# On-line sequential hemodiafiltration (OL-S-HDF): a new therapeutic option

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## SUMMARY

Background: *On line haemodiafiltration provides the greatest clearance for low and high-molecular weight uremic toxins, which is associated with a lower risk of mortality in our patients. Nowadays, there's increasing evidence about the need of achieving at least 20 litters ultrafiltration in postdilution mode and 70% reduction of beta-2-microglobulin (B2M), however it requires a vascular access's high blood flow. Unfortunately, we do not succeed in these objectives because of our patients being older, diabetic and with poor vascular access; in this situation high blood flows are more difficult to get at the expense of lower postdilution exchange volumes. The aim of this study was to assess the efficiency of OL-S-HDF to obtain an equivalent ultrafiltration volume as 20 L in OL-postdilution-HDF (OL-P-HDF). OL-S-HDF initially begins in postdilution mode changing to predilution once the transmembrane pressure (TMP) reached 250 mmHg.*

Methods: *We performed one high-flux HD session (HF-HD), one OL-P-HDF session and one OL-S-HDF session in each of the 16 adult patients who participated during 3 consecutive weeks. We compared the clearance rates of low and middle molecules such as urea, creatinine, B2M, myoglobulin and levels of albumin and haematocrit between the 3 different techniques. We measured the pre-filter pressure (PFP) by a manometer set before the dialyzer.*

Results: *The main characteristics of the sessions are described in table N°1. There wasn't significant difference in Kt/V, urea and creatinine removal between the three techniques. B2M and myoglobulin's clearance rates were significantly higher in both hemodiafiltration modes than in HF-HD ($p = 0.000$), however we didn't find differences between OL-P-HDF and OL-S-HDF. There was a direct correlation between PFP and TMP along the sessions in every technique ($p < 0.05$). We found that PFP was better than TMP to correlate with pre-dialysis levels of albumin and haematocrit and also with the haemoconcentration percentage at the end of the sessions.*

Conclusions: *This study confirms that OL-S-HDF is as good as OL-P-HDF and it could be a useful technique to treat patients with suboptimal access's blood flow to get to achieve ultrafiltration volumes within the objectives. PFP could offer extra information than TMP.*

Key words: *On line haemodiafiltration. Transmembrane pressure. Blood flow. B2-microglobulin. Myoglobulin.*

## RESUMEN

**La hemodiafiltración en línea proporciona una alta eficacia depurativa de moléculas de mediano y gran peso molecular. Existe consenso sobre la necesidad de conseguir al menos 20 L de ultrafiltración en postdilución y tasas de reducción de B2-microglobulina mayores del 70%. Desafortunadamente muchos pacientes tienen un acceso vascular inadecuado siendo muy difícil lograr esos volúmenes de ultrafiltración sin complicaciones clínicas. El objetivo de este trabajo fue conseguir un volumen de ultrafiltración equivalente a 20 L en postdilucional, mediante la técnica «Secuencial» (HDF-OL-S) que comienza siendo postdilucional y cuando la PTM alcanza los 250 mmHg se trasforma en predilucional. Se realizó una sesión de hemodiálisis de alto flujo (HD-HF), una de hemodiafiltración postdilucional (HDF-OL-P) y otra sesión en modo secuencial a 16 pacientes durante 3 semanas consecutivas, en la sesión de mitad de semana. Se compararon los rendimientos de eliminación de pequeñas y medianas moléculas entre las diferentes técnicas. Se midió la presión prefiltro (PPF) mediante manómetro predializador. No encontramos diferencias en el Kt/V, tasa de reducción de urea y de creatinina entre las 3 técnicas. La tasa de reducción de B2-microglobulina y mioglobina fue significativamente mayor tanto en HDF-OL-P como en HDF-OL-S con respecto a la HD-HF, no habiendo diferencias entre ambas técnicas de HDF. Existió una correlación directa entre PTM y PPF a lo largo de la sesión en todas las técnicas. La PPF horaria se correlacionaba mejor que PTM con los niveles basales de albúmina sérica, hematocrito y porcentaje de hemoconcentración al final de la diálisis. La HDF-OL-S es una técnica de hemodiálisis con los mismos beneficios de la postdilucional que permite lograr volúmenes de ultrafiltración dentro de los objetivos planteados. Creemos podría ser útil en pacientes con flujos sanguíneos limitados para lo cual habría que diseñar nuevos estudios. La PPF aporta información complementaria a la PTM.**

*Palabras clave:* Hemodiafiltración en línea. Presión transmembrana. Flujo sanguíneo. B2-microglobulina. Mioglobina.

## INTRODUCTION

On-line hemodiafiltration (OL-HDF) is a dialysis procedure that adds to diffusive transport characteristic of standard hemodialysis (HD) a significant amount of convective transport. Convective transport allows for an increased clearance of me-

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dium and large-sized molecules, difficult to remove by diffusion.[1] Retention of these uremic molecules has traditionally been associated to various chronic complications in patients on hemodialysis. Several studies have shown decreases in these complication when procedures with greater convective transport are used.[2-6] The disparity in the clinical results of HDF procedures reported in the literature may be accounted for by the different convective component. Hemodiafiltrations of 6-8 L of ultrafiltrate per session are often compared to HDs greater than 20 L. It was recently reported that the relative mortality risk could be decreased in patients treated with HDF with a high convective transport, as compared to either low or high-flux HD.[7,8]

On-line postdilutional HDF (OL-P-HDF) is the most efficient renal clearance procedure in clinical practice, being more efficient, the higher the infusion rate is. In this regard, agreement begins to exist about the need for achieving at least 20 L of ultrafiltration (UF)[9] and B2-M clearance rates higher than 70%.[4,10] However, postdilutional infusion is limited by the progressive plasma hemoconcentration in the dialyzer.[11]

When a filtration coefficient of 25% of real Qb is exceeded in the OL-P-HDF procedure, a hemoconcentration will be induced in the dialyzer that will interfere with diffusion, with a subsequent decrease in clearance of small molecules and a trend to coagulability in capillaries, which may further decrease clearance.[12] Coagulation of the whole blood circuit may sometimes occur. TMP increases, and extreme values (> 300 mmHg) are associated to protein denaturation and hemolysis, with irreversible reduction in dialyzer efficacy.[13]

To solve these problems, systems combining the advantages of both modalities (pre and postdilution) and attempting to minimize their disadvantages have been devised. Such systems include the mixed OL-HDF[14] and mid-dilutional[15,16] procedures, but are not still available or require special materials that increase the costs. There are also sequential convective procedures combining hemofiltration and hemodiafiltration which have been shown to improve the hemodynamic tolerance of patients, as well as the clearance rates of molecules of medium molecular weight.[17]

Patients whose vascular access allows for a real blood flow (Qb) of 400 mL/min in OL-P-HDF will have no problems for maintaining 100 mL/min of UF without technical problems, thus achieving 24 L of convective transport in a 4-hour session. Many patients currently have an inadequate vascular access, particularly those with indwelling catheters. UF would therefore have to be reduced to 60 mL/min or to be converted into predilutional. Since predilutional OL-HDF has a 1/2 to 1/3 lower performance than postdilutional OL-HDF for medium-sized molecules,[9] UF rates as high as 300 mL/min (18 L/h) and commensurate infusions, which cannot be achieved by all machines, would be required.

In an attempt to achieve ultrafiltrations equivalent to 20 L in postdilution for potential future application to patients with limited Qbs, we developed a procedure called «on-line sequential HDF» (OL-S-HDF). OL-S-HDF starts with infusion in postdilution, at an approximate rate of 100 mL/min, and once TMP reaches 250 mmHg, infusion is manually changed to predilution, increasing the infusion rate by 50% until the end of the session (fig. 1). Hence the term «sequential», because infusion would not be simultaneous, but sequential over time, not requiring any filters or monitors different from the usual ones. Our purpose was to analyze the performance of the OL-S-HDF procedure in the clearance of small and medium-sized molecules, and to compare it to high-flux hemodialysis (HD-HF) and OL-P-HDF.

## STUDY DESIGN

This was a controlled, prospective study where 16 patients in a chronic hemodialysis program were randomly dialyzed using HD-HF, OL-P-HDF, and OL-S-HDF. Patients continued on their standard dialysis technique three times weekly, and the above procedures were performed in each patient in the mid-week session for three consecutive weeks. Procedures were analyzed and compared to each other.

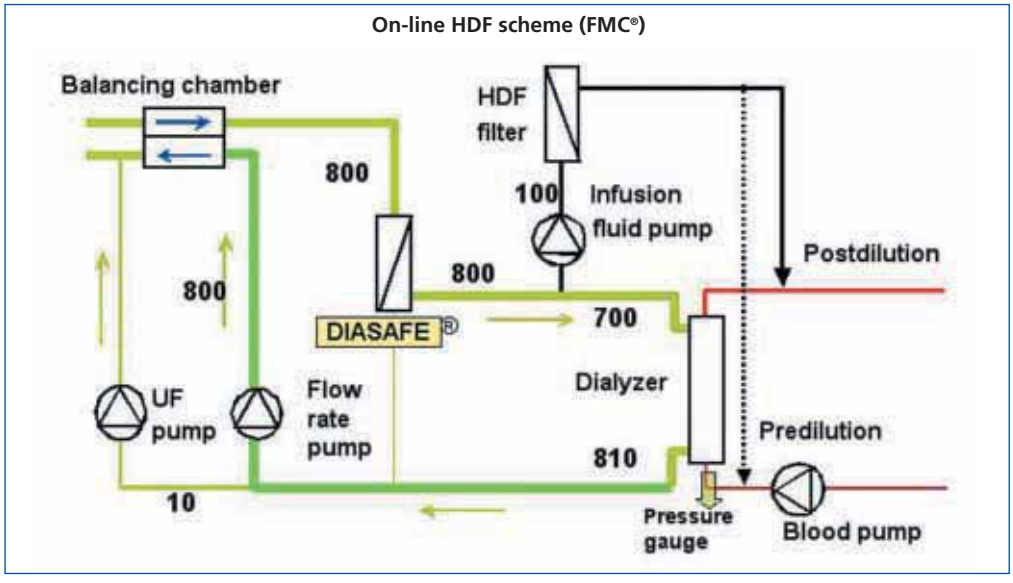


**Figure 1.** Scheme depicting the modified on-line hemodiafiltration (HDF) procedure from Fresenius Medical Care® (FMC). UF pump: Ultrafiltration pump.

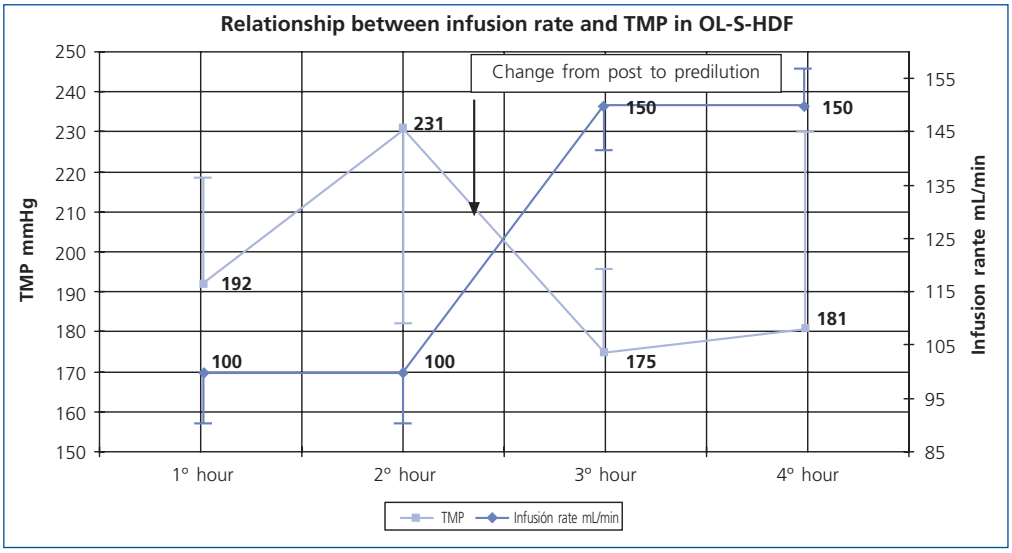


**Figure 2.** Temporal representation of change from post to predilution infusion and its relationship to transmembrane pressure (TMP) in the on-line sequential hemodiafiltration (OL-S-HDF) procedure. Values are given as mean and standard deviation.

## PATIENTS

Sixteen stable adult patients diagnosed of chronic kidney disease undergoing dialysis three times a week at the Hemodialysis Unit of Hospital G. U. «Gregorio Marañón» participated in the study.

Inclusion criteria were: age ranging from 18 and 80 years; hemoglobin levels within normal ranges according to European guidelines for anemia management;[18] vascular access with a Qb[3] 300 mL/min; and urea recirculation within normal limits (less than 12%, measured at low flow). Patients provided consent for the study. Poor dialysis tolerance was an exclusion criterion.

## MATERIALS

A Fresenius® model H400-S equipment fitted with an OCM device (online clearance monitor, ionic dialysance) and BVM (blood volume monitor), and a HF80S dialyzer (polysulfone, 1.8 $m^2$; Fresenius®, Hamburg, Germany) were used in all sessions. A portable digital pressure gauge (Nagano®) was placed between the blood pump and dialyzer to measure pre-filter pressure (PFP).

## METHODS

In all sessions studied, the theoretical blood flow rate adequate for achieving an real Qb (calculated by the equipment from pre-pump negative pressure) of 400 mL/min was kept. If this figure was not achieved, Qb was increased until a pressure –200 mmHg was induced in the pre-pump arterial line. A bath flow rate (Qd) of 800 mL/min, a dialysis fluid with a calcium concentration of 3 mEq/L, and a total conductivity of 14 mS/cm were used. Session duration was as usual for each patient.

In OL-P-HDF sessions, an infusion rate of 25% of real Qb was used. OL-S-HDF sessions started in postdilutional phase, programming an infusion rate of 100 mL/min without exceeding 30% of Qb, and when TMP reached 250 mmHg, the infusion fluid was transferred to predilution at an infusion rate 50% higher than the previous one (fig. 2).

The following laboratory parameters were measured before and after dialysis: urea, creatinine, B2-microglobulin, myoglobin, albumin, and hematocrit (Hct). The post-dialysis sample was taken from the arterial line after reducing pump speed to 50 mL/min for 2 minutes.

## DATA COLLECTION

The following were measured and recorded during each session: calculated real Qb, arterial line pressure (AP), venous line pressure (VP), TMP, PFP, and changes in plasma volume (by BVM) every hour. To measure the efficacy of the different procedures, clearance rates of urea, creatinine, B2-microglobulin, and myoglobin were calculated. The final Kt was measured in all sessions using the OCM (ionic dialysance) and Kt/V was estimated, calculating V by the Watson formula. Kt/V was calculated from pre- and post-session urea levels using the Daugirdas (1993) and Maduell formulas.

Percent hemoconcentration (HC) was calculated at the end of session using the following equation: [(Post-dialysis Hct x 100)/Pre-dialysis Hct]-100. To use this formula, hematocrit was measured before dialysis in the arterial line and at the end of dialysis at dialyzer outlet.

## STATISTICS

Normal values were expressed as the mean (± standard deviation). The value interval was sometimes recorded. A Chi-square test or a Fisher's exact test when appropriate were used to compare qualitative variables. Differences between means were tested using an analysis of variance (ANOVA). Normalized variables were correlated to each other (Pearson's correlation coefficient). A value of $p < 0.05$ was considered statistically significant. Data were analyzed using SPSS software version 12 for Windows.

## RESULTS

The 16 patients, 9 females and 7 males, had a mean age of 62 (± 14) years, a mean dry weight of 67 (± 9) kg, and a mean

**Table I. Characteristics of dialysis sessions**

| | HD-HF | OL-P-HDF | OL-S-HDF | p |
|---|---|---|---|---|
| Effective Qb (mL/min) | 381 ± 34 | 373 ± 27 | 370 ± 32 | NS |
| Infusion rate (mL/min) | 0 | Post 95 ± 4 | Post 99 ± 11<br>Pre 148 ± 18 | NS |
| Total UF vol (L/sesión) | NA | 23.4 ± 3 | 14.7 ± 5 en Post<br>17 ± 6 en Pre | 0.000 |
| Hct (%) | 34.7 ± 3 | 35 ± 5 | 35.4 ± 4 | NS |
| % HC | 15 ± 6 | 38 ± 22 | 21 ± 9 | 0.003* |

Qb:actual blood flow. Post: postdilution. Pre: predilution. Total UF vol: total ultrafiltrate volumen (infusion fluid + ultrafiltrate). Hct: hematocrit. % HC: percent hemoconcentration at end of dialysis. ([Post-dialysis Hct x 100)/Pre-dialysis Hct]-100). HD-HF: High-flux hemodialysis. OL-P-HDF: On-line post-dilutional hemodiafiltration. OL-S-HDF: On-line sequential hemodiafiltration. NS: not significant. NA: not applicable. *Significant differences between the three procedures.

Hct of 35% (± 4.2). All patients were stable and had been more than 6 months on dialysis. Four patients were diabetic and two had an indwelling catheter, while all other patients had a functioning arteriovenous fistula.

Dialysis duration was 219 (± 15) minutes (min. 195-max. 240). Mean transition time from post to predilution in OL-S-HDF from session start was 127 (± 33) minutes (min. 60 - max. 165, and had an inversely correlated to baseline hct levels ($p = 0.005$)

Table I shows data of all three procedures. No significant differences were found in the real Qb reached in the three procedures or in pre-dialysis hematocrit values. Infusion volume was significantly higher in OL-S-HDF than in OL-P-HDF. Hemoconcentration (%HC) was more important in OL-P-HDF than in OL-S-HDF, in which it was in turn higher than in HD-HF.

No differences were found in Kt (ionic dialysance), Kt/V, and urea and creatinine clearance rates between the three procedures, while the clearance rates of B2-microglobulin and myoglobin were significantly greater for both OL-P-HDF and OL-S-HDF as compared to HD-HF ($p < 0.000$). There were no differences between both HDF procedures (table II).

A direct correlation existed between TMP and PFP during the session in all procedures ($p < 0.05$), with a TMP pressure of 145 mmHg corresponding to a PFP of 395 mmHg. Both pressures gradually increased towards the end in OL-P-HDF (figs. 3 and 4). Hourly PFP was found to have a positive correlation with baseline serum albumin levels ($p < 0.03$), Hct values ($p < 0.01$), and percent hemoconcentration in the patient at end of dialysis ($p < 0.01$), this finding was not demostrated for TMP. Clearance rate of β2-microglobulin and myoglobin had an inverse correlation with TMP and PFP ($p = 0.003$ and 0.01).

No clinical complications occurred in any of the sessions studied. Only the presence of some clotted capillary at the end of the OL-P-HDF sessions required an increase in heparin dose in this procedure.

## DISCUSSION

OL-HDF is the most complete clinical hemodialysis procedure currently available.[19] The postdilutional modality achieves the best performance in terms of clearance of uremic toxins.[14] To achieve adequate results with this modality, ultrafiltrations higher than 20 L should be achieved.[9] In patients with an optimal vascular access, blood flow rates higher than 400 mL/min may be achieved, which would allow for reaching that volume in about 4 hours, maintaining a 25% filtration fraction.

As shown by the study results, clearance and removal of small molecules such as urea and creatinine are similar in HD-HF and OL-HDF procedures. In some optimal cases with low filtration fractions and not very high hematocrit values, up to a 10% increase may be achieved.

**Table II. Clearance rate of small and medium-sized molecules and Kt/V during dialysis**

| | HD-HF | OL-P-HDF | OL-S-HDF | p |
|---|---|---|---|---|
| Urea | 77 ± 6% | 79 ± 5% | 80 ± 8% | NS |
| Creatinine | 68 ± 8% | 72 ± 6% | 71 ± 8% | NS |
| B2-M | 61 ± 7% | 75 ± 9% | 77 ± 5% | 0.000*/** |
| Myoglobin | 12 ± 15% | 42 ± 14% | 33 ± 18% | 0.000*/** |
| Kt/V | 1.6 ± 0.1 | 1.6 ± 0.2 | 1.6 ± 0.3 | NS |

HD-HF: high-flux hemodialysis. OL-P-HDF: on-line post-dilutional hemodiafiltration. OL-S-HDF: on-line sequential hemodiafiltration. B2-M: B2-microglobulin. Kt/V: dialysis dose. NS: not significant.
* Comparing both OL-HDF procedures to high-flux HD.
** No significant differences were seen between OL-P-HDF and OL-S-HDF.

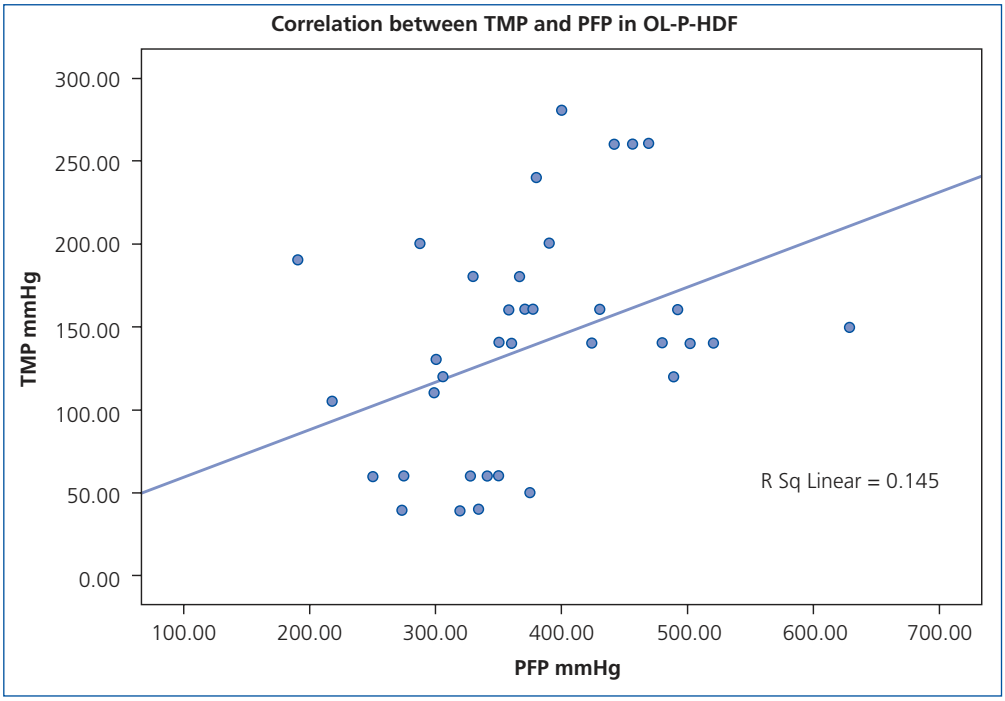


**Figure 3.** Correlation between transmembrane pressure (TMP) and prefilter pressure (PFP) in the on-line postdilutional hemodiafiltration (OL-P-HDF) procedure. Values are given in mmHg.

Anyway, these procedures are not intended to increase clearance of small molecules, but that of medium and big molecules, and an up to 70% increase was indeed seen in the clearance rates of B2-microglobulin and myoglobin with OL-HDF procedures. It should be emphasized that the dialyzer used in this study achieves in itself a significant level of B2-microglobulin removal in hemodialysis because by retrofiltration causes a true internal OL-HDF.

The number of patients with vascular access and high blood flow rates are now almost a minority. With theoretical blood flow rates of approximately 300 mL/min it is very difficult to achieve 20 L of ultrafiltration in a standard time of four hours. When an attempt is made to increase postdilutional infusion to 100 mL/min, multiple technical problems occur, including TMP elevation, partial or total clotting of the system, and a decreased dialytic performance. In our study, these problems were detected and related better with PFP than with TMP though, as previously stated, these two pressures are significantly related. Factors contributing to the occurrence of these problems include high hematocrit values, hyperproteinemia, and hyperlipidemia. On the other hand, if an attempt is made to increase pump flow, we may contribute to the occurrence of complications such as a marked decrease in arterial line pressure or, which is the same thing, a decrease in the real Qb/theoretical Qb ratio and recirculation of vascular access.

In our study, the factor correlating best to PFP increase was hematocrit and progressive hemoconcentration during dialysis. PFP was also related to baseline albuminemia. PFP sometimes reached levels higher than 700 mmHg. In future OL-HDF machines it would be helpful to have a pressure gauge to measure PFP, which is sometimes more useful than TMP. While many of our patients have high hematocrit values and normal albumin levels, if a 25% filtration fraction is respected no clinical complications occur in OL-P-HDF, as shown in our study.

In some cases where PFP and TMP are markedly increased, a greater interference probably exists between both types of transport, with a decrease in diffusive transport leading to a decreased clearance of small molecules. This phenomenon was documented in this study also for medium-sized molecules such as B2-microglobulin and myoglobin, when clearance rates were inversely related to PFP and TMP. The increase in protein layer in the capillary membrane when a high filtration fraction was applied would explain this phenomenon.

OL-S-HDF was shown to be better than HD-HF but similar to OL-P-HDF for removing medium-sized molecules. The sequential procedure would thus be similar but not superior to the postdilutional procedure, and would therefore not be recommended for stable patients and with optimal Qbs. There are, however, patients with limited Qbs (< 300 mL/min) who do not reach the desired 20 L in the scheduled OL-P-HDF time. Though this study included patients with relatively limited Qbs (mean Qb of 370 mL/min and only 31% of patients with Qb < 350 mL/min), we think that in patients with Qb < 300 mL/min, OL-S-HDF could be a therapeutic alternative to achieve higher volumes with similar clearances.

When switching from postdilutional to predilutional infusion, the UF-infusion rate was increased by 50%, but we think that to achieve a better performance in patients with limited Qbs such rate could be further increased, even doubled, with no complications. It should be noted that the predilutional system does not involve an increased use of dialysis fluid, though compensated systems adjusting fluid to blood flow currently exist.

From the technical viewpoint, change in the infusion site is simple and does not require any accessory, so that it does not involve any additional cost. Based on the foregoing, we think that OL-S-HDF could be a useful hemodialysis procedure in

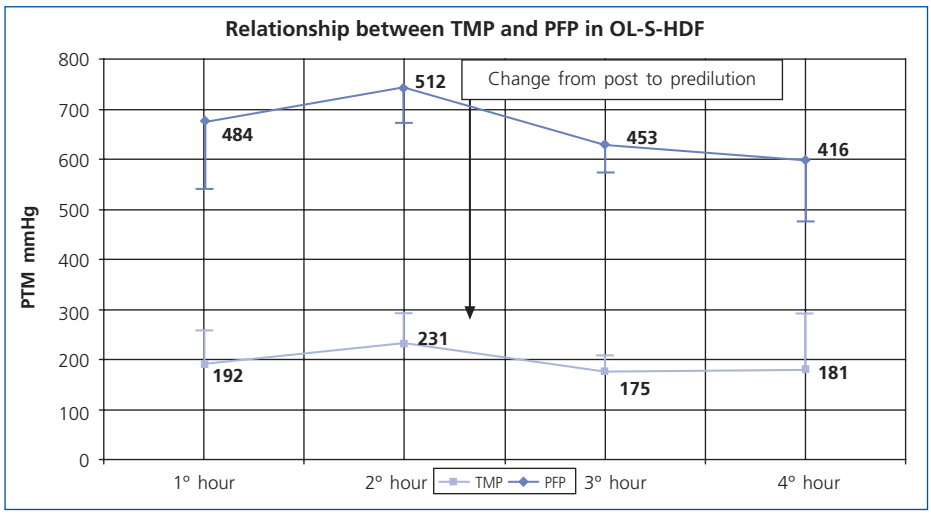


**Figure 4.** Relationship between transmembrane pressure (TMP) and prefilter pressure (PFP) in the on-line sequential hemodiafiltration (OL-S-HDF) procedure. The time of change from post to predilution is represented with an arrow. Values are given as mean and standard deviation.

patients with limited blood flow rates (< 300 mL/min). Further studies of this procedure should therefore be designed.

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