STUDY OF DILUTION MODES AND TRANSMEMBRANE PRESSURE UNDER DIFFERENT OPERATIONAL CONDITIONS IN CVVH

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INTRODUCTION

The landmark CRRT dose trial (Ronco et al, Lancet 2000) was performed in the post-dilution CVVH mode. The clinical benefits provided by CVVH for both pre-dilution and post-dilution may be related to middle molecule (MM) clearances. Other dose/outcome trials used different CRRT modes which may influence MM clearance.

The purpose of this experimental CRRT study was to measure the clearance of small solutes (urea, creatinine), MM surrogates (vancomycin, inulin) and the transmembrane pressures (TMP) in different dilution modes, degree of pre-dilution, and flow conditions along with MM sieving coefficient (SC) values over extended periods in CRRT. Our results find that small molecular solute clearance increased as the percentage of pre-dilution decreased but the SC for middle molecular weight solutes decreased drastically due to protein cake formation. The data obtained by varying pre and post dilution percentages are predictable for small solutes. Higher clearance values for MM can be achieved in Pre and PBP under low TNP rather than in Post. In order to access the high middle molecule clearance in high volume CVVH, longer experimental times are necessary and further understanding of potential degradation in clearance over clinically relevant durations of filter used is required.

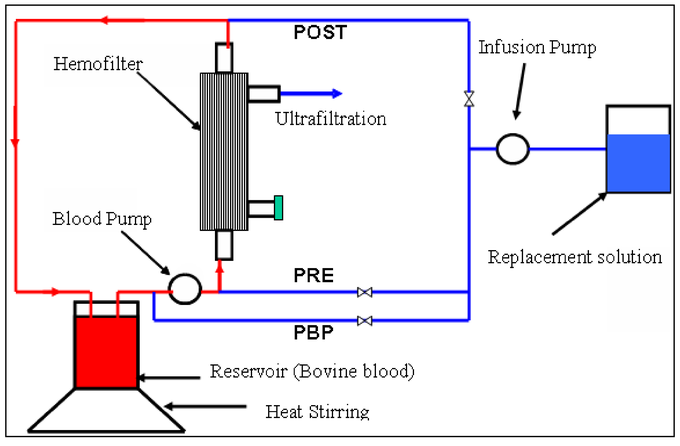
EXPERIMENTAL CONDITIONS

- 6 liters bovine blood (Hct ~ 35%, 34ºC-36ºC) was used as blood compartment fluid.
- An isovolemic fluid exchange was used, such that ultrafiltration rate and replacement fluid rate (Q_R) were the same
- Post dilution, pre-dilution and pre-pump dilution with following three operational conditions:
  - Blood flow rate: 190 mL/min, Replacement flow rate: 2 L/hr.
  - Blood flow rate: 290 mL/min, Replacement flow rate: 3 L/hr.
  - Blood flow rate: 380 mL/min, Replacement flow rate: 4 L/hr.
- Different dilution percentages of 0% (pure POST), 25%, 50%, 75%, and 100% (pure PRE) with a blood flow rate of 290 mL/min and replacement fluid (RF) rate of 3 L/hr.
- Machine: Prismaflex, “Treatment” duration = 240 minutes.
- Hemofilter: 1.4 m^2 Polyarylethersulfone (HF1400, Gambro/Baxter)
- N = 3 for each filter/flow rate, dilution mode combination
- Solutes:

  Small molecular solutes surrogates: Urea (MW: 60); Creatinine (MW: 113)

  Middle molecules solutes surrogates: Vancomycin (MW: 1448); Inulin (MW: 5200)

Figure 1 Experimental System



DATA ANALYSIS

• Clearance (K) determination

Small molecular solutes: Average of instantaneous blood-side values measured at 0, 15, 30, 60, 120, 180, and 240 min

Middle molecular solutes: Based on decrease in reservoir solute concentration as a function of time

• Assays

Small molecular solutes: Cobas Mira (Colorimetric Assays)

Middle molecular solutes: Vancomycin: Cobas Mira (EMIT Assay); Inulin: Spectrophotometer (UV 520 nm)

• Statistical analysis was performed using “Anova Single Factor”, with results expressed as mean ± SD

• Difference was considered statistically significant at $p < 0.05$ *

RESULTS

Table 1 Variation of Urea and Creatine Clearances (mL/min) with Operational Conditions

	POST		PRE		PBP	
	U	C	U	C	U	C
Condition 1	34.0 ±2.0	34.0 ±1.0	27.0 ±0.8	27.8 ±1.0	25.3 ±1.9	26.0 ±0.5
Condition 2	54.0 ±1.2	55.0 ±0.7	35.1 ±0.7	35.5 ±0.3	36.4 ±0.7	35.7 ±1.4
Condition 3	71.0 ±2.0	71.0 ±1.0	52.1 ±1.7	51.6 ±0.6	49.5 ±5.6	52.8 ±3.6
P-value	6.5E-09	3.7E-09	1.1E-06	4.5E-08	4.3E-04	1.9E-05

Table 2 Variation of Inulin and Vancomycin Clearance (mL/min) with Operational Conditions

	POST		PRE		PBP	
	I	V	I	V	I	V
Condition 1	26.8 ±2.3	30.6 ±4.6	26.0 ±4.7	25.2 ±1.2	24.5 ±0.9	23.7 ±0.5
Condition 2	34.7 ±5.6	36.7 ±3.8	33.6 ±3.1	31.9 ±0.6	36.4 ±0.9	33.7 ±1.5
Condition 3	48.5 ±4.1	43.8 ±3.6	44.4 ±6.5	46.3 ±0.9	47.2 ±1.8	46.7 ±0.6
P-value	0.0014	0.02	0.014	5.36E-07	2.1E-06	2.33E-07

POST: post dilution; PRE: pre dilution; PBP: pre pump dilution; I: inulin, V: vancomycin

Figure 2 Comparison of Vancomycin and Inulin SC with Time at Different Dilution Modes under Condition #1

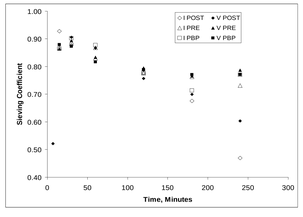


Table 3 Measured TMP (mmHg) Values for Different Dilution Modes and Flow Conditions

	Condition1	Condition 2	Condition 3
POST	116.1 ±5.6	137.2 ±13.6	155.7 ±12.0
PRE	73.7 ±0.4	84.7.1 ±2.3	95.5 ±2.3
PP	65.5 ±1.8	83.6 ±0.7	101.3 ±11.3

DISCUSSIONS

- There are significant changes ($p < 0.001$) of urea and creatinine clearance with different experimental conditions. There is significant decrease ($p < 0.01$) of urea and vancomycin clearance from post-dilution mode to pre-dilution mode and from post-dilution mode to pre-pump-dilution model. But there is no significant difference between pre-dilution and pre-pump-dilution mode. The clearance changes with time for urea and creatinine had no significant effect for all the operational conditions and dilution modes (results were not presented here).
- Consistent with previous studies, the post-dilution mode provided the highest clearances under all flow conditions for the SMW solutes. However, high blood flow rates (~300 mL/min and above) were necessary to achieve high dose while also maintaining an acceptable filtration fraction. Solute clearances were not different in traditional pre-dilution and pre-blood pump administration of replacement fluid. Equivalence was possible due to automatic blood pump speed compensation of the Prismaflax system, the absence of which would have resulted in lower clearances in the pre-pump mode.
- There are significant increases ($p < 0.001$) of inulin and vancomycin clearance with different experimental conditions. No significant change ($p > 0.05$) of inulin clearance between post-dilution and pre-dilution mode, post-dilution and pre-pump-dilution model, and pre-dilution and pre-pump-dilution mode were observed.
- There are significant changes of inulin and vancomycin SC with time. But the change in SC with time in post-dilution mode are the most significant ($p < 10^{-9}$) among other two dilution modes. In the PRE and PBP modes, inulin and vancomycin follow a similar trend in the variation of SC with time. This indicates that PRE and PBP dilution modes have high shear force which reduces boundary layer on membrane surface.
- In the PRE & PBP, the clearance of middle molecular weight solutes (inulin vancomycin) are almost the same as in POST but in PRE & PBP, the TMP values are low when compared to that in POST.

CONCLUSIONS

1. Small MW solute clearance increased as the extent of predilution decreased. 2. Middle MW SC decreased substantially (especially in POST) with time, most likely due to secondary membrane effects. 3. Higher clearance values for MMW solutes can be achieved in PRE and PBO rather than in POST, but under low TMP.

ACKNOWLEDGMENT

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