**Online Hemodiafiltration**

By Francisco Maduell

Although the physical and chemical concepts of diffusion and convection are well known, dialysis has been carried out mainly by diffusion during its first four decades. This form of dialysis, hemodialysis (HD), has ensured the survival of millions of patients with advanced kidney disease worldwide and has met the increasing needs generated in the 50 years since dialysis was considered for long-term renal replacement therapy. The delay in incorporating convection techniques as routine treatment has technological and economic reasons. Hemofiltration (HF) or hemodiafiltration (HDF) modalities require the use of dialyzers of high permeability and, at the same time, monitors with volume control and a dual pump. Replacement fluid is a further cost, is the main reason for abandoning HF, and was a key constraint on the initial HDF technique, with volumes ranging between 3 and 10 L. In the 1990s, the introduction of online HDF techniques using the dialysis fluid itself as a replacement solution has meant a revolution in HD units. It has taken another 10 years to renovate and upgrade water treatment, introduce specific monitors, and incorporate safety filters to ensure ultrapure dialysate.

What is hemodiafiltration?

The European Dialysis working group (EUDIAL) revisited the definition of hemodiafiltration (1) as the blood clearance treatment that combines diffusive and convective transport using a high-flux dialyzer with an ultrafiltration coefficient (KUF) >20 mL/min Hg/mm2, a sieving coefficient for β2-microglobulin >0.6, and a percentage of effective convective transport greater than 20 percent of the total processed blood. Convolution was defined as the sum of the replacement volume and the intradialytic weight loss achieved.

Can I provide online hemodiafiltration?

To answer this question, complete the checklist in Table 1. If the answer to all of the questions is yes, you are able to provide this treatment modality. If the answer to one or more of the questions is no, the treatment cannot be started until each point has been resolved. This checklist does not include training, because the current technology has been greatly simplified and is easy to use.

Why should we systematically implement online hemodiafiltration?

Online HDF (OL-HDF) can be indicated for all patients receiving hemodialysis, because there are no contraindications. Online HDF techniques constitute progress toward renal replacement therapy that is most similar to the native kidney. These techniques offer a higher clearance of uremic substances with a greater range of molecular size.

The possible clinical benefits that convection techniques can provide are better control of hyperphosphatemia, malnutrition, inflammation, anemia, infectious complications, joint pain, amyloidosis associated with dialysis, intradialytic tolerance, insomnia, irritability, restless leg syndrome, polyneuropathy, and itching.

Does online hemodiafiltration improve survival?

Observational studies, adjusted for demographic and comorbidity factors, have shown that a lower risk of death is associated with online HDF (2–5). In addition, three large prospective randomized clinical trials (RCTs) have been conducted to compare survival outcomes in prevalent patients. The CONTRAST study randomized 714 patients to low-flux HD or OL HDF and at the end of the study the two groups showed no difference in survival (6). Similarly, in the Turkish HDF study, 782 patients were randomized to HF HD or OL HDF and the outcome was not affected by treatment allocation (7). However, the ESHOL study randomized 906 patients to HF-HD or OL HDF, and the allocation to OL HDF was associated with a 30 percent reduction in all-cause mortality (8).

Association between survival and convective volume

In all large RCTs, the convective volume seemed to be an important issue. A post hoc analysis of the CONTRAST study showed that in the group of patients with the highest delivered convolution volume (upper tertile >21.95 L), mortality was 39 percent lower than in patients randomized to LF-HD (6). In a Turkish study, the median value of substitution volume in the OL-HDF group was 17.4 L, and when patients were stratified according to this threshold, those in the high-efficiency OL-HDF group were associated with a 46 percent risk reduction for overall mortality and a 69 percent risk reduction for cardiovascular mortality (7). In post hoc analyses of the ESHOL study, mortality in the intermediate tertile (23.1–25.4 L per session) and upper tertile (>25.4 L) was significantly lower than that in patients randomized to HD: 40 percent and 45 percent risk reduction for overall mortality, respectively (8).

Convective dose prescription

Convective target volume should therefore be the maximum possible for the individual characteristics and parameters of each patient dialysis. Based on the results of secondary analyses of the main clinical trials, the current recommendation of the optimal dose of OL-HDF, in postdilutional mode with a thrice-weekly treatment schedule, would be a convective volume >23 L per session. However, bear in mind that this recommendation is based in secondary analysis, and therefore there could be a selection bias. Patients receiving greater convective volume are those in better overall condition, with good vascular access and less diabetes or cardiovascular disease. In the absence of more conclusive scientific evidence, it seems a reasonable and affordable recommendation that should be confirmed with future clinical trials.

**Blood flow**

The main limiting factor for convective volume is Qb. In postdilution mode, the maximum recommended infusion flow is 53 percent of the Qb value. Achieving adequate convective volumes may be complicated in patients with limited Qb. Some authors have suggested that the prescription of Qb is more a matter of treatment policy in each dialysis unit than the characteristics of the patients themselves (13).

**Dialyzer**

New dialysis machines that allow an automatic infusion flow (Qi) to maximize the convective volume have reduced the risk of hemocoagulation and have increased convective volume (14–15).

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**Dialyzer**

Online HDF needs high-flux dialyzers. Currently, dialyzers are available with large convective capacity, with KUF between 40 and 100 mL/Hg/mm Hg. This means that with a transmembrane pressure of 200 mm Hg, allowing Qi of 133 to 333 mL/min, Qi is much higher than that which can actually be used. Therefore, a dialyzer with KUF > 45 mL/Hg/mm Hg is not a limiting factor in the convective volume, and the differences obtained in the purification capacity would be minimal.

**Dialysis duration**

Increase in the duration of dialysis will always be a valid alternative to increase in convective volume.

Is it time to change from diffusion techniques to online hemodiafiltration?

We are fully convinced that now is the time to change to convective techniques. First, the available scientific evidence supports that this treatment increases overall and cardiovascular survival. Second, technological develop-

Table 1. Checklist to evaluate whether a dialysis unit can provide online hemodiafiltration

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>Do you have adequate financial reimbursement?</td>
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<tr>
<td>Do you have proper water treatment for ultrapure water?</td>
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<tr>
<td>Do you have access to high-flux dialyzers?</td>
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<tr>
<td>Do you have appropriate machines for OL-HDF?</td>
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<tr>
<td>Can you use two safety filters on these machines to obtain ultrapure dialysate?</td>
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<td></td>
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<tr>
<td>Can you request monthly microbiological cultures and endotoxin determinations?</td>
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</tbody>
</table>

Abbreviations: HDF = hemodialfiltration; OL = online.
Continuous Renal Replacement Therapy: The Rise of the New Machines

By Lakhmir S. Chawla

Continuous renal replacement therapy (CRRT) is relatively young; the first continuous venovenous CRRT systems were deployed widely in the late 1990s. The early machines were an enormous improvement over continuous arteriovenous systems. However, the early machines did not have the corresponding accessories available, and many nephrologists can recall “brewing” lactate-buffered dialysis and replacement solutions to operate CRRT in the early days. Some of us even resorted to using peritoneal dialyse in CRRT. In the past 15 years, the need for customized fluids has been rare, and multiple bicarbonate buffered commercial solutions are now available. In addition, the accessories for short-term dialysis such as double-lumen catheters, anticoagulation options, and replacement fluid solutions have all been upgraded over the past 15 years. Now, CRRT, which was once a laborious and complex procedure, has become much easier and safer. So what does the field need now? Next-generation machines.

The first-generation CRRT machines were the Prisma and the Diapact. At the time, these machines were embraced because of their ability to perform venovenous procedures more safely. During this time, the primary goal was to get control of the patient’s volume and electrolytes without hemodynamic instability. The publication of the “Ronco paper” in The Lancet in 2000 pushed many clinicians to try to achieve a higher dose of CRRT.

These first-generation machines did not have flow capacities for blood or effluent flow rates that met the needs of many clinicians, and the second-generation machines were brought into the intensive care unit with the capacity to achieve these higher flow targets. After publication of the Randomized Evaluation of Normal versus Augmented Level of Replacement Therapy trial and Acute Renal Failure Trial Network, the consensus dose for CRRT was set at 20 to 25 mL/kg/h. However, questions about hemofiltration versus diffusion remain unanswered, and some still believe that extended daily dialysis is adequate compared with CRRT.

In any case, for most clinicians in the United States, CRRT is performed with the PrismaFlex (Baxter Medical), the NxStage System One (NSO, NxStage Medical), or the Diapact System (B-Braun). Both PrismaFlex and NSO have the ability to run much higher effluent flow rates. Both platforms can also perform plasmapheresis, and the PrismaFlex can be used with the MARS system (Gambro) to conduct albumin dialysis. The key technological differentiator of the NSO compared with the PrismaFlex and the Diapact System is its use of a disposable cartridge containing all of the blood and fluid pathways, including a volumetric fluid management system. This volumetric system balances fresh replacement fluid or dialysate with effluent coming from the dialyzer and removes excess fluid (net ultrafiltration) from the patient. The PrismaFlex and the Diapact System both use gravimetric scales. The PrismaFlex machine features five pumps (blood, dialysate, pre–blood pump replacement solution, post–blood pump replacement solution, and effluent), four scales (one each for effluent and dialysate, two for replacement solutions) and a disposable set with preconnected high-flow dialyzers and fluid circuitry. The Diapact System has three pumps with a wide range of blood flows and dialysate flows. Fluid handling and ultrafiltration control is gravimetric, with one scale.

But now the new machines are coming. A looming question is whether these current platforms are sufficient or whether new capabilities and features are required. The names and timelines of the new machines have not been officially announced, but at the bedside we can expect new versions of the PrismaFlex and the NSO in the next 24 months. In addition, Spectral Medical, Inc., has indicated its intention to introduce a CRRT machine to the North American market in the next 18 months, called the S.A.M. (Spectral Apheresis Machine). The S.A.M. system uses a synchronized piston pump system run by four internal cam shafts that also run the pump clamps. The S.A.M. system is a small, easy-to-use, open platform for CRRT and hemoperfusion. In the pediatric world, the CARPEDIEM machine (Belico), which debuted in Europe, looks to enter the US market. CARPEDIEM was specifically designed for neonatal CRRT and has very low priming volumes, blood flow rates as low as 5 mL/min, and incredibly accurate scales (error ≤ 1 g), making it appealing for use in low-weight children as well.

What features can we expect with these new machines, and will the new machines bring features to the bedside to improve only delivery of the therapy or will they also have new capabilities to improve outcomes? Inasmuch as the new machines and their new features remain unknown, I conducted an informal poll at the Critical Care Nephrology meeting in Vicenza, Italy, in June 2015 and asked which new features were most desirable. The top answers were reduced cost, smaller footprint, increased versatility, and portability. Interestingly, many thought leaders said the addition of an online monitor for hematocrit, calcium, or both would be an important advancement. In short, the new machines are coming soon, and we can hope that the manufacturers of the new devices will deliver.