very reproducible per patient (coefficient of variation 3.9 ± 0.6 and $3.3 \pm 0.3\%$, respectively) and they greatly varied across patients ($31\text{--}42$ mL/h⁻¹/mmHg and $82\text{--}100$ mL/min, respectively). $G_{K_{D-UF-max}}$ and its associated Q_{UF} decreased during dialysis treatment ($P < 0.01$). The $G_{K_{D-UF-max}}$ decrease was related to weight loss ($R^2 = 0.66$; $P = 0.0015$).

Conclusions: $G_{K_{D-UF}}$ is a reliable and accurate method to assess the water permeability of a system *in vivo*. It varies according to

dialysis setting and patient-related factors. It is an objective parameter evaluating the forces driving convection and identifies any diversion of the system during the treatment procedure. It is applicable to low- or high-flux dialysis as well as pre- or post-dilution HDF. Thus, it may be used to describe the characteristics of a dialysis system, is suitable for clinical use and may be of help for personalized prescription.

Keywords: haemodiafiltration, high convection volumes, $G_{K_{D-UF-max}}$

INTRODUCTION

Two randomized controlled trials (RCTs) testing the supposed benefits of haemodiafiltration (HDF) on survival observed such beneficial effects only in a *post hoc* analysis when convection volumes were high (>17 or 22 L following the studies) [1, 2]. In a third RCT by Maduell *et al.* [3], applying high convection as the treatment of choice was associated with observed a significant improvement in survival over classical high-flux dialysis. These reports and subsequent confirmatory work have definitely influenced the opinion of the renal community, and the belief is growing that post-dilutional online HDF (OL-HDF) with high convection volumes (HC-HDF) is the best treatment, at the present time, to improve patient's survival prospects [4, 5].

High convection volumes can be obtained only with high-flux/highly permeable dialyzers and require increased transmembrane pressure (TMP). During the treatment procedure,

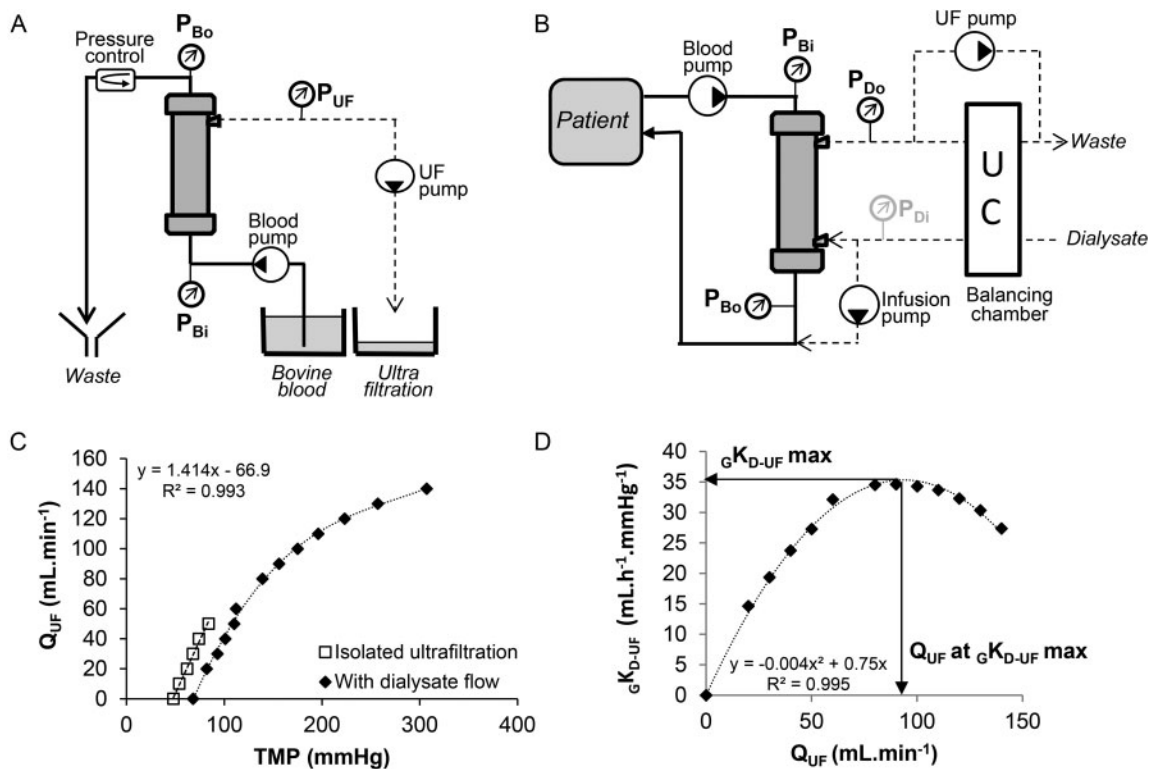


FIGURE 1: Methods and results of K_{UF} and $gK_{D-UF-max}$ determinations. (A and B) Schematics of the setting to determine K_{UF} . (A) The *in vitro* setting proposed by the FDA [15, 16] to assess K_{UF} for high-permeability dialyzers. It is an isolated ultrafiltration system (with no dialysate), where K_{UF} is determined by the slope of Q_{UF}/TMP points (see C). (B) The *in vivo* setting presently used in clinics, which is closed with an ultrafiltration controller (balancing chambers). (C) Q_{UF} increases linearly with TMP in isolated ultrafiltration, the *in vivo* K_{UF} of the dialyzer is the slope of this line ($K_{UF} = 1.414 \times 60 = 85$ mL/h/mmHg) (open squares). The straight line is shifted to the right and parallel when introducing a dialysate flow (same slope and therefore same K_{UF} according to Keshaviah's calculations). The shift may be explained, at least in part, by the hydrostatic pressure linked to dialysate flow and the oncotic pressure modifications linked to blood flow. When measurements of Q_{UF} higher than those proposed by Keshaviah's were performed, the Q_{UF} -TMP relationship no longer followed a straight line function. It bent and tended to plateau. (D) Plotting the values of gK_{D-UF} (Q_{UF}/TMP)/ Q_{UF} for these *in vivo* measurements described the parabolic distribution of gK_{D-UF} . The vertex of the parabola is $gK_{D-UF-max}$ and the corresponding Q_{UF} is the highest Q_{UF} that can be obtained for the minimal TMP.

particularly when high convection is requested, fouling of the membrane may occur, altering the efficacy of the system [6] and provoking a sustained increase of the TMP necessary to obtain the requested volumes. This results in alarms and system instability. Some attempts have been made to control this situation, and several systems automatically decrease the ultrafiltration flow when TMP is considered too high [6–12]. Dialysis stability is then obtained at the price of decreasing the total convection volume below that initially prescribed, without informing the physician in charge of the treatment. Therefore, new approaches to increase the stability of the system and minimize its deviation in terms of water permeability are needed.

The recently described gK_{D-UF} and $gK_{D-UF-max}$ [13] are promising parameters to support maintaining the system at its optimal filtration conditions. gK_{D-UF} follows a parabolic function when increasing convection flow, defining a maximum level of gK_{D-UF} , which is the vertex of the parabola. The Q_{UF} at which $gK_{D-UF-max}$ is observed is the highest ultrafiltration flow obtained per TMP unit in that system [14].

Since gK_{D-UF} is an objective parameter of the water permeability of a dialysis system, it can be used to monitor convection flow and help in identifying any potential diversion of the

system during the treatment procedure when high convective volumes are requested.

To deepen our understanding of this parameter, we assessed the reproducibility of gK_{D-UF} , $gK_{D-UF-max}$ and its associated Q_{UF} and observed that these parameters are accurate and reproducible enough to be used in clinics.

MATERIALS AND METHODS

Patients

Fifteen stable dialysis patients treated in the dialysis centre of Néphrologie Dialyse St Guilhem in Sète (France) were included in the study (Table 1). They were dialyzed three times a week with online HDF Dialog+ (BBraun, Melsungen, Germany) and DBB 07 (NIKKISO, Tokyo, Japan) machines, using ultrapure double reverse osmosis water. Their vascular accesses were native arteriovenous fistulas (14 patients) and jugular catheters (1 patient). They had been on dialysis for >3 months and had no active disease during the study. They were able to understand the study and gave signed informed consent to participate in it. The study protocol was approved by the Comité de Protection des Personnes of Nîmes (2011.10.05 bis;

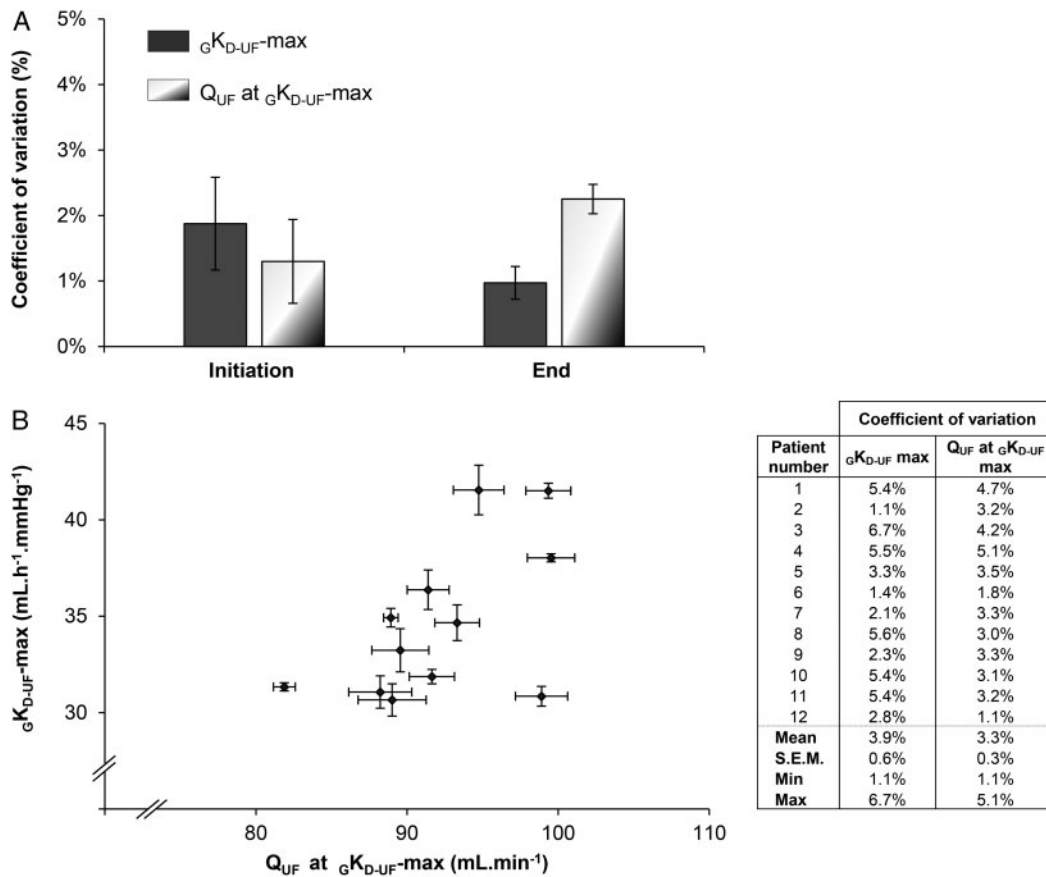


FIGURE 2: $GK_{D-UF-max}$ and Q_{UF} at $GK_{D-UF-max}$ reproducibility. (A) GK_{D-UF} was consecutively determined three times at the initiation and just before the end of the dialysis session in three patients. The coefficient of variation (CV) was calculated for each patient and the mean \pm SEM of individual CVs is plotted. It can be observed that coefficients of variation the CV was $<3\%$. The variability of the measure of the value of $GK_{D-UF-max}$ decreased with the dialysis session, whereas the variability of the value of Q_{UF} at which $GK_{D-UF-max}$ is obtained was remarkably low at the beginning. (B) The points represent the mean of a minimum of four GK_{D-UF} measures for 12 patients and the bars are the SEM. The measurements were performed at the beginning of the first session of the week during four consecutive weeks. The blood flow was 370 ± 33 mL/min (mean \pm SD), with a range of 300–400 mL/min. It can be observed that the cross-patient variation may be important ($>30\%$), while the values observed for a given patient are in a narrow range (small SEM lines).

Table 1. Patient characteristics

Characteristics	Patients (N = 15)
Sex ratio	8 males/7 females
Age (years), mean \pm SEM	73 \pm 12
Body weight after dialysis (kg), mean \pm SEM	71 \pm 2
Serum proteins (g/L), mean \pm SEM	62.8 \pm 1.2
Haematocrit (%), mean \pm SEM	35.5 \pm 1.4
Haemoglobin (g/dL), mean \pm SEM	11.1 \pm 0.3
Initial renal disease, n	
Diabetic nephropathy	4
Glomerulonephritis	2
Nephroangiosclerosis	3
Polycystic renal disease	2
Other/unknown	4
Vascular access, n	
Native arterio-venous fistula	14
Jugular catheter	1
Blood flow (mL/min), mean \pm SEM	373 \pm 8

registration number at the French Agency AFSSAPS 2011-A01092-39).

Polysulfone high-flux dialyzers (Xevonta Hi 18, Amembris and Diacap Hips 18, 1.8 m², B Braun Avitum, Melsungen,

Germany) were used. Total dialysate production flow was checked for every dialysis monitor and set at 600 mL/min in post-dilution. In pre-dilution; it was set at 500 mL/min plus the infusion flow (maximum 700 mL/min).

Convection flows assessed

GK_{D-UF} was determined for all patients at increasing convection flows. To establish $GK_{D-UF-max}$, the infusion flow rate was set at 0 mL/min and then modified stepwise by 10 mL/min from 50 to 100 or 110 mL/min. After ~ 1 -min stabilization, TMP was recorded and GK_{D-UF} was calculated with Q_{UF} :

$$Q_{UF} = \text{infusion flow (mL.min}^{-1}\text{)} + \text{weightloss(mL.min}^{-1}\text{)}$$

$$GK_{D-UF}(\text{mL/h/mmHg}) = Q_{UF} \times 60 / \text{TMP}$$

To prevent excess haemoconcentration in post-dilution, the last step was limited to a Q_{UF} value of 30% of the blood flow (Q_b). The vertex of the parabolic function (GK_{D-UF}/Q_{UF}) is $GK_{D-UF-max}$. The corresponding total convection flow is $GK_{D-UF-max}$ associated Q_{UF} (and corresponds to the x value of the $GK_{D-UF-max}$ point). A specific software was developed to

quickly determine $G_{K_{D-UF-max}}$ and its associated Q_{UF} at bedside.

TMP was given by the dialysis machines with three (B BRAUN Dialog+) or four (NIKKISO DBB 07) pressure sensors. The pressure sensors to assess TMP were located at the inlet and outlet of the blood side, the outlet of the dialysate side of the dialyser and, in the case of four-point readings, the dialysate inlet (Figure 1B). In order to increase the accuracy of TMP measurements and standardize them, *in vitro* experiments were performed.

The *in vitro* studies consisted in putting the dialysate tubing in an open volume (a laboratory plastic beaker, at the same height as the dialyzer where pressure = 0) and reading the measurements of the monitor for TMP. A correction factor for each machine could then be obtained, which was the deviation of the TMP readout of the machine from zero during these calibration studies. Following these studies, we decided to incorporate our correction factor to correct the readouts given by the machines during $G_{K_{D-UF}}$ determinations at bedside.

All pressures were measured outside the dialyzer, and the resultant given by the dialysis monitor was corrected as described to obtain the TMP value. Although the precise values of hydrostatic and oncotic pressures within the dialyzer are not determined, they are incorporated in the TMP readings. As a result, the parabolic function between Q_{UF} and $G_{K_{D-UF}}$ holds true regardless of the oncotic pressure or haematocrit levels, which influence the absolute value of the vertex but not the shape of the curve.

Statistics

Statistical analyses were performed using SAS 9.2 (SAS, Cary, NC, USA). P-values <0.05 were considered significant. Values are given as mean \pm standard error of the mean (SEM).

RESULTS

Parabolic distribution of the $G_{K_{D-UF}}$ and Q_{UF} relationship in high-flux settings with ultrafiltration control

The $G_{K_{D-UF}}$ determinations were repeatedly performed at the beginning of dialysis sessions in 15 patients. The parabolic distribution of $G_{K_{D-UF}}$ was systematically observed with high correlation indexes ($R^2 = 0.995 \pm 0.001$ $N = 150$ determinations). The worst fit that was observed had an R^2 value of 0.958 and the best was 0.999. The parabolic function held true in both post-dilutional and pre-dilutional HDF. Figure 1 shows the schematics of the setting to measure K_{UF} *in vitro* (Figure 1A) and *in vivo* with an ultrafiltration controller (Figure 1B). In isolated ultrafiltration (Figure 1C), the P/Q Q_{UF} over TMP function describes a straight line when limited to 50 mL/min (the US Food and Drug Administration proposes 30 mL/min [15]), the slope of which is K_{UF} based on Keshaviah *et al.* [17]. Adding a dialysate flow shifted the straight line to the right and increasing the filtration rate bent the line towards a plateau (Figure 1C). Finally, when $G_{K_{D-UF}}$ was calculated and plotted

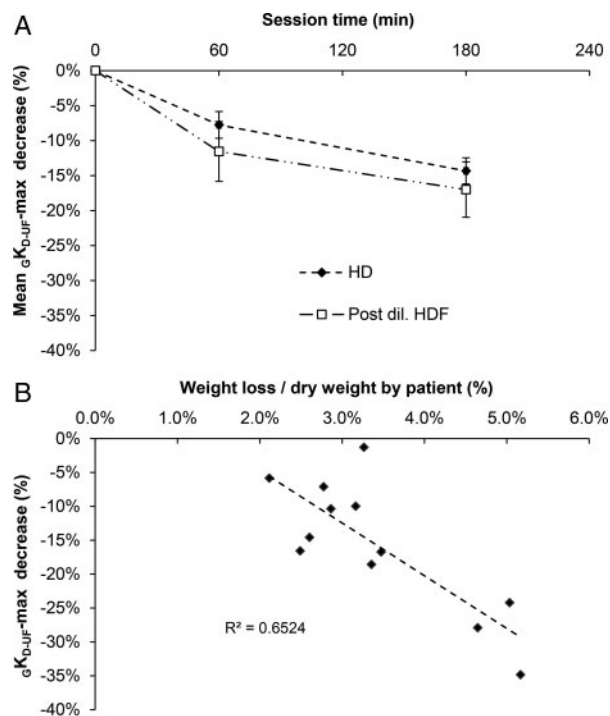


FIGURE 3: Mean $G_{K_{D-UF-max}}$ variations during the treatment. (A) The influence of the dialysis technique and time on $G_{K_{D-UF-max}}$. The same patients were treated with either haemodialysis (HD) or HDF. $G_{K_{D-UF}}$ was measured at the beginning of the treatment and at 60 and 180 min; HD and HDF are plotted. The absolute value of $G_{K_{D-UF-max}}$ decreased during the treatment and, although not significantly different, there was a trend towards a greater decrease for HDF. (B) The influence of body weight loss on $G_{K_{D-UF-max}}$ variation during dialysis. The change in $G_{K_{D-UF-max}}$ (% difference of initial and 180 min) was significantly correlated with body weight loss] in percentage of total body weight; $R^2 = 0.65$ ($P < 0.001$), showing that patient factors (among which, probably refilling) influence the decrease of $G_{K_{D-UF-max}}$ during the dialysis session.

over Q_{UF} , the parabolic function appeared with its vertex, $G_{K_{D-UF-max}}$ (Figure 1D).

Reproducibility and variability of $G_{K_{D-UF-max}}$ and its associated Q_{UF} :

Reproducibility for a given patient. $G_{K_{D-UF-max}}$ and its related Q_{UF} were reproducible within a dialysis session. $G_{K_{D-UF}}$ showed a coefficient of variation (CV) of $1.9 \pm 0.7\%$ when consecutively determined at the beginning of the dialysis session and $1.0 \pm 0.3\%$ at the end of the dialysis session (Figure 2A). The reproducibility of $G_{K_{D-UF-max}}$ associated Q_{UF} was good, with CVs of 1.3 ± 0.6 and $2.3 \pm 0.2\%$ at the beginning and end of the dialysis session, respectively (Figure 2A).

$G_{K_{D-UF-max}}$ and its related Q_{UF} determined at the initiation of dialysis were reproducible from one dialysis session to the following one for every patient (Figure 2B). The average CV for $G_{K_{D-UF-max}}$ was $3.9 \pm 0.6\%$ (highest 6.7%). The average CV for $G_{K_{D-UF-max}}$ associated Q_{UF} was even lower ($3.3 \pm 0.3\%$; highest 5.1%; table in Figure 2B).

Variability across patients. $G_{K_{D-UF-max}}$ varied across patients, from 31 to 42 mL/h⁻¹/mmHg (36% increase;

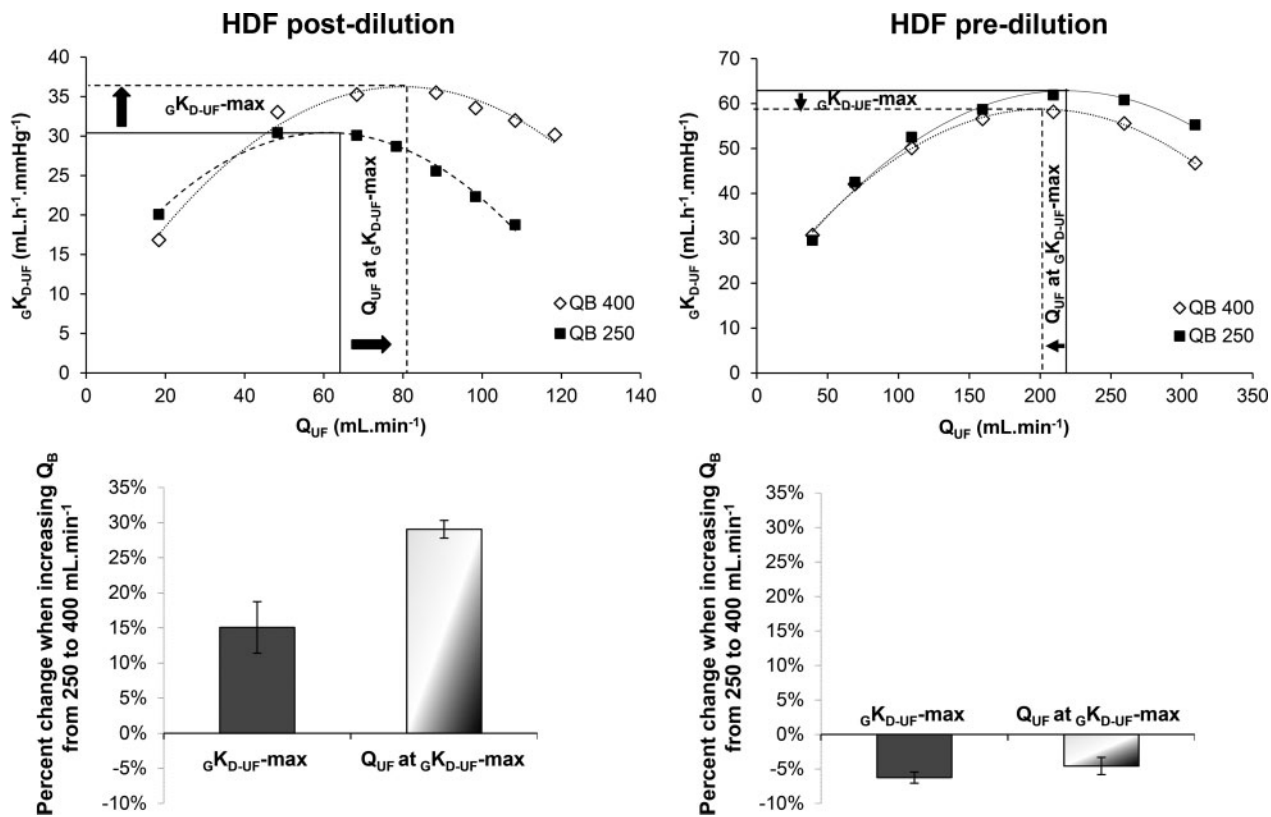


FIGURE 4: Effect of blood flow and infusion site on G_{KD-UF} . The upper panels display the measurements of G_{KD-UF} in a patient treated with two different blood flows [$Q_b = 250$ mL/min (full squares) and $Q_b = 400$ mL/min (open diamonds)] and using two different infusion sites [post-dilution (left-hand side) and pre-dilution (right-hand side)]. The lower panels show the effect of increasing blood flow on $G_{KD-UF-max}$ and its associated Q_{UF} . Both significantly increased in post-dilution HDF (left-hand side), while they decreased in pre-dilution HDF (right-hand side) ($N = 6$ and $P < 0.05$ for all), although to a lesser extent.

Figure 2B). $G_{KD-UF-max}$ associated Q_{UF} ranged from 82 to 100 mL/min (22% increase; Figure 2B).

Factors influencing $G_{KD-UF-max}$ and its associated Q_{UF} :

Patient characteristics. Across patients, the mean $G_{KD-UF-max}$ was negatively associated with plasma protein concentration (Spearman $\rho = -0.77$; $P = 0.004$), haematocrit ($\rho = -0.63$; $P = 0.03$) and haemoglobin ($\rho = -0.58$; $P = 0.04$).

Time of dialysis session. The G_{KD-UF} parabola assessed at the start of the dialysis session was repeated after 1 and 3 h of dialysis, showing a significant decrease in $G_{KD-UF-max}$ both during haemodialysis and HDF ($P < 0.001$ for both; Figure 3A). More importantly, this decrease affected the absolute value of $G_{KD-UF-max}$ more than the associated Q_{UF} . Correlation studies showed that the $G_{KD-UF-max}$ change was significantly correlated to weight loss ($R^2 = 0.65$; $P < 0.001$; Figure 3B). These data show that variations in G_{KD-UF} during the dialysis session are patient dependent.

Blood flow and infusion site. For six patients, $G_{KD-UF-max}$ was determined in four different conditions (pre- and post-dilution HDF each with 250 and 400 mL/min blood flows). The parabolic shape was always observed. Increasing blood flow significantly increased $G_{KD-UF-max}$ and its associated Q_{UF} in post-

dilution HDF, whereas the opposite was observed in pre-dilution (Figure 4).

DISCUSSION

Determining $G_{KD-UF-max}$ is a new method to assess the convection characteristics of a dialysis system that is more adapted to the presently used technology (high convection flows, high-permeability dialyzers, closed ultrafiltration circuit and ultrafiltration controllers) [13] than the ones advised by certain regulatory authorities [16], which were designed for low-permeability dialyzers and open systems [17].

Establishing the value of $G_{KD-UF-max}$ and its associated Q_{UF} at the beginning of the dialysis procedure provides an objective method to identify the best situation in terms of convection individually for every patient. Since it is a global measure *in vivo* [13], it takes into account all the parameters known to modulate ultrafiltration internally, alongside the dialyzer (haematocrit, total protein and elicited oncotic pressure) [18]. By determining $G_{KD-UF-max}$, one can identify the setting with the highest convection for the minimal TMP constraints.

Given the instability observed when requesting very high ultrafiltration flows, the use of $G_{KD-UF-max}$ in clinics is promising to minimize the increase in TMP and consequent alarms while maintaining a high ultrafiltration flow. However, before

the expected contribution of $G_{K_{D-UF-max}}$ to high-flux haemodialysis and HDF is proved, it was important to address the reproducibility and/or variability of the method, as well as the factors influencing this variability. The present work provides all this information and shows that determining $G_{K_{D-UF}}$ is easily performed, reliable, reproducible and has very low coefficients of variation. It is patient-specific, showing that the convection characteristics of a dialysis system may vary by a patient effect, and indeed stresses the value of a personalized prescription of convection. It further shows that the parabolic function also holds true in pre-dilution HDF. The opposite effect on $G_{K_{D-UF}}$ following the increase in blood flow observed in pre- and post-dilution HDF, while maintaining the same infusion flow, is certainly influenced by variations in viscosity [19] at the dialyzer entrance (an increase in blood flow in pre-dilution results in an increase in viscosity by changing the volume/volume blood-infusate proportion, thereby decreasing $G_{K_{D-UF}}$). While this explains the observed decrease in water permeability, it does not indicate total removal efficacy of the system, which is decreased in pre-dilution HDF [20].

The values of convection obtained in post-dilution at $G_{K_{D-UF-max}}$ in the example given in Figure 4 were ~ 80 mL/min when Q_b was 400 mL/min (20% blood processed), whereas they were 62 mL/min when Q_b was 250 mL/min (25% blood processed). These results may be somewhat lower than those usually obtained with automated systems [9, 11, 12]. If the target convection volume (or flow) is higher than that obtained in the $G_{K_{D-UF-max}}$ situation in a given setting, it is possible for the prescriber to increase the dialyzer surface area, to change the dialyzer and/or, if the patient is treated with post-dilution HDF and the vascular access allows it, to increase blood flow (as shown in Figure 4). Doing so, the dialysis system can be maintained in the $G_{K_{D-UF-max}}$ situation while allowing higher convection volumes. Alternatively, prescribers may want to obtain the aimed convection volume by setting the system at a Q_{UF} exceeding that of the $G_{K_{D-UF-max}}$. Determining $G_{K_{D-UF}}$ still informs the prescriber on the level of pressure constraints the system will undergo to obtain the prescribed convection volume. Using $G_{K_{D-UF}}$ determinations is a completely different approach than limiting the convection to be prescribed (or obtained) to a percentage of blood flow or imposing a TMP threshold that may be used by other automated systems. We would propose to measure $G_{K_{D-UF}}$ at the beginning of the session to use the value for prescription. The physician will prescribe at the $G_{K_{D-UF-max}}$, or lower or even higher than $G_{K_{D-UF-max}}$, and subsequently $G_{K_{D-UF}}$ determinations may be repeated at any time during the dialysis session to identify any modification appearing during the treatment time.

In presently used clinical settings, determining $G_{K_{D-UF}}$ is a promising tool guiding how to increase convection volume while maintaining system stability as long as possible. $G_{K_{D-UF}}$ is the first objective parameter that has been proved to be applicable to both pre- and post-dilution HDF. Thus it may be of assistance for physicians prescribing high convection post-dilution HDF as well as for those aiming to further increase convection volume using pre-dilution HDF. Finally, $G_{K_{D-UF}}$ may also be of assistance to describe the convective characteristics of a dialysis

system very much in line with what is required by the regulatory bodies (FDA, EMA).

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CONFLICT OF INTEREST STATEMENT

A.F., N.G., F.D., C.G. and A.A. are employees of RD Néphrologie, a spin-off of the CNRS (France), owner of the patent protecting the rights on the exploitation of GKD-UF. I.S., F.V., P.B. and M.F.S. have declared no conflicts of interest.

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Longitudinal trends in serum ferritin levels and associated factors in a national incident hemodialysis cohort

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ABSTRACT

Background: The rise in serum ferritin levels among US maintenance hemodialysis patients has been attributed to higher intravenous iron administration and other changes in practice. We examined ferritin trends over time in hemodialysis patients and whether iron utilization patterns and other factors [erythropoietin-stimulating agent (ESA) prescribing patterns, inflammatory markers] were associated with ferritin trajectory.

Methods: In a 5-year (January 2007–December 2011) cohort of 81 864 incident US hemodialysis patients, we examined changes in ferritin averaged over 3-month intervals using linear mixed effects models adjusted for intravenous iron dose, malnutrition and inflammatory markers. We then examined ferritin trends across strata of baseline ferritin level, dialysis initiation year, cumulative iron and ESA use in the first dialysis year and baseline hemoglobin level.

Results: In models adjusted for iron dose, malnutrition and inflammation, mean ferritin levels increased over time in the overall cohort and across the three lower baseline ferritin strata. Among patients initiating dialysis in 2007, mean ferritin levels

increased sharply in the first versus second year of dialysis and again abruptly increased in the fifth year independent of iron dose, malnutrition and inflammatory markers; similar trends were observed among patients who initiated dialysis in 2008 and 2009. In analyses stratified by cumulative iron use, mean ferritin increased among groups receiving iron, but decreased in the no iron group. In analyses stratified by cumulative ESA dose and baseline hemoglobin, mean ferritin increased over time.

Conclusions: While ferritin trends correlated with patterns of iron use, increases in ferritin over time persisted independent of intravenous iron and ESA exposure, malnutrition and inflammation.

Keywords: ferritin, hemodialysis, iron, longitudinal trends

INTRODUCTION

As the main storage molecule for iron [1, 2], serum ferritin is a protein related to both iron and oxygen metabolism [3], and it is widely used as a parameter to screen for iron deficiency and overload in chronic kidney disease (CKD) patients [4].