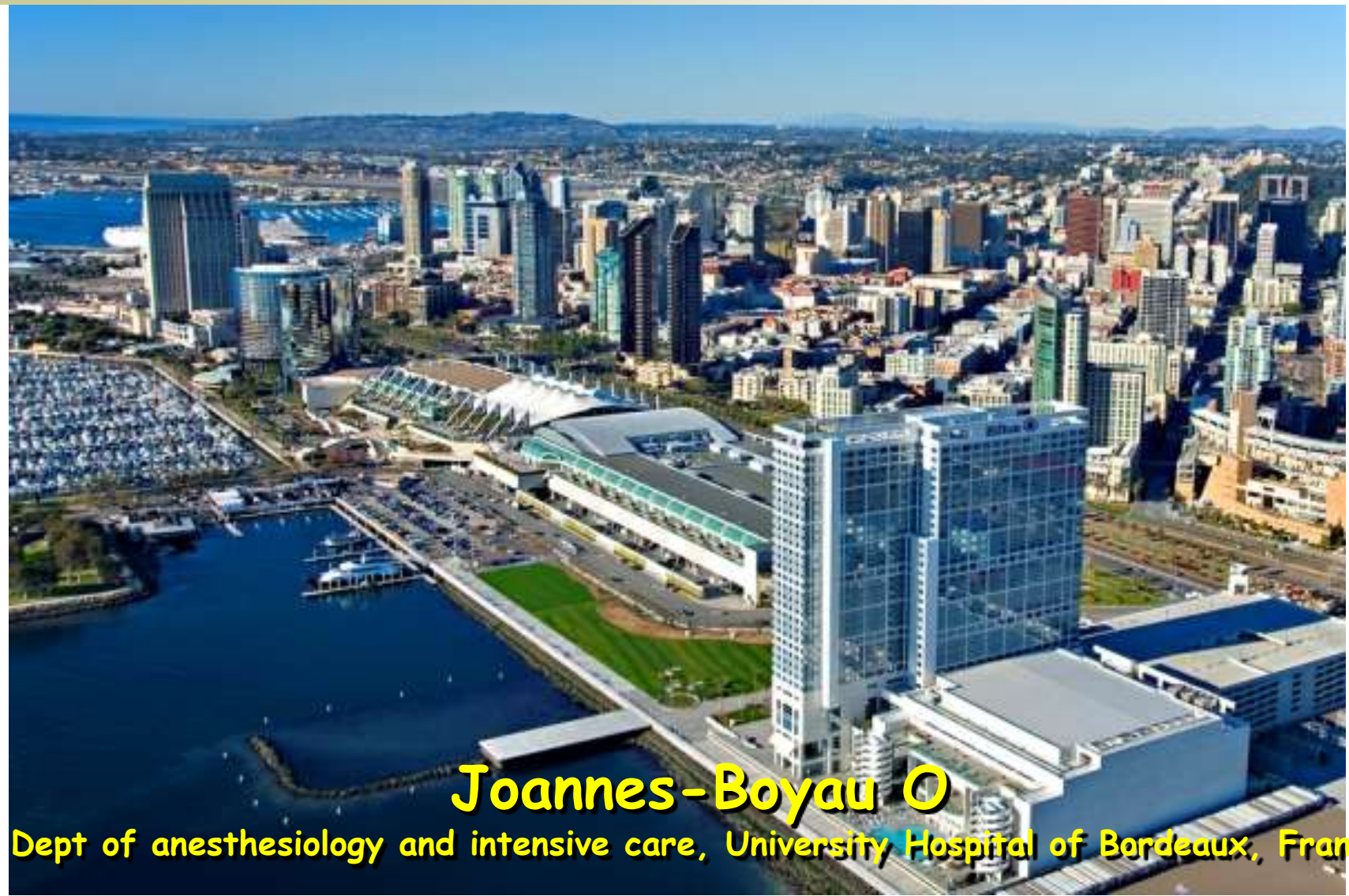
Anticoagulation in CRRT

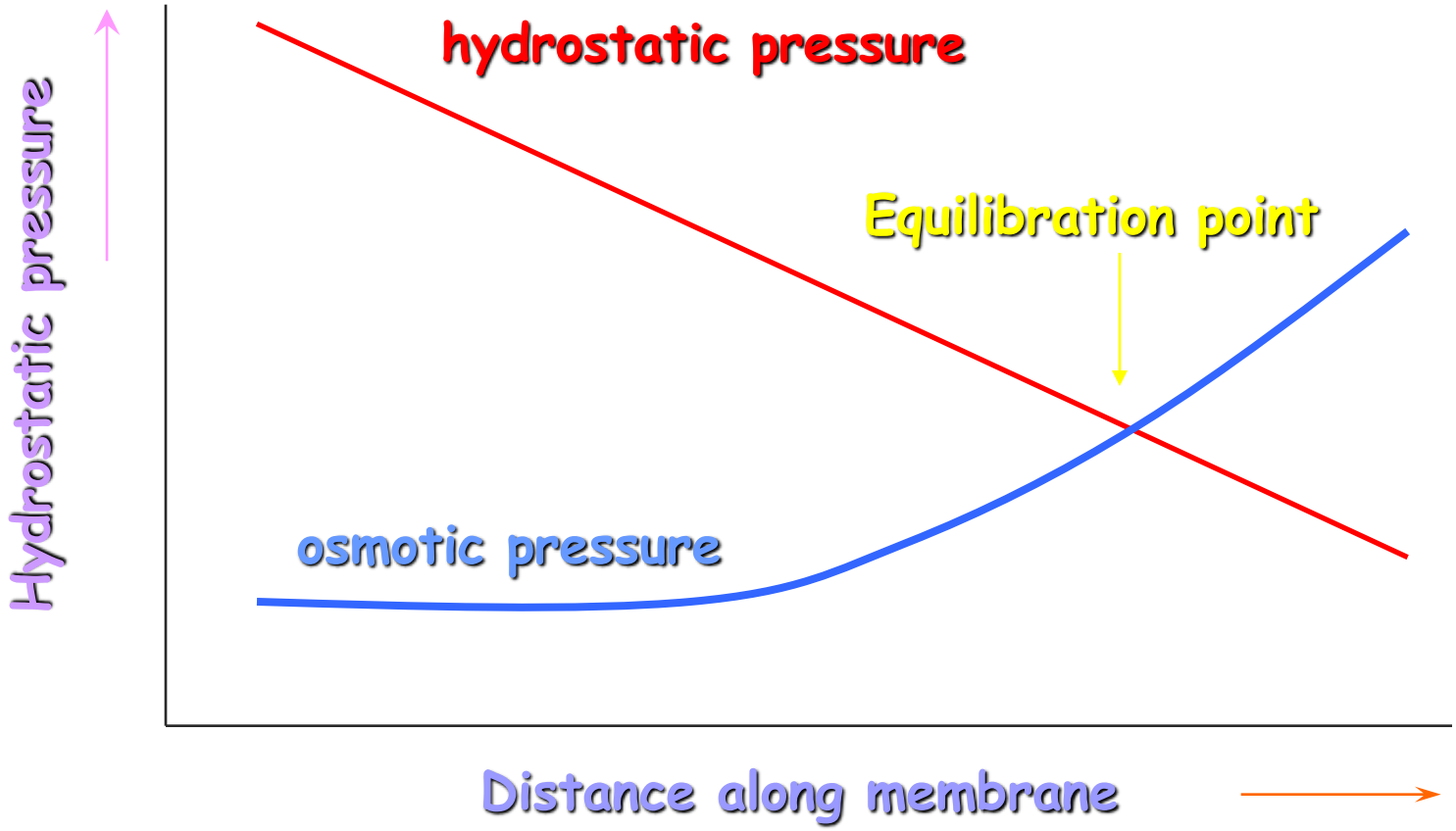


Joannes-Boyau O

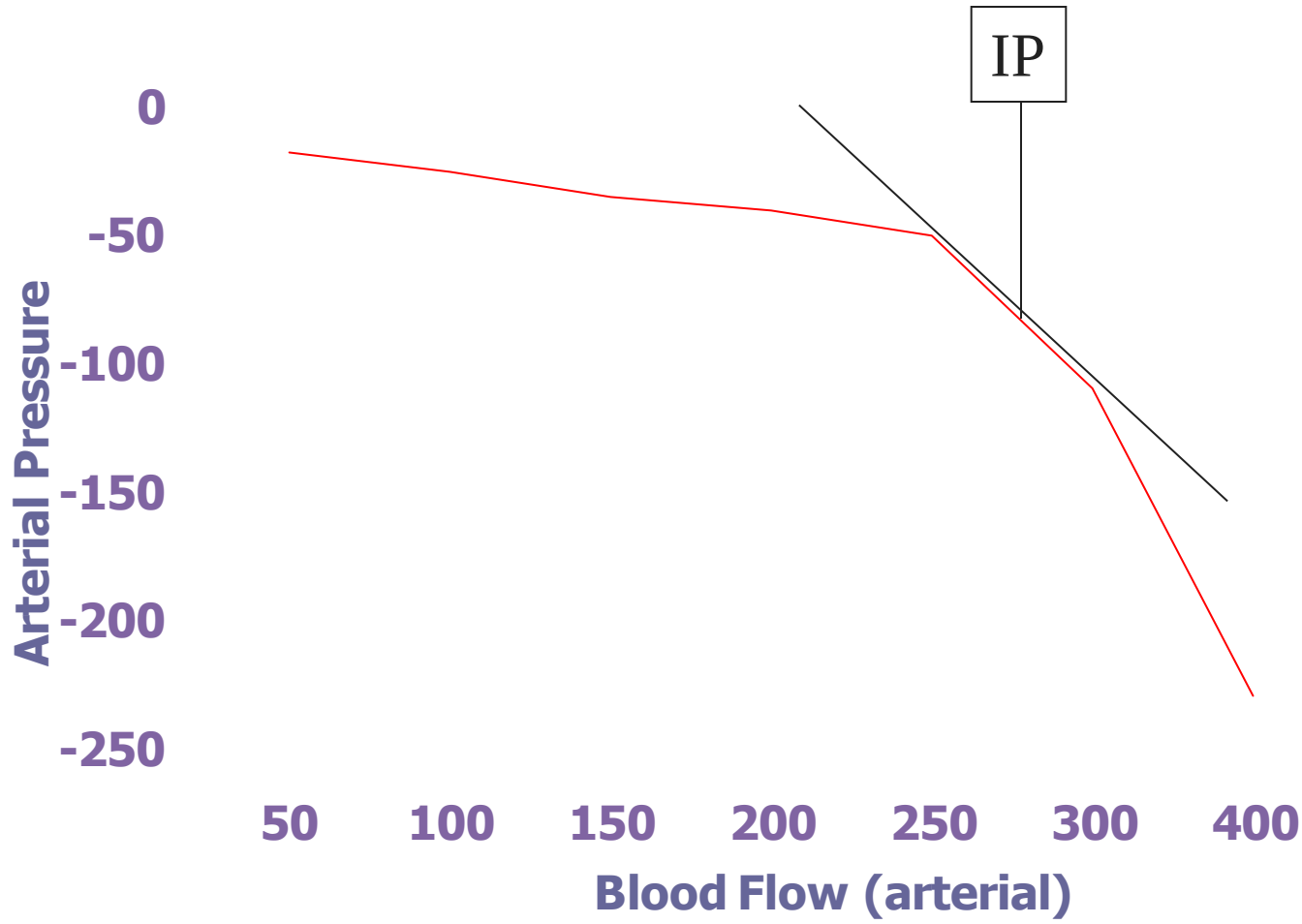
Dept of anesthesiology and intensive care, University Hospital of Bordeaux, France

CRRT SAN DIEGO 2012

Convection


hydrostatic pressure
Equilibration point
osmotic pressure
Hydrostatic pressure
Distance along membrane

Blood flow / KT

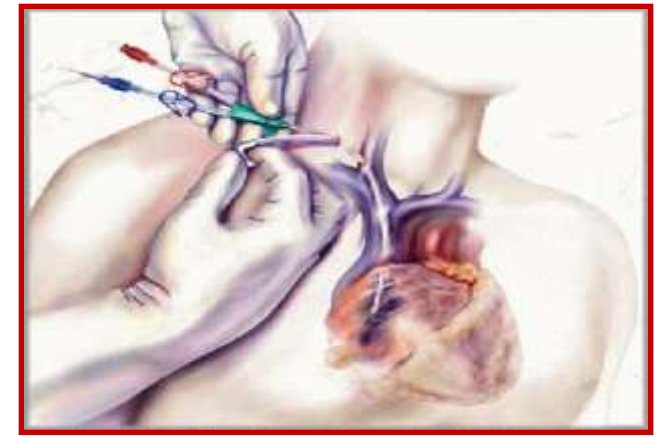


Check Vascular Access

Caruana et al. Am Jkidney Dis. 9; 1987; 497-501

Canaud et al. Nephron 1986; 43:133-8.

- Diameter, length and types of catheters
  - Type: Material features
    - Silicone elastomer and polyurethane
    - Canaud et al (1986) promoted a parallel double catheterisation
  - Diameter and blood flow
    - 8.5 French : 150-200 ml/min BF
    - 11 French : 250-300 ml/min BF
    - 14 French : 450-500 ml/min BF
  - Recirculation
    - Increased in dual catheters +/- 10 %
    - Especially if femoral access is less than 20 cm
    - Avoid reverse AV connection

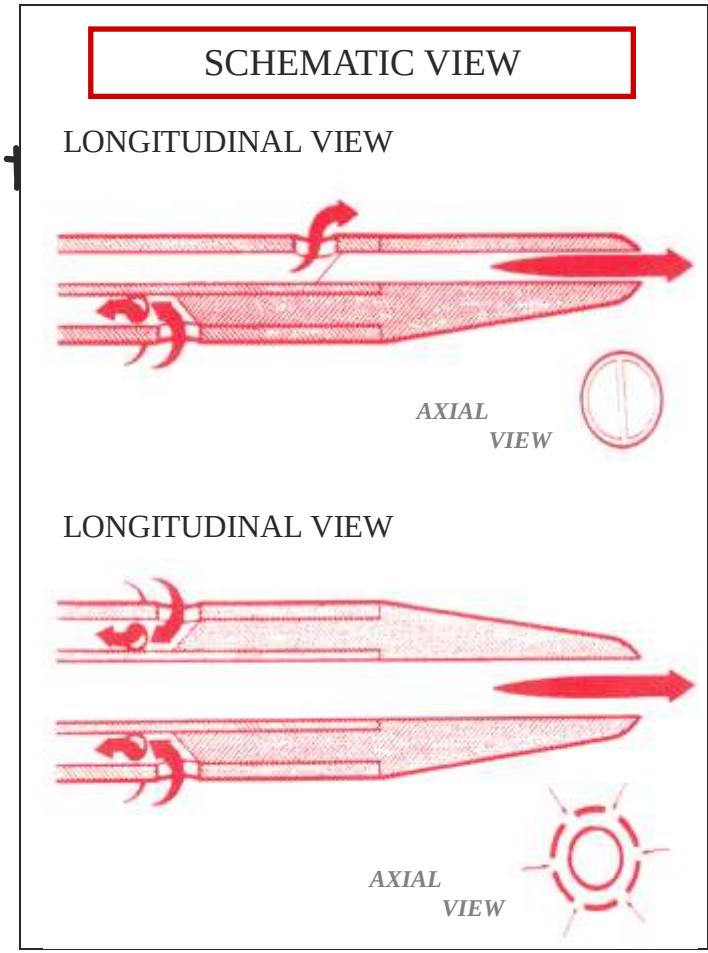


Check Vascular Access

Denys et al. N Engl. J Med 1991, 324 ;566.

Wynckel et al. Kidney Int 1992, 42:235.

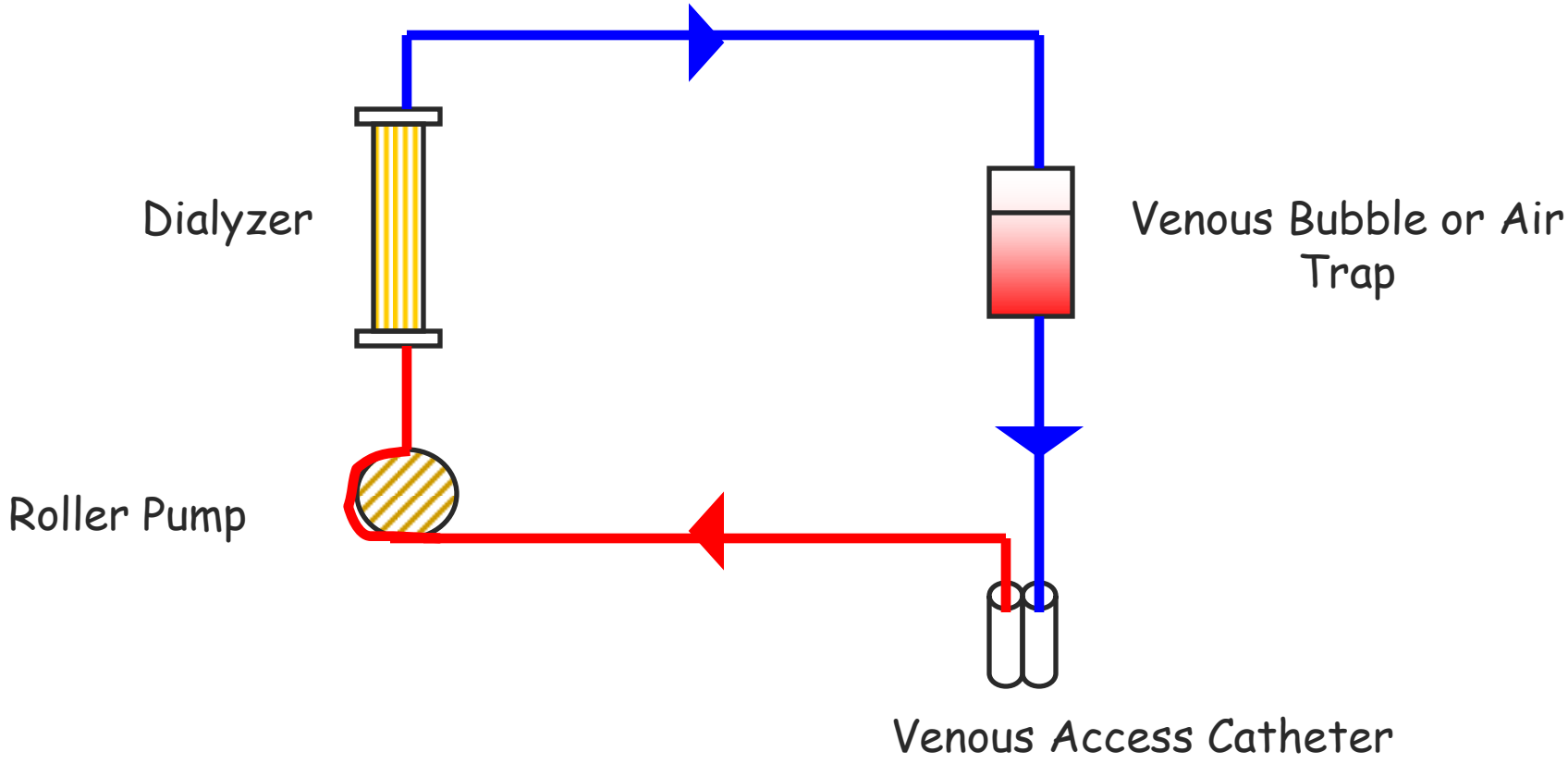
- Catheter insertion site
  - Best site : right internal jugular
  - But in practice : femoral is the easiest approach
  - Avoid left internal jugular at both subclavian
  - Doppler ultrasound technique is very useful
- Diameter, length and types of catheters
  - Length - Right int. jugular : 15 cm.
    - Femoral : 20-24 cm.
  - Diameter : 14 French.
  - Type coaxial : 360° arterial intake



Treatment Characteristics Affecting Filter Life

- Arteriovenous vs Venovenous
- Vascular Access
- Diffusion versus Convection
- Filtration Fraction
- Blood Flow
- Membrane Material and Geometry
- Circuit Alarms

Areas of Clot Development in the CRRT Circuit



Davies H. Australian Critical Care 2006

Case report

- Mr D. 59 years old, admitted in emergency
- High abdominal pain with fever
- CT-Scan = peritonitis with pneumoperitoneum
- Surgery in emergency
  - Colitis on diverticula inflammation
  - Spontaneous perforation
  - Stercoral peritonitis
- ICU admission after surgery

ICU clinical parameters

- Intubated/Ventilated/sedated
- Hemodynamic instability despite adequate fluid filling
- Catecholamine requirement at 0.5 µg/kg/h
- Hemodynamic parameters (Echo + PICCO):
  - MAP 65 mmHg, CI 5 L/min, SVRI 1135
  - EF 85 %
  - SVV 9 %
  - SVO_2 74 %

ICU biological parameters

- WBC : 11 500; CRP : 555
- Platelets : 120 000, PT : 70%, ACT : 37/34
- Lactates 3,71; Creatinine 120 µmol/l; Urea 12,5 mmol/l
- K^+ 4.8; Na^+ 144
- Last 12h diuresis = 0.4 ml/kg/h
- Hepatic data are normal

High volume hemofiltration

- Hemofiltration parameters
  - 70 ml/kg/h (5.6 L in 1/3 pre-dilution, 2/3 post-dilution)
  - 200 ml/min blood flow
  - Anticoagulation by UFH : 7 UI/kg/h (500 UI/h)
  - Catheter in right femoral : 15 cm, 12 French
  - Arterial press = -75 mmHg, venous press = 110 mmHg

Two early thrombosis in the first 12 hours

Clotting problem

- 70 ml/kg/h (5.6 L in 1/3 pre-dilution, 2/3 post-dilution)
- 200 ml/min blood flow **FF = 40%**
- Anticoagulation by UFH : 7 UI/kg/h (500 UI/h)
- Catheter in right femoral : 15 cm, 12 French
- Arterial press = -75 mmHg, venous press = 110 mmHg

Troubleshooting

- 70 ml/kg/h (5.6 L in 1/3 pre-dilution, 2/3 post-dilution)
- 330 ml/min blood flow
- Anticoagulation by UFH : 7 UI/kg/h (500 UI/h)
- Catheter in right femoral : 15 cm, 12 French
- Arterial press = -200 mmHg, venous press = 150 mmHg

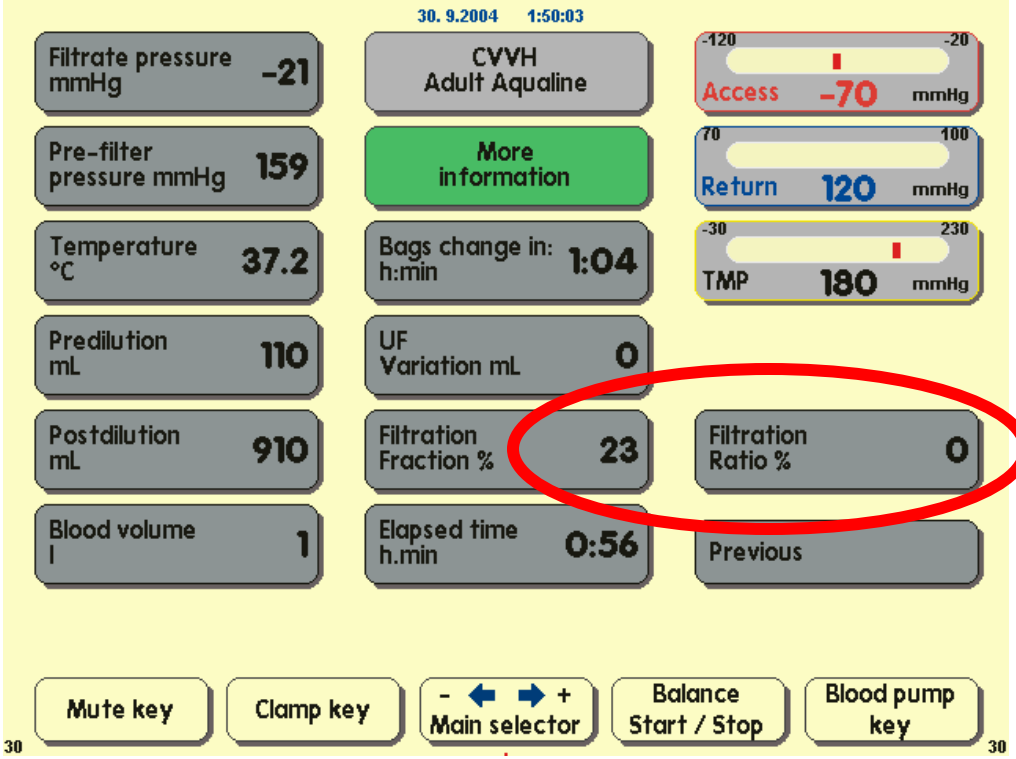
Two early thrombosis in the first 12 hours

Troubleshooting

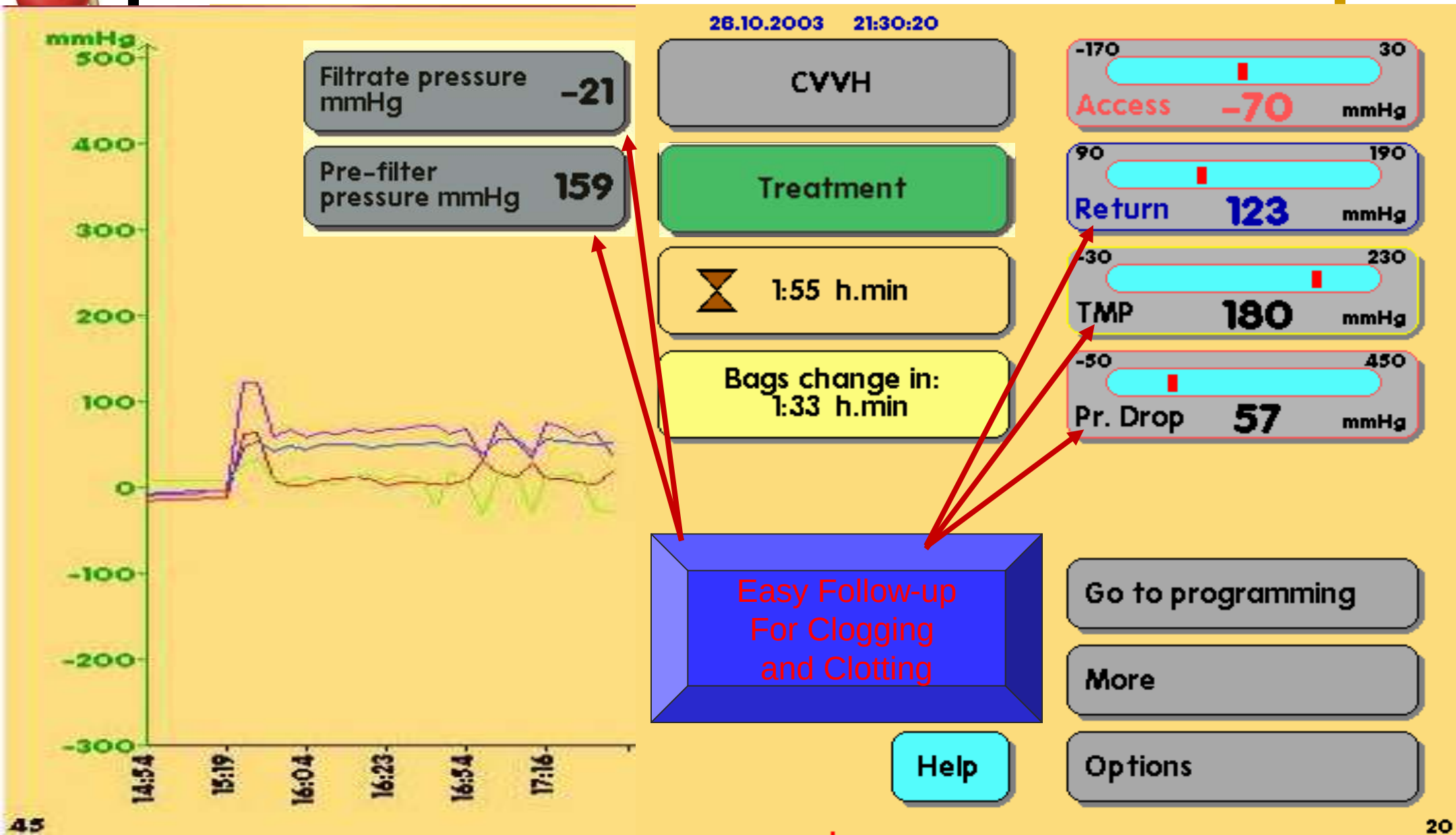
- 70 ml/kg/h (5.6 L in 1/3 pre-dilution, 2/3 post-dilution)
- **330** ml/min blood flow
- Anticoagulation by UFH : 7 UI/kg/h (500 UI/h)
- Catheter in right femoral : **24** cm, **13.5** French
- Arterial press = -75 mmHg, venous press = 110 mmHg

Catheters

Blood flow / Filtration Ratio



Check Pressures



Anticoagulation?

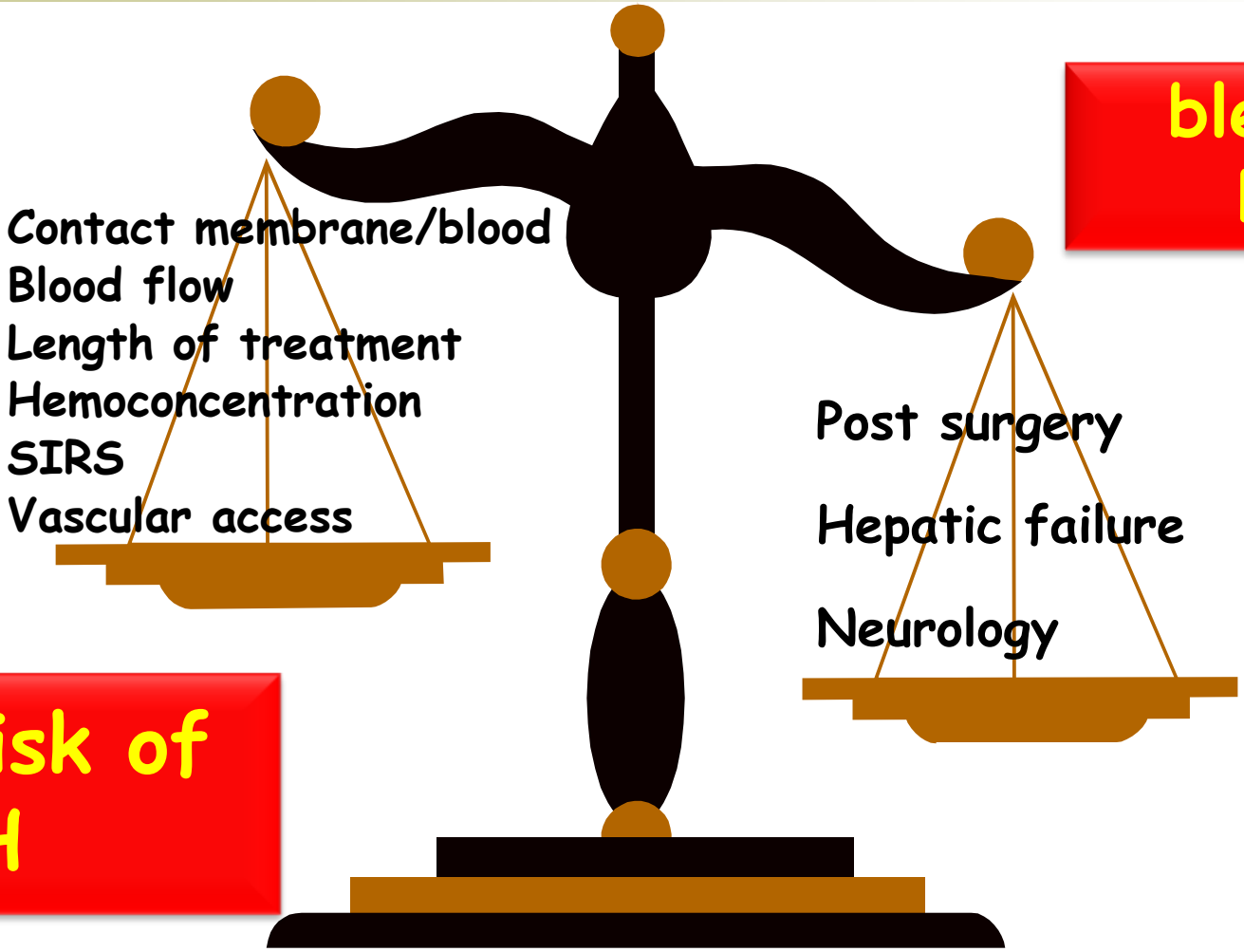
Evaluation criteria

- Permeability Index (UF/TMP)
- UF Volume
- Transmembrane pressure
- Membrane lifespan (Thrombosis, length…)

Origin of filter's thrombosis

- 50% = Catheters (site, nursing, local cause…)
- 37% = Coagulation problems
- 13% = Technique

Anticoagulation?



bleeding Risk

Clotting risk of CVVH

BALANCE BENEFICE / RISK

Which Anticoagulant?

Unfractionated HEPARINE

Heparin

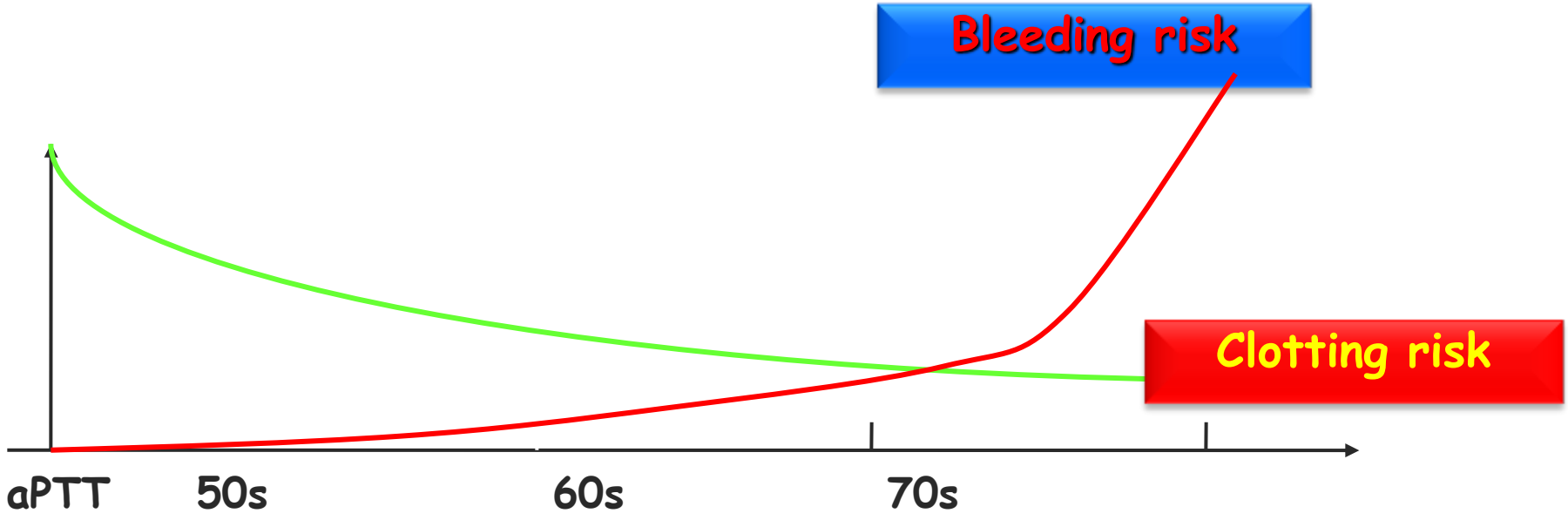
- **Unfractionated heparin (UFH)**

  - Adjusted Dose → Platelet > or < 50.000
  - Adjusted Dose → APTT (ACT) or heparin blood concentration
  - Adjusted Dose → risk of hemorrhage
  - Adjusted Dose → Weight

  - Co-factor : AT often reduced in septic patients

  - Doses = Bolus 15-30 UI/kg and 5-15 UI/kg/h

Heparin = Risk?



Moriniere P et al. Blood Purif..

- HIT

Héparine : Risk ?

N ENGL J MED 359;1 WWW.NEJM.ORG JULY 3, 2008

Intensity of Renal Support in Critically Ill Patients with Acute Kidney Injury

The VA/NIH Acute Renal Failure Trial Network*

Anticoagulant — no. of treatments (%)		
None	1736 (54.6)	1666 (59.7)
Heparin	645 (20.3)	530 (19.0)
Citrate	649 (20.4)	495 (17.7)
Other	148 (4.7)	98 (3.5)

Supplementary Table 5. Reported Complications Associated with Study Therapy – All Modalities of Renal Replacement Therapy (RRT) *

Event	Intensive Management Strategy (N=563)		Less-Intensive Management Strategy (N=561)		P-Value
	number (percent)				
Study days	7572		7227		
RRT treatments	6681		4921		
Reported serious adverse events (SAEs)					
	Patients	***Events***	***Patients***	***Events***	
Bleeding	7 (1.2)	9 (0.1)	6 (1.1)	6 (0.1)	0.79

Héparine : Risk?

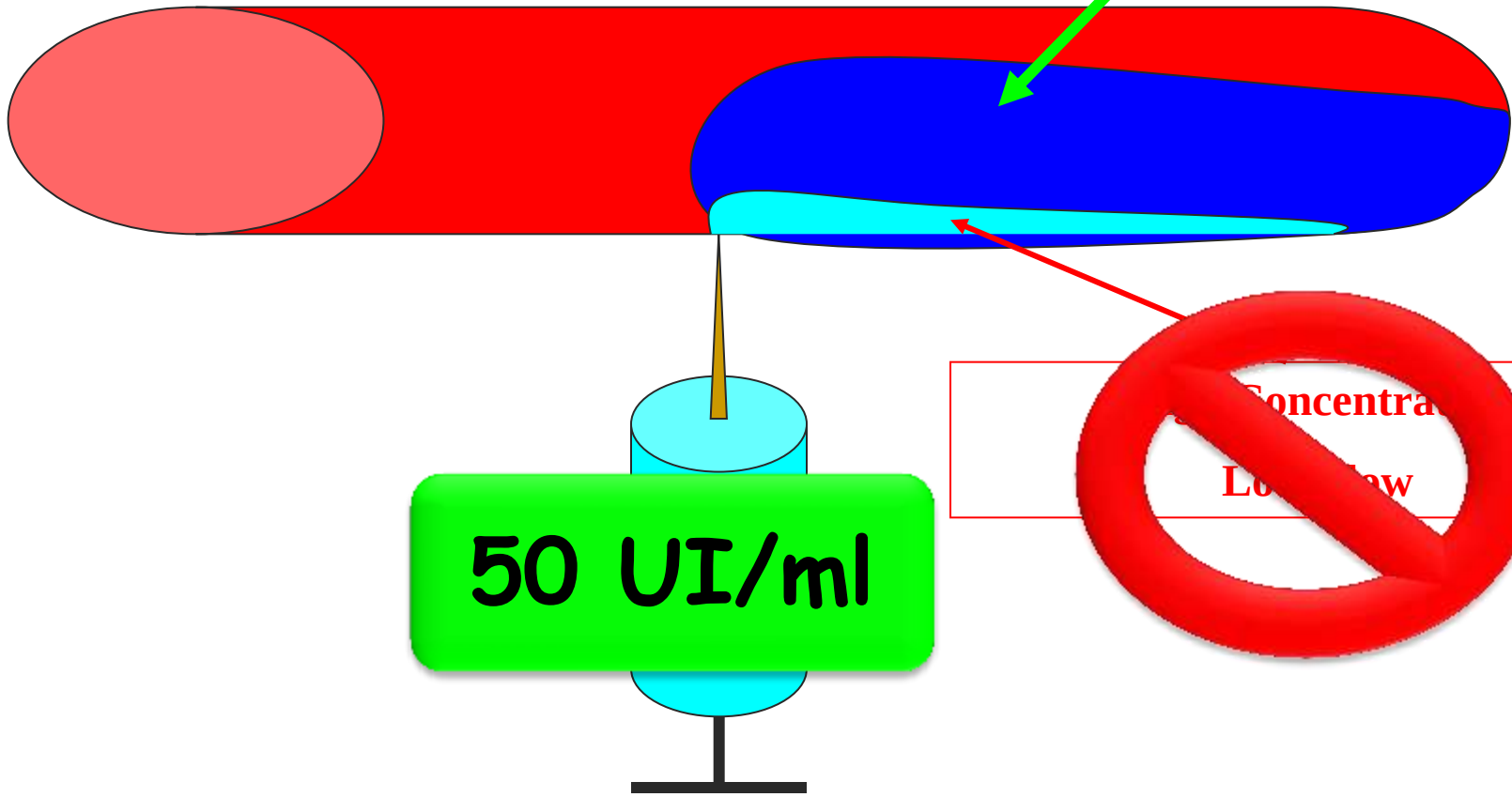
rium syndrome, one case of cerebral edema, one of rectal bleeding, one of cardiac arrest, and one of too rapid correction of hyponatremia) that were considered by the site investigators to be potentially related to treatment (Table 4). In the lower-intensity group, there were five serious adverse events (three cases of heparin-induced thrombocytopenia, one case of hypoxemia, and one of car-

Type of a			
Prefil			0.87
No a			0.05
Hepa			0.25
Syste			0.52
Othe			0.42
One or m			
No. o			0.77
No. of episodes	4	5	—

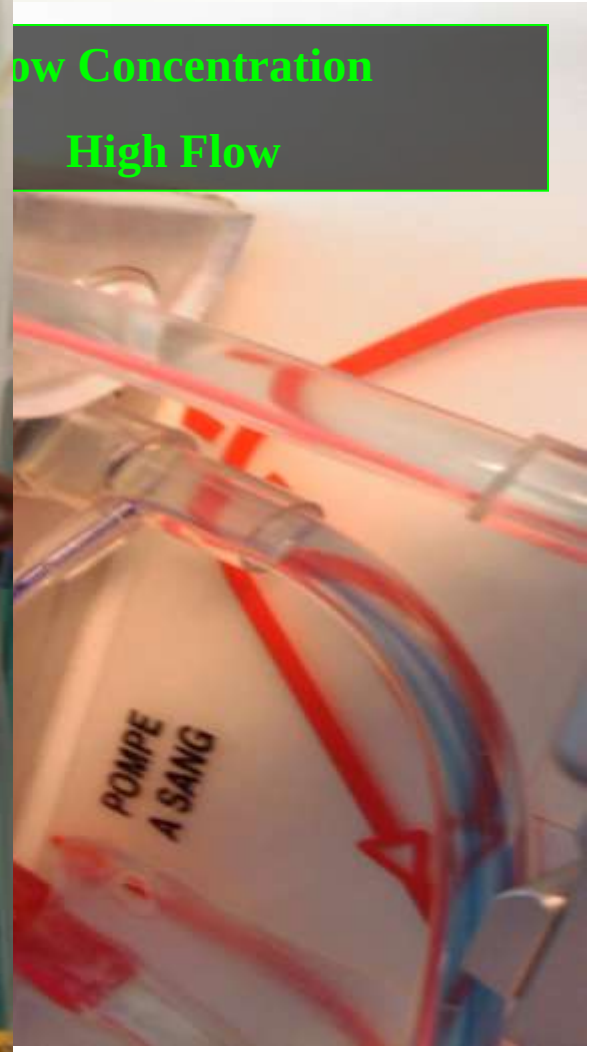
Heparine

Low Concentration

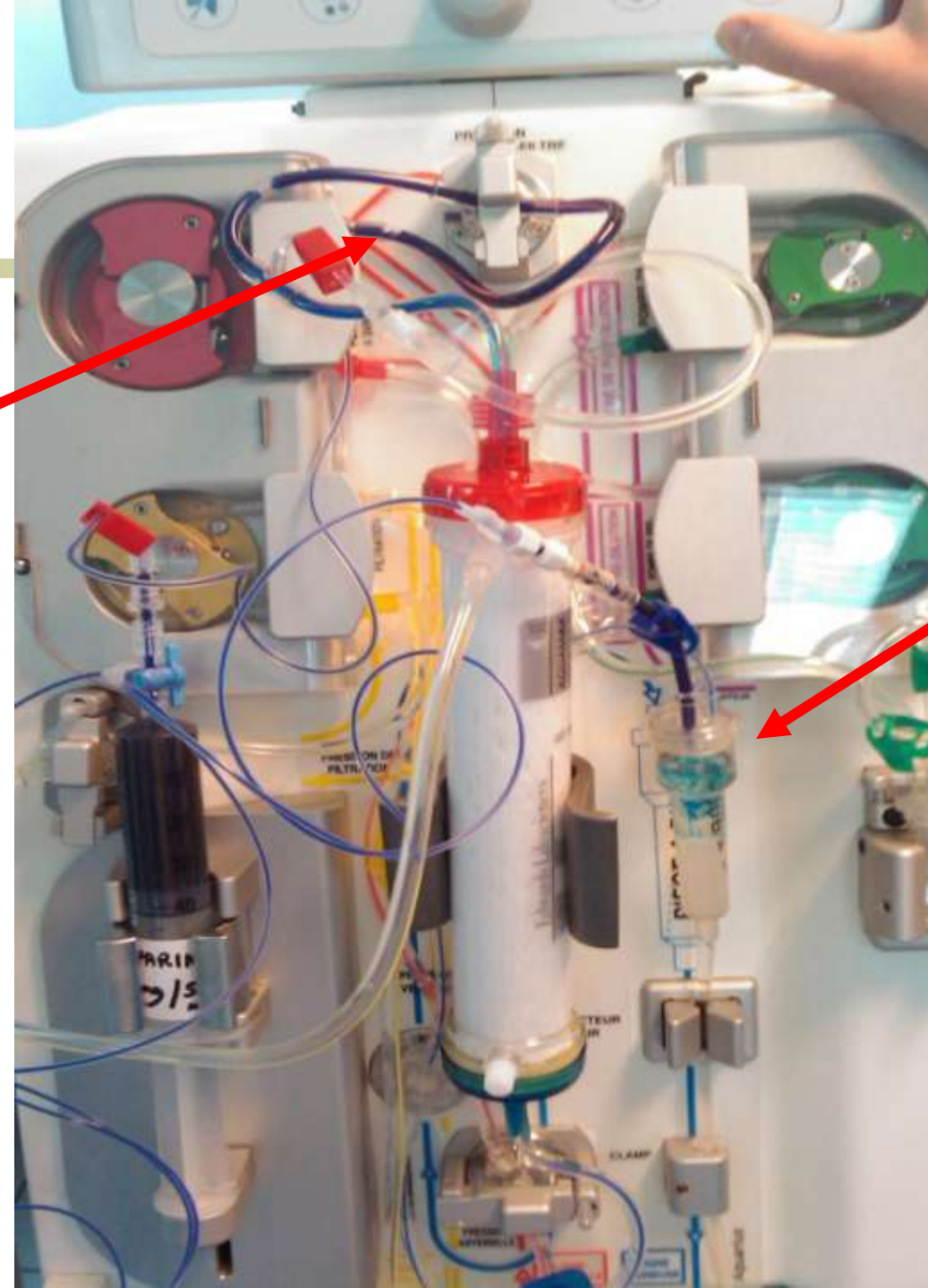
High Flow




High Concen
Low Flo
POMPE


ow Concentration
High Flow
POMPE
A SANG

Bubble Trap trouble



2/3

1/3

ICU biological parameters

- WBC : 11 500; CRP : 555
- Platelets : 120 000, PT : 70%, ACT : 37/34
- Lactates 3 [illegible] l/l; Urea 12,5 mmol/l
- K^+ 4.8; Na[illegible]
- Last 12h diuresis = 0.4 ml/kg/h
- Hepatic data are normal

AT : 32%

New thrombosis in the next 12 hours

Antithrombin supplementation for anticoagulation during continuous hemofiltration in critically ill patients with septic shock: a case-control study

Damien du Cheyron[1], Bruno Bouchet[1], Cédric Bruel[2], Cédric Daubin[1], Michel Ramakers[1] and Pierre Charbonneau[1]

Crit Care 2006

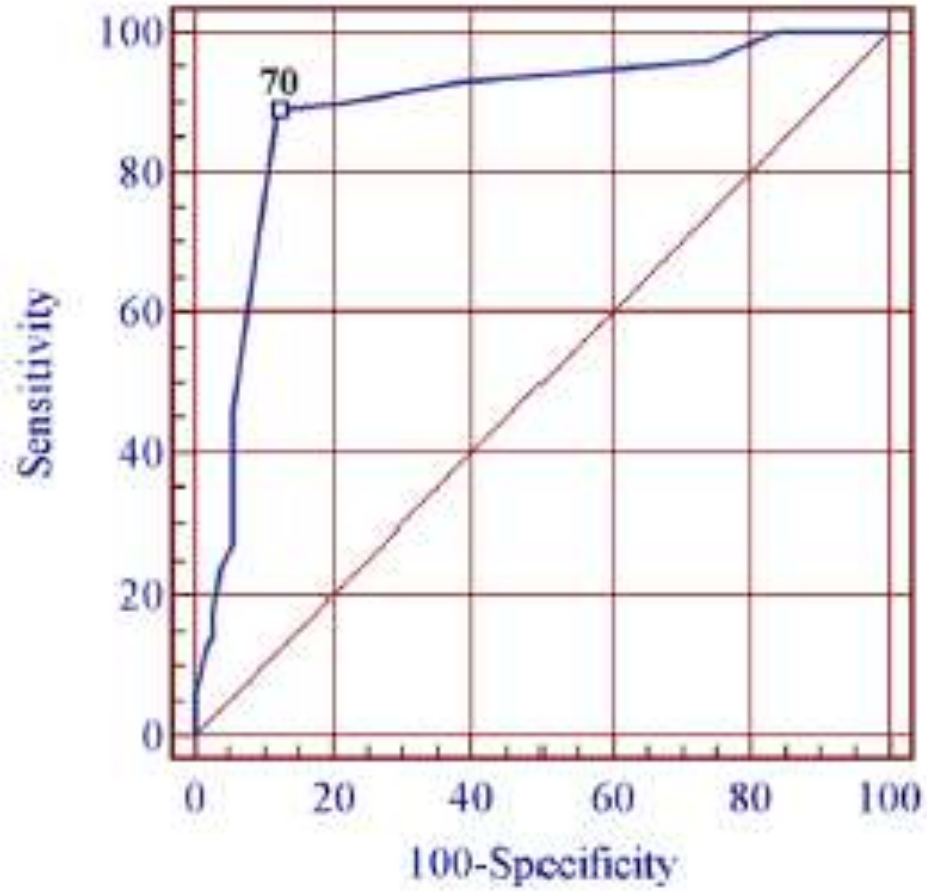
- Retrospective study, 4 years, 2 phases :
  - Phase I : 55 patients followed with 40 deficit in AT (<70%) without supplementation
  - Phase II : 38 Patients with a deficit in AT, supplementation
- Supplementation by Bolus of 50 UI/kg
- Patients treated by CVVH or CVVHDF
- All septic with organ failure

Antithrombin supplementation for anticoagulation during continuous hemofiltration in critically ill patients with septic shock: a case-control study

Damien du Cheyron[1], Bruno Bouchet[1], Cédric Bruel[2], Cédric Daubin[1], Michel Ramakers[1] and Pierre Charbonneau[1]

Crit Care 2006

Figure 1



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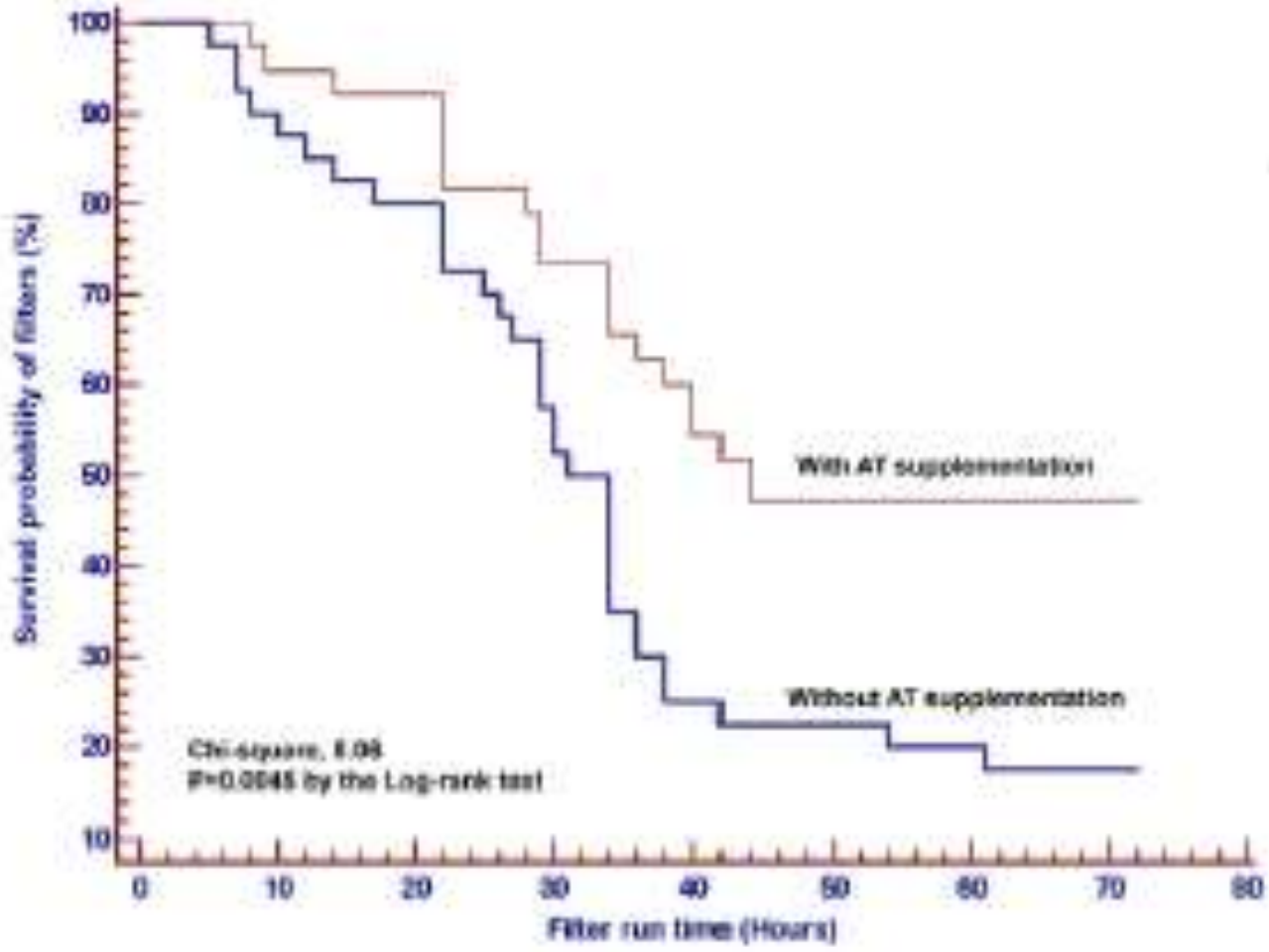
Crit Care 2006

Figure 3



Acquired Deficit of Antithrombin and Role of Supplementation in Septic Patients During Continuous Veno-Venous Hemofiltration

Mathieu Lafarcle,* Olivier Joannes-Boyau,* Patrick M. Honoré,† Bernard Gauche,‡ Hubert Grand,‡ Catherine Fleureau,* Hadrien Rose,* and Gérard Janvier*

ASAIO 2008

- Correlation between AT activity level and filter lifespan ?
- Interest of AT supplementation for filter lifespan ?
- Risk of bleeding
- Transfusion needed ?
- Comparison between continuous infusion and Bolus methods
- Cost / efficacy

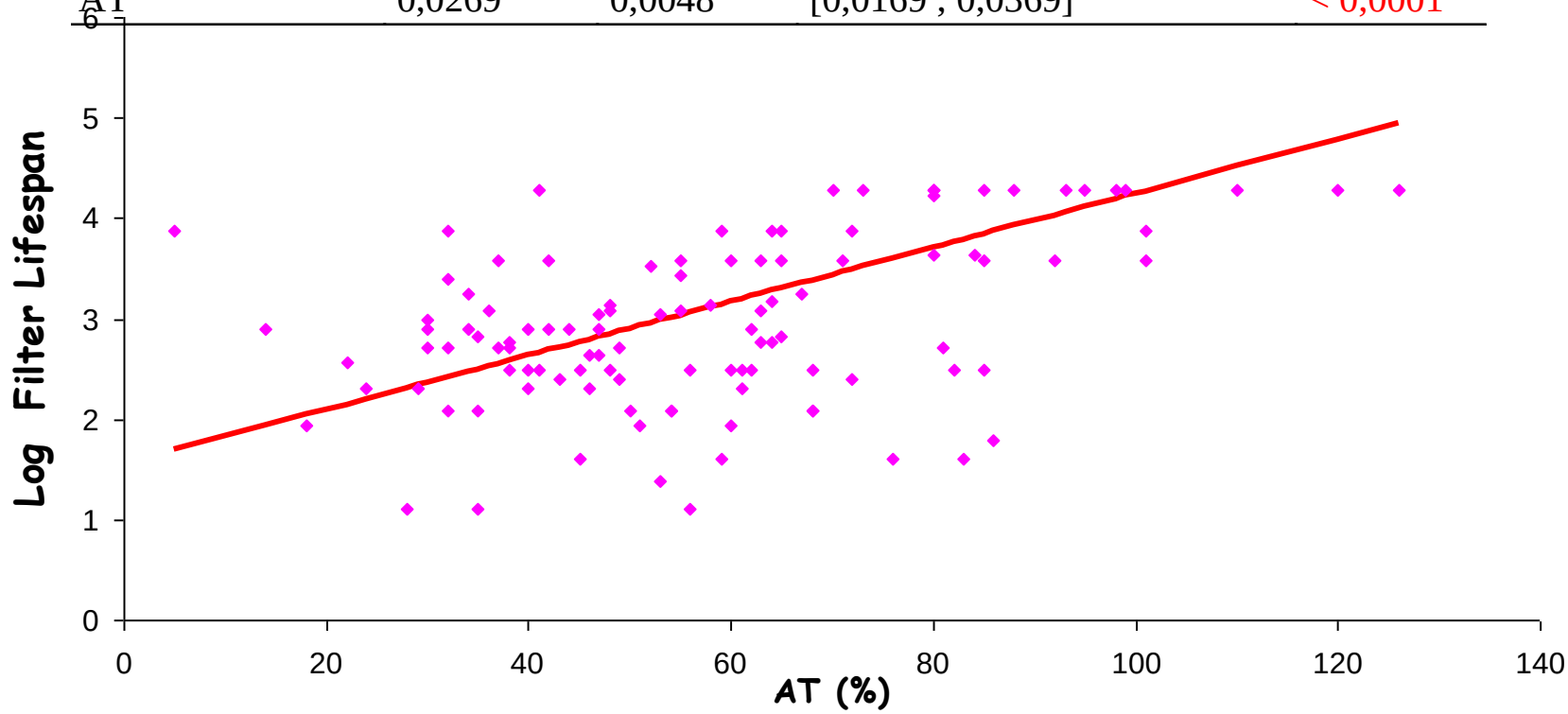
Acquired Deficit of Antithrombin and Role of Supplementation in Septic Patients During Continuous Veno-Venous Hemofiltration

Mathieu Lafarcle,* Olivier Joannes-Boyau,* Patrick M. Honoré,† Bernard Gauche,‡ Hubert Grand,‡ Catherine Fleureau,* Hadrien Rose,* and Gérard Janvier*

ASAIO 2008

Relationship Log Filter Lifespan / AT activity level

Parameter	Estimation	Ecart-type	confidence Interval 95%	p-value
Intercept	1,5565	0,2981	[0,9325 ; 2,1805]	< 0,0001
AT	0,0269	0,0048	[0,0169 ; 0,0369]	< 0,0001



Which Anticoagulant?

Unfractionated HEPARIN ⟺ High bleeding risk

SAFE

Regional HEPARINISATION ?

Which Anticoagulant?

- **Regional heparinization**
  - More filter thrombosis
  - Risk of hemorrhage

Bellon J, Cabrol et al, Masson, Paris, 1989.
Tang SD et al. *ASAID Transaction* 1992.

Which Anticoagulant?

Unfractionated HEPARINE ⟺ SAFE

Regional HEPARINISATION ⟺ Technical problems

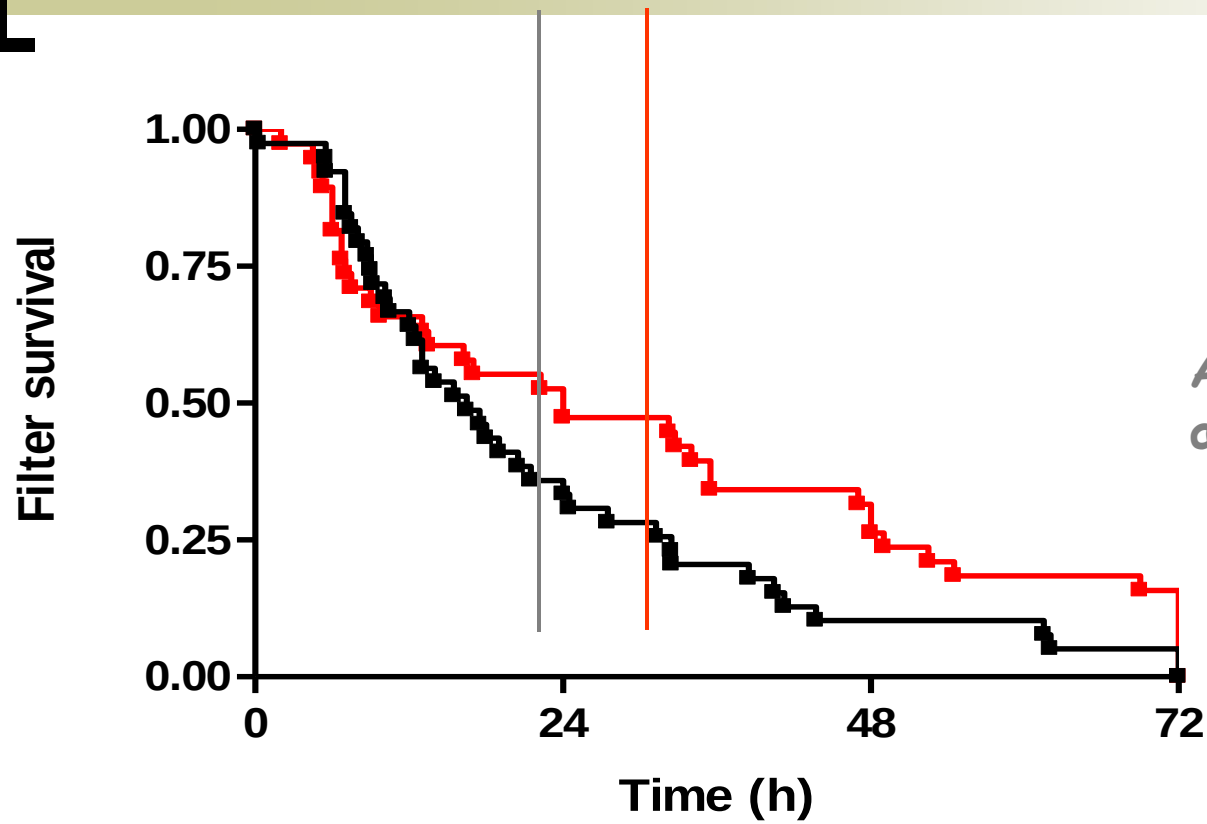
LMWH?

Which Anticoagulant?

- **LMWH**
  - . Anti Xa activity and less anti-thrombin activity.
  - . Reduce the risk of hemorrhage.
  - . Usually used in patients with chronic renal failure.
  - . Less used in ICU :
    - . Difficulty of monitoring.
    - . Accumulation in patients with acute renal failure.
    - . Partially neutralized by protamine.

De Pont AC, et al. *Crit Care Med.* 2000
Reeves JH, et al. *Crit Care Med.* 1999

Heparin vs enoxaparin

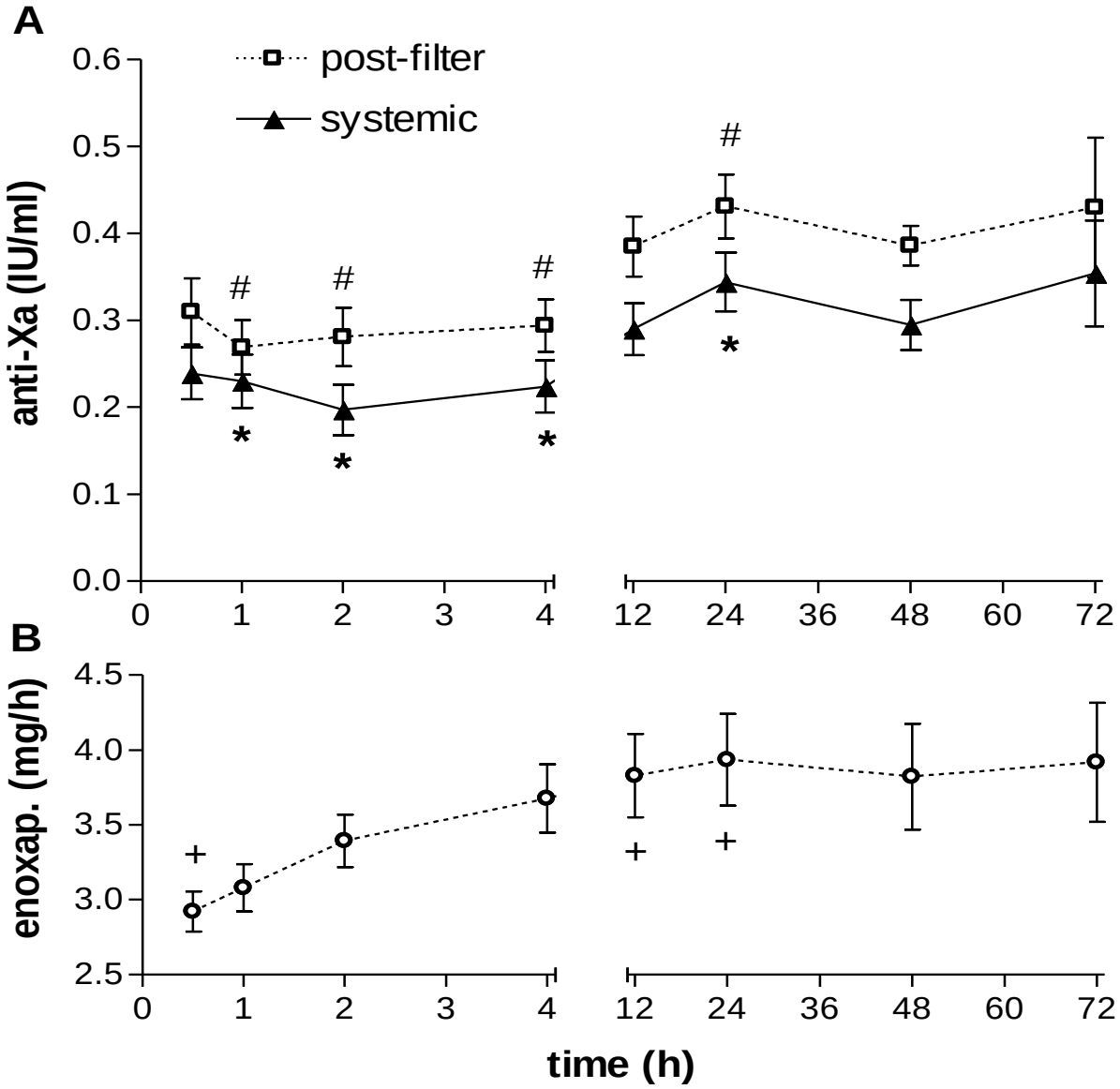


Anti Xa = 0.25-0.30 IU/ml
aPTT = 40-45 sec

	heparin	enoxaparin	
filter life (mean ± SEM)	21.7 ± 3.0 h	30.6 ± 4.0 h	p=0.017
steady state dose	590 ± 46 IU/h	3.6 ± 0.2 mg/h	

Joannidis M et al, Intensive Care Med 2007

Heparin vs enoxaparin



Day cost

Heparin	Enoxaparin
270€	240€

Bleeding

Heparin	Enoxaparin
1 (2,5%)	1 (2,5%)

Joannidis M et al; Intensive Care Med 2007

Which Anticoagulant?

Unfractionated HEPARINE	⟺	SAFE
Regional HEPARINISATION	⟺	Technical problems
LMWH	⟺	Not easy in ICU
PROSTACYCLIN ?		

Prostacyclin?

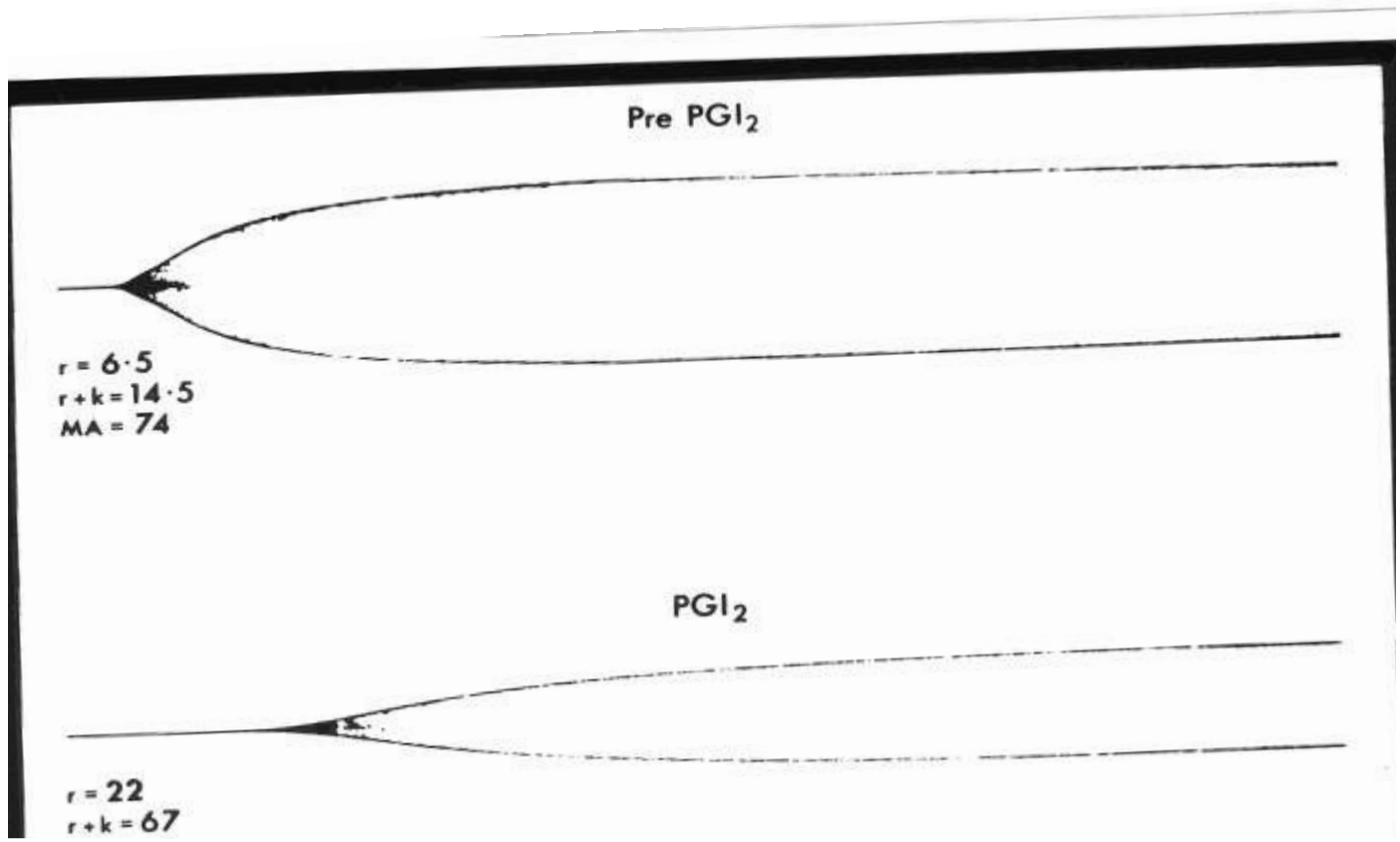
	Nb of filters / patients / Day
Heparin (low dose) alone	1,7 ± 0,2
Heparin + PG-E1 (5 ng/kg/min)	1,1 ± 0,1
Heparin + PG-E1 (20 ng/kg/min)	0,7 ± 0,2

Kozek-Langenecker SA, et al. *Crit Care Med.* 1998

Dramatic reduction of Heparin dose requirement with 5ng of PG

Silvester W, Honoré PM. *Blood Purif 1997*

Prostacyclin

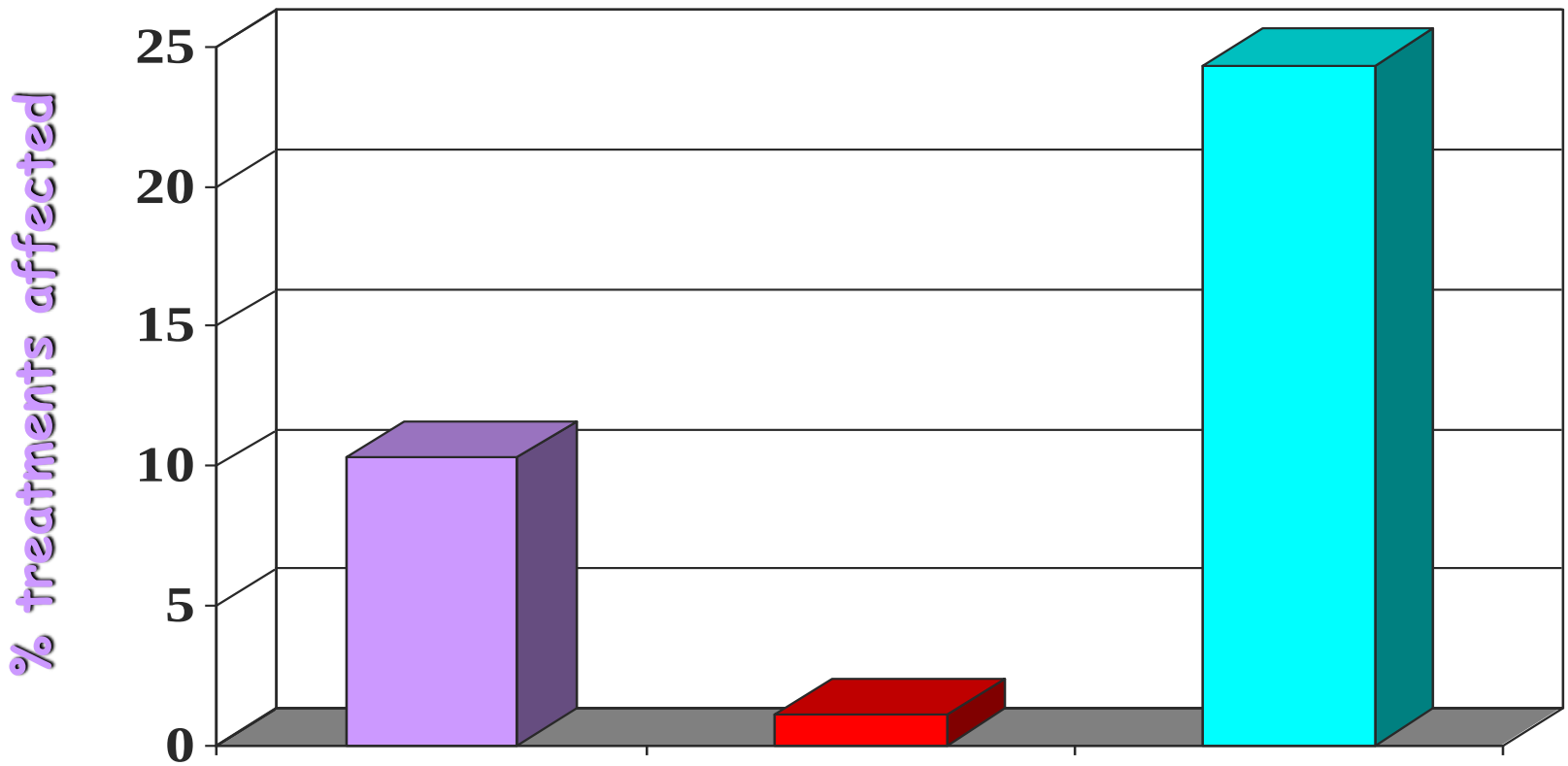


pre

PGI_2
5 ng/kg.min

PGI_2 for SLED

Fiacadori et al NephrolDialTransplant 2007



Parma
35 ICU pts
185 SLED
Start
3 ng/kg.min
iv Then
6 ng/kg.min
into circuit

Which Anticoagulant?

- **Prostacyclin (PGI2)**
  - Platelet aggregation inhibitor
  - Strong Vasodilator activity
  - In association with LMWH or UFH
  - Cost

Which Anticoagulant?

Unfractionated HEPARINE	⟺	SAFE
Regional HEPARINISATION	⟺	Technical problems
LMWH	⟺	Not easy in ICU
PROSTACYCLIN	⟺	Bleeding risk ↘ Hypotensive effect ↗
CITRATE ?		

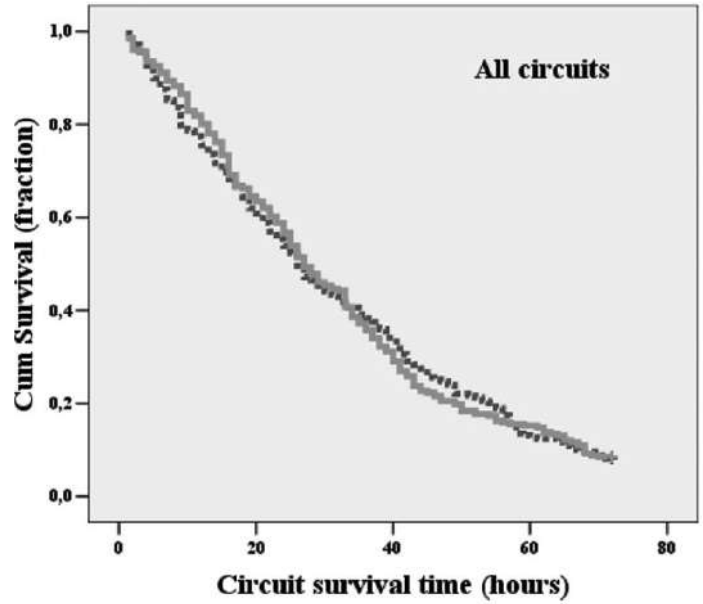
Citrate anticoagulation for continuous venovenous hemofiltration*

Heleen M. Oudemans-van Straaten, MD, PhD; Rob J. Bosman, MD; Matty Koopmans, RN;

Crit Care Med 2009 Vol. 37, No. 2

Table 3. Safety, efficacy, and clinical outcomes

	Citrate (n = 97)	Nadroparin (n = 103)	*p*
Safety			
Adverse events needing discontinuation of study anticoagulant, n (%)	2 (2)	20 (19)	<0.001
Bleeding, n (%)	6 (6)	16 (16)	0.08
Heparin-induced thrombocytopenia, n (%)	3 (3)	4 (3)	0.90



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Crit Care Med 2009 Vol. 37, No. 2

	Citrate (n = 97)	Nadroparin (n = 103)	*p*
Mortality			
All randomized patients			
Mortality hospital (%) (95% CI)	42 (31–51)	57 (48–67)	0.02
Mortality 3-month (%) (95% CI)	48 (38–58)	63 (53–72)	0.03
Per protocol patients			
Mortality hospital (%) (95% CI)	41 (31–51)	57 (48–67)	0.03
Mortality 3-month (%) (95% CI)	45 (35–55)	62 (53–72)	0.02

Which Anticoagulant?

Unfractionated HEPARINE	⟺	SAFE
Regional HEPARINISATION	⟺	Technical problems
LMWH	⟺	Not easy in ICU
PROSTACYCLIN	⟺	Bleeding risk ↘ Hypotensive effect ↗
CITRATE	⟺	Best anticoagulant in ICU BUT…

without Anticoagulation

- Hemofiltration with pre-dilution
- Repeated rinsing of hemofiltration circuit
- Regional anticoagulation by Citrate ?

Tan HD, et al. *Intensive Care Med.* 2000

Uchino S, Bellomo R, et al. *ASAIO J.* 2004

Anticoagulation Free Protocols

Study	Design	Pts*	CRRT Modality	BF (ml/min)	Effluent (L/hr)	Catheter	Mean Filter Life hrs (median)**
Bellomo et al 1993	RCT	10	CVVHD	150	1	Femoral	40.9 (26)
Martin et al 1994	Retrosp	37	Post-dil CVVH	100-150	0.8-1.3	N/A	22.1 (19.2)
Tan et al 2000	Prosp	12	Pre-dil CVVH	200-300	2	13.5 F	32
Holt et al 2002	Prosp	14	CVVHD	200	N/A	10.8 F	33.2 (21)
Moribito et al 2003	Prosp	22	CVVHD CVVHDF CVVH	100-150	N/A	12 F	10 pts (switched to AC) :12 12 pts: 38.3 (30)
Uchino et al 2004	Prosp	35	Pre- and Post dil CVVH	200	2	13.5 F	19.3

*All patients with coagulopathies

**Circuit survival similar or longer than in patient without coagulopathy receiving UFH

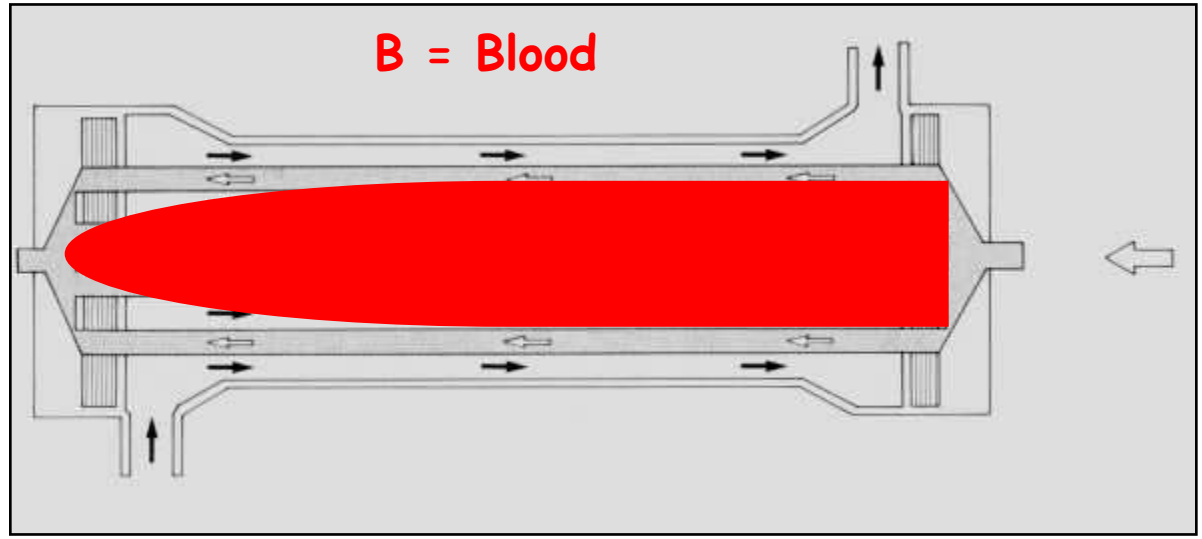
Summary

- Check list :
  - Catheter
  - Filtration fraction
  - Pressures
  - Stop treatment during nursing

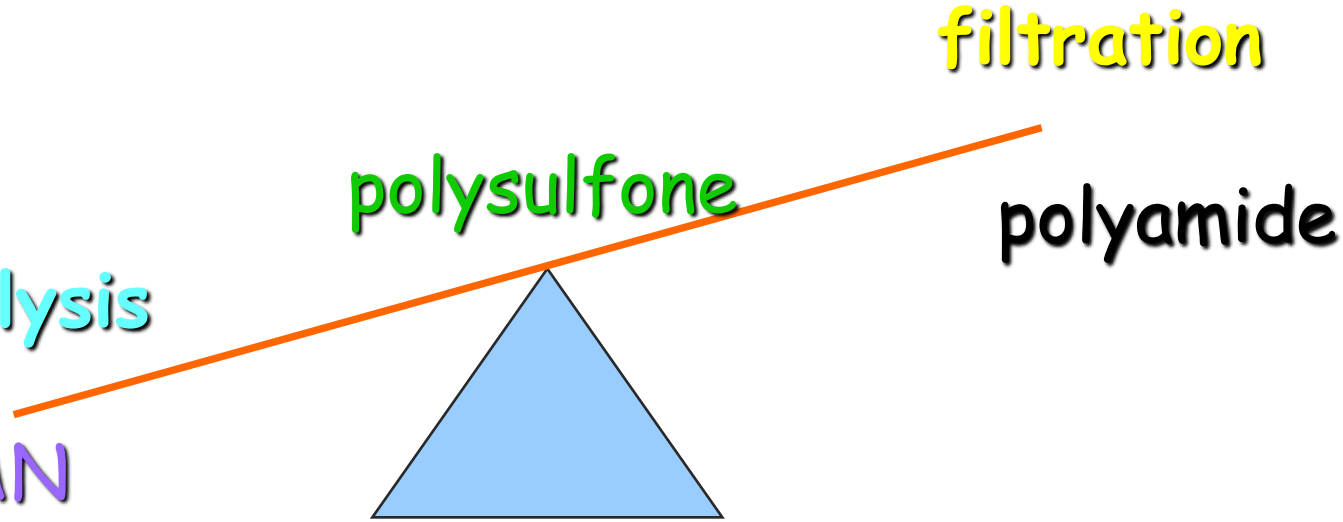
Summary

- Anticoagulation Only one third of thrombosis problems
- More difficulties in septic patients (AT, CIVD...)
- Choose the anticoagulant :
  - Lowest half-life
  - Easy to Neutralize
  - According to ICU habits

Capillary dialyser



Membranes


filtration
polysulfone
polyamide
dialysis
PAN
modified cellulose


capillary fibre
long
short
narrow diameter
large diameter


Bordeaux
place de la Bourse, June 2010
Thank you