Hemodiafiltration versus Mixed Hemodiafiltration: What's Place ?

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2ième Symposium Infirmier romand en Néphrologie

Disclosure

Speaker name: **Prof. Bernard Canaud**

☐ I have the following potential conflicts of interest to report:

☐ Consulting

☒ **Employment in industry (FMC)**

☐ Shareholder in a healthcare company

☐ Owner of a healthcare company

☐ Other(s)

☐ I do not have any potential conflict of interest

Outlook of the Presentation

1. What is optimal in convective therapies ?
   – Convective dose : postdilution HDF as reference
2. What's matter in HDF ?
   – Dilution mode : Post - Pre - Mixed - Mid
3. Why mixed-HDF is necessary ?
   – Medical & engineering rationale
4. How to use mixed-HDF ?
   – Technical aspects
   – Nursing & Doctor perspectives
5. What indications ?
6. What results ?
7. Take home message

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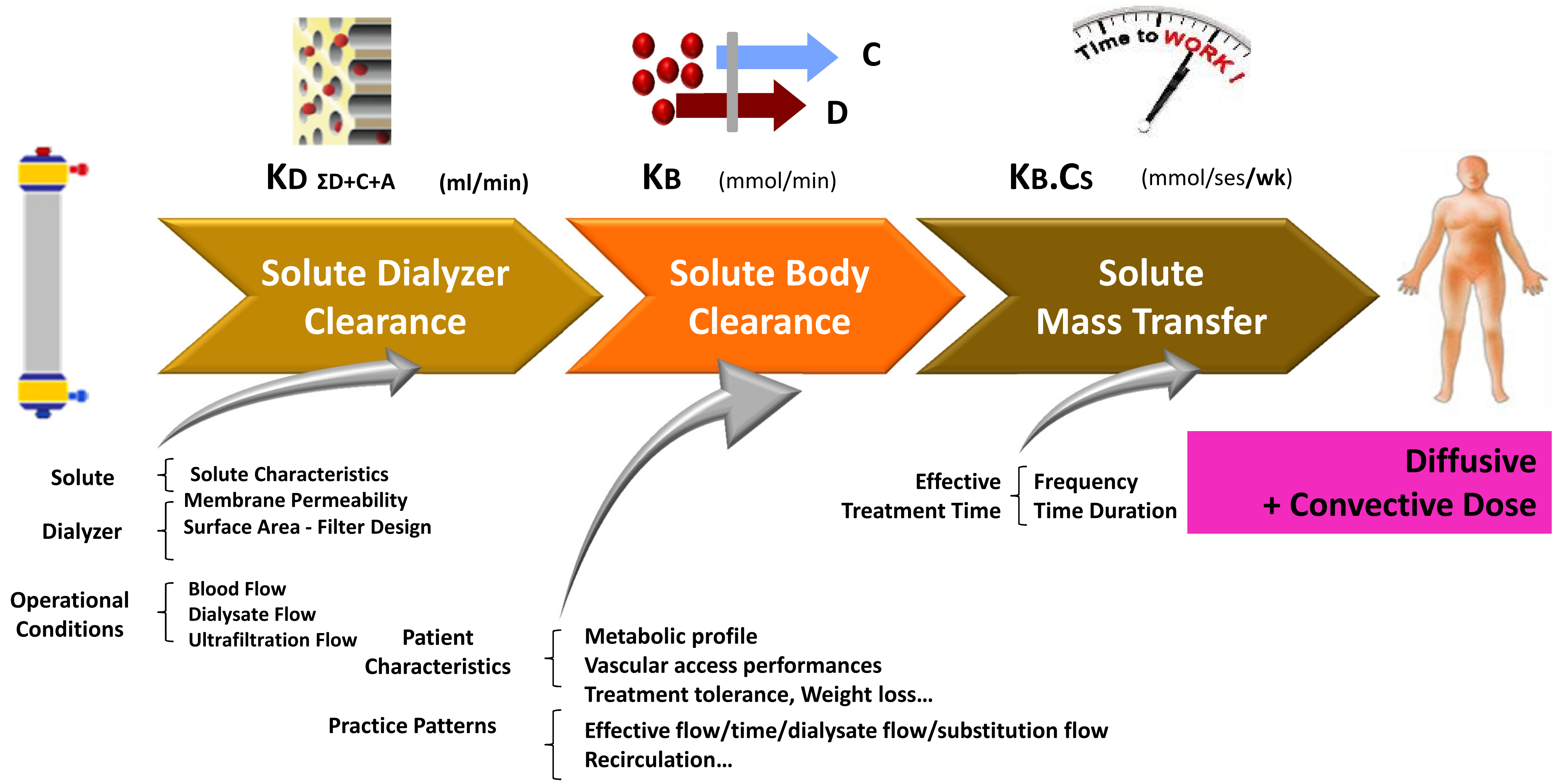
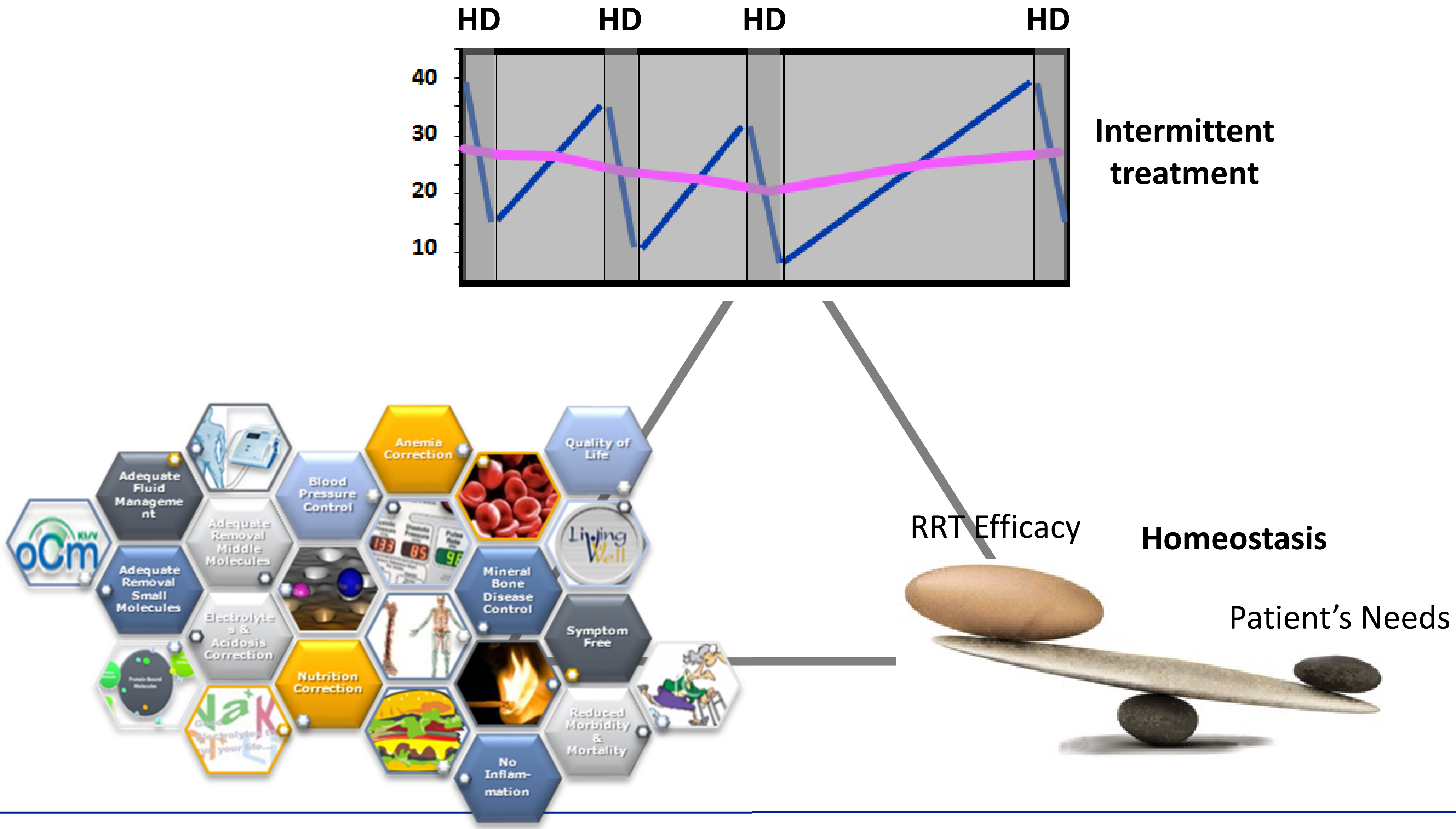
From Dialyzer Clearance to Body Mass Transfer

Effective Solute Mass Removal per Session

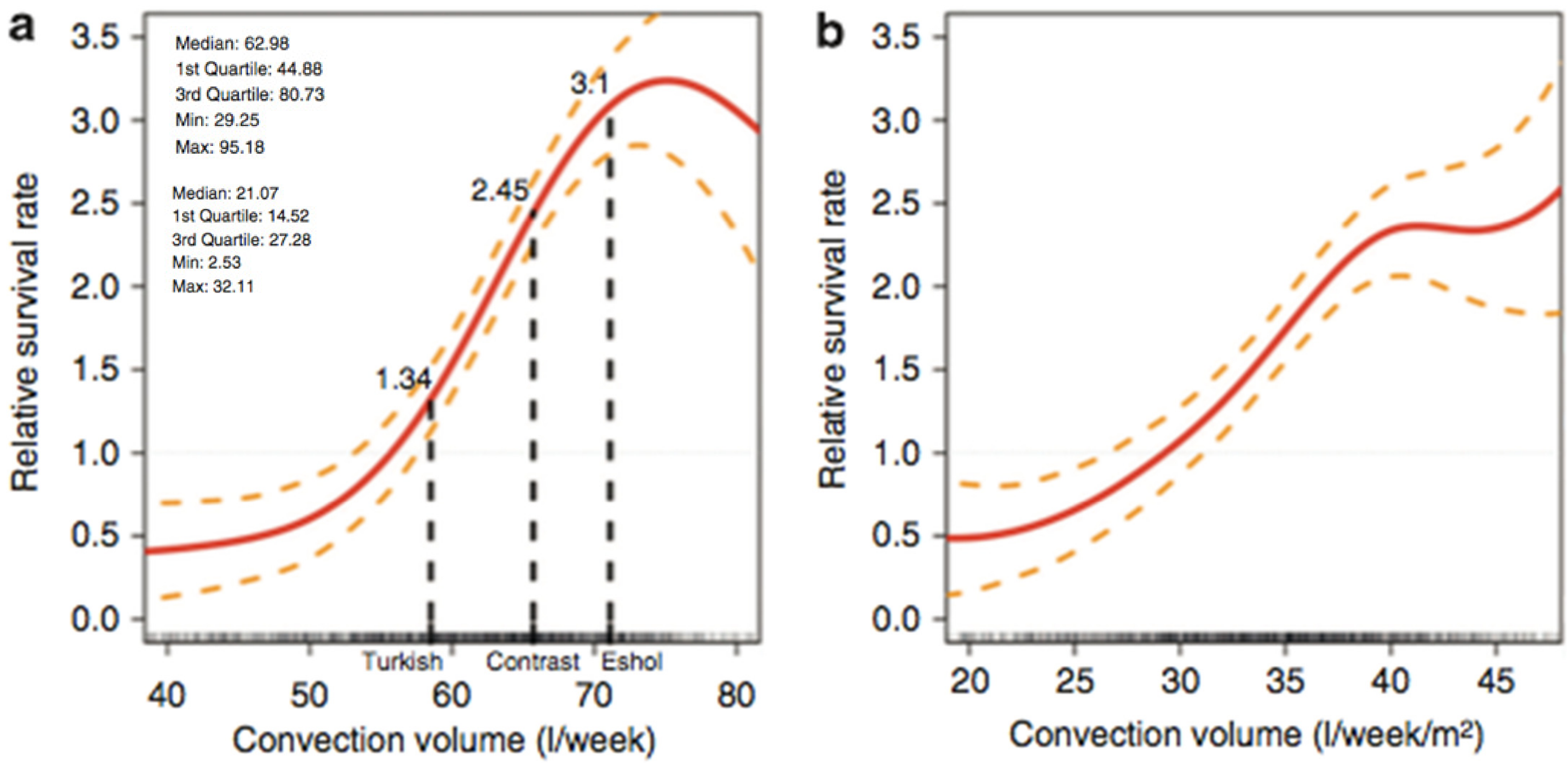


From Mass Transfer to Patient Needs

RRT Adequacy: Effective Solute Mass Removal per Week

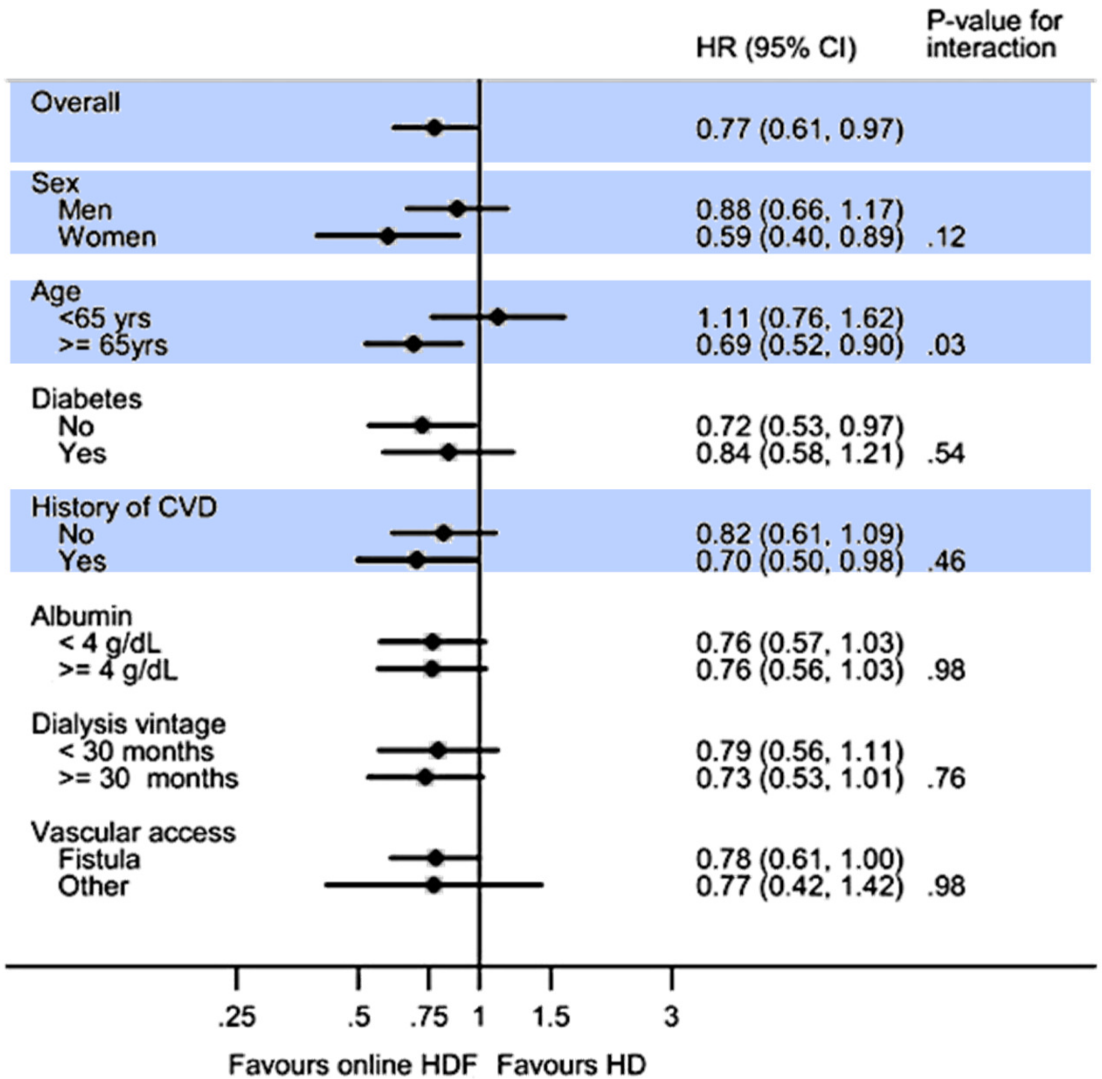


Cubic Spline Analysis of Relative Survival Rate Vs Convection Volume Non Adjusted



Canaud B et al, *Kidney Int.* 2015;88:1108-1116

HRs for CardioVascular Mortality In Patients Receiving HDF Versus HD, Overall and in Subgroups



-23%

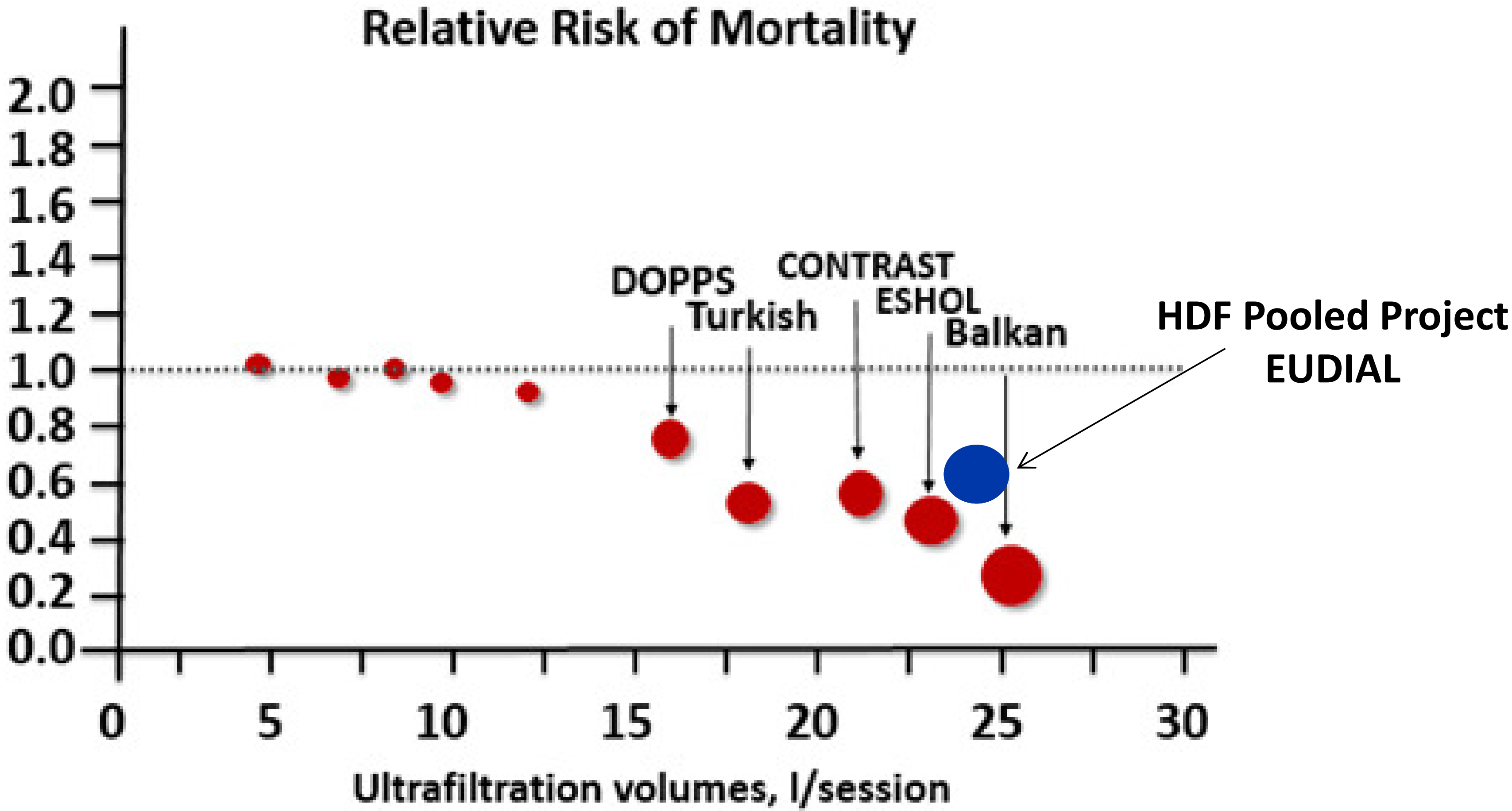
-41%

-31%

-30%

2793 prevalent ESKD pts

Simulated Benefits of Convective Volume on Relative Risk of Mortality in CKD Patients



Imamovic G et al, 'Rational for Improved Patients' Survival on Hemodiafiltration' in *InTech* Chapter, 2016 In Press

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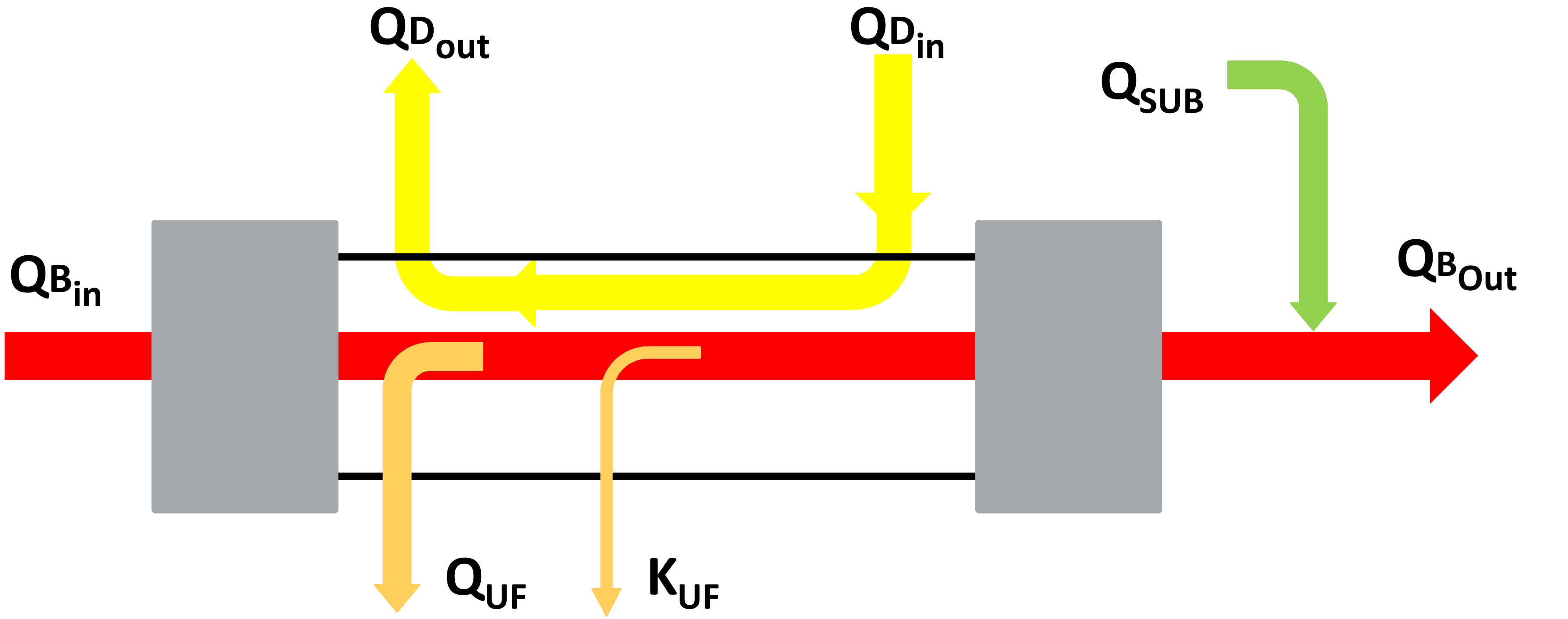
Post-dilution Hemodiafiltration



QB_{IN} = Blood Flow In
QB_{OUT} = Blood Flow Out
QD_{IN} = Dialysate Flow In
QD_{OUT} = Dialysate Flow Out

Sieving Coefficient = CS_B/CS_F

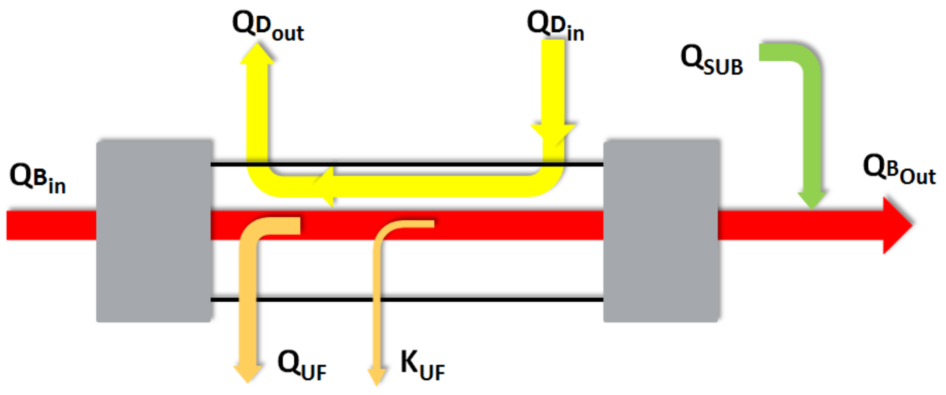
QUF = Ultrafiltration Rate
QSUB = Substitution Rate
Kuf = WL/t_{HD} Weight Loss
QF = Total Ultrafiltration Rate
DF = Dilution Factor
S = Sieving Coefficient

Tattersall JE et al, *Nephrol Dial Transplant.* 2013 ;28(3):542-50

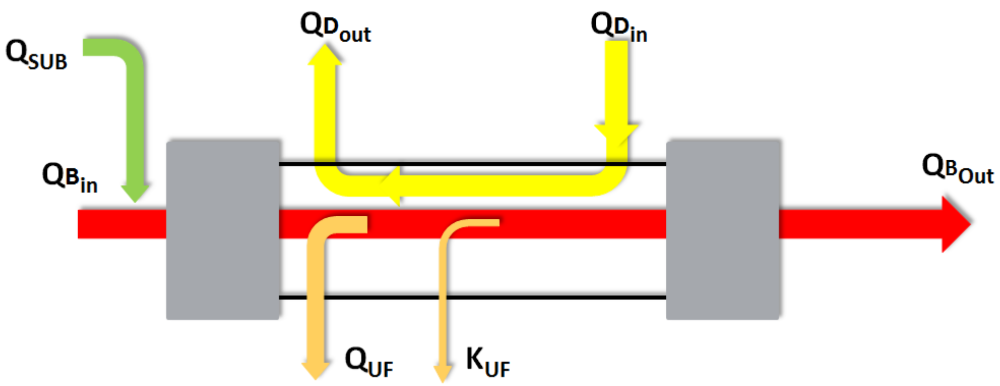
Different Modalities of HDF

Defined from Substitution Sites

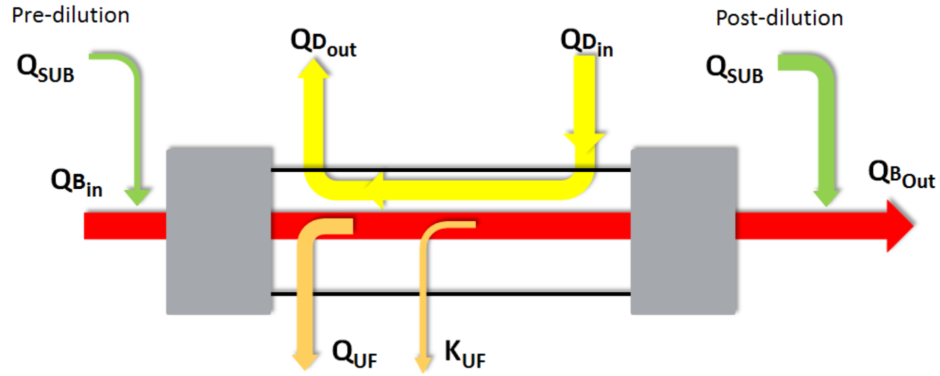
Post-Dilution HDF



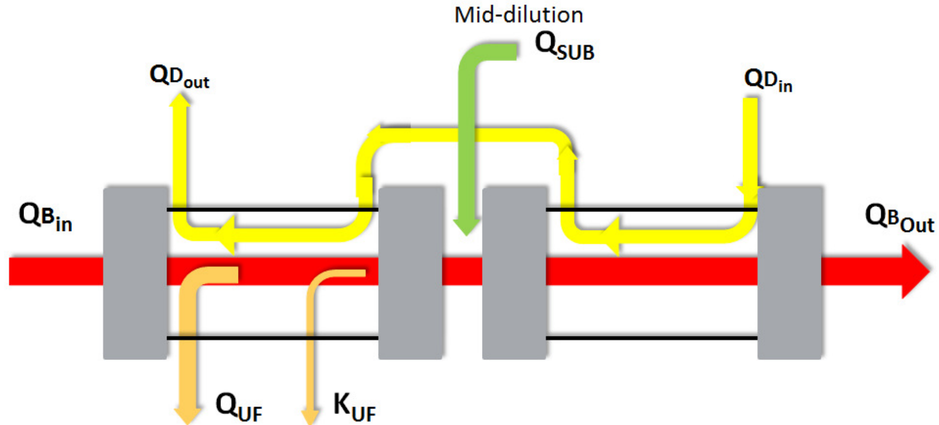
Pre-Dilution HDF



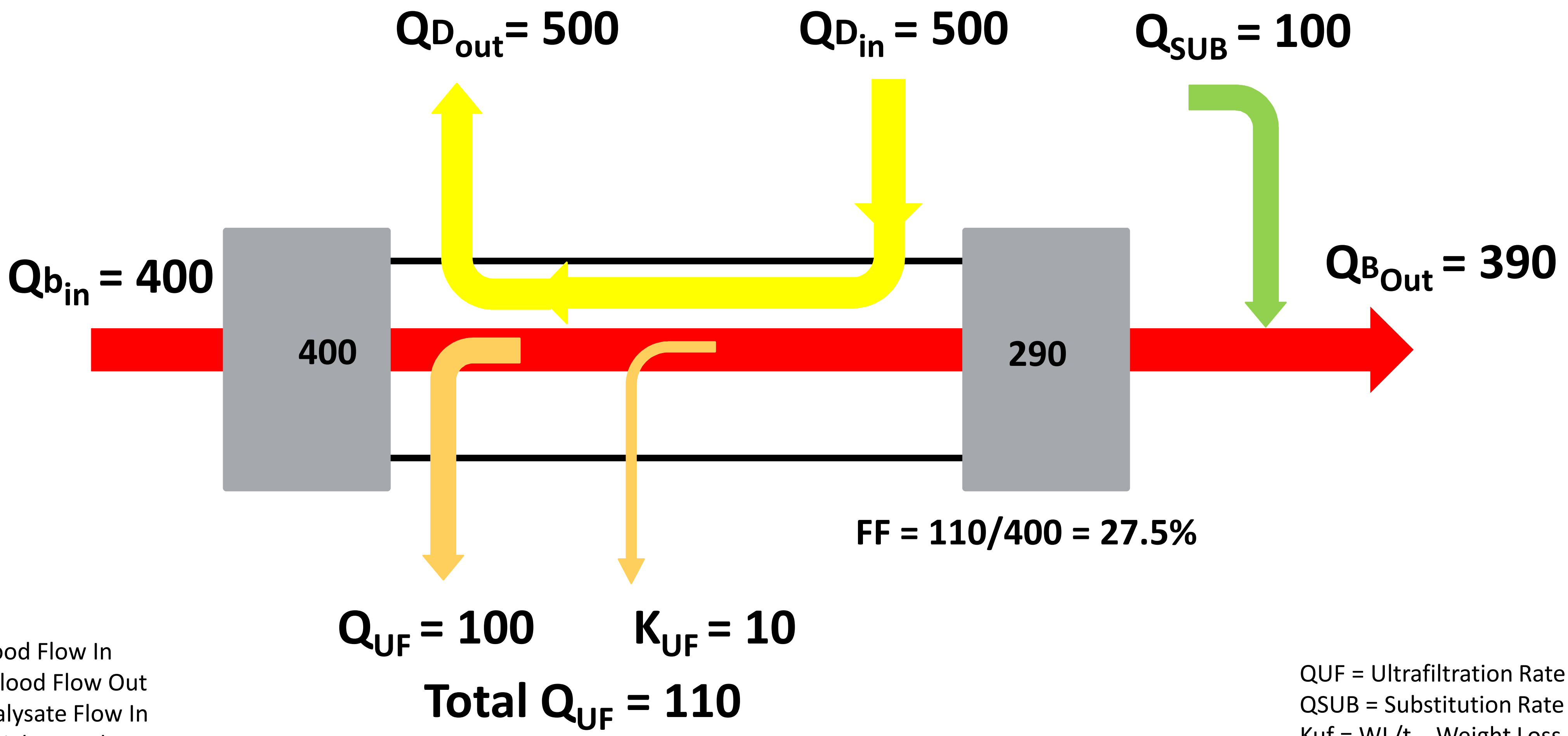
Mixed-Dilution HDF



Mid-Dilution HDF



Postdilution Hemodiafiltration
Flow and Fluid Transfer



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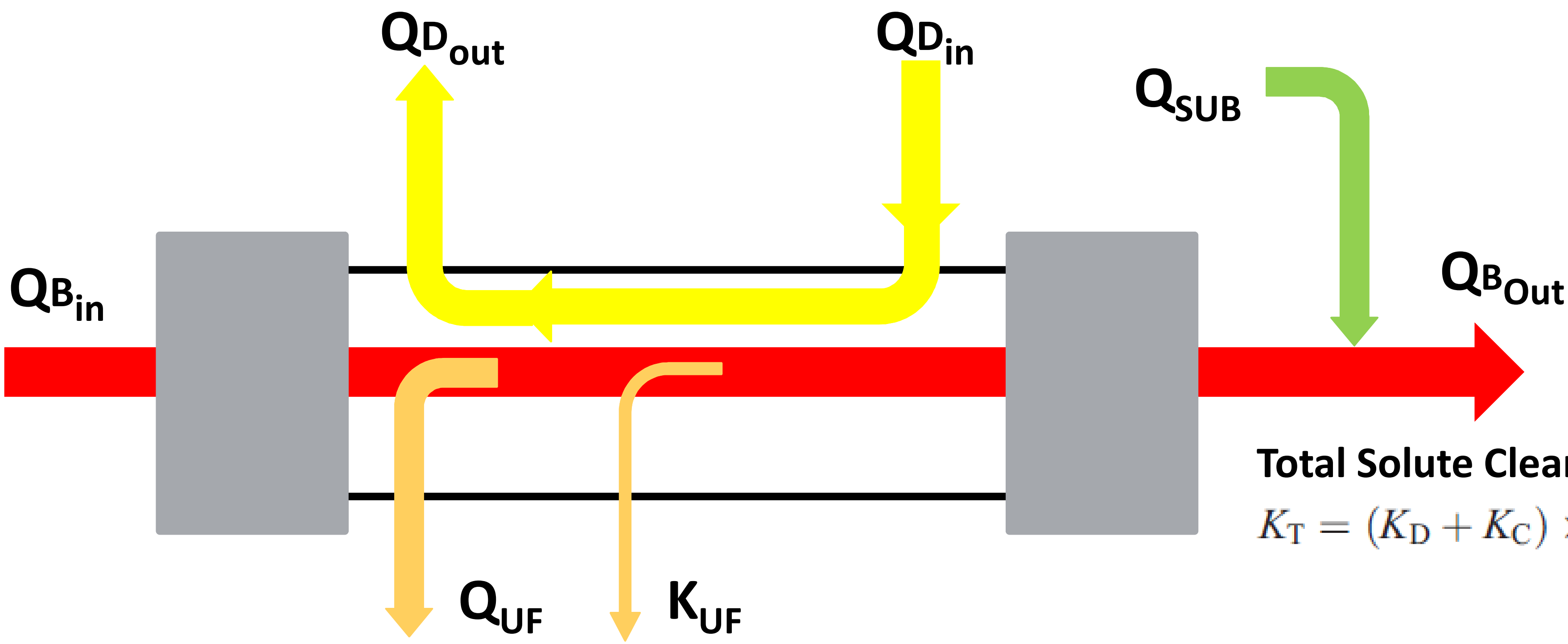
Kuf = WL/t_{HD} Weight Loss

Postdilution Hemodiafiltration

$$K_D = \frac{1 - e^{K_oA \times [(Q_b - Q_d)/(Q_b \times Q_d)]}}{(1/Q_b) - (1/Q_d) \times e^{K_oA \times [(Q_b - Q_d)/(Q_b \times Q_d)]}}$$

Diffusive Clearance, KD

KoA = Solute Mass Transfer Coefficient
QD_{IN} = Dialysate Flow In
QD_{OUT} = Dialysate Flow Out



Total Solute Clearance

$$K_T = (K_D + K_C) \times \mathrm{DF}$$

QB_{IN} = Blood Flow In
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QD_{OUT} = Dialysate Flow Out

Sieving Coefficient = CS_B/CS_F

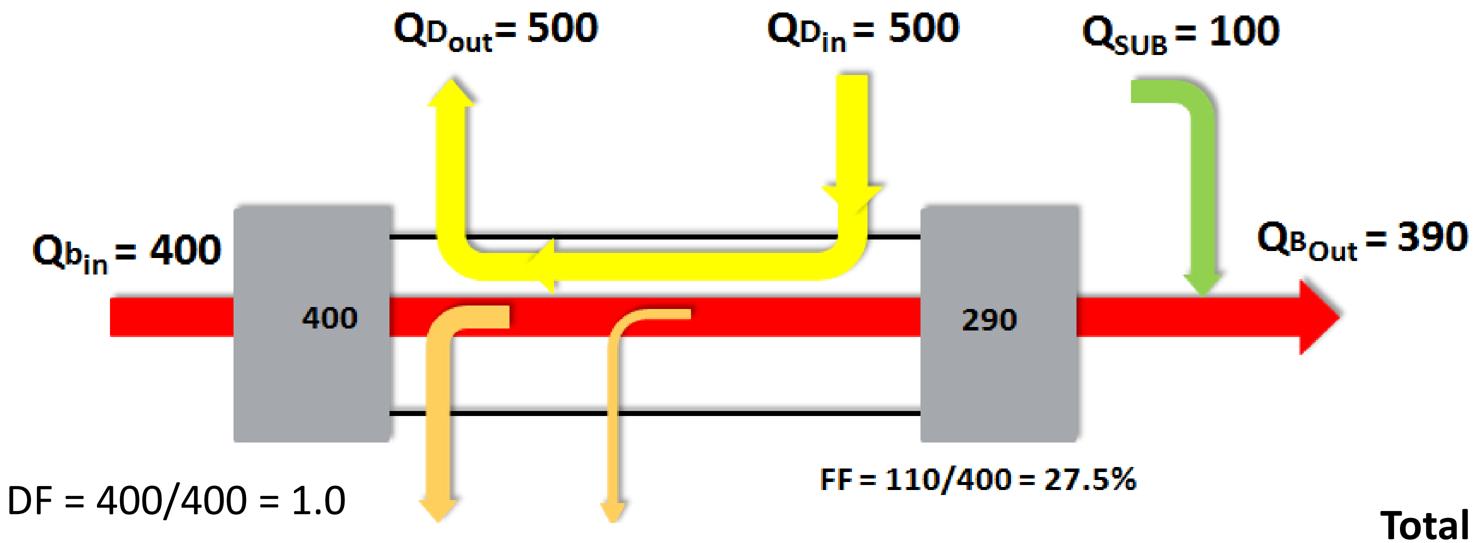
Convective Clearance, KC

$$K_C = \frac{Q_b - K_D}{Q_b} \times Q_f \times S$$

QUF = Ultrafiltration Rate
QSUB = Substitution Rate
Kuf = WL/t_{HD} Weight Loss
QF = Total Ultrafiltration Rate
DF = Dilution Factor
S = Sieving Coefficient

Tattersall JE et al, *Nephrol Dial Transplant.* 2013 ;28(3):542-50

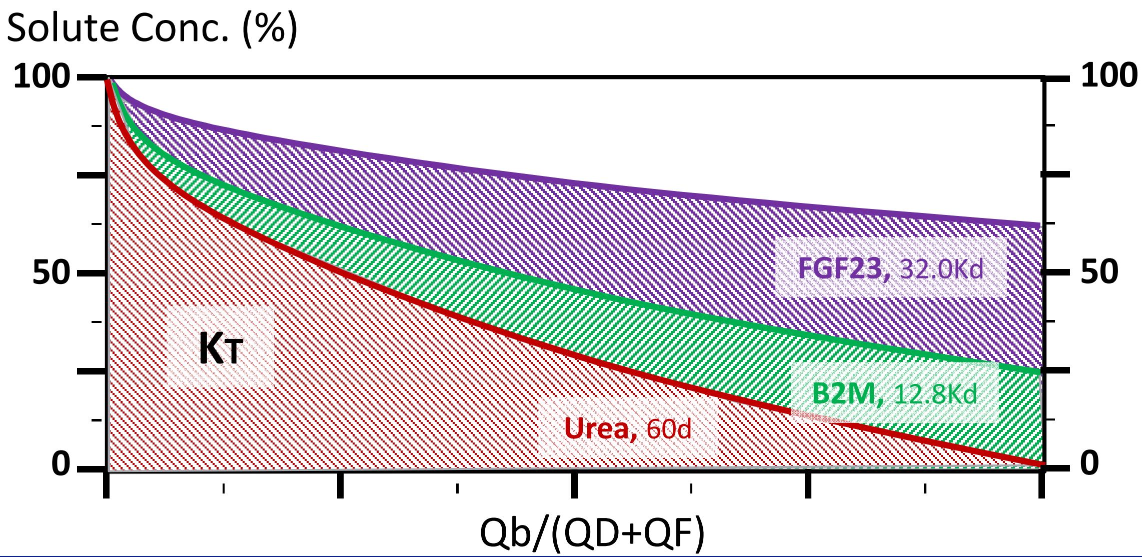
Postdilution Hemodiafiltration
Solute Profile & Convective Clearance



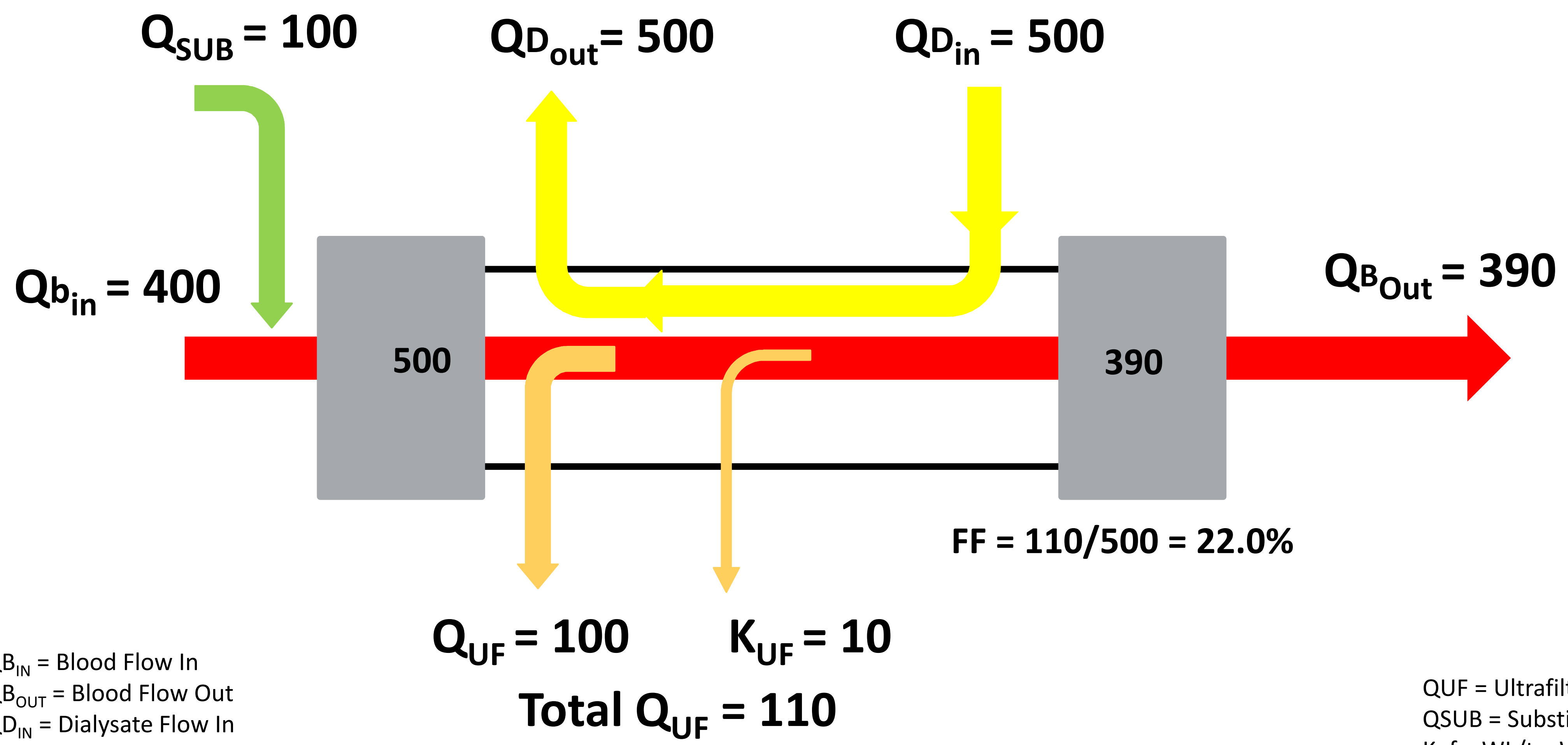
Total Solute Clearance

$$K_T = (K_D + K_C) \times \text{DF}$$

DF = 1.0



Predilution Hemodiafiltration
Flow and Fluid Transfer



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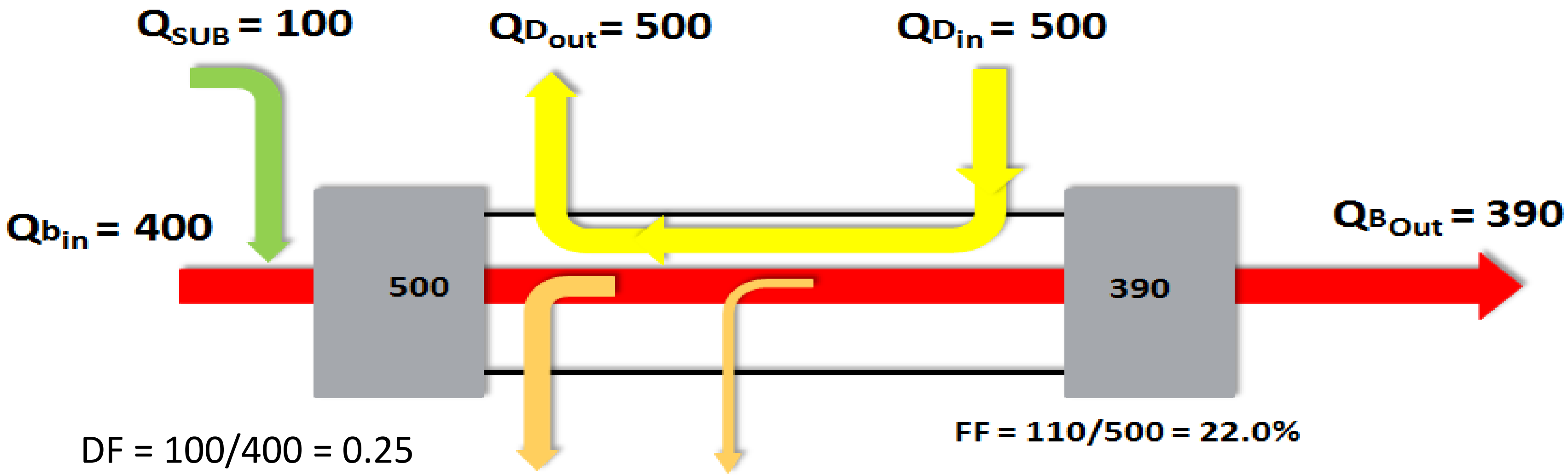
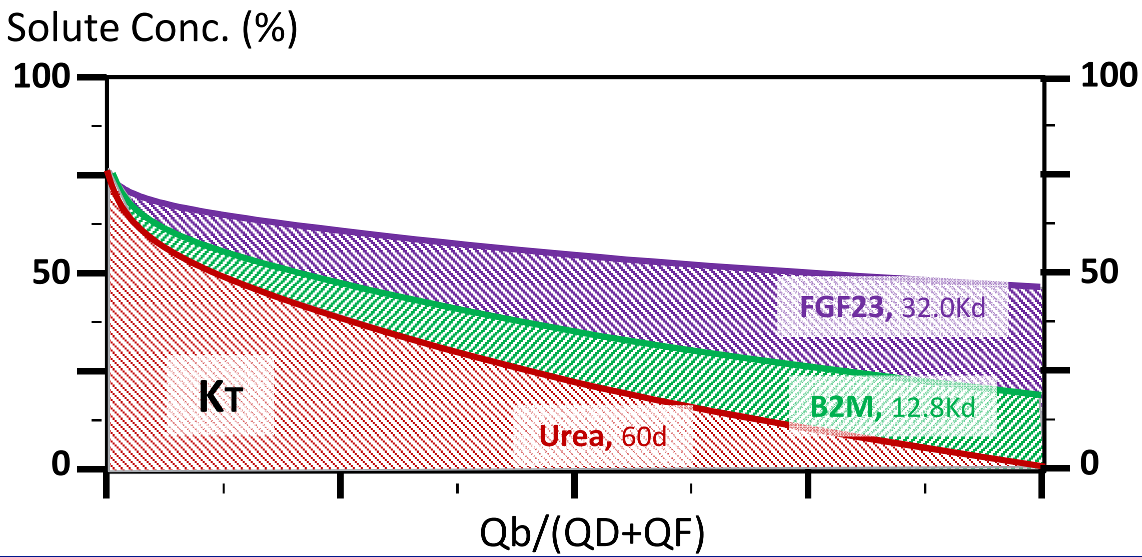
Predilution Hemodiafiltration

Solute Profile & Convective Clearance





Total Solute Clearance

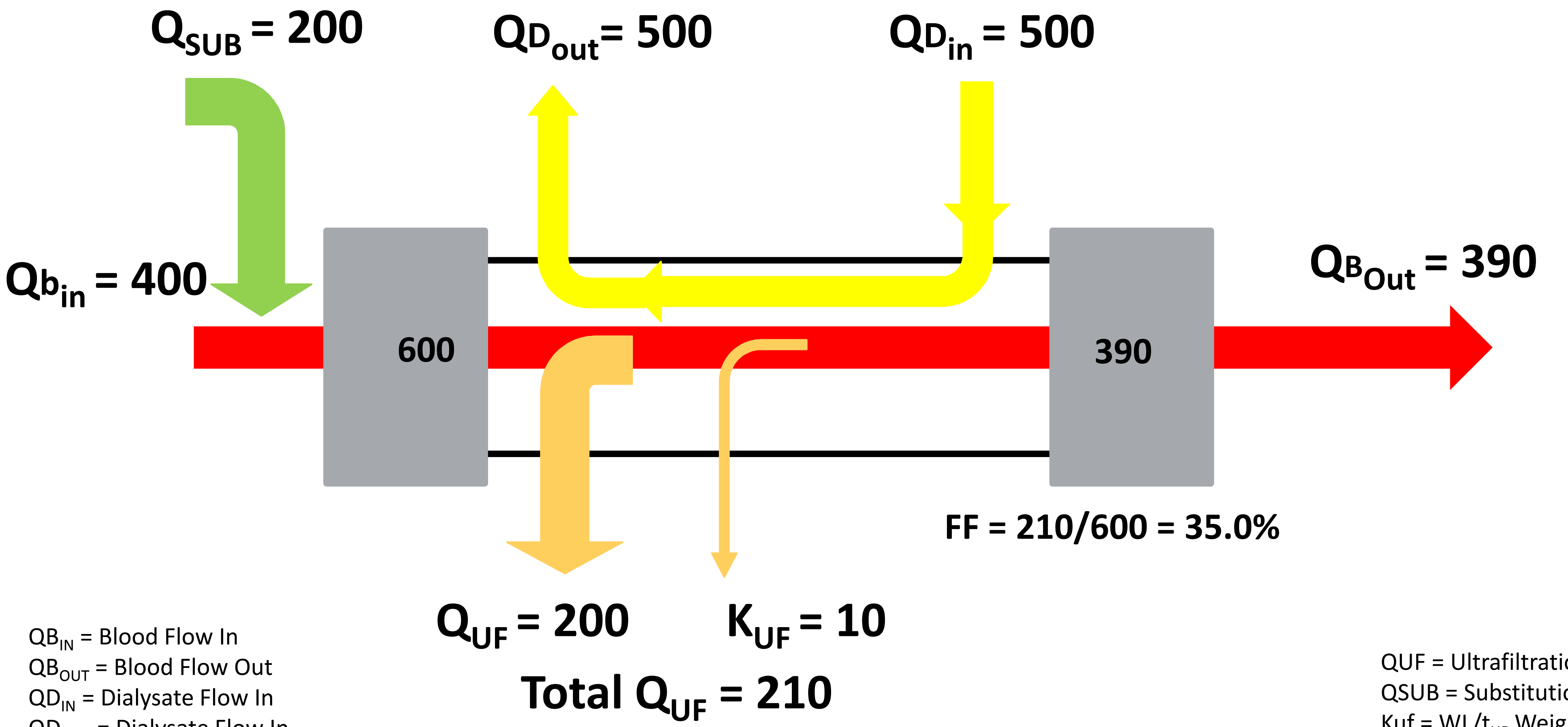
$$K_T = (K_D + K_C) \times \mathrm{DF}$$

DF = 0.25

$$K_C = \frac{Q_b - K_D}{Q_b} \times Q_f \times S$$

↗Q_f & ↗Q_{SUB}

Predilution Hemodiafiltration
Flow and Fluid Transfer Matching Post-HDF



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Advantages & Disadvantages of Substitution Modalities

Post-dilution HDF

Pro:

- High solute clearance & removal
  - Small, Middle & High MW solutes
- Reduce consumption of substitution volume

Con:

- Hemoconcentration
  - Increase protocrit & hematocrit
  - Increase viscosity & oncotic pressure
  - Fibers and membrane fouling
- Reduce hydraulic & solute membrane permeability
  - Increase transmembrane pressure
  - Reduce sieving coefficient
  - Fibers clotting
  - Potential alarms
- Increase membrane stress
  - Potential albumin leakage

Pre-dilution HDF

Pro:

- Hemodilution
  - Decrease protocrit & hematocrit
  - Reduce viscosity & oncotic pressure
  - Reduce fibers & membrane fouling
- Facilitate protein-bound solute clearance & removal
- Preserve hydraulic & solute membrane permeability
- Reduce membrane stress

Con:

- Reduce solute clearance & removal
  - Small > Middle & High MW solutes
- Increase consumption of substitution volume

Mixed-dilution HDF

Pro:

- Avoid drawbacks of both post & pre-dilution methods

Con:

- Require specific hardware equipment
  - Two infusion pumps
  - Specific blood tubing set
- Require specific software & algorithm
  - Accounting for hematocrit & protocrit changes
  - Adjusting post/pre infusion ratio keeping transmembrane pressure in target
  - Increase consumption of substitution volume

Some Clinical Indicators for Choosing Best Substitution Modality

Favorable to Post-HDF

- Good vascular access flow
- High blood flow
- Hematocrit 30-35% or Hb 10-11g/dl
- Albumin concentration (35-40g/l)
- Standard weight loss or UFR <15ml/Hr/kg
- No inflammation, No active infection
- No paraproteinemia
- No hyperlipidemia, no hypertriglyceridemia
- No hyperviscosity: fibrinogen <3g/l, leukocytes $<5.10^3$, Platelets $<150.10^3$
- No clotting disorders
- Unfavorable probing

Favorable to Pre or Mixed-HDF

- Poor vascular access flow or veno-venous access
- Low blood flow (<300ml/min)
- Hematocrit >35% or Hb >12g/dl
- Albumin concentration >40g/l
- High weight loss or UFR >15ml/Hr/kg
- Inflammation, Active infection
- Paraproteinemia
- Hyperlipidemia, Hypertriglyceridemia
- Hyperviscosity
- Clotting disorders

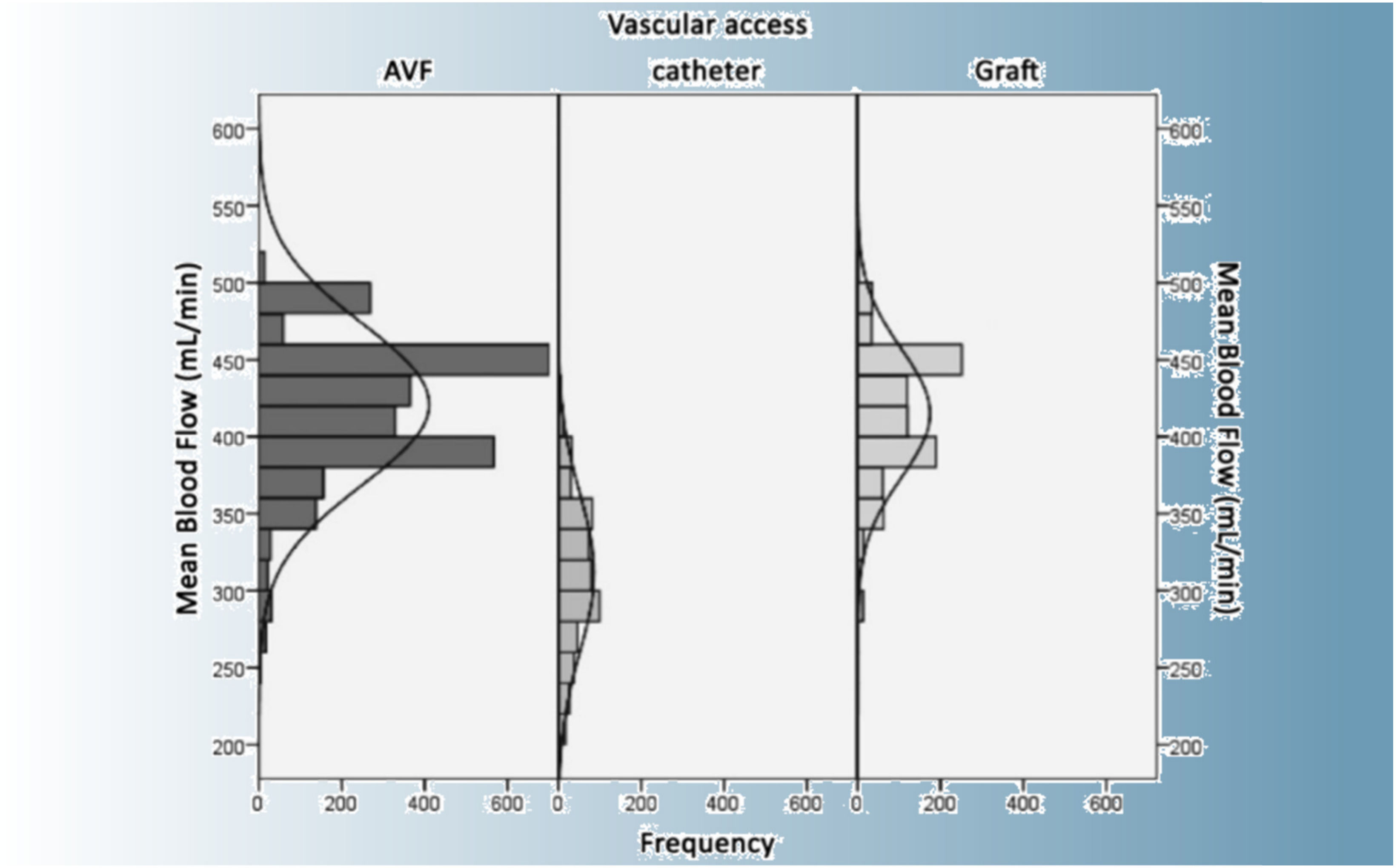
Convective Dose Delivered in Postdilution HDF with Automatic Ultrafiltration Control (AutoSub⁺)

	FX Cordiax 60	FX Cordiax 600	FX Cordiax 800	FX Cordiax 100	ALL
Patients (N)	325	2572	121	464	3315
Sessions (N)	10022	78177	3740	4888	106827
Age (years)	61.7 ± 14.8	64.8 ± 13.7	61.1 ± 12.6	63.5 ± 13.2	64.5 ± 13.7
Gender (Female, %)	47.2	38.5	17.9	34.9	39.2
BMI (kg/m²)	25.2 ± 4.9	26.4 ± 5.5	30.1 ± 6.7	27.7 ± 6.3	24.4 ± 5.5
Kt/V	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Substitution fluid volume (l/treatment)	22.6 ± 4.3	24.8 ± 4.6	25.0 ± 3.9	31.6 ± 7.2	24.8 ± 6.2
Convection volume (l/treatment)	25.1 ± 4.1	27.3 ± 4.6	28.1 ± 3.9	37.0 ± 6.7	27.4 ± 6.3
Mean Filtration Fraction (%)	29.6 ± 3.9	28.0 ± 3.8	30.3 ± 3.8	32.2 ± 4.4	28.3 ± 4.1
Sessions with substitution fluid volume ≥21 L (%)	70.2	84.4	89.7	92.8	81.5

	FX Cordiax 60	FX Cordiax 600	FX Cordiax 800	FX Cordiax 100
Substitution fluid volume (l/treatment)	22.6 ± 4.3	24.8 ± 4.6	25.0 ± 3.9	31.6 ± 7.2
Convection volume (l/treatment)	25.1 ± 4.1	27.3 ± 4.6	28.1 ± 3.9	37.0 ± 6.7
Mean Filtration Fraction (%)	29.6 ± 3.9	28.0 ± 3.8	30.3 ± 3.8	32.2 ± 4.4
Sessions with substitution fluid volume ≥21 L (%)	70.2	84.4	89.7	92.8

Marcelli D et al, *Int J Artif Organs* 2015; 38(5):244-50.

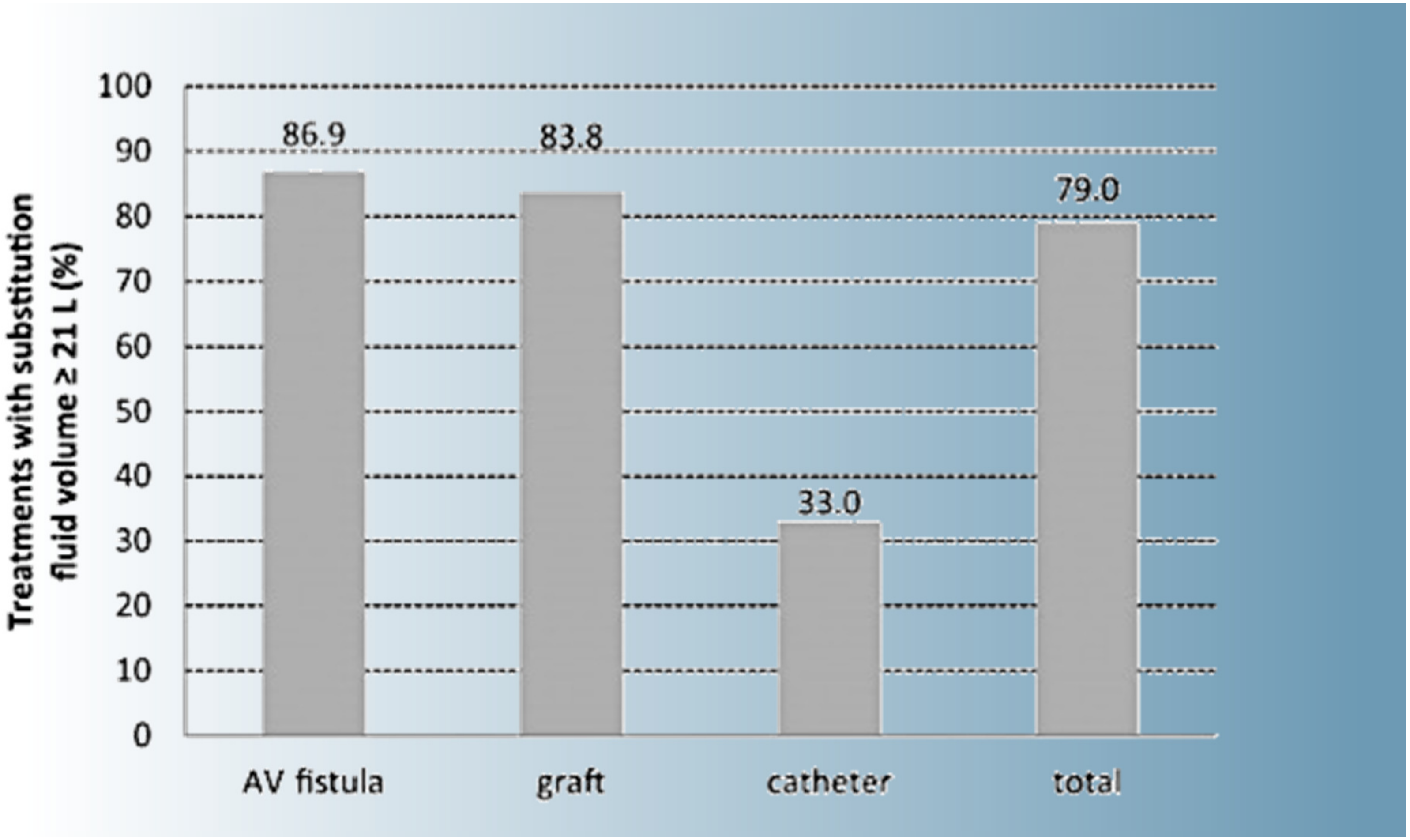
Modifiable Factors with Achievement of Optimal Convective Dose in Postdilution HDF



4176 sessions - 366 patients on postdilution HDF
1-month observational cohort study

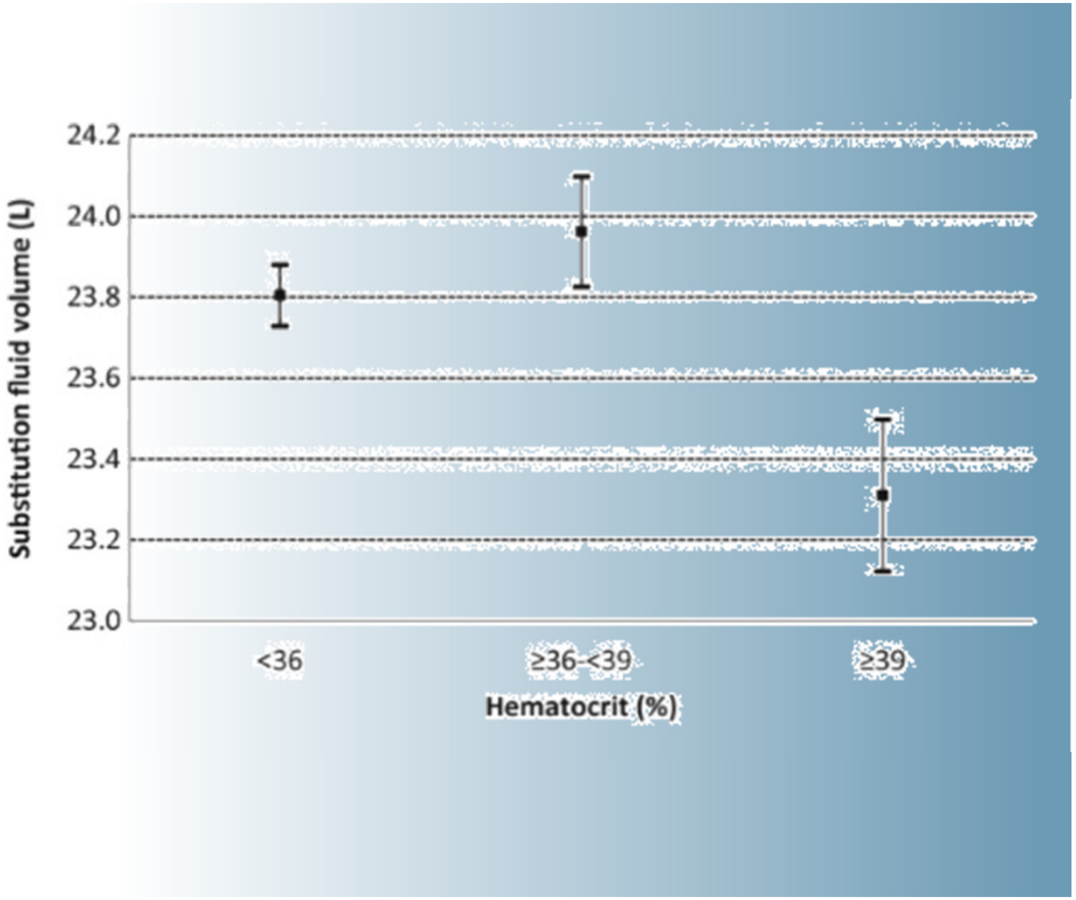
Marcelli D et al, *Artif Organs* 2015, 39(2):142–149

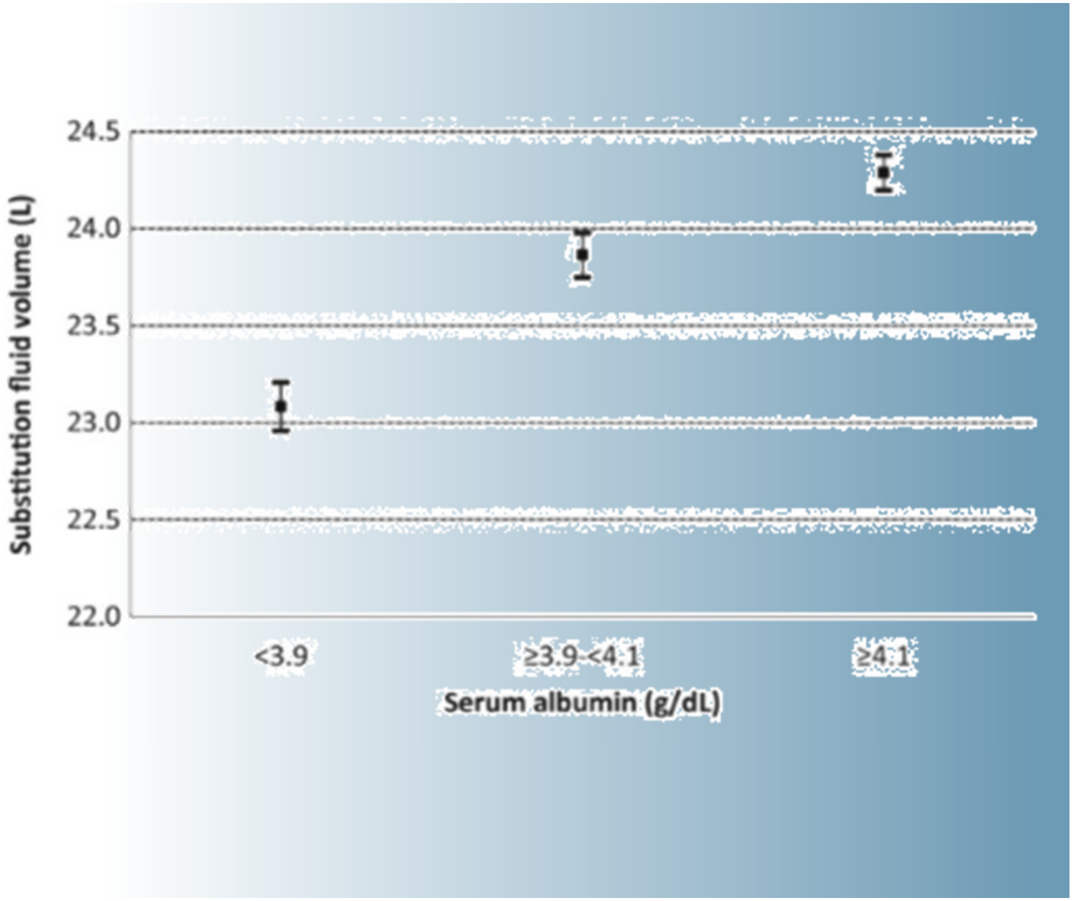
Vascular Access Type and Achievement of Optimal Convective Dose in Postdilution HDF



Marcelli D et al, *Artif Organs* 2015, 39(2):142–149

Hematocrit & Albumin and Achievement of Optimal Convective Dose in Postdilution HDF





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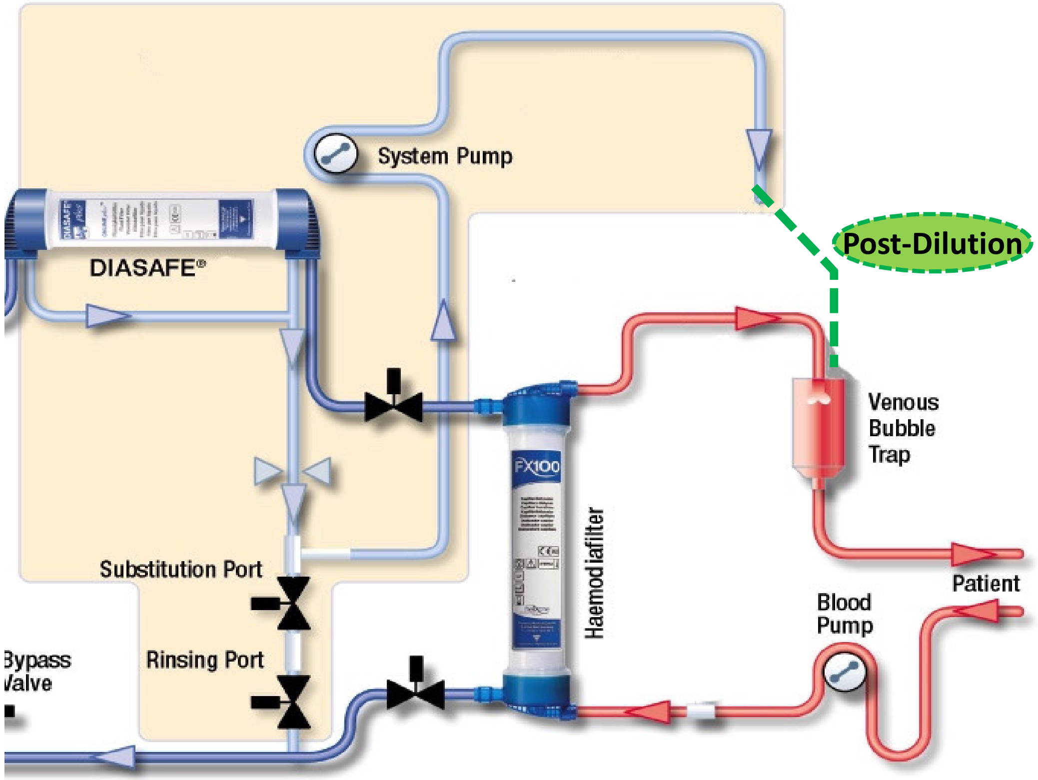
Mode of Substitution Matters

Post-Dilution HDF:
reference



Manual versus Automated Delivery

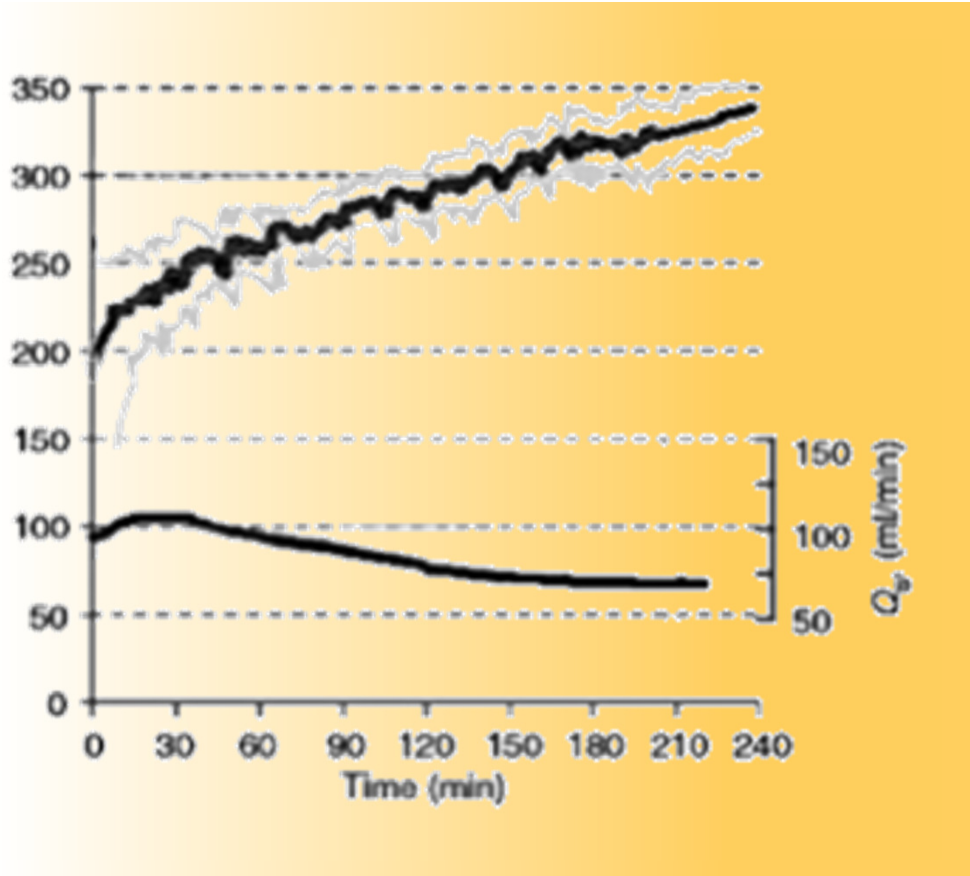
Manual Management

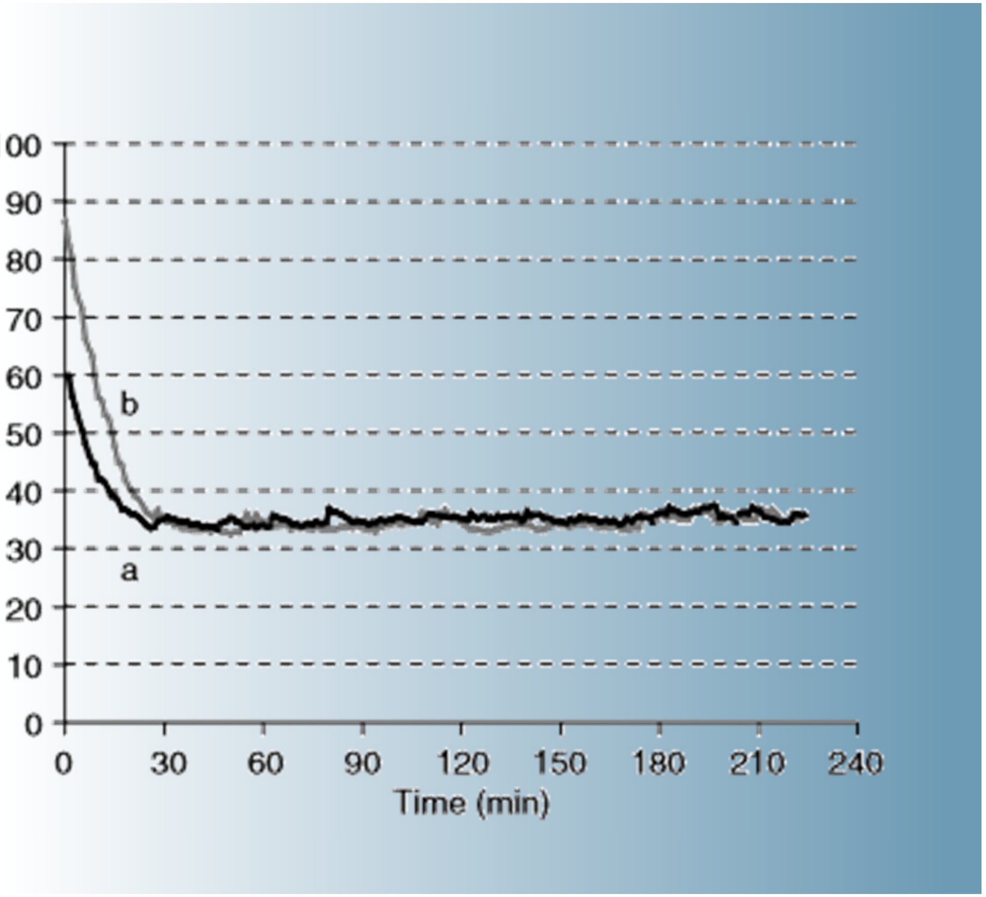
Ultrafiltration Control

Substitution Flow and TMP Profiles

HF80 filter and Manual Post-HDF

HF80S, Manual Post-HDF

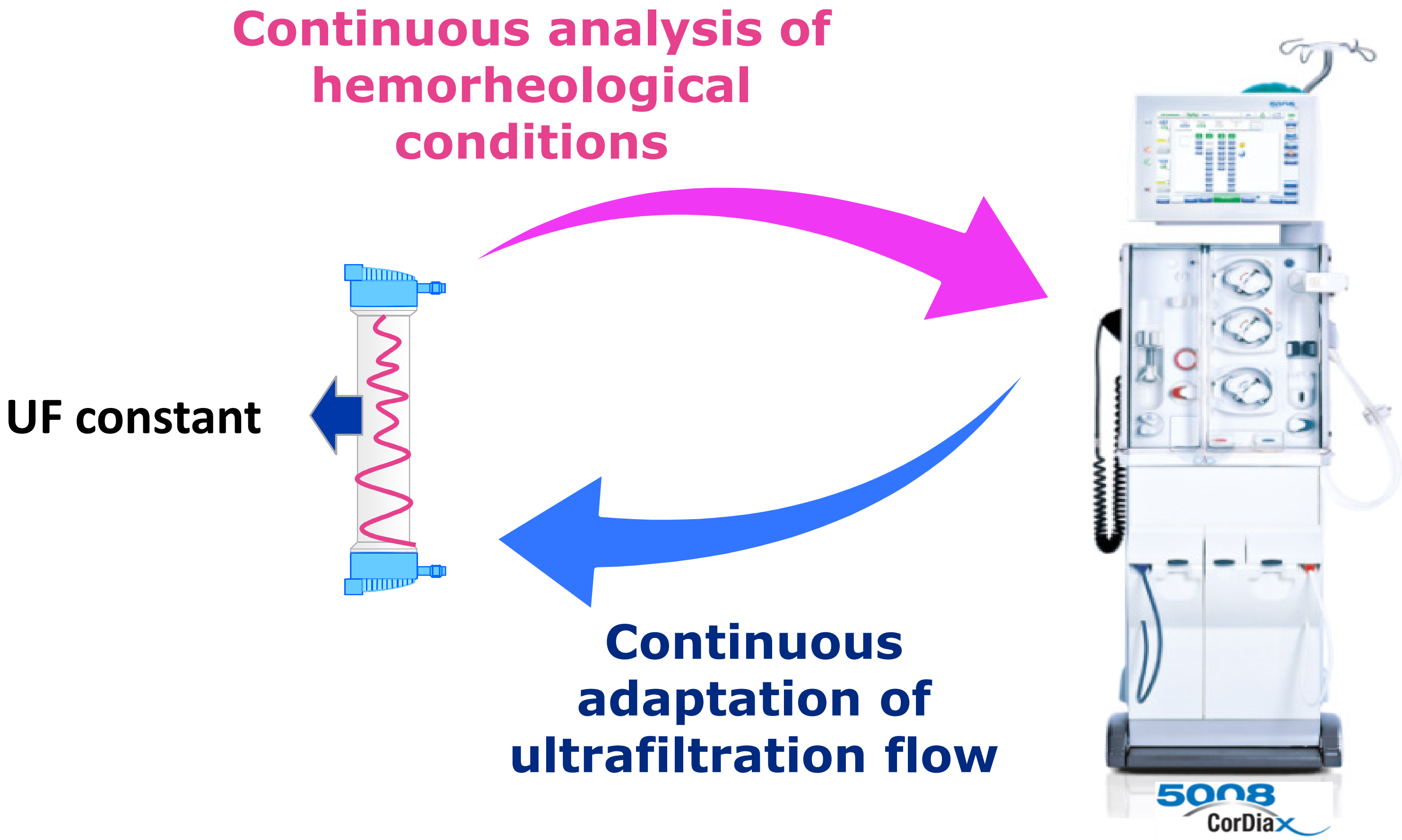




Vaussenat F et al, ASAIO J. 1997 ;43(6):910-5.

Vaussenat F et al, Nephrol Dial Transplant. 2000;15(4):511-6.

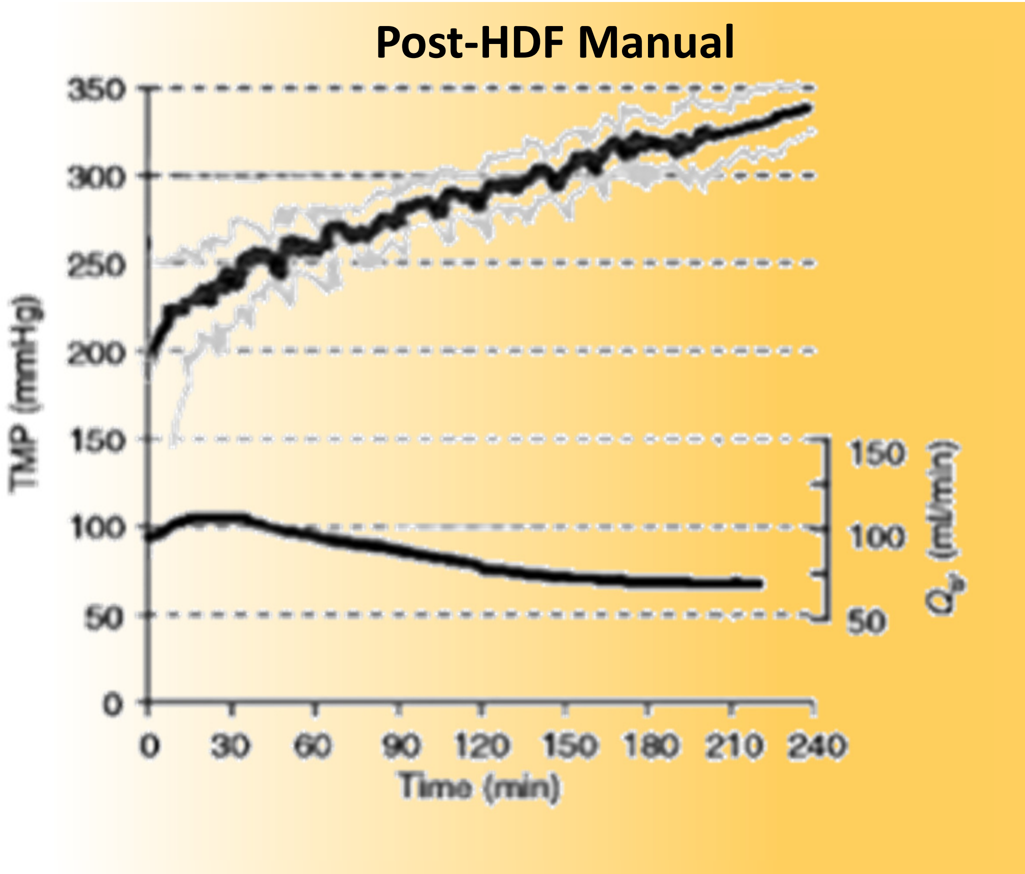
Innovative Technology & Intelligent HDF Machine Facilitate Achievement of High Convective Volume

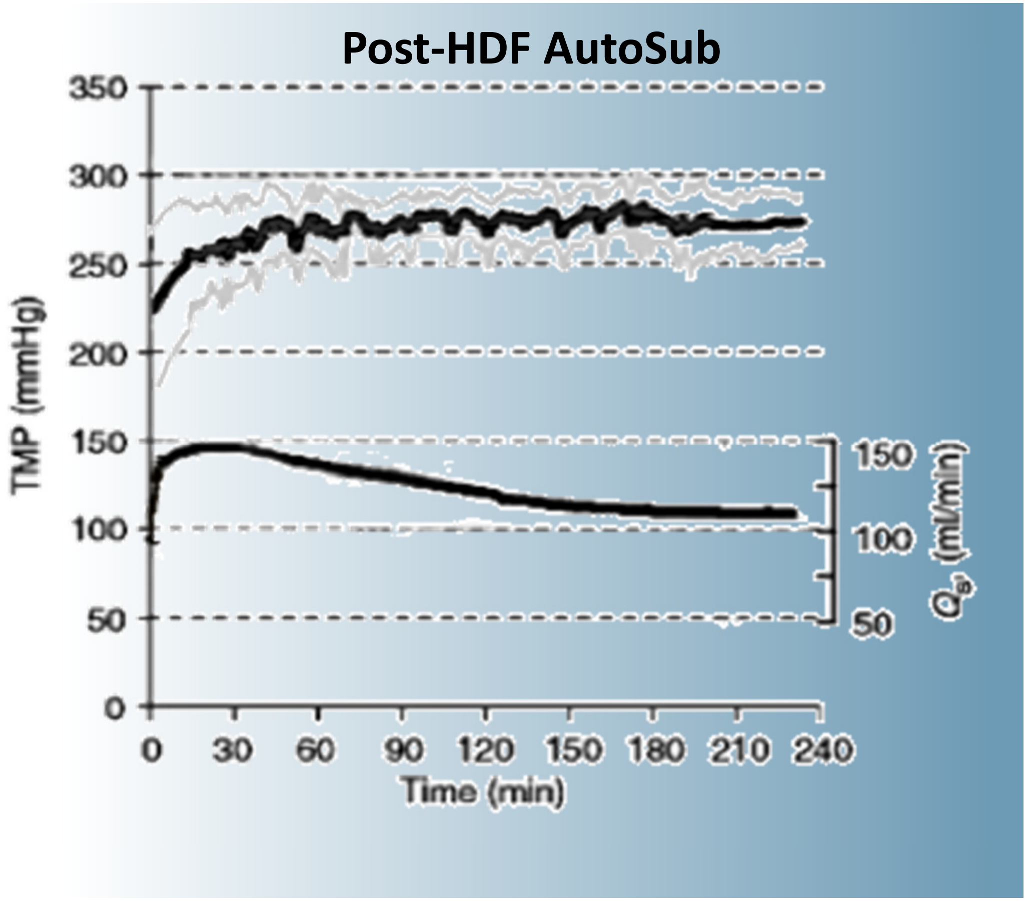


Ultrafiltration control by AutoSub*plus* with FX CorDiax

Substitution Flow and TMP Profiles

Post-HDF Manual vs Pre-HDF AutoSub





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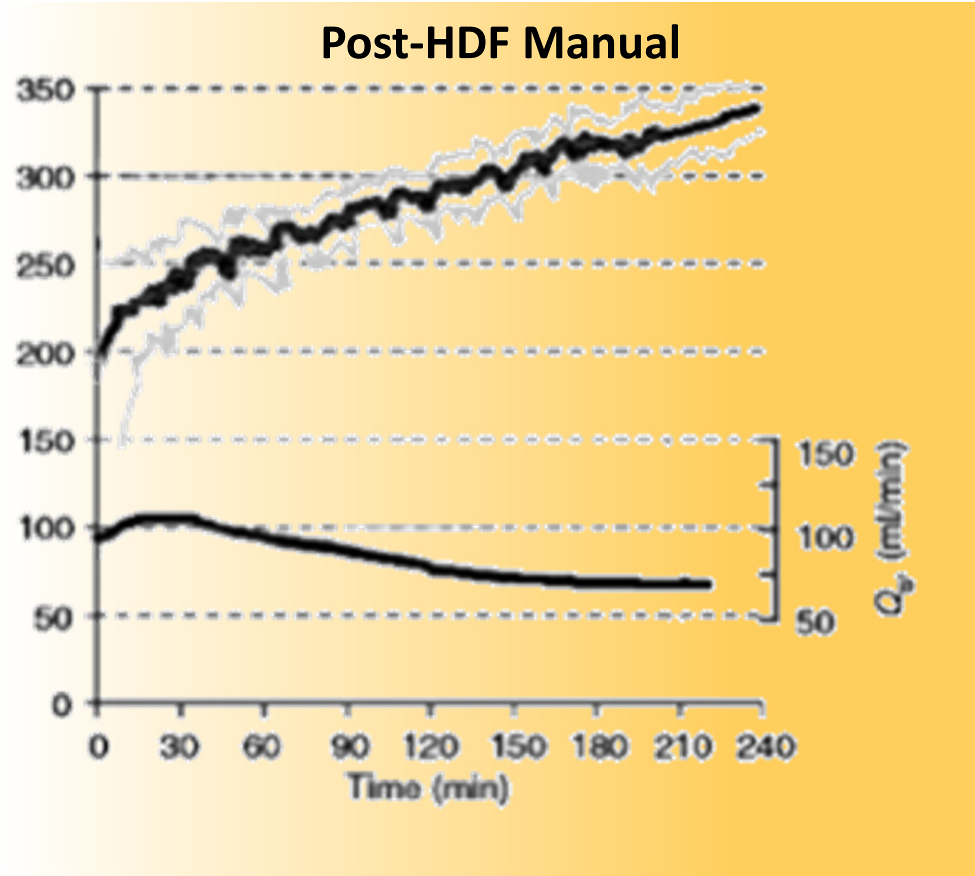
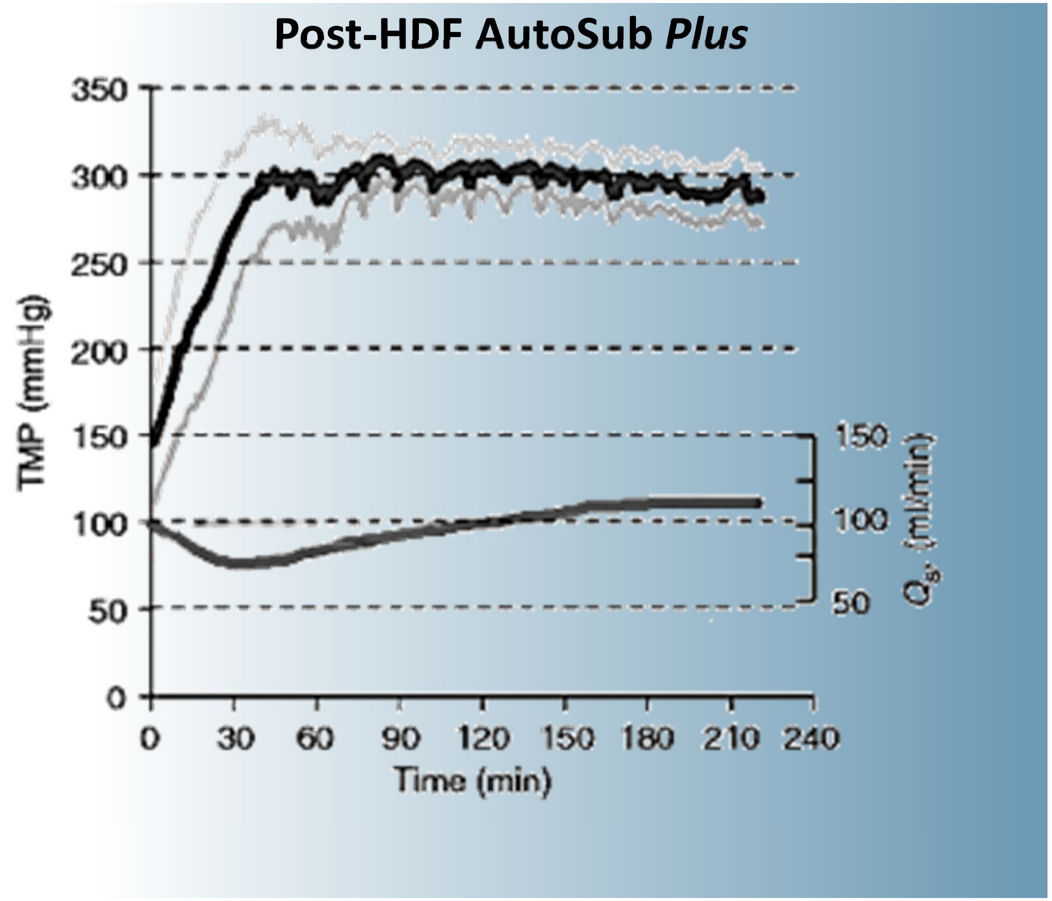
Substitution Flow and TMP Profiles

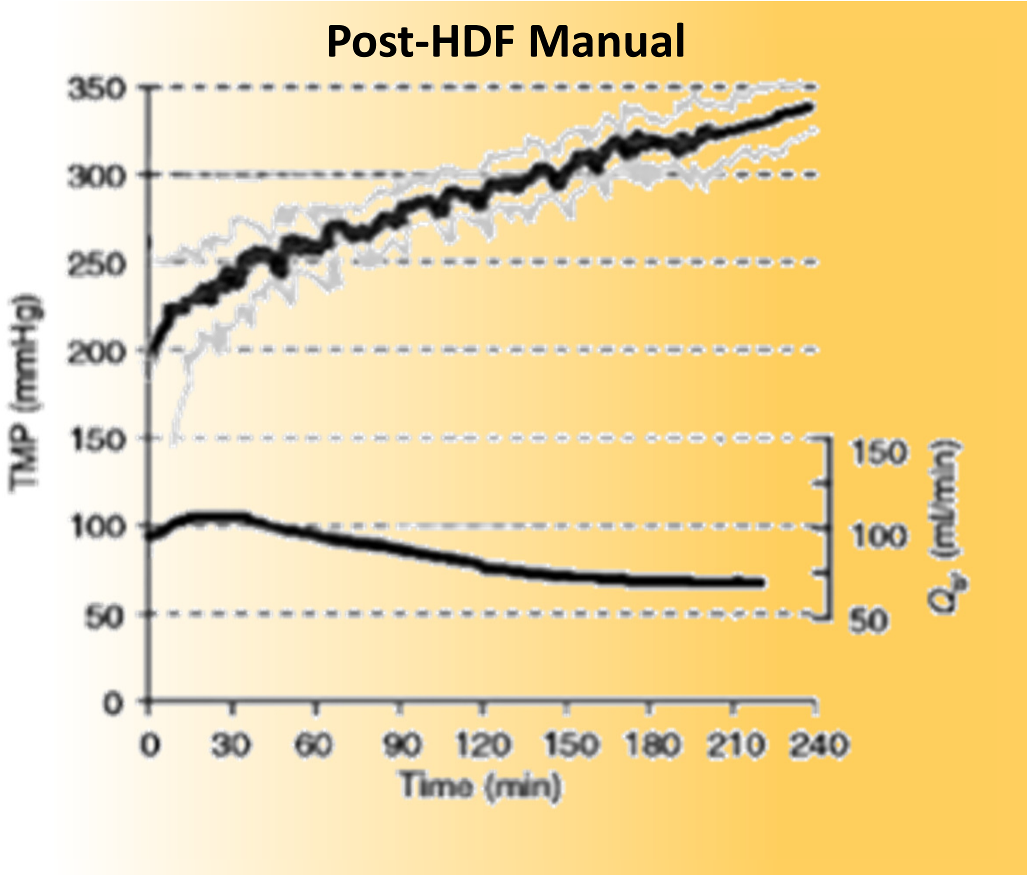
Post-HDF Manual vs Post-HDF AutoSub *Plus*

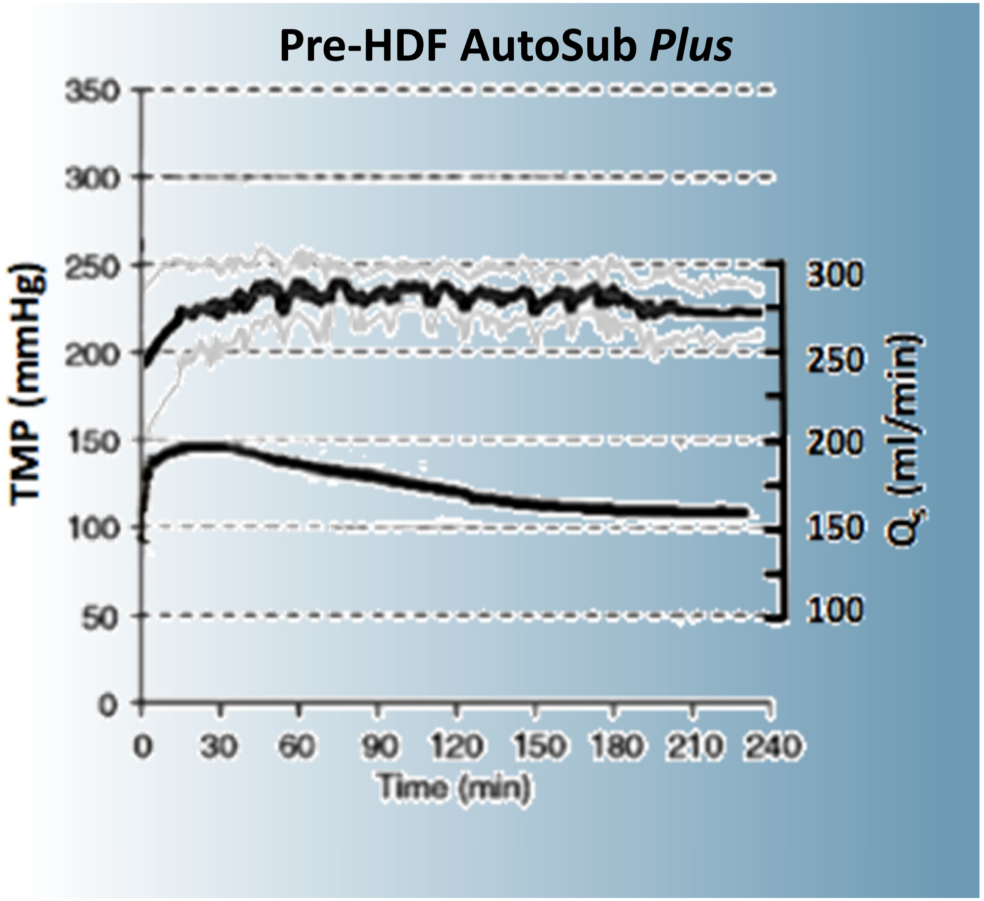




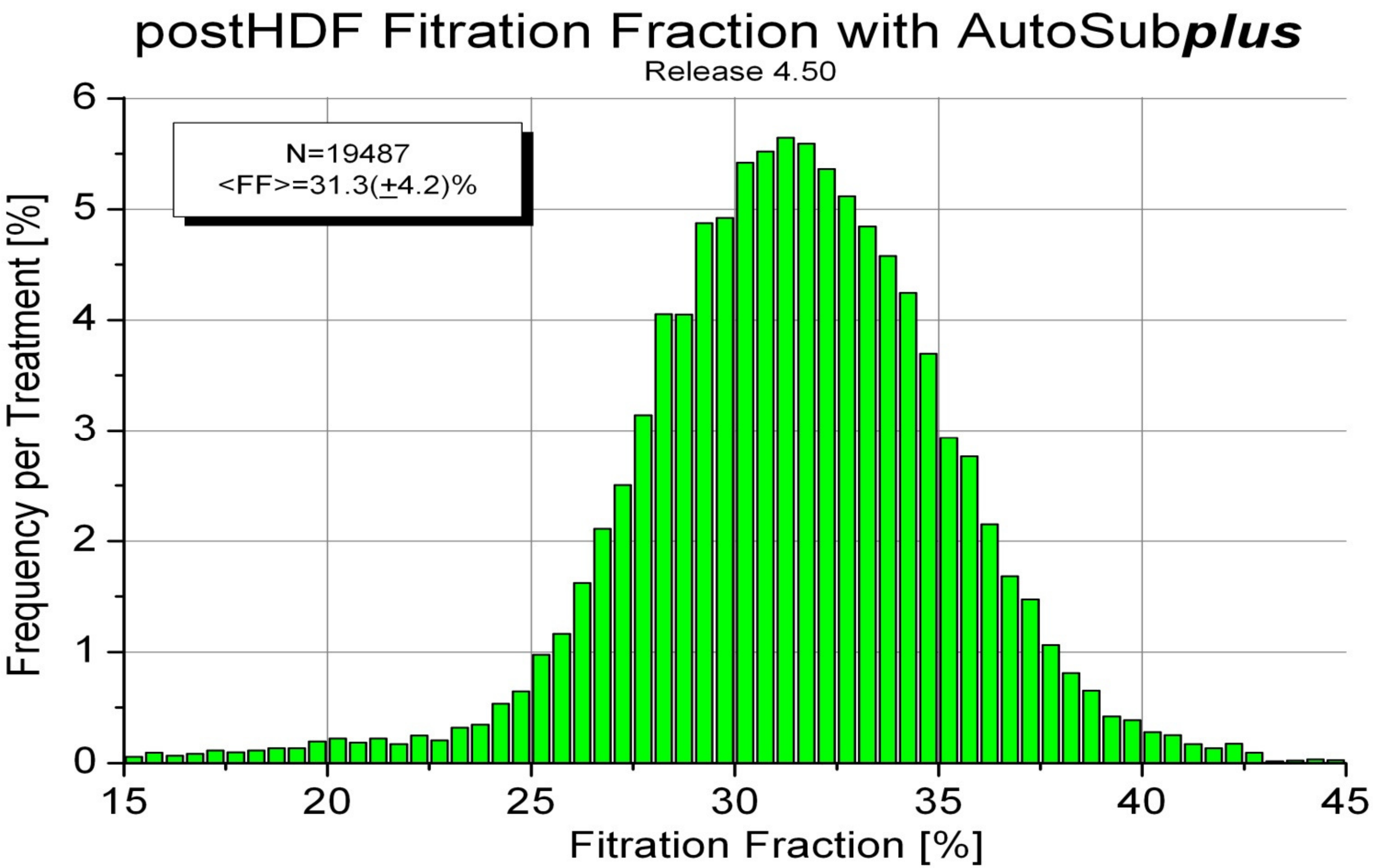
Substitution Flow and TMP Profiles

Post-HDF Manual vs Pre-HDF AutoSub *Plus*





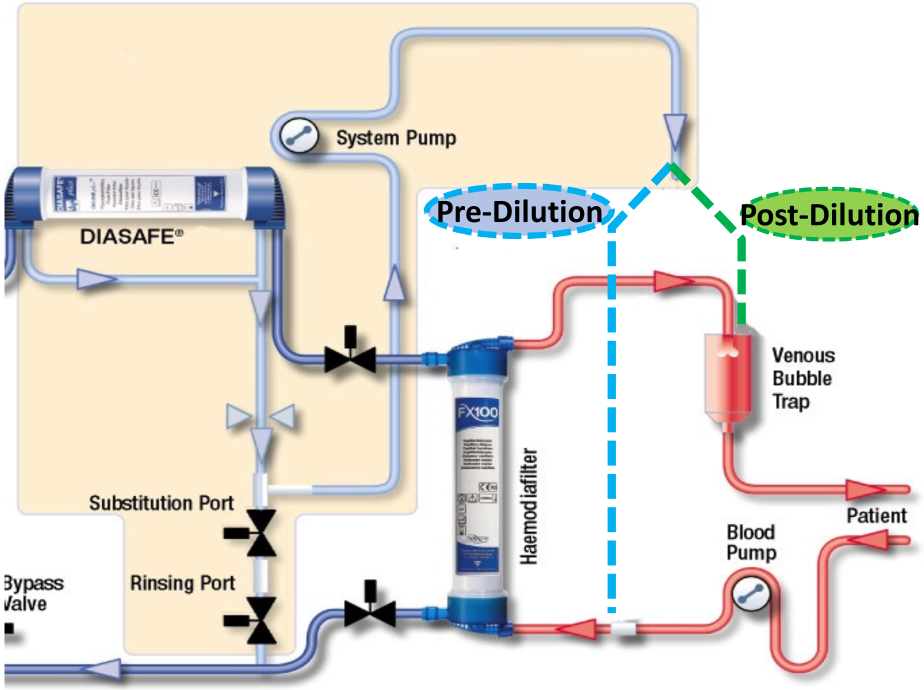
Automatic Control of Ultrafiltration by AutoSub Plus
Increases Filtration Fraction and Convective Volume



Marcelli D et al, *Int J Artif Organs* 2015; 38(5):244-50.

Mode of Substitution Matters

Mixed-Dilution HDF:
as alternative



Automated Delivery

↓

TMP Control

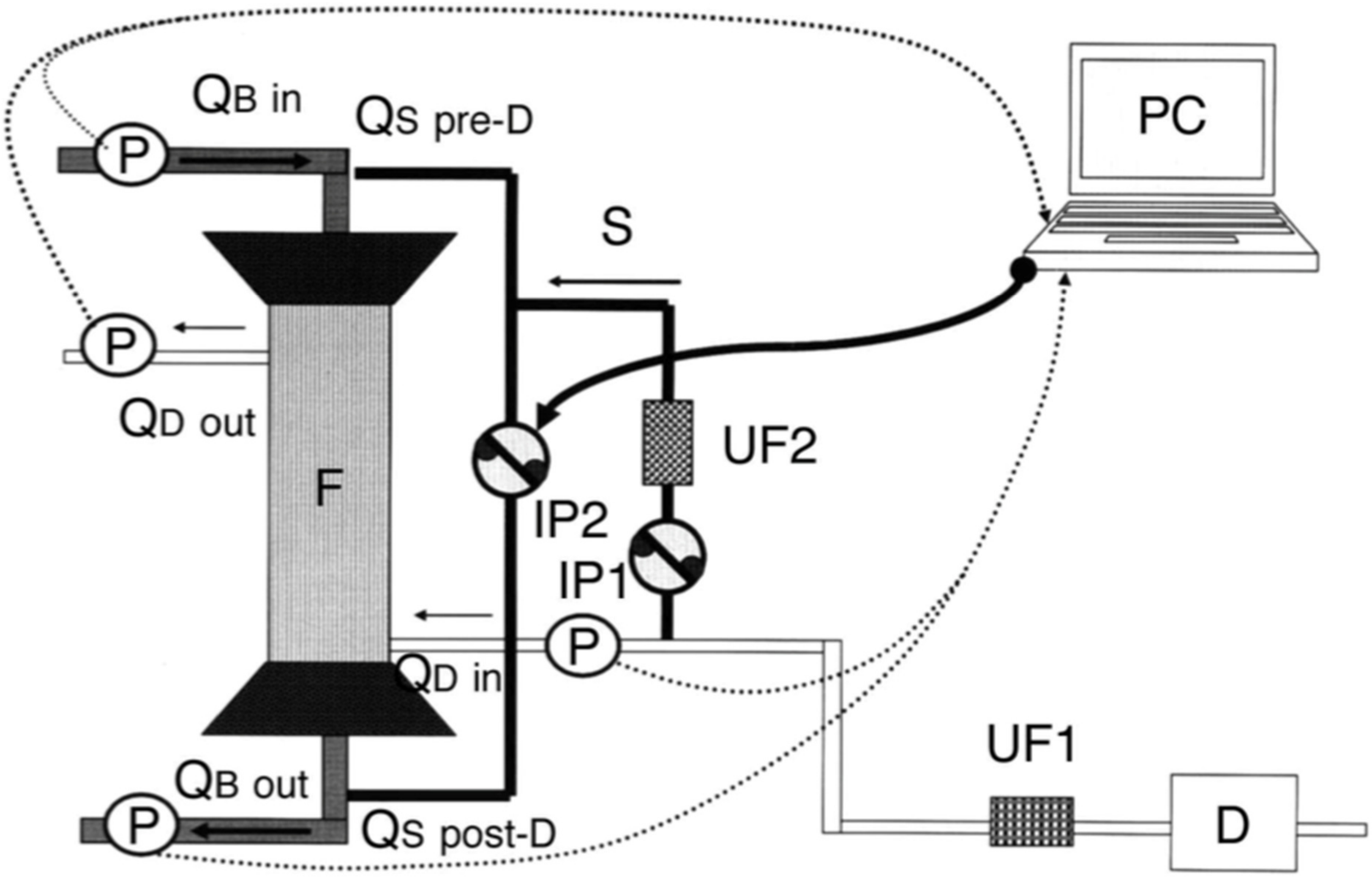
↓

Substitution Adjustment

↓

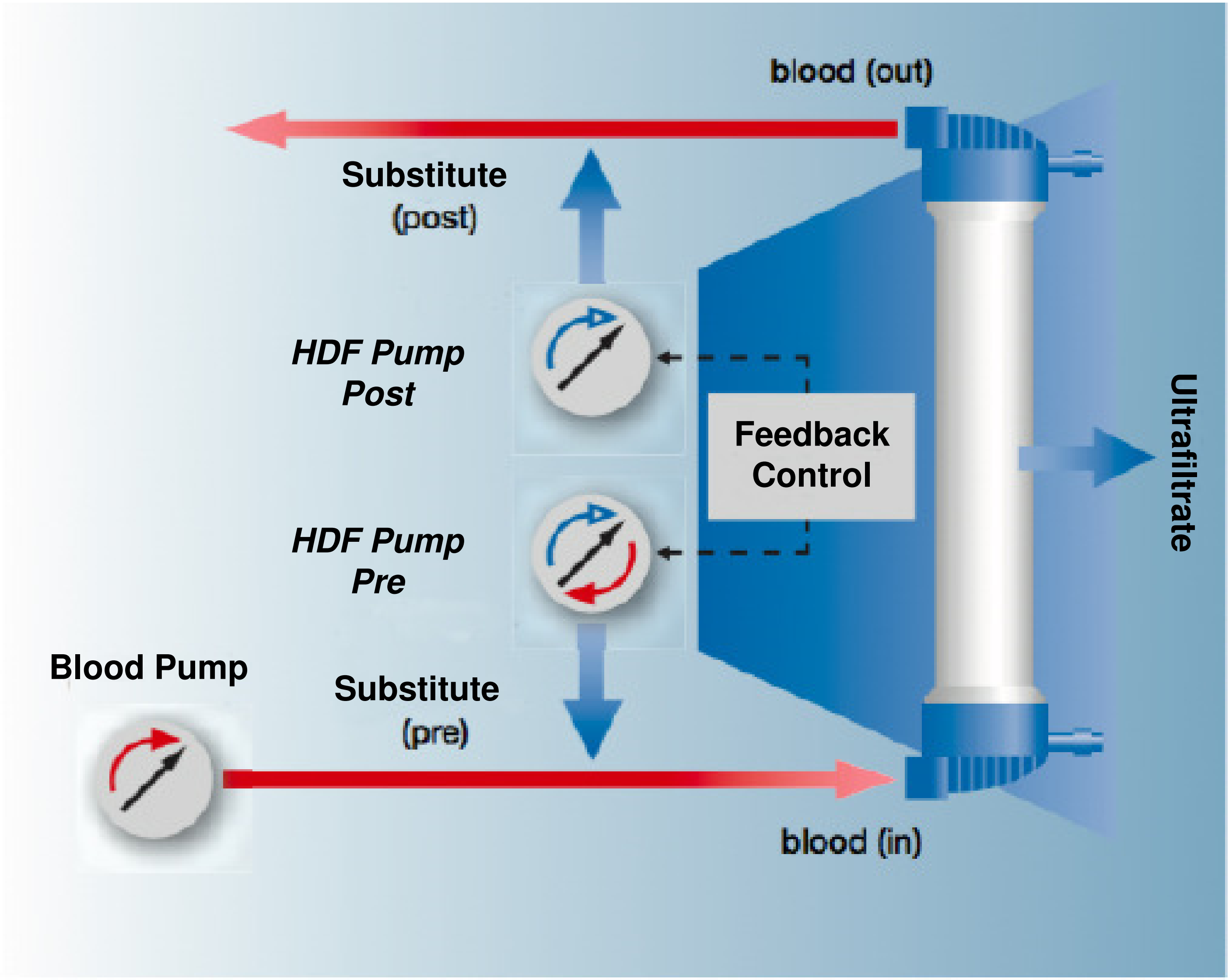
Ultrafiltration Control

Mixed-Dilution Hemodiafiltration
Original Setting During Clinical Trial



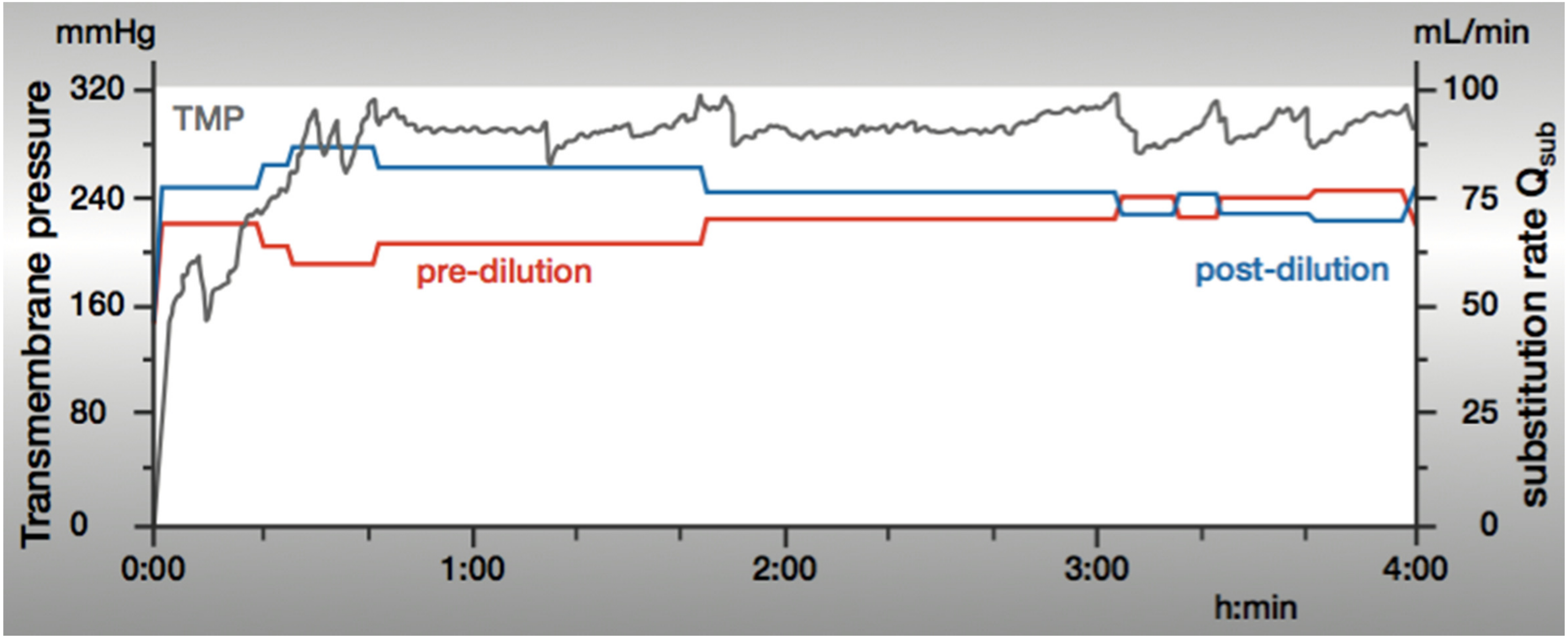
Pedrini LA et al, *Kidney Int.* 2003;64:1505–1513

Mixed-Dilution Hemodiafiltration



Pedrini LA et al, *Kidney Int.* 2003;64:1505–1513

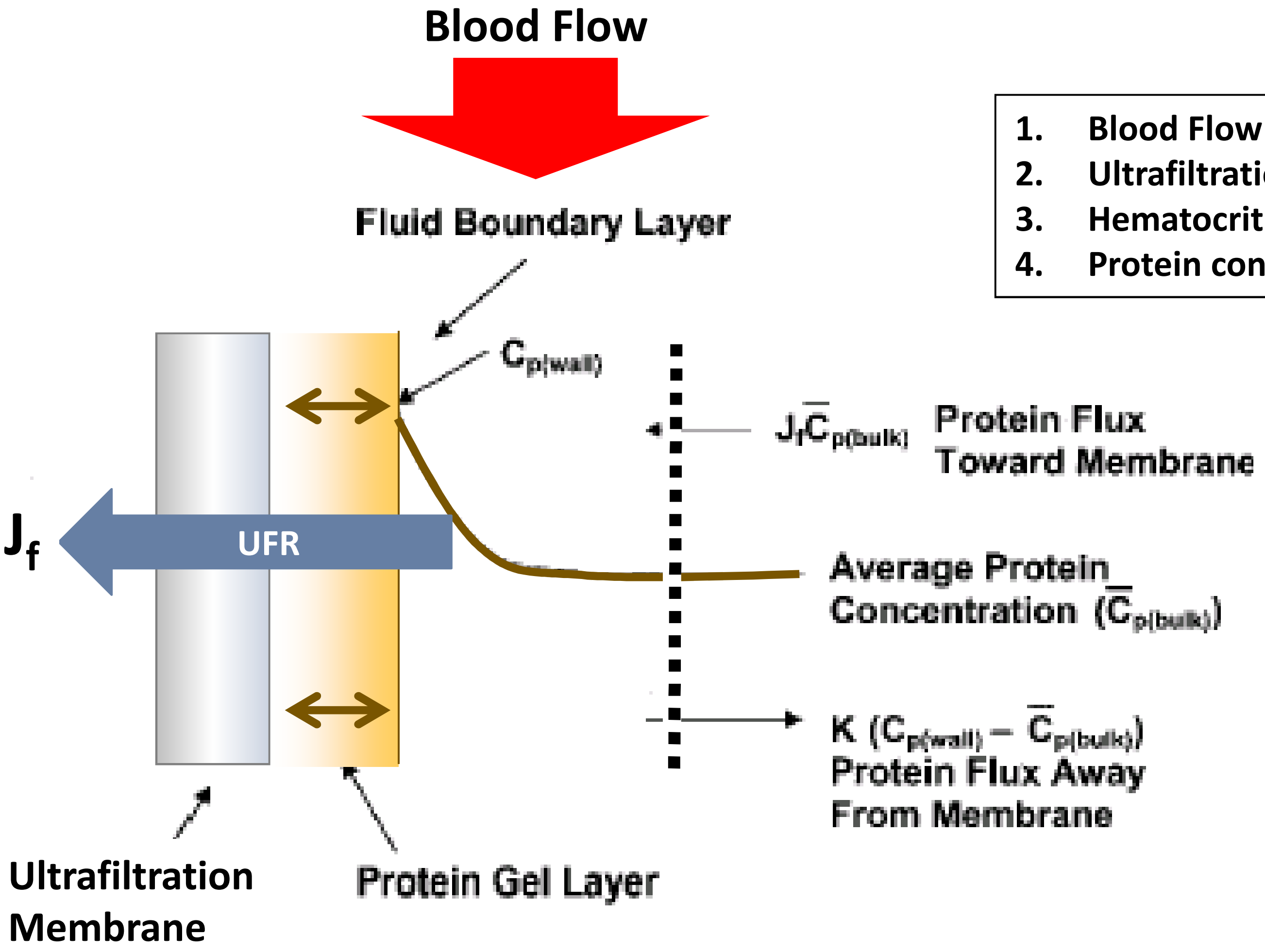
Typical Behavior of Substitution Flow (post/pre) in Mixed-HDF



Pedrini LA et al, *Kidney Int.* 2006;69:573–579

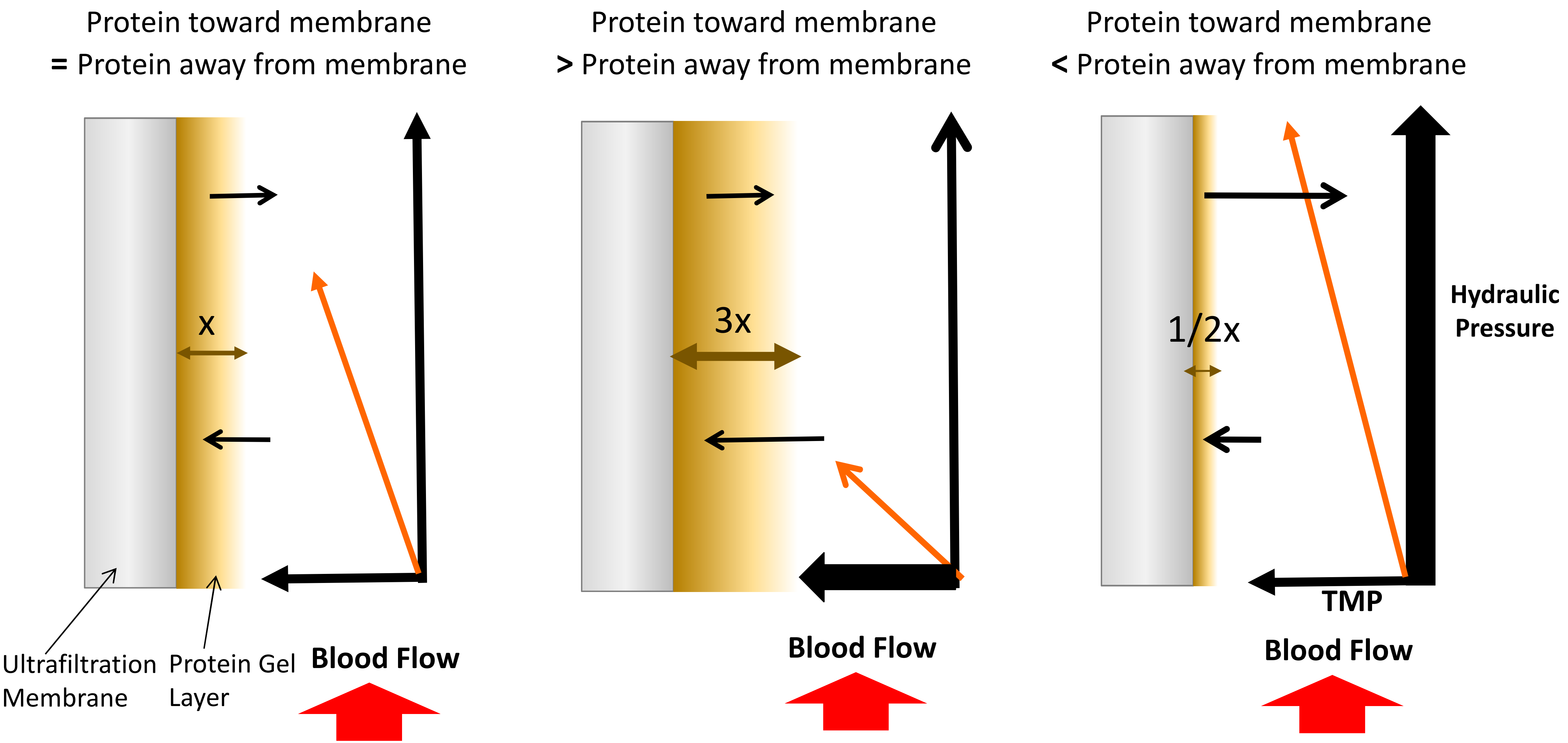
Protein Cake Formation onto the Membrane

Protein Gel Layer Formation During Convective Therapy



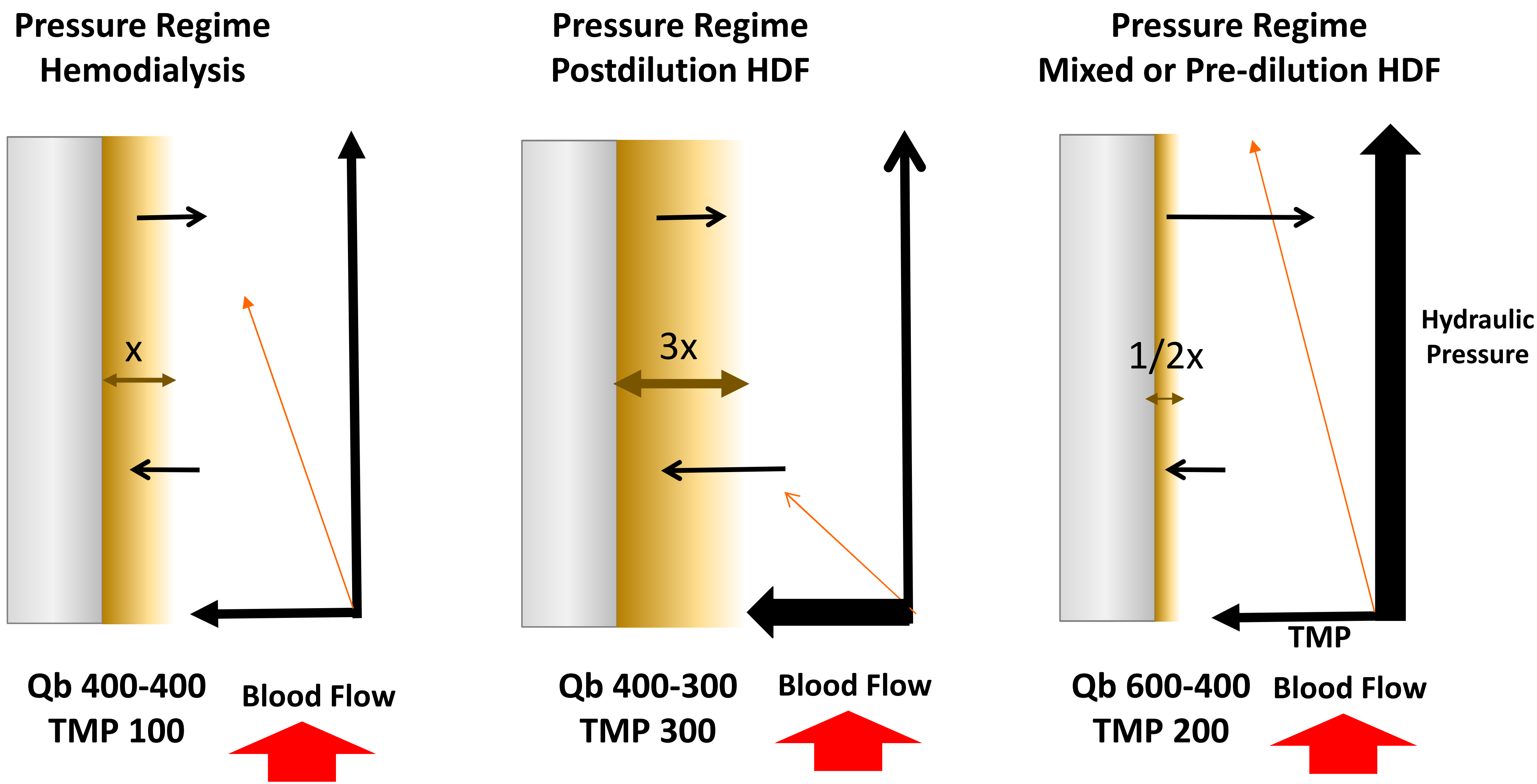
1. **Blood Flow**
2. **Ultrafiltration**
3. **Hematocrit**
4. **Protein concentration**

Protein Gel Layer Formation
Effects of Blood Flow, Shear Rate/Stress & TMP

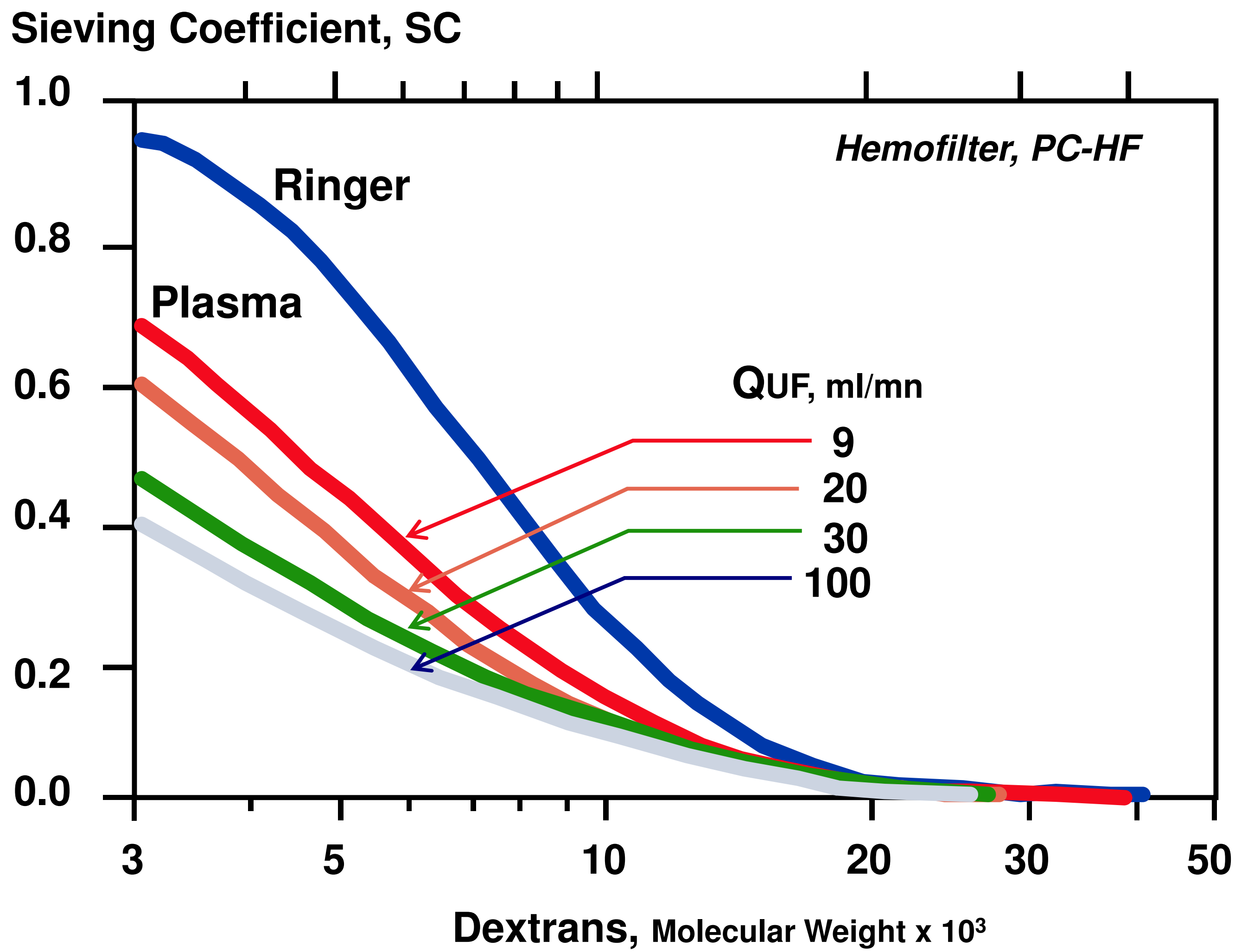


Protein Gel Layer Formation

Hemodialysis, Postdilution vs Mixeddilution HDF



Ultrafiltration Flow & Protein Gel Layer Formation
Reduces Solutes Sieving Coefficient



Henderson LW et al, *ASAIO*

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   - **Medical & engineering rationale**
4. How to use mixed-HDF ?
   - Technical aspects
   - Nursing & Doctor perspectives
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6. What results ?
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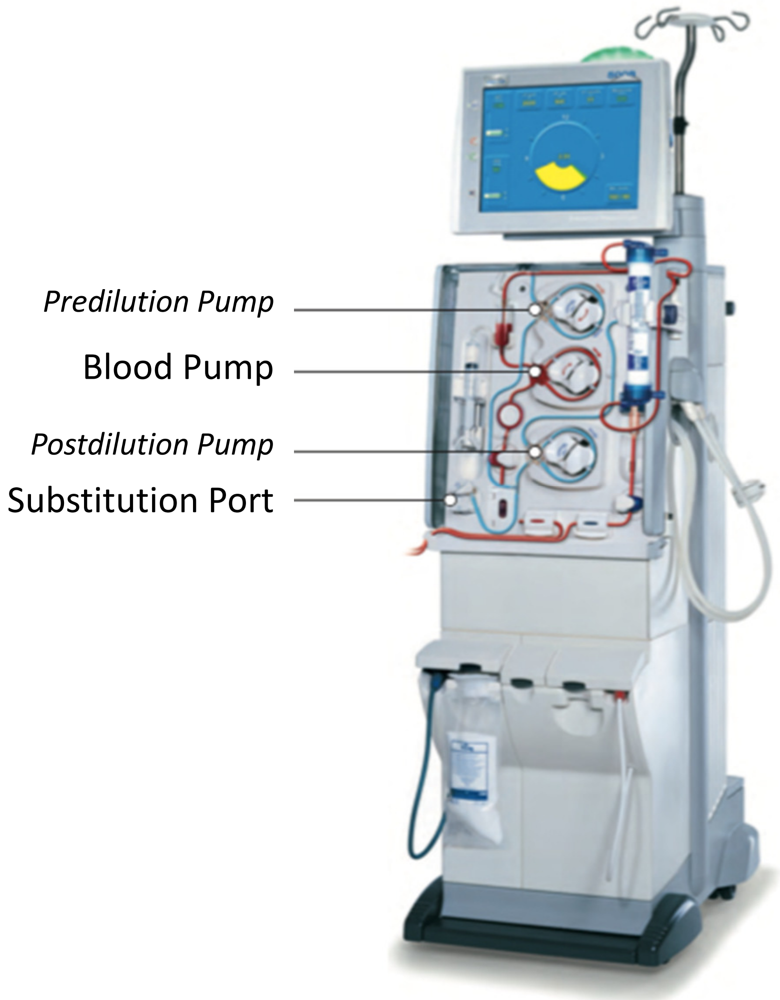
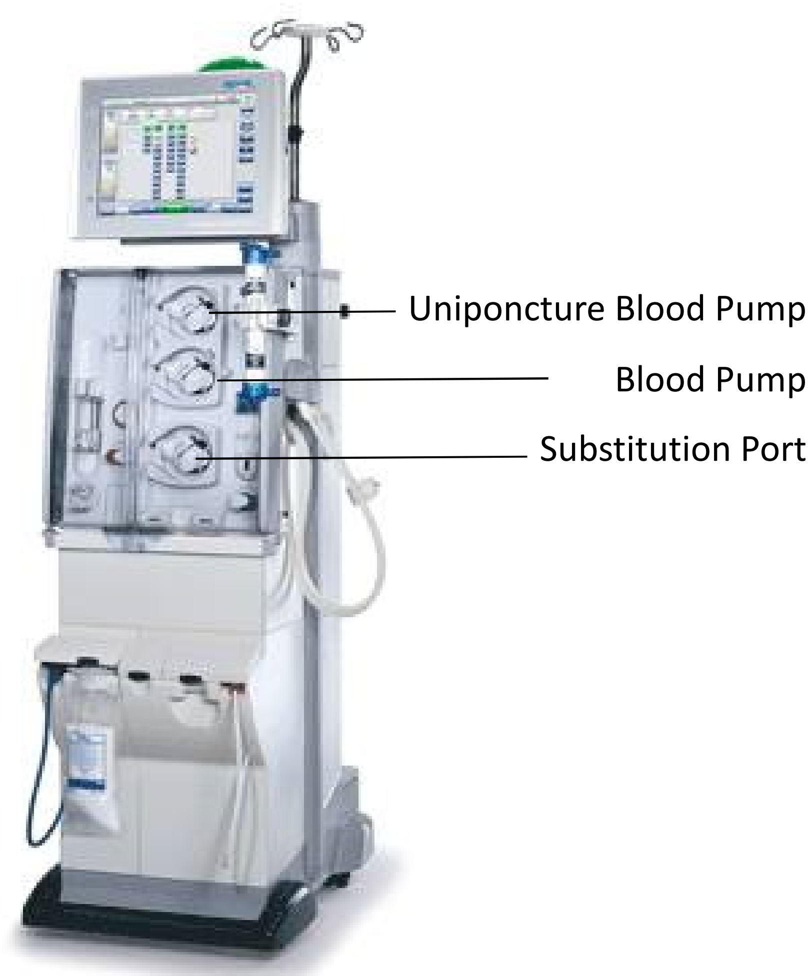
Mixed-Dilution HDF Machine vs Standard HDF



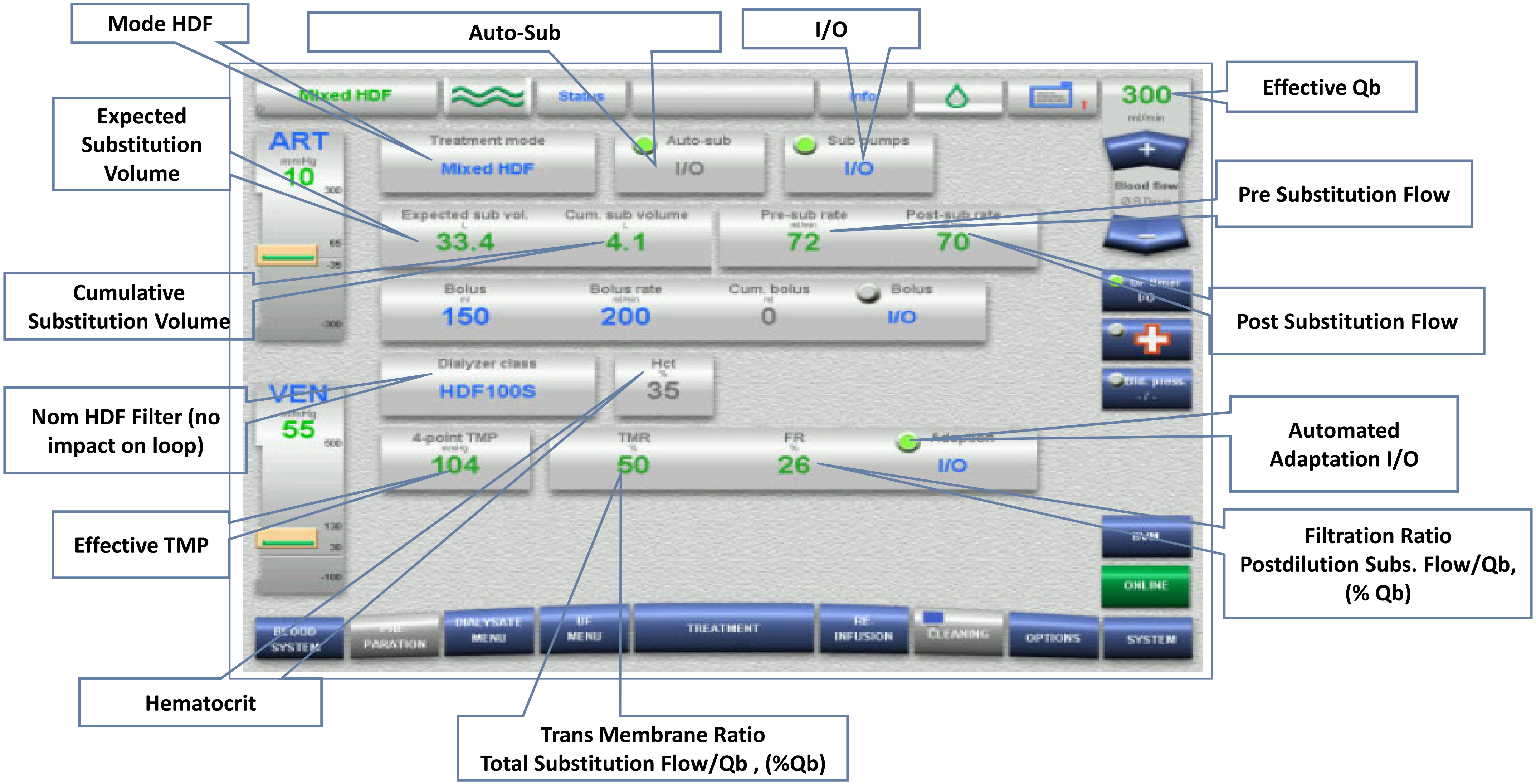
5008 Mixed HDF



5008 & 5008S HDF Post or Pre-HDF

Mixed-Dilution HDF Machine

Prescription & Monitoring Screen



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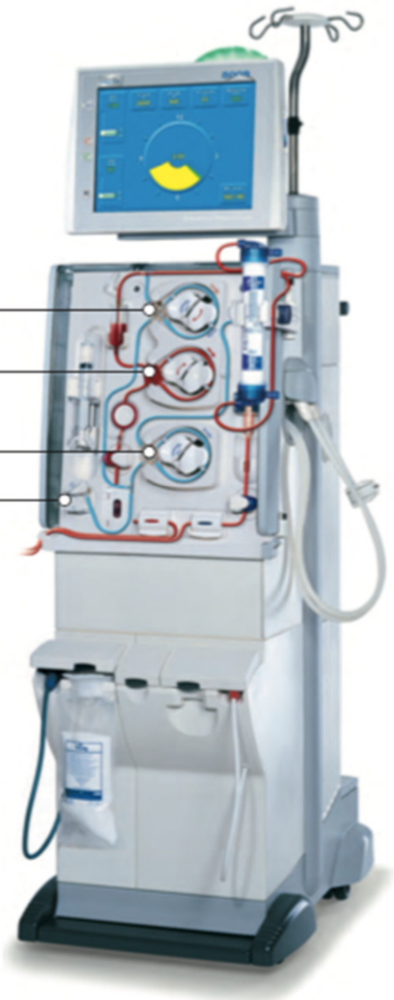
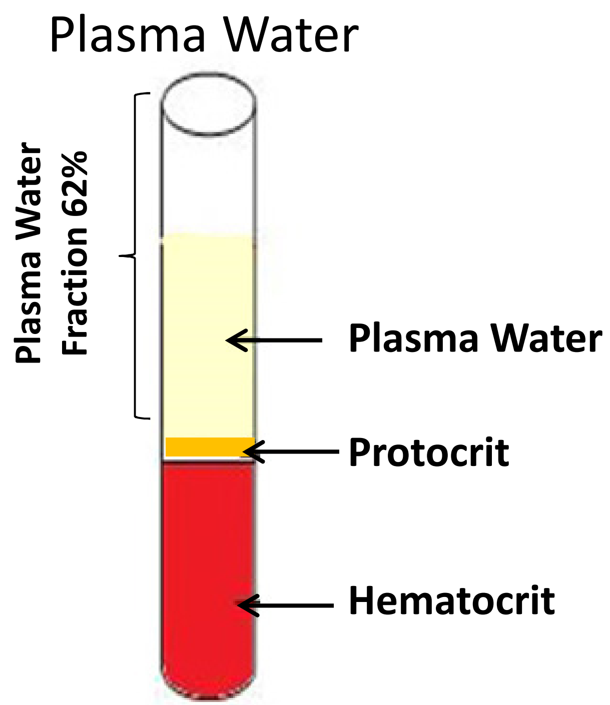


5008 Mixed HDF

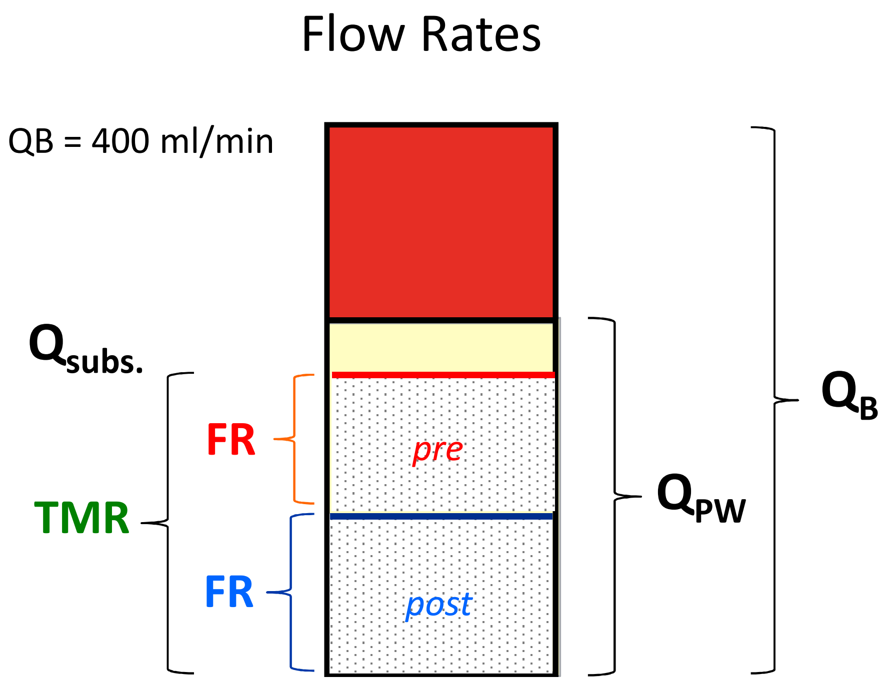
5008 & 5008S HDF Post or Pre-HDF

Plasma Water and Water Flow Rates



H = 33 %
(Hb = 11 g/dl)
TP = 70 g/l

TMR : Transmembrane Ratio
FR : Filtration Ratio

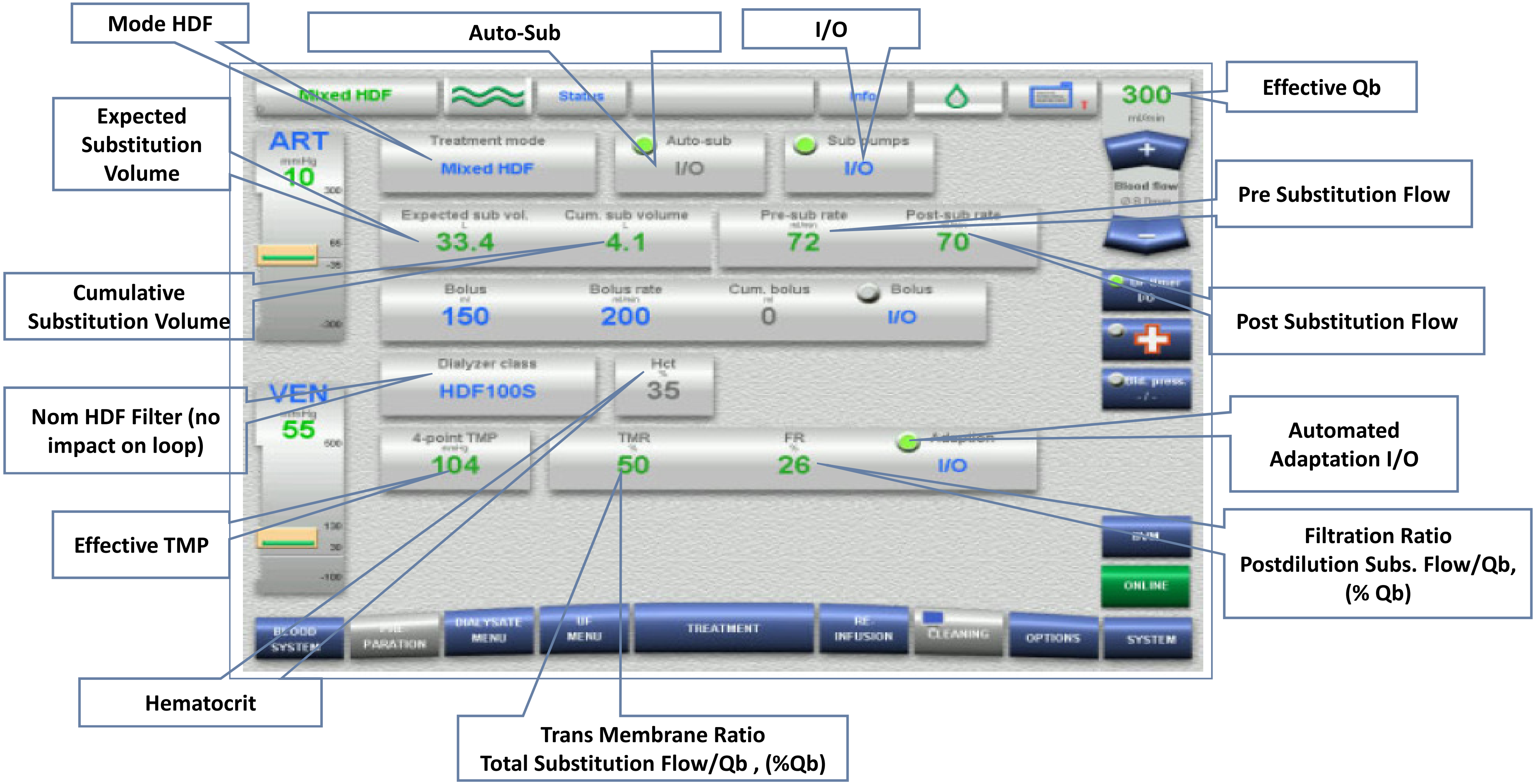


Plasma Water Fraction = (1 – H) x (1 – PT)
Plasma Water Fraction = (1 – 0,33) x (1 – 0,07) = **0,62**

Plasma Water Flow = QB x Plasma Water Fraction
Plasma Water Flow = 400 x 0.62 = **248 ml/min**

Mixed-Dilution HDF Machine

Prescription & Monitoring Screen



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HDF Predilution vs Mixeddilution with Low Blood Flow

VA: 31 AVF, 7 CVC
G : 22 M, 16 F
73.8 ±12.8ys
Dry weight 74.1±10.7 kg
HD : 4:00 x 3 wk

38 ESKD patients – 6 centers

Low blood flow ≤300ml/min

↓

Cross-Over RCT

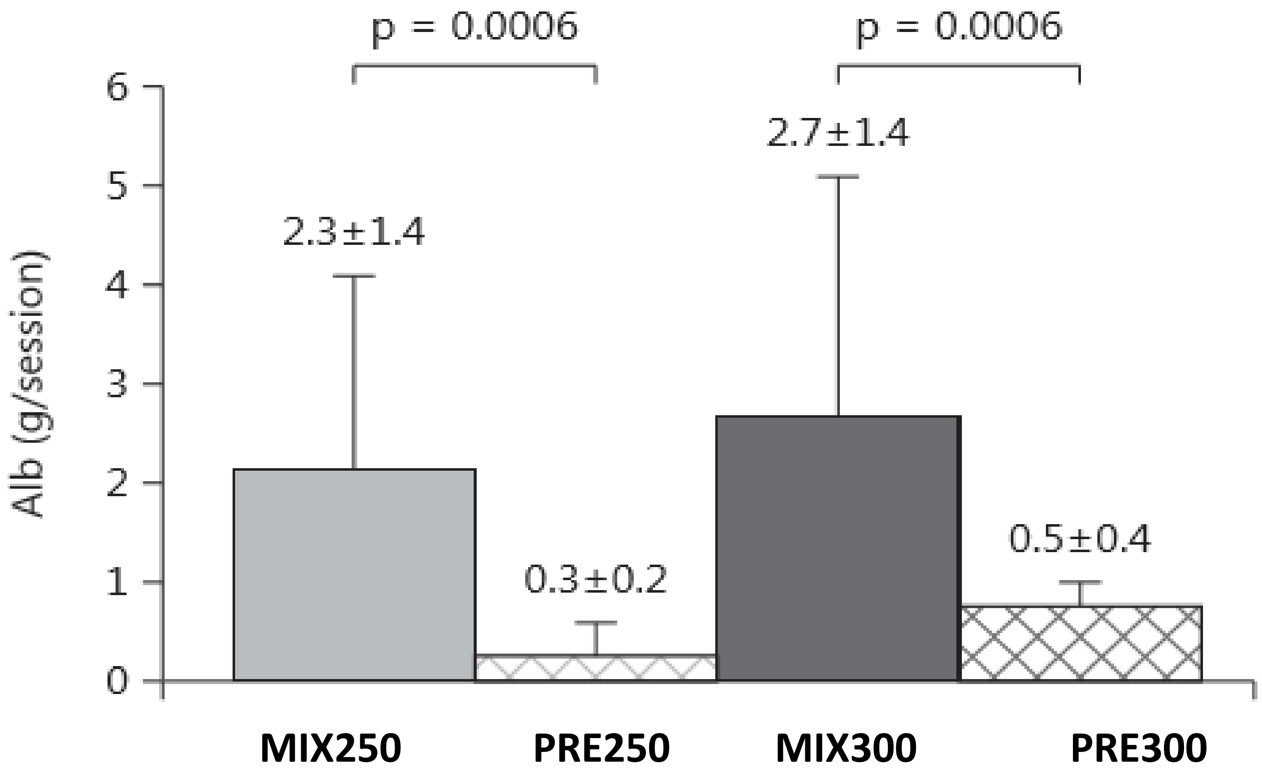
HDF pre Qb250	**HDF pre Qb350**	**HDF mixed Qb250**	**HDF mixed Qb300**

FX1000HDF

eKt/v, PR-P, PR-B2M, PR-Myogl.
Albumin Lost

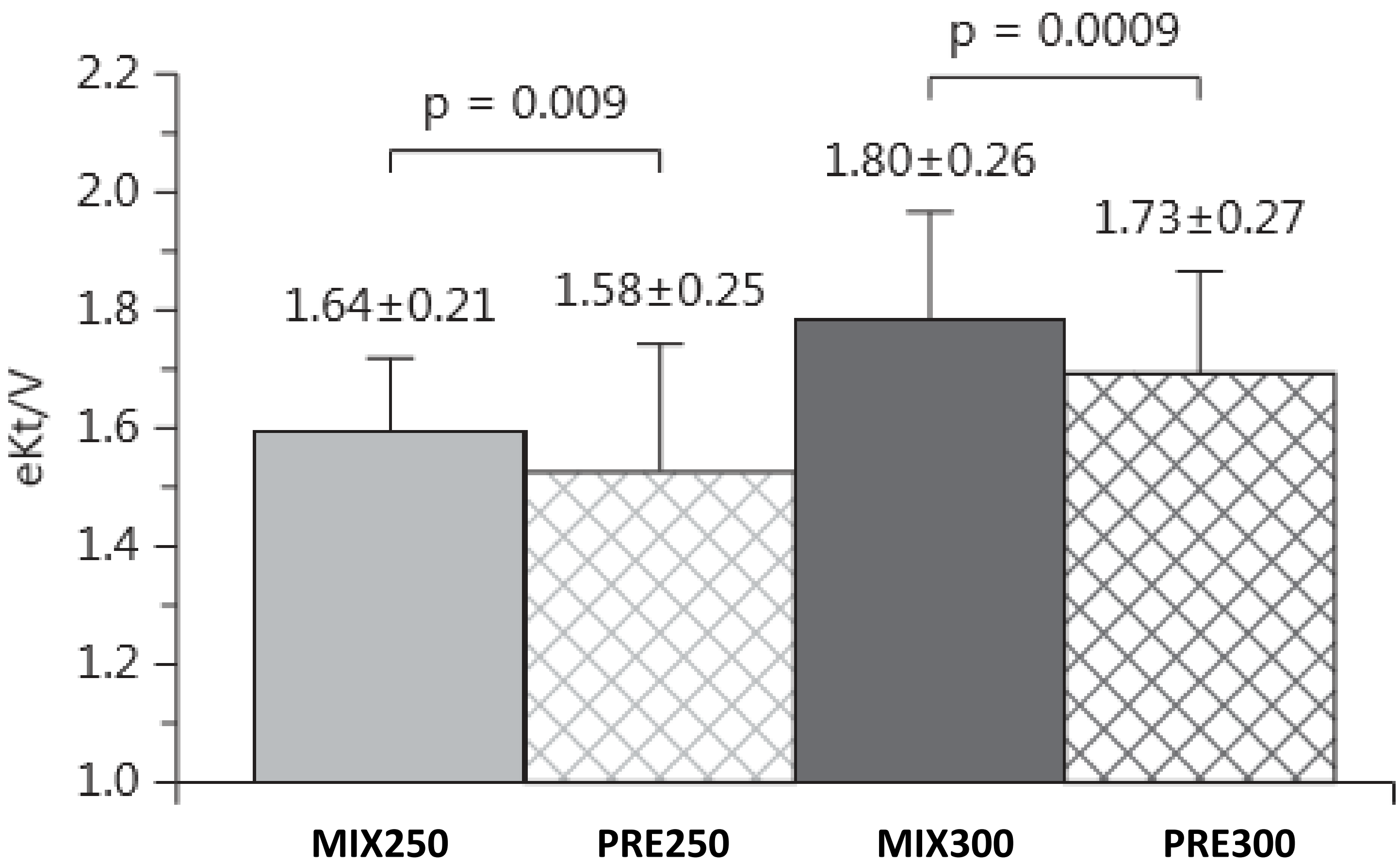
Potier J et al, *Blood Purif* 2013;36:78–8

Albumin Lost per Session



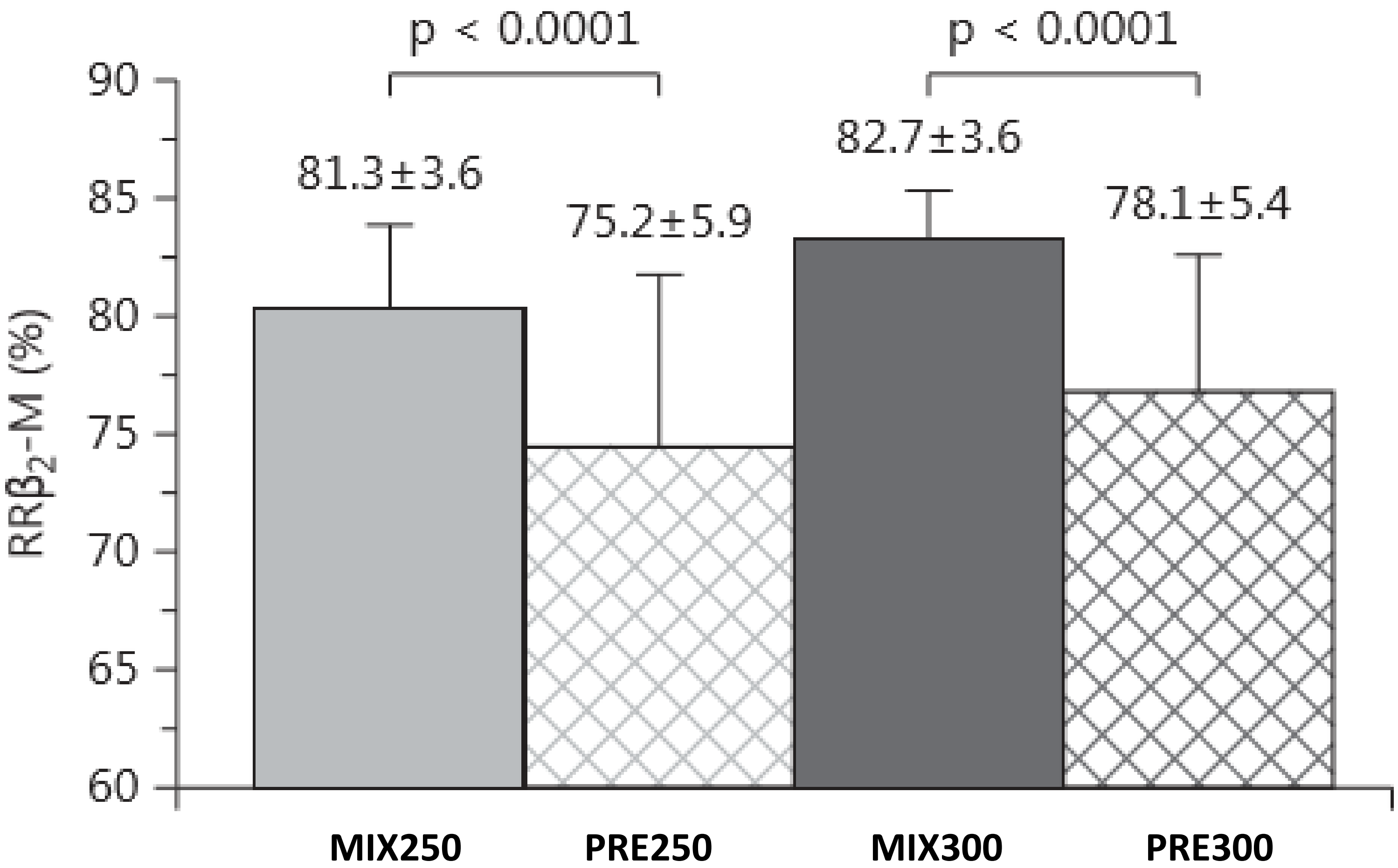
Potier J et al, *Blood Purif* 2013;36:78–8

eKt/V



Potier J et al, *Blood Purif* 2013;36:78–8

Percent Reduction of B2-Microglobulin



Potier J et al, *Blood Purif* 2013;36:78–8

Substitution Volumes Achieved in the Different Modalities

	PRE250	PRE300	MIX250	MIX300
UF/4 h, ml	2,463±576	2,449±641	2,436±774	2,377±736
PBV, l	57.3±1.9	68.5±2.5	57.4±1.8	67.6±3.3
VS_{Total}, l	36.5±7.6	41.3±10.9	23.8±1.9	28.5±2.4
VS_{Pre}, l	36.5±7.6	41.3±10.9	7.0±0.7	10.1±3.0
VS_{Post}, l			16.8±1.7	18.4±2.8
VS Post eq., L	18.2±3.8	20.7±5.5	27.3±2.3	33.5±3.9

PBV, processed blood volume
UF, weight loss
VS total, total ultrafiltration per session
VS pre, ultrafiltration in predilution
VS post, ultrafiltration in postdilution

Potier J et al, *Blood Purif* 2013;36:78–8

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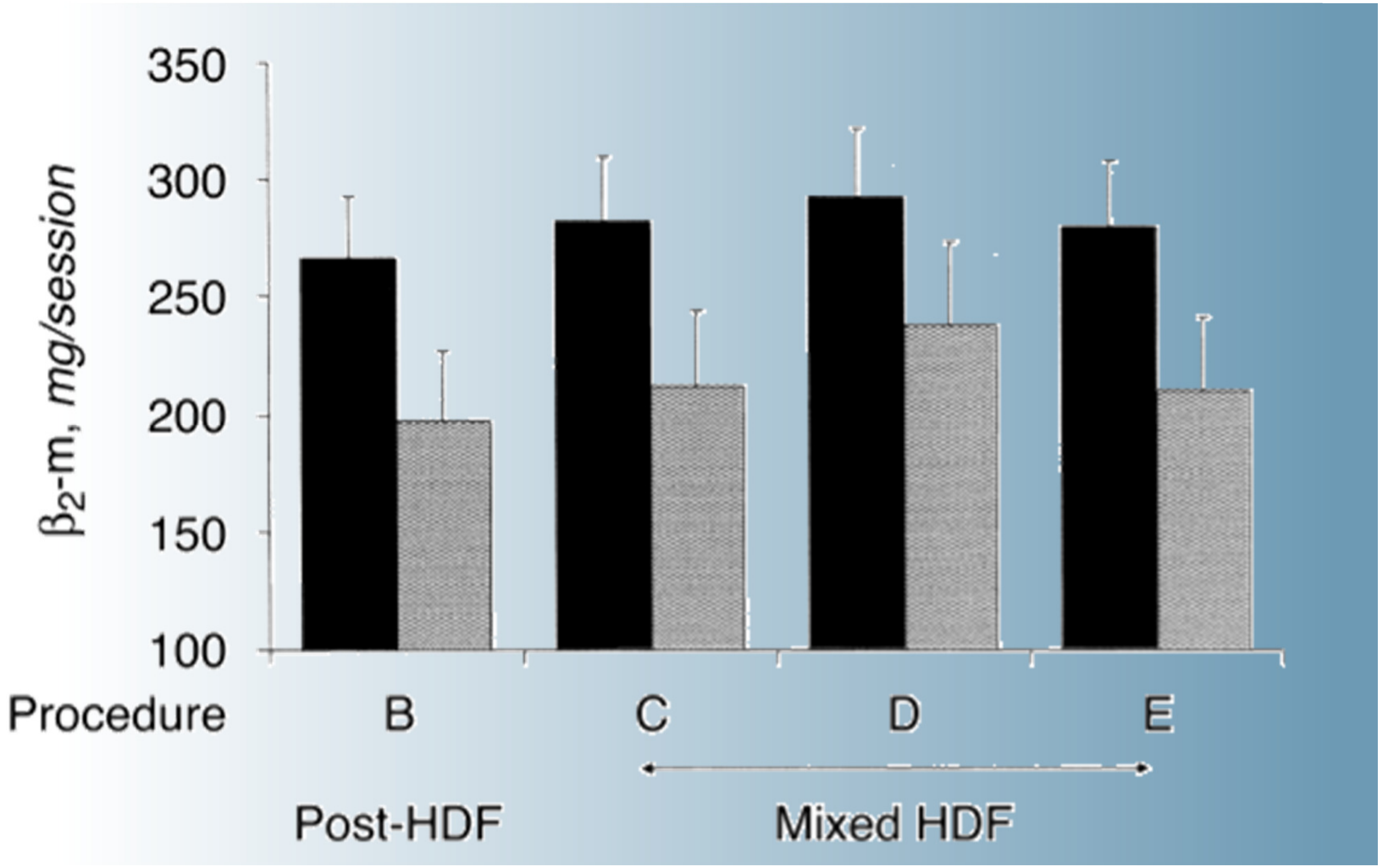
ß2-Microglobuline Removal Post vs Mixed-HDF with Different Regimes



Direct dialysis quantification by dialysate collection

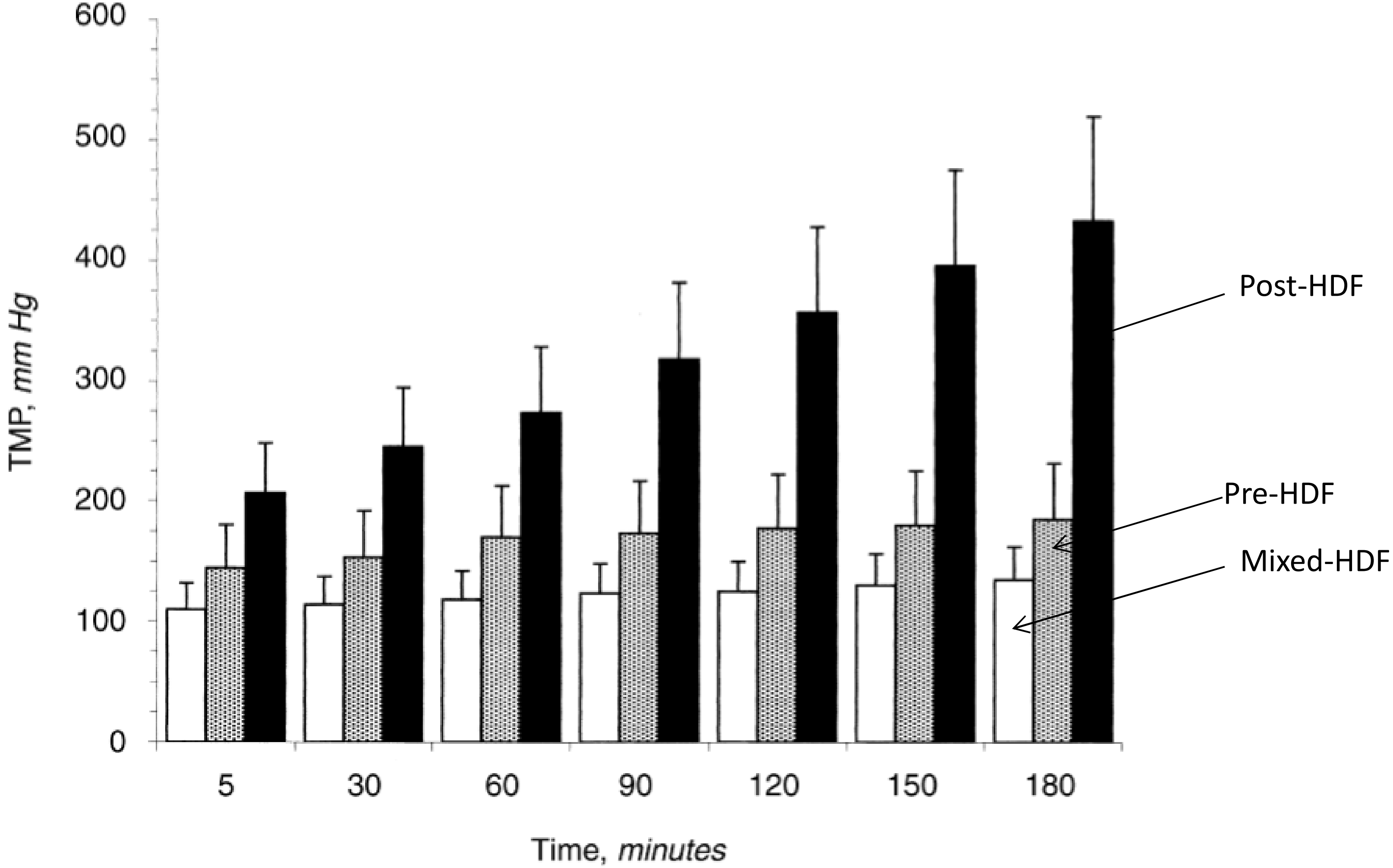
Pedrini LA et al, *Kidney Int.* 2003;64:1505–1513

Performances Comparison Post vs Mixed-HDF

		Hemodialysis	Post-hemodiafiltration	Mixed hemodiafiltration		
		Procedure A (N = 20)	Procedure B (N = 20)	Procedure C (N = 20)	Procedure D (N = 20)	Procedure E (N = 20)
Q_{PWin}	Start	227 ± 35	231 ± 34	230 ± 35	227 ± 36	229 ± 36
	End	210 ± 32	212 ± 31	212 ± 33	209 ± 35	210 ± 35
$Q_{Spre\text{-}D}$	Start	—	—	65 ± 28	135 ± 41	201 ± 29
	End	—	—	98 ± 41	174 ± 57	260 ± 60
$Q_{Spost\text{-}D}$	Start	—	145 ± 20	122 ± 18	114 ± 17	108 ± 15
	End	—	124 ± 22	90 ± 20	78 ± 28	48 ± 35
FF	Start	—	0.67 ± 0.05	0.67 ± 0.06	0.71 ± 0.04	0.74 ± 0.02
	End	—	0.64 ± 0.07	0.64 ± 0.05	0.67 ± 0.05	0.68 ± 0.05

Pedrini LA et al, *Kidney Int.* 2003;64:1505–1513

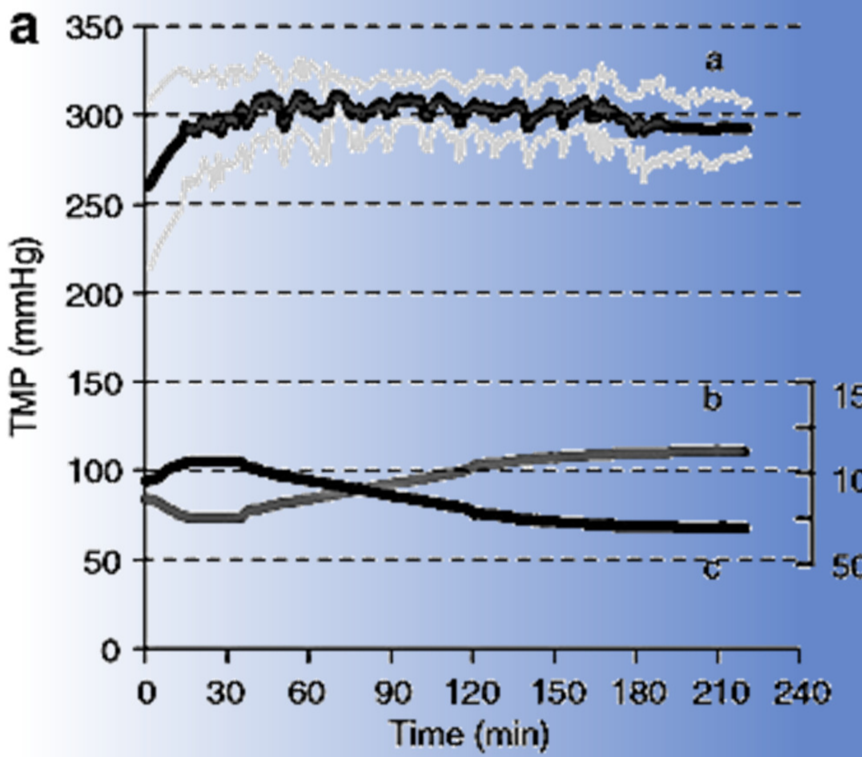
Transmembrane Pressure Behavior According to HDF Modalities



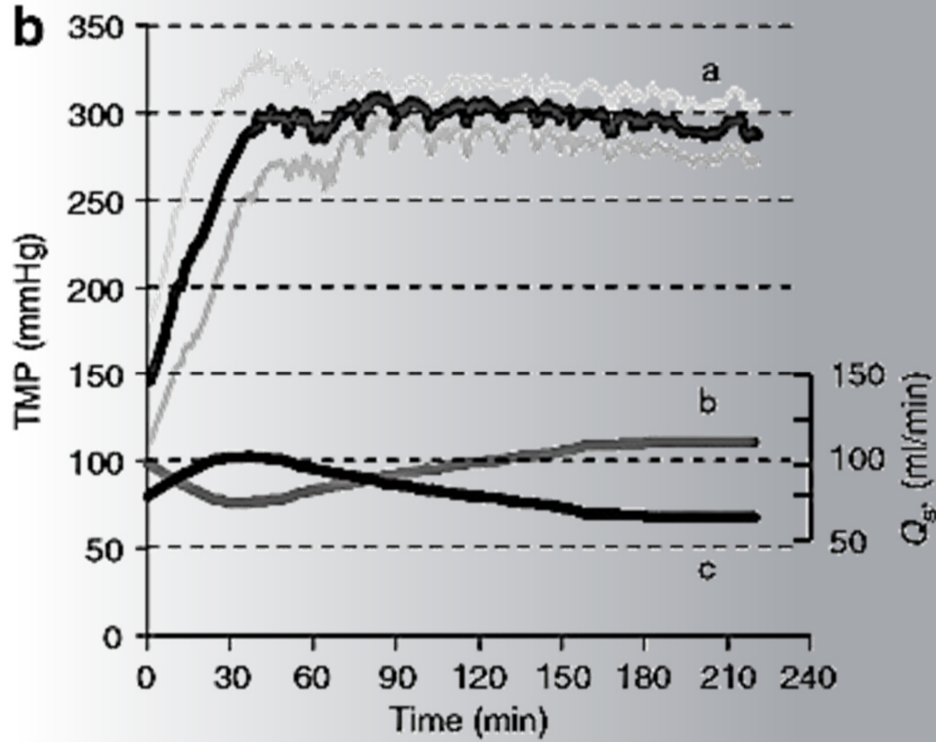
Pedrini L et al, *Kidney Int.* 2000;58:2155–2165

Transmembrane Modulation to Optimize Performances and Reduce Albumin Loss

Constant TMP at around 300mmHg



Profiled TMP



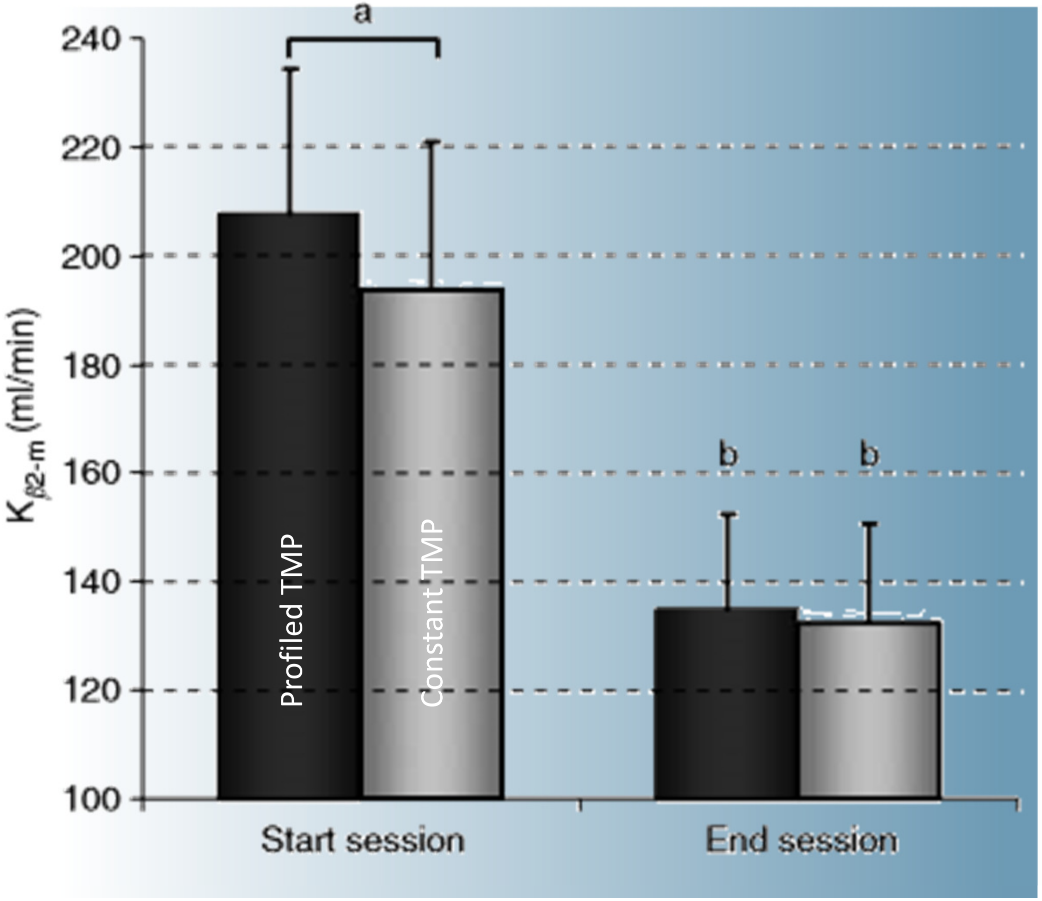
Pedrini L et al, *Kidney Int.* 2006;69:573-579

Albumin Loss at the Start and the End of HDF with Different Procedures

	Constant TMP N=12	Profiled TMP N=12	P-value[a]
Mass in dialysate (g)			
Start – 30 min	0.98 ± 0.18	0.62 ± 0.14	<0.0001
30 min – end	4.26 ± 0.78	3.36 ± 1.15	<0.05
Total	5.24 ± 0.77	3.98 ± 1.19	<0.001
Rate of loss (mg/min)			
Start – 30 min	32.6 ± 6.0	20.6 ± 4.7	<0.0001
30 min – end	22.7 ± 2.7[b]	17.8 ± 5.5	<0.01
Total	24.1 ± 2.1	18.2 ± 4.9	<0.001

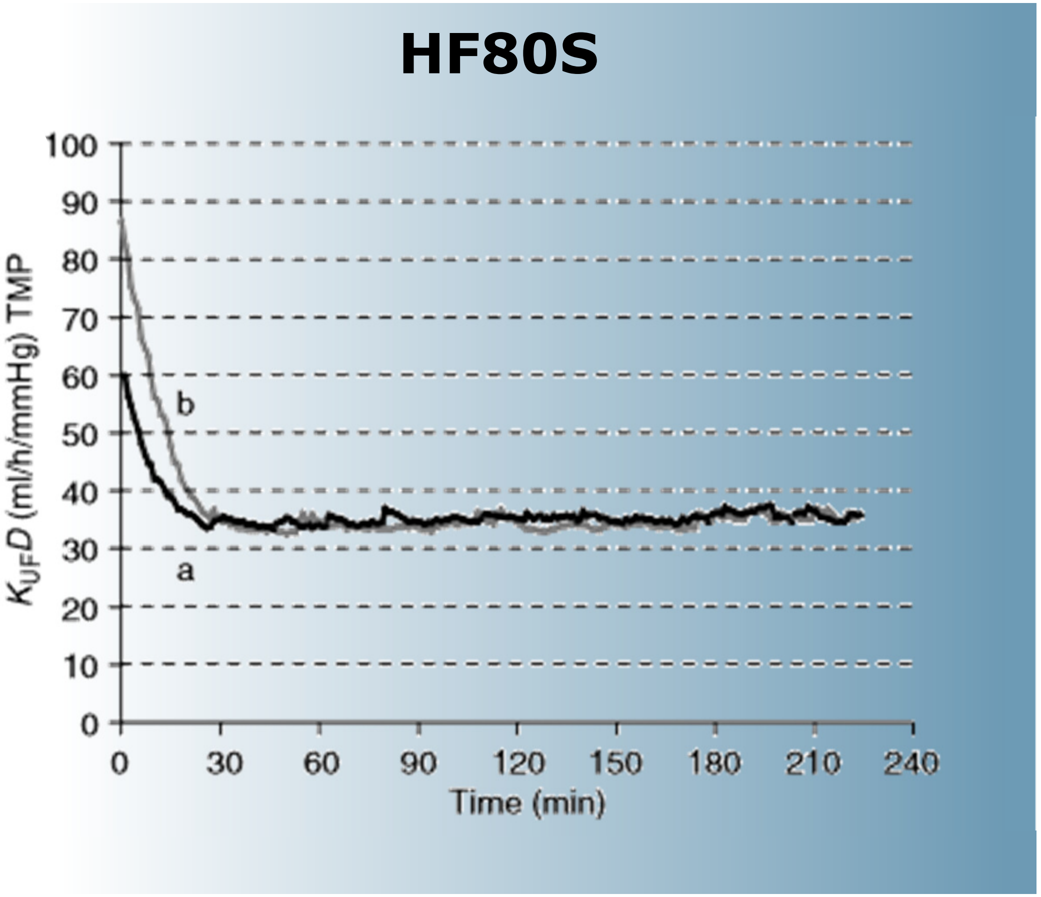
Pedrini L et al, *Kidney Int.* 2006;69:573-579

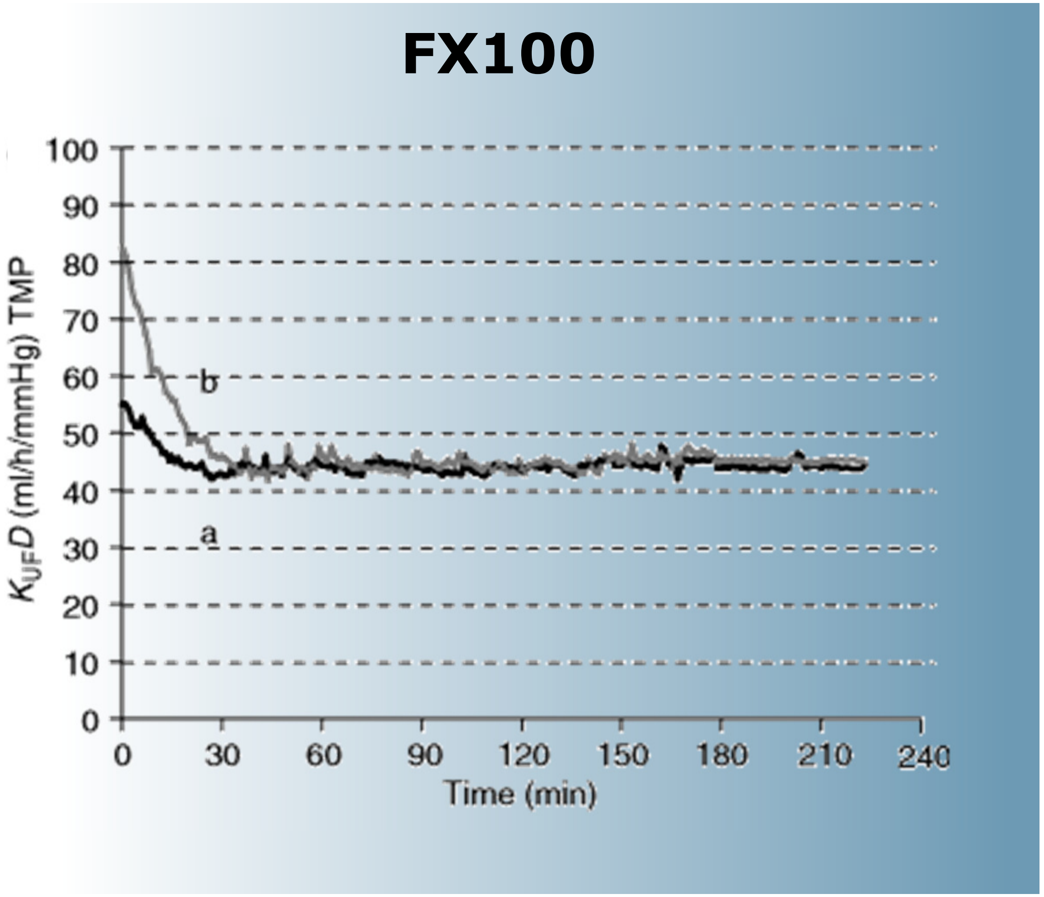
Instantaneous ß2-M Clearance at the Start and the End of HDF



Pedrini L et al, *Kidney Int.* 2006;69:573-579

Behavior of Ultrafiltration Coefficient (KUF)





a. Constant TMP
b. Profiled TMP

KUF = QUF/TMP

Pedrini L et al, *Kidney Int.* 2006;69:573-579

Pilot Study

- Prospective open randomized study
- 6 stable anuric ESKD patients on regular RRT
- Treatment schedule 3 x 240 min per week
- All AVF – Needles 15 gauges
- Cordiax HDF5008, FMC
- Qb = 350 ml/min - Qd = 600 ml/min - Qsub = AutoSub
- Study protocol

  Each patient explored over two sessions one week apart : HD vs HDF
  - 2 pat **HD** Cordiax100 - **HFD POST** Cordiax1000 (AS)
  - 2 pat **HD** Cordiax100 - **HFD PRE** Cordiax1000 (AS)
  - 2 pat **HD** Cordiax100 - **HFD MIXED** Cordiax1000 (Auto)

  Pre and post dialysis blood samples
  - Percent reduction of selected solutes normalized for hemoconcentration

*Approved by Medical Ethical Committee of CH Caen

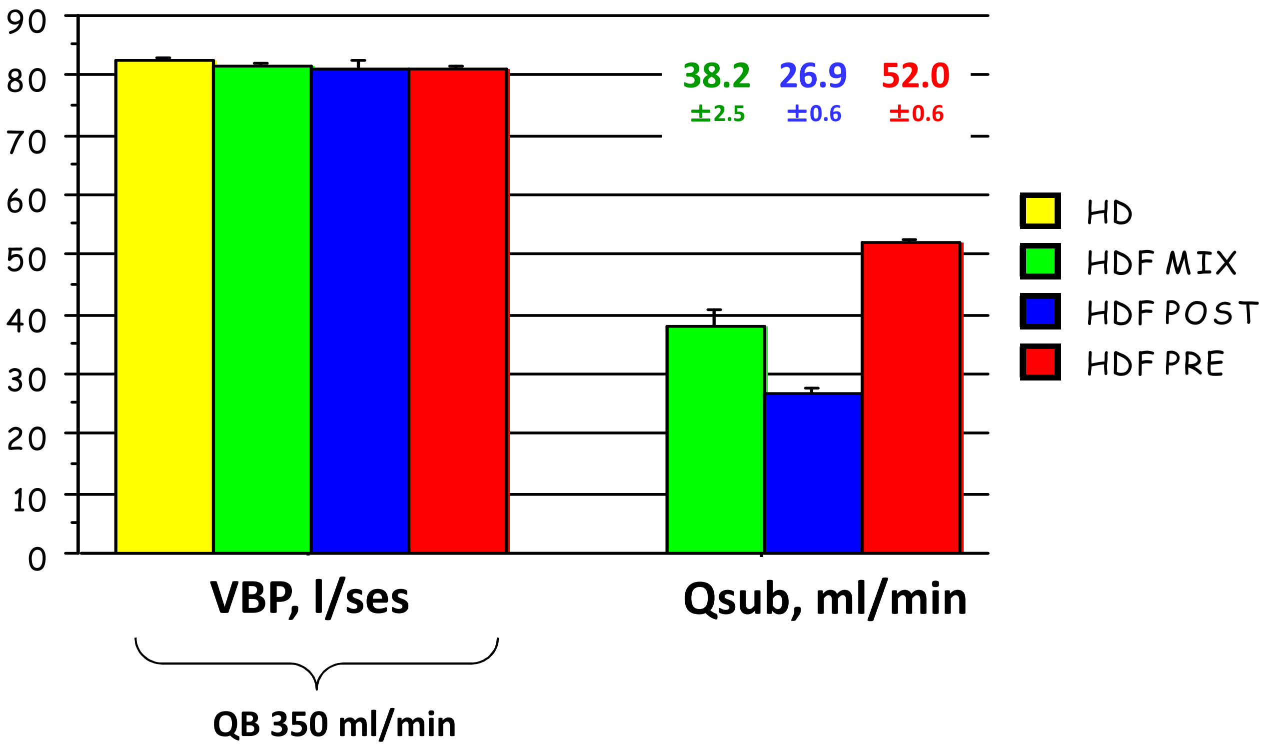
Courtesy Dr J Potier, Cherbourg

Characteristics of FX Dialyzers

	FX100	Cordiax 100	FX1000	Cordiax 1000
Membrane material	Helixone	Helixone plus	Helixone	Helixone plus
Surface Area, m^2	2.2	2.2	2.2	2.3
KoA Urea, ml/min	1354	1545	1354	1421
Diameter, µm	185	185	210	210
Kuf, ml/h/mmHg	73	68	75	76
SC-ß2M	0.8	**0.9**	0.8	**0.9**
SC-Myog		0.5		0.5
SC-Alb	0.001	**<0.001**	0.001	**<0.001**

Courtesy Dr J Potier, Cherbourg

Prescription and Operational Conditions

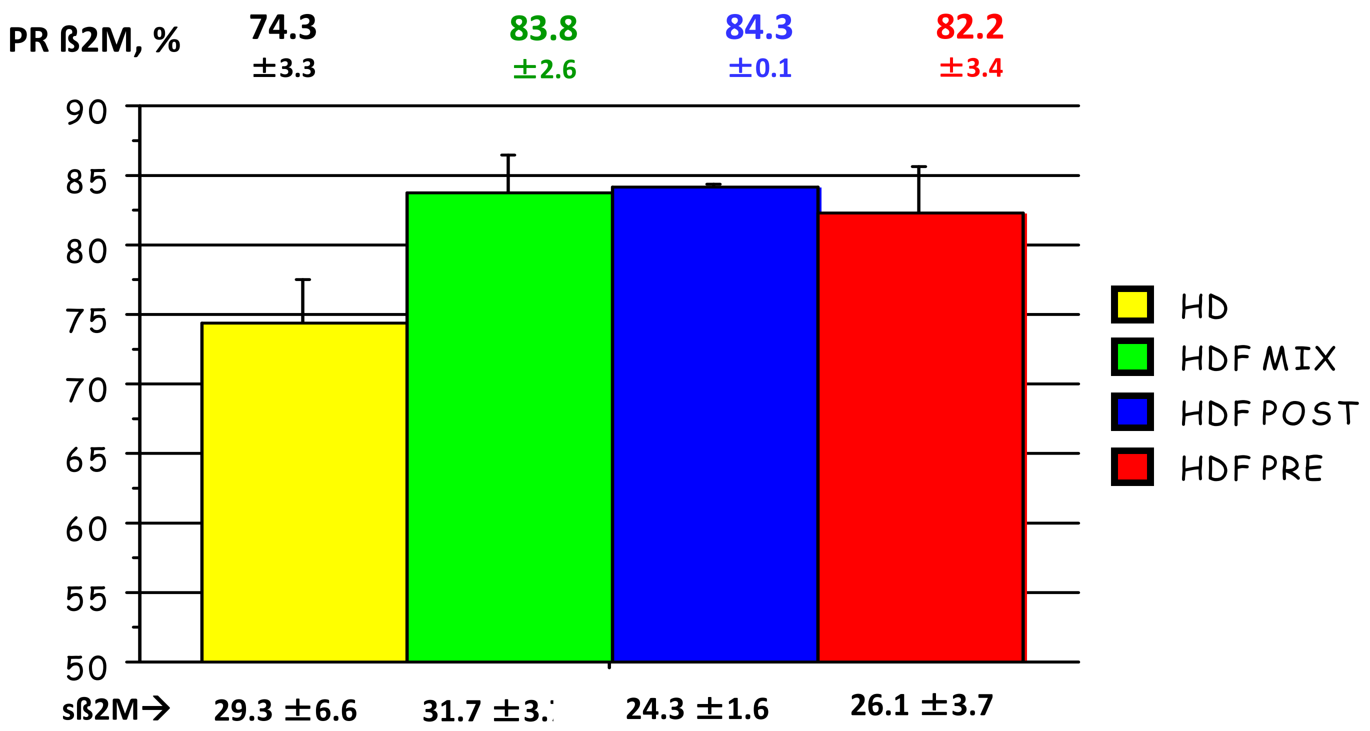


Blood flow, QB (ml/min)
Volume Blood Processed, VBP (l/ses)
Substitution Flow, QSub (ml/min)
Volume Substituted, VS (l/ses)

Dialysis duration 240 min
Substitution flow prescription
- **QSub Pre = Qsub Post x 2**
- **Qsub Mixed = QSub Post x 1.4**

Courtesy Dr J Potier, Cherbourg

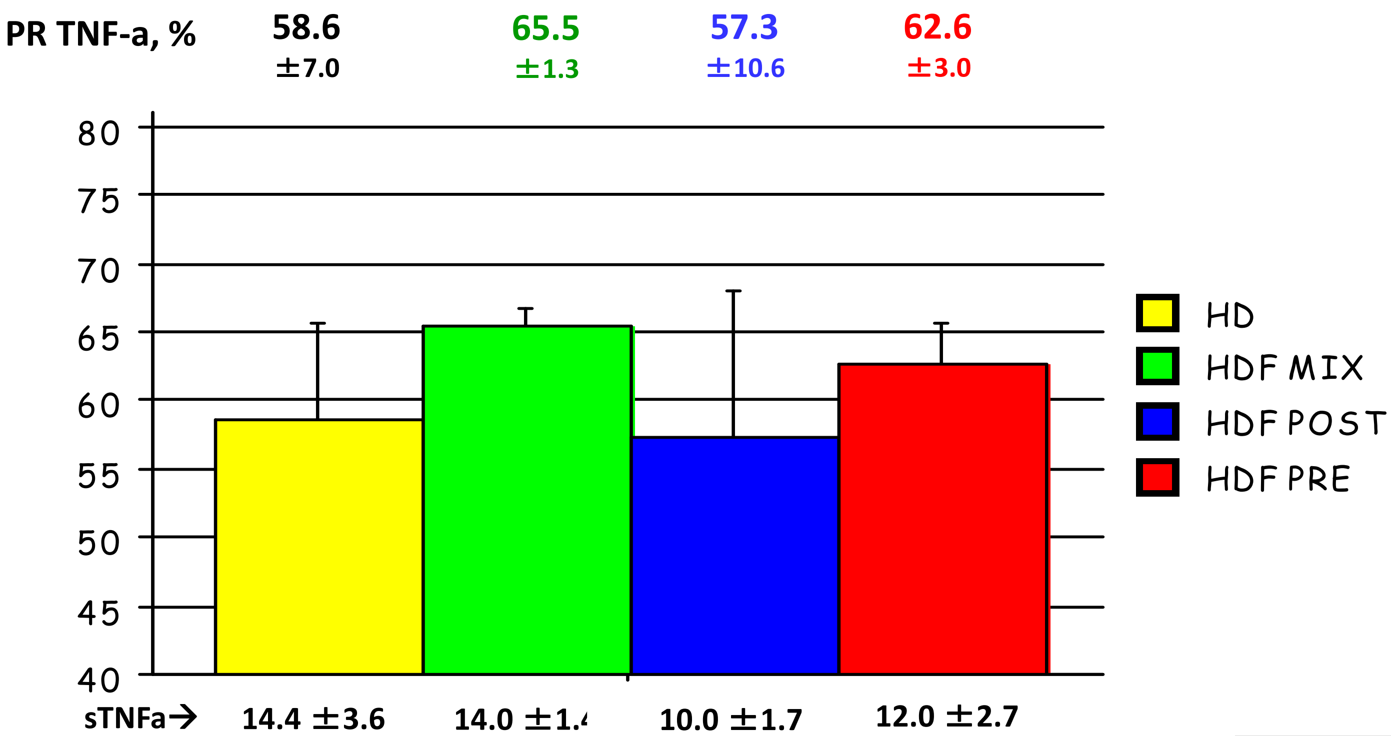
ß2-Microglobulin, 12.8Kda



Nephelometry
N <2.4mg/L
X±SD 28.3±5.4 (21,2 à 38)

Courtesy Dr J Potier, Cherbourg

TNF α, 17-50 KDa

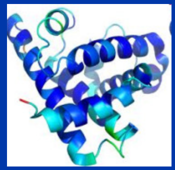


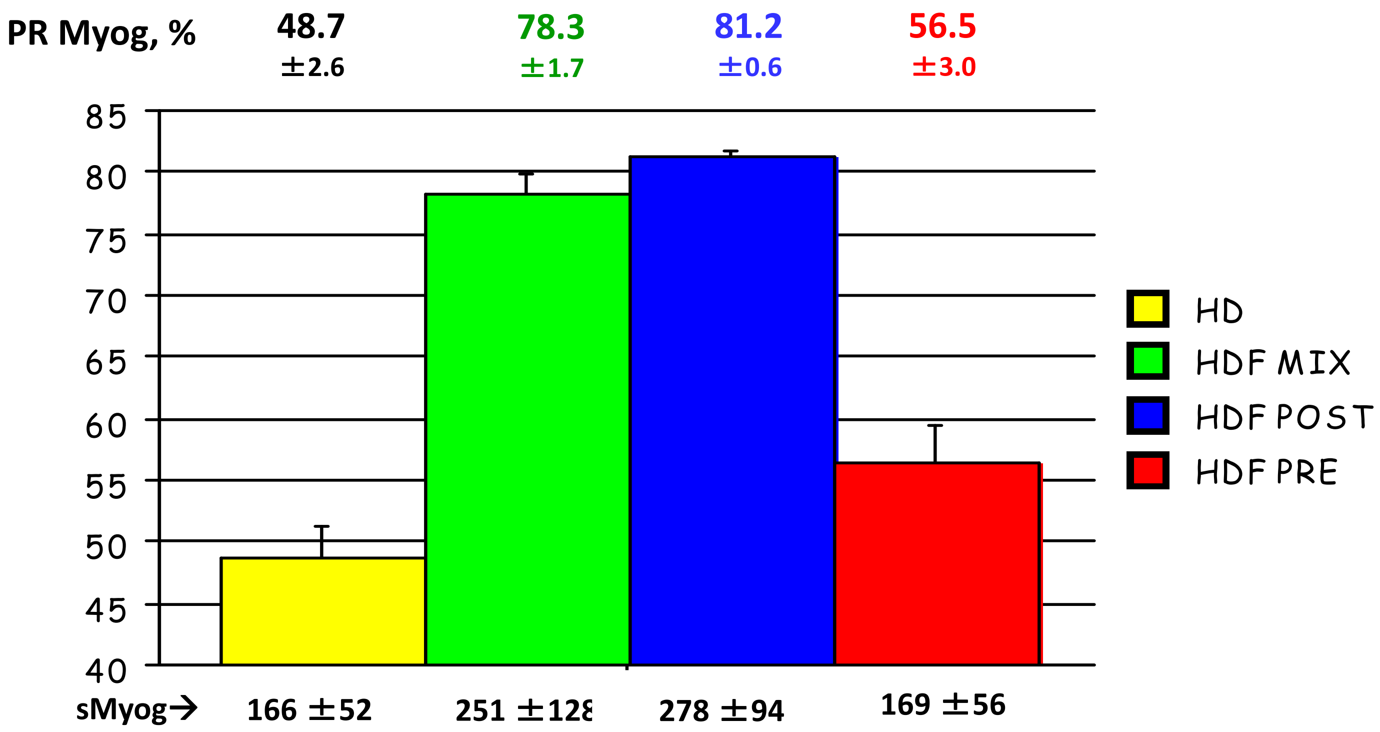
Elisa R&D

N: < 1.9 pg/mL

X±SD: 12.3 ±3.2 (8.8 à 19.4)

Myoglobin, 17.2KDa

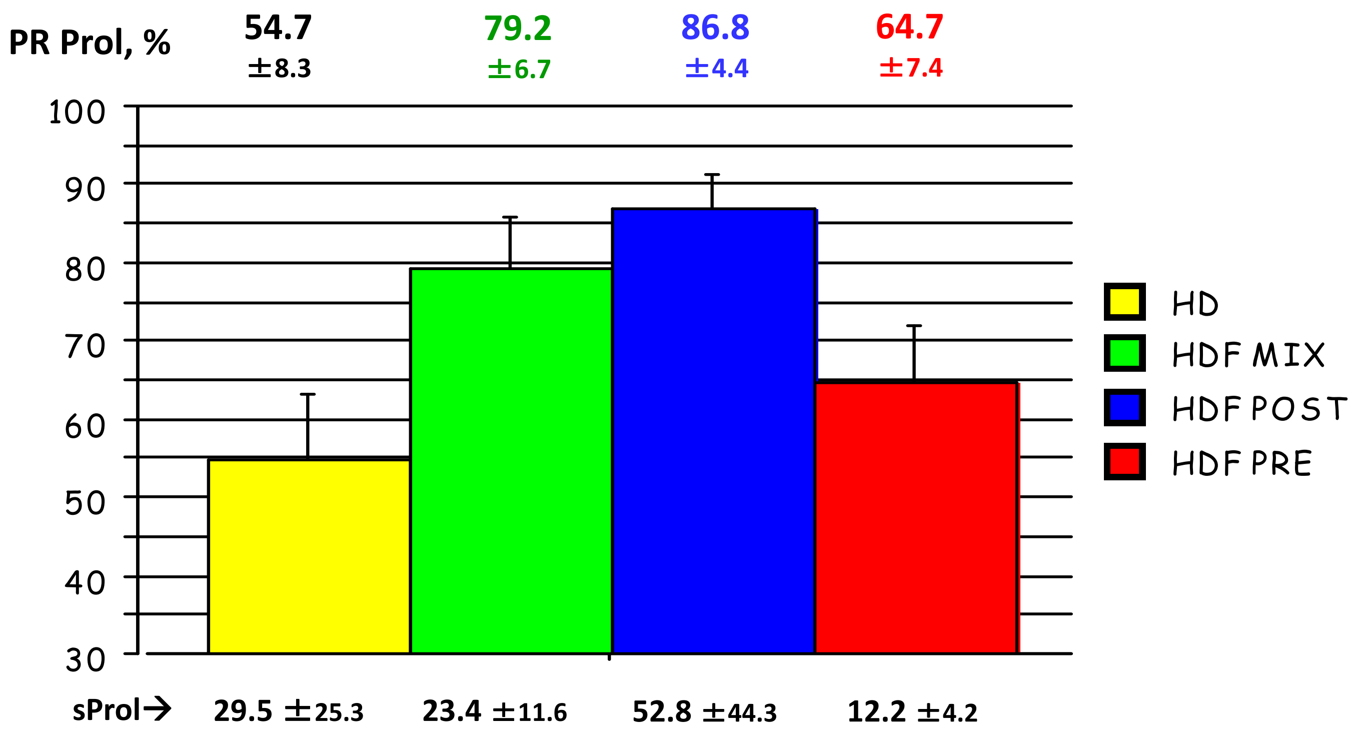




Nephelometry
N : 24-72 ng/mL
X±SD: 199 ±79 (88 à 345)

Courtesy Dr J Potier, Cherbourg

Prolactin, 23.0 KDa



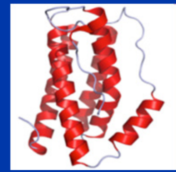
ELISA Biomerieux

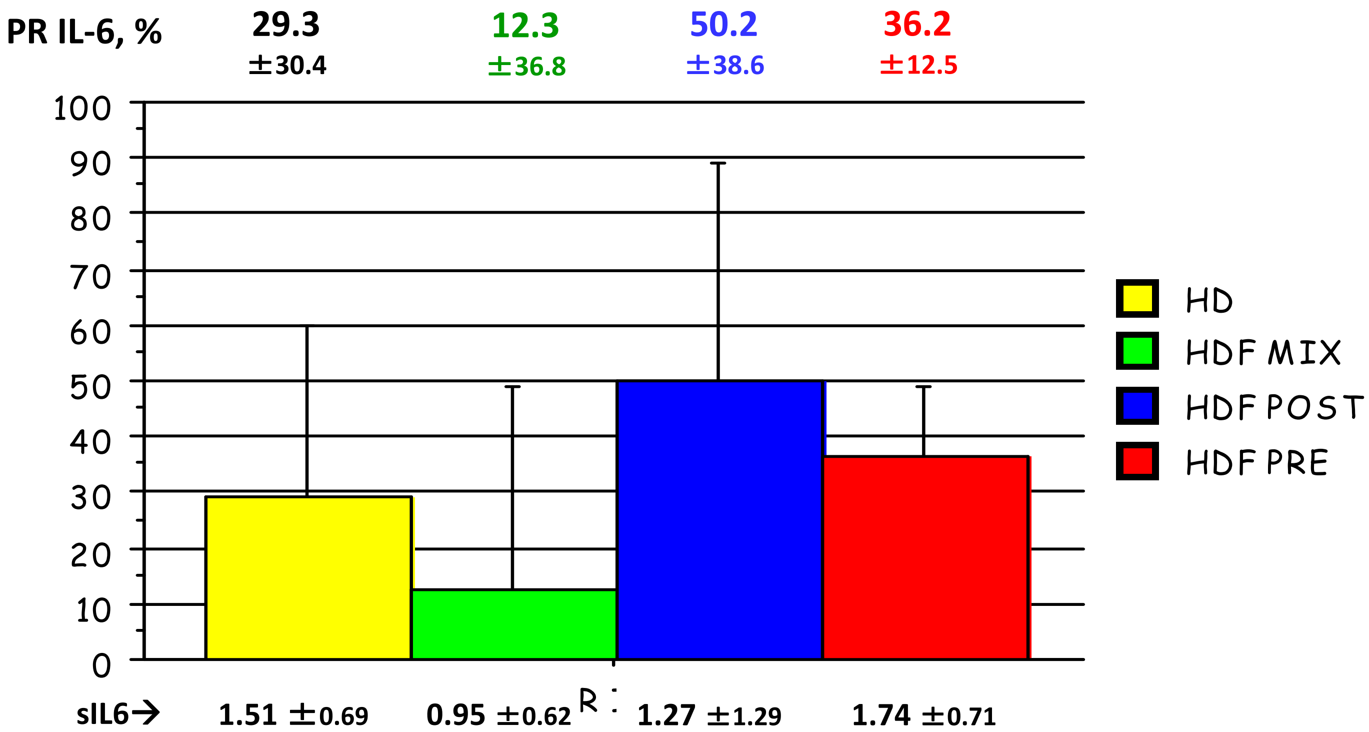
N M 2 à 15 – F 3-20 ng/mL

X±SD 29.5 ±25.3 (9.2 à 84.1)

Courtesy Dr J Potier, Cherbourg

IL-6, 24.5KDa





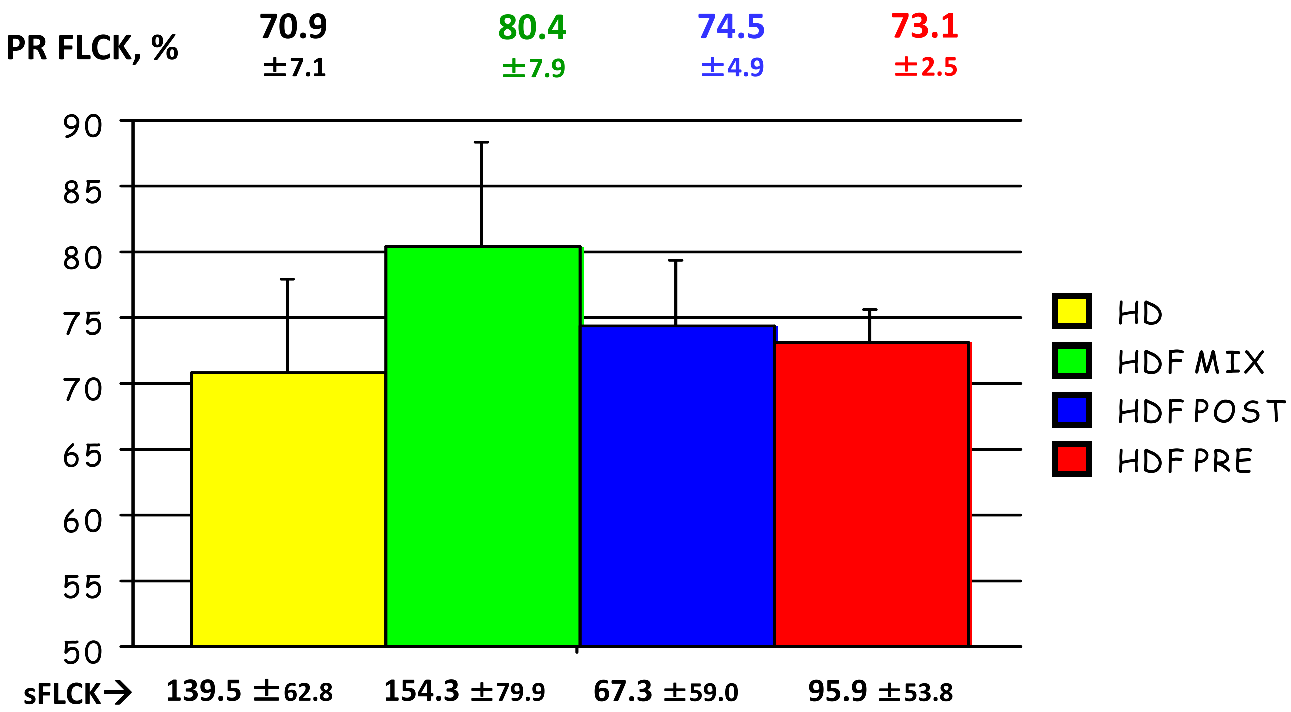
Elisa R&D

N < 2.1 pg/mL

X±SD: 1.41 ±0.72 (0.35 à 2.47)

Courtesy Dr J Potier, Cherbourg

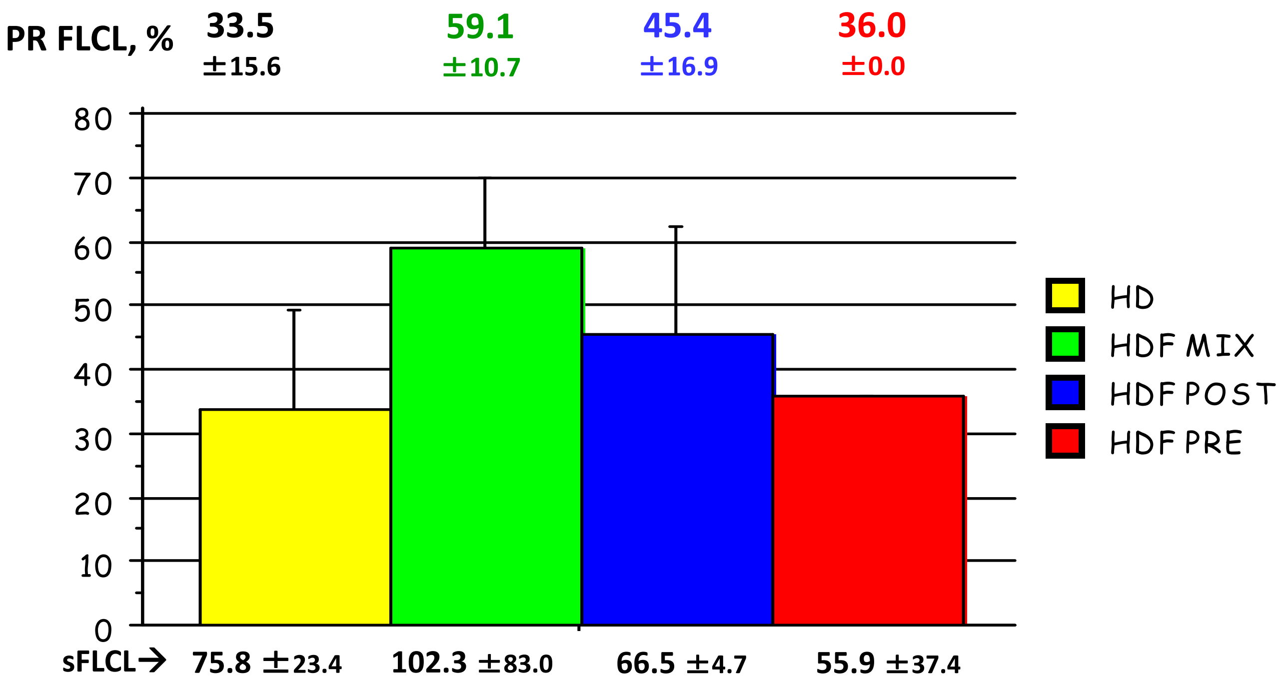
Free Light-Chain Kappa, 25.0KDa



Free Lite
N 3.3 à 19.4mg/L
X±SD 122.7 ±63.1 (25.5 à 229)

Courtesy Dr J Potier, Cherbourg

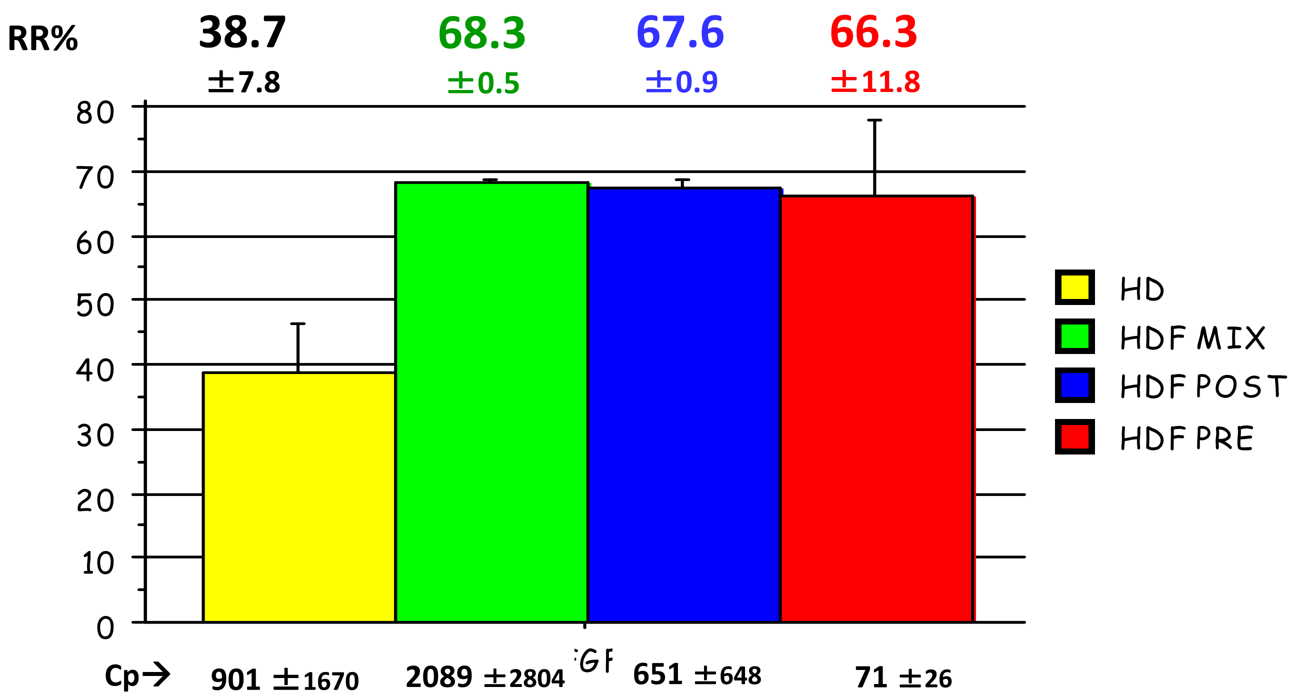
Free Light Chain Lambda, 50.0KDa



Free Lite
N 5.7 à 26.3 mg/L
X±SD 75.3 ±35.9 (29.4 à 161)

Courtesy Dr J Potier, Cherbourg

FGF23, 32.KDa

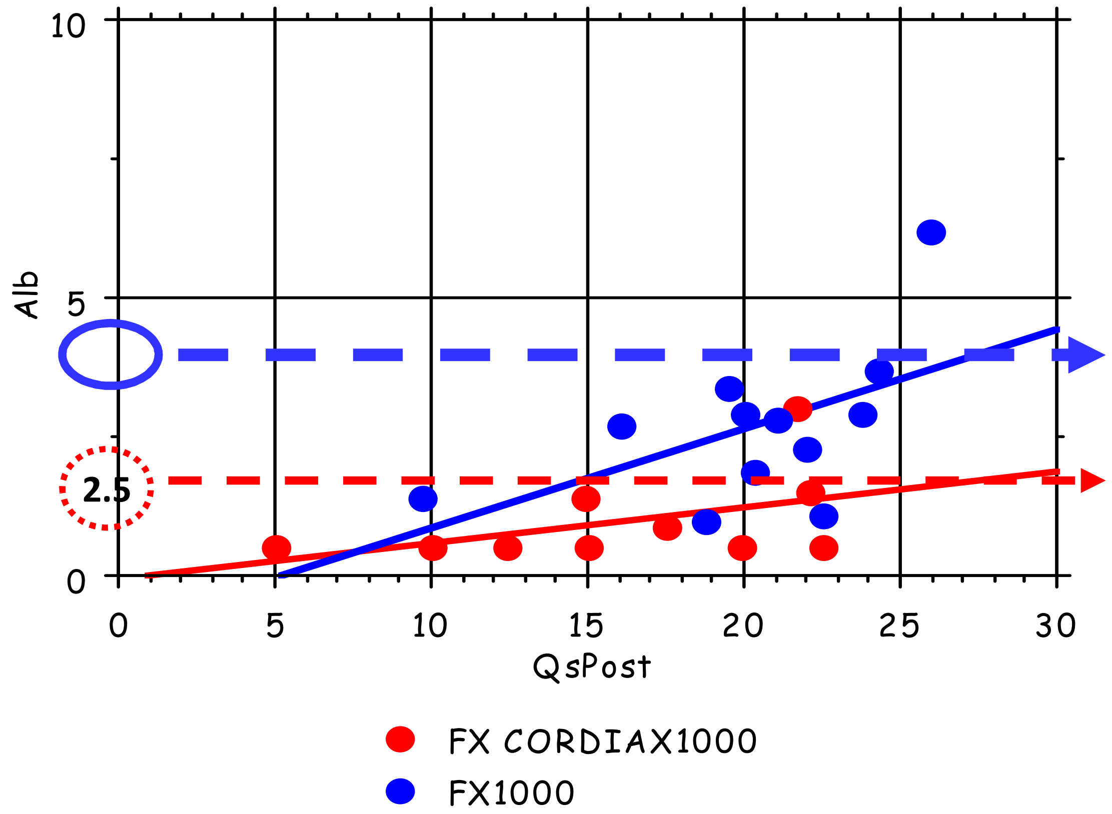


Elisa merck/millipore
N: pg/mL
X±SD 919 ±1558 (52 à 4280)

Courtesy Dr J Potier, Cherbourg

Albumin Loss as Function of QSubstitution

FX1000HDF vs Cordiax1000



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Take Home Message

- Benefits of HDF are depending on convective dose delivered
- Postdilution HDF is still the reference method for convective therapies in RRT
- Minimum threshold total ultrafiltered volume to improve better outcome is closed to $40L/m^2$/wk or $70L/1.73m^2$
- Automated ultrafiltration control by AutoSub*Plus* permits to achieve this volume in more than 75% of CKD patients
- Mixed-HDF main facilitate implementation of HDF in the remaining 25% of CKD patients with hemorheologic unfavorable profile
- Poor blood flow, catheters, elderly and kids may benefit from mixed-HDF
- Long-term studies are still missing to define specific indications and benefits