Impact of pre-dilution and flushing on continuous renal replacement therapy

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ABSTRACT

Introduction: Infusing the replacement solution before the filter (pre-dilution) and regular flushing have not been accounted for in conventional mathematical equations. Their effects on various continuous renal replacement therapy (CRRT) parameters, such as ultrafiltration fraction and urea clearance, have not been well studied. We incorporated these parameters into mathematical equations to help in understanding and prescribing CRRT.

Methods: We built a mathematical model to evaluate the plasma flow rate, filter fluid inflow rate with pre- and post-dilution and ultrafiltration rate, plasma clearance of urea, and ultrafiltration fraction.

Results: In pre-dilutional therapy, the volume of replacement needed to be increased in order to achieve the target plasma clearance rate. The extra volume needed increased exponentially with higher target plasma clearance rate. The higher the targeted plasma clearance in relation to blood flow rate (Qb), the greater the increase. Increasing blood flow rate reduced the ultrafiltration fraction for both pre- and post-dilution therapy. It had no effect on plasma clearance with post-dilution therapy but significantly improved the clearance in pre-dilution therapy. Higher haematocrit resulted in higher ultrafiltration fraction in both pre- and post-dilution therapy. Higher haematocrit had no effect on plasma clearance with post-dilution therapy but slightly reduced clearance in pre-dilution therapy. For a given total volume of ultrafiltration, flushing reduced plasma clearance with both pre- and post-dilution therapy. Flushing slightly reduced ultrafiltration fraction of post-dilution therapy but minimally increased the ultrafiltration fraction of pre-dilution therapy. This mathematical model could be utilised in prescribing Qb and replacement rate based on targeted plasma clearance, ultrafiltration fraction, fluid removal rate and haematocrit. There was close approximation of predicted and measured urea plasma clearance.

Conclusion: Pre-dilution therapy reduced urea clearance significantly and this needed to be compensated for by increasing the volume of ultrafiltration or Qb. Flushing was of limited benefit and may reduce urea clearance. In prescribing haemofiltration, Qb and replacement rate could be determined with this model.

Keywords: continuous renal replacement therapy, flushing, haemofiltration, mathematical modelling, pre-dilution haemofiltration, ultrafiltration fraction

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INTRODUCTION

Filter clotting can be a major problem with continuous renal replacement therapy (CRRT), especially when heparin is not used, for example, in patients with disseminated intravascular coagulation (DIVC) or active bleeding. In continuous veno-venous haemofiltration (CVVH), replacement solution may be infused before the filter, i.e. pre-dilution, or after the filter, i.e. post-dilution. Flushing may also be done by infusing a set volume of fluid rapidly at regular intervals before the filter. Pre-dilution and regular flushing have been widely used locally to prevent filter clotting in CRRT. However, these are not accounted for in conventional mathematical equations, and their effect on various CRRT parameters such as ultrafiltration fraction and urea clearance is not well studied. We aimed to incorporate these into mathematical equations to help us understand and prescribe CRRT better.

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Table I. Comparison of pre- and post-dilution replacement rate for same plasma clearance with Qb=150 ml/min.

Supply haematocrit (%)	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0
Blood pump (ml/min)	150.0	150.0	150.0	150.0	150.0	150.0	150.0	150.0
Replacement rate – pre-dilution (ml/hour)		1,190.0		2,930.0		5,730.0		10,960.0
Replacement rate – post-dilution (ml/hour)	1,000.0		2,000.0		3,000.0		4,000.0	
Fluid removal rate (ml/hour)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Output: predicted								
Ultrafiltration fraction (%)	15.9	15.9	31.7	31.7	47.6	47.6	63.5	63.5
Plasma clearance (ml/hour)	1,000.0	1,000.9	2,000.0	1,999.9	3,000.0	3,000.7	4,000.0	4,000.5

Table II. Effect of Qb on ultrafiltration fraction and plasma clearance.

Supply haematocrit (%)	30.0	30.0	30.0	30.0
Blood pump (ml/min)	150.0	200.0	150.0	200.0
Replacement rate – pre-dilution (ml/hour)			1,000.0	1,000.0
Replacement rate – post-dilution (ml/hour)	1,000.0	1,000.0		
Fluid removal rate (ml/hour)	0.0	0.0	0.0	0.0
Output: predicted				
Ultrafiltration fraction (%)	15.9	11.9	13.7	10.6
Plasma clearance (ml/hour)	1,000.0	1,000.0	863.0	893.6

METHODS

Formulae were developed (Appendix A) for the following:

1. Plasma flow rate (PFR)
2. Filter fluid inflow rate (FFIR)
3. Fluid removal rate (FRR)
4. Ultrafiltration rate (UF)
5. Plasma clearance (PC)
6. Ultrafiltration fraction (UFF)

In CVVH, the solute flux or clearance (C) across the membrane is the product of the ultrafiltration rate (UF) and the ratio between the concentration of the solute in the ultrafiltrate and in plasma water, i.e. the solute's sieving coefficient (S). $C = UF \times S$. S is equal or close to 1 for urea. Hence, for post-dilution therapy, the urea clearance equals the ultrafiltration rate.

The derivation of replacement rate in pre-dilution and post-dilution therapy with calculation based on targeted plasma clearance and fluid removal rate is shown in Appendix B. The derivation of r, ratio of post- versus pre-dilution rate to achieve the same targeted plasma clearance rate is explained in Appendix C. Both appendices D and E serve to assist in haemofiltration prescription, based on targeted plasma clearance, ultrafiltration fraction, and fluid removal rate. The derivation of calculated plasma flow rate from targeted plasma clearance and ultrafiltration fraction is demonstrated in Appendix D. The derivation of pre-dilution replacement rate based on targeted plasma clearance, ultrafiltration fraction and fluid removal rate are shown in Appendix E. The effect of flushing on plasma clearance and ultrafiltration fraction in mathematical model is shown in Appendix F.

The Microsoft Excel programme was used to calculate the ultrafiltration fraction and urea clearance, based on various CRRT prescriptions. Different scenarios could be tested with the programme to understand the impact of blood flow rate, haematocrit (HCT), pre- and post-dilution, and flushing on ultrafiltration fraction and clearance. For a given clinical scenario, various prescriptions could be tested and adjusted to try to achieve certain targets e.g. ultrafiltration fraction of less than 20% and urea clearance of more than 35 ml/kg/hour. Eventually, a mathematical model was built to calculate the required blood flow rate (Qb) and replacement rate in order to achieve targeted plasma clearance, ultrafiltration fraction and fluid removal rate. We evaluated the predicted and measured urea clearance in the intensive care unit patients.

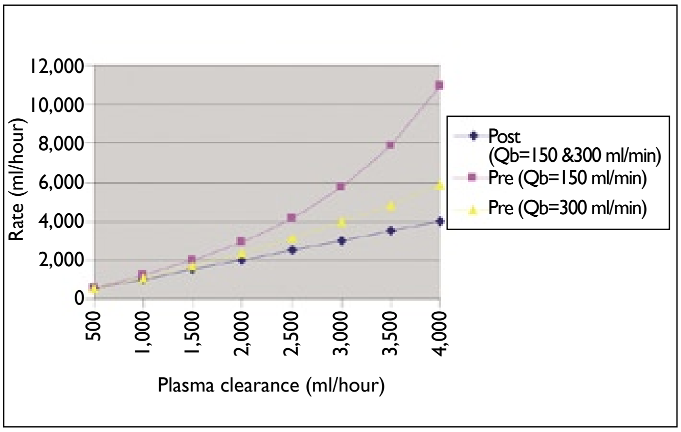

Fig. 1 Pre- versus post-dilution replacement at various plasma clearance values (with HCT = 30% FRR = 0).

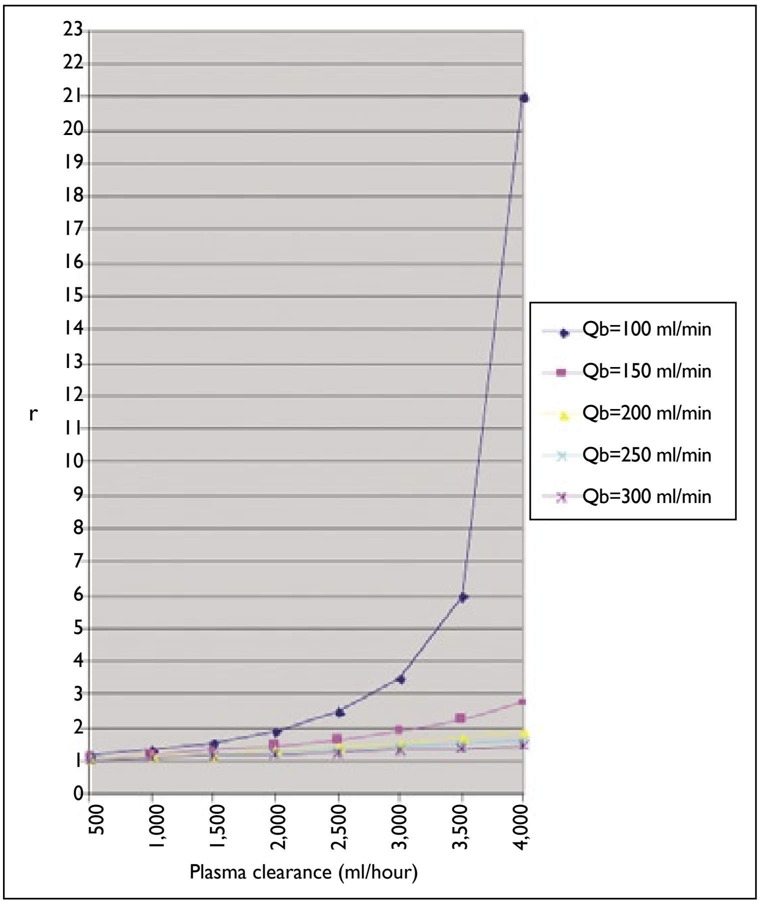

Fig. 2 Ratio (r) of pre- versus post-dilution replacement rate at various plasma clearance values with various Qb rates.

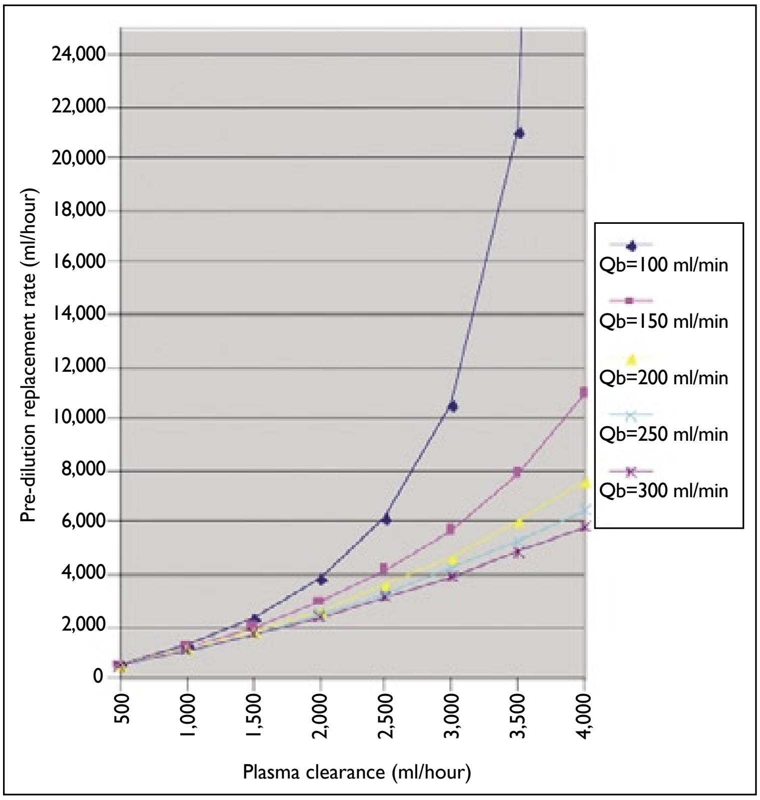

Fig. 3 Pre-dilution replacement rate based on Qb with HCT = 30% and fluid removal rate (FRR) = 0.

RESULTS

We first evaluated the effect of pre- and post-dilution on ultrafiltration volume needed to achieve targeted plasma clearance with this invented software. In comparing the pre- and post-dilution replacement rate needed to achieve same plasma clearance of urea, a higher pre-dilution replacement rate was needed to achieve the same plasma clearance of urea as shown in the mathematical modelling (Appendix C) and the illustrations (Fig. 1 and Table I). Thus, the higher the targeted plasma clearance, the equivalent pre-dilution replacement rate had to be increased exponentially to achieve the same targeted plasma clearance.

As shown in Formula 6 of Appendix A, increasing blood flow rate reduced the ultrafiltration fraction for both pre- and post-dilution. As shown in Formula 5 of Appendix A, increasing blood flow rate significantly improved the plasma clearance in pre-dilution therapy because of the higher ratio of actual plasma flow rate to filter fluid inflow rate (PFR/FFIR) approaching 1. This was essential for large-sized patients with need of high plasma clearance rate. Increasing blood flow rate had no effect on plasma clearance with post-dilution therapy (PFR/FFIR = 1) (Table II).

Thus, the ratio (r) of pre- and post-dilution replacement rate was reduced with increasing plasma flow rate (Figs. 1 & 2, and comparing Tables I & III). The higher the plasma flow rate, the closer r was to 1 (Fig. 2). The calculated pre-dilution replacement rate based on Formula 10 of Appendix B is shown in Fig. 3. The pre-dilution replacement rate rose exponentially with increasing plasma clearance. This exponential rise was lesser with increasing blood flow rate.

Table III. Comparison of pre- and post-dilution replacement rate for same plasma clearance with Qb=300 ml/min.

Supply haematocrit (%)	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0
Blood pump (ml/min)	300.0	300.0	300.0	300.0	300.0	300.0	300.0	300.0
Replacement rate – pre-dilution (ml/hour)		1,090.0		2,380.0		3,940.0		5,860.0
Replacement rate – post-dilution (ml/hour)	1,000.0		2,000.0		3,000.0		4,000.0	
Fluid removal rate (ml/hour)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Output: predicted								
Ultrafiltration fraction (%)	15.9	15.9	31.7	31.7	47.6	47.6	63.5	63.5
Plasma clearance (ml/hour)	1,000.0	1,000.9	2,000.0	1,999.9	3,000.0	3,000.7	4,000.0	4,000.5

Table IV. Comparison of pre- and post-dilution replacement rate for same plasma clearance with fluid removal rate of 100 ml/hour.

Supply haematocrit (%)	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0
Blood pump (ml/min)	150.0	150.0	150.0	150.0	150.0	150.0	150.0	150.0
Replacement rate – pre-dilution (ml/hour)		1,070.0		2,780.0		5,540.0		10,680.0
Replacement rate – post-dilution (ml/hour)	900.0		1,900.0		2,900.0		3,900.0	
Fluid removal rate (ml/hour)	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Output: predicted								
Ultrafiltration fraction (%)	15.9	15.9	31.7	31.7	47.6	47.6	63.5	63.5
Plasma clearance (ml/hour)	1,000.0	1,000.1	2,000.0	1,998.2	3,000.0	3,001.0	4,000.0	3,999.6

Both the calculated pre- and post-dilution replacement rate requirement altered with changes in fluid removal rate, although the ratio of pre- versus post-dilution replacement rate was the same (Formulae 10 & 13 of Appendix B and Table IV). Thus, in pre-dilutional therapy, the effect of fluid removal rate on reducing required replacement fluid was little in low plasma clearance, but increased to considerable amount in high plasma clearance. The ultrafiltration fraction for both the pre- and post-dilution replacement therapy were equal for the same plasma clearance and same plasma flow rate in the above scenarios, as a result of relationship described in Formula 6 of Appendix A.

Higher haematocrit resulted in higher ultrafiltration fraction in both pre- and post-dilution therapy, as shown in Formula 6 of Appendix A. Higher haematocrit had no effect on plasma clearance with post-dilution therapy, as PFR/FFIR was constantly 1. Nevertheless, in pre-dilution therapy, a higher haematocrit reduced the ratio of PFR/FFIR, and thus reduced clearance in pre-dilution therapy. The reduction, however, was small (Table V).

There were interesting findings regarding the effect of flushing. Flushing reduced the actual plasma flow rate, as the supply was channelled to flushing fluid. During the conventional method of flushing, we needed to switch the blood supply to flushing fluid. We also needed to remove all flushing fluid with equal amount of fluid removal rate. For a given total volume of ultrafiltration (Appendix F), flushing reduced plasma clearance with both pre- and post-dilution therapy. For post-dilution therapy, flushing reduced the ultrafiltration fraction but the reduction was very small. For pre-dilution therapy, flushing may actually increase the ultrafiltration fraction, because of the increasing ultrafiltration rate contributed by the increasing fluid removal rate to remove flushing fluid. However, the effect was again very small (Table VI).

We next applied different scenarios to understand the influence of choice of therapy, weight and haematocrit. The need of increasing replacement rate to achieve the targeted plasma clearance and subsequently increasing the blood pump in order to decrease the ultrafiltration fraction is shown in Table VII. As a continuation from Table VII, higher replacement rate and blood pump were needed in heavier patients (Table VIII). On the other hand, patients with a higher haematocrit needed a higher blood pump in order to decrease the ultrafiltration fraction (Table IX). Besides, higher blood pump improved the plasma clearance in pre-dilutional therapy.

It was essential to verify the above formulae with comparison of predicted and measured urea clearance

Table V. Effect of haematocrit on plasma clearance and ultrafiltration fraction.

Supply haematocrit (%)	20.0	30.0	20.0	30.0
Blood pump (ml/min)	150.0	150.0	150.0	150.0
Replacement rate – pre-dilution (ml/hour)			1,000.0	1,000.0
Replacement rate – post-dilution (ml/hour)	1,000.0	1,000.0		
Fluid removal rate (ml/hour)	0.0	0.0	0.0	0.0
Output: predicted				
Ultrafiltration fraction (%)	13.9	15.9	12.2	13.7
Plasma clearance (ml/hour)	1,000.0	1,000.0	878.0	863.0

Table VI. Impact of flushing on plasma clearance and ultrafiltration fraction.

Supply haematocrit (%)	30.0	30.0	30.0	30.0
Blood pump (ml/min)	150.0	150.0	150.0	150.0
Replacement rate – pre-dilution (ml/hour)			1000.0	900.0
Replacement rate – post-dilution (ml/hour)	1,000.0	900.0		
Flushing rate (ml/hour)		100.0		100.0
Fluid removal rate (ml/hour)		100.0		100.0
Output: predicted				
Fluid extraction rate (minus flushing) (ml/hour)	0.0	0.0	0.0	0.0
Ultrafiltration fraction (%)	15.9	15.8	13.7	13.8
Plasma clearance (ml/hour)	1,000.0	984.2	863.0	861.7

Table VII. Increasing replacement and Qb to achieve the targeted plasma clearance and ultrafiltration fraction.

Input	Post- vs pre-		Increase replacement		Increase Qb		
Weight (kg)	50	50	50	50	50	50	50
Supply haematocrit (%)	30	30	35	35	30	30	30
Blood pump (ml/min)	180	180	180	180	240	240	240
Pre-dilution (ml/hour)	0	1,000	0	2,100	0	0	2,100
Post-dilution (ml/hour)	1,000	0	2,100	0	2,100	1,700	0
Fluid removal rate (ml/hour)	100	100	100	100	100	100	100
Output: predicted							
Predicted venous haematocrit	30.3	30.3	35.3	35.3	30.2	30.2	30.2
Ultrafiltration fraction (%)	14.6	12.9	31.3	24.1	21.8	17.9	18.1
Plasma clearance (PC) (ml/hour)	1,100.0	971.5	2,200.0	1,693.4	2,200.0	1,800.0	1,820.7
PC/weight per hour (ml/hour/kg)	22.0	19.4	44.0	33.9	44.0	36.0	36.4
Aim achieved (PC/Wt >35 ml/kg, clot if UFF <20%)	PC/Wt low	PC/Wt low	PCok, clot	PC/Wt low	PCok, clot	Achieved	Achieved

of CRRT in the intensive care unit setting. The above formulae were evaluated in the intensive care unit of the Sarawak General Hospital, Kuching, Malaysia, and close approximation was found between the predicted and measured urea clearance of CVVH (Table X). Eventually, we invented formulae to help in prescribing replacement rate and blood pump rate, based on targeted plasma clearance and fluid removal rate. With Formula 15 from Appendix D, we could derive the plasma flow rate. For post-dilution replacement therapy, with the Formula 13 of Appendix B, we could derive the required replacement rate for given targeted plasma clearance and fluid removal rate. While for pre-dilution replacement

Table VIII. Increasing blood pump and replacement in heavier patients.

Parameter Input	Higher weight		Higher Qb & replacement	
Weight (kg)	60	60	60	60
Supply haematocrit (%)	30	30	30	30
Blood pump (ml/min)	240	240	270	270
Pre-dilution (ml/hour)	0	2,100	0	2,500
Post-dilution (ml/hour)	1,700	0	2,000	0
Fluid removal rate (ml/hour)	100	100	100	100
Output: predicted				
Predicted venous haematocrit	30.2	30.2	30.2	30.2
Ultrafiltration fraction (%)	17.9	18.1	18.5	18.8
Plasma clearance (PC) (ml/hour)	1,800.0	1,820.7	2,100.0	2,130.3
PC/weight per hour (ml/hour/kg)	30.0	20.3	35.0	35.5
Aim achieved (PC/Wt >35 ml/kg, clot if UFF <20%)	PC/Wt low	PC/Wt low	Achieved	Achieved

therapy, with the Formula 16 from Appendix E, we could derive the required replacement rate.

Illustrative example

The following is an example of how these formulae could be utilised in the clinical scenario.

A 50 kg patient with haematocrit of 25% was admitted with acute renal failure. Post-dilution replacement with fluid removal rate of 100 ml/hour, targeted plasma clearance of 35 ml/kg and ultrafiltration fraction of 15% was planned.

Targeted plasma clearance is 1,750 ml/hour.

From Formula 13 of Appendix B, post-dilution replacement is calculated as 1,650 ml/hour.

From Formula 15 of Appendix D, plasma flow rate is calculated as 194 ml/min.

Thus, as from Formula 1 of Appendix A, Qb is $194/(1 - 0.25) = 260$ ml/min.

To find out the replacement rate required in pre-dilution therapy in the above example:

From Formula 16 of Appendix E, pre-dilution replacement is $(1{,}750 - 100)/(1 - 0.15) = 1{,}941$ ml/hour.

To find out the replacement rate required in combined pre- and post-dilution replacement therapy with equal plasma clearance contributed by both dilution:

To halve the plasma clearance of post-dilution replacement: $1{,}650/2 = 825$ ml/hour.

From Formula 9.1 of Appendix B, pre-dilution replacement is 971 ml/hour.

The above flow rate can be adjusted to the closest available flow rate in the CRRT machine.

DISCUSSION

Continuous haemofiltration[1] with convective solute loss has been utilised to improve the outcome of acute renal failure patients. CVVH has been shown to have better survival outcome in comparison to arterio-venous access, probably due to the more predictable blood flow[2]. Ronco et al[3] demonstrated the need of increasing ultrafiltration rate beyond at least 35 ml/hour/kg for post-dilution replacement therapy. Pre-dilutional therapy has less risk of filter clotting but reduces the clearance significantly[4]. Constant effluent over plasma urea level has been observed in a previous study[5]. However, it would be essential to solve the issue of pre-dilution with a mathematical model and to quantify its effect on plasma clearance and ultrafiltration fraction[5-8].

Our model demonstrated the need for adjusting pre-dilution replacement rate in consideration of targeted plasma clearance. This was because pre-dilution was not as volume-effective as post-dilution therapy in achieving the same target plasma clearance in terms of replacement volume rate. The filtered fluid was a mixture of plasma and replacement fluid in pre-dilution therapy, whereas in post-dilution, only the plasma was filtered. The effect of mixing became more obvious when we increased the target plasma clearance. Thus, in predilutional therapy, the volume of replacement needed to be increased exponentially, in order to achieve the same targeted plasma clearance rate of equivalent post-dilution replacement rate.

Increasing the blood flow rate reduced the ultrafiltration fraction for both pre- and post-dilution, and significantly improved the clearance in pre-dilution therapy, especially in large-sized patients with high target plasma clearance. On the other hand, increasing the blood flow rate had no effect on plasma clearance with post-dilution therapy. Fluid removal rate also affected the required replacement rate, as demonstrated

Table IX. Higher Qb for high haematocrit.

Input	High haematocrit		Increase Qb	
Weight (kg)	60	60	60	60
Supply haematocrit (%)	40	40	40	40
Blood pump (ml/min)	270	270	300	300
Pre-dilution (ml/hour)	0	2,500	0	2,500
Post-dilution (ml/hour)	2,000	0	2,000	0
Fluid removal rate (ml/hour)	100	100	100	100
Output: predicted				
Predicted venous haematocrit	40.2	40.2	40.2	40.2
Ultrafiltration fraction (%)	21.6	21.3	19.4	19.5
Plasma clearance (PC) (ml/hour)	2,100.0	2,068.1	2,100.0	2,111.3
PC/weight per hour (ml/hour/kg)	35.0	34.5	35.0	35.2
Aim achieved (PC/Wt >35 ml/kg, clot if UFF <20%)	PCok, clot	PC/Wt low	Achieved	Achieved

Table X. The predicted and measured urea clearance of continuous renal replacement therapy.

Case no.	Qb (ml/min)	HCT (%)	Pre-replacement rate (ml/hour)	Post-replacement rate (ml/hour)	FRR (ml/hour)	Predicted plasma clearance (ml/hour)	Urea clearance measurements Quf.E/P * (ml/hour)	Modified Fick's Principle ** (ml/hour)
1.	125	30.8	400	0	0	371.4	389.7	460.3
2.	150	25.7	0	1,400	80	1,480.0	1,315.6	
3.	100	30.9	1,500	100	0	1,174.9		1,122.6

* Quf: ultrafiltration rate; E: effluent urea level; P: plasma urea level.

** Modified formula of Fick's principle is documented in Appendix G.

in the mathematical model, although the ratio of pre- versus post-dilution replacement rate was the same. The effect of fluid removal rate on reducing required replacement fluid became greater with higher plasma clearance. Higher haematocrit resulted in a higher ultrafiltration fraction in both pre- and post-dilution therapy. Higher blood pump could then be utilised to decrease the ultrafiltration fraction. A higher HCT could also reduce clearance in pre-dilution therapy.

Understanding that plasma clearance is the product of ultrafiltration fraction times Qb/FFIR is of utmost importance. We have shown that plasma flow rate and replacement rate should be adjusted according to the goal setting of plasma clearance, while maintaining a good level of ultrafiltration fraction (Tables VII-IX). Flushing the system at least once per hour with 100 ml of saline appears to reduce system clotting[9,10]. In our mathematical model, flushing reduced the plasma clearance with both pre- and post-dilution therapy. For post-dilution therapy, flushing reduced ultrafiltration fraction but the reduction was very small. For pre-dilution therapy, flushing may actually increase the ultrafiltration fraction, although the effect was again very small. Thus, mathematically, flushing had little effect in improving haemofiltration circuit longevity.

In prescribing haemofiltration for both pre- and post-dilution replacement therapy, Qb could be determined by the targeted plasma rate, ultrafiltration fraction and HCT, as shown in Formula 15 from Appendix D. In post-dilution replacement therapy, the replacement rate could be determined by targeted plasma clearance and fluid removal rate in post-dilution replacement rate, as shown in Formula 13 from Appendix B. On the other hand, in pre-dilution replacement therapy, replacement rate could be determined by targeted plasma clearance, fluid removal rate and ultrafiltration fraction, as shown in Formula 16 from Appendix E. In prescribing combination therapy of pre- and post-dilution, replacement rate can be calculated with formulae from appendix B to achieve targeted plasma clearance.

We incorporated all these formulae into a software programme, which enabled us to prescribe appropriate replacement therapy for targeted plasma clearance per body weight, ultrafiltration fraction and fluid removal rate, according to body weight and HCT of the patient. We have re-evaluated these formulae and found close approximation between the predicted and measured urea plasma clearance. Lastly, the above formulae could be adjusted with 93% of plasma flow rate, or according to the plasma protein level[11]. Nevertheless, the trend of predicted plasma clearance of urea will not vary much from our results.

In conclusion, pre-dilution therapy can reduce urea clearance significantly, and this needs to be compensated for by increasing the volume of ultrafiltration or increasing the blood flow rate. Flushing is of limited benefit and may reduce urea clearance. Blood flow rate and replacement rate can be determined with above mathematical model to achieve the targeted plasma clearance and ultrafiltration fraction.

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Appendix A

Plasma flow rate, PFR (ml/hour) = [Qb (ml/min) × 60 – FLUSH (ml/hour)] × (1 – HCT)

or

$$\text{PFR (ml/min)} = (\text{Qb} - \text{FLUSH}/60) \times (1 - \text{HCT}) \qquad \text{(Formula 1)}$$

where Qb is defined as blood pump rate,
HCT is defined as haematocrit, and
FLUSH is defined as flushing rate.

$$\text{Filter fluid inflow rate, FFIR} = \text{PFR} + \text{FLUSH} + \text{PRE} \qquad \text{(Formula 2)}$$

where PRE is defined as pre-dilution replacement rate.

$$\text{Fluid removal rate, FRR} = \text{FLUSH} + \text{Fluid extraction rate} \qquad \text{(Formula 3)}$$

$$\text{Ultrafiltration rate, UF} = \text{PRE} + \text{POST} + \text{FRR} \qquad \text{(Formula 4)}$$

where PRE is defined as pre-dilution replacement rate, and
POST is defined as post-dilution replacement rate.

$$\text{Plasma clearance, PC (ml/hour)} = \text{UF} \times \frac{\text{PFR}}{\text{FFIR}} \qquad \text{(Formula 5)}$$

$$\text{Note : PC} = (\text{PRE} + \text{POST} + \text{FRR}) \times \frac{(\text{Qb} \times 60 - \text{FLUSH}) \times (1 - \text{HCT})}{(\text{Qb} \times 60 - \text{FLUSH}) \times (1 - \text{HCT}) + \text{PRE} + \text{FLUSH}}$$

$$\text{Ultrafiltration fraction, UFF} = \frac{\text{UF}}{\text{FFIR}} \qquad \text{(Formula 6)}$$

$$\text{Note : UFF} = \frac{\text{PRE} + \text{POST} + \text{FRR}}{(\text{Qb} \times 60 - \text{FLUSH}) \times (1 - \text{HCT}) + \text{PRE} + \text{FLUSH}}$$

Appendix B

In pre-dilution replacement therapy, from Formula 5 of Appendix A,

$$PC = (PRE + POST + FRR) \times \frac{PFR}{FFIR}$$

$$PC \times FFIR = PRE \times PFR + POST \times PFR + FRR \times PFR$$

From Formula 2,

$$PC \times PRE + PC \times PFR + PC \times FLUSH = PRE \times PFR + FRR \times PFR + POST \times PFR \qquad \text{(Formula 7)}$$

$$PRE = \frac{PFR \times (PC - FRR - POST) + PC \times FLUSH}{PFR - PC} \qquad \text{(Formula 8)}$$

In pre-dilution replacement setting without flushing, this formula can be simplified as:

$$PRE = \frac{PFR \times (PC - FRR - POST)}{PFR - PC} \qquad \text{(Formula 9.1)}$$

In pre-dilution replacement setting without post-dilution, this formula can be simplified as:

$$PRE = \frac{PFR \times (PC - FRR) + PC \times FLUSH}{PFR - PC} \qquad \text{(Formula 9.2)}$$

In pre-dilution replacement setting without flushing and post-dilution, this formula can be simplified as:

$$PRE = \frac{PFR \times (PC - FRR)}{PFR - PC} \qquad \text{(Formula 10)}$$

From Formula7,

$$POST = \frac{PC\,(PRE + PFR + FLUSH)}{PFR} - PRE - FRR \qquad \text{(Formula 11)}$$

In post-dilution replacement setting without flushing, this formula can be simplified as:

$$POST = PC + \frac{PRE}{PFR} - PRE - FRR \qquad \text{(Formula 12.1)}$$

In post-dilution replacement setting without pre-dilution, this formula can be simplified as:

$$POST = PC + \frac{FLUSH}{PFR} - FRR \qquad \text{(Formula 12.2)}$$

In post-dilution replacement setting without flushing and pre-dilution, this formula can be simplified as:

$$POST = PC - FRR \qquad \text{(Formula 13)}$$

Appendix C

To achieve a given plasma clearance rate in a setting without flushing, in comparing pre- and post-dilution therapy, let r = ratio of pre-dilution over post-dilution replacement rate. From Formulae 10 and 13,

$$r = \frac{PRE}{POST}$$

$$= \frac{PFR}{PFR - PC} \qquad \text{(Formula 14)}$$

Appendix D

In pre-dilution replacement therapy, from Formulae 2, 6 and 10, and after numerous mathematical operations*, we derive

$$PFR = \frac{PC}{UFF} \qquad \text{(Formula 15)}$$

In post-dilution replacement therapy, from Formula 5, PC = UF,

and from Formula 6, $PFR = \frac{UF}{UFF} - PRE$,

Considering Formulae 4 and 13,

$$\therefore PFR = \frac{(POST + FRR)}{UFF}$$

$$PFR = \frac{PC}{UFF}$$

Thus, Formula 15 is applicable for both pre- and post-dilution replacement therapy.

* Note: In pre-dilution therapy

From Formulae 2 and 6,

$$PRE(1 - UFF) = PFR \times UFF - FRR$$

$$PRE = \frac{PFR \times UFF - FRR}{1 - UFF}$$

From Formula 10,

$$PRE = \frac{PFR \times (PC - FRR)}{PFR - PC}$$

$$\therefore \frac{PFR \times (PC - FRR)}{PFR - PC} = \frac{PFR \times UFF - FRR}{1 - UFF}$$

$$PFR \times PC + PFR \times FRR \times UFF = PFR^2 \times UFF + FRR \times PC$$

$$UFF \times [PFR^2 - PFR \times (FRR + \frac{PC}{UFF})] = -FRR \times PC$$

$$\begin{aligned}(PFR - \frac{FRR \times UFF + PC}{2 \times UFF})^2 &= -\frac{FRR \times PC}{UFF} + (\frac{FRR \times UFF + PC}{2 \times UFF})^2 \\ &= -\frac{FRR \times PC}{UFF} + \frac{(FRR \times UFF)^2 + 2PC \times FRR \times UFF + PC^2}{4 \times UFF^2} \\ &= \frac{-4UFF \times FRR \times PC + (FRR \times UFF)^2 + 2PC \times FRR \times UFF + PC^2}{4 \times UFF^2} \\ &= \frac{(PC - UFF \times FRR)^2}{4UFF^2}\end{aligned}$$

$$PFR - \frac{FRR \times UFF + PC}{2 \times UFF} = \frac{PC - UFF \times FRR}{2 \times UFF}$$

$$\begin{aligned}PFR &= \frac{FRR \times UFF + PC}{2 \times UFF} + \frac{PC - UFF \times FRR}{2 \times UFF} \\ &= \frac{PC}{UFF}\end{aligned}$$

Appendix E

From Formulae 10 and 14,

$$PRE = \frac{PC - FRR}{1 - UFF} \qquad \text{(Formula 16)}$$

Appendix F

UF = replacement rate + FRR = replacement rate + flush

In pre-dilutional therapy,

$$PC = UF \times \frac{(Qb \times 60 - FLUSH) \times (1 - HCT)}{(Qb \times 60 - FLUSH) \times (1 - HCT) + PRE + FLUSH}$$

$$= UF \times \frac{(Qb \times 60 - FLUSH) \times (1 - HCT)}{(Qb \times 60 - FLUSH) \times (1 - HCT) + (UF - FLUSH) + FLUSH}$$

$$= UF \times \frac{(Qb \times 60 - FLUSH) \times (1 - HCT)}{(Qb \times 60 - FLUSH) \times (1 - HCT) + UF}$$

In post-dilutional therapy,

$$PC = UF \times \frac{(Qb \times 60 - FLUSH) \times (1 - HCT)}{(Qb \times 60 - FLUSH) \times (1 - HCT) + FLUSH}$$

$$\text{Ultrafiltration fraction, UFF (\%)} = \frac{UF}{FFIR}$$

In pre-dilutional therapy,

$$UFF = \frac{UF}{(Qb \times 60 - FLUSH) \times (1 - HCT) + UF}$$

In post-dilutional therapy,

$$UFF = \frac{UF}{(Qb \times 60 - FLUSH) \times (1 - HCT) + FLUSH}$$

Appendix G

We developed the mathematical equation[7] below to measure urea clearance as a modified formula of Fick's Principle.

Erythrocyte water flow rate, EWFR = Haematocrit $\times$ (Qb $-$ flushing) $\times$ 0.72

Erythrocyte water flow rate with bound urea, $EWFR_{urea}$ = Haematocrit $\times$ (Qb $-$ flushing) $\times$ 0.8

Supply rate (ml/hour) = (Qb (ml/min) $\times$ 60) $-$ Flushing rate

Return rate (ml/hour) = (Qb (ml/min) $\times$ 60) $-$ Fluid removal rate $-$ Flushing rate

Supply or return, Plasma flow rate, PFR = (Supply rate or return rate) $\times$ (1 $-$ Haematocrit)

Plasma water flow rate, PWFR = PFR $\times$ 0.93

Supply or return blood water flow rate, SWR or RWR = Supply or return PWFR + EWFR

Supply or return blood water flow rate for urea, SWR_{urea} or RWR_{urea}

= Supply or return PWFR + $EWFR_{urea}$

$$\text{Urea clearance, } K_{urea} \text{ (ml/hour)} = \frac{[(SWR_{urea} \times \text{Supply BU}) - (RWR_{urea} \times \text{Return BU})]}{\text{BU of Supply}}$$

$$\text{Net urea clearance, } K_{urea} \text{ (ml/hour)} = \frac{[(SWR_{urea} \times \text{Supply BU}) - (RWR_{urea} \times \text{Return BU})]}{\text{Systemic BU}}$$