DIALYZER DIFFUSIVE CLEARANCE OPTIMIZATION BY A NON-REGENERATED RECIRCULATING DIALYSATE SYSTEM

M. Prado*, L.M. Roa**

* Biomedical Engineering Group, University of Seville, Seville, Spain
** Biomedical Engineering Group, University of Seville, Seville, Spain

mpradovelasco@ieee.org, laura@esi.us.es

Abstract: This paper summarizes the major findings obtained by our group regarding a novel non-regenerated recirculating dialysate system (RDS) for improving the diffusive clearance in hollow-fiber dialyzers. The study presents firstly the mathematical foundation that gives the conditions under which RDS can be applied. The RDS is compared subsequently to three well-known two-chamber dialysis systems, showing that it can be a competitive technique for optimizing the dialysis efficiency when the diffusive mass-transfer of the dialyzer is exhausted. Simulation results show that the efficiency of the RDS increases by a factor of 5 to 8 with respect to the efficiency of the single dialyzer, when this one operates with a number of transfer units equal to 0.1. The RDS acts removing the bottleneck associated with the dialysate phase, in such a way that the dialyzer efficiency could even be controlled by the blood-membrane phases. This outcome could be exploited by using membranes with higher diffusive coefficients.

Introduction

Diffusion is the dominant mechanism in the clearance of small and medium molecular weight uremic solutes in patients with end state renal disease submitted to periodic hemodialysis. This fact together with the strong correlation between the dose of urea clearance delivered to a patient and the relative risk of mortality and morbidity, underlies the importance of keeping a proper diffusive efficiency in a dialysis system [1,2].

However, as the clearance dose recommended by the Kidney Dialysis Outlines Quality Initiative (K/DOQI) is proportional to body weight, large patients have a greater risk to be under-dialyzed than the others [3]. Increase the clearance by enlarging the membrane mass-transfer area, *A*, is limited by the associated reduction in diffusive mass-transfer coefficients [4]. This fact makes expensive and even insufficient the use of high-efficiency dialyzers. As an example, Dennison published a study-case that shows the insufficiency of high-efficiency dialyzers for achieving the required dialysis dose for a large patient [5].

The limitation of high efficiency dialyzers to achieve high enough dialysis doses in large patients pushed the research on arrangements of two dialyzers. The efficiency of this solution was happily shown in the cited case-study from Dennison, who really achieved the required dose by means of an in-series array of dialyzers [5]. However this solution is still costly and complex, and presents some drawbacks [6], as the undesirable backfiltration (dialysate flux directed to the blood compartment) and fiber clotting. We are committed to note that backfiltration can be used as a mechanism for on-line infusion of substitution fluid in hemodiafiltration, but this technique requires ultrapure dialysate and the analysis exceeds the scope of this paper.

Diffusive mass-transfer seems limited by the dialysate phase in modern dialyzers, in such a way that the product overall mass-transfer coefficient by the effective mass-transfer area, K_0A, grows with the dialysate flow rate, Q_d, but does not with the blood flow rate, Q_b, as many studies show [4,7-9].

This bottleneck could be reduced by increasing Q_d as necessary, but this solution is cost-prohibitive.

This paper first summarizes the major mathematical result that supports the way in which a new recirculating dialysate system (RDS) for optimizing the diffusive clearance of a dialyzer operates. This system is based on the increase of the total Q_d by means of recirculation. The mathematical statement presented is called theorem of applicability of the RDS [10].

The second part of this paper presents the outcomes of a digital simulation comparison study between the RDS and three two-chamber dialysis systems. The reliability of the mathematical models used in this work has been carefully justified in previous articles [10,11].

Materials and Methods

The following section presents a summary of the RDS physical foundation [10]. The subsequent Section states the necessary and sufficient conditions that must be fulfilled to guarantee the improvement of the diffusive clearance of a particular dialyzer by means of the RDS.

The mathematical theory has been applied to four types of commercial dialyzers (2 Cuprophan dialyzers from Gambro™, 2 polysulfone (PS) dialyzers from Fresenius™), for blood flow rates Q_b = 300, 500, and 800 ml/min. The last high value exceeds the maximum blood flow rate that can be extracted from a normal vascular access, however it allows showing the behaviour of the RDS around the intermediate value Q_b = 500 ml/min, and in addition it throws light regarding

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the combined use of the RDS with blood recirculating dialysis systems [11]. A more exhaustive description of this issue exceeds the scope of this paper. The overall mass-transfer resistances of these selected dialyzers were written as a function of Q_d, using in-vitro measurements published in [7,12]. All of them followed a linear law into the experimental range [10,11]. The mean squared error (MSE) of the linear regression was below 9.5 % in all of the cases.

The operating points of these dialyzers will be presented over the graphs resulting from the simulation experiments accomplished for comparing the RDS to the three two-chamber dialysis systems depicted in Fig. 1.

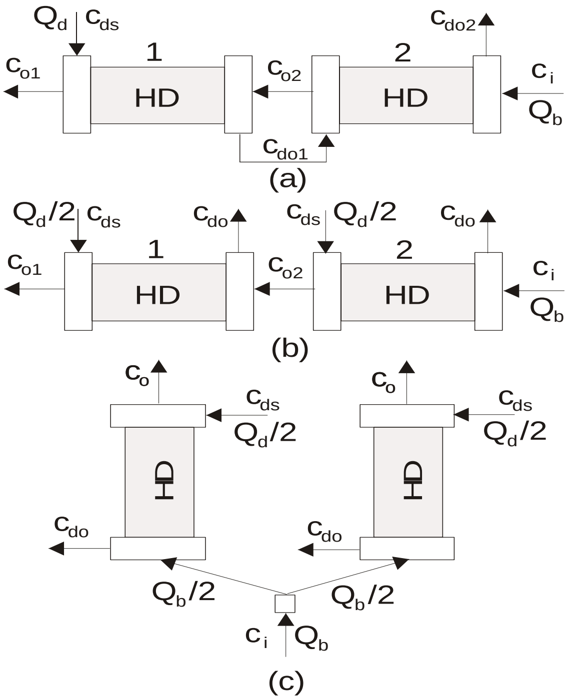

Figure 1: Iconic diagrams of in-series dialyzers arrangement (HDS) (a), in-series dialyzers arrangement with independent dialysate fluid circuits (BD) (b), and in-parallel dialyzers arrangement (HDP) (c).

Diagrams show blood and fresh dialysate flow rates, Q_b and Q_{ds}, respectively, as well as solute concentrations at blood and dialysate lines, c and c_d, respectively. Dialyzers are labelled as 1 and 2, according to their order in the dialysate pathway. Subscripts i refer to the dialyzer blood inlet, whereas s refers to the dialyzer fresh dialysate inlet. Subscripts o refer to blood and dialysate outlets of the dialyzer, and they are numbered according to the dialyzer number.

The comparative analysis between double-chamber systems and the RDS that we present here takes into account the dependence of their diffusive efficiencies upon four parameters [11]. These are the dimensionless parameters, NTU_b, $INTU_b$, and NTU_{bm}, which are defined in the following section, and the ratio between the operating flow rates, $R_s = Q_b/Q_{ds}$. The simulation experiment explores a wide range of dialyzers and operating conditions by means of these dimensionless parameters, which range the intervals [0.1, 3] and [-0.05, -2] for NTU_b and $INTU_b$, respectively. We considered the value of R_s that maximizes the efficiency of the RDS in each point (NTU_b, $INTU_b$, NTU_{bm}). The third value of this 3-tuple, NTU_{bm}, was fixed as 5 and 10, in each of the two simulation experiments performed.

The largest improvements in the efficiency provided by the evaluated dialysis systems with respect to the efficiency of the single dialyzer are presented in shaded contour graphics. The area in these graphics is divided in regions associated with the dialysis system that provides the highest efficiency.

Description of the RDS

This Section summarizes the theoretical foundation of the RDS. A more complete and comprehensive description can be seen in [10].

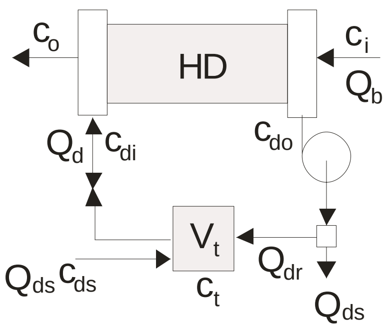

Figure 2: Iconic diagram of the RDS. The dialysate pump, well-stirred tank, and dialysate input resistance (clockwise) are represented by a circle, a rectangle, and two opposed arrows.

The variables follow the same nomenclature of Fig. 1. Q_{dr} is the recirculating dialysate flow rate and $Q_d = Q_{ds} + Q_{dr}$ is the total dialysate flow rate. Variables c_t and V_t are solute concentration and fluid volume of the well-stirred tank, where the fresh dialysate is added and mixed. The value of Vt is taken approximately equal to the dialyzer dialysate volume, guarantying the steady-state operation of the system [10].

We are interested in solutes with mass-transport across membrane mainly governed by diffusion and without membrane adsorption. Under these conditions, if the dialyzer operates in steady-state and the overall mass-transfer coefficient, K_0, is independent of the position along the hollow fiber streamline, the solute removal of the RDS can be formulated using the unidimensional theory of diffusive mass-transport [13], as:

$$\dot{m} = \varepsilon_d^{RDS} \cdot Q_{ds} \cdot \left(c_i - c_{ds} \right) = \varepsilon^{RDS} \cdot Q_b \cdot \left(c_i - c_{ds} \right), \quad (1)$$

where ε_d^{RDS} and ε^{RDS} are the dialysate- and blood-side diffusive efficiencies of the RDS, respectively.

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These ones can be written as [10]:

$$\varepsilon^{RDS} = \frac{1}{Q_b / Q_{ds} + \mathrm{EAD}(Q_d)} \qquad \varepsilon_d^{RDS} = \frac{Q_b}{Q_{ds}} \varepsilon^{RDS}, \qquad (2)$$

where the function EAD is given by:

$$\mathrm{EAD}(Q_d) = \frac{1 - Q_b / Q_d}{1 - e^{-\mathrm{NTU}(1 - Q_b / Q_d)}} \qquad (3)$$

The dimensionless number NTU(Q_d) is known as the number of transfer units of the dialyzer, and it is defined as NTU(Q_d) = $K_0A(Q_d)/Q_b$ [10]. Considering that the relationship between the effective overall diffusive mass-transfer resistance, R_t, and Q_d is linear, according to several experimental studies [4,7], the dimensionless number NTU may be formulated as [11]:

$$\frac{1}{\mathrm{NTU(Q_d)}} = \frac{1}{\mathrm{NTU}_b} + \mathrm{INTU}_b \cdot (\frac{Q_d}{Q_b} - 1) \geq \frac{1}{\mathrm{NTU}_{bm}}, \quad (4)$$

where the dimensionless groups $\mathrm{NTU_b}$, $\mathrm{INTU_b}$, and $\mathrm{NTU_{bm}}$ do not depend on $\mathrm{Q_d}$, as shown their definition equations:

$$\mathrm{NTU}_b = \frac{A}{Q_b R_{tb}} \qquad \mathrm{INTU}_b = \frac{R'_t Q_b^2}{A} \qquad \mathrm{NTU}_{bm} = \frac{A}{Q_b R_{tbm}} \qquad (5)$$

The variable R_{tb} is the overall mass-transfer resistance at $Q_d = Q_b$, and R_{tbm} is the effective resistance of blood-membrane phases. From (5) is clear that NTU grows with Q_d, it has an upper limit in $\mathrm{NTU_{bm}}$, and satisfies $\mathrm{NTU(Q_d = Q_b) = NTU_{bm}}$.

Applicability of the RDS

Given a countercurrent dialyzer operating with a blood flow rate Q_b, and overall diffusive mass-transfer resistance R_t, linearly related to Q_d, the maximum diffusive efficiency of the RDS will be higher than the diffusive efficiency of the associated single dialyzer, if and only if the following conditions are verified [10]:

1. Regarding the NTU-derived parameters.

a. $\mathrm{INTU_b}$ is negative.

b. $\mathrm{NTU_b}$ is lower than $\mathrm{F_b(INTU_b)}$, which is equal to:

$$F_b(\mathrm{INTU}_b) = \begin{cases} \infty & \text{if} \quad \mathrm{INTU}_b \leq -\frac{1}{2} \\ P(\mathrm{INTU}_b) & \text{if} \quad -\frac{1}{2} \leq \mathrm{INTU}_b \leq 0, \end{cases} \qquad (6)$$

where a least squares fitting-based analytical formula for $P(INTU_b)$ is (MSE < 1 %):

$$P(\mathrm{INTU}_b) = 1.43 - \frac{0.0162}{\mathrm{INTU}_b} + \frac{0.0470}{\mathrm{INTU}_b + 0.5} + 3.68 \cdot \mathrm{INTU}_b^{\,2} \qquad (7)$$

c. The fulfilment of conditions (a) and (b) guarantees that the RDS will present an unique couple of non-null values of dialysate flow rates where its efficiency reaches a minimum and maximum, Q_{d1} and Q_{d2}, respectively, provided that R_{tbm} = 0. However, in general R_{tbm} is not cero, and the existence and uniqueness of the two local extremes are kept if $Q_{d1} < Q_{dbm}$, where Q_{dbm} is given as the solution of $R_t(Q_{dbm})=R_{tbm}$.

If the three previous conditions are met, the RDS will provide the maximum efficiency for the following total dialysate flow rate, Q_d*:

$$Q_d^* = \min(Q_{d2}, Q_{dbm}) \qquad (8)$$

2. Regarding the fresh-dialysate flow rate.

The maximum available dialysate flow rate, Q_{ds}, must verify $Q_d^{**} < Q_{ds} < Q_d^*$, where Q_d^{**} is the unique solution of $\varepsilon^{RDS}(Q_d^*) = \varepsilon^{RDS}(Q_d^{**})$.

Results and discussion

The blood-side diffusive efficiencies of all the studied dialysis systems, built upon the Gambro™ GFE 9 and GFE 15, and the Fresenius™ F5 and F8, are shown in Table 1. We used the values of $\mathrm{Q_{ds}}$ that maximize the improvement of the efficiency given by the RDS. The efficiency of the RDS is presented together with the total dialysate flow rate $Q_d = Q_{ds} + Q_{dr}$, which was taken equal to optimal value, Q_d*, as described in the previous Section. A previous work proved the possibility to select Q_{ds} and Q_{dr} in an independent manner [10].

The average increments of BD and HDP systems were 21.2 % and 24.4 %. These values are slightly higher that the average increments of 15 % obtained in a recent in-vivo study [14], in agreement with the higher mass-transfer resistance of the blood phase under in-vivo conditions. The HDS obtained the highest increment of efficiency in all of the cases, whereas the RDS accomplished similar values that the HDS for medium and high Q_b, that is, when the diffusive capacity of the dialyzer is exhausting.

The operating points associated with rows in Table 1 have been added to Fig. 3, which presents the outcomes of the simulation experiment previously described.

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Table 1: Blood-side efficiencies of the dialysis systems assessed, ε^{RDS}, ε^{HDS}, ε^{BD}, and ε^{HDP}, as well as the blood side efficiency of the single dialyzer, ε. The first two columns show the operating flow rates. The percentage of increment of the efficiency with respect to that of the single dialyzer is presented between brackets. Flow rates are in ml/min.

Dialyzer	Q_b	Q_{ds}	NTU_{bm}	[Q_d, ε^{RDS}]	ε^{HDS}	ε^{BD}	ε^{HDP}	ε
GFE 15	800	1294	1.25	[2500, 0.55 (11)]	0.70 (41)	0.64 (28)	0.66 (32)	0.50
GFE 15	500	1371	2.00	[2500, 0.73 (6)]	0.88 (28)	0.82 (19)	0.84 (22)	0.69
GFE 15	300	1696	3.33	[2500, 0.90 (1)]	0.99 (10)	0.96 (8)	0.97 (8)	0.89
GFE 9	800	1753	0.75	[4250, 0.45 (13)]	0.61 (53)	0.57 (44)	0.58 (46)	0.40
GFE 9	500	1810	1.20	[4250, 0.61 (10)]	0.79 (41)	0.75 (34)	0.76 (36)	0.56
GFE 9	300	1979	2.00	[4250, 0.80 (5)]	0.94 (23)	0.91 (20)	0.92 (21)	0.76
F 8	800	662	2.25	[1280, 0.54 (30)]	0.56 (37)	0.48 (16)	0.50 (21)	0.41
F 8	500	643	3.60	[1280, 0.68 (19)]	0.76 (32)	0.65 (14)	0.68 (19)	0.58
F 8	300	669	6.00	[1212, 0.82 (4)]	0.94 (19)	0.85 (8)	0.88 (12)	0.79
F 5	800	637	1.25	[1320, 0.44 (33)]	0.48 (45)	0.42 (26)	0.43 (30)	0.33
F 5	500	626	2.00	[1320, 0.60 (25)]	0.67 (40)	0.58 (22)	0.60 (26)	0.48
F 5	300	626	3.33	[1320, 0.76 (13)]	0.86 (28)	0.78 (16)	0.81 (20)	0.67

In accord with the behavior observed in Table 1, the zone where the RDS outperforms the other dialysis systems grows with NTU_{bm}. The simulation experiment has been limited to the operating region where RDS is applicable, which explains why diagrams are bounded by the function $F_b(INTU_b)$.

As shown in that figure, the increments of the efficiency reach values between 560 % and 825 %, approximately. These increments are sensitive enough to NTU_b, as indicates the density of isolines in this operating region.

Considering that the boundary between RDS and HDS zones moves to the left bottom corner when NTU_{bm} goes down from 5 (it is indicated in the right diagram of Fig. 3) nearly all the operating points associated with Table 1 would be really placed in the HDS zone, due to their NTU_{bm} values (see Table 1). The points associated with the same dialyzer are connected by a directed line, which defines the operating trajectory of the dialysis system when Q_b grows. All these trajectories move forward the RDS zone. Accordingly, the increment of efficiency of the RDS grows with Q_b for any particular dialyzer.

Summarizing, the RDS surpassed the remaining techniques for operating conditions characterized by a low value of the *diffusive mass-transfer area / blood flow rate ratio*. The increments of diffusive clearances were above 100 % in a significant zone of the operating domain. These outcomes suggest that RDS could be considered a good cost-efficiency technique for optimizing the diffusive clearance of present low-flux dialyzers.

Moreover, in-vitro experiments performed on high-efficiency (HE), high-flux (HF), and even blood recirculating systems (BR), indicate that their functional domains tend to move inside the RDS region, as shown in Fig. 4. These movements are joined to an increase of the increment of the efficiency provided by the RDS [11].

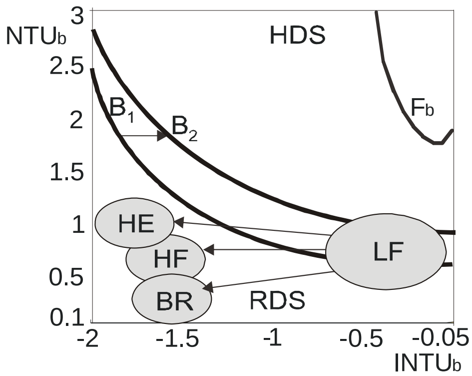

Figure 4: Sketch of the operating region divided in HDS and RDS zones. It presents the operating region related to the low-flux dialyzers (LF), high-flux dialyzers (HF), high-efficiency dialyzers (HE), and blood-recirculating dialysis systems (BR). The boundary between zones moves to the right (B_1 to B_2) when NTU_{bm} grows.

Conclusion

The RDS is a technique for optimizing the diffusive clearance of a dialyzer based on the hypothesis that the efficiency will be mainly controlled by the dialysate phase. This assumption has been widely verified for dialyzers currently used in hemodialysis.

The present paper has presented a summary of the major outcomes regarding the RDS obtained by our group. The reliability of the methodological approach followed in this study is founded on the accuracy of the unidimensional theory of diffusive mass-transport for dialyzers working in-vitro with diffusion as dominant mechanism.

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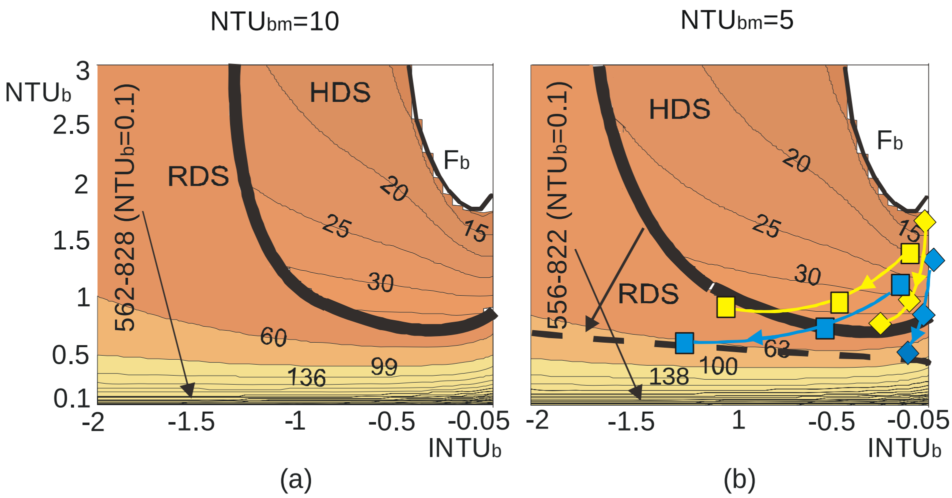

Figure 3: Shaded contour graphics showing the percentage increment of the blood side efficiency (upon isolines) accomplished by the best optimization technique among HDS, HDP, BD and RDS, at the operating point (NTU_b, $INTU_b$, NTU_{bm}, $R_s = Q_b = Q_{ds}$), for the optimal R_s, when $NTU_{bm} = 10$ (a) and 5 (b). The operating region is divided in two zones associated with the best efficiency method (thick black line). Diagram (b) indicates the movement of this boundary line when NTU_{bm} decreases from 5 (dashed line), as discussed in text. The operating points of commercial dialyzers from Table 1 are shown in (b) by yellow rhombus marks (GFE 15), blue rhombus marks (GFE 9), yellow square marks (F 8), and blue square marks (F5). Directed lines connect each group of marks, showing the evolution of the operating point when Q_b grows.

The outcomes show that the RDS is the best dialysis system for low values of NTU_b, that is, when dialyzers operate under exhaustion conditions.

Although low-flux dialyzers do not take advantage of the full potential of the RDS, in-vitro experiments over HF, HE and BR dialysis systems suggest that the diffusive clearance of these ones could be better maximized by this novel technique.

We are currently developing a prototype of this system, in parallel with the generalization of the problem to consider a multi-solute optimization system, as well as the inclusion of ultrafiltration and adsorption mechanisms, with the aim of combining the RDS with other dialysis therapies.

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