RIGHT THERAPY CONTEST 2019

Patient outcomes with adsorptive therapies
Patients with inflammation and malnutrition

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THE RIGHT THERAPY CONTEST 2019

Although randomized clinical trials represent the best way to assess the safety and performance in a clinical setting, there is a growing interest in the role of real-world clinical data for evidence generation. Those data are generated by daily use of devices in standard conditions without specific inclusion or exclusion criteria; all patients are eligible.

For this reason, in November 2018 Medtronic established the Right Therapy Contest to give healthcare professionals a forum to collaborate and share clinical best practice on the application of adsorptive blood purification therapies. We believe treatment personalization — the right therapy — can potentially lead to improved outcomes.

During the contest period, we received 39 case reports on hemodialysis patients treated with Bellco adsorptive extracorporeal therapies, as part of standard clinical practice.

The Medtronic (Bellco) Scientific Affairs Team assembled an independent panel of three European clinicians, who were selected based on their scientific curricula, expertise, and experience with Bellco filtration adsorption therapies. It was important that among their credentials, they also had extensive knowledge of uremic toxins and the effect on patients on dialysis, and at least:

- Two publications on Bellco adsorptive therapies and/or extracorporeal blood purification therapies
- 10 publications in peer-reviewed international journals

The panel evaluated all submissions based on the following criteria:

- Originality and uniqueness of cases
- Scientific quality
- Clinical or patient Impact
- Presentation and comprehensibility

The closing date for submissions was May 5, 2019, 23.59 CET. Case reports submitted after this date were not considered.

The cases reported represent real-world evidence of the adsorptive therapy in clinical practice, according to patient clinical need, and under the supervision of the clinicians involved. This booklet contains all case reports and/or clinical experiences that were submitted as part of the Right Therapy contest.1

The procedures and techniques described do not represent all medically acceptable protocols; physicians should always use their professional discretion and follow hospital protocol.

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† All clinicians granted approval and permission for publication.
Uremic Toxins — A Tale of Numerous Stories
Björn Meijers, M.D., Ph.D., University Hospitals, Leuven, Belgium

Chronic kidney disease (CKD) is one of the most important health epidemics of our time. More than 10% of the general population is affected and its prevalence continues to rise. As kidney function is paramount for body homeostasis, loss of kidney function results in significant morbidity and high preterm mortality. In recent decades, major advances have been made to reduce mortality and morbidity of affected individuals. Important innovations include the development of hemodialysis, peritoneal dialysis as well as kidney transplantation. While kidney transplantation is an excellent therapeutic option for suitable transplant recipients, access is hampered by donor shortage. Globally, the majority of end-stage kidney disease (ESKD) patients with access to renal replacement therapies relies on hemodialysis for survival.

The development and deployment of hemodialysis, kidney transplantation and many other scientific breakthroughs has dramatically altered the course of uremia. Once encompassing all symptoms and signs related to the loss of kidney function, we now consider uremia to include only those pathophysiological consequences that are not (yet) manageable by therapeutic intervention. Of note, patients still suffer from remnant uremia and have unacceptably high morbidity and mortality rates (e.g. significantly exceeding mortality of colon cancer, or after myocardial infarction). Unresolved issues include malnutrition, systemic inflammation, atherosclerosis (MIA syndrome) as well as mineral-bone disorder.

Uremia is characterized by the retention of organic waste solutes. To the extent that these retained solutes contribute to the syndrome of uremia, these are considered uremic toxins. A simple definition of such solutes would be “any organic solute in the blood that: (i) accumulates in patients with chronic kidney disease resulting in a blood concentration exceeding concentrations found in individuals with a normal kidney function, (ii) adversely affecting physiological function(s), thereby (iii) contributing to morbidity and/ or mortality.” Gradually, the list of putative and known uremic toxins has expanded and now includes several hundreds of solutes. Historically, these have been classified according to physicochemical properties describing their behavior during dialysis, i.e., low vs. high molecular weight and the degree of protein binding.

This classification, while of value, has several limitations: (i) It focuses on patients with end-stage kidney disease, as it is based on solute behavior during dialysis. It is however quite clear that human physiology is already affected by uremia at less severe loss of kidney function. Most epidemiological studies demonstrate worsening of hard clinical endpoints once the (estimated) glomerular filtration rate is reduced to below 60 mL/min/1.73 m2. (ii) The physicochemical classification focuses only on epuration of uremic retention solutes, but not on its source. Typically, uremic retention solute concentrations have a large interindividual dispersion, while intraindividual variation over time is limited. Exploration of contributing factors in patients at advanced stages of CKD point to variations in metabolism and adsorption. This is particularly true for uremic retention solutes derived from the gut microbial metabolism. (iii) The physicochemical classification assumes that molecular weight is an important classifier for uremic retention solutes. However, during conventional dialysis dialysance is dependent on diffusion over a semi-permeable membrane. According to the Stokes-Einstein equation, the diffusion constant is not dependent on the molecular weight. Rather, it is dependent on the inverse of the hydrophilic radius.
\[ D = \frac{R T}{N 1/6 \pi \eta} \]

equation 1

Stokes-Einstein equation (\( D \), diffusion constant; \( R \), gas constant; \( T \), absolute temperature; \( \eta \), viscosity; \( p \), hydrophilic radius).

This implies that uremic retention solutes with an identical molecular weight, but different hydrophilic radius cannot have the same dialysance, and thus will behave different during dialysis. This also implies that simply increasing pore size will not result in significant augmentation of diffusive transport of uremic retention solutes with a large hydrophilic radius.

(iv) The dialytic clearance of solutes is not only dependent on the dialysance, but also on the kinetic behavior. Relevant factors include the distribution volume and the equilibration rate between different compartments. (v) The physicochemical model is primarily focused on conventional hemodialysis. The dialytic clearance is much less dependent on molecular size (not weight!) during convective therapies. Also, this model is not well-suited to describe solute behavior during adsorptive techniques.

We have previously proposed a genealogical classification, typing uremic retention solutes on their source or origin.\(^{10}\) One can discriminate three groups: exogenous, endogenous, and microbial-human co-metabolites. This classification is quite useful to direct therapies aimed at prevention of accumulation. Most research efforts now go to the gut microbial metabolism derived uremic retention solutes.

Ideally, a genealogical classification would be combined with a classification based upon epuration during extracorporeal therapies. Factors that need to be taken into account are diffusive vs. convective transport, degree of adsorption, degree of protein-binding, and kinetics (distribution volume, multi-compartmental distribution). To date, there is no generally accepted classification that takes into account all these issues. One of the major challenges is that typically, several techniques are combined, as most dialysis sessions combine diffusion with at least a small amount of convection (the ultrafiltration volume), or larger volumes of convection (hemodiafiltration). Even less is known about the role of adsorption. Proof of principle experiments have demonstrated that extracorporeal epuration efficacy of several uremic retention solutes can be boosted by adsorption. Adsorption can also be applied in combination with conventional dialysis.

We are only beginning to understand the complexities of uremia. Our knowledge of the uremic retention solutes and its role in uremic toxicity has expanded in large part thanks to the development of hemodialysis and peritoneal dialysis. Therefore, careful evaluation of novel techniques and its effects on patients with end-stage kidney disease may provide additional insights and challenge current paradigms.
References


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Microinflammation and Endothelial Damage

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Non-traditional risk factors such as uremic toxin accumulation, inflammation, oxidative stress, and endothelial dysfunction are associated with chronic kidney disease (CKD) and may contribute to the accelerated atherosclerosis and cardiovascular complications.\(^1,2\) The uremic toxins activate monocyte-derived dendritic cells, CD14+CD16+ or CD14++CD16+, which release proinflammatory cytokines that damage the endothelium and decrease circulating bone marrow-derived endothelial progenitor cells (EPC).\(^2,3,4\) Inflammation may promote atherogenesis suggesting that cardiovascular mortality is closely associated with the inflammatory status which is present in hemodialysis (HD) patients.\(^1,3,5\) In fact, CRP and IL-6 predicted overall and cardiovascular mortality.\(^2\) Chronic inflammation has been related to the cell activation induced by the dialysis modality, dialysis membranes, and contamination of the dialysis fluid, as well as the accumulation of uremic toxins (figure 1). Our group has reported that chronic inflammation in CKD is accompanied by an increase in the percentage of CD14+/CD16+ monocytes. The inflammatory activity increased the expression of intracellular cytokines that induced activation and death of endothelial cells. There was a relationship between increased CD14+/CD16+ and endothelial damage which suggests that these cells may play an important role in the coupling of inflammation and endothelial damage. Therefore, the reduction in CD14+/CD16+ inhibitory monocytes may constitute a therapeutic goal in the treatment of CKD.\(^3,6,7\)

OL-HDF is a highly effective dialysis modality that expands the spectrum of removed uremic toxins. In a prospective, crossover study, we showed that in patients on OL-HDF there was a decrease of CD14+CD16+ which was paralleled to a reduction of intracellular cytokines and short telomere cells.\(^8\) All these factors may contribute to reducing uremic complications and possibly mortality. On the other hand, it has been recently reported that circulating endothelial microparticles (EMP) may be considered as a potential new risk factor in the occurrence of cardiovascular events and provides evidence for using EMP as a surrogate marker of endothelial dysfunction.\(^7,9\)

The increasing of EMP in CKD patients is comparable with the those in patients with endothelial dysfunction pathologies. This may suggest use of this marker as a possible new indicator of endothelial dysfunction in uremic patients.\(^6,10\) We evaluated the effect of convective transport on microinflammation and endothelial damage.\(^9\) The reduction of CD14+CD16+ cells was correlated with an improvement of both EMP and EPCs. Therefore, it is possible to speculate that monocyte-derived dendritic cells may have an additional effect on endothelial activation and injury leading to release microparticles in the circulation, and stimulation of the bone marrow to increase the production of circulating EPC.\(^7,8\) In addition, we have observed that the accumulation of senescent monocytes may explain, in part, the development of chronic inflammation and atherosclerosis in elderly subjects and in patients with CKD.\(^3\)

The amelioration of the micro-inflammatory status using high convective transport seems to reduce endothelial damage. However, it is important to stress that OL-HDF did not achieve normal values.\(^9\) Therefore, it seems reasonable to look for more effective therapeutic alternatives.
In a prospective single-center crossover study, we compared HFR-Supra and OL-HDF effects on uremic toxins and inflammatory, endothelial status, or oxidative stress markers. Relative to OL-HDF, HFR-Supra was associated with greater indoxyl sulfate removal and lesser abnormalities in all other study variables, namely circulating interleukin-6, tumor necrosis factor-alpha, proportions of activated proinflammatory (CD14+CD16, CD14++CD16) monocytes, endothelial progenitor cells, apoptotic endothelial microparticles, vascular endothelial growth factor, vascular cellular adhesion molecule, angiopoietins 2 and 1, Annexin V, and superoxide dismutase. Our investigation provides hypothesis-generating results suggesting that compared with OL-HDF, HFR improves protein-bound toxin removal, inflammatory, endothelial status, and oxidative stress. These potential benefits may have a positive impact on improving cardiovascular mortality and survival of HD patients. However, it is necessary to conduct studies with a large number of patients followed for a long period of time to confirm these results. A key aspect is to define what type of patients can have a greater benefit of this type of dialysis.

**Figure 1.**

**Microinflammatory status associated to HD**

Factors potentially modifiable
References


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The Ideal Extracorporeal Treatment for Patients with End-Stage Renal Disease (ESRD)

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ESRD is characterized by the retention of a huge number of waste solutes with a wide range of molecular weights (MW). A number of these solutes are bound to proteins — mostly albumin. The toxicity of a number of these waste products has been demonstrated. The ideal extracorporeal treatment for patients suffering from ESRD would be able to eliminate efficiently all these uremic toxins — including those bound to albumin.

During hemodialysis (HD) — and derived methods — the elimination of uremic toxins is dependent on diffusion/convection over a semi-permeable membrane. This is roughly dependent of the MW of the toxin, or more precisely of the Stokes-Einstein radius of the molecule.

During conventional HD — like that used in the 1960’s — uremic toxins diffuse across a semi-permeable membrane of low porosity along their concentration gradient. Hence, only toxins with a small Stokes-Einstein radius could be eliminated.

As soon as technological improvements of HD monitors allowed a good control of ultrafiltration (UF) — elimination of salt and water — semi-permeable membranes of greater porosity began to be used, allowing to get rid of uremic toxins with a somewhat greater radius (« high flux » HD). In an attempt to increase the elimination of toxins with a higher MW, techniques of hemodiafiltration (HDF) were developed later on. Here, an important volume of plasma water (typically circa 20 liters) is pushed through the membrane and replaced by a fresh substitution fluid. So, additional uremic toxins of the plasma water can be eliminated by convection through the membrane.

However, those HDF techniques have clear limitations: (i) uremic toxins with higher Stokes-Einstein radius and those bound to proteins are not cleared (ii) whether HDF is associated with improved patient prognosis is a matter of debate. (iii) replacement fluid is made under the responsibility of the nephrologist which poses legal problems (iv) we have shown recently that dialysance of myoglobin — a high MW molecule retained in uremia — is not inferior during HD with a modern HD membrane such as the Phylter Up from Bellco as compared to high volume HDF.

Hence, new methods must be developed to significantly improve the efficiency of uremic toxins elimination. One interesting way to do so consists of using adsorption membranes.

Interestingly, several high flux membranes used in classical HD had already demonstrated interesting adsorption capabilities with clinical benefits. For instance, the AN69 polyacrylonitrile developed by Hospal is able to adsorb 2-microglobulin and limit the risk of HD-associated amyloidosis. More recently, the polymethylmethacrylate (PMMA) membrane has demonstrated its capacity to adsorb the immunoglobulins light chains and has even been used successfully to treat patients with myeloma and acute renal failure. However, in these examples the adsorption capacity is of course limited due to the small surface membrane.
An interesting approach consists of combining the use of a membrane of very high porosity with an adsorption device. The very porous filter allows the production of ultrafiltrate rich in uremic toxins of a wide range of Stokes-Einstein radius and albumin-bound toxins. This toxin-rich ultrafiltrate is then regenerated by the passage through a huge surface adsorption cartridge. The regenerated ultrafiltrate is then reinfused to the patient.

This method is used in the HFR technique (HDF with endogenous ultrafiltrate reinfusion, Medtronic) to treat ESRD patients and CPFA (Coupled Plasma Filtration Adsorption, Medtronic) to treat patients with severe sepsis. In these techniques the adsorption device is built from resin. It has been shown that this resin adsorbs a wide range of uremic toxins without adsorbing a number of useful molecules such as albumin and hydrosoluble vitamins. The surface of the adsorption cartridge is enormous, and it has been shown that it holds its adsorption capacity even by the end of treatment. Theoretically this method could also be used in a number of accidental/voluntary intoxication for which no efficient treatment is available.

A number of clinical studies with HFR and CPFA have yielded encouraging results. So, HFR can efficiently eliminate light chains in patients suffering myeloma kidney. Moreover, in HD patients suffering idiopathic inflammation — considered as a good surrogate of mortality — inflammation is significantly improved already after 4 months of HFR therapy. In intensive care unit patients with severe sepsis vital prognosis is significantly improved in those patients treated with high volume CPFA.

Of course, the use of adsorption such as in HFR (with a high cut-off plasma filter, such as with the Sinclair 0.2 system) in combination with a high efficiency high flux hemodialysis membrane would yield the opportunity to clear efficiently uremic toxins with a very wide range of Stokes-Einstein radius while detoxifying also plasma albumin.

References


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The Effect Of HFR-Aeq on Hemodynamics and Middle Molecule Clearance: A Case Report.

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Background
Hemodiafiltration with Endogenous Reinfusion Aequilibrium (HFR-Aeq) is a dialysis technique characterized by a resin cartridge with adsorptive power that aims to better reproduce the kidney physiology, mimicking both glomerular and tubular functions. Thus, HFR-Aeq combines diffusion, convection, and adsorption. Dialysis patients are challenging. Intradialytic Hypotension (IDH) often characterizes our dialytic population and represents one of the major causes of cardiovascular mortality. In addition, the clearance of some uremic toxins, such as Beta2-microglobulin (B2M), relates with mortality as well. The European Best Practice Guidelines have recommended the use of B2M as a marker for middle molecules and it could be used as a marker to guide routine chronic hemodialysis therapy.

Methods
We selected a female patient, 82 years old, with end stage renal disease (ESRD) due to Autosomal Dominant Polycystic Kidney Disease (ADPKD). She is also affected by hypothyroidism and hyperlipidemia. However, chronic hypotension has represented the main life-limitation in this patient. Online Hemodiafiltration (HDF) three times a week was the dialytic prescription until she was shifted to HFR-Aeq, last March. We carefully monitored vitals, and laboratory tests were collected from arterial blood lines both at the start and at the end of a single dialysis session, including B2M, PTH, LDL Cholesterol, LDH and CRP. We sought to explore if HFR-Aeq could impact hemodynamics such as significantly reduce uremic toxins middle molecules. T-Test was applied for statistics.

Results
Statistically significant elevation of both Systolic (119±10.21) and Diastolic (93±8) blood values were recorded (fig. 1), with no IDH episodes along HFR-Aeq sessions. Furthermore, the patient self-reported a clear improvement of her life autonomy. B2M (fig. 2), was significantly decreased at the end of each session, with a p-value of 1.54E-06. PTH and LDL cholesterol were significantly reduced as well with respectively a p-value of 8.42E-04 (PTH) and 5.99E-04 (LDL Chol). No statistical differences were recorded about LDH and CRP levels.

Conclusions
Our observation demonstrates a significant improvement of both systolic and diastolic blood pressure values during HFR-Aeq sessions, with more stable intradialytic hemodynamics, such as during patient daytime. Our observation generates additional data supporting the idea that HFR-Aeq may lead to a better outcome in hemodialysis patients, stabilizing hemodynamics and removing uremic toxins middle molecules. Longer-term studies are needed.
References


HFR Aequilibrium Improves Intradialytic Hypotension in Hemodialysis Patients


**Background**
Intradialytic hypotension is the major clinical problem during hemodialysis treatment. HFR-Aequilibrium, a profiled hemodiafiltration supported by the Natrium sensor for the sodium measure, can reduce intradialytic hypotension. We present a clinical case with an observational period of 6 months, exactly 3 months with standard treatment followed by 3 months of HFR-Aequilibrium using Flexya dialysis machine.

**Methods**
A 52-year-old female patient with lupus nephritis started hemodialysis treatment in our Renal Unit at the age of 21. She also had epilepsy due to lupus encephalopathy. At the age of 29, after 8 years of dialysis treatment, she received a donor kidney transplant from a deceased patient. Ten years later, at the age of 39, she was submitted to ureterocystoneostomy for vesico-ureteral reflux. At the age of 40, her renal function declined because of antibody mediated rejection. At the age of 48, she started hemodialysis treatment in another Renal Unit for end-stage renal disease and after one year she joined two waiting lists for renal transplant. At the age of 50, she had intermittent claudication. Peripheral arterial disease of the lower extremities was diagnosed, and she was submitted to percutaneous transluminal angioplasty and stent placement in external iliac artery. About one year ago she decided to continue hemodialysis treatments in our Renal Unit. At first, we continued standard treatment, but then she switched from standard treatment to HFR-Aequilibrium because of intradialytic hypotension.

**Results**
She showed improvement of intradialytic cardiovascular stability because we registered a rate of 15% of sessions with nurse intervention for hypotension (6 of 39) during standard treatment vs. 3% of sessions with HFR-Aequilibrium (1 of 39). In the last year we switched 12 patients from standard treatment to HFR-Aequilibrium improving the quality of dialysis sessions with an interesting reduction of hypotensive episodes from 11% with standard treatment to 3% with HFR-Aequilibrium. Hypotensive prone patients with more than one episode per month had a reduction of nurse intervention for hypotension from 21% to 4% of sessions using HFR-Aequilibrium. (figure 1)

**Conclusions**
HFR-Aequilibrium, using Flexya dialysis machine, improves intradialytic cardiovascular stability in our patients, as shown in this clinical case and in our observational analysis of 12 patients.
### References


PATIENTS WITH CARDIOVASCULAR RISK

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Background
The hemodiafiltration with endogenous reinfusion (HFR) is the selective extracorporeal technique that combines adsorptive resins to convection and diffusion. It offers a proper solution to the most common problems of inflammation and malnutrition. In effect, it has already been observed that HFR, both because of the use of synthetic membranes and because of its resin cartridge, can adsorb pro-inflammatory markers and reduce oxidative stress. The purpose of this work was to examine the effect of HFR compared to standard bicarbonate hemodialysis (BHD) on a hemodialyzed patient with cardiovascular instability.

Methods
We evaluated one uremic patient, 62-years-old, almost five years in hemodialysis secondary to nephroangiosclerosis. Native AV fistula with Qb 300 mL/min and Qd 500 mL/min. The work was divided into two periods of observation: a) BHD for five months; b) HFR for five months. We analysed the trend of average values of CRP, albumin, PTH, and Hb. Even the dialysis treatment adequacy index (Kt/V) was highlighted. All the treatments were delivered with Flexya dialysis monitor (Medtronic) in a tri-weekly session, lasting four hours.

Results
As shown in Table 1, HFR compared to BHD was associated with a greater removal of uremic toxins testified by the increase of Kt/V. Average increase in serum albumin levels of 0.2 g/dL while average reduction of 0.4 mg/dL in CRP values occurred. The PTH value was also reported as halving during HFR, despite the patient maintained the same therapy (paricalcitol Zemplar 5 µg. 2 vials/week). It meant that a more adequate calcium-phosphorus metabolism with a better correction of hyperparathyroidism occurred. Furthermore, there was an improvement of Hb values in conjunction with a reduction in the use of erythropoietin. It therefore let us reduce health costs. We should however point out the long-term advantages related to a lower progressive drop of blood pressure (BP). Systolic and diastolic BP were kept higher throughout the HFR (150/90 vs. 90/60 mmHg), guaranteed to reach the target dry weight with fewer dialysis intolerance symptoms. In BHD, instead, symptomatic intradialytic hypotension (IDH) episodes were higher, causing a significant number of saline infusions and stop UF during the treatment itself. During BHD period, the patient reported symptomatic dizziness, fatigue, tiredness, and breathlessness too, even at home. In HFR, he no longer had fatigue and was able to carry out daily activities with less tiredness. The patient started to travel again, because he was more self-confident and stronger. He also dealt with hemodialysis sessions much more comfortably.
**Conclusions**

In hemodialysis patients with severe inflammation, the change in treatment from BHD to HFR was associated with a rapid improvement of inflammation markers and cardiovascular symptoms and tolerance. Moreover, a reduction of PTH values was reached, while Hb values increased. The results of this work support the importance of verifying, through extended studies, the long-term impact of HFR of high-risk and difficult-to-treat BHD patients. Because of the convective removal and the greater biocompatibility of HFR, HFR could help to decrease both IDH and general malaise on a hemodialyzed patient. This could have an important impact in patients’ life expectancy and quality of life.

<table>
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<th>5 months - BHD</th>
<th>5 months - HFR</th>
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Table 1. Comparison between 5 months – BHD and HFR period on Kt/V, albumin, CRP, PTH and Hb average values

**References**


Patients With Cardiovascular Risk

Resolution of Symptomatic Intra-Dialytic Hypotension Episodes by HFR-Aequilibrium
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Background
One of the most frequent and dangerous complications occurring during hemodialysis is intra-dialytic hypotension (IDH). IDH significantly interferes with the delivery of an adequate dialysis dose but also causes a sudden and critical hypoperfusion of the cerebral, cardiovascular, and mesenteric districts. The most common cause of IDH is an ultrafiltration rate that exceeds an adequate plasma refilling rate. For this reason, HFR-Aequilibrium, a biofeedback system, has been implemented to continuously profile sodium concentration of the dialysis solution and ultrafiltration rate during dialysis sessions to improve intradialytic hemodynamic stability.

Methods
A 65-year-old male patient has been treated with dialysis thrice a week for end-stage renal disease secondary to nephroangiosclerosis since December 1st, 2016. For 18 months (April 2017–October 2018), the patient has been treated in a sequential 6-month period (April–October 2017) with bicarbonate hemodialysis (BD), hemodiafiltration with endogenous reinfusion (HFR) (October 2017–April 2018) and HFR with coupled sodium and ultrafiltration profiling (HFRAEQ) (April–October 2018). BD, HFR and HFRAEQ were all performed by Flexya dialysis monitor, Bellco Medtronic. Symptomatic intradialytic hypotension was defined as any fall in systolic and diastolic blood pressure during dialytic treatment requiring nurse intervention (ultrafiltration rate reduction or temporary ultrafiltration discontinuation, infusion of saline solutions or plasma expanders, anticipated termination of dialysis session). Parameters as incidence of symptomatic IDH, difference between interdialytic weight gain and total dialytic ultrafiltration, mean interdialytic weight gain in relation to estimated dry body weight and pre-dialysis systolic blood pressure have been evaluated during the first month (T0) and the last month (T6) of each six-months period.

Results
The incidence of IDH episodes was 31% at T0 and 50% at T6 on BD, 50% at T0 and 33% at T6 on HFR and fell to 0% both at T0 and T6 on HFRAEQ (Fig. 1). The interdialytic weight gain in relation to estimated dry body weight was 4.15±0.77 kg at T0 and 3.62±0.55 kg at T6 on BD, 4.57±0.90 kg at T0 and 4.34±0.68 kg at T6 on HFR, 4.19±0.68 kg at T0 and 2.77±0.41 kg at T6 on HFRAEQ, showing a significant lower weight gain in HFRAEQT6 (P<0.0001 for HFRAEQT6 vs BDT0, HFRT0, HFRT6, HFRAEQT0) (Fig. 2). The difference between interdialytic weight gain and total dialytic ultrafiltration was 1.3±0.6 kg at T0 and 0.6±0.6 kg at T6 on BD, 1.7±0.9 kg at T0 and 1.6±0.9 kg at T6 on HFR, 0.9±0.7 kg at T0 and -0.2±0.3 kg at T6 on HFRAEQ, showing a significant lower difference in HFRAEQT6 (P<0.0001 for HFRAEQT6 vs BDT0, HFRT0, HFRT6; P<0.001 for HFRAEQT6 vs HFRAEQT0) (Fig. 3). Pre-dialysis systolic blood pressure was 111±13 mmHg at T0 and 125±16 mmHg at T6 on BD; 112±15 mmHg at T0 and 113±9 mmHg at T6 on HFR; 116±15 mmHg at T0 and 126±12 mmHg at T6 on HFRAEQ.
Conclusions

HFR-Aequilibrium proved to be more effective than bicarbonate hemodialysis in improving cardiovascular stability, reducing the incidence of symptomatic IDH, the interdialytic weight gain and the difference between interdialytic weight gain and total dialytic ultrafiltration, not affecting overall blood pressure control.
References


HFR-Aequilibrium Reduces Intradia
tic Hypotensive Events and Allows Significant
Ultrafiltration Volumes on Hypotensive Patients
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Background
Dialysis on hypotensive patients with a significant target of ultrafiltration volume can lead
to intradialytic hypotensive events. HFR-Aequilibrium technique is a form of endogenous
hemodiafiltration that, using a mathematical model and a sensor, handles the ultrafiltration rate
and the sodium balance automatically, modifying the total conductivity throughout the dialysis.
This biofeedback system is useful to avoid hypotensive events.

Methods
A 65-year-old female patient has been treated with hemodialysis thrice a week for end-stage
renal disease since September 2009. The patient showed post-ischemic dilated cardiopathy
with a 30% ejection fraction, became carrier of biventricular ICD-PM due to supraventricular
tachycardia and has been subjected to total thyroidectomy for multinodular struma. Both
nephrectomy and dilated cardiopathy acted directly on hypotension status of the patient. For
almost a month the patient has been treated in AFB technique, afterwards in HFR-Aequilibrium,
performed by dialysis monitor Formula (Bellco Medtronic), for more than one year. The following
parameters have been evaluated for one year in HFR-Aequilibrium treatment: incidence of
symptomatic intradialytic hypotension, pre- and post-dialysis blood pressure, ultrafiltration
volumes and dry body weight. Data have been evaluated during the first month (T0), the sixth
month (T6) and the last month (T12) in HFR-Aequilibrium.

Results
The incidence of symptomatic hypotensive episodes was 7% at T0 and 0% at T6 and T12 (Fig.
1). Pre-dialysis systolic blood pressure (SP-PRE) was 85±9 mmHg at T0, 82±9 mmHg at T6
and 83±5 mmHg at T12; post-dialysis systolic blood pressure (SP-POST) was 92±4 mmHg at
T0, 89±6 mmHg at T6 and 87±8 mmHg at T12; pre-dialysis diastolic blood pressure (DP-PRE)
was 56±6 mmHg at T0, 52±8 mmHg at T6 and 55±7 mmHg at T12; post-dialysis diastolic
blood pressure (DP-POST) was 59±6 mmHg at T0, 56±8 mmHg at T6 and 58±6 mmHg at T12;
no significant differences have been noticed between the several groups of blood pressures
(Fig.2). Ultrafiltration volumes (Fig. 3) were 2.4±0.4 kg at T0, 2.8±0.5 kg at T6 and 2.9±0.5 kg
at T12, showing a significant higher ultrafiltration volume in T12 (p<0.05, T12 vs. T0). The dry
body weight (Fig. 4) was 55.2±0.2 kg at T0, 54.1±0.1 kg at T6 and 51.3±0.3 kg at T12, showing a
significant decrease in T6 and T12 (p<0.0001, T12 vs. T6, T12 vs. T0, T6 vs. T0).
Conclusions

HFR-Aequilibrium proved to be a strong biofeedback system to maintain cardiovascular stability and to reduce the incidence of symptomatic intra-dialytic hypotension. It gave the opportunity to apply significant growing ultrafiltration volumes and to reduce dry body weight, not affecting overall blood pressure control, during the single dialysis session and all over time.
References


Nava-Rebollo A, Grande-Villoria J, Department of Nephrology, Complejo Asistencial de Zamora, SACYL, Zamora, Spain.

Background
Chronic inflammation is a risk factor for cardiovascular disease among hemodialysis (HD) patients. This inflammatory state is characterized by failure to thrive, uncontrolled BP, endogenous erythropoietin (EPO) resistant anemia, hypoalbuminemia, elevated plasma C-reactive (CRP) protein levels, which are well-known risk factors for increased morbidity and mortality on dialysis. Prognosis in HD patients could be improved by decreasing the circulating concentration of pro-inflammatory substances. Hemodiafiltration with endogenous reinfusion (HFR) is a highly biocompatible dialysis technique, that combines the processes of diffusion, convection, and adsorption, able to adsorb proinflammatory cytokines and to decrease amino acids and antioxidants loss. Case: An adult man with hypertension and end-stage renal disease secondary to primary Focal Segmental Glomerulosclerosis, on maintenance HD for 12 months via a right internal jugular tunneled catheter, with a nonfunctioning kidney allograft transplanted four years earlier. He refused transplantectomy and arteriovenous fistula surgical creation. During the firsts 12 months under HD, he was treated with standard bicarbonate hemodialysis (BHD) with a high-flux polynephron membrane with 2.1 m² of surface. Despite dismissing major causes of anemia, we observed an increasing necessity of EPO, and refractory hypertension in spite of maximal dosage of four antihypertensive agents and dry weight adjusted by bioimpedance. Both, HD catheters and failed renal allografts, as foreign body exposure, are well-known to contribute a proinflammatory state in HD patients.

Methods
Suspecting chronic inflammation status was leading EPO resistance and uncontrolled hypertension, the patient was switched from BHD to HFR Supra with a super-high-flux membrane and adsorption with a high-adsorption capacity cartridge. No changes in other dialytic parameters. Clinical variables, including inflammatory markers, were assessed monthly before midweek session. Erythropoietin resistance index (ERI) was defined as the weekly weight-adjusted EPO dose (U/kg per week)/Hb level (g/dL). Data was compared at baseline (last month in BHD) and after four and eight months of HFR.

Results
We observed a progressive reduction of CRP, in EPO dosage and ERI, to maintenance of target Hb levels after eight months, and an increment in dry weight, albumin and ferritin levels, as improvement in nutritional status. Furthermore, a better BP control was noticed, despite a reduction in antihypertensive treatment (Table 1). There were no hypotension episodes or hospitalization during follow up.
Table 1: Main clinical, laboratory and therapeutic features at baseline, 4 month postHFR and 8 month postHFR.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline standard BHD</th>
<th>HFR Supra 4 month</th>
<th>HFR Supra 8 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPO dosage (UI/week)</td>
<td>27000</td>
<td>9000</td>
<td>3000</td>
</tr>
<tr>
<td>ERI (U/kg per week)/Hb (g/dL)</td>
<td>39.82</td>
<td>11.63</td>
<td>4.11</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.3</td>
<td>13.1</td>
<td>11.3</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.4</td>
<td>3.7</td>
<td>4.1</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>88.7</td>
<td>7.2</td>
<td>4.1</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>1572</td>
<td>953</td>
<td>456</td>
</tr>
<tr>
<td>Dry weight (Kg)</td>
<td>60.3</td>
<td>60.8</td>
<td>64.5</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>188</td>
<td>135</td>
<td>128</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>92</td>
<td>88</td>
<td>82</td>
</tr>
<tr>
<td>Number antihypertensive drugs</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Conclusions
This real case shows that the HFR Supra is a HD modality that could help in management in a significant subgroup of complex dialysis patient at high proinflammatory risk. HFR Supra improves chronic inflammation state, allowing proinflammatory biomarkers removal, resulting in lower EPO resistance and better BP control and nutritional status. Furthermore, it could suppose a significative economic shaving in EPO and antihypertensive drugs. Finally, this convective technique has a beneficial impact contributing to a better clinical situation, and probably, reduces long-term cardiovascular morbidity supporting the importance of verifying, by ad hoc studies.

References
Isonatric Dialysis Biofeedback in Hemodiafiltration with Online Regeneration of Ultrafiltrate (HFR) in Hypertensive Hemodialysis Patients: A Randomized Controlled Study.


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Background
Dialysis biofeedback in hemodiafiltration with online regeneration of ultrafiltrate (HFR) could help to improve arterial hypertension. We evaluated the impact of isonatric HFR (HFR-iso) on hypertension control compared to conventional HFR.

Methods
The Isodial study is a prospective multicenter, open-label, controlled, and randomized study (15). Patients from ten French and Belgian dialysis centers were included. After a run-in period of one week, patients having an arterial blood pressure >140/90 mmHg were randomized either to conventional HFR (control treatment) or to Isonatric HFR (intervention treatment) with a 1:2 allocation ratio. Patients had 24 dialysis sessions during eight weeks in their treatment group. The randomization was centrally carried out according to a randomization list. This study received approval from the local ethics committee (CPP Ile de France VI) and all the patients gave written informed consent to participate. End points: The primary end point was the variation between the first and the last dialysis session of the predialytic mean systolic blood pressure (SBP) measured three times at each session before any connection to the hemodialysis circuit. Inclusion and exclusion criteria: Patients were included in the study if they met the following criteria: older than 18 years old, dialyzed for more than three months, treated three times a week for 3.5 to 5 hours, having a systolic arterial blood pressure greater than 140 mm Hg or a diastolic blood pressure greater than 90 mm Hg evaluated at dialysis start for at least two of the three dialysis sessions in the week of the run-in period, absence of acute adverse medical events during the three last months and having signed the informed consent. Pregnant women, patients with a life-threatening disease, those with an acute illness during the last three months, patients included in another study protocol and patients with a psychiatric disease were not included. Hemodialysis treatment: Hemodialysis treatment was performed according to the following guidelines: 3.5 to 5 hours, prescribed blood flow rate, dialysate temperature <37°C and ultrafiltration rate to reach the dry weight in the two groups of treatment. Dialysate conductivity was set during the run-in period for the conventional HFR arm (control group) and was not modified during the study protocol. In HFR-iso (treatment group), the dialysate conductivity was automated and driven by the monitor to reach a patient conductivity equal to the value measured at 15 minutes of dialysis and using ultrafiltration and sodium profiles.
Sample size calculation: For an arterial blood pressure standard deviation of 15 mm Hg, the possibility to demonstrate a difference of 10 mmHg of the predialytic SBP between the two therapies with a power of 80% was reached with 28 patients per group. Considering a dropout rate of 10%, we planned to include 70 patients, 23 in the control group and 47 in the isonatric group. Statistics data was expressed as mean (± standard deviation) for quantitative variables and frequency (%) for qualitative variables. For normally distributed quantitative variables, the t-test was used, while for the non-normally distributed variables (variation of the defined daily dose of antihypertensive drugs, number of sessions with at least one hypotension and/or intolerance criteria), the Wilcoxon signed-rank test was performed to compare the variation in parameters between the first and the last dialysis session. Fisher’s exact-test was used to assess differences in frequency of qualitative variables. The course of the systolic arterial blood pressure during follow-up was analyzed using linear mixed models with time as both a fixed and random effect (degree of freedom estimated using Satterthwaite approximation) and the treatment effect characterized by a group* time interaction. To identify factors that influence the blood pressure, a covariance analysis was conducted with systolic arterial blood pressure as dependent variable and gender, age, dry weight, presence of diabetes or co-morbidities and total defined daily dose of antihypertensive treatment at baseline as independent variables. Influence of these variables on the evolution was tested via interactions between the given factor and the time variable.

Fig. Course of the predialytic systolic blood pressure according to the treatment group (for a mean age of 69 years)

In the isonatric HFR group, the intercept was 157.5 ± 3.8 mmHg and the slope was -0.12 ± 0.08 mmHg per day (p = 0.021). In the conventional HFR group, the intercept was 147.7 ± 2.6 mmHg and the slope was 13 ± 0.05 mmHg per day (p = 0.121). The conventional HFR group being the reference, the estimates were 9.9 ± 4.7 (p = 0.041) for the group, 0.3 ± 0.2 (p = 0.207) for the day, 0.1 ± 0.1 (p = 0.476) for the age, -0.3 ± 0.1 (p = 0.012) for the interaction time*group and -0.01 ± 0.00 (p = 0.053) for the interaction time*age.
Results
47 hemodialysis patients were included and randomized (ratio 2/1) HFR-iso versus HFR during 24 dialysis sessions. In the isonatric HFR group (32 patients, 768 dialysis sessions), the predialytic SBP decreased from S1 to S4 of 9 ± 20 mmHg and increased of 5 ± 24 mmHg in the HFR group (15 patients, 360 dialysis sessions), variation that differed between the two groups (ΔS1-S24, p = 0.035; interaction group*time, p=0.012, figure). The DBP (HFR-iso -3 ± 14 mmHg vs HFR 5 ± 13 mmHg; p=0.088), the DDD of antihypertensive treatment and the dry weight did not vary significantly during the study. The number of sessions complicated by symptomatic hypotension was similar in the 2 groups.

Conclusions
Isonatric HFR improved blood pressure control without increasing dialysis hypotension episodes.

References
Effect of on-line hemodiafiltration with endogenous reinfusion (HFR) Aequilibrium on Sjogren’s syndrome hemodialysis patient

F. D’Angelo, G. Gaudiano, U.O.S Dipartimentale di Nefrologia e Dialisi Osp. S. Giovanni Chiaromonte (PZ), Italy.

Background

Sjogren’s syndrome is an autoimmune disease. Most people with Sjogren’s syndrome are women. It usually starts after age 40. In Sjogren’s syndrome, it attacks the glands that make tears and saliva. Sjogren’s can also affect other parts of the body, including joints, lungs, kidneys, blood vessels, digestive organs, and nerves. In the present report, we evaluated the benefits of hemodiafiltration with endogenous reinfusion HFR-Aeq of a patient with Sjogren’s syndrome in hemodialysis treatment.

Methods

We considered the following subject. A woman of 67 years, with chronic kidney disease (CKD) secondary to Sjogren’s syndrome and Hashimoto’s Thyroiditis. The patient (whose hypertension was affected) was undergoing thrice-weekly chronic standard hemodialysis bicarbonate (BHD) treatment since 2015, without any residual renal function. Despite her characteristic hypertension, during BHD treatment, the patient showed intra and inter-dialytic hypotension (IDH), which is one of the major clinical problems for hemodialysis treatment.  

The hemodiafiltration with endogenous reinfusion (HFR) consists of a dual dialyzer with an adsorbent resin cartridge between chambers. The regenerated ultrafiltrate is used as a substitution fluid and combines adsorption, convection, and diffusion. HFR-Aequilibrium (HFR-Aeq) is an evolution of the HFR dialysis therapy, with dialysate sodium concentration and ultrafiltration rate profiles elaborated by an automated procedure. In November 2017 we switched our patient from BHD to HFR–Aeq., reporting the medical interventions and the symptoms. All dialysis sessions lasted 240 minutes. The HFR–Aeq. treatments were delivered with Formula Therapy Bellco and Flexya Next dialysis monitor (Medtronic).

Results

During BHD treatment, the patient complained of general sickness with frequent headache even at home. A relevant number of post-dialysis cramps even after the end of hemodialysis treatment occurred. Reduction of the dry weight was frequently used to reduce cramps and headache, however without improving her conditions. In HFR-Aeq we observed a rapid improvement of dry weight, interdialytic weight gain. Symptomatic hypotension episodes were significantly lower on HFR–Aeq versus BHD. A significative reduction of erythropoietin dose also occurred. There was an improvement of inflammatory status, because of the resin cartridge and its adsorptive power. The switch from BHD to HFR–Aeq was associated with a rapid improvement in patient’s quality of life (QoL) in terms of energy/fatigue, pain, and physical functioning. She started to work again, even in the day of dialysis treatment.
Conclusions
In our center we wanted to analyze the impact of HFR–Aeq on the intradialytic tolerance and inflammatory state of a patient suffering from Sjogren’s Syndrome. We collected encouraging results on the use of this method to improve patient’s QoL and to address the common problems of IHD and tolerance symptoms. Ultrafiltration and sodium profiles in HFR–Aeq were definitively combined to avoid IHD. The finding of this work supports the importance of verifying the long-term impact of HFR–Aeq on patient outcomes.

References
Benefits of the Biofeedback HFR-Aequilibrium on Intra-Dialytic Hypotension

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Background
Intradialytic hypotension (IDH) remains the most frequent complication during hemodialysis treatment. It is well known that HFR-Aequilibrium (HFR-Aeq.) represents one of the most powerful treatments to avoid IDH. Through dynamic profiles of ultrafiltration and conductivity of the dialysate, it ensures a better refilling and reduction of the complications during the treatment. It also results in a successful therapeutic solution for patients with malnutrition and inflammation. Through this clinical report, we wanted to evaluate the impact of HFR-Aeq. on the intradialytic tolerance and IDH on two patients (around 50 years), both on renal transplant list.

Methods
Patient (pt.) 1, in bicarbonate hemodialysis (BHD) treatment since 2008, suffering from anemia secondary to Myelodysplasia with intra and inter-symptomatic hypotension. In the last months hypotensive episodes were always more frequent; moreover, the pt. started to complain of cramps at the end of BHD treatment, lack of appetite and a strong thirst. Pt. 2, 57 years, with CKD secondary to IgA Glomerulonephritis, from October 2018 in BHD treatment. The pt., previously normotensive, began to present episodes of intra and inter-dialytic hypotension; it occurred, not only during the treatment, but even at home. We saw an anxiety-depressive syndrome with poor acceptance of the disease. The pt. stopped driving; a deeper sense of fatigue prevented her from having any physical activity. In November 2018, the frequency of IDH and dialysis intolerance symptoms for both pts. was so high that we decided to shift them from BHD to HFR- Aeq. All the HFR-Aeq. treatments were delivered with Flexya™ Next dialysis monitor (Medtronic).

Results
During the last 24 weeks, IDH incidence drastically decreased for both pts., with a relative risk reduction of dialysis complicated by hypotension of -30 % and -35% respectively. The effect of reducing IDH was evident also by the lower number of interventions made by the nurses during the HFR-Aeq. sessions. A marked reduction of saline infusions stop UF and premature interruption of the treatment due to IDH was obtained during the profiling dialysis to both patients. During HFR-Aeq., a more than -30 % relative risk reduction of any intervention due to IDH occurrence was observed. During HFR-Aeq. for both pts., systolic and diastolic blood pressure were more stable on significantly higher values, also during the last treatment hour, the most critical one. Pt. 1 no longer presented hypotensive episodes at home, while pt. 2 became more self-confident and started to work and drive again. Moreover, inflammatory indices appeared reduced in the weeks following the treatment.
Conclusions
HFR-Aeq treatment led to an improvement in the QoL of both patients; but it also significantly improved hemodialytic sessions’ stability. These positive findings increasingly mark the importance to customize therapies, through some biofeedback systems, like the plasma sodium HFR-Aeq. The dialysate sodium concentration and UF profiles, elaborated by this mathematical model, led us to achieve the planned weight loss and reach the desired target post-dialysis plasma sodium concentration, avoiding the dialysis intolerance symptoms.

References
Use of Hemodiafiltration with Endogenous Reinfusion (HFR) Aequilibrium as a Response to Arterial Hypertension

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Background
Hypertension is a common cardiovascular complication in hemodialysis patients and its treatment is challenging. It is one of the most common diseases in industrialized countries; it affects about 20% of the adult population and represents one of the major clinical problems of modern times. Hypertension rarely has noticeable symptoms. But if untreated, it increases a risk of serious problems such as heart attacks and strokes. The meta-analysis on anti-hypertensive treatment in hemodialysis patients evidenced that its control is associated with an all cause 20% and cardiovascular 29% survival improvement. Dialysis biofeedback in hemodiafiltration with online regeneration of ultrafiltrate (HFR) could help to improve arterial hypertension. HFR Aequilibrium (HFR-Aeq.) is a profiled dialysis which creates coupled ultrafiltration and sodium conductivity profiles in order to achieve the planned weight loss (WL) and reach the desired target post-dialysis plasma sodium concentration. The aim of the present report was to evaluate the impact of HFR-Aeq. (sodium profiling) in comparison with the standard BHD technique on arterial hypertension and dialysis hemodynamic intolerance.

Methods
We have analyzed one patient, 65-years-old, with average values of 150/85 mmHg of blood pressure (BP) under a triple antihypertensive therapy (Amlodipine 10 mg, Carvedilol 25 mg, Clonidine 150 mg) for 15 years, in hemodialysis with standard HD bicarbonate (BHD) treatment since 2014. In BHD, the patient had shown dialysis intolerance and worsening of arterial hypertension. In November 2018, she was switched from BHD to HFR-Aeq., the profiled dialysis supported by the Natrium sensor for the pre-dialysis Na+ measure. The clinical course was monitored for six months by means of pre- and post-treatment blood gases, pre- and post-dialysis arterial blood pressure, body weight, BMI, dialysis data (HFR setting + Natrium reading) and bio-humoral data. All the treatments were delivered with Flexya™ Next dialysis monitor (Medtronic).

Results
After 24 weeks of HFR-Aeq. treatment there was an improvement of intradialytic hemodynamics and systolic BP values. Predialytic BP decreased more in HFR-Aeq. than in BHD. The daily dose of antihypertensive treatment was modified and reduced (suspension of clonidine). Inflammatory indices appeared reduced in the weeks following the treatment, too. We observed that HFR-Aeq. improved arterial BP control without increasing dialysis hypotension episodes. A subjective improvement in quality of life has taken place.
**Conclusions**

A better control of arterial BP and a decrease of the interdialytic weight gain were obtained. As a mode that also decreases the sodium dialysate patient gradient, our hypothesis was that the use of biofeedback Aeq. would help to improve hypertension control with fewer dialysis intolerance symptoms. This could have an important impact in every day dialysis practice.

**References**


Chronic Inflammation, Malnutrition, and Vascular Damage in Hemodialysis: What Role for Hemodiafiltration with Endogenous Reinfusion (HFR)? Description of a Case.

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Background
Chronic inflammation is common in uremic patients in hemodialysis treatment and is associated with increased morbidity and mortality, as well as poor quality of life. In this type of patient, inflammation is a cause of both cardiovascular disease and malnutrition, a clinical triad that finds its synthesis in the definition of MIA (malnutrition-inflammation-atherosclerosis) syndrome. Hemodiafiltration with endogenous reinfusion (HFR), combining three purification mechanisms (diffusion, convection, and absorption) has shown to reduce micro-inflammation phenomena improving endothelial damage and oxidative stress, as well as optimizing the nutritional status minimizing the loss of vitamins and amino acids during treatments.

Methods
We describe the case of a 76 year-old female patient, suffering from terminal uremia secondary to polycystic nephropathy, in standard hemodialysis treatment for about six years. The patient, suffering from diabetes mellitus with micro (retinopathy and nephropathy) and macrovascular complications (chronic ischemic heart disease, chronic arteriopathy in the lower limbs), underwent, in June 2018, in acute ischemia of the right lower limb. The patient had consequent need for surgical amputation of leg and subsequent infection of the stump with septic state. At the end of the antibiotic therapy, performed for at least two months, the main blood chemistry parameters showed severe signs of malnutrition and inflammation that persisted until October 2018. Since then, HFR has been started instead of standard hemodialysis. In the following months, the patient went towards a progressive improvement of the general conditions, improving the appetite resulting, as a consequence, in a more adequate nutritional status and to a reduction of the inflammatory state.

Results
Six months after the beginning of the HFR we detected a progressive increase in the values of albuminemia, pre-albuminemia, lymphocyte count, cholesterol levels, azotemia and phosphoremia, demonstrating an improvement in the nutritional status of the patient. The increasing levels of creatinine oriented us towards an increasing deposition of muscular masses. The progressive decrease in the levels of C-reactive protein also associated with a greater mobilization of iron from the deposits (increase of transferrin levels) demonstrated the better control of the inflammatory state. The data is also associated with the patient’s good general condition, which also refers to a significantly improved quality of life. Details in Figures 1 and 2.
Figure 1.

Figure 2.
Conclusions
Our case highlights a clear improvement in the clinical and hematobiochemical parameters concerning the nutritional and inflammatory status of a hemodialysis patient suffering from severe malnutrition-inflammation-atherosclerosis syndrome (MIA syndrome), six months after replacing the standard dialysis treatment with hemodiafiltration with endogenous reinfusion (HFR). On the basis of the scientific literature related to this topic, we therefore consider it essential to reserve this type of treatment to malnourished, inflamed, and cardiovascular patients in order to optimize as much as possible, improving first and foremost the quality of life.

References
Case Report of IgG4 disease and HFR2
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Background
The patient followed for diabetes became insulin-intolerant in 04/2010. Nephrological management in 05/2010 for acute renal failure in the course of urinary sepsis. The development will objectify a chronic interstitial nephritis on urological dysfunction of the retroperitoneal fibrosis type. Further histological analyses will objectify an infiltration of the interstitium by IgG4 positive plasmocytes. The patient is therefore diagnosed with IgG4 syndrome. In addition, calcium oxalate crystals had also been found in kidney biopsy. The patient has recently been waiting on the kidney transplant list. Hemodialysis began in 04/2011. She was switched to the HFR technique on 15/05/2018.

Methods
We analyzed the sessions until early April (02/04/2019) The patient received 136 prescriptions of HFR. The number of HFR sessions actually performed was 111, 15 out of 136 sessions in HDF, 9 in HD. The average purification volume of the sessions under HFR was 11.9 L with a purification infusion index of 14.5%.

Results
Retrospective observation shows a small variation in the CRP but there are three episodes of acute phase (late August 2018, late September 2018, January 2019) during the HFR observation. The albumin level shows an increase after the introduction of the HFR technique. Concerning other biological elements concerning this patient, we did not observe any variation in beta2microglobulin levels. There is a trend towards a decrease in neutrophilia and a moderate decrease in total lymphocytes. The oxalemia study was not continued for technical reasons.
Conclusions
The technique shows an improvement in albumin status, a tendency to leukocyte variation, probable controls of cytokinic variation. In the context of inflammatory autistic immune pathology, variations in lymphocyte populations could be studied. The absorption of oxalate is to be reviewed but requires a standardized dosing capacity.
Effects of HFR on the Cardiovascular Instability and Inflammation Status on Hemodialyzed Patient

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Background
Inflammation is a common occurrence in end stage renal disease (ESRD), playing an important role in the cardiovascular morbidity and mortality of these patients. Hemodiafiltration with endogenous reinfusion (HFR) is a highly biocompatible dialysis technique. It demonstrated good maintenance of the nutritional status with improved impact on microinflammation. The aim of the present report was to evaluate the impact of 6-months HFR run in period in comparison with 6-months standard bicarbonate dialysis (BHD) run in period on the overall and cardiovascular intradialytic stability of a hemodialyzed patient.

Methods
We enrolled our patient in ESRD, characterized by an important inflammatory and malnutritional status, in presence of stasis liver and severe cardiopathies and vasculopathies (both mitral and aortic valvular heart disease). The patient had ascitic fluid associated to a high intra and post-dialysis vascular instability. By what, frequent symptomatic pressure drops occurred during hemodialysis. Three-weekly BHD and HFR dialysis sessions were associated (delivered with Flexya dialysis monitor Medtronic). The parameters listed were strictly maintained in both BHD and HFR: Qb 280 ml/min, Qd = 500 ml/min, duration of the treatment = 4 hours. Hemodialysis treatment adequacy (Kt/V), cardiovascular stability (in terms of blood pressure), serum levels of CPR and albumin were evaluated.

Results
The table 1 shows the results, both during HFR and BHD, in terms of average of CRP, albumin and Kt/V values. A progressive and significant reduction of serum CRP and a corresponding increment of the serum albumin were more evident during HFR window. Moreover, Kt/V significantly increased in HFR. About cardiovascular stability, the values registered during HFR significantly differed from BHD ones. During the HFR period, systolic blood pressure (SBP) values were slightly higher at any time measure correspondent of BHD values (120-110 vs. 90-80). As for the SBP, the HFR was associated with more stable diastolic blood pressure (DBP) values (70 vs. 50 mmHg). Also, heart rate (HR) values during HFR were significantly higher, with the absence of intradialytic arrhythmias (frequent, rather, in BHD). In BHD, instead, symptomatic hypotension (IDH) episodes were significantly higher, with recurrent stop UF. The patient complained of cramps and dyspnea even for small efforts. Furthermore, there were persistent edemas in both legs.

Table 1. Comparison of average values of CRP, Albumin and Kt/V between 6 months - BHD and HFR run in period

<table>
<thead>
<tr>
<th></th>
<th>Baseline: BHD</th>
<th>6 months - BHD period</th>
<th>Switch to HFR</th>
<th>6 months - HFR period</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>2,5 mg/L</td>
<td>1,4 mg/L</td>
<td>0,9 mg/L</td>
<td></td>
</tr>
<tr>
<td>ALBUMINE</td>
<td>2,9 mg/L</td>
<td>3,2 g/dL</td>
<td>3,4 g/dL</td>
<td></td>
</tr>
<tr>
<td>Kt/V</td>
<td>0,9</td>
<td>0,8</td>
<td>1,6</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions
The HFR contributed significantly to improve the patient’s clinical condition, in terms of stability and quality, reducing the inflammatory status. A better adequacy of dialysis session (Kt/v 1.6) was reached. Thanks to its benefits, HFR led us to work within duration treatment, getting the target dry weight, without any premature interruption of the treatment (frequent, instead, in BHD). It allowed us to reduce leg edema. During the HFR period, the patient started to show a relative physical well-being both during dialysis and at home (no dyspnea), managing to fulfill everyday needs; it was a strong impact on his quality of life. Although limited to a single patient, this work suggests to us that HFR could help to avoid intolerance symptoms in hemodialysis patients and reduce the inflammatory status, while preserving the nutritional one. Larger, longer-term studies are necessary to confirm our results and to determine impact on patient outcomes.

References
Reduction of Proinflammatory Biomarkers and Erythropoiesis Stimulating Agents (ESAs) Consumption in Hemodiafiltration Reinfusion (HFR) – Treated Patient: A Case Report

L. Di Lullo, G. Barbera, V. Barbera, C. Feliziani, G. Otranto, A. Santoboni, Department of Nephrology and Dialysis, “L. Parodi – Delfino” Hospital, Colleferro, Italy

**Background**

Chronic inflammation is a major issue in chronic kidney disease (CKD) patients and it can be accountable for several clinical and biochemical abnormalities in such patients’ population. Patients undergoing chronic hemodialysis often present high levels of proinflammatory cytokines (IL - 1β, TNF-α, IL – 6) and other molecules that can interfere with erythropoiesis such as hepcidin. High levels of circulating hepcidin could be accountable for a reduction in response to ESA, leading clinicians to prescribe high ESAs dosages. Standard hemodialysis cannot be sufficient to resolve clinical pictures directly linked to heavy inflammatory status. Hemodiafiltration with endogenous reinfusion (HFR) represents a dialysis technique that uses the endogenous reinfusion fluid and simultaneously perform three fundamental mechanisms of extracorporeal depuration: diffusion, convection and adsorption leading to specific removal of inflammation – related biomarkers.

**Methods**

Our patient is a 55-year-old male who started renal replacement therapy (RRT) in 2016 probably due to uncontrolled arterial hypertension leading to end–stage renal disease (ESRD) in four years by his first nephrologist’s referral. The patient also presented an intricate cardiovascular involvement with bilateral carotid artery obstructive disease, dyslipidemia, anemia, and high plasmatic levels of proinflammatory biomarkers (C–reactive protein, IL-1β, TNF-α, IL – 6 and hepcidin). After three years of high–flux hemodialysis and online hemodiafiltration (during which inflammatory pattern was not affected and hemoglobin’s target was never achieved), patient was shifted to HFR Supra treatment (Polysulfone filter for diffusion, Polyphenylene Super High Flux filter for convection and 50 ml hydrophobic interaction resin to also provide IL – 6 and Complement D – factor removal).

**Results**

After 6 and 12 months of HFR Supra treatment patient showed a dramatic improvement of inflammatory and nutrition status with a significant statistical increase of albumin (from 2.6 g/dl to 3.2 and 3.9 g/dl) and hemoglobin levels (from 9.6 g/dl to 11.2 and 12.1 g/dl). At the same time IL-1β, TNF-α, IL–6 plasmatic levels significantly dropped, respectively, by 32–35 and 38% together with a reduction in hepcidin levels (from 12.4 ng/ml to 3.8 and 2.6 ng/ml) (Fig. 1). Together with these results, CRP also decreased from 5.8 to 1.1 and 0.9 mg/dl (hs–CRP) (Fig. 2) thus indicating an improvement in inflammatory pattern. Patient also showed a bilateral reduction of fibrocalcific plaques’ extension on common carotid artery together with significant improvement in lipidic profile with a 20% increase in HDL cholesterol and a 35% decrease in LDL – cholesterol levels. Finally, a reduction in ESAs’ consumption was observed (from Darbepoetin 40 mcg/weekly to Darbepoetin 20 mcg/weekly).
Conclusions
HFR and especially HFR Supra can represent a further chance in some hemodialysis patients with high rates of inflammation. Reduction in ESAs’ consumption has been achieved with evident economic impact on renal replacement treatment’s additional costs.

References
Anemia and Inflammation: Advantage from HFR Treatment. A Case Report


Background
An 88-year-old male with chronic kidney disease (CKD) secondary to membranous nephropathy (MN). On June 2015 in dialysis with a Tesio catheter in right jugular vein. The patient has different comorbidities: Arterial hypertension complicated by organ damage (retinopathy and cardiopathy), chronic ischemic cardiopathy NSTEMI (2018), he’s using a pacemaker due to second-degree atrioventricular block (AV block) and aortic stenosis with moderate paroxysmal atrial fibrillation, multiple myeloma IgG Kappa and Previously acquired Von Willebrand’s disease. Pure aplasia of the red series, anemia needing frequent transfusion support, positivity to anti-EPO antibodies, previously total prostatectomy for carcinoma, ankylosing spondylitis, and gonarthrosis. All those co-pathologies determine a constant inflammatory status that, associated with anti-EPO antibodies, causes persistent anemia that needs frequent blood transfusions. The standard hemodialytic treatment did not achieve improvement on inflammatory status nor on the number of early blood transfusions. After one year of standard treatment the patient shifted on hemodiafiltration with endogenous reinfusion therapy (HFR), with the aim to improve inflammatory status by efficacy removal of inflammatory mediators as well as free light chains removal and to reduce the number of transfusions per year.

Methods
The patient underwent standard bicarbonate hemodialysis (HD) from June 2015 to June 2016, using a 1.8 m² dialyzer in Polyethersulfone (Qb=300 mL/min, Qd= 500 mL/min). Then he was shifted on HFR from July 2016 and is still under treatment with HFR (Qb=300 mL/min, Qd=500 mL/min). The iron supplementation was stable, requiring blood transfusion every time the Hb values became less than 8 g/dL.

Results
The following table shows results on the laboratory parameters and numbers of blood transfusion by years.
<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dL)</td>
<td>8.85 ± 0.75</td>
<td>9.03 ± 0.75</td>
<td>9.82 ± 0.84</td>
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<tr>
<td>HT</td>
<td>26.63 ± 1.54</td>
<td>25.53 ± 2.38</td>
<td>30.76 ± 2.53</td>
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<tr>
<td>Iron (μg/dL)</td>
<td>58 ± 2.8</td>
<td>59.6 ± 3.36</td>
<td>62 ± 20.1</td>
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<tr>
<td>Transferrin (mg/dL)</td>
<td>179 ± 12</td>
<td>173.6 ± 7.96</td>
<td>181 ± 4.8</td>
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</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>560 ± 62</td>
<td>259.8 ± 125</td>
<td>227.6 ± 211</td>
<td></td>
</tr>
<tr>
<td>Sat (%)</td>
<td>18 ± 9.9</td>
<td>24 ± 1.4</td>
<td>25 ± 3</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>13 ± 8.3</td>
<td>11.2 ± 4.6</td>
<td>12.6 ± 5.4</td>
<td></td>
</tr>
<tr>
<td>Folic Acid (μg/L)</td>
<td>6.2</td>
<td>4.6</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Vit B12 (ng/L)</td>
<td>330</td>
<td>303</td>
<td>328</td>
<td></td>
</tr>
<tr>
<td>Total Proteins (g/L)</td>
<td>5.8 ± 0.07</td>
<td>6.45 ± 0.21</td>
<td>6.7 ± 0.29</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>3.2 ± 0.2</td>
<td>3.67 ± 0.14</td>
<td>3.63 ± 0.17</td>
<td></td>
</tr>
<tr>
<td>Blood trans (N)</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions**

This case report demonstrates that personalizing the dialytic treatment has real clinical advantages and leads to a marked improvement in the quality of life of patients. Here, the use of a method such as HFR, which determines absorption from the ultrafiltrate of a series of uremic toxins implicated in the mechanisms of inflammation, contained the inflammatory status and drastically reduce the need for transfusions in a patient diagnosed with myeloma, medullary aplasia and with anti-EPO antibodies. Laboratory data shows that Hb and HT have progressively improved over time, CRP is slightly reduced but is also influenced by intercurrent phenomena, while ferritin has normalized, and finally nutritional parameters have clearly improved.
Reversal of MIA Syndrome with HFR
Gesuete A, Guida CC, Aucella F, Department of Nephrology and Dialysis, Research Hospital "Casa Sollievo della Sofferenza", San Giovanni Rotondo, Italy

Background
Patients ongoing chronic haemodialysis are frequently affected by malnutrition inflammation atherosclerosis (MIA) syndrome. Standard dialysis treatments do not treat and reverse this syndrome that may define a bad clinical outcome. Hemodiafiltration with endogenous reinfusion (HFR) is a dialysis technique, highly biocompatible, able to adsorb proinflammatory cytokines and to decrease amino acids and antioxidant loss. These features could be helpful in dialysis patients.

Methods
A patient suffering from chronic progressive renal failure due to membranous nephropathy started dialysis treatment with bicarbonate dialysis three times a week. After eight months of this dialysis regimen, the patient showed an inflammation status, high level of serum phosphorus and of inflammatory marker as C-reactive protein (CRP). Moreover, the patient was also hypotension prone, with a mean incidence of four intradialytic hypotension episodes every month. So, we switched the patient to an alternative treatment with online hemodiafiltration with endogenous reinfusion (HFR) without any other change in the dialysis regimen (same dialysis rhythm, number of sessions, length of sessions, blood and dialysate flow, pharmacological therapy). We reevaluate the patient after six months of this new dialysis regimen.

Results
Six months after the switch from standard bicarbonate dialysis to hemodiafiltration with endogenous reinfusion there was a clear decrease of CRP level (0.93–0.48), an improvement of serum albumin (3.6–3.8), a decrease in serum phosphorus (6.0–4.6) and an improvement in dialysis efficiency (Kt/V 1.027–1.24). The patient also showed improvement in dialysis hemodynamic, without any hypotensive feature during HFR treatment.

Conclusions
In maintenance HD patients affected by overt and idiopathic chronic inflammation, switching from BHD to HFR allows a marked improvement of inflammatory status as testified by a significant decrement of serum levels of CRP coupled with a significant increase of albumin. This is of paramount clinical relevance because a significant percentage of patients had no identifiable preventable or treatable causes, identifying idiopathic chronic inflammation. So, for these patients, currently, no pharmacological intervention is specifically targeted. Chronic inflammation may result from specific identified sources, such as occult infections, membrane bio-incompatibility, poor quality of dialysis water, volume overload, inadequate dialysis, and protein wasting, but there are patients without these features. In conclusion, in HD patients affected by idiopathic chronic inflammation, the switch from BHD to HFR is associated with a rapid improvement of inflammation markers. One of the features of chronic inflammation in HD patient is ESA resistance, however our follow-up was probably too short to detect this possible beneficial effect.
**References**


Effect of Hemodiafiltration with Endogenous Reinfusion on Chronic Inflammation in Maintenance Hemodialysis Patients: Case Report of Two Patients

Philippe Durieux. Centre hospitalier de Wallonie Picarde Service de Néphrologie- Unité d’hémodialyse, Tournai, Belgium.

Background
Chronic inflammatory condition is a frequent problem in hemodialysis patients, generally resulting from the interaction between blood constituents and the hemodialysis membrane. Interaction of the dialysis membrane with the components of blood has the potential to induce an inflammatory response and to lead to numerous long-term clinical sequelae: anemia, denutrition, malaise, increased cardiovascular risk, etc. Hemodiafiltration with endogenous reinfusion (HFR) is a dialysis technique, highly biocompatible, able to adsorb proinflammatory cytokines. These features could be helpful in maintenance hemodialysis patients affected by idiopathic chronic inflammation. Hemodiafiltration reinfusion (HFR) treatment is an alternative dialysis technique that uses the endogenous reinfusion fluid and performs, simultaneously and separately, the three mechanisms of extracorporeal depuration: diffusion, convection, and adsorption.

Methods
The aim of the observational study was to evaluate potential HFR impact on chronic inflammation in two maintenance hemodialysis patients in our dialysis center. The most usual dialysis technique performed in our center is hemodiafiltration on line (HDF on line) with ultrapure dialysate performed by double reverse osmosis coupled with electrodeionization. We assess biologic parameters before (six months) and after HFR initiation (five months): C-reactive protein as inflammatory marker, prealbumin, serum albumin as nutritional marker, hemoglobin, and erythropoiesis-stimulating agent’s needs (darbepoetin-alpha). We report two cases of male patients who presented chronic inflammation condition of indeterminate origin. The first patient (A), a 69-year-old man, is in maintenance hemodialysis in our center from December 2016. He presented an ischaemic cardioapthy with coronary artery bypass grafting in 1986, hypertension and calcified pleural plaques, evidence of occupational exposure to asbestos. We also noted a well-differentiated prostatic adenocarcinoma, Gleason 6 (3 + 3 - very low risk prostate cancer). The initial dialysis technique was post-dilution hemodialysis on line, from December 2016 to September 2018. The second patient (B), a 52-year-old man, is in maintenance hemodialysis in our center from January 2018, treated by HDF on line. This severe obese patient experienced chronic nephrolithiasis of struvite stones with chronic pyelonephritis and end-stage renal disease. We changed dialysis technique from HDF on line to HFR on September 2018 (patient A, still continuing) and on September 2018 to February 2019 (patient B) in order to evaluate the HFR impact on chronic inflammatory condition. See Table 1 Characteristics of the patients at baseline.

Results
See Fig. 1 Results Adverse events during HFR: Patient A: acute non-complicated diverticulitis of the sigmoid colon (January 2019) Patient B: acute pyelonephritis (February 2019).
Figure 1. Results

<table>
<thead>
<tr>
<th></th>
<th>Patient A</th>
<th>Patient B</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE (years)</td>
<td>69</td>
<td>52</td>
</tr>
<tr>
<td>GENDER</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>DIALYSIS INITIATION</td>
<td>December 2016 HDF on line</td>
<td>January 2018 HDF on line</td>
</tr>
<tr>
<td></td>
<td>September 2018 HFR</td>
<td>October 2018 to February 2019 HFR</td>
</tr>
<tr>
<td>NEPHROPATHY</td>
<td>Hypertension</td>
<td>Chronic pyelonephritis</td>
</tr>
<tr>
<td>PRIOR CVD</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>DIABETE</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>HYPERTENSION</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>BMI</td>
<td>32.8 kg/m²</td>
<td>62 kg/m²</td>
</tr>
<tr>
<td>VASCULAR ACCESS</td>
<td>Native arterio-venous fistule</td>
<td>Native arterio-venous fistule</td>
</tr>
<tr>
<td>CONVECTIVE VOLUME (HDF technique)</td>
<td>29 liters</td>
<td>22.7 liters</td>
</tr>
<tr>
<td>MEMBRANE</td>
<td>High flux synthetic membrane</td>
<td>High flux synthetic membrane</td>
</tr>
<tr>
<td></td>
<td>POLYPHENYLENE 2.2 m²</td>
<td>POLYPHENYLENE 2.2 m²</td>
</tr>
<tr>
<td>CONVECTIVE VOLUME (HFR technique)</td>
<td>14 liters</td>
<td>12.7 liters</td>
</tr>
<tr>
<td>MEMBRANE</td>
<td>Double-chamber dialyzer</td>
<td>Double-chamber dialyzer</td>
</tr>
<tr>
<td></td>
<td>constituted by a high-flux membrane</td>
<td>constituted by a high-flux membrane</td>
</tr>
<tr>
<td></td>
<td>(polyphenylene, 0.7 m²) in convective chamber and a low-flux membrane (polyphenylene 1.95 m²) in diffusive chamber</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Characteristics of the patients at baseline

<table>
<thead>
<tr>
<th></th>
<th>Patient A</th>
<th>Patient B</th>
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</thead>
<tbody>
<tr>
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<td>GENDER</td>
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<td>DIALYSIS INITIATION</td>
<td>December 2016 HDF on line</td>
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<td>Hypertension</td>
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<td></td>
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<tr>
<td></td>
<td>(polyphenylene, 0.7 m²) in convective chamber and a low-flux membrane (polyphenylene 1.95 m²) in diffusive chamber</td>
<td></td>
</tr>
</tbody>
</table>

Double-chamber dialyzer constituted by a high-flux membrane (polyphenylene, 0.7 m²) in convective chamber and a low-flux membrane (polyphenylene 1.95 m²) in diffusive chamber
**Conclusions**

HFR dialysis technique did not seem to improve inflammatory status as testified by a significant decrement of serum levels of CRP coupled with a significant increase of albumin of the two picked patients who were previously in maintenance hemodialysis by HDF on line dialysis technique. We did not observe any significative difference in term of inflammatory condition nutritional status. During the HFR techniques, both patients underwent adverse serious infectious events that makes hazardous interpretation of the results.

**References**


Hemodiafiltration with On-Line Endogenous Reinfusion (HFR) and Cytokines (CK) Removal: A Center Experience
Losappio V, Perulli R, Cataneo F, Maiorano A, Teri A, Godeas G, Coviello N, Stallone G, Grandaliano G, Nephrology Dialysis and Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy.

Background
Chronic Kidney Disease (CKD) is a growing disease affecting over 497.5 million adults in the world. It has been associated with increased risks of end-stage renal disease (ESRD), cardiovascular disease (CVD), and death. CK seems to play a key role in CKD pathogenesis and its complications (CVD, malnutrition, cancer, bone disease). Moreover, an angiogenic factor as vascular endothelial growth factor (VEGF) seems to be related to CKD progression. According to their molecular weight, CK are not efficiently removed with standard hemodialysis (HD). HFR is a dialytic method which combines diffusion, convection, and adsorption through a high permeability membrane and cartridge resin. The inflammatory mediators (i.e. IL-6 or p-cresol), are adsorbed through HFR cartridges.

Methods
We switched to HFR 2 patients (Pt). Pt A, a 61-year-old, affected by IgAN, ischemic heart disease (IHD), with a history of two kidney transplants (first one in 1985 and the second one in 2000), started HD in 2018. Pt B, a 74-year-old with a previous diagnosis of spinocellular epithelioma of the lower lip (1977) and of melanoma (1999), IHD, started HD in 2014. Blood samples (BS) were collected before starting HFR (T0) and one month later (T1). During the first HFR session, whole BS were collected through blood lines before starting and at the end of the treatment. At T1, BS were collected before the HFR session and at the end, with a second sample collected through specific blood lines (provided by Medtronic) before and after the cartridge, 5 minutes after starting HFR without ultrafiltration and with a 100 ml/min Qb and at 230 minutes later. Every BS was tested for: IL1α, IL1β, IL2, IL4, IL6, IL8, IL10, TNF α, IFNγ, VEGF, EGF, MCP1. Each session lasted 4 hours, Pt were clinically stable during the evaluated month (no infection or CVD) and were comparable for comorbidities and clinical features.

Results
During the single HFR session at enrollment and at 30 days, we observed a consistent relative reduction rate (RR) of both IL8 (RR A -38.06%; RR B -35.2%) and VEGF (RR A -17.9%; RR B -38.1%) and not significant variation of MCP1 (RR A +3.12%; RR B 1.92%). Moreover, we compared the RR of CK level between the baseline value before switching and the value measured immediately before the last 30-days HFR. We confirmed a cumulative RR for IL8 in both Pt (RR A -35.09%; RR B -34.53%). Contrarily, VEGF (RR A -0.66%; RR B +14.97%) and MCP1 (RR A -38.58%; RR B +5.78%) were not reduced in both patients. Finally, we would test the direct adsorptive capacity of the cartridge. We confirmed the adsorption of IL6 (RR A -47.6%; RR B -64.22%) as reported in literature and demonstrated the adsorption of IL8 (RR A -78.5%; RR B -85.82%), VEGF (RR A -99.8%; RR B -22.4%) and MCP1 (RR A -99.9%; RR B -99.9%). Results are showed in Table 1 and Table 2.
### Table 1. Cytokine values at the switch, at one-month from switch and at the end of the first treatment and before starting the last one of the monthly follow-up

<table>
<thead>
<tr>
<th>Time Period</th>
<th>IL-18</th>
<th>IL-2</th>
<th>IL-6</th>
<th>IL-8</th>
<th>IL-10</th>
<th>TNF-α</th>
<th>IL-4</th>
<th>IL-1α</th>
<th>VEGF</th>
<th>MCP-1</th>
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<tr>
<td>TA0 start</td>
<td>9.15</td>
<td>19.11</td>
<td>21.7</td>
<td>103.08</td>
<td>6.82</td>
<td>6.77</td>
<td>42.33</td>
<td>3.63</td>
<td>445.02</td>
<td>739</td>
</tr>
<tr>
<td>TA0 4 hours</td>
<td>7.86</td>
<td>14.33</td>
<td>27.55</td>
<td>63.94</td>
<td>8.31</td>
<td>9.61</td>
<td>10.31</td>
<td>3.4</td>
<td>365.11</td>
<td>762.13</td>
</tr>
<tr>
<td>RRA</td>
<td>-14%</td>
<td>-25%</td>
<td>+26.9%</td>
<td>-38.06%</td>
<td>+21.84%</td>
<td>+41.9%</td>
<td>-75.6%</td>
<td>-6.3%</td>
<td>-17.9%</td>
<td>+5.12%</td>
</tr>
<tr>
<td>TB0 start</td>
<td>10.5</td>
<td>21.25</td>
<td>36.66</td>
<td>109.7</td>
<td>22</td>
<td>13.75</td>
<td>9.76</td>
<td>4.3</td>
<td>483.09</td>
<td>582.94</td>
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<tr>
<td>TB0 4 hours</td>
<td>7.2</td>
<td>17.2</td>
<td>36.8</td>
<td>71.03</td>
<td>19.3</td>
<td>14.6</td>
<td>8.74</td>
<td>4.4</td>
<td>299.8</td>
<td>594.15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time Period</th>
<th>IL-18</th>
<th>IL-2</th>
<th>IL-6</th>
<th>IL-8</th>
<th>IL-10</th>
<th>TNF-α</th>
<th>IL-4</th>
<th>IL-1α</th>
<th>VEGF</th>
<th>MCP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRB</td>
<td>-31.4%</td>
<td>-18.86%</td>
<td>+0.5%</td>
<td>-35.2%</td>
<td>-12.2%</td>
<td>+6.18%</td>
<td>-10.45%</td>
<td>+2.32%</td>
<td>-38.01%</td>
<td>+1.92%</td>
</tr>
</tbody>
</table>

### Table 2. Before and after adsorbent cartridge during the one-month follow-up HFR session (Pre C: before cartridge; Post C: post cartridge)

<table>
<thead>
<tr>
<th>Time Period</th>
<th>IL-18</th>
<th>IL-2</th>
<th>IL-6</th>
<th>IL-8</th>
<th>IL-10</th>
<th>TNF-α</th>
<th>IL-4</th>
<th>IL-1α</th>
<th>VEGF</th>
<th>MCP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>TA0 Pre C</td>
<td>7.03</td>
<td>16.82</td>
<td>9.81</td>
<td>10.0</td>
<td>6.11</td>
<td>8.25</td>
<td>10.13</td>
<td>4.34</td>
<td>51.8</td>
<td>275.9</td>
</tr>
<tr>
<td>TA0 C</td>
<td>7.13</td>
<td>19.11</td>
<td>3.4</td>
<td>8.69</td>
<td>5.93</td>
<td>0.1</td>
<td>9.95</td>
<td>3.96</td>
<td>54.32</td>
<td>33.0</td>
</tr>
<tr>
<td>RRA</td>
<td>+14.2%</td>
<td>+15.61%</td>
<td>-65.34%</td>
<td>-13.1%</td>
<td>-2.94%</td>
<td>-98.78%</td>
<td>-1.77%</td>
<td>-7.9%</td>
<td>+8.46%</td>
<td>-88.03%</td>
</tr>
<tr>
<td>TA4 Pre C</td>
<td>6.16</td>
<td>19.43</td>
<td>11.63</td>
<td>18.0</td>
<td>6.29</td>
<td>7.93</td>
<td>7.78</td>
<td>3.96</td>
<td>53.0</td>
<td>271.5</td>
</tr>
<tr>
<td>TA4 Post C</td>
<td>6.49</td>
<td>18.15</td>
<td>5.14</td>
<td>2.15</td>
<td>6.11</td>
<td>4.84</td>
<td>11.36</td>
<td>4.3</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>RRA</td>
<td>+5.35%</td>
<td>-6.58%</td>
<td>-55.8%</td>
<td>-88%</td>
<td>-2.86%</td>
<td>-38.96%</td>
<td>+46.01%</td>
<td>+8.58%</td>
<td>-99.8%</td>
<td>-99.96%</td>
</tr>
<tr>
<td>TA0 Pre C</td>
<td>7.03</td>
<td>16.82</td>
<td>9.81</td>
<td>10.0</td>
<td>6.11</td>
<td>8.25</td>
<td>10.13</td>
<td>4.34</td>
<td>51.8</td>
<td>275.9</td>
</tr>
<tr>
<td>TA4 Post C</td>
<td>6.49</td>
<td>18.15</td>
<td>5.14</td>
<td>2.15</td>
<td>6.11</td>
<td>4.84</td>
<td>11.36</td>
<td>4.3</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>RRA</td>
<td>-7.88%</td>
<td>+7.9%</td>
<td>-47.6%</td>
<td>-78.5%</td>
<td>0%</td>
<td>-41.33%</td>
<td>+12.14%</td>
<td>-0.91%</td>
<td>-99.8%</td>
<td>-99.9%</td>
</tr>
<tr>
<td>TB0 Pre C</td>
<td>5.47</td>
<td>16.14</td>
<td>12.3</td>
<td>14.53</td>
<td>5.93</td>
<td>6.77</td>
<td>11.02</td>
<td>4.91</td>
<td>7.00</td>
<td>238.0</td>
</tr>
<tr>
<td>TB0 C</td>
<td>6.49</td>
<td>19.74</td>
<td>11.49</td>
<td>2.15</td>
<td>0.1</td>
<td>4.98</td>
<td>11.53</td>
<td>4.5</td>
<td>59.09</td>
<td>152.0</td>
</tr>
<tr>
<td>RRA</td>
<td>+18.64%</td>
<td>-22.3%</td>
<td>-6.58%</td>
<td>-85.2%</td>
<td>-98.3%</td>
<td>-26.44%</td>
<td>+4.62%</td>
<td>-8.35%</td>
<td>-15.58%</td>
<td>-55.88%</td>
</tr>
<tr>
<td>TB4 Pre C</td>
<td>6.49</td>
<td>14.7</td>
<td>9.47</td>
<td>5.82</td>
<td>7.5</td>
<td>6.77</td>
<td>9.39</td>
<td>3.29</td>
<td>50.54</td>
<td>278.0</td>
</tr>
<tr>
<td>TB4 Post C</td>
<td>7.45</td>
<td>13.95</td>
<td>4.4</td>
<td>2.06</td>
<td>6.47</td>
<td>4.84</td>
<td>12.03</td>
<td>4.18</td>
<td>54.32</td>
<td>0.1</td>
</tr>
<tr>
<td>RRB</td>
<td>+14.79%</td>
<td>-5.1%</td>
<td>-53.53%</td>
<td>-64.6%</td>
<td>-13.73%</td>
<td>-28.5%</td>
<td>+28.11%</td>
<td>+27.05%</td>
<td>+7.47%</td>
<td>-99.96%</td>
</tr>
<tr>
<td>TB0 Pre C</td>
<td>5.47</td>
<td>16.14</td>
<td>12.3</td>
<td>14.53</td>
<td>5.93</td>
<td>6.77</td>
<td>11.02</td>
<td>4.91</td>
<td>7.00</td>
<td>238.0</td>
</tr>
<tr>
<td>TB4 Post C</td>
<td>7.45</td>
<td>13.95</td>
<td>4.4</td>
<td>2.06</td>
<td>6.47</td>
<td>4.84</td>
<td>12.03</td>
<td>4.18</td>
<td>54.32</td>
<td>0.1</td>
</tr>
<tr>
<td>RRB</td>
<td>36.19%</td>
<td>-13.56%</td>
<td>-64.22%</td>
<td>-85.82%</td>
<td>+9.1%</td>
<td>-28.5%</td>
<td>+9.16%</td>
<td>-14.86%</td>
<td>-22.4%</td>
<td>-99.9%</td>
</tr>
</tbody>
</table>
Conclusions
We observed a possible modulation in VEGF, IL8 and MCP1, supposing a cumulative effect over time. The cartridge demonstrated a high efficacy in removing CK although the in vivo cumulative effect is less evident. HFR could play a role in modulating inflammation and in reducing ESRD major complications.

References
Reduction of Inflammatory State in an Old Hemodialysis Patient After Initiation of Online-HFR Therapy


Background
Inflammation is highly prevalent in patients on hemodialysis (HD) and it has a great impact on survival and hospitalization. Besides chronic kidney disease complications, attention should be paid to the dialysis technique itself. The benefits of hemodiafiltration (HDF) are associated with enhanced clearance of middle molecules by convection, whereas albumin loss using high volume exchange is a possible disadvantage. On-line hemodiafiltration with endogenous reinfusion (HFR) combines diffusion and convection as it occurs in HDF, however the two techniques are strikingly different. HFR is a promising option to control inflammation and malnutrition in HD.

Methods
We described a case of a 79-year-old female who started Bicarbonate Hemodialysis in August 2014 due to ESRD of unknown etiology through an internal jugular tunneled catheter. Her past medical history included high blood pressure and a hysterectomy complicated by ileostomy creation in 2015. In August 2018, she started to report having a fever with chills after every dialysis session. The fever occurred 3–6 hours after the end of dialysis and lasted 12–16 hours. It reached the peak of 38°C and was self-limiting. Although the fever was never recorded during dialysis, inflammation was biochemically documented by an increase of C-reactive protein, ferritin, and erythrocyte sedimentation rate. Central line and peripheral blood cultures were repeatedly performed and showed no significant results. The patient underwent several investigations to exclude any neoplastic and infective underlying diseases (total body CT-scan, PET scan and oncomarkers). All test results were normal. Given the persistency of fever of unknown origin and hyporexia with 5.5% weight loss (2.5 Kg over eight months' time), on the 16th of March 2019, the decision to shift dialysis prescription from standard bicarbonate HD to HFR was taken. Notably, dialysis adequacy was satisfactory, treatment was performed at an effective blood flow of 300 ml/min and the dialysis session lasted four hours three times a week. No changes in medications nor in drug dosage were made at the time of the shift. Both biochemical tests and SF-36 were assessed one month prior and after HFR was started.

Results
Shortly after HFR was initiated, the patient experienced a reduction in several markers of inflammation and uremia and increase in serum albumin and hemoglobin (table 1). Evaluation of health status showed either amelioration or no changes in the eight scales measured through SF-36 (table 2). No further episodes of hyperpyrexia after dialysis were reported and the trend to weight loss was reversed. Although it is often subclinical in elderly, inflammation has great impact on health and QOL. HFR was useful to control the HD-related inflammation and resulted in patient well-being and better nutritional parameters. The main limitations were the impossibility to measure IL-6 and to provide evidence of long-term improvement.
Conclusions
In hemodialysis patients, HD-related factors should always be investigated as triggers of inflammation. In our case, HFR resulted in a successful strategy to reverse a persistent inflammatory status with clinically relevant benefits and significant improvement in the individual quality of life.

<table>
<thead>
<tr>
<th>Parameter (unit of measurement)</th>
<th>Before HFR</th>
<th>After HFR</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine (mg/dl)</td>
<td>6.01</td>
<td>5.79</td>
<td>-3.7%</td>
</tr>
<tr>
<td>Blood Urea Nitrogen (mg/dl)</td>
<td>57</td>
<td>52</td>
<td>-8.8%</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>1074</td>
<td>672</td>
<td>-37.4%</td>
</tr>
<tr>
<td>Erythrocyte Sedimentation Rate (mm)</td>
<td>72</td>
<td>62</td>
<td>-13.9%</td>
</tr>
<tr>
<td>Serum Albumin (g/L)</td>
<td>36</td>
<td>39</td>
<td>+8.3%</td>
</tr>
<tr>
<td>C-reactive Protein (mg/L)</td>
<td>21.7</td>
<td>8.8</td>
<td>-59.7%</td>
</tr>
<tr>
<td>β2 - microglobulin (mcg/ml)</td>
<td>44.1</td>
<td>40.2</td>
<td>-8.8%</td>
</tr>
<tr>
<td>Hemoglobin **(g/dl)</td>
<td>10.3</td>
<td>10.8</td>
<td>+4.9%</td>
</tr>
<tr>
<td>Body temperature after dialysis session (°C)</td>
<td>38.0</td>
<td>36.8</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Questionnaire about quality of life SF-36</th>
<th>Before HFR</th>
<th>After HFR</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning (%)</td>
<td>20</td>
<td>40</td>
<td>Improvement</td>
</tr>
<tr>
<td>Role limitations due to physical health (%)</td>
<td>0</td>
<td>0</td>
<td>No difference</td>
</tr>
<tr>
<td>Role limitations due to emotional problems (%)</td>
<td>0</td>
<td>100</td>
<td>Improvement</td>
</tr>
<tr>
<td>Energy/fatigue (%)</td>
<td>35</td>
<td>50</td>
<td>Improvement</td>
</tr>
<tr>
<td>Emotional well-being (%)</td>
<td>52</td>
<td>56</td>
<td>Improvement</td>
</tr>
<tr>
<td>Social functioning (%)</td>
<td>37.5</td>
<td>50</td>
<td>Improvement</td>
</tr>
<tr>
<td>Pain relief (%)</td>
<td>22.5</td>
<td>77.5</td>
<td>Improvement</td>
</tr>
<tr>
<td>General health (%)</td>
<td>25</td>
<td>25</td>
<td>No difference</td>
</tr>
</tbody>
</table>
HFR Supra Resolved Refractory Itch in a Dialysis Patient
L. Gobbi, G. Scaparrotta, M. Rigato, L.A. Calò, Nephrology University of Padua, Italy.

Background
Chronic itch (CI) is one of the most distressing conditions that substantially impair quality of life (QOL). CI is associated with many diseases of hepatic, renal, or hematological origin. Several pruritogens including bile salts (BS) have been hypothesized to be involved in the pathogenesis of CI, however the definite mechanism is still to be clarified and currently available medications are ineffective.

Methods
QOL was assessed by EuroQol 5 Dimensions 5 level (EQ5D5L). Dialysis adequacy was estimated by Kt/V and reduction ratios.

Results
In 04/2018 a 52-year-old man was referred to our unit to start renal replacement therapy (RRT). 5 years before, he underwent OLTx after a history of cirrhosis-HCC due to HCV. The first OLTx was complicated by primary graft dysfunction and 3 days later he underwent a second OLTx with good graft function; his renal function was normal. From 03/ to 08/2015 he was treated with sofosbuvir with HCV negativization. Hepatic function was good, but he developed CKD II complicated with sub-nephrotic proteinuria. In 12/2016 the patient developed graft rejection treated with corticosteroids; posttransplant bile duct anastomotic stenosis was diagnosed with an increase of BS and cholestasis index and the appearance of occasional itch; cholestyramine and ursodeoxycholic acid were introduced. CKD worsened to IIIb with nephrotic range proteinuria. In 03/2017 CKD was complicated by the occlusion of the right renal artery, which contributed to CKD progression to IV; the itch become more intense. In the following months, CKD worsened to ERSD; blood tests and kidney biopsy could not lead to a clear diagnosis. In 03/2018 right radiocephalic fistula was made up to allow bicarbonate dialysis, which was started in 04/2018. Liver function remained stable except for the elevated level of BS; CI became very distressing with a heavily compromised QOL. Due to continuous scratching, in fact, he couldn’t work, couldn’t practice simple daily activities, and even people stood away from him thinking he was infectious. QOL was evaluated by EQ5D5L 11342 VAS 41. Phosphorus (P) was well controlled by residual diuresis, hemodialysis, and sevelamer. In 09/2018, RRT was switched to HFR with a slight improvement of CI. P and hepatic function were good, EQ5D5L improved to 11241 VAS 51. In 11/2018 RRT was switched with HFR Supra which significantly reduced CI and BS -67%, β2 microglobulin -42%, Serum amyloid -64% and Interleukin 6 -9%, with consequent improvement of QOL (EQ5D 5L further improved to 11121 VAS 73). Albumin plasma levels remained quite stable 46 g/L. The continuous scratching stopped, and he could work without losing focus on his activities and could stay in the company of other people without discomfort.
This case shows that Supra cartridge retained BS and likely other pruritogens. The EQ5D5L scores illustrate how the HFR Supra definitively improved QOL significantly reducing up to almost resolving the CI. Although in this case itch could have a multifactorial origin (uremia, liver chronic rejection, immunosuppressive therapy) and the identification of the main pruritogens can be difficult. HFR Supra has demonstrated a clear effect in resolving the patient’s CI with its very distressing QOL, in reducing the inflammatory state and it may definitely represent a valid therapeutic approach in case of CI in dialysis patients.

Table 1. Plasmatic level before and after HFR Supra treatment

<table>
<thead>
<tr>
<th></th>
<th>Pre HFR Supra</th>
<th>Post HFR Supra</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile salts, umol/L</td>
<td>34</td>
<td>11.1</td>
</tr>
<tr>
<td>β2-microglobuline, mg/L</td>
<td>32.2</td>
<td>18.7</td>
</tr>
<tr>
<td>Serum amyloid A, mg/L</td>
<td>7.97</td>
<td>2.83</td>
</tr>
<tr>
<td>Interleukin 6, ng/L</td>
<td>10.1</td>
<td>9.2</td>
</tr>
</tbody>
</table>

Conclusions

This case shows that Supra cartridge retained BS and likely other pruritogens. The EQ5D5L scores illustrate how the HFR Supra definitively improved QOL significantly reducing up to almost resolving the CI. Although in this case itch could have a multifactorial origin (uremia, liver chronic rejection, immunosuppressive therapy) and the identification of the main pruritogens can be difficult. HFR Supra has demonstrated a clear effect in resolving the patient’s CI with its very distressing QOL, in reducing the inflammatory state and it may definitely represent a valid therapeutic approach in case of CI in dialysis patients.
References


Hemodiafiltration with Online Regeneration of Ultrafiltrate for Severe Nevirapine Intoxication in a HIV-Infected Patient

Service of Nephrology, CUB Hospital Erasme, Bruxelles, Belgium.

Background
Nevirapine, a non-nucleoside reverse transcriptase inhibitor, is one of the commonly used drugs in HIV infections. Its use has been complicated by several side effects including life-threatening toxic epidermal necrosis or severe hepatotoxicity. Unfortunately, no efficient treatment of such complications is available.

Methods
We describe the case of a patient with severe toxic epidermal necrosis developing within nine days of starting nevirapine, and the successful attempt at nevirapine plasma removal by hemodiafiltration with online regeneration of ultrafiltrate (HFR), a blood purification procedure combining hemodialysis with adsorption capacities of a resin cartridge.

Results
After one session of HFR (three hours), the evolution of the TEN was dramatically halted and skin lesions started to regress significantly during the following days. The patient was discharged after 48h of favorable clinical observation. The NVP blood levels were monitored during the HFR session (figure 1). Plasma concentrations of NVP were determined by a fully validated high-performance liquid chromatography (HPLC)/mass spectrometer method as described elsewhere (1). We compared this rate of blood elimination to that of the spontaneous elimination reported among 9 HIV-infected patients (1). During HFR, the NVP plasmatic elimination rate was -21.82 +/- 4.94 ng/ml per hour. NVP blood levels were therefore decreased by 36.5% after 3h of HFR and were still falling after HFR reaching 220 ng/ml after 12h after HFR (figure 2). In comparison, the rate of spontaneous plasmatic NVP clearance was significantly slower reaching only -4.55 +/- 1.31 ng/ml per hour (n=9), which is 5 times slower than HFR in our case (P 0.039; figure 1). Finally, we incubated two different set concentrations of NVP (40 µg/ml and 20 µg/ml) with hydrophobic styrene of the HFR cartridge (1 ml) in vitro. NVP concentrations were measured every hour for 4 hours. As expected, HFR resin adsorbed NVP very efficiently with a rate of elimination equal to -3494 ng/ml and -2357 ng/ml per hour for 40 and 20 µg/ml NVP respectively. Moreover, after only 1 hour of incubation in the presence of HFR resin in vitro, levels of NVP were undetectable.

Conclusions
This case report illustrates the interest of the HFR in acute intoxication and poisoning. Accordingly the role of HFR should be further investigated.
References

Use HFR-Supra for Porphyria Cutanea Tarda Treatment in Hemodialysis Patient


Background

We present the case of a 53-year-old man on long-term haemodialysis since July 2008 secondary to diabetic nephropathy. His previous medical history included type 2 diabetes with poor metabolic control, morbid obesity, hypertension (HTN), severe mixed dyslipidaemia, secondary hyperparathyroidism, hyperuricaemia and Child-Pugh B7 chronic alcoholic liver disease. In August 2016, he developed erosive, vesicular, painful lesions on his upper limbs, abdomen, and lower limbs which became worse when exposed to the sun. Tests for faecal protoporphyrins were positive (53 μg/g) and skin biopsy was compatible with the diagnosis of porphyria cutanea tarda (PCT). The patient began joint follow-up with dermatology. However, his lesions became worse (especially on his upper limbs) and were associated with severe joint pain.

In July 2017, it was decided to start treatment with chloroquine, with improvement of the lesions and pain until he became asymptomatic. After three months of treatment, without modifying his life habits or his usual treatment, he had a new flare-up of very painful skin lesions associated with arthralgia and limited mobility in the interphalangeal joints of both hands. After consultation with dermatology, it was decided to change conventional high-flux haemodialysis to haemodiafiltration with ultrafiltrate regeneration by resin adsorption (Supra-HFR), with clear improvement of skin lesions after three sessions and virtual resolution of the lesions and pain after two weeks of treatment. Protoporphyrins were again determined after three months on this technique to confirm clinical-biological correspondence, with clear improvement with respect to previous determinations, as shown in Table 1.

Methods

Supra-HFR is an extrarenal purification technique that combines conventional, adsorption, and diffusion. It has been used with good results in multiple myeloma,1 in the control of inflammatory markers due to a decrease in proinflammatory cytokines (NOS, IL-6 and p-Cresol),2–4 and has even been used for the control of intradialytic HTN5 and nevirapine poisoning in the treatment of HIV.6

Results

Table 1 Changes in laboratory results according to treatment. alt-text: Table 1 - December 2016: High-flux HD -> Faecal protoporphyrins (NL: 0–8 μg/g) 53 μg/g faeces. - September 2017: High-flux HD + chloroquine -> Faecal protoporphyrins (NL: 0–8 μg/g) 38.5 μg/g faeces - March 2018: Supra-HFR + chloroquine -> Faecal protoporphyrins (NL: 0–8 μg/g) 8.5 μg/g faeces HD: haemodialysis; NL: normal limits; Supra-HFR: haemodiafiltration with ultrafiltrate regeneration by adsorption in resin.
Table 1.

Conclusions
Our case is the first to describe a possible role of the Supra-HFR technique in the treatment of metabolic diseases such as PCT. Clinical trials are needed to confirm this effect plus experimental studies to determine the mechanism by which it is produced. One hypothesis would be that this technique could remove the inflammatory molecules deriving from oxidative stress secondary to the overproduction and accumulation of porphyrins, with the consequent improvement of the patient’s symptoms.

References
Improvement of Itching in Patients Suffered from Liver Disease Undergoing Hemodialysis with HFR-SUPRA

Di Liberato L, Pezzutto A, Bonomini M. Nephrology and Dialysis Unit, SS Annunziata Hospital, Chieti, Italy.

Background
Itching in patients undergoing hemodialysis has a complex pathogenesis not fully understood yet. In patients suffering from liver disease and end-stage renal disease in haemodialysis, biliary acids levels increase in blood. This increase has been correlated to pruritus onset. We chose two patients in thrice weekly haemodialysis affected by HCV-related cirrhosis treated with lactulose, rifaximin, branched-chain amino acids to control hepatic encephalopathy. The patients have been treated with antihistamines to control pruritus, the second one also took cholestyramine. In literature, few studies have evaluated the removal of biliary acids by hemodialysis.

Methods
We made a first dosage of biliary acids through the resin at time 0. Biliary acids reference values were 0–4 μmol/L. We dosed biliary salts and ammonium at 0, 4, 12 weeks, respectively. At the beginning of the study (and the 6th week), patients itching was evaluated through 5D-itch scale, asking also if the patient had found benefit on pruritus compared to the previous six months (when he started HFR-SUPRA).

Results
Samples pre- and post-resin collected at 30 minutes after starting HFR-SUPRA treatment at time zero documented a reduction of biliary salts concentrations in the patient 2 (1.8 μmol/L pre-resin vs <0.2 μmol/L post-resin), while in the patient 1 both biliary salts concentrations have resulted under the laboratory detectable value (see Table 1). The six biliary acids samples collected before and after HFR-SUPRA session showed a reduction of biliary acids concentration in both patients (patient 1: pre–HD median value: 6.66 μmol/L; post–HD median value: 3.76 μmol/L; patient 2 pre–HD median value: 42.63 μmol/L; post–HD median value: 23.43 μmol/L) (see fig.1 and table 2). At six months, however, itching had not improved. We sampled ammonium before and after HFR SUPRA session at time 0 and at fourth weeks; we documented ammonium reduction in both patients (see table 3). At the 12th weeks branched-chain amino acids were stopped; patients took only lactulose and rifaximin. At the fourth week since the suspension, we observed stable ammonium values (see table 3).

Fig. 1: Serum biliary acids levels before and after HFR SUPRA session at baseline, at 4th weeks and at 12th weeks.

Fig. 2: Median ammonium levels before and after HFR SUPRA session in the five months of treatment.
Conclusions
We have explored the possibility of removing bile acids and ammonium through HFR SUPRA and its impact on pruritus. In spite of bile acids and ammonium removal, patients have not reported an improvement of itching evaluated with modified 5D-itch scale. This is because uremic pruritus in liver cirrhosis has a complex pathogenesis not only attributable to biliary acids retention. We have also documented ammonium stable values with HFR SUPRA after stopping branched-chain amino acids infusion at the end of haemodialysis session: this represents a possible benefit in patient undergoing haemodialysis with important interdialytic weight gain. Our study has several limitations: 1) limited number of patients; 2) absence of control group; 3) pre- and post-resin ammonium sampling in order to evaluate the removal by convection and/or adsorption rather than only removal by diffusion. Therefore, in spite of advantages and the drawbacks reported above, our study paves the way to further evaluation about the “tailoring” of haemodialysis therapy in patient suffered from cirrhosis with pruritus and hyperammonemia.

References
HFR Therapy in Two Patients with Calcific Uremic Arteriolopathy (Calciphylaxis): A Single Unit Experience

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Background
We describe the cases of two haemodialysed patients with type 2 diabetes treated with insulin who developed life-threatening manifestations of calciphylaxis. Therapeutic approaches are limited especially in dialysis patients and include among others intensification of dialysis sessions to normalize calcium x phosphorous product, lowering calcium dialysate, the use of calcium-free phosphate binder, the withdrawal of vitamin K antagonist or the use of thiosulfate of sodium.1 Despite some of these approaches, the bilateral skin lesions of their legs worsened in the two patients. These lesions progressed to very painful ulcers threatening the viability of their legs. Therefore, we tried another strategy of haemodialytic therapy integrating diffusive, convective, and adsorptive features: HFR therapy.

Methods
The two patients had history of diabetes type 2 treated with insulin. They don’t take any vitamin K antagonists. The first patient had a history of obesity and hyperphosphataemia (between 1,65 and 2.75 mmol/l the months preceding the symptoms). But when we started the HFR treatment PTH and phosphate levels were low because of malnutrition (PTH: 31.5 ng/l (11-67) and Phosphate 0,74 mmol/l (0,81-1.45). The other patient had a well-controlled calcium x phosphorous product without secondary hyperparathyroidism. The two patients had a context of chronic inflammation (patient 1: crp 42.5 mg/l (<5 mg/l); patient 2: 31.5 mg/l, respectively, when we started HFR and malnutrition (patient 1 prealbumin level: 0,18 g/l (0,2-0,4); patient 2: 0,14g/l).We conducted a short trial over four weeks of respectively 21 sessions of three or four hours by each sessions of HFR in the first patient and 22 sessions in the second patient associated with general wound management.

Results
Despite these dialytic treatments associated with high clearance performance due to high cut-off membrane with adsorptive, selective purification and improved biocompatibility characteristics, we observe no any improvement of the lesions. The evolution of inflammatory and malnutrition markers were uninterpretable due to existing confounding factors. Unfortunately, a transfemoral amputation of the left leg was performed in the first patient at the end of the HFR treatment and the lesions of the contralateral leg improved very slowly after a few weeks of interdisciplinary treatment including pain control, topical treatment, surgical treatments and antibiotics. The bilateral skin lesions of the second patient with the same combined strategy healed very slowly and we don’t think that the dialytic therapy influenced the course of the illness.
Conclusions
In conclusion, there is no approved single therapy for calciphylaxis despite an interdisciplinary approach. That’s why we had expectations about a new strategy of dialysis integrating diffusion, convection, and adsorption: the HFR treatment. Despite hypothetical advantages (biocompatibility, performance, and opening new era of perspectives in malnutrition and chronic inflammation), the use of HFR therapy during four weeks in two patients don’t improve manifestations of uremic calciphylaxis.

References
Hemodiafiltration with Endogenous Reinfusion as a Possible New Ally for the Control of Secondary Hyperparathyroidism

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Background
The current dialysis population is characterized by many fragile patients with several comorbidities. In the age of personalized medicine, the evolution of dialysis therapy is characterized by the search of a highly efficient depuration and a high clinical tolerance. In this perspective, hemodiafiltration with endogenous reinfusion (HFR) can be used to optimize toxin removal. HFR is a form of hemodiafiltration with a 2-chamber filter that allows separating convection and diffusion and in which the reinfusion fluid consists of the endogenous ultrafiltrate purified by adsorption through a sorbent cartridge. In particular, HFR is ranked among the most effective methods in phosphate removal, and it also appears to induce a deceleration in bone turnover in patients suffering from secondary hyperparathyroidism (SHPT).

In addition, the recent development of HFR Aequilibrium (HFR-Aeq), which implements the HFR therapy with an advanced biofeedback system to control sodium balance, has proved to be effective in stabilizing the intradialytic hemodynamics with a lower incidence of dialysis intolerance symptoms. In this study, we report the case of a 45-year-old woman in maintenance hemodialysis for five years and treated with acetate free biofiltration (AFB) for her susceptibility to intradialytic hypotension. A serious dialysis inefficiency with marked hyperphosphatemia (hyper-P) and poor dietary and pharmacological compliance prompted us to shift the treatment from AFB to HFR-Aeq aiming for better phosphate removal and to improve the dialysis tolerance.

Methods
Beta2-microglobulin (B2M), C-Reactive protein (CRP), albumin levels were collected every two months. Furthermore, given that the patient was affected by SHPT with parathyroid hyperplasia candidate for parathyroidectomy, P, PTH and alkaline phosphatase (AP) values were also monitored. Finally, in order to evaluate the tolerability of dialysis therapy we counted the number of dialysis sessions in which intradialytic hypotensive episodes occurred and the number of early interrupted dialysis sessions.

Results
All the data collected is shown in Table 1. An important deceleration in bone turnover characterized by reduction of the AP and PTH was observed in the HFR-Aeq period than in the AFB period. Better control of P and no change in phosphate chelating agents and calcimimetics were also detected. In addition, B2M, CRP and Albumin values were slightly reduced (Figure 1). Finally, the number of hypotensive episodes and early interrupted treatments due to hemodynamic instability and intolerance of the patient resulted lower with HFR-Aeq than with AFB.
Conclusions
The case of our patient confirms that HFR-Aeq, when compared to AFB, promotes a better control of P, thanks to the higher efficiency of phosphorus removal, and has a higher tolerability. In addition, we can speculate that HFR is also associated with an independent effect on bone metabolism (i.e., not related to variations in P) probably due to its low inflammatory impact due to the use of an ultrapure endogenous reinfusion. The role of HFR as an additional treatment option for hyper-P and bone turnover activated by SHPT should be investigated in further clinical trials.

References
The Solution in a Kit

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Background
Uremic toxins and chronic inflammation are associated with elevated cardiovascular risk and reduced survival in patients with end-stage renal disease (ESRD). Hemodiafiltration with endogenous reinfusion (HFR) is a highly biocompatible dialysis technique that combines three depurative mechanisms: diffusion, convection, and absorption through a resin cartridge. HFR significantly reduces the concentration of pro-inflammatory toxins with a marked improvement in quality of life.

Methods
This paper reports the clinical situation of a 70-year-old man with a medical history of diabetes mellitus type II, dyslipidemia, hypertension, heart disease, smoking, and ESRD. After ambulatory follow-up of a year, renal replacement therapy (RRT) with bicarbonate hemodialysis (BHD) was started. After three months of BHD the patient was switched to HFR-AEQUILIBRIUM (HFR-AEQ).

Results
After three months of BHD, plasma C-reactive protein (CRP) level was by far exceeding normal values (CRP >5 mg/L) as well as B2-microglobulin, parathyroid hormone (PTH) and homocysteine plasma levels, respectively >20 mg/L, >500 pg/mL and >15 µmol/L. Furthermore, episodes of intradialytic hypotension (IDH) were frequent. After 3 months of HFR-AEQ reduction of plasma levels of CRP (<20 mg/L) were observed. Also, a progressive and significant reduction of plasma PTH and homocysteine were evident. HFR-AEQ reduced the frequency of IDH.

Conclusions
HFR is a highly biocompatible dialysis technique that combines three depurative mechanisms: diffusion, convection, and absorption. Because of the resin cartridge, it can adsorb proinflammatory agents effectively. This case reports a rapid improvement in levels of inflammation markers after the switch from BHD to HFR. The application of HFR-AEQ based on Profiler kinetic model (sodium balance) improved the intradialytic tolerance and reduction of IDH in comparison with BHD.

References