TMP revisited: the importance of plasma colloid osmotic pressure in high-flux dialysers

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With high-flux dialysers and volume-controlled machines, transmembrane pressure (TMP) is no longer used to prescribe and control the adjustment of patient volume but still used to monitor filter function and membrane integrity. A drop in TMP at given operation characteristics indicates a leak or even a rupture in the membrane, while an increase in TMP indicates a loss in hydraulic permeability, most likely because of gradual clogging of the filter by formation of secondary membranes or obstruction of individual capillary fibers. Monitoring dialyser function is of special interest in different forms of haemofiltration and haemodiafiltration, where ultrafiltration rates are allowed to reach very high values exposing all components of the process to substantial strain. High ultrafiltration rates and excessive filtration fractions bear the risk of cell damage or activation [1] and filter failure [2]. Thus, there is increased interest to monitor driving pressures and to obtain objective criteria for safe operation of such treatment modes [3, 4].

In this issue of the journal, Ficheux et al. [5] describe that the ratio of ultrafiltration rate (Q_{uf}) to TMP in high-flux dialysers has a distinct maximum within a narrow range of ultrafiltration rates for a wide range of operating conditions. The Q_{uf}/TMP ratio is interpreted as the ultrafiltration coefficient K_{uf} of the dialyser. This maximum is easily identified during the actual treatment and the authors suggest that the ultrafiltration rate and/or the TMP associated with this maximum indicates a region for optimal ultrafiltration treatment. Indeed, this could be an interesting approach to improve convective techniques.

The relationships between ultrafiltration, treatment (blood flows, dialysate flows and pressures), filter (flow resistance, filter hydraulic permeability and fibre geometry) and patient parameters (blood composition with regard to haematocrit and plasma protein concentration) are rather complex and the interested reader is referred to more detailed discussions of this subject [6–8]. These relationships have been examined using mathematical models [9–13]. We therefore assumed that such an approach could be helpful to better understand the Q_{uf}/TMP maximum observed by Ficheux et al. [5]. The model to address this question was adapted from models published elsewhere [9,13]. The source code of this model that does not account for effects caused by concentration polarization and/or deposition of proteins is provided in the supplementary material and can be used with Berkeley-Madonna, a numerical integrator available from the Internet (Berkeley Madonna X, version 8.3.15, http://www.berkeleymadonna.com).

For a given set of parameters comparable to those described in the technical note, the dialysate inflow pressure was varied to cover a TMP range from 0 to 300 mmHg, a common upper limit in convective techniques [3,4]. The nominal filtration coefficient K_{uf} of the dialyser was 100 mL/h/mmHg, as provided by the manufacturer, and assumed to represent the hydraulic permeability times the active membrane surface area of the dialyser. As expected, Q_{uf} steadily increased with increasing TMP, but the increase was less pronounced for TMP exceeding 100 mmHg (Figure 1a, full line). As a consequence, the slope (ΔQ_{uf}/ΔTMP) of the Q_{uf} to TMP relationship was not constant but continuously decreased from ~83 to 7 mL/h/mmHg (Figure 1b, full line).

Interestingly, in spite of a constant K_{uf} assumed in the model, the ratio of Q_{uf}/TMP plotted versus Q_{uf} (Figure 2a, full line) or TMP (Figure 2b, full line) showed a shape and a maximum comparable to that presented in the technical note [5]. The ratio of Q_{uf}/TMP reached maximum values of 41 mL/h/mmHg at a Q_{uf} of 90 mL/min and at a TMP of 102 mmHg. Thus, the experimental observation presented in the technical note was successfully replicated by the mathematical model describing internal filtration and backfiltration in a high-flux dialyser.

Contrary to expectations, the simulations showed that there was a large discrepancy between the constant K_{uf} of the dialyser (100 mL/h/mmHg), the slope of the Q_{uf} to TMP relationship (Figure 1b, full line) as well as the ratio of Q_{uf}/TMP (Figure 2, full lines). A comparison of slopes (Figure 1b) and ratios (Figure 2b) helps to resolve part of the problem. The slope of a functional relationship between two variables (ΔQ_{uf}/ΔTMP in this case) is not identical to the ratio of these variables (Q_{uf}/TMP). Slope and ratio are only identical for the linear case and in the absence of an intercept. The actual relationship between Q_{uf} and TMP is nonlinear with a non-
The discrepancy between the ratio $Q_{uf}/\Delta TMP$, the slope $\Delta Q_{uf}/\Delta TMP$ and the constant $K_{uf}$ of the dialyser essentially originates from simplifications in estimating the true filtration pressure. For the dialyser where pressures are distributed because of flow and filtration, net $Q_{uf}$ is proportional to the average filtration pressure $\bar{p}_{fil}$:

$$Q_{uf} = K_{uf} \bar{p}_{fil}. \quad (1)$$

As hydrostatic pressures are assumed to linearly decrease within each compartment, the arithmetic mean of in- and outflow pressures ($p_{in}, p_{out}$) to and from blood (subscript b) and dialysate (subscript d) compartments is considered a good surrogate of mean compartment pressure and the difference of both as a good surrogate of the average hydrostatic pressure gradient. In applications with artificial kidneys, the hydrostatic pressure gradient is also know as TMP:

$$\text{TMP} = \frac{p_{b,in} + p_{b,out} - p_{d,in} + p_{d,out}}{2} \quad (2)$$

This formula was also used in the simulations discussed above.

In practice, however, TMP is determined from only two pressures measured in each compartment, such as venous line and dialysate inflow pressures. Such reduced information is insufficient to monitor the changing hydrostatic pressure to flow relationships within a dialyser over the course of a whole treatment [4]. The simplification inherently assumes a constant and/or zero pressure drop in both blood and dialysate compartments. The pressure drop, however, is in the magnitude of 100 and 50 mmHg in blood and dialysate compartments, respectively, and increases with blood and dialysate flow [6]. Moreover, hydrostatic pressures are not measured at the exact entrance and/or exit of the capillary fibers. The conduits between fibres and pressure sensors usually have large diameters and one would not assume a large pressure loss, but the flow distributors for blood and dialysate at the dialyser ends exert a significant flow resistance [13].

If the membrane is impermeable for macromolecules, the average filtration pressure also includes a plasma colloid osmotic component $\pi$ opposing filtration [3], so that

$$\bar{p}_{fil} = \text{TMP} - \pi \quad (3)$$

Plasma colloid osmotic pressure accounts for major nonlinear effects in the relationship between pressure and filtration, especially in high-flux dialysers. The measurement of colloid osmotic pressure requires dedicated transducers and is not routinely done in haemodialysis. While it may be reasonable to assume a more or less constant colloid osmotic pressure between 20 and 25 mmHg for arterial blood entering the extracorporeal circuit, plasma colloid osmotic
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pressure easily exceeds 50 mmHg or more within high-flux dialysers and in postdilution haemodiafiltration. At a filtration fraction of 50% reached in the experiments of Ficheux et al. [5], plasma protein concentration will double and at a protein concentration of 140 g/L, plasma colloid osmotic pressure is expected to reach values of 85 mmHg [14]. In high-flux dialysers, this magnitude is no longer negligible. Unlike TMP, the average colloid osmotic pressure is expected to reach values of 85 mmHg [14]. In high-flux dialysers and in postdilution haemodiafiltration. At a filtration pressure easily exceeds 50 mmHg or more within high-flux dialysers (Kuf) is not a fixed value, it follows a parabolic function: the new concept of Kuf max. Nephrol Dial Transplant 2011; 26: 636–640.)

It follows from this analysis that a focus on hydrostatic pressures alone, while excluding the effects of plasma colloid osmotic pressure, is inappropriate to determine and monitor the filtration coefficient of high-flux dialysers and probably insufficient to optimally control the process of convective dialysis therapies using high ultrafiltration rates. The relevance of plasma colloid osmotic pressure is also supported by the experimental observation that the Quf/TMP maximum in [5] varied between patients where plasma protein concentration and hematocrit are more likely to be different rather than between treatments done in the same patient.

While the Quf/TMP versus Quf relationship indeed shows a maximum also in the mathematical model, this ratio clearly does not represent the filtration coefficient of the dialyser. The speculation that the Quf/TMP maximum is caused by the onset of protein deposition and membrane fouling can be questioned as the maximum can be explained by failure to include the effects of plasma colloid osmotic pressure and relying on hydrostatic pressures only. It is therefore questionable whether the ratio Quf/TMP and its maximum will be useful to detect the optimum Kuf of the dialyser. Whether the maximum will be helpful to guide ultrafiltration therapy remains to be studied.

A measurement of the true driving pressures has the potential to detect deteriorating filtration characteristics. This, however, requires new technology for its online measurement.

Supplementary data
Supplementary data is available online at http://ndt.oxfordjournals.org.

Conflict of interest statement. None declared.

(See related article by Ficheux et al. The ultrafiltration coefficient of a dialyser (Kuf) is not a fixed value, and it follows a parabolic function: the new concept of Kuf max. Nephrol Dial Transplant 2011; 26: 636–640.)

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5. Ficheux A, Kerr PG, Brunet P et al. The ultrafiltration coefficient of a dialyser (Kuf) is not a fixed value; it follows a parabolic function: the new concept of Kuf max. Nephrol Dial Transplant 2011; 26: 636–640

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