# Medical Insights of Hemodiafiltration

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Hemodiafiltration, a dialysis method that was implemented in clinics many years ago and that combines the two main principles of hemodialysis and hemofiltration—diffusion and convection—has had a positive impact on mortality rates, especially when delivered in a high-volume mode as a surrogate for a high convective dose. The achievement of high substitution volumes during dialysis treatments does not only depend on patient characteristics but also on the dialyzer (membrane) and the adequately equipped hemodiafiltration machine.

hemodiafiltration dialysis treatment

## 1. Necessity of Advanced Treatment Options for End-Stage Kidney Disease Patients to Improve Outcomes

Advances in technical and medical treatment options are of paramount importance for patients with end-stage kidney disease (ESKD) based on their high morbidity and mortality rates [1][2][3][4][5]. In a recent study with ESKD patients treated with hemodiafiltration (HDF), more than 90% suffered from metabolism and nutrition disorders, including type 2 diabetes mellitus [6]. Vascular disorders, such as hypertension, were reported for approximately 85% of patients, and cardiac disorders/coronary artery disease were reported for approximately 65% of patients. These comorbidities are both a sequel and an origin of ESKD. According to investigators, hypertensive and large vessel diseases (48%) and diabetes mellitus (21%) are the two leading root causes of ESKD.

In this context, cardiovascular complications are a leading cause of death in ESKD patients [3][7][8][9][10][11]. Male patients with ESKD on hemodialysis have an overall incidence of myocardial infarction of approximately 2.13 per 100 patient-years [12], which is approximately 3.5 times the risk of a comparable male population of >65 years old and not on hemodialysis [13]. The overall mortality rate in this population is approximately 6 times higher than in the general population [14]. This risk is also driven by vascular calcification caused by hypercalcemia and a dysregulation of the parathyroid hormone [15][16]. Moreover, diabetes mellitus and protein–energy wasting (PEW) are major problems among dialysis patients and major predictors of morbidity and mortality [17][18][19][20][21]. One major component of PEW is anorexia, which affects up to 50% of ESKD patients [22]. Anorexia may be caused by underdialysis, which, in turn, affects taste. A randomized study of 30 patients showed that an adaptation of the dialysis dose from a low initial Kt/V of 0.82 ± 0.19 to 1.32 ± 0.21 increased protein uptake (estimated by the protein catabolic rate, or PCR) by 26%, whereas the PCR remained constant in the control group with the unchanged dialysis procedure [23]. It is, thus, important to achieve the recommended dialysis target doses to avoid the PEW syndrome, e.g., by using highly efficient dialysis modalities. In addition to protein intake, protein loss should be considered, as the sieving properties of dialyzers may contribute to the PEW syndrome if they leak elevated amounts of albumin [6][24]. Thus, efficient dialysis may alleviate comorbidities associated with negative clinical outcomes in ESKD patients. This should include the elimination of middle- and large-sized uremic toxins, such as β2-microglobulin or inflammatory cytokines, and prevent the loss of essential proteins, such as albumin.

## 2. Hemodiafiltration vs. Other Modalities: Impact on Performances as Short-Term Surrogate Marker of Efficiency

Hemodiafiltration (HDF) has become the renal replacement therapy of choice in Europe and in Asian countries due to its superior performance vs. HD, i.e., the clearance and removal of uremic toxins, improved intradialytic hemodynamic stability, including fewer periods with cardiac and vascular stresses, and reduced inflammation [25][26][27][28][29]. The present section compares the performance characteristics of HDF with those of other treatment modalities.

Superior performance originates from combining the physical principles of diffusion known from HD and convection [30][31][32]. Online HDF outperforms low-flux HD in the removal of middle molecular weight uremic toxins, such as β2-microglobulin, myoglobin, and leptin [33][34][35][36]. For β2-microglobulin, however, high-flux HD may achieve comparable results as online HDF [37][38]. Furthermore, HDx (expanded HD) with medium cut-off (MCO) membranes and forced internal filtration by design has been described as an additional treatment modality. MCO membranes may achieve nominally similar solute clearances, and they possess good removal capacities for molecules up to approximately 50 kDa, with an albumin loss of below 5 g per HD session [39][40]. In a large survey among 71 Italian nephrologists, four questions were dedicated to MCO membranes [41]. Using the Delphi method of sequential questionnaires and defining a consensus as a level of agreement of ≥66%, the experts agreed that MCO membranes were associated with reduced systemic inflammation, improvement of dialysis-related anemia, better clearance for middle-to-high molecular weight uremic toxins, and improved treatment hemodynamics. However, the experts did not see a consistent association between MCO membranes and reduced mortality, especially from cardiovascular causes (a borderline positive consensus of 66%).

To describe the performance and safety of different dialysis modalities, Maduell and Broseta performed a selective review of the published clinical study data [42]. As an indicator of performance, they defined a global removal score as the average removal rates of β2-microglobulin, myoglobin, prolactin, α1-microglobulin, and α1-acid glycoprotein minus the removal rate for albumin. Post-dilution HDF possessed the highest mean removal score, followed by HDx, which was superior to pre-dilution HDF and high-flux HD. Low-flux HD presented the lowest global removal score, which was less than half that of post-dilution HDF. When analyzing the removal rates depending on blood flow (Qb) and substitution volume, post-dilution HDF proved superior to HDx, even with low Qb and a substitution volume not smaller than 17–18 L per session [43][44][45]. Regarding safety, the authors stressed that MCO membranes must only be used in HDx and not in HDF. Here, >20 g of albumin could be lost per session, whereas dialyzers dedicated to HDF may sieve as little as <2 g [6][46]. Furthermore, in the CARTOON trial, a randomized trial comparing HDx and post-dilution HDF, the coronary calcium scores, a surrogate for cardiovascular outcomes, remained stable in the HDF group and deteriorated significantly under HDx [47][48].

Good dialysis performance could also be linked to the improvement of other complications in dialysis patients. A cross-sectional study among 82 non-diabetic dialysis patients compared the effects of HD and HDF on the insulin resistance index [49]. The study found that insulin resistance was significantly correlated with the β2-microglobulin reduction rate and HDF was associated with lower insulin resistance compared to HD. This indicates that HDF, which is generally superior in the β2-microglobulin reduction rate to standard HD, might preserve insulin sensitivity in non-diabetic patients on renal replacement therapies or improve insulin resistance in diabetic patients. Furthermore, HDF is associated with less inflammation compared to standard HD, as shown by the lower levels of CRP, interleukin 6 (IL-6), and homocysteine. This could be linked to the better elimination of some inflammatory compounds, such as advanced glycosylation end products (AGEs), which accumulate in patients with ESKD and activate monocytes to release IL-6, TNF-α, and interferon-γ [34][50][51][52][53].

In this context, it is important to note that for efficient HDF treatments, suitable high-flux dialyzers are essential to allow for strong performance throughout the complete treatment time [24][54]. Several randomized controlled trials have been performed to compare the performance of different dialyzers among post-dilution HDF [6][55][56]. The trials found higher mean β2-microglobulin reduction rates for the dialyzers with synthetic membranes (>67% over a 4 h session) compared to dialyzers with cellulose triacetate-based membranes (51%). The dialyzers with polysulfone-based membranes achieved β2-microglobulin reduction rates of >70% in all of the trials. Here, the dialyzer possessing the most hydrophilic membrane and the lowest protein fouling showed the best removal of middle-sized molecules.

A recent cross-over study in ten stable HD patients by Vanommeslaeghe et al. compared the membrane fiber patency and performance in post-dilution HDF between a cellulose-based asymmetric triacetate (ATA) dialyzer (Solacea 19H) and a polysulfone dialyzer (FX CorDiax 800) [57]. The ATA dialyzer maintained open fibers over the dialysis sessions, whereas the polysulfone dialyzer showed a declining patency towards the end of the dialysis. The performance was generally in line with the fiber patency. These results appear to contradict the trials cited above and the laboratory data [24][58], where polysulfone dialyzers were superior to cellulose-based dialyzers. However, the study by Vanommeslaeghe et al. submitted the dialyzers to a fiber-blocking stress test that is not relevant for current clinical practices in that the dose of anticoagulation was reduced to one-fourth of the regular dose. Furthermore, the polysulfone dialyzer was a predecessor to the current model with improved hydrophilicity and fiber patency [24][58].

## 3. Impact on Morbidity and Mortality as Hard Clinical Endpoint to Support Larger Use of Hemodiafiltration

The most current clinical evidence suggests that HDF offers better clinical outcomes regarding the survival rate of dialysis patients as compared to standard HD, especially when delivered in high-volume mode. This section summarizes the clinical evidence with regards to morbidity and mortality.

As discussed above, the addition of convection to the basic mechanism of HD (diffusion) improves the clearance of middle molecular weight solutes during online HDF. This additional correction of the uremic environment in HDF is associated with decreased cardiovascular damage and, subsequently, lower cardiovascular morbidity and mortality [59]. This hypothesis was tested in four large randomized controlled trials (RCTs), all of which were performed in Europe. However, none of the studies provided undisputable results to the basic question of whether HDF is superior or not [33][37][38][60][61].

In an individual patient data meta-analysis (IPD-MA), the European pooling project combined the four RCTs (N = 2793 patients) that compared HDF (N = 1400, post-dilution mode) to standard HD (N = 1393) on clinical outcomes [25]. This analysis found that there was a 14% reduction in all-cause mortality and a 23% reduction in cardiovascular mortality when treated on HDF as compared to standard HD, which the authors classified as a substantial effect. The other causes of death, including sudden death and non-cardiac events, such as fatal infections and malignancies, were equally distributed between the HD and HDF groups. An interesting aspect of all four trials was that the actually delivered dosage of convective volume showed a considerable non-intended range caused by variations in everyday clinical practice. This fact and the patients' given height and weight made it possible to perform post-hoc analyses on the possible associations between the convective volume standardized to body surface area (BSA) and survival outcomes. Therefore, the group of HDF patients was divided into the following three tertiles by delivered convective volume: low volume of <19 L, middle volume of 19–23 L, and high volume of >23 L per session. With respect to all-cause mortality, there was evidence of a dose–response relation. The highest delivered BSA-adjusted volume (>23 L per 1.73 $m^2$ BSA per session) was associated with a 22% reduction in all-cause mortality and a reduction of 31% in cardiovascular mortality after an adjustment for age, gender, albumin, creatinine, history of CV diseases, and history of diabetes. These 23 L were based on the lower limit of the highest tertile in this meta-analysis. Based on these results, many subsequent publications have recommended a minimum convection volume of 23 L/1.73 $m^2$ BSA per session for HDF treatments [25][26]). Furthermore, scaling of the ultrafiltration volume to BSA allows for the adjustment of the dialytic convective dose to a patient's metabolic needs and the comparison of populations with various anthropometric profiles (i.e., European, Asian, or American populations).

Bernard Canaud and co-workers reached a comparable conclusion in an observational study (N = 2293) [62]. Here, the recommended convection volume was approximately 70 L per week, i.e., approximately 23 L per session, and, again, the data suggested a dose–response relation between the convective volume and the relative survival rate.

Another large observational study from Japan, among 5000 pairs of patients treated with HD or pre-dilution online HDF (the usual HDF mode in Japan), investigated the association of HD versus HDF (low and high volume) with all-cause and cardiovascular mortality [63]. In the pre-dilution mode, the substitution volume usually doubles. Thus, the high-volume HDF in the study was at about 50 L per session, and the low-volume HDF was at 25 L per session. Based on this definition, the 12-month all-cause mortality in the high-volume HDF group was significantly lower than that in the low-volume HDF group. Interestingly, when comparing the HD and high-volume HDF, the survival curves for all-cause mortality and cardiovascular mortality diverged very fast, which suggested a rapid effect.

Recently, the French Renal Epidemiology and Information Network Registry, which was started in 2002 with the aim to generate real-world evidence data for HDF and HD [64], also confirmed in a large observational study (REIN Registry) the superiority of HDF vs. HD with regards to all-cause and cardiovascular mortality [65].

In contrast, a French RCT [61], which focused on 381 elderly patients (above 65 years of age), and a newer analysis of Dialysis Outcomes and Practice Study (DOPPS) data of 8567 patients [66] did not find a significant difference in either all-cause or cardiovascular mortality between HDF and HD or between HDF patients with convective volumes below versus above 20 L per session.

Using a more detailed analysis of 2793 patients from the European pooling project, the authors investigated whether the benefits of HDF regarding cardiovascular mortality depend on the type of cardiovascular disease, i.e., cardiac cardiovascular disease, non-cardiac cardiovascular disease, or unclassified cardiovascular disease [25]. This analysis showed that the reduction in cardiovascular mortality in the HDF mode was solely explained by the cardiac part of cardiovascular mortality.

Thus, most studies found HDF, at least when delivered in high-volume mode, to be associated with a reduction in all-cause mortality. This was mainly explained by a reduction in cardiovascular and, more specifically, cardiac mortality [67][68].

## 4. Mechanisms for Beneficial Effects of Hemodiafiltration

This evidence on the beneficial effects of HDF raises a question regarding the possible mechanisms of the observed effects on improved survival reported for HDF. In a recent review article, two groups of associated effects—direct and indirect effects—were discussed with regards to cardiovascular function and structure [30]. Regarding the direct factors, data from observational and interventional multicenter studies show a reduction in the frequency of intradialytic hypotension episodes in convective therapies, such as HDF or HF vs. HD, a better hemodynamic stability [69][70][71][72][73], and an improvement in cardiac remodeling during HDF treatments [74][75]. A better hemodynamic stability appears not to be related to the better $Na^+$ balance achievable by HDF vs. high-flux HD [76]. Other direct effects may include the following: a reduction in chronic inflammatory states [53][74][77][78], oxidative stress [78][79][80], or an improvement of endothelial function and cardiovascular stiffness [81][82][83]. Furthermore, the direct effects can also be a reduction in the progression of atherosclerosis [78][84], sympathetic tone (nerve) activity [85], arrhythmogenicity, or the circulation of cardiotoxic uremic toxins [81][86]. Importantly, these direct effects may affect each other. Indirect effects in this context comprise a better correction of anemia [87][88], a better nutritional state [89][90], an improvement in physical activity [91][92], a better quality of life [93][94][95], and maintenance of residual kidney function [96][97]. It is highly difficult or basically impossible to separate these effects and identify a common underlying effect. It is most likely a complex of various interrelated effects that overall result in a beneficial effect on clinical endpoints. In this context, patient-related factors precluding a sufficiently high convective volume exchange may play a role. A retrospective study performed by Davenport identified low post-sessional intracellular water, low serum albumin, diabetes mellitus, and higher co-morbidity as indicators for low convective volumes. As these factors are not easily remediable, the patients affected may not be able to achieve the higher convection volume reported to be associated with improved patient survival [98].

In summary, the effects on the removal of middle molecules and large soluble molecules, inflammation, intradialytic morbidity, endothelial function, blood pressure regulation, and oxidative stress are the factors with the clearest evidence in the literature at present [30][99].

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