HEMODIAFILTRATION
Evolution of Techniques: from Rationale to Clinical Results

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HDF is an extracorporeal renal replacement technique utilizing a highly permeable membrane, in which diffusion and convection are conveniently combined to enhance solute removal in a wide spectrum of molecular weights. UF exceeds the desired fluid loss in the patient and therefore, replacement fluid must be administered to achieve the target fluid balance. Different modalities of HDF are today applied in clinical practice, however the common denominator of such therapy is the combination of diffusion and convection to achieve solute and volume control.

HISTORICAL NOTICES

In the early times of dialysis, several pioneers began to analyze the potential use of multiple mass separation processes to achieve blood purification. In 1967 Henderson published the first paper on the use of UF and fluid replacement (diafiltration) as a method of blood cleansing. In 1969, Miller and Shinaberger demonstrated the feasibility of diafiltration. In 1977 for the first time, the term HDF was used by Leber et al. The new dialysis method consisted on the combination of hemofiltration (HF) and conventional hemodialysis (HD) using high flux membranes with a transmembrane pressure of 300-500 mmHg and a dialysate flow rate of 900 ml/min. Due to the combination of convective mass transfer and diffusion, the clearance value of both small and larger molecules were significantly higher than during HF or HD alone with the same membrane. The removal of excess water from the patient was better tolerated. At least two advantages have been ascribed to HDF since the beginning: 1) easy removal of excess water from the patient and 2) clearance of solutes in a wide spectrum of molecular weight. In 1977, another investigator, Dr. Kunitomo, demonstrated the feasibility of HDF thanks to the most recent technological innovations that included UF control systems, highly permeable hollow fiber dialyzers and replacement solutions prepared in bags. These advances made possible the spreading of the technique that gained popularity in Europe and opened the way to the modern technology of HDF and its application as a routine renal replacement therapy.

TECHNIQUES

Hemodiafiltration is a combination of hemodialysis and hemofiltration. The combination of convection with a high flux thin membrane allows for simultaneous removal of small and large solutes. The relative contribution of convection to overall solute removal increases progressively with increasing molecular weight. These concepts have been implemented in clinical practice leading to different forms of hemodiafiltration. We can summarize the practical applications of hemodiafiltration over the years as follows:

Classic Hemodiafiltration (HDF): This technique is based on an average reinfusion rate of 9 liters per sessiontypically in post dilution. Fluids are contained in commercial bags. A blood flow higher than 300 ml/min is required to generate sufficient rates of ultrafiltration at acceptable transmembrane pressure gradients. The required equipment includes an ultrafiltration control system, a reinfusion pump and a scale continuously weighing the reinfusion bags. This technique was used for many years before on-line modalities were available. In some cases, the amount of reinfusion was as low as 3 liter/session (soft HDF) as in the case of Biofiltration (a ready-to-use proprietary technique from Hospal, France) or up to 15 liter per session as in the case of the so-called Hard HDF.

Acetate Free Biofiltration (AFB) : This is a special form of hemodiafiltration in which even small traces of acetate were completely eliminated both from dialysate and replacement fluid. The average amount of replacement fluid is titrated based on the blood bicarbonate level and varied between 6 and 9 liters per session.

High Volume hemodiafiltration (HardHDF) : In this form of classic hemodiafiltration, the amount of fluid exchange is 15 liters/session or more. Because of the high ultrafiltration rate, high blood flows are required and replacement solution is sometimes infused in pre-dilution mode. While this partially decreases the efficiency of the therapy, it allows for an optimal blood flow distribution in the hemodialyzer and a lower protein concentration polarization at the blood membrane interface.

On-Line Hemodiafiltration(OLHDF) : The high cost of commercially prepared replacement fluids in bags and an improvement in the technology of on-line dialysate preparation have stimulated the development of a novel technique called On-Line hemodiafiltration. Freshly prepared ultrapure dialysate is taken from the dialysate inlet line, processed with multiple filtration steps and then reinfused as replacement fluid. In this way, large amounts of inexpensive replacement solution are generated and hemodiafiltration can be performed with very high fluid turnover (up to 30-40 liters/session). Fluid reinfusion can be pre- or post-dilution, or even both in different proportions. Older HDF machines can be embedded with software and system controls to perform on-line HDF.

Internal Filtration HDF (iHDF) : The water fluxes in hollow fiber hemodialyzers are characterized by a proximal filtration and a distal backfiltration. This is because a positive transmembrane pressure gradient is present in the proximal part of the fiber bundle, while in the distal part, the transmembrane pressure gradient may become negative. In some circumstances proximal water flux can be enhanced: by applying a constriction in the middle of the fiber bundle. When this is accomplished by placing an obstruction to dialysate flow in the dialysate compartment or by reducing the inner diameter of the fibers, internal filtration can reach values of 40-50 ml/min in a 1.8 square meter dialyzer. The ultrafiltration control system of the machine operates a fluid balance increasing the relative amount of backfiltration. This form of therapy is internal hemodiafiltration.

Paired Filtration Dialysis (PFD) : This technique of hemodiafiltration, developed in Italy, is based on two filters placed in series: the first is a hemofilter and removes fluid and solutes by convection; the second is a hemodialyzer in which solutes are predominantly removed by diffusion . Replacement fluid is infused between the two units. This therapy minimizes the interactions between convection and diffusion, prevents backfiltration in the hemodialyzer and makes ultrafiltrate available for on-line measurements as a surrogate for plasma water. Recently further evolution of this concept has led to the HFR(Hemodiafiltration on-line with endogenous reinfusion) and PHF (Paired hemodiafiltration on-line with exogenous reinfusion) techniques. HFR is a PFD where the ultrafiltrate produced is purified by adsorption through a resin/charcoal unit and utilized subsequently as a replacement fluid. In PHF, the fist unit is used to backfilter some fresh dialysate acting as ultrapure on-line filtered replacement fluid.

Mid-dilution hemodiafiltration (MDHDF) : Recently, special filters with two longitudinal compartments have been developed to create a technique called mid-dilution HDF. Blood flows in the first compartment producing a certain amount of ultrafiltration; at the end of the compartment blood is redirected countercurrent in the second blood compartment. On the venous end of the dialyzer, in place of the venous port is a special chamberdesigned to receive replacement fluid infusion and to reconstitute blood composition. Blood then leaves the dialyzer alongside the arterial entry. Dialysate in this system flows 50% countercurrent to blood and 50% co-current to blood.

Double High Flux Hemodiafiltration (DHFHDF) : This technique also utilized two high flux dialyzers in series. Filtration takes place on the proximal filter while backfiltration takes place in the distal unit. High blood flows have been utilized for this technique and its high efficiency has allowed treatments under 2 hours/session.

Push-Pull Hemodiafiltration (PPHDF) : this technique utilizes the mechanism of alternating filtration and backfiltration, produced by alternating pre- and post-filter pumps. When the post filter pump is stopped filtration occurs, and when the pre-filter pump is stopped the negative pressure induced in the blood compartment produces backfiltration.

FLUID PURITY AND BIOCOMPATIBILITY

HDF combines the use of a high-flux synthetic membrane with low bioreactive profile with ultrapure dialysis fluid. Online preparation of sterile and pyrogen-free solutions for infusion during HDF require a hygienically designed and maintained flow path. Sterility is assured by ultrafilters with known retention capacity, placed in strategic positions and dimensioned to remove bacteria and endotoxinsl. Strict application of recommendations for the maintenance of online HDF equipment guarantees the safety of this method. Microbiologic safety of online-HDF has been shown in long-term clinical studies, with neither cytokine-inducing activity in the fluid nor pyrogenic reactions in patients despite the infusion of large volumes of fluid in every session.

Biocompatible membranes and ultrapure fluid reduce bioactivation of circulating leukocytes induced by blood-hemodialyzer interaction. The high UF rates also result in protein-coating of the membrane, increasing biocompatibility. Prevention of inflammation is now becoming a crucial concern to reduce the incidence of dialysis-related complications of malnutrition, anemia and atherosclerosis. Several prospective studies have shown the release of pro-inflammatory mediators (IL-1, IL-6, tumor necrosis factor) resulting from patient- hemodialyzer interaction is significantly reduced for patients receiving online HDF. HDF patients in the DOPPS study demonstrated a lower microinflammatory profile. Dyslipidemia profile oxidative stress and advanced glycosylation end products (AGE) have also been reported to contribute to the accelerated atherosclerosis seen in end stage renal disease (ESRD). The regular use of high-flux membranes in HD or in HDF has been shown to improve the lipid profile, reduce oxidative stress and decrease AGE concentrations. This may be in part due to improved biocompatibility of the online HDF system.

SUMMARY

Despite technological advances, treatment with HD and diffusive solute removal are characterized by high mortality and many complications. We must seek better therapies for our patients. Treatment modalities involving convection, such as HDF, allow the removal of a broader spectrum of uremic solutes, with more efficient clearance of middle molecules. The technology of online preparation of ultrapure dialysate and reinfusate fluid has reduced the cost and complexity of HDF, while assuring safety and efficacy. Online HDF has many potential clinical advantages over high-flux HD that may improve the overall quality of renal replacement therapy and improve the survival of ESRD patients. There is a need for further confirmation of these encouraging findings with large prospective controlled trials wih adequate sample size and follow-up. Furthermore, a full understanding of the mechanism and potential benefits of each specific technique can allow clinicians to obtain the best possible result from their application.