2016

Anticoagulation régionale au Citrate

Bases théoriques & Application pratique

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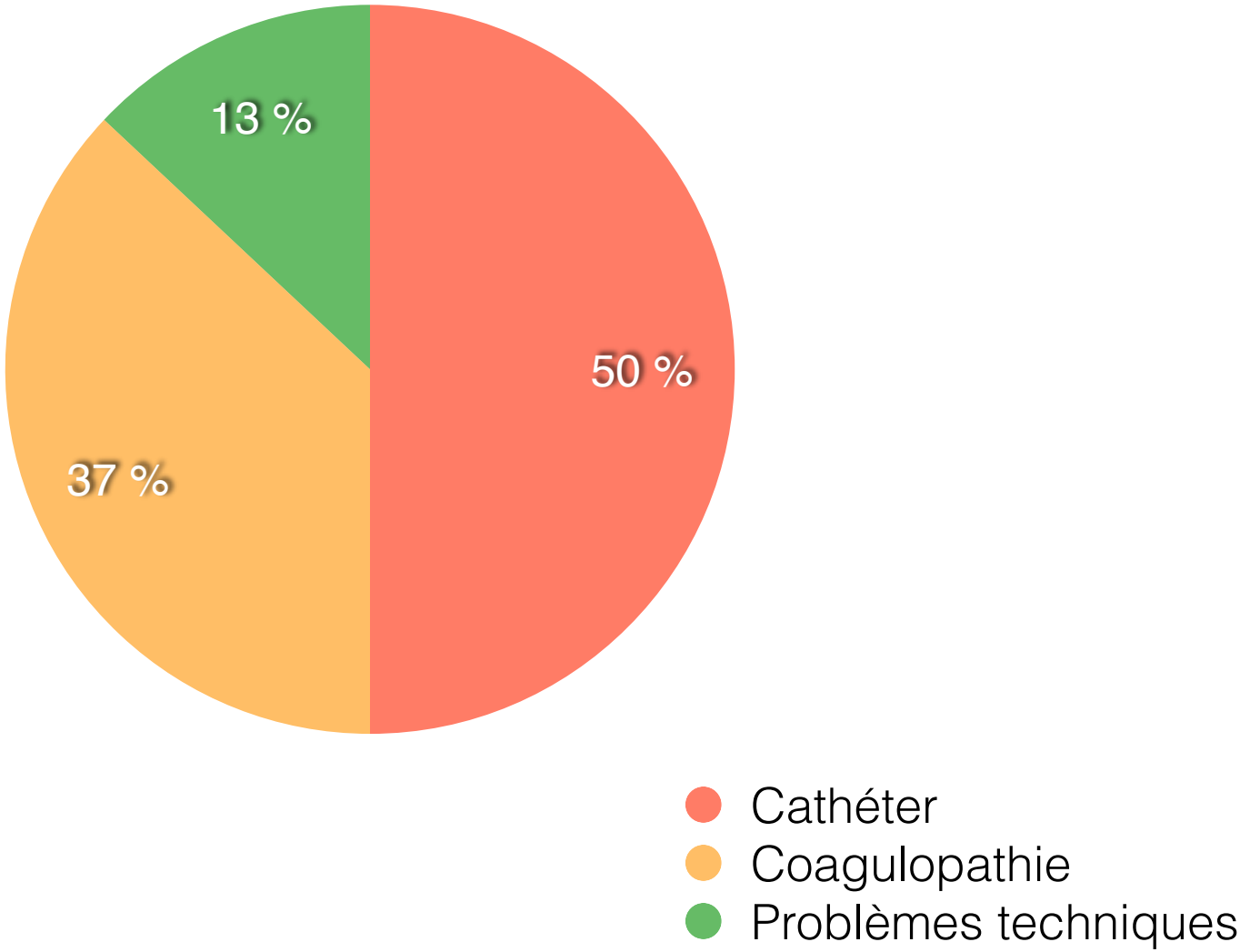
Causes des thromboses de Filtres



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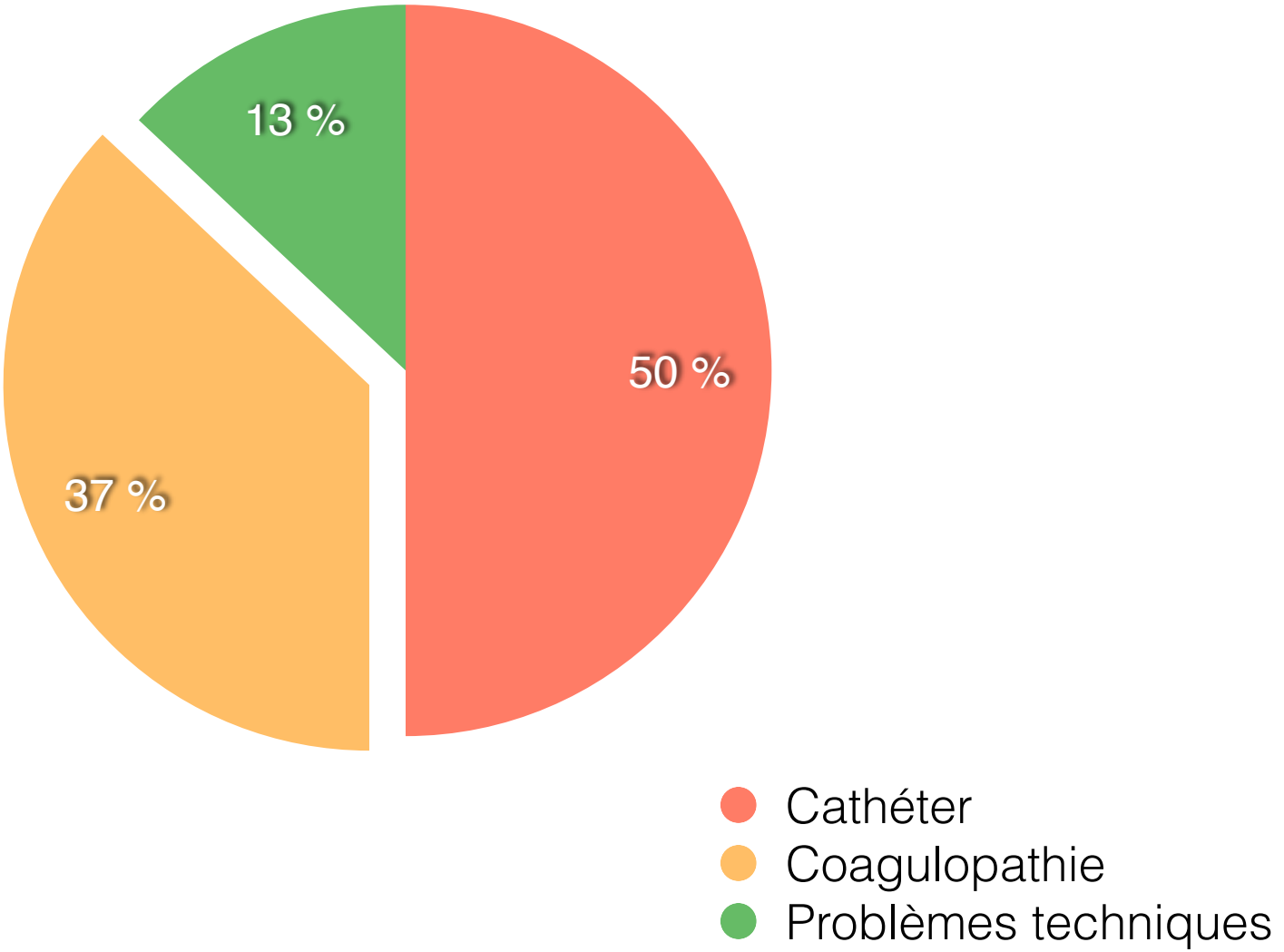


Pourquoi Anticoaguler le circuit ?

Pourquoi Anticoaguler le circuit ?

Préserver les performances du Filtre (ST 150)

Augmenter la durée de vie de l'EERC

Eviter la spoliation sanguine

Conséquence de la coagulation du Filtre

Baisse de la dose de Filtration et/ou de Dialyse

Augmentation des pertes sanguines

Transfusion, coût, risques

Perte de Temps pour les IDE

Insatisfaction, désinvestissement de l'EERC

Cahier des charges
de la meilleure Anticoagulation pour l'EERC

1/2-vie courte

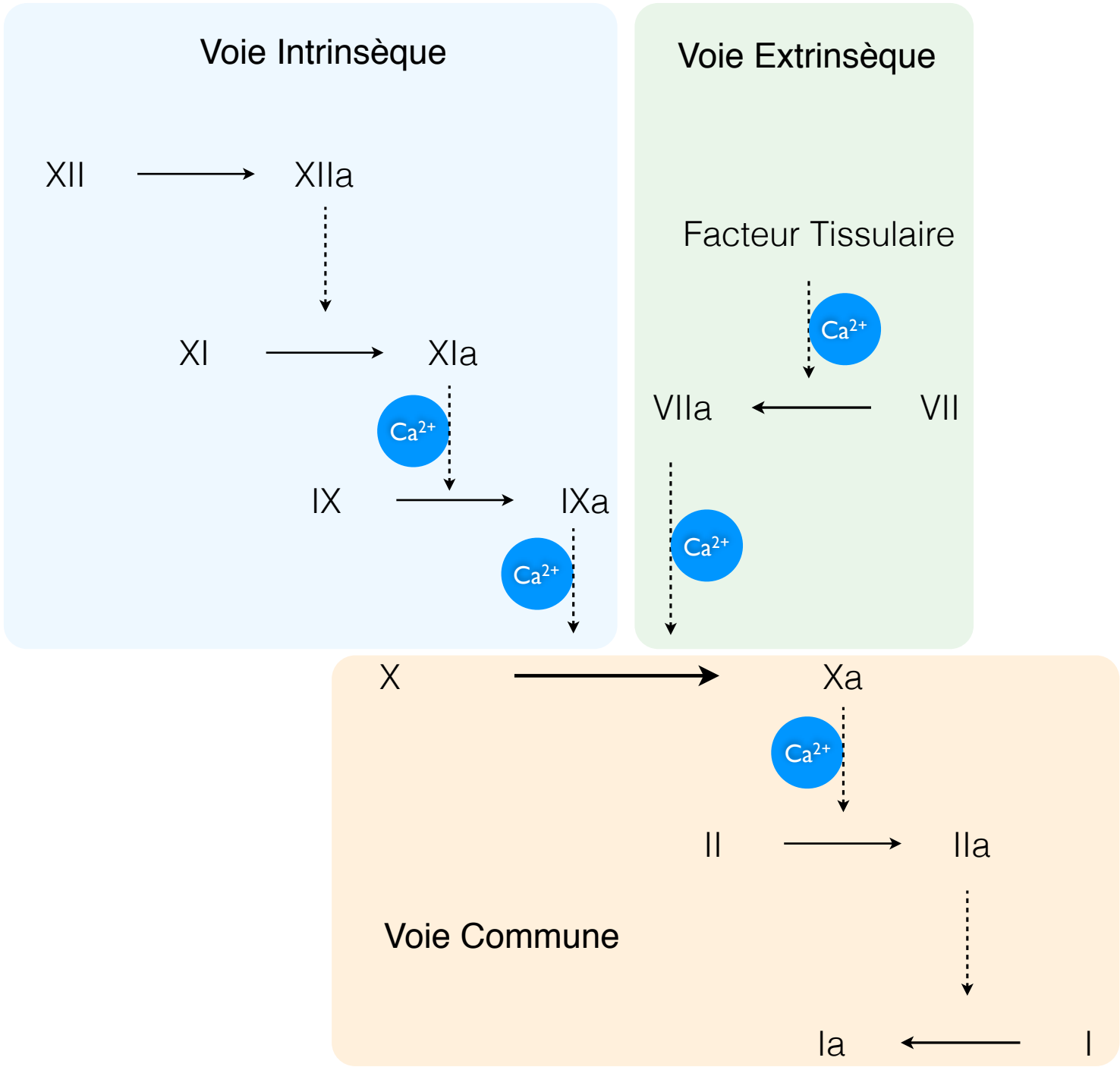
Action limitée au circuit

Facile à surveiller

Pas d'effet secondaire systémique

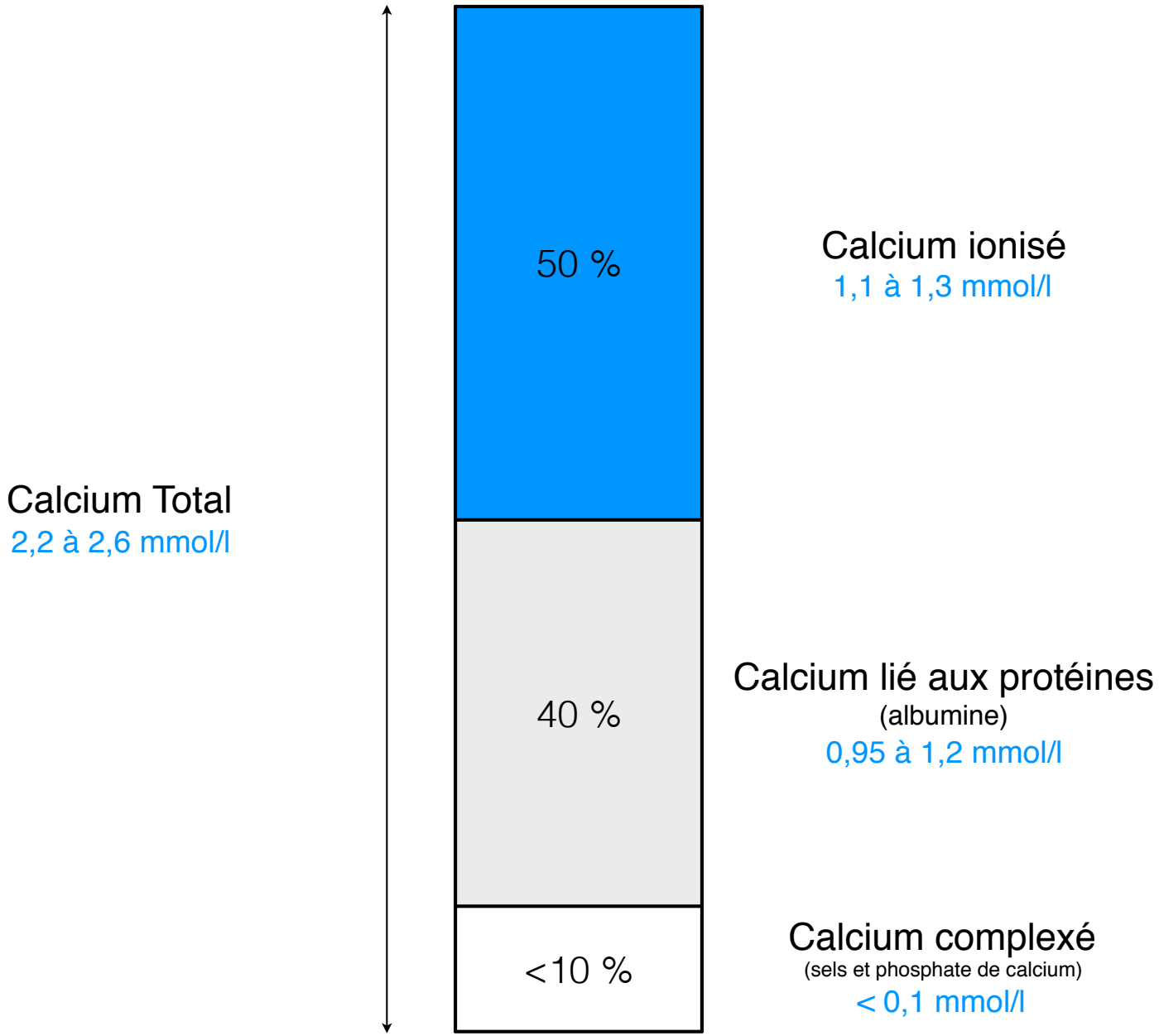
Antagoniste disponible

Aucun ne remplit tous ces critères

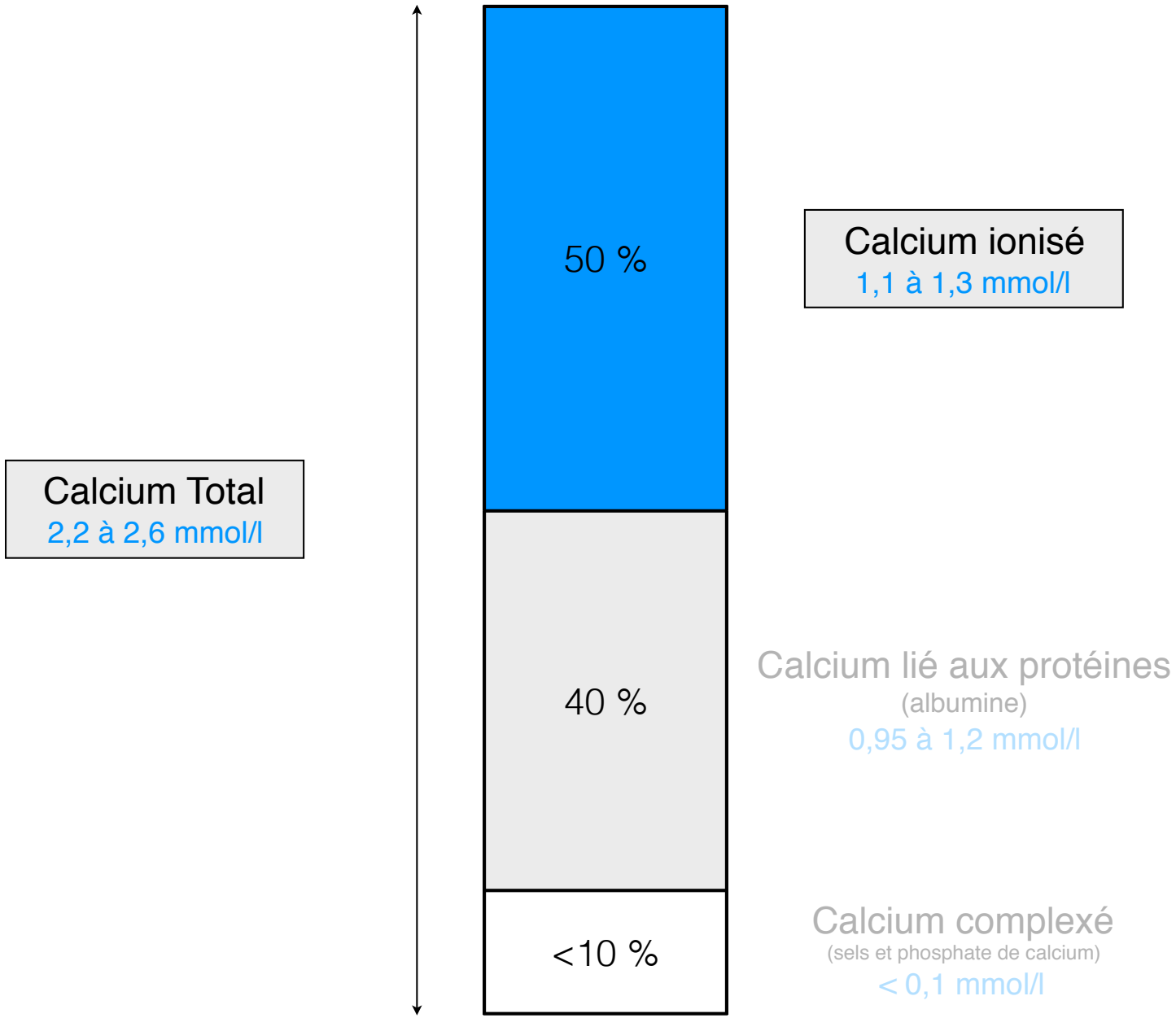

Voie Intrinsèque
XII
XIIa
XI
XIa
Ca2+
IX
IXa
Ca2+
Voie Extrinsèque
Facteur Tissulaire
Ca2+
VIIa
VII
Ca2+
X
Xa
Ca2+
II
IIa
Voie Commune
Ia
I

Facteur I	Fibrinogène
Facteur II	Prothrombine
Facteur III	Facteur Tissulaire : Thromboplastine Tissulaire
Facteur IV	**Calcium**
Facteur V	Pro-accélérine
Facteur VI	Accélérine (ancien Facteur Va)
Facteur VII	Proconvertine : Accélérateur de conversion de la prothrombine sérique (ACPS)
Facteur VIII	Facteur Anti-Hémophilique (FAH) et Globuline anti-Hémophilique (GAH)
Facteur IX	Facteur Christmas : Composant de la Thromboplasmine plasmatique (CTP)
Facteur X	Facteur Stuart - Prower
Facteur XI	Facteur Rosenthal, Antécédent de laThromboplastine plasmatique (ATP)
Facteur XII	Facteur Hageman, Facteur de Contact
Facteur XIII	Facteur Stabilisant de la Fibrine, Fibrinase

Le Calcium


Calcium Total
2,2 à 2,6 mmol/l
50 %
40 %
<10 %
Calcium ionisé
1,1 à 1,3 mmol/l
Calcium lié aux protéines
(albumine)
0,95 à 1,2 mmol/l
Calcium complexé
(sels et phosphate de calcium)
< 0,1 mmol/l

Le Calcium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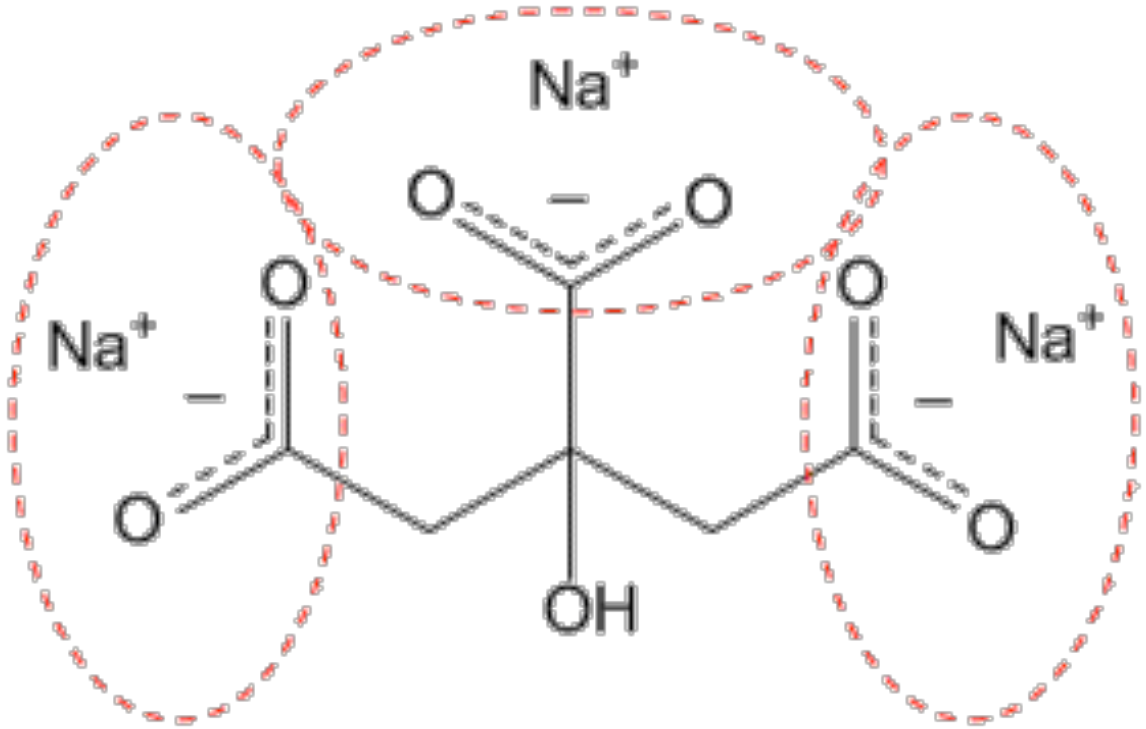
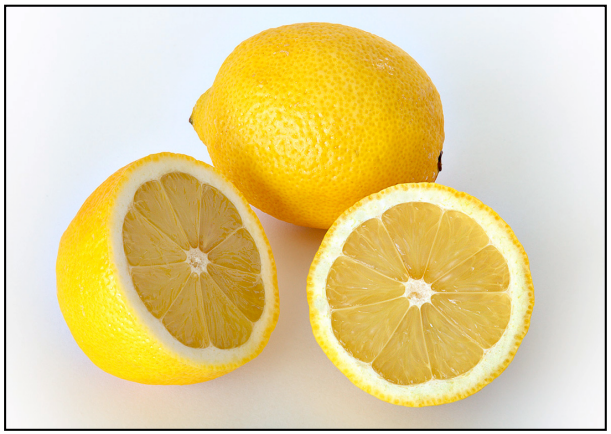
Le Citrate



Sel d’Acide Citrique Tri-Sodique

Le Citrate

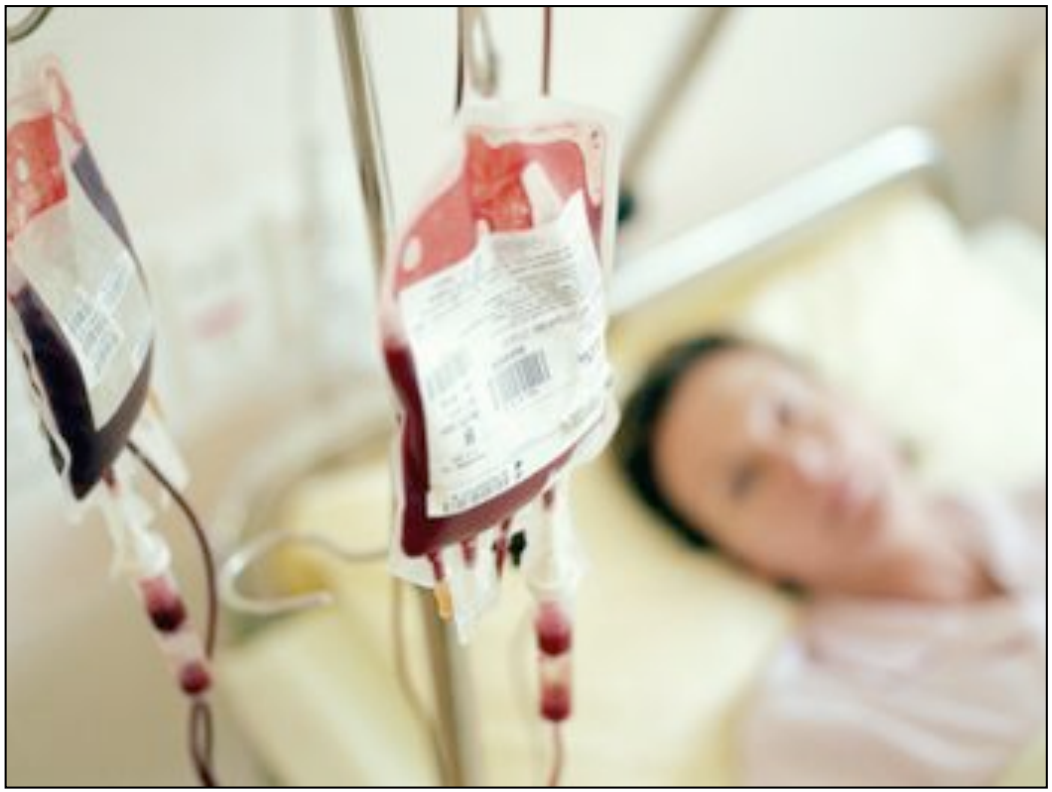


Chélateur du Ca^{2+}

Libère 3 Na^{+}

Complexe Ci-Ca^{2+}

Le Citrate



Le Citrate

PrismoCitrate 18/0

Le Citrate

5 litres

Ci-Na[3]	18 mmol/l
Ac Citrique	0 mmol/l
Na^+	140 mmol/l
Cl^-	86 mmol/l
Glucose	0 mmol/l
K^+	0 mmol/l

PrismoCitrate 18/0

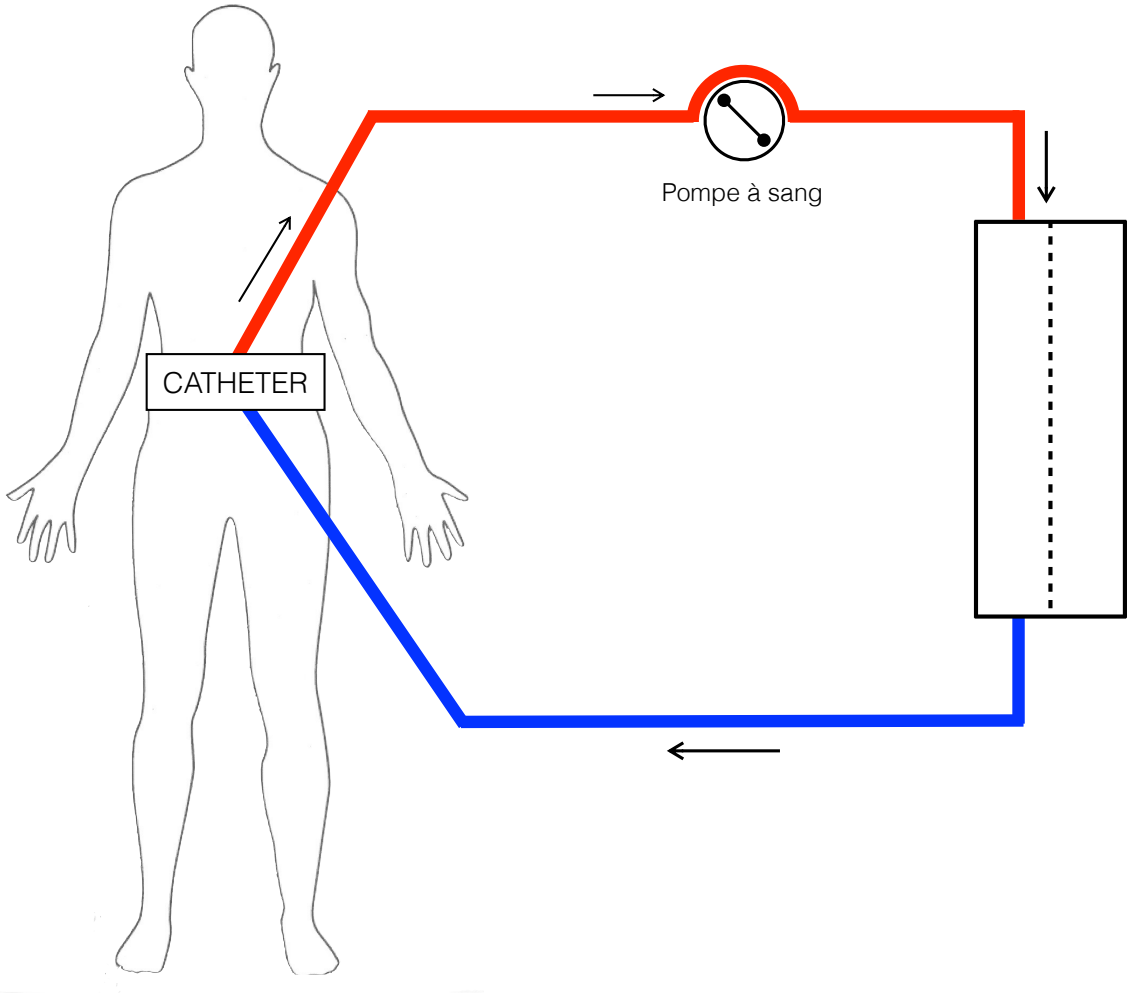
Pourquoi «régionale»?

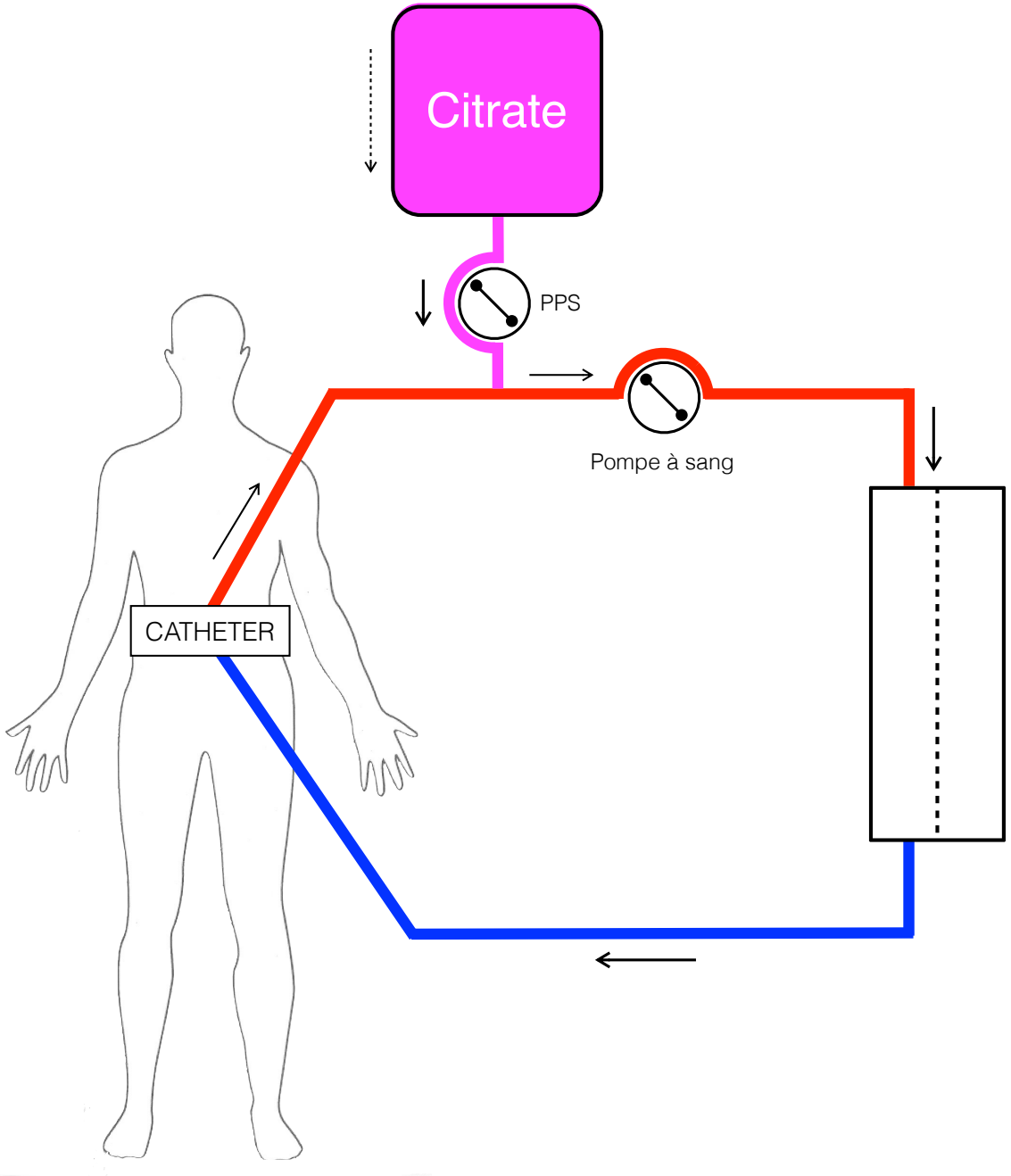
Car on anticoagule exclusivement le montage extra-corporel

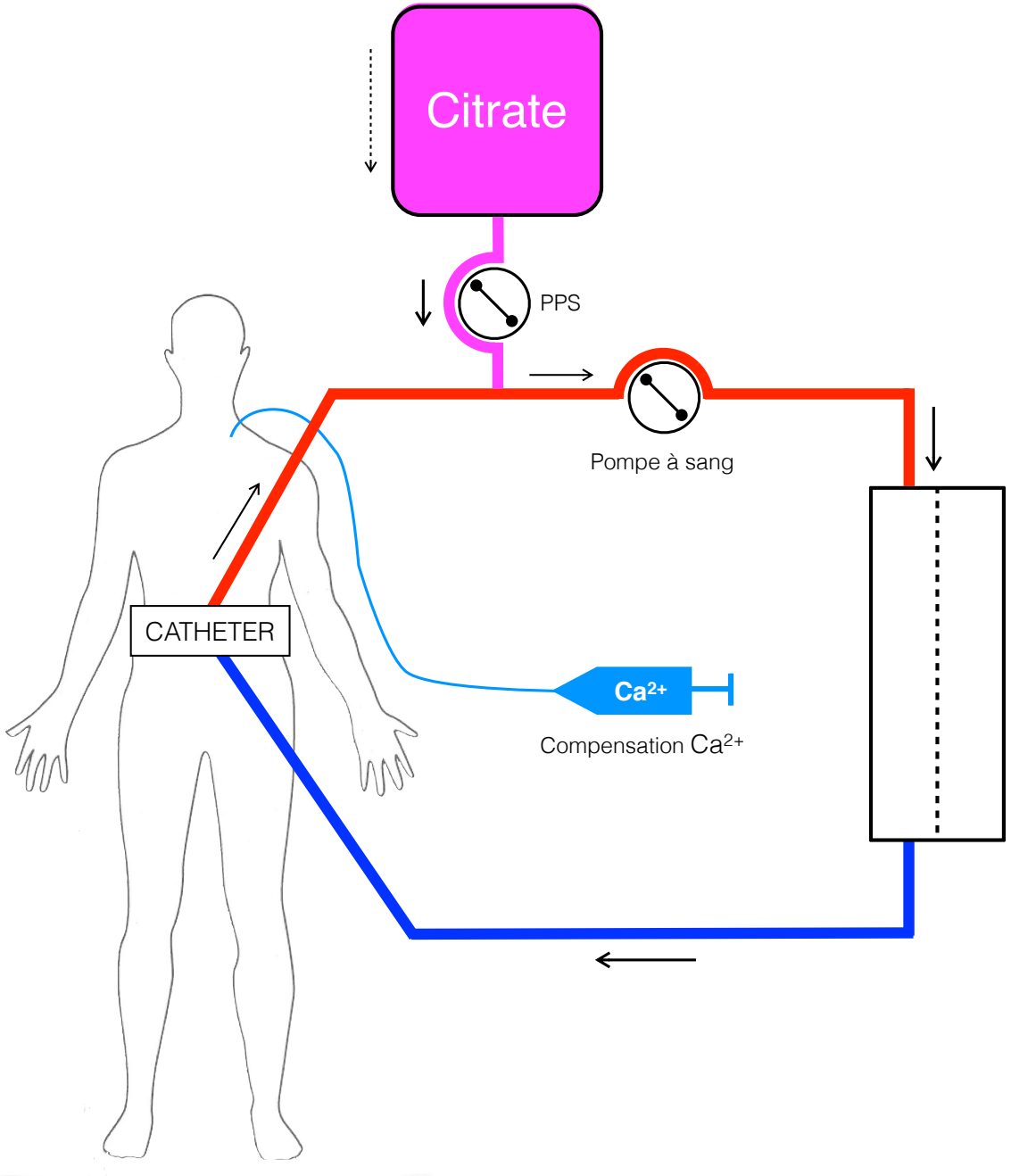
Pas d’anticoagulation systémique

Comment ?

Comment ?




Citrate
PPS
Pompe à sang
CATHETER


Citrate
PPS
Pompe à sang
CATHETER
Ca2+
Compensation Ca2+

La Machine

La Machine

Prismaflex®

5 Pompes

4 Pesons

Formation pratique

Logiciel mis à jour

PSE intégré

Indications de l'anticoagulation au Citrate

Tous les patients devant bénéficier d'une EERC

et

Présentant un saignement actif
Traumatisés, saignements digestif....

Présentant un risque hémorragique
Post Chirurgie (Neuro, Hépatique), TC, Thrompopénie

Présentant une allergie à l'héparine

Contre-Indications de l'anticoagulation au Citrate

Insuffisance hépato-cellulaire sévère

mais...

Seuils non définis dans la littérature

Seuils communément admis
TP< 50 %
FV < 50 %

Quid des patients en défaillance aiguë ou chronique ?

Pas de seuil (TP et FV) défini précisément dans la littérature…

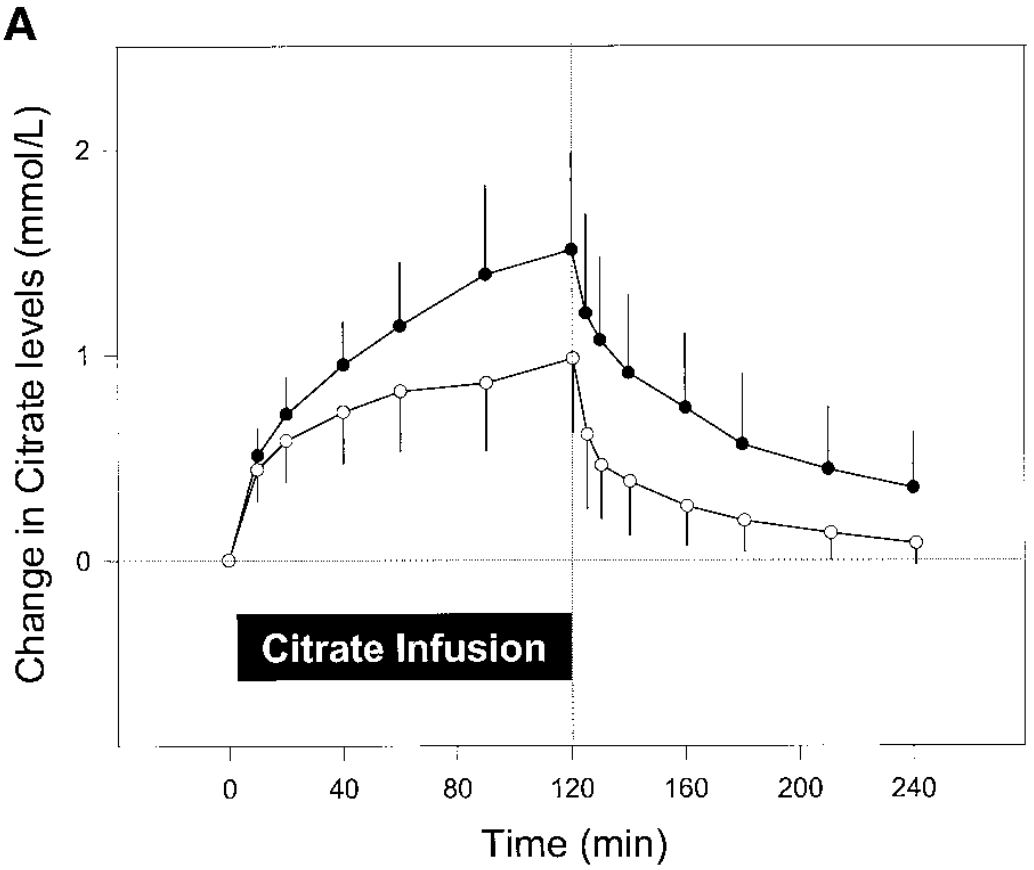
↓

Réflexion sur la balance « Bénéfice - Risque »
au cas par cas

Citrate pharmacokinetics and metabolism in cirrhotic and noncirrhotic critically ill patients

Ludwig Kramer; Edith Bauer; Christian Joukhadar; Wolfram Strobl; Alexandra Gendo; Christian Madl; Alfred Gangl

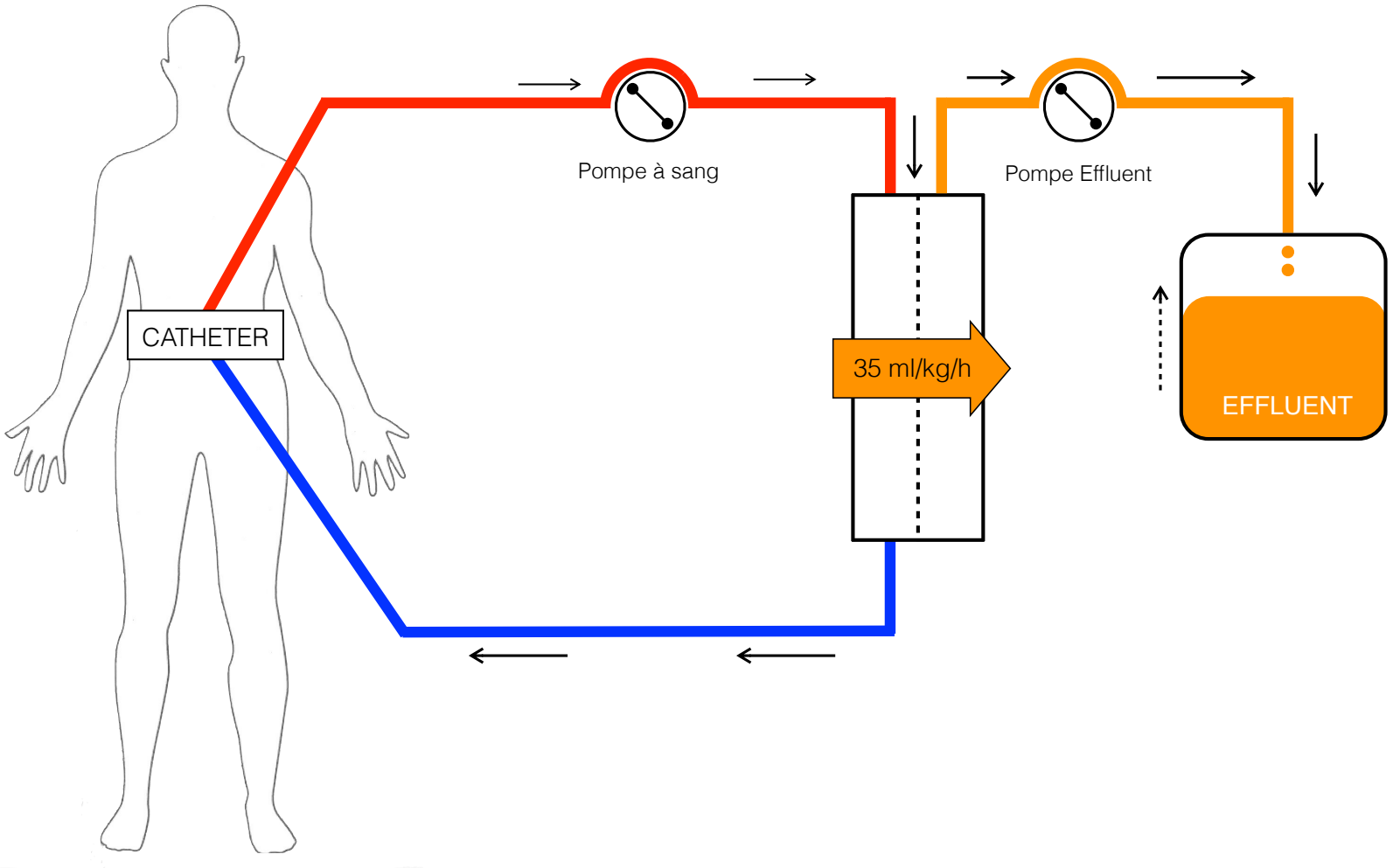
Crit Care Med 2003 Vol. 31, No. 10

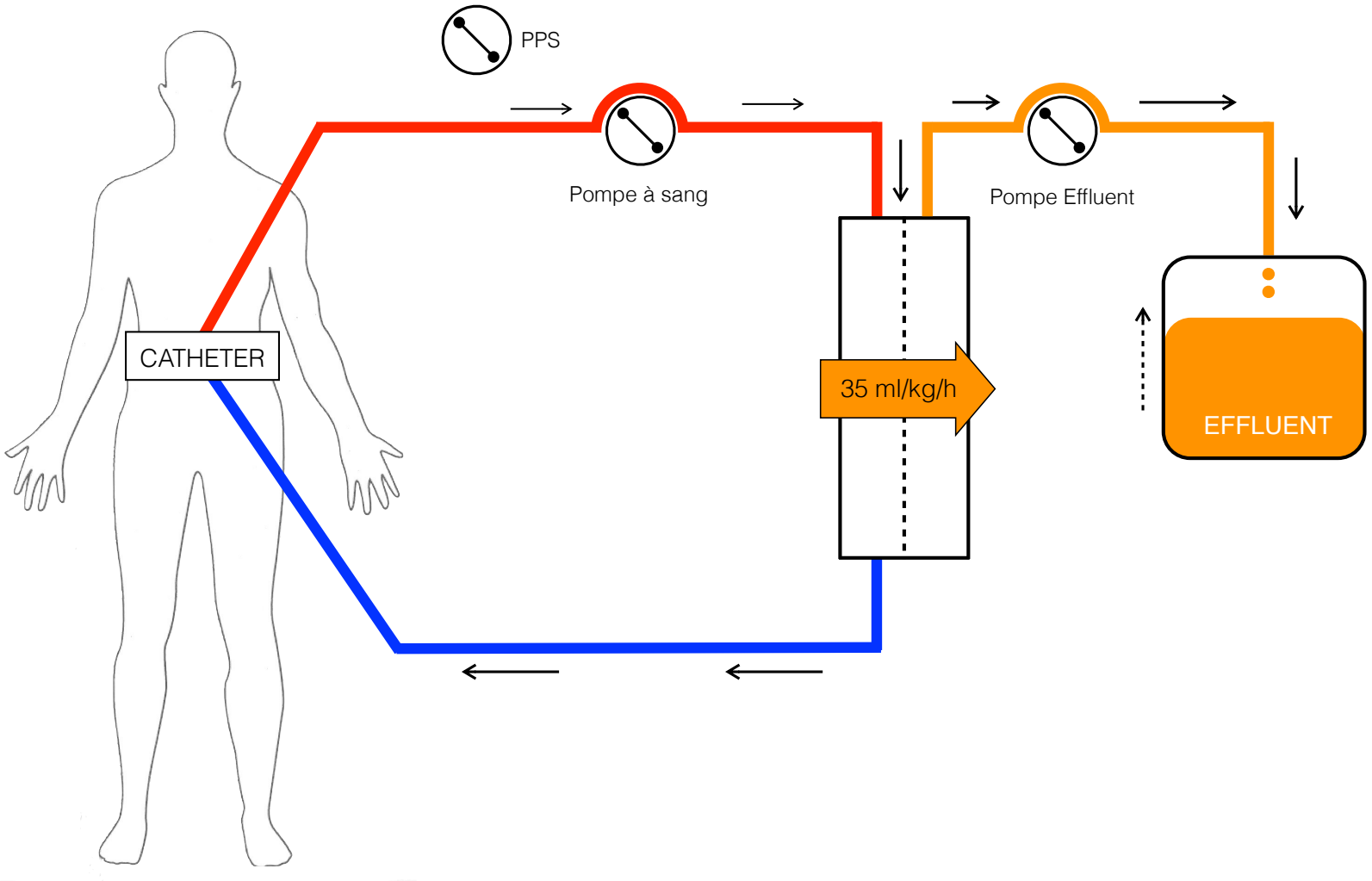


Protocole du Service

Le Montage

CVVH exclusif
dans un premier temps...


Pompe à sang
Pompe Effluent
CATHETER
35 ml/kg/h
EFFLUENT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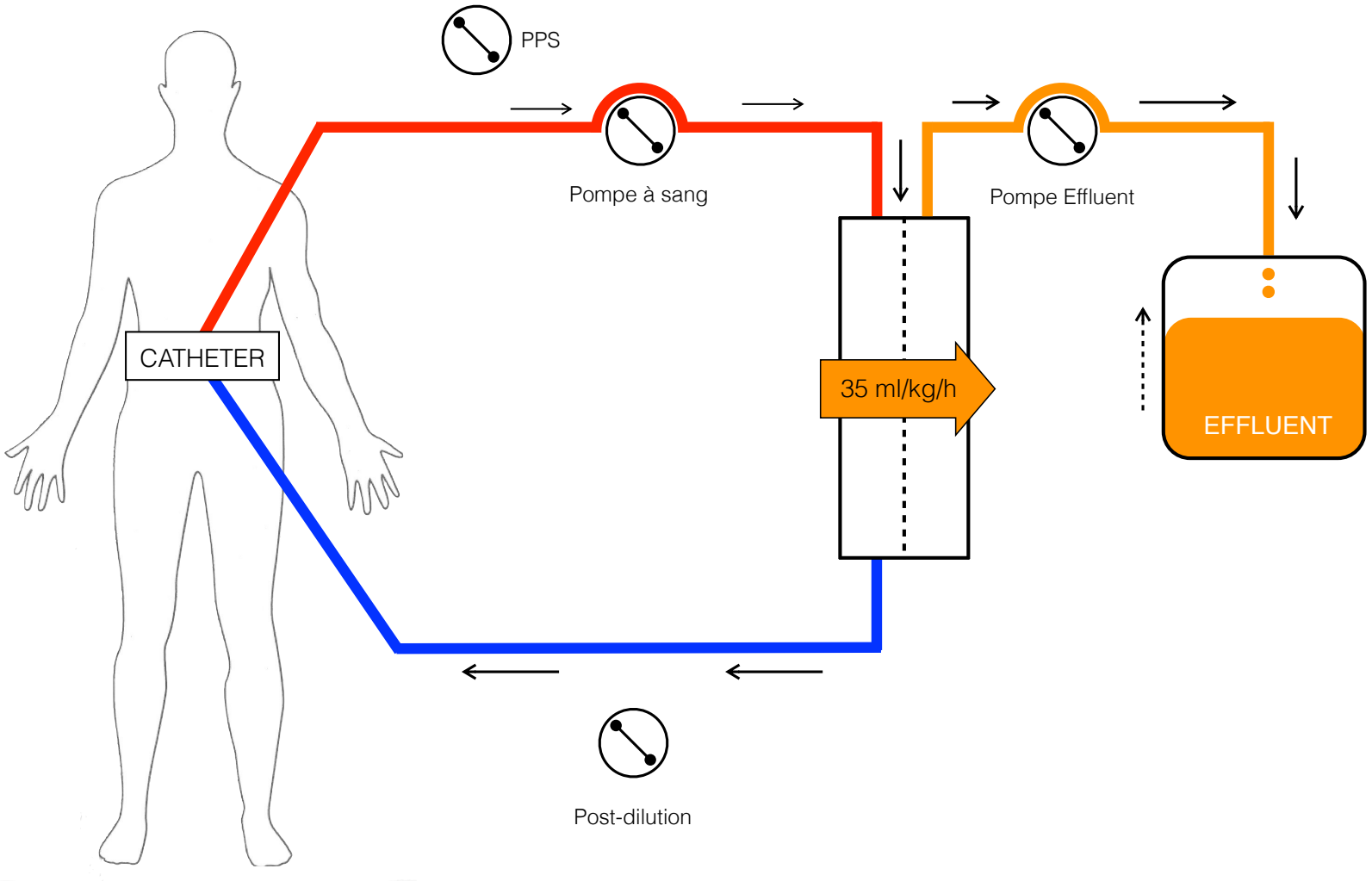
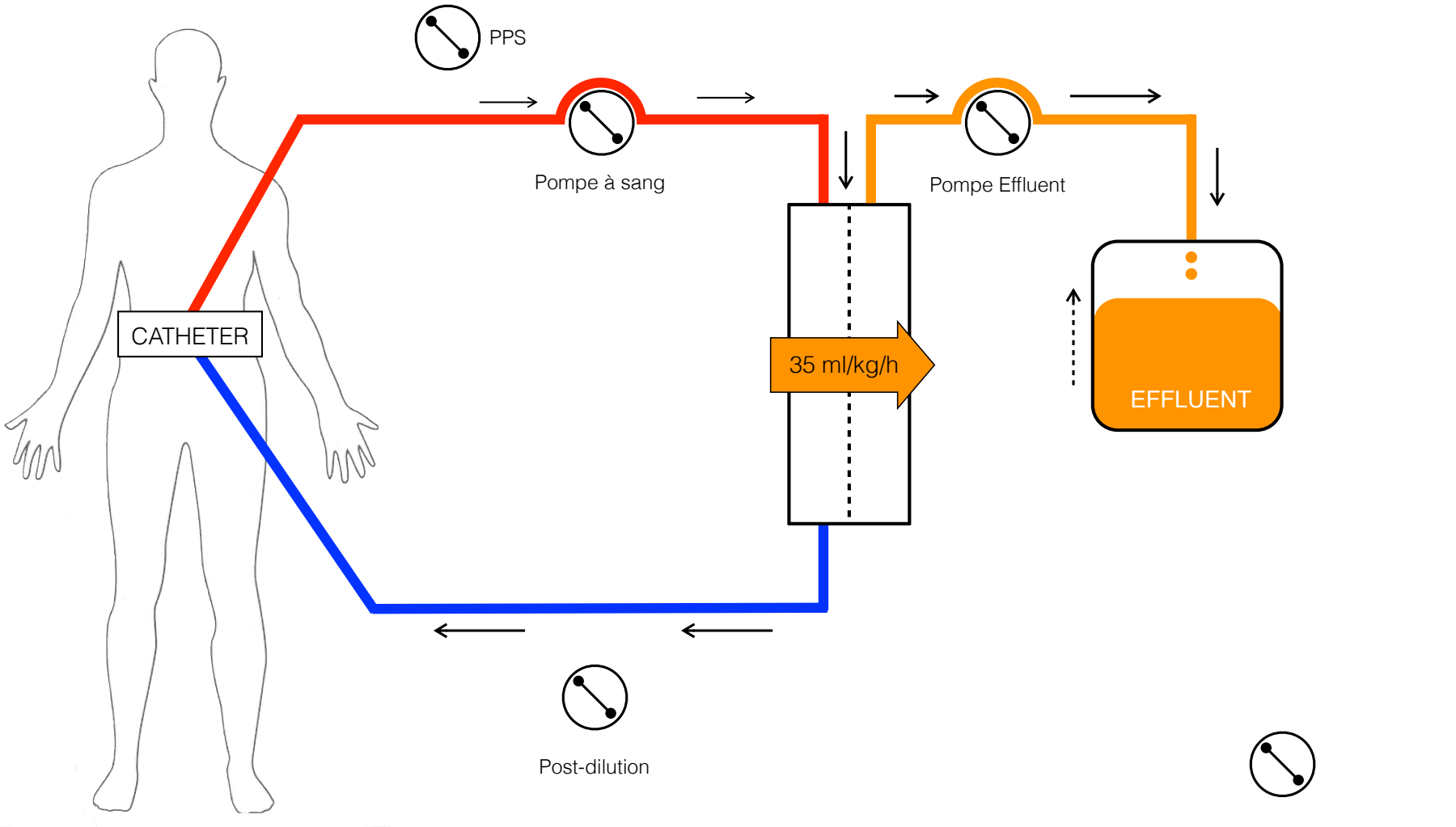
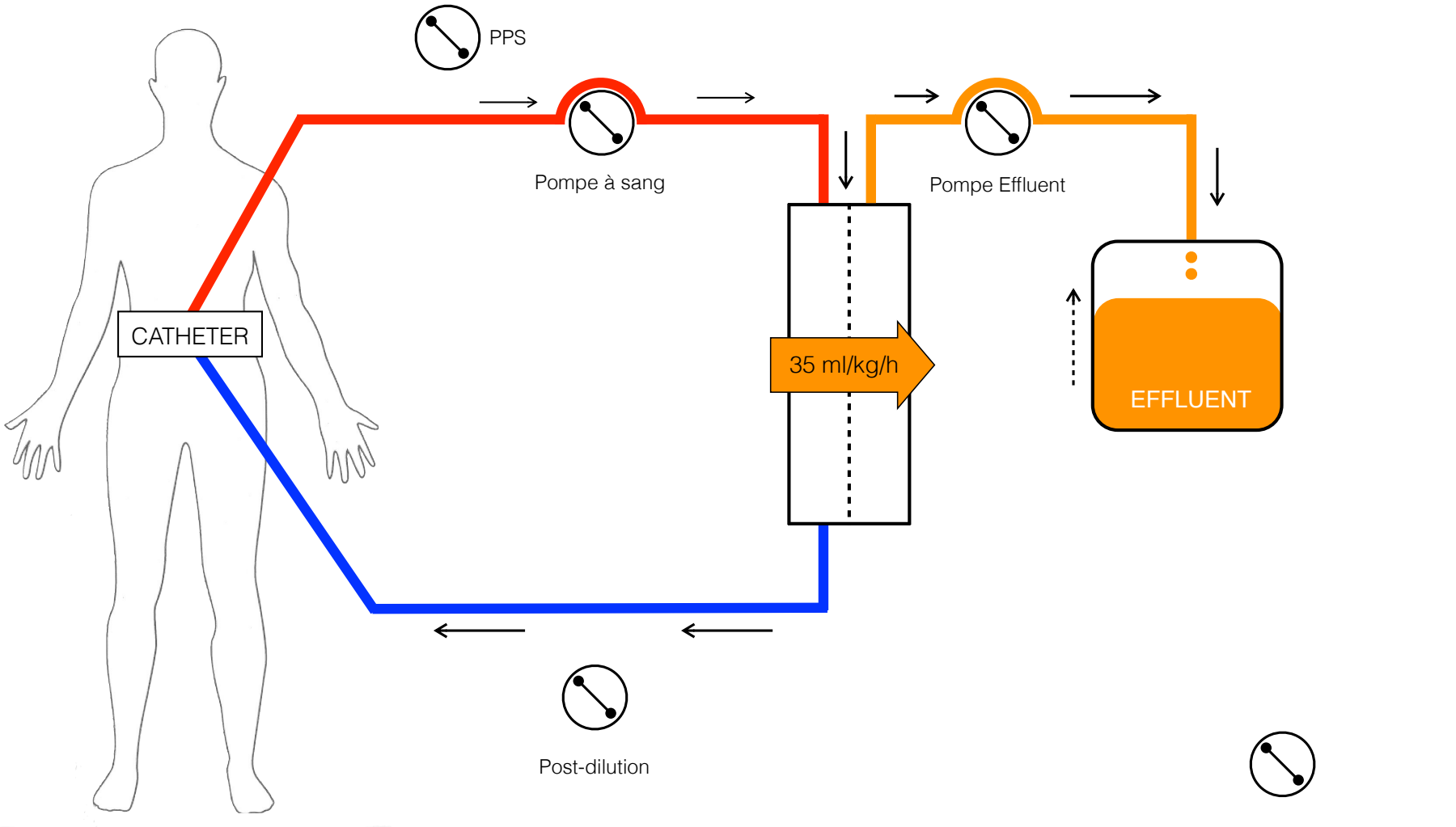
EFFLUENT


PPS
Pompe à sang
Pompe Effluent
CATHETER
35 ml/kg/h
EFFLUENT
Post-dilution


PPS
Pompe à sang
Pompe Effluent
CATHETER
35 ml/kg/h
EFFLUENT
Post-dilution
Dialysat ou Pré-dilution ou Post-dilution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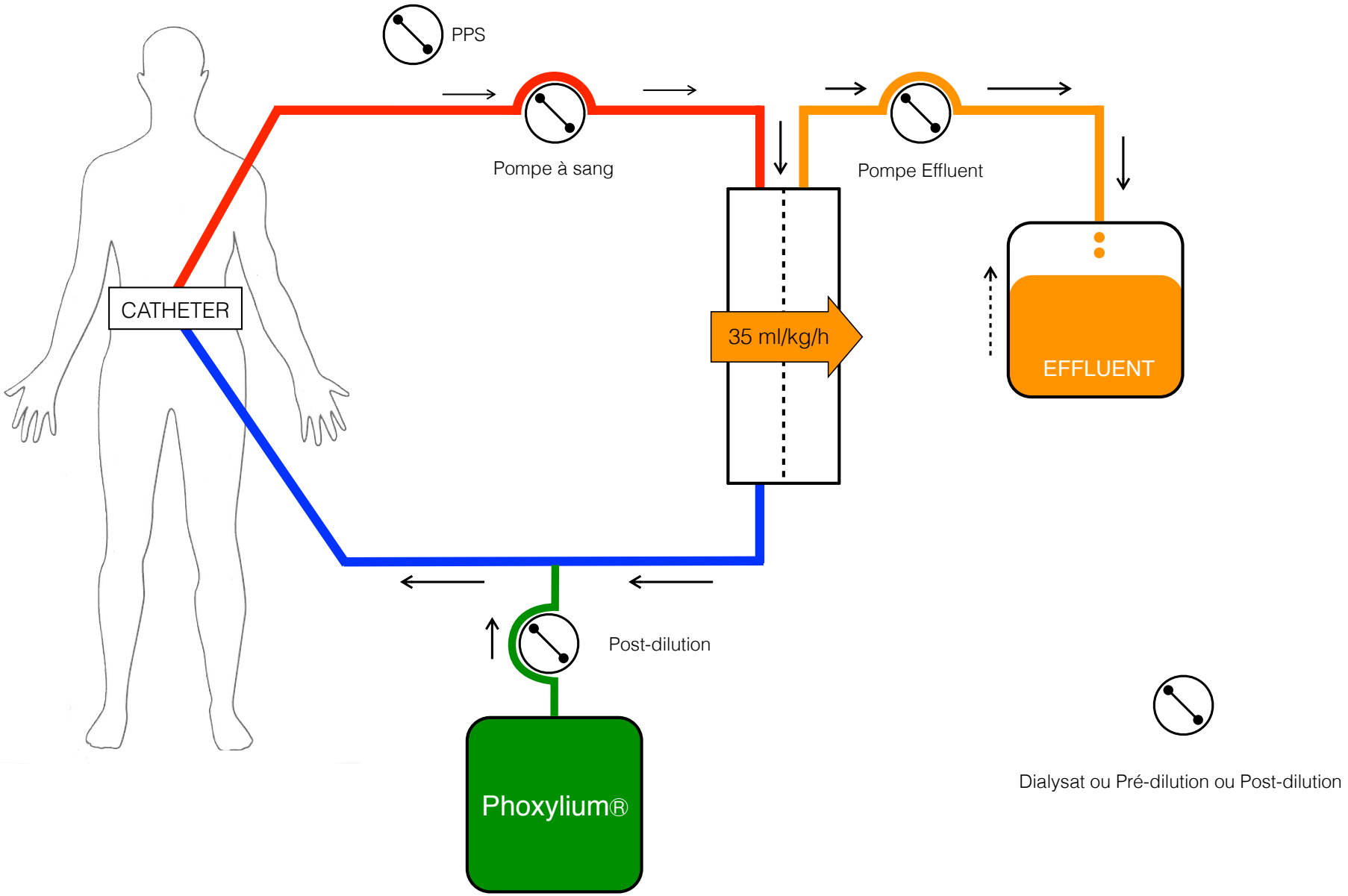
PPS
Pompe à sang
Pompe Effluent
CATHETER
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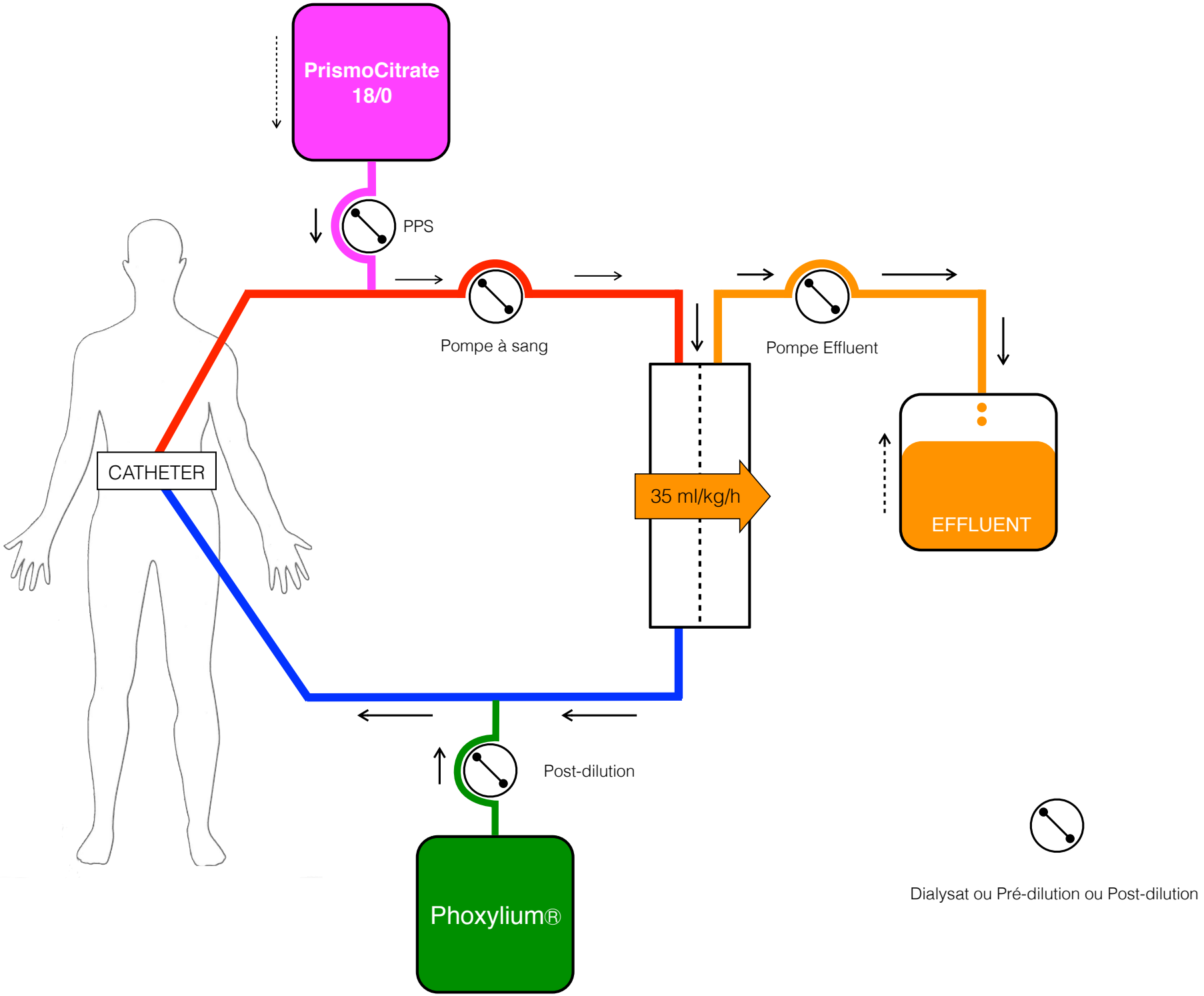
EFFLUENT
Post-dilution
Phoxylium®
Dialysat ou Pré-dilution ou Post-dilution


PrismoCitrate 18/0
PPS
Pompe à sang
Pompe Effluent
CATHETER
35 ml/kg/h
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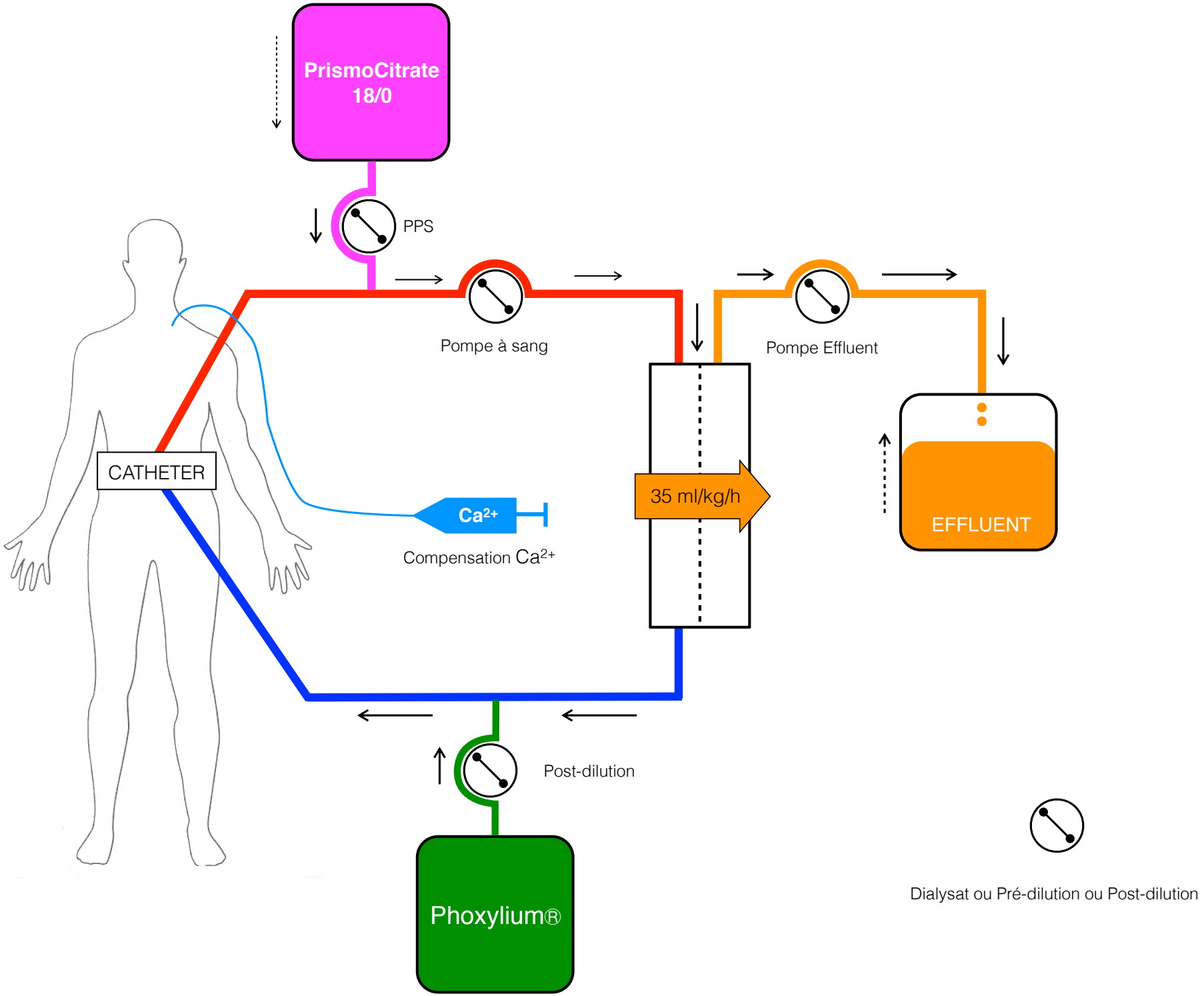
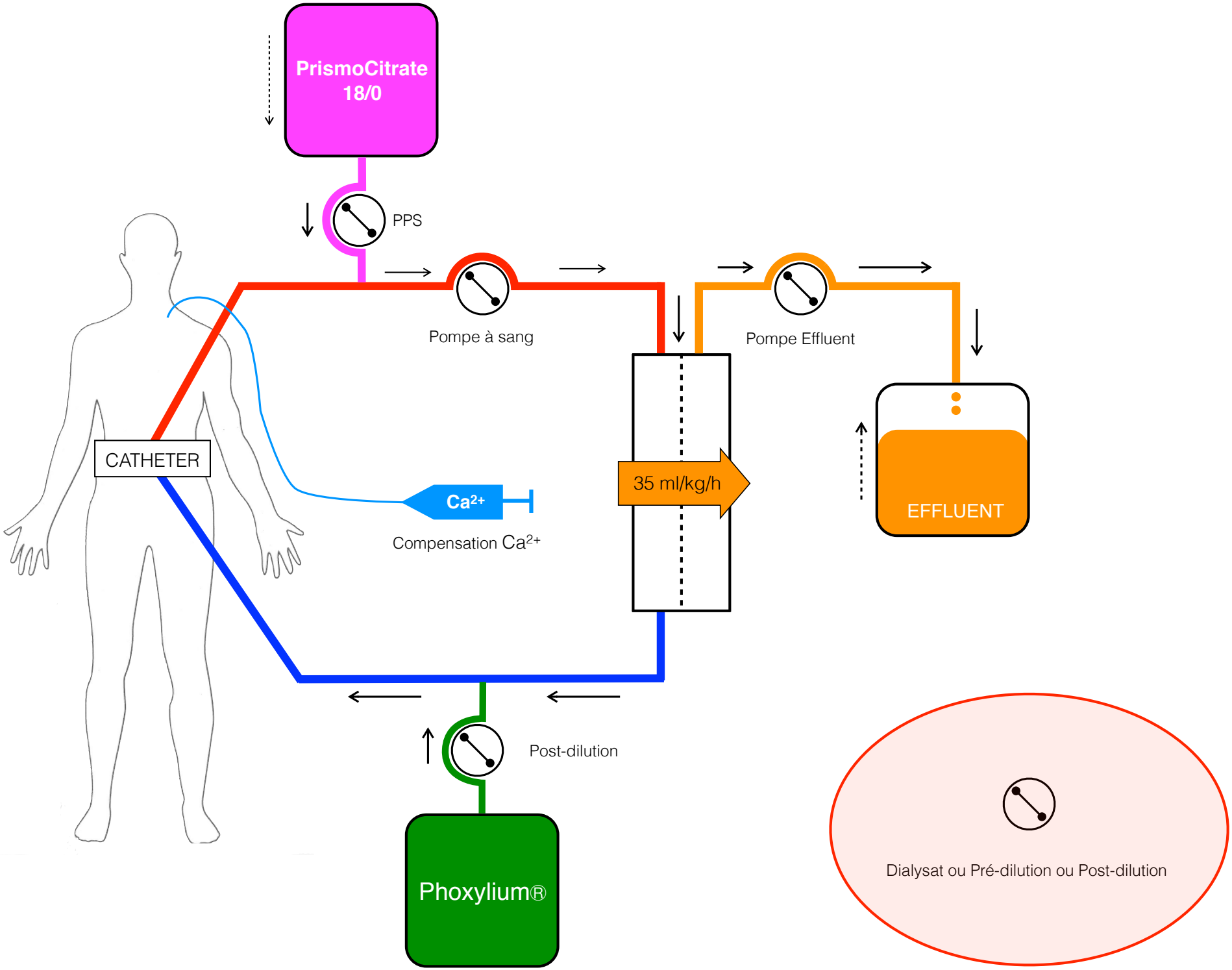
Post-dilution
Phoxylium®
Dialysat ou Pré-dilution ou Post-dilution


PrismoCitrate 18/0
PPS
Pompe à sang
Pompe Effluent
CATHETER
Ca2+
Compensation Ca2+
35 ml/kg/h
EFFLUENT
Post-dilution
Phoxylium®
Dialysat ou Pré-dilution ou Post-dilution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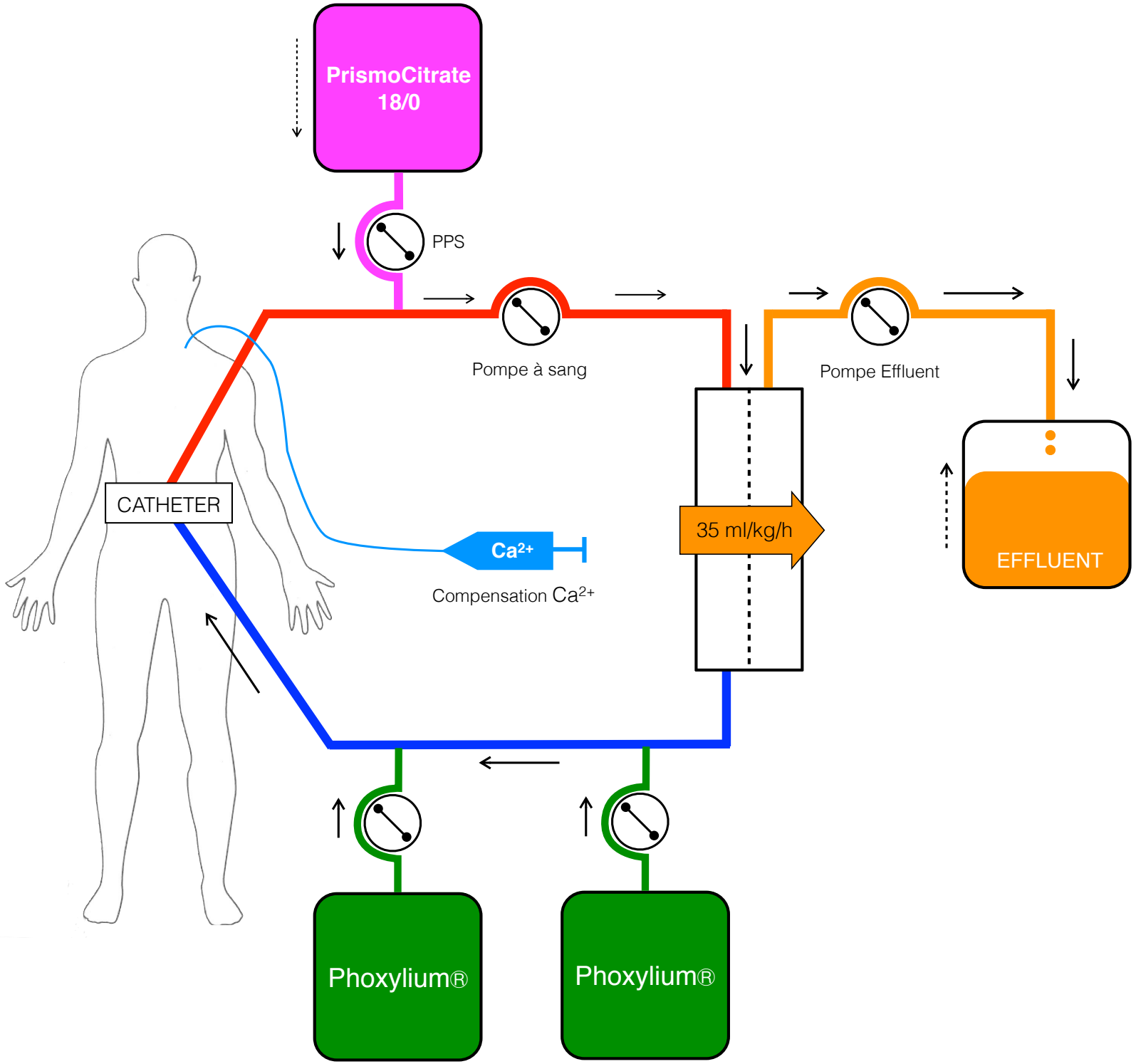
Dialysat ou Pré-dilution ou Post-dilution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PPS
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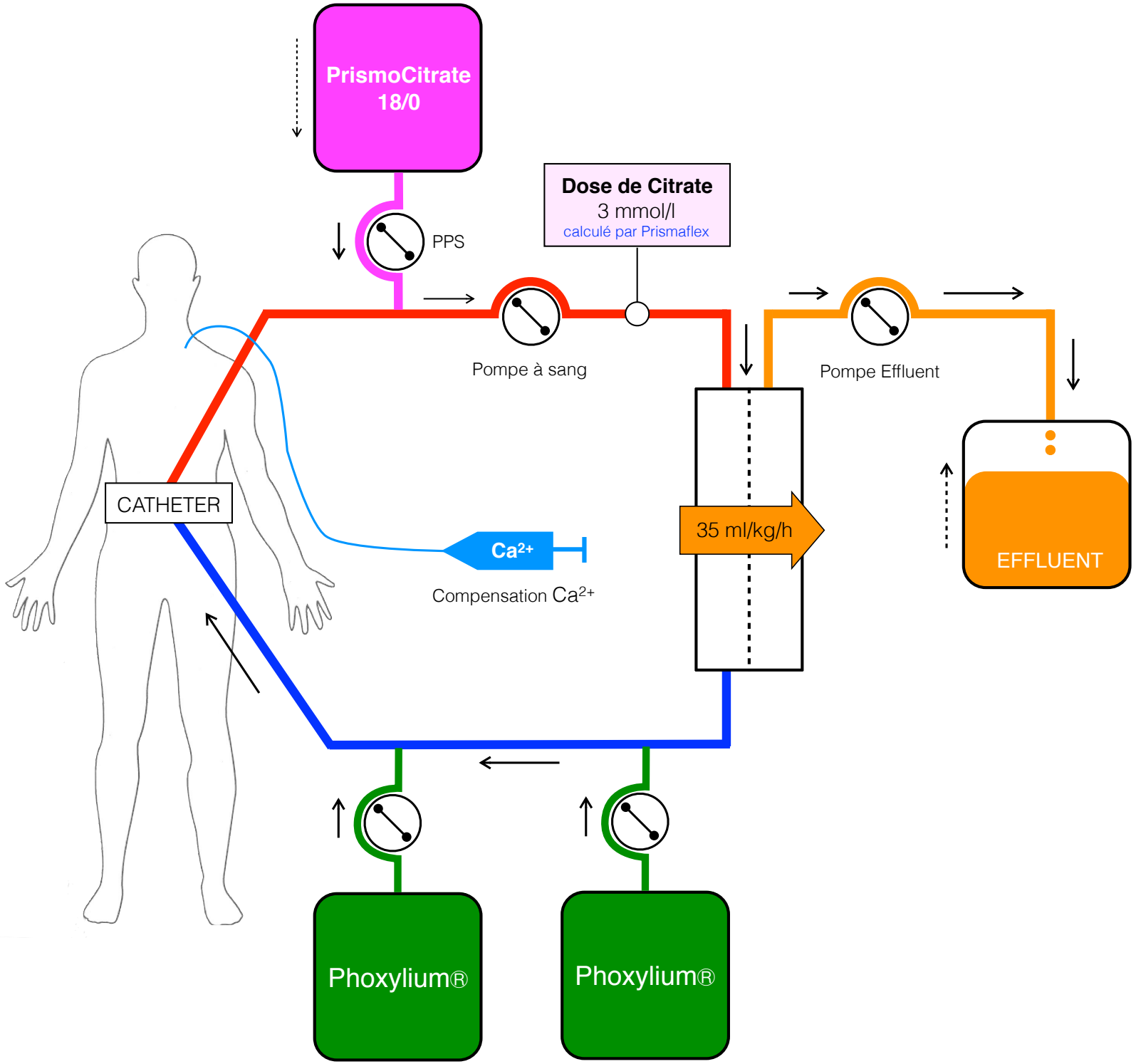
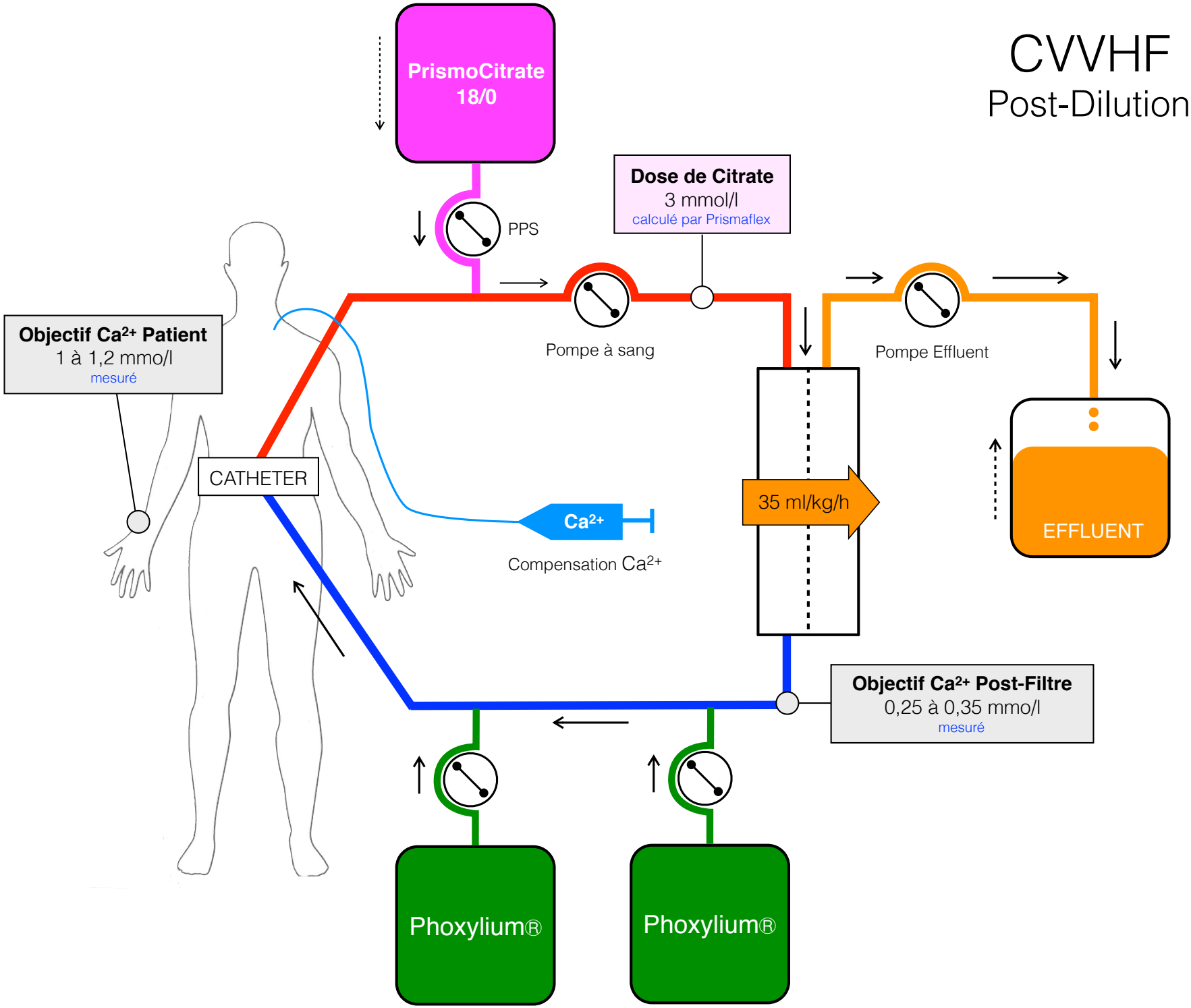
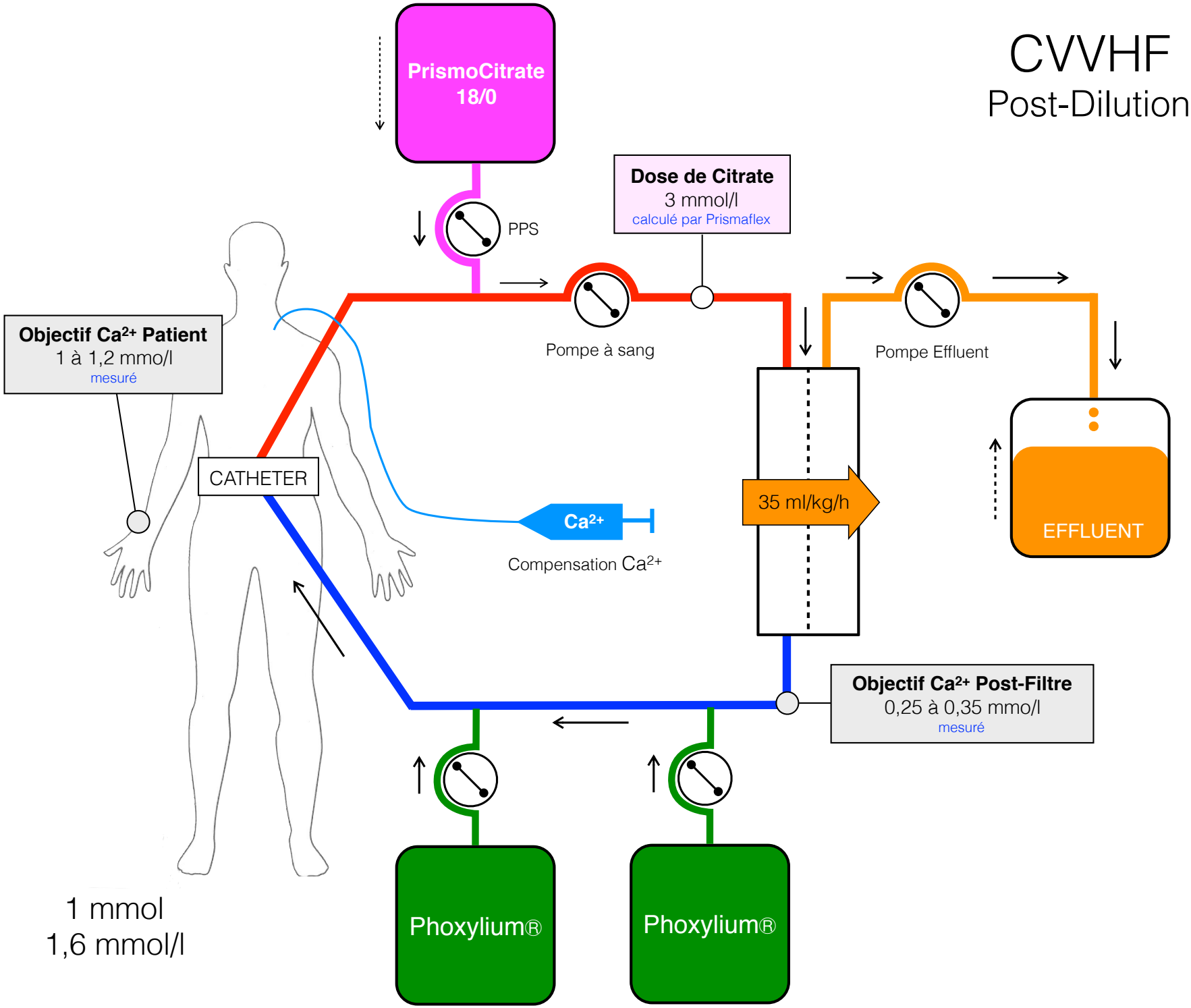
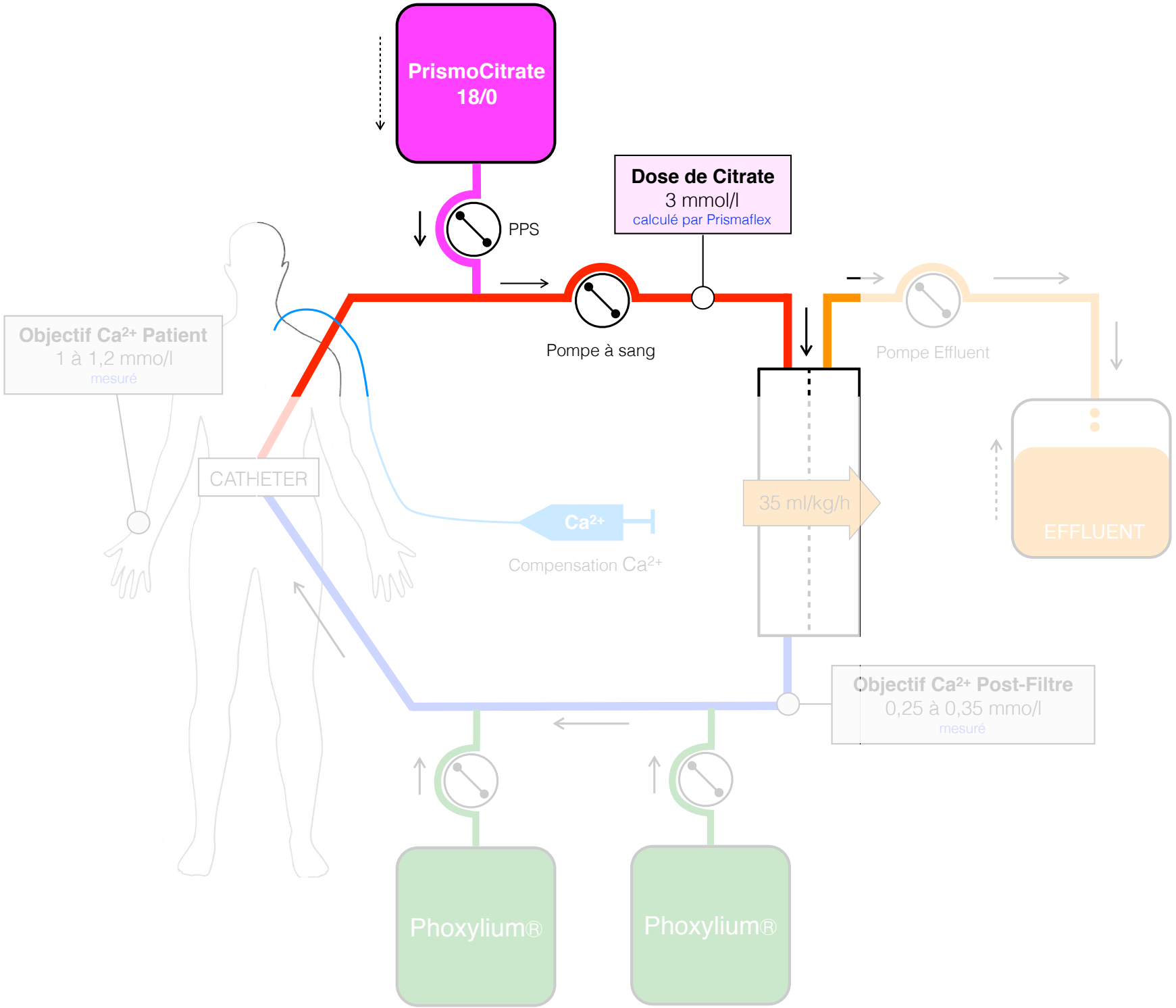
CATHETER
Ca2+
Compensation Ca2+
35 ml/kg/h
EFFLUENT
Phoxylium®
Phoxylium®


PrismoCitrate
18/0
PPS
Dose de Citrate
3 mmol/l
calculé par Prismaflex
Pompe à sang
Pompe Effluent
CATHETER
Ca2+
Compensation Ca2+
35 ml/kg/h
EFFLUENT
Phoxylium®
Phoxylium®

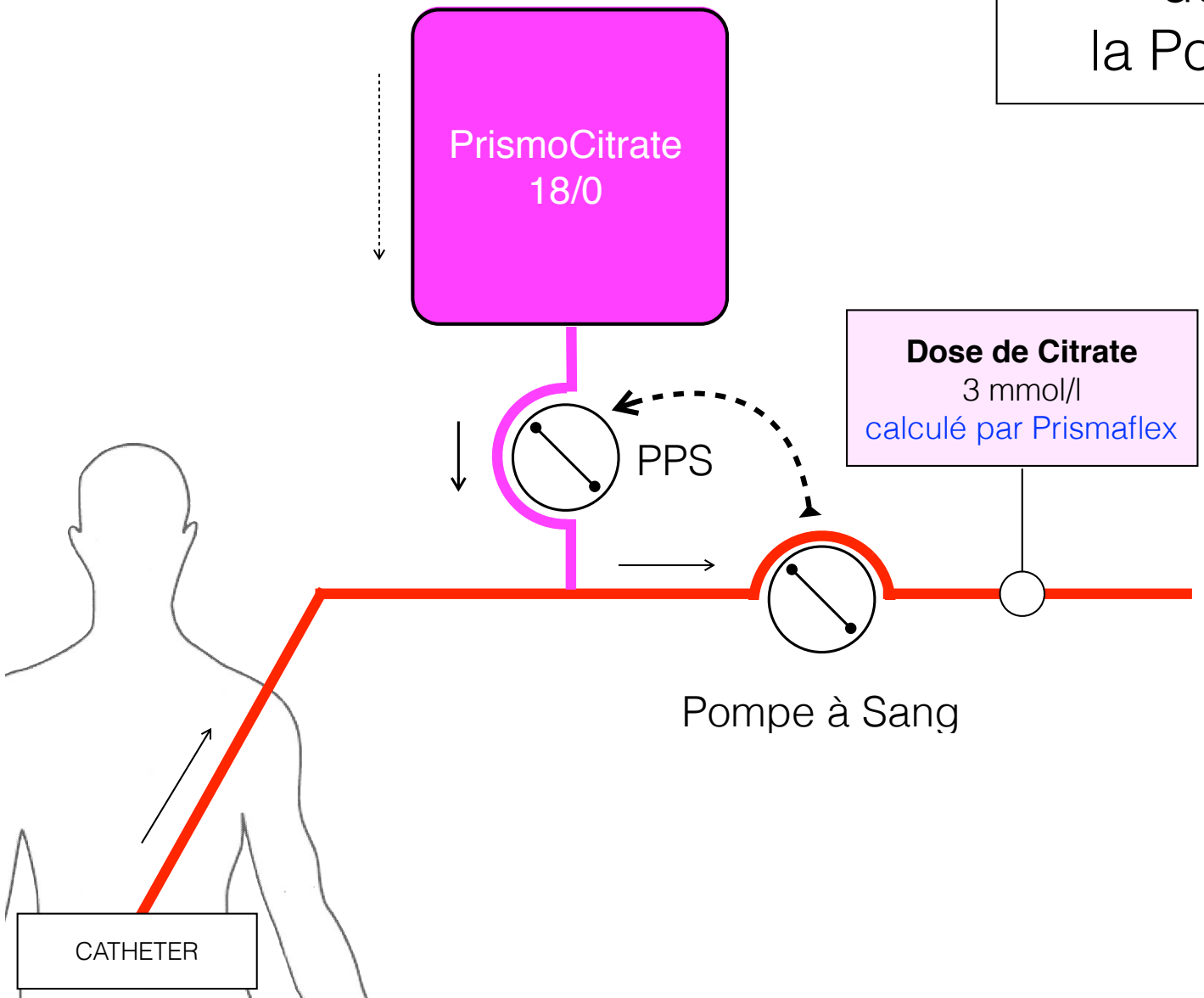
CVVHF
Post-Dilution



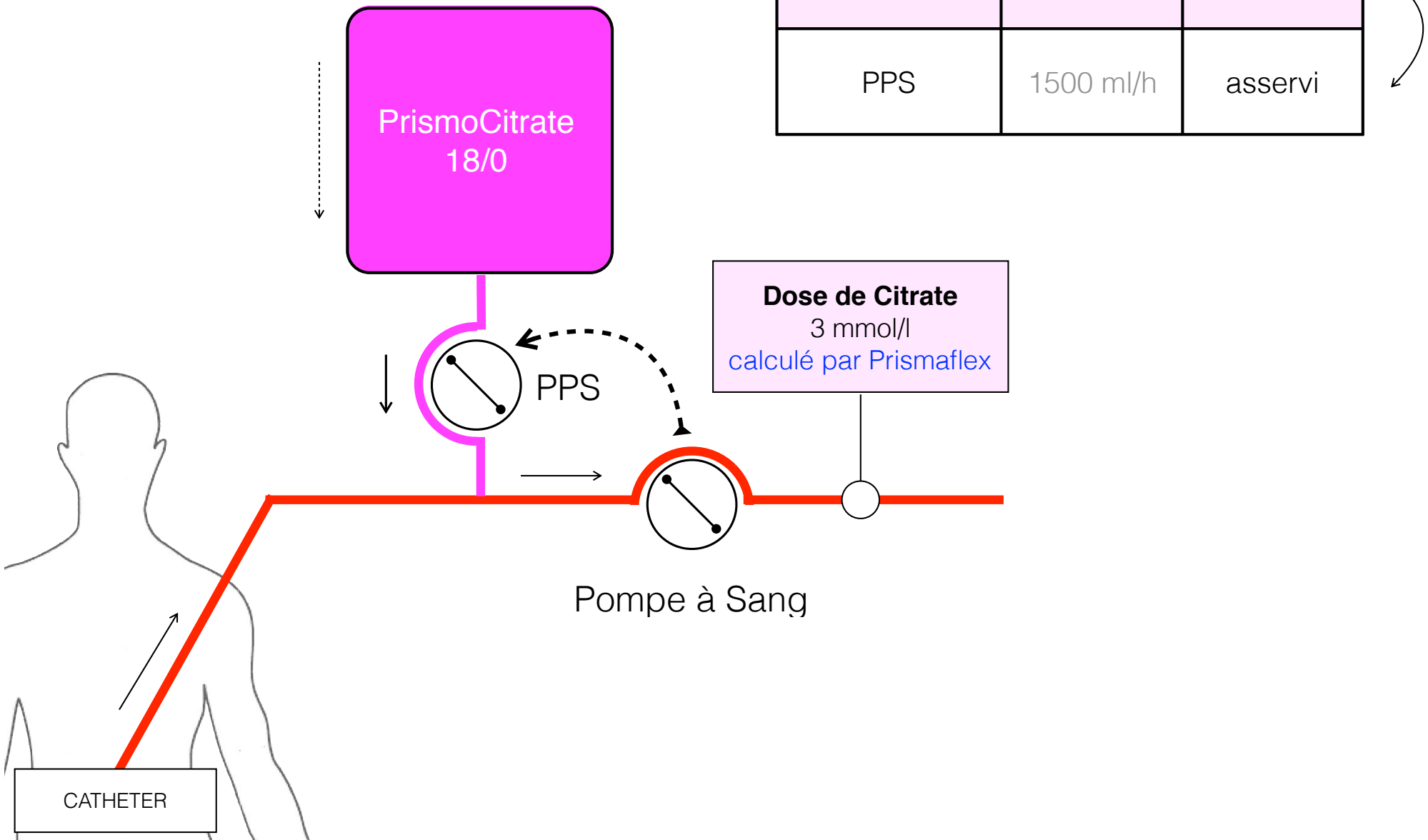

CVVHF
Post-Dilution
PrismoCitrate
18/0
PPS
Dose de Citrate
3 mmol/l
calculé par Prismaflex
Objectif Ca2+ Patient
1 à 1,2 mmo/l
mesuré
Pompe à sang
Pompe Effluent
CATHETER
Ca2+
Compensation Ca2+
35 ml/kg/h
EFFLUENT
Objectif Ca2+ Post-Filtre
0,25 à 0,35 mmo/l
mesuré
Phoxylium®
Phoxylium®
1 mmol
1,6 mmol/l


PrismoCitrate
18/0
PPS
Dose de Citrate
3 mmol/l
calculé par Prismaflex
Pompe à sang
Pompe Effluent
Objectif Ca2+ Patient
1 à 1,2 mmo/l
mesuré
CATHETER
Ca2+
Compensation Ca2+
35 ml/kg/h
EFFLUENT
Objectif Ca2+ Post-Filtre
0,25 à 0,35 mmo/l
mesuré
Phoxylium®
Phoxylium®

Asservissement
de la PPS à
la Pompe à Sang

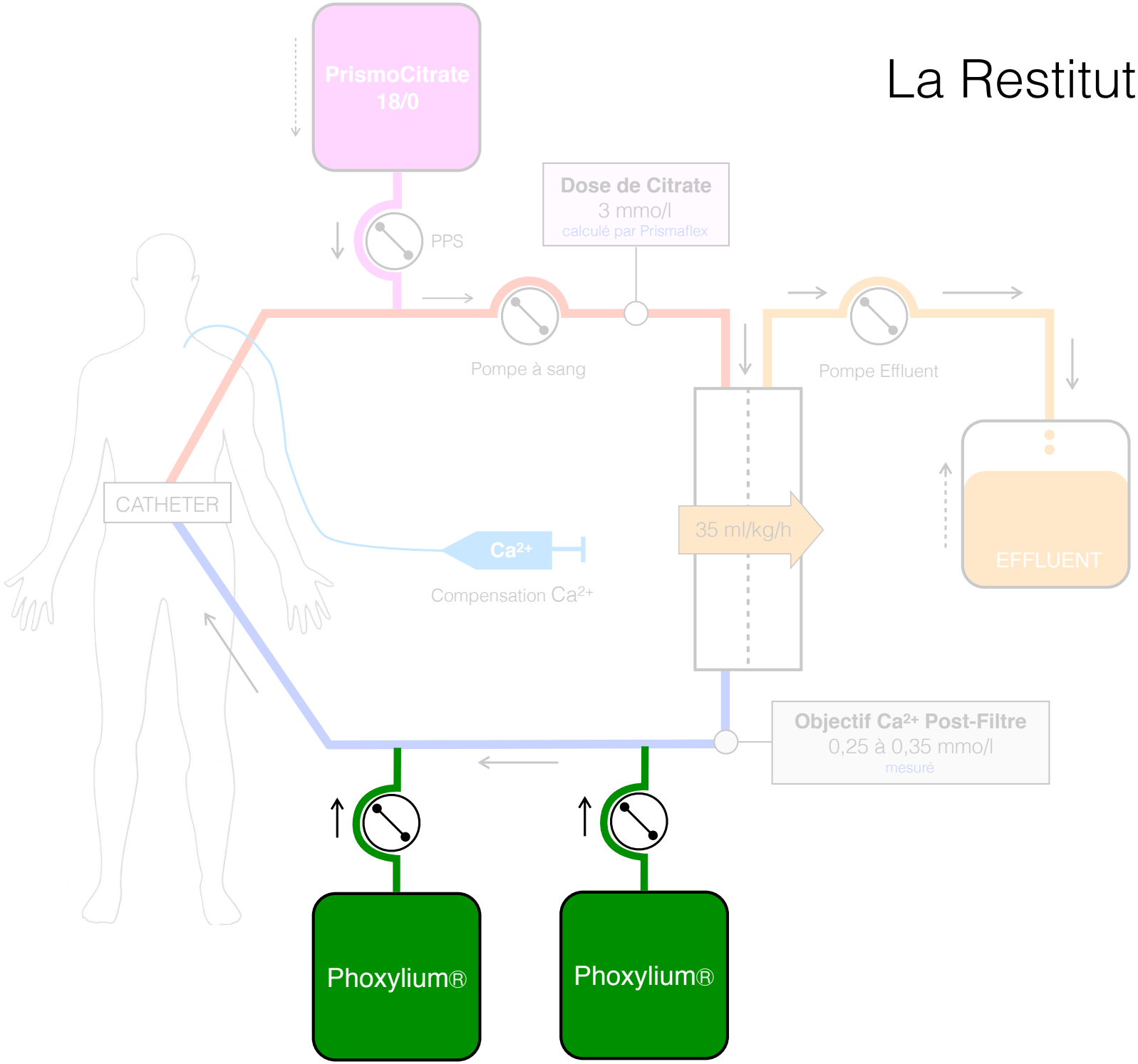


Dose de Citrate	3 mmol/l	Prescrit
Pompe à Sang	150 ml/mn	Prescrit
PPS	1500 ml/h	asservi



Les Solutés

La Restitution



La Restitution

	Phoxylium®
Ca++	1,25 mmol/l
Mg2+	0,6 mmol/l
Na+	140 mmol/l
K+	4 mmol/l
Cl-	115,9 mmol/l
HPO_4^{2-}	1,2 mmol/l
HCO3-	30 mmol/l
Lactates	0

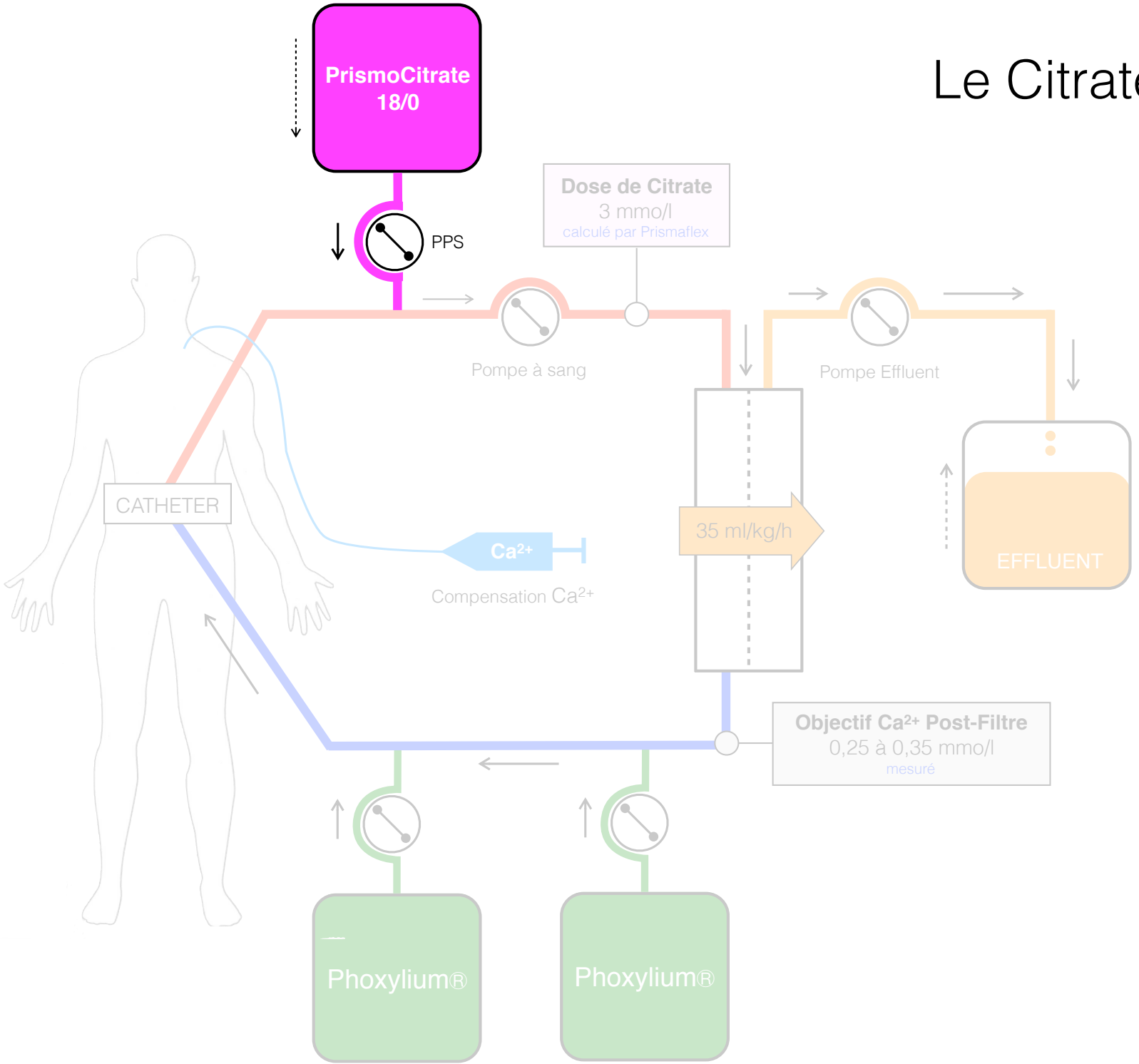
Phoxylium®

La Restitution

	Phoxylium®	Hémosol B0®
Ca++	1,25 mmol/l	1,75 mmol/l
Mg2+	0,6 mmol/l	0,5 mmol/l
Na+	140 mmol/l	140 mmol/l
K+	4 mmol/l	0
Cl-	115,9 mmol/l	109,5 mmol/l
HPO_4^{2-}	1,2 mmol/l	0
HCO3-	30 mmol/l	32 mmol/l
Lactates	0	3

Phoxylium®

Le Citrate


PrismoCitrate 18/0
PPS
Dose de Citrate
3 mmol/l
calculé par Prismaflex
Pompe à sang
Pompe Effluent
CATHETER
Ca2+
Compensation Ca2+
35 ml/kg/h
EFFLUENT
Objectif Ca2+ Post-Filtre
0,25 à 0,35 mmol/l
mesuré
Phoxylium®
Phoxylium®

Le Citrate

5 litres

Ci-Na^{3}	18 mmol/l
Ac Citrique	0 mmol/l
Na^{+}	140 mmol/l
Cl^{-}	86 mmol/l
Glucose	0 mmol/l
K^{+}	0 mmol/l

PrismoCitrate 18/0

Le Set

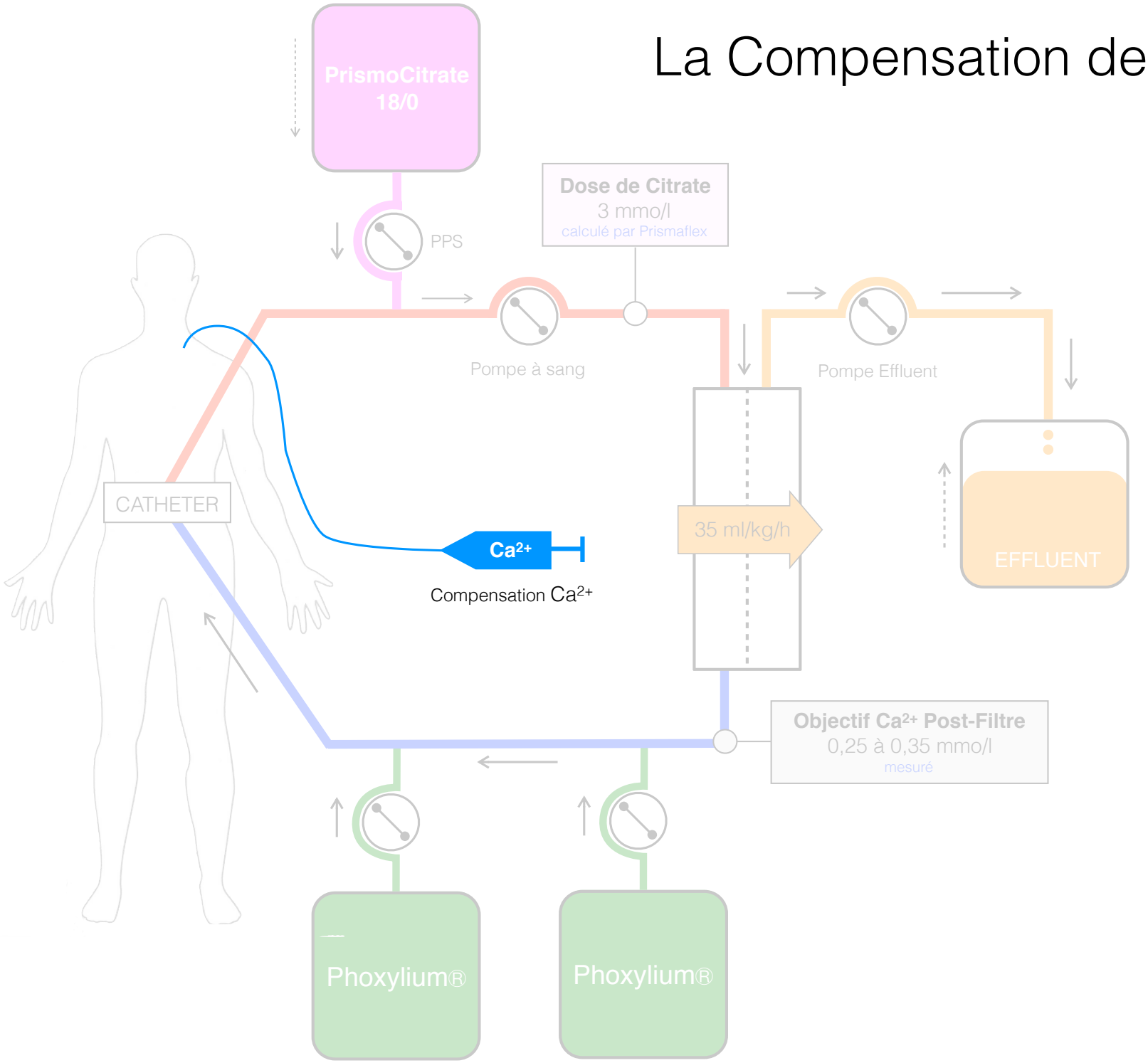
Membrane et Tuyaux

Lecteur Code-Barre,
la machine connait la
clairance du filtre

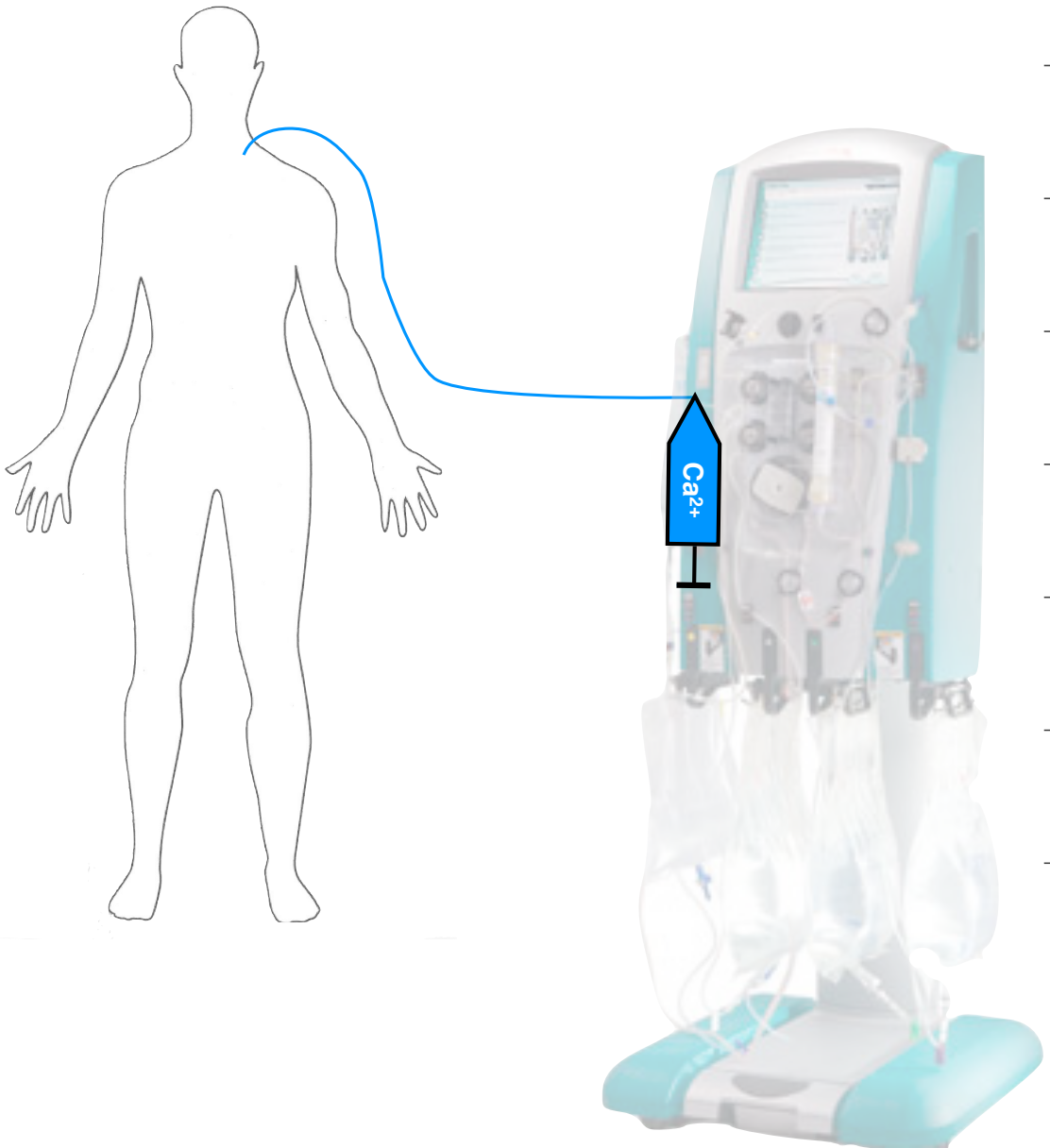
ST 150

AN 69ST

La Compensation de Ca^{2+}

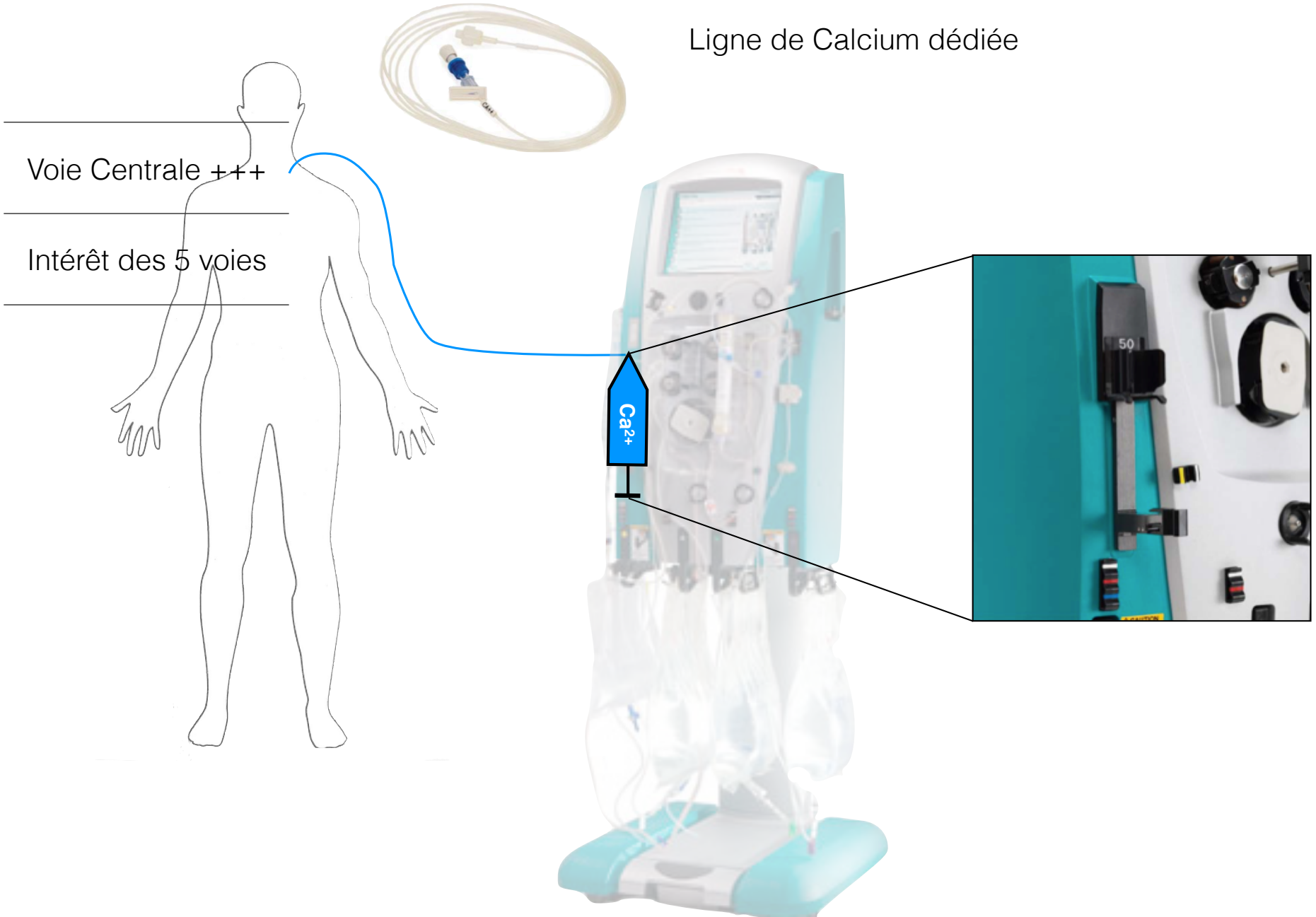


La Compensation de Ca^{2+}



Intégré à Prismaflex®
Exprimée en % de compensation
5 à 200 %
Débuter à 100 %
Incrément de 10 %
Chlorure de Ca^{2+} 10 %
«Asservi»

La Compensation de Ca^{2+}



Concernant la Compensation de Ca^{2+} en cas d'EER au Citrate

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En **AUCUN CAS** sur une voie veineuse périphérique

Car risque MAJEUR de nécrose cutanée sur une voie périphérique

Toxicité directe du chlorure de calcium sur les veines de petit calibre et de faible débit

---

TOUJOURS sur une voie **dédiée** d'un cathéter veineux central

Ne pas faire d'anticoagulation au citrate si cet impératif n'est pas remplit

L'anticoagulation régionale au citrate n'est ni une thérapeutique, ni une urgence

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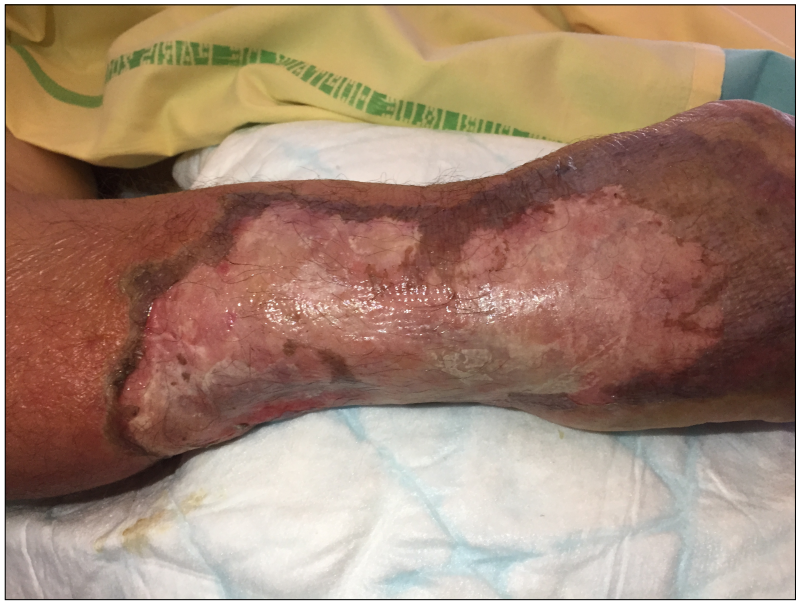
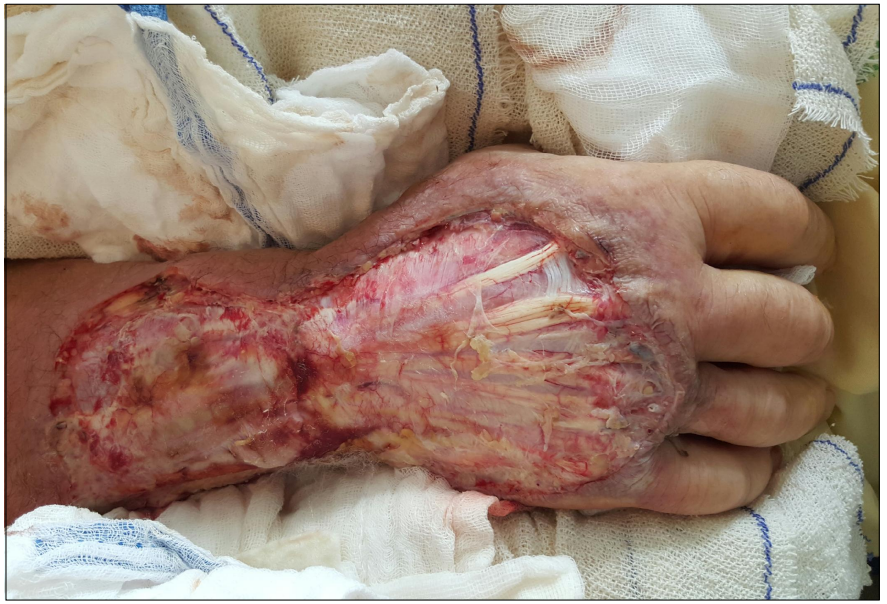




«Rien ne sert de courir, il faut partir à point»

Débuter l'EER citrate en normocalcémie est une bonne chose!

Il faut prendre le temps de corriger une calcémie avant de débuter une EER citrate

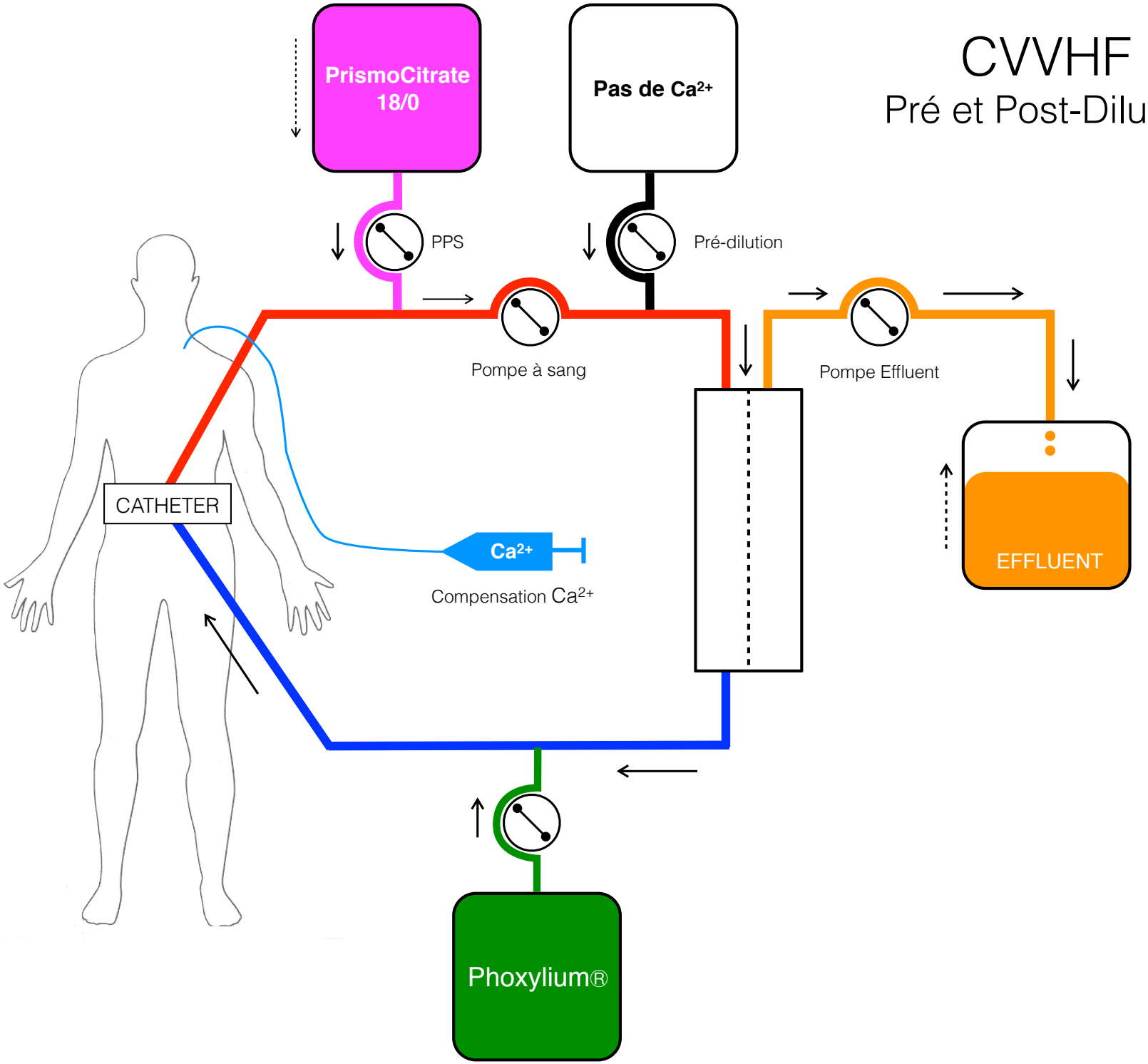
Que prescrire ? ... en pratique

Machine	Prismaflex®
Mode	CVVHF (Imposé)
Anticoagulation	PrismoCitrate 18/0
Dose de Citrate	3 mmol/l
Débit sang	150 ml/min
Dose de filtration	30 à 40 ml/kg/h
Restitution en post exclusive	1500 ml/h
Compensation Calcium	100 % à l'initiation
Solutés de restitution	Phoxylium® +/ Na +/- Bicar +/- K+ et...
Déplétion	.... ml/h
La surveillance	

Weight (kg)	Blood flow rate (ml/min)	Citrate (ml/h)	Replacement Post dilution (ml/h)	Prescribed dialysis dose
50	100	1350	500	37 ml/kg/h
55	100	1350	500	34 ml/kg/h
60	100	1350	750	35 ml/kg/h
65	100	1350	750	32 ml/kg/h
70	150	1500	1500	43 ml/kg/h
75	150	1500	1500	40 ml/kg/h
80	150	1500	1500	38 ml/kg/h
85	150	1500	1500	35 ml/kg/h
90	150	1500	1500	33 ml/kg/h
95	150	1500	1500	32 ml/kg/h
100	150	1500	1500	30 ml/kg/h
105	200	1650	2000	35 ml/kg/h
110	200	1650	2000	33 ml/kg/h
115	200	1650	2000	32 ml/kg/h
120	200	1650	2000	30 ml/kg/h

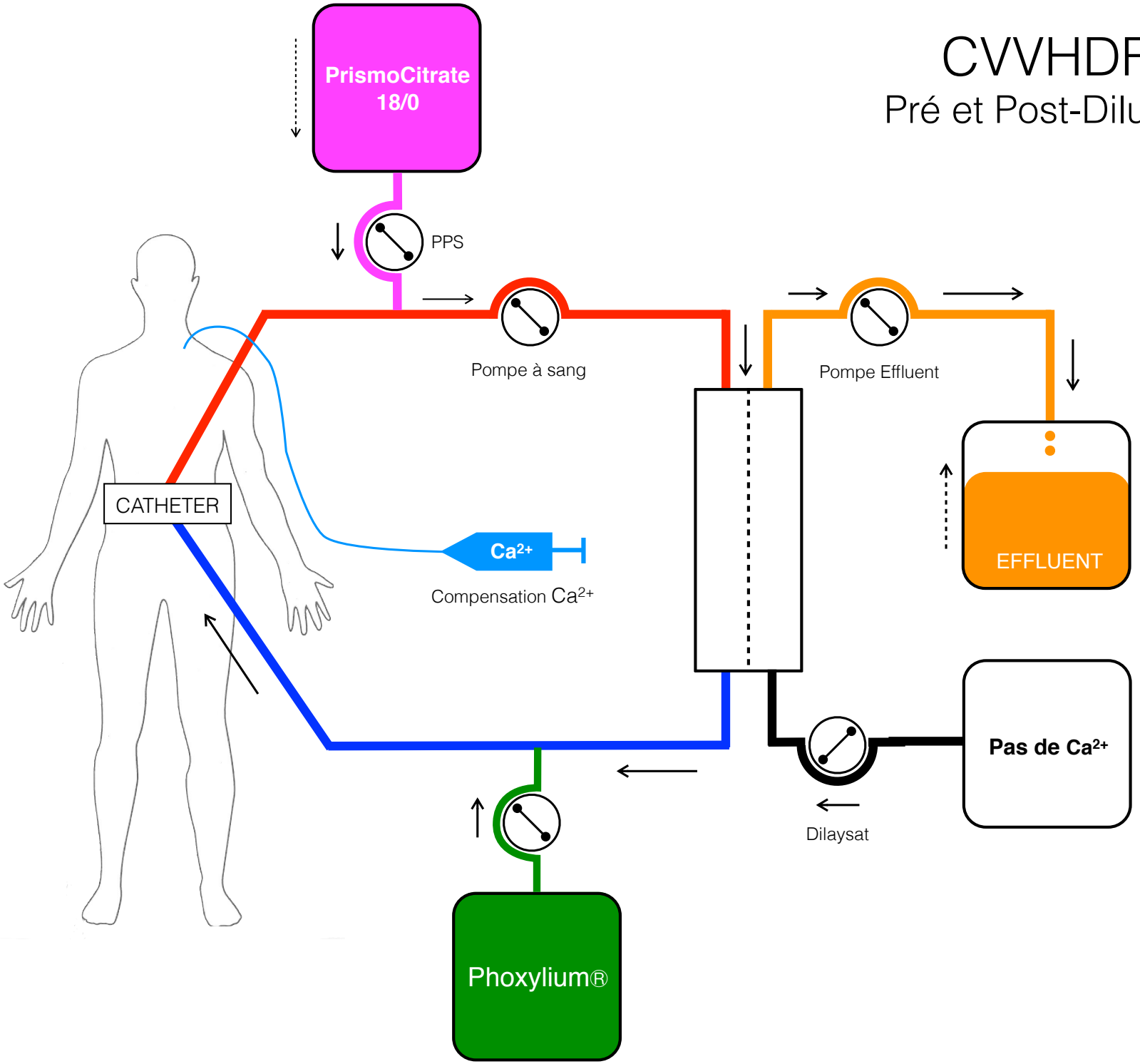
Les autres protocoles... ce sera pour plus tard

CVVHF
Pré et Post-Dilution



CVVHDF

Pré et Post-Dilution



Les Complications

Hypocalcémie

Alcalose métabolique

Hypernatrémie

Intoxication au citrate

Acidose métabolique
et/ou
Accumulation de Citrate

Hypocalcémie

Alcalose métabolique

Hypernatrémie

Intoxication au citrate

Acidose métabolique
et/ou
Accumulation de Citrate

Hypocalcémie (ionisé)
< 0,95 mmol/l

Tétanie, Hypotension et Arythmie cardiaque

⬇

Dose de citrate trop élevée

Compensation de Ca2+ trop faible

Non respect du protocole

Défaut de surveillance

Peut survenir même en l’absence d’insuffisance hépatique

Hypocalcémie

Alcalose métabolique

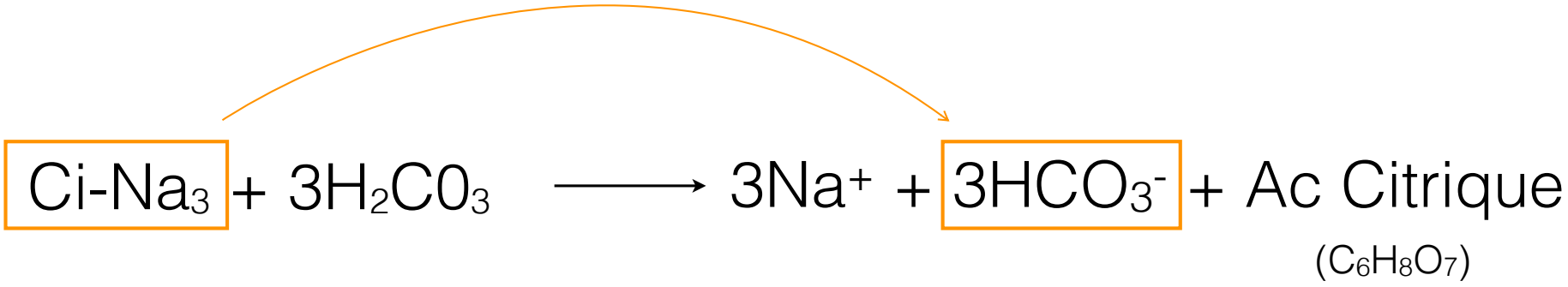
Hypernatrémie

Intoxication au citrate

Acidose métabolique
et/ou
Accumulation de Citrate

Le citrate (acide faible) s'associe à l'acide carbonique pour donner :

3 ions Na^+
du Bicarbonate
de l'Acide citrique.

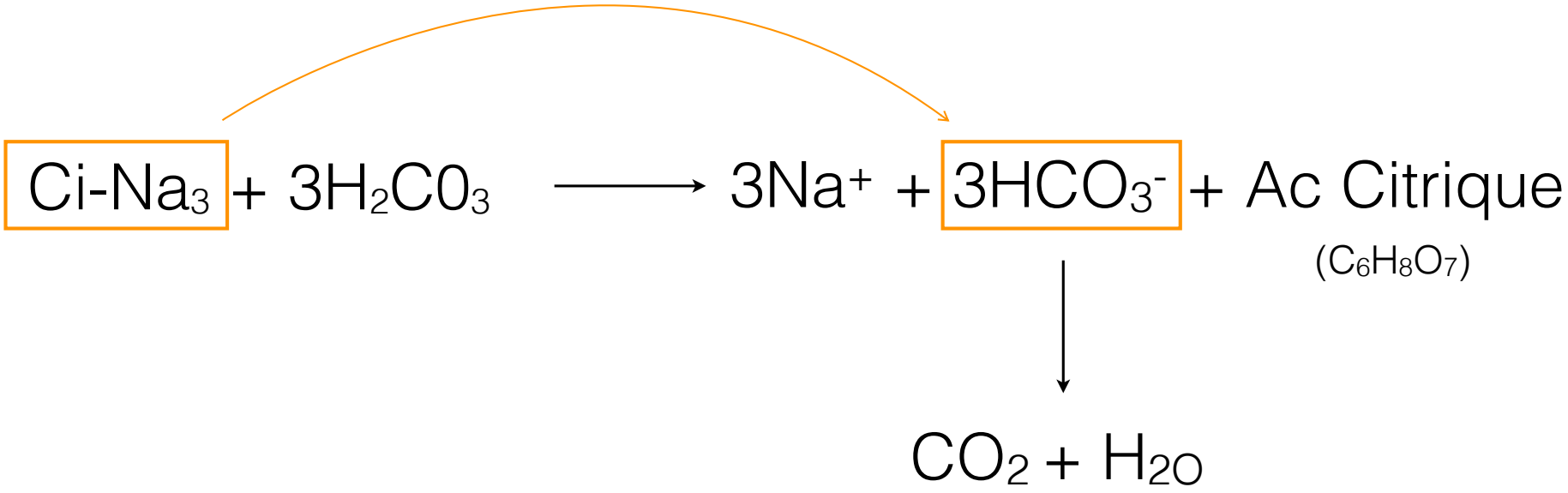


1 mmol de Citrate donne 3 mmol de Bicar

Métobolisme plasmatique, hépatique, musculaire et rénal

Le citrate (acide faible) s'associe à l'acide carbonique pour donner :

3 ions Na^+
du Bicarbonate
de l'Acide citrique.



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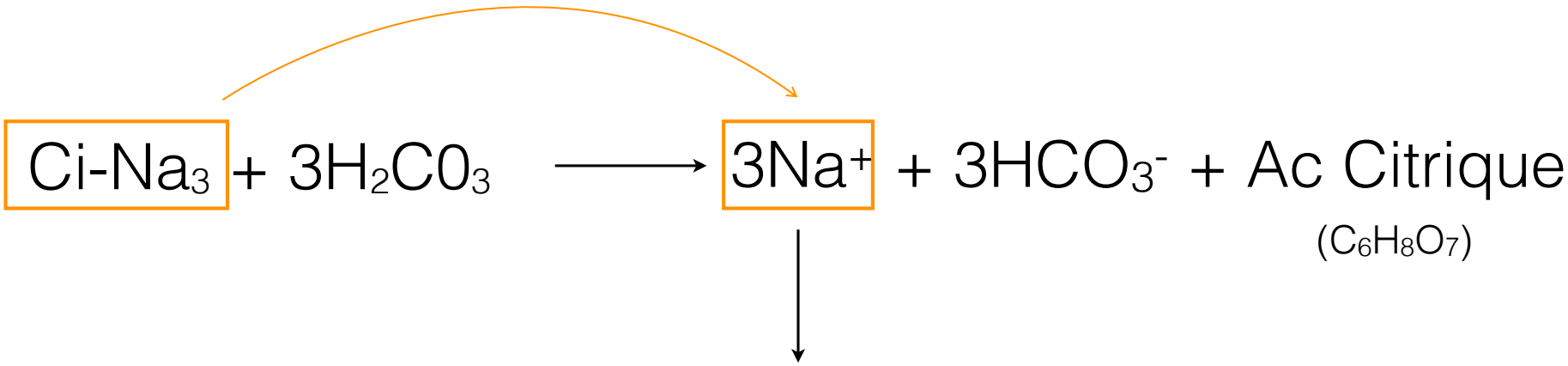

Augmentation de la DIF
Stewart

Hypocalcémie

Alcalose métabolique

Hypernatrémie

Intoxication au citrate

Acidose métabolique
et/ou
Accumulation de Citrate

Le citrate (acide faible) s'associe à l'acide carbonique pour donner :

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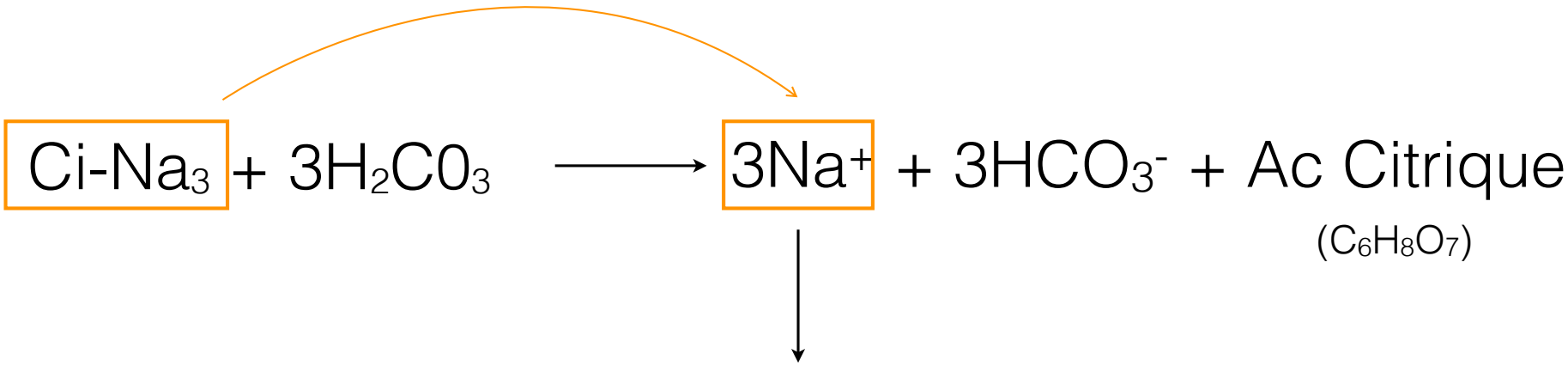

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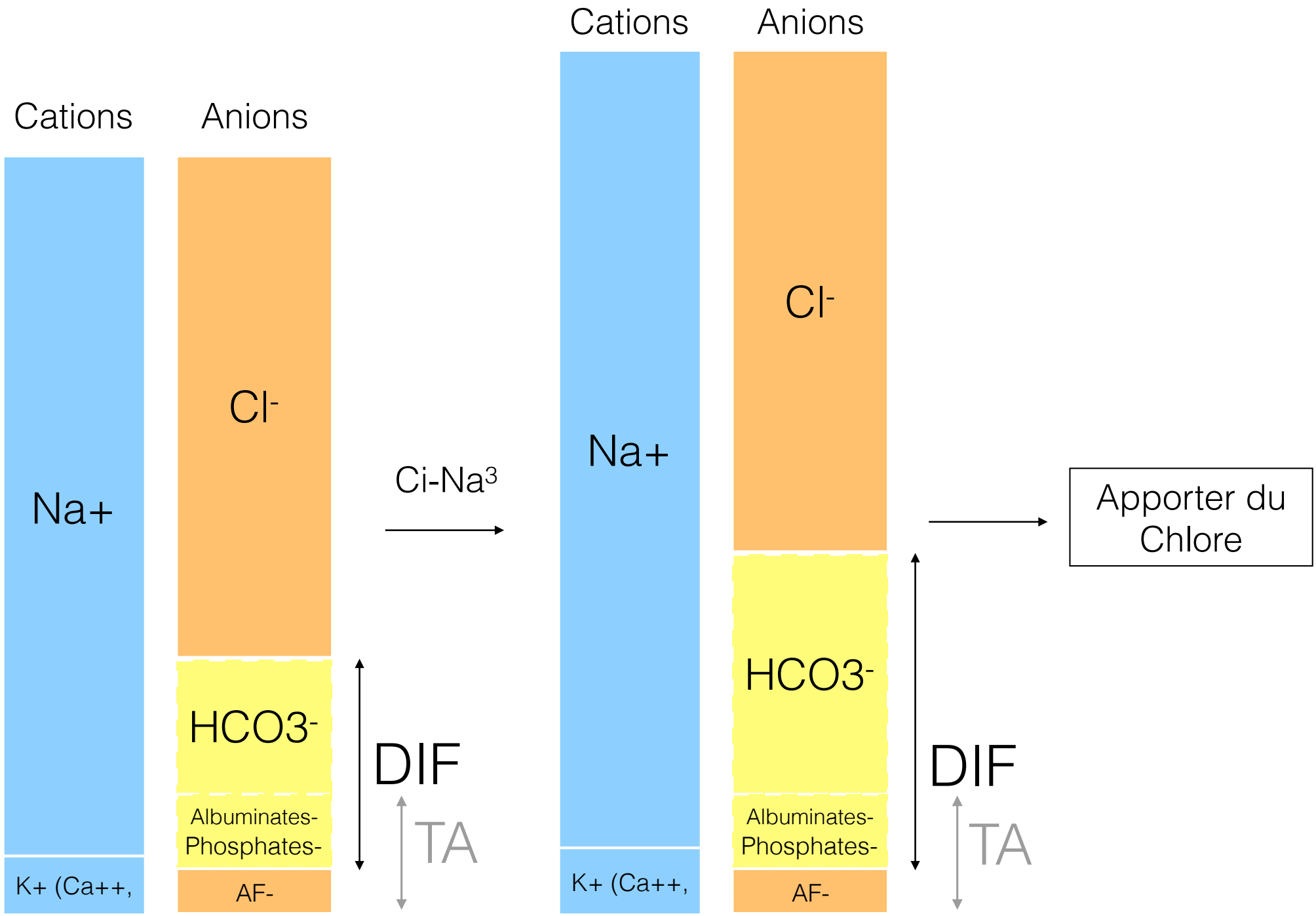

Cations
Anions
Na+
Cl-
HCO3-
Albuminates-
Phosphates-
AF-
K+ (Ca++,
DIF
TA
Ci-Na3
Cations
Anions
Na+
Cl-
HCO3-
Albuminates-
Phosphates-
AF-
K+ (Ca++,
DIF
TA
Apporter du Chlore

Hypocalcémie

Alcalose métabolique

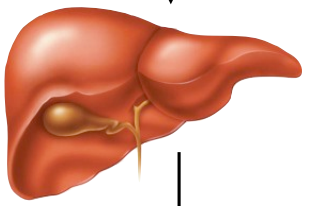
Hypernatrémie

Intoxication au citrate

Acidose métabolique
et/ou
Accumulation de Citrate

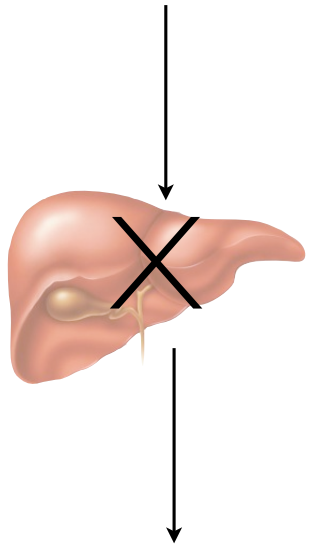
$Ci\text{-}Na_3 + 3H_2C0_3 \rightleftharpoons 3Na^+ + 3HC0_3^- +$ Ac Citrique ($C_6H_8O_7$)

1 mmol de Citrate donne
1 mmol d'Ac Citrique



$H_20 + CO_2$

$Ci\text{-}Na_3 + 3H_2C0_3 \longrightarrow 3Na^+ + 3HC0_3^- +$ Ac Citrique ($C_6H_8O_7$)



$H_20 + CO_2$

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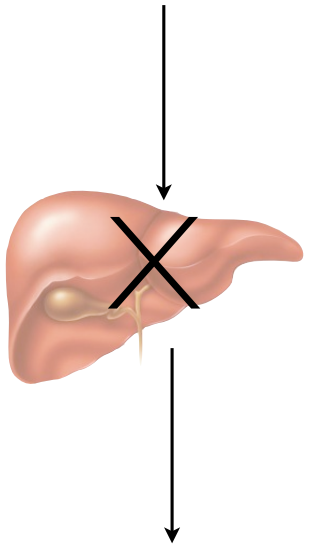
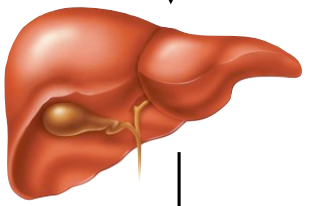


$H_20 + CO_2$

Acidose métabolique

$Ci\text{-}Na_3 + 3H_2C0_3 \rightleftharpoons 3Na^+ + 3HC0_3^- +$ Ac Citrique ($C_6H_8O_7$)

Accumulation de Citrate



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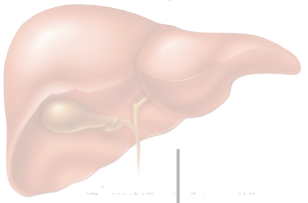
Accumulation de Citrate



$H_20 + CO_2$

Si le citrate est infusé plus rapidement qu'il n'est éliminé par dialyse ou par voie métabolique

Accumulation de Citrate

Le citrate en excès se lie au calcium

Hypocalcémie (ionisé)
(< 0,95 mmol/l)

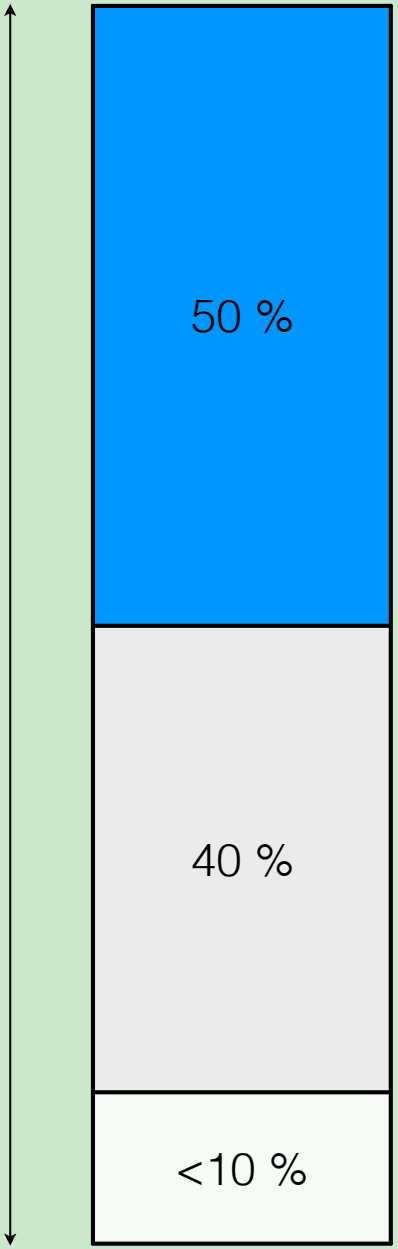
Accumulation de complexe Ci-Ca^{2+}

Augmentation du Ca Complexé

$$\frac{\text{CaTotal}}{\text{Ca}^{2+}} \leq 2{,}5$$

Situation Normale

Accumulation de Citrate



Calcium Total
2,2 à 2,6 mmol/l

Calcium ionisé
1,1 à 1,3 mmol/l

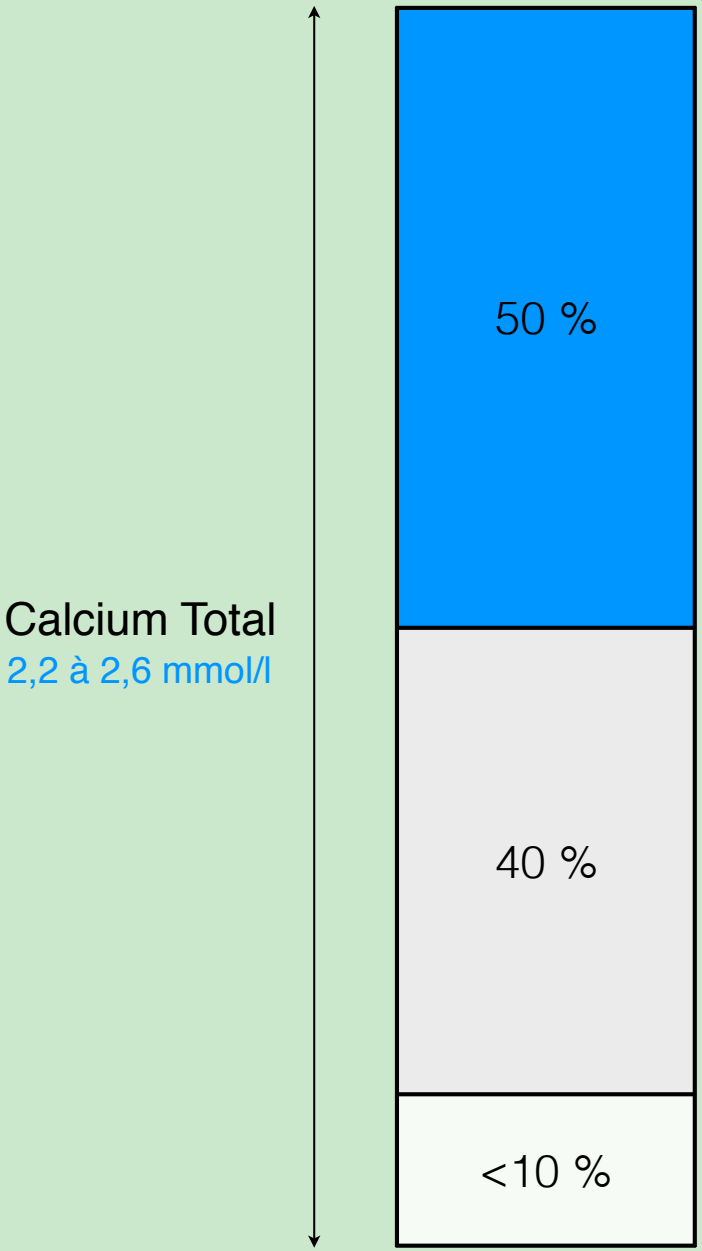
Calcium lié aux protéines
(albumine)
0,95 à 1,2 mmol/l

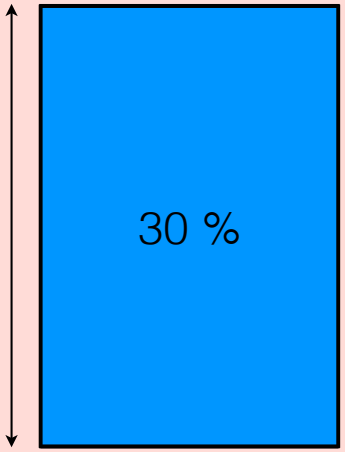
Calcium complexé
(sels et phosphate de calcium)
< 0,1 mmol/l

$\frac{\text{CaTotal}}{\text{Ca}^{2+}} \leq 2{,}5$

Situation Normale

Accumulation de Citrate



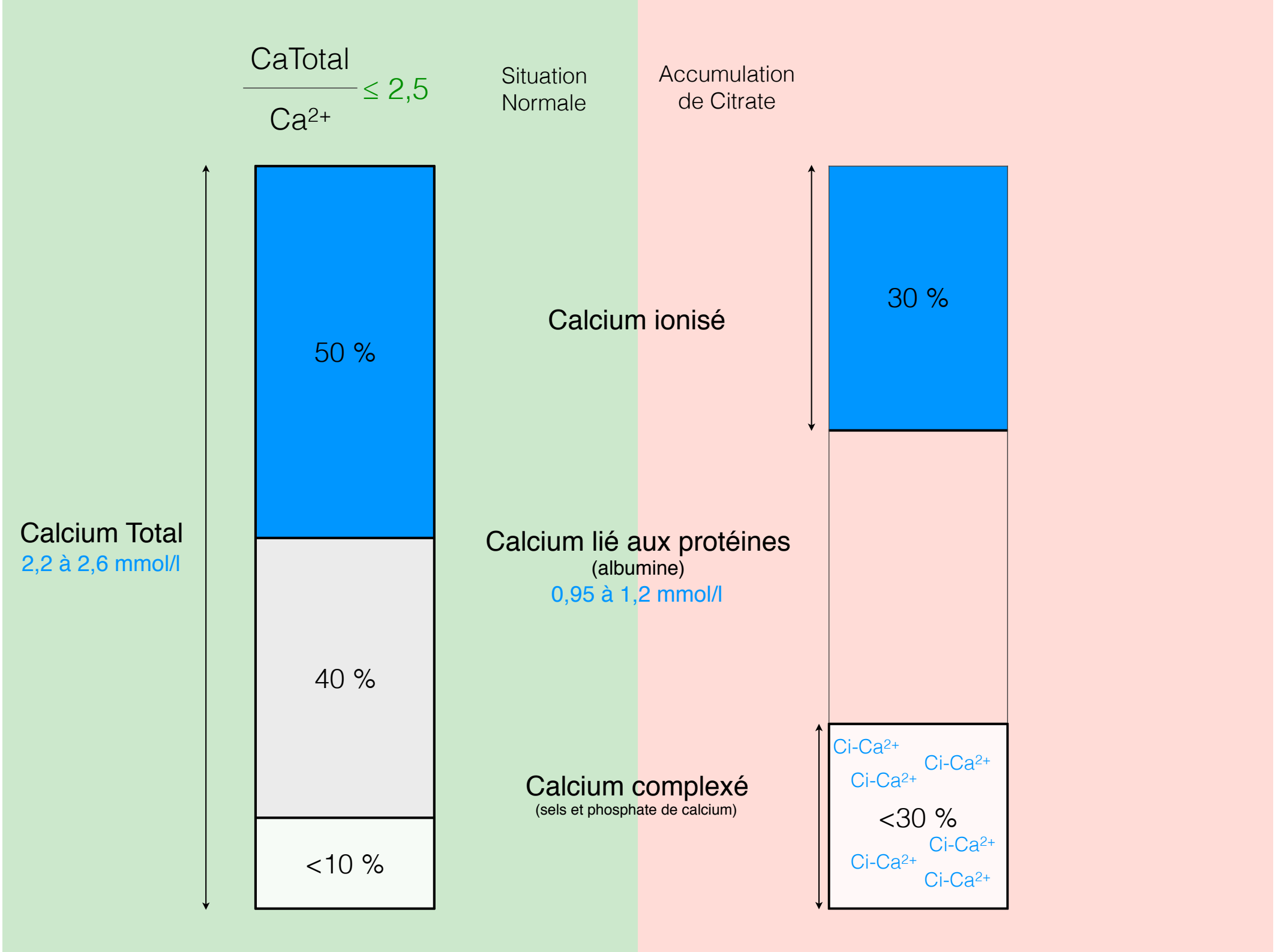


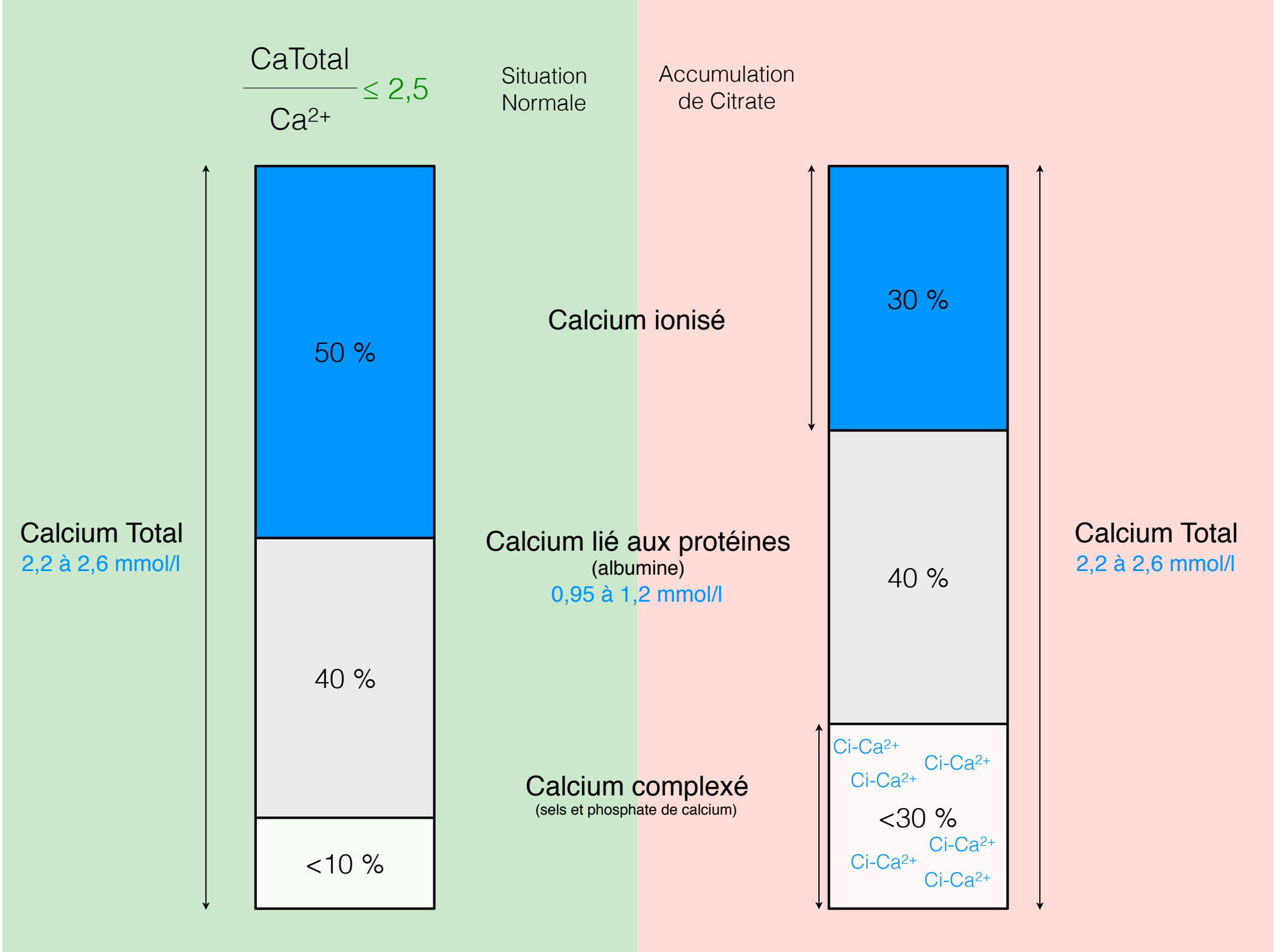
Calcium Total
2,2 à 2,6 mmol/l

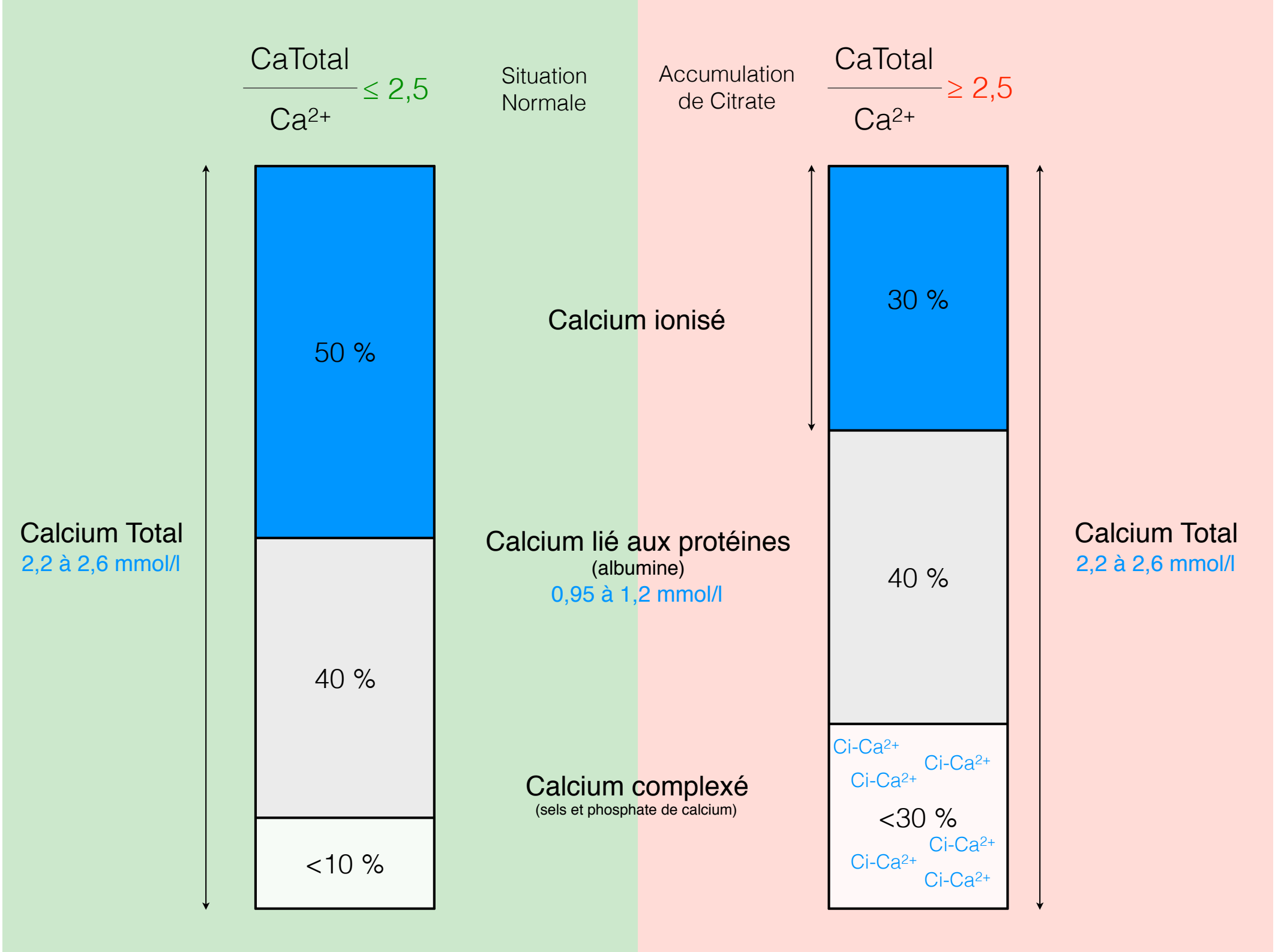
Calcium ionisé

Calcium lié aux protéines
(albumine)
0,95 à 1,2 mmol/l

Calcium complexé
(sels et phosphate de calcium)
< 0,1 mmol/l


CaTotal / Ca2+ ≤ 2,5
Situation Normale
Accumulation de Citrate
Calcium Total
2,2 à 2,6 mmol/l
50 %
40 %
<10 %
Calcium ionisé
30 %
Calcium lié aux protéines
(albumine)
0,95 à 1,2 mmol/l
Calcium complexé
(sels et phosphate de calcium)
Ci-Ca2+
Ci-Ca2+
Ci-Ca2+
<30 %
Ci-Ca2+
Ci-Ca2+
Ci-Ca2+


CaTotal / Ca2+ ≤ 2,5
Situation Normale
Accumulation de Citrate
Calcium Total
2,2 à 2,6 mmol/l
50 %
40 %
<10 %
Calcium ionisé
Calcium lié aux protéines
(albumine)
0,95 à 1,2 mmol/l
Calcium complexé
(sels et phosphate de calcium)
30 %
40 %
Ci-Ca2+
Ci-Ca2+
Ci-Ca2+
<30 %
Ci-Ca2+
Ci-Ca2+
Ci-Ca2+
Calcium Total
2,2 à 2,6 mmol/l


CaTotal / Ca2+ ≤ 2,5
Situation Normale
Accumulation de Citrate
CaTotal / Ca2+ ≥ 2,5
Calcium Total
2,2 à 2,6 mmol/l
50 %
40 %
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Calcium lié aux protéines
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0,95 à 1,2 mmol/l
Calcium complexé
(sels et phosphate de calcium)
30 %
40 %
Ci-Ca2+
Ci-Ca2+
Ci-Ca2+
<30 %
Ci-Ca2+
Ci-Ca2+
Ci-Ca2+
Calcium Total
2,2 à 2,6 mmol/l

Monitorage une fois par jour

$$\frac{\text{CaTotal}}{Ca^{2+}}$$

Monitorage une fois par jour

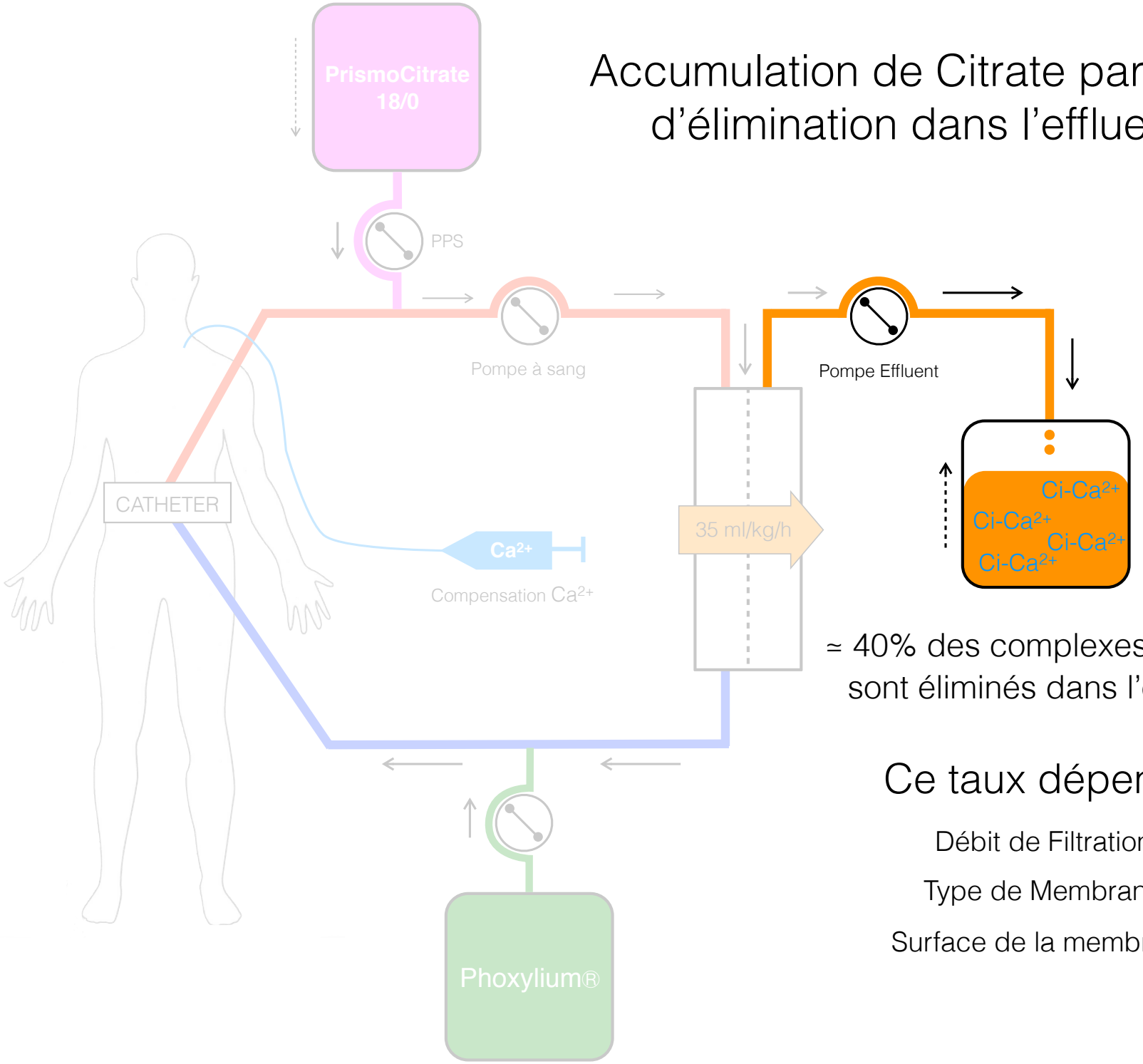
$$\frac{\text{CaTotal}}{\text{Ca}^{2+}} \geq 2{,}5$$

Accumulation de Citrate

Stop Citrate

MAIS conserver l'épuration +++

Accumulation de Citrate par défaut d'élimination dans l'effluent...



≃ 40% des complexes Ci-Ca^{2+} sont éliminés dans l'effluent

Ce taux dépend :

Débit de Filtration

Type de Membrane

Surface de la membrane

Hypomagnésémie

Le Citrate est aussi chélateur du Magnésium

Avec une moindre affinité que pour le Calcium

Ionogrammes réguliers et supplémentation quotidienne

La Surveillance

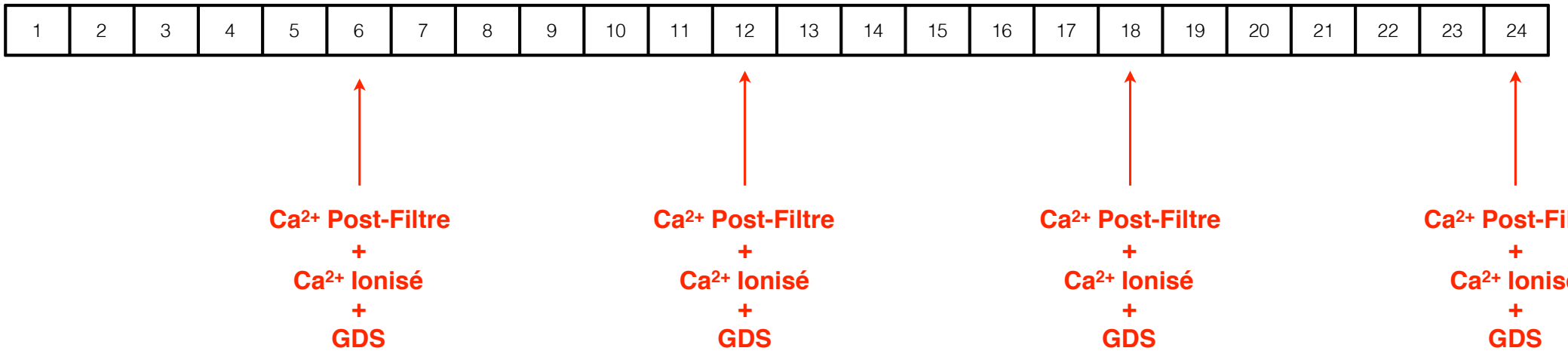
La surveillance clinique est la même que chez tous les patients sous EER

/6h	GDS artériel, Ca ionisé patient Ca ionisé post-filtre
/12h	Iono sang complet
/24h	Ca Total Ca Ionisé

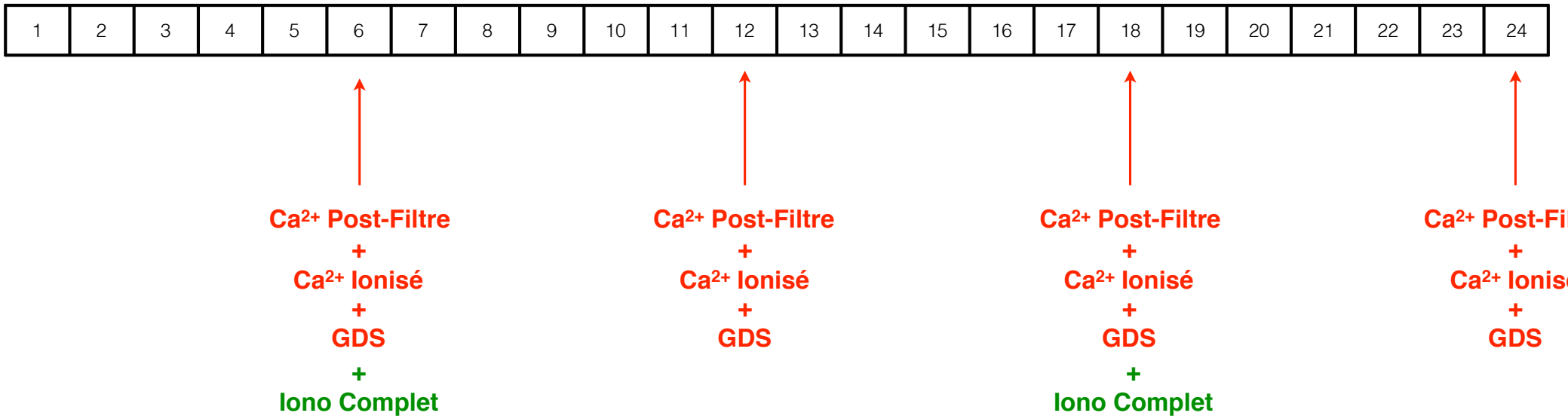
La surveillance clinique est la même que chez tous les patients sous EER

/4h
Le premier jour

/6h	GDS artériel, Ca ionisé patient Ca ionisé post-filtre
/12h	Iono sang complet
/24h	Ca Total Ca Ionisé

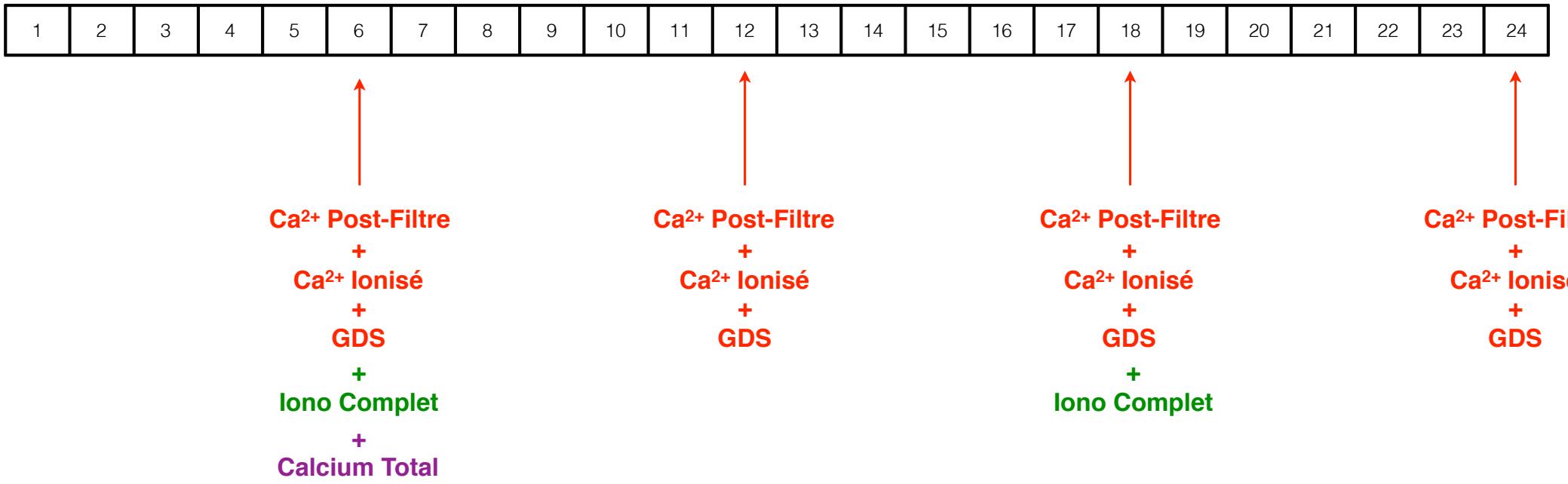


/6h GDS artériel,
Ca ionisé
Ca ionisé post-filtre



/6h GDS artériel,
Ca ionisé
Ca ionisé post-filtre

/12h Iono sang complet



/6h	GDS artériel, Ca ionisé Ca ionisé post-filtre
/12h	Iono sang complet
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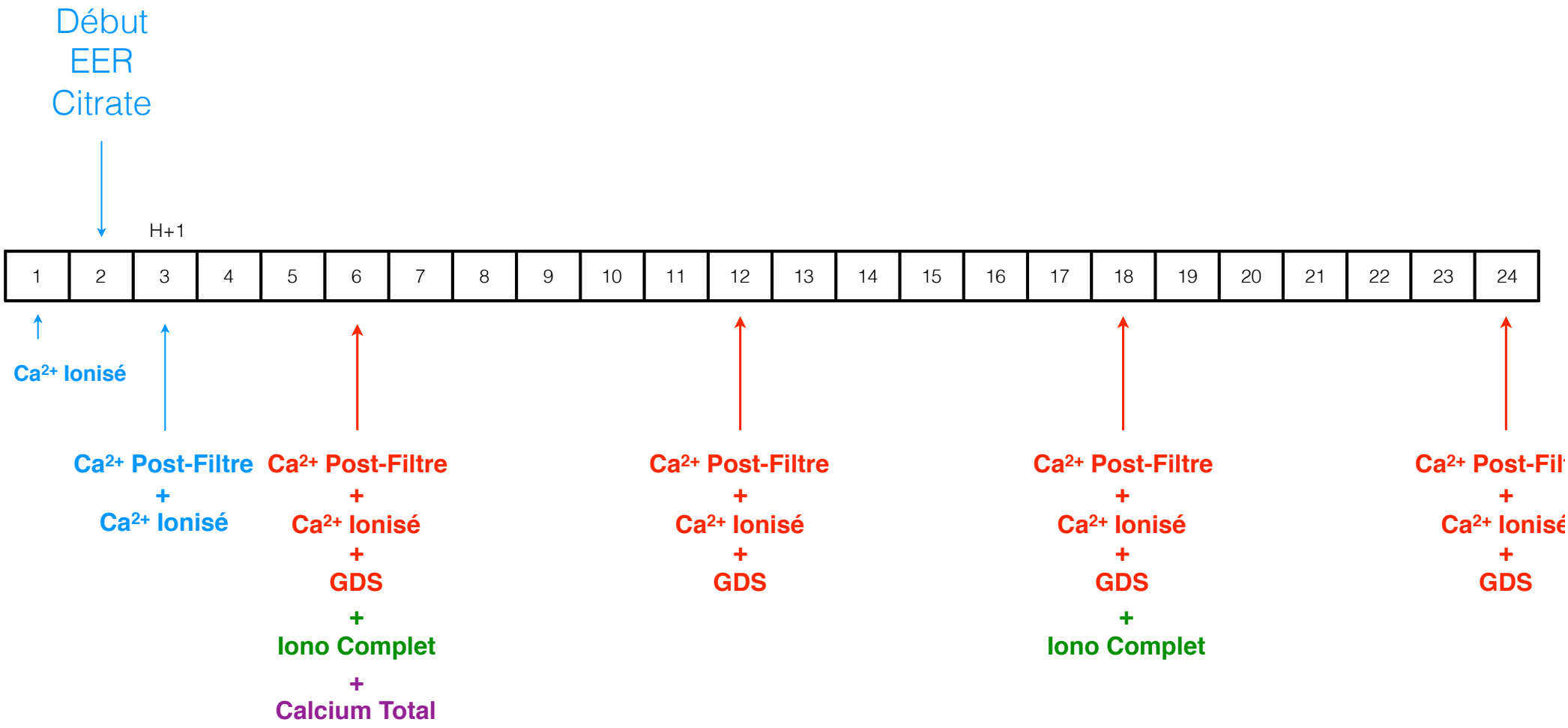

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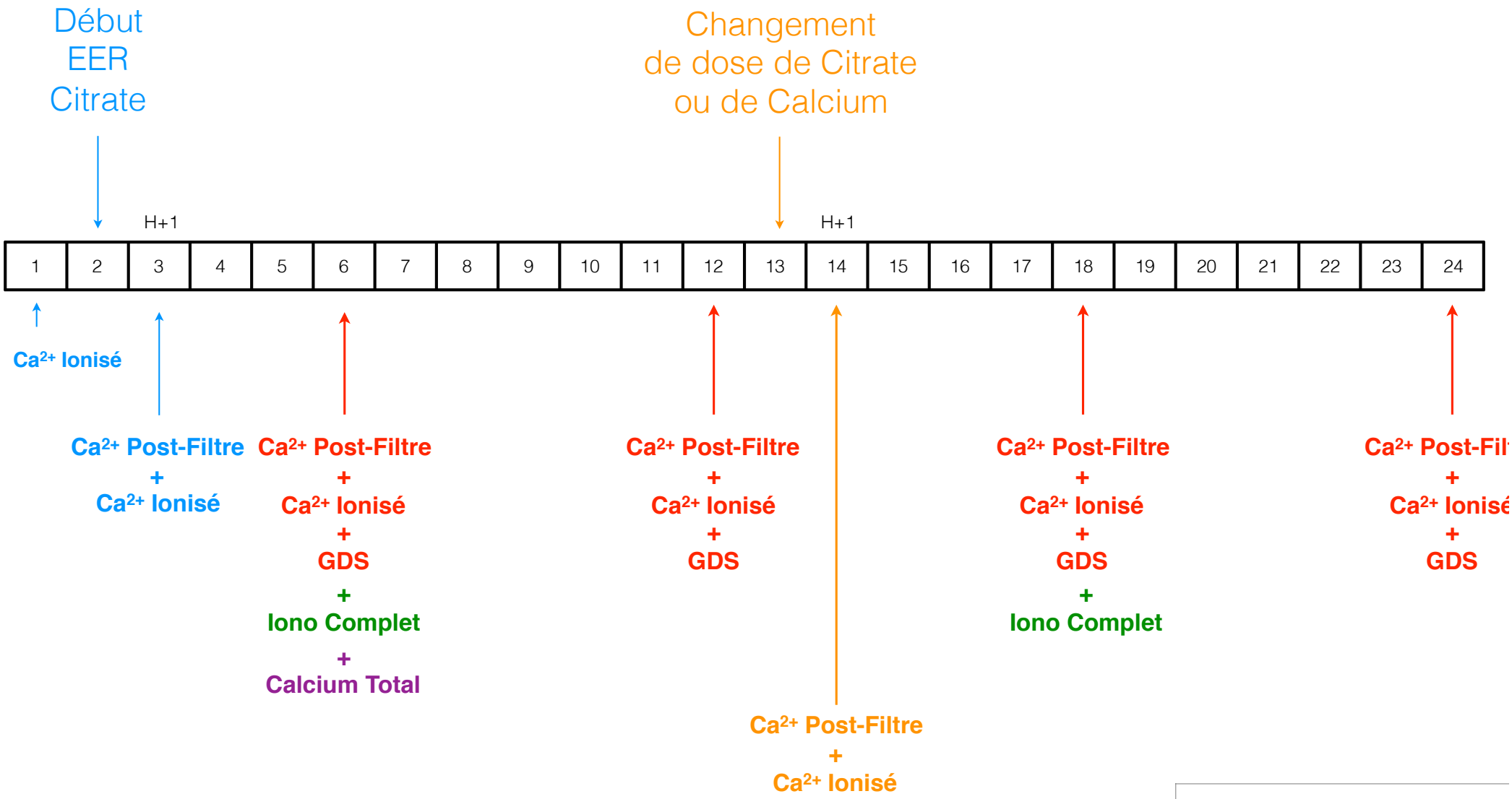


/6h	GDS artériel, Ca ionisé Ca ionisé post-filtre
/12h	Iono sang complet
/24h	Ca Total Ca Ionisé

Objectif Ca^{2+} Post-Filtre
0,25 à 0,35 mmo/l

Mesure du Ca^{2+} Post-Filtre/6h	< 0,25 mmol/l	0,25 à 0,35 mmol/l	> 0,35 mmol/l
	↓	↓	↓
Adaptation de la <u>Dose de Citrate</u>	↘ de 0,5 mmol/l	pas de changement	↗ de 0,5 mmol/l

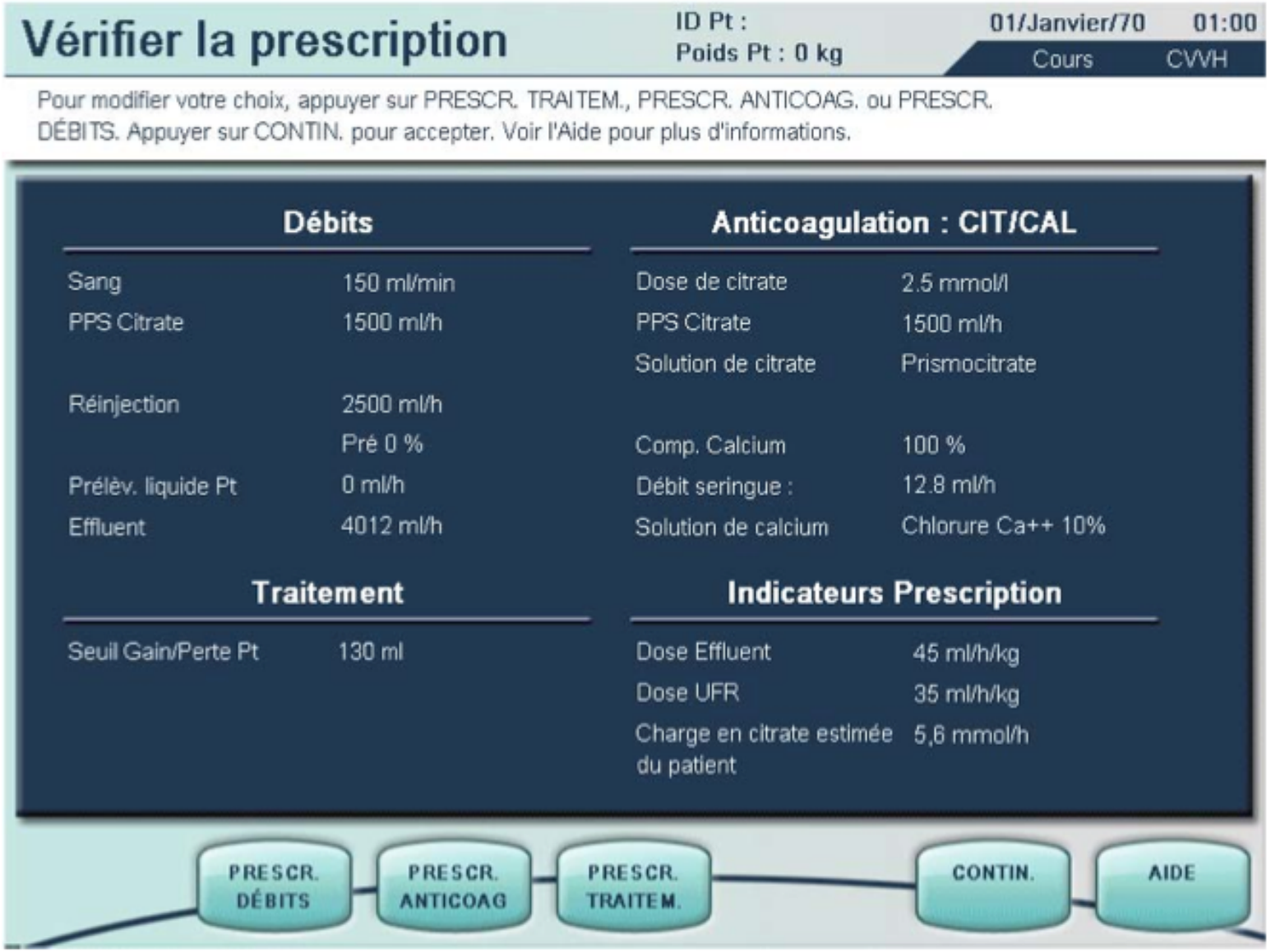
Objectif Ca^{2+} Patient
1 à 1,2 mmo/l

Mesure du Ca^{2+} Patient/6h	< 1,0 mmol/l	1 à 1,2 mmol/l	> 1,25 mmol/l
	↓	↓	↓
Adaptation de la <u>Dose de Ca^{2+}</u>	↗ de 10 %	pas de changement	↘ de 10 %

L’adaptation de la posologie de citrate et de calcium peut être réalisée par **l’IDE** au vu des résultats des GDS/6h.

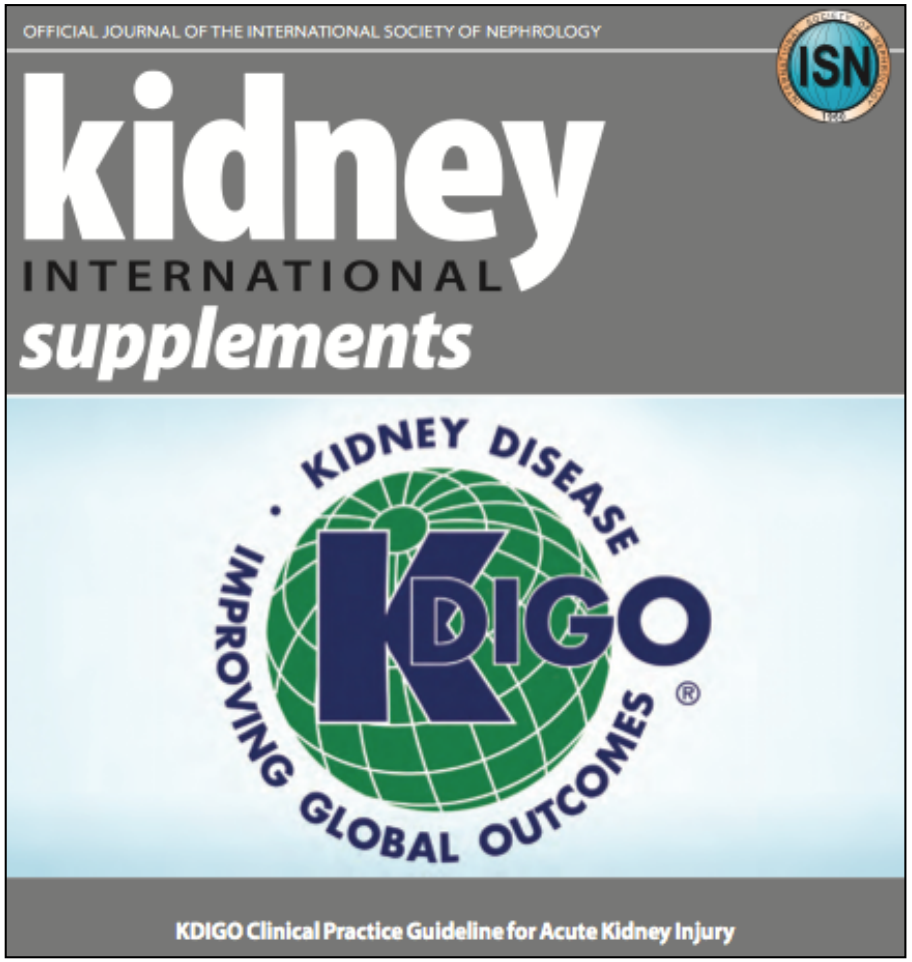
En revanche, en cas d’alcalose ou d’acidose métabolique, la décision de modifier les débits sera prise par le **médecin**.

La Surveillance en cours de Traitement



Recommandations

2012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INTERNATIONAL
supplements
KIDNEY DISEASE
IMPROVING GLOBAL OUTCOMES
KDIGO
KDIGO Clinical Practice Guideline for Acute Kidney Injury

Clinical Guidelines

nephron Clinical Practice

Nephron Clin Pract 2012;120:c179–c184
DOI: 10.1159/000339789

Published online: August 7, 2012

KDIGO Clinical Practice Guidelines for Acute Kidney Injury

Arif Khwaja

Sheffield Kidney Institute, Northern General Hospital, Sheffield, UK

Table 3. Key recommendations for dialysis interventions for treatment of AKI

Recommendation	Evidence level
Anticoagulation	
Use anticoagulation in RRT as long as no impaired coagulation/bleeding risk	1B
Unfractionated or low-molecular-weight heparin for intermittent RRT	1C
Regional citrate preferred for CRRT	2B
Unfractionated or low-molecular-weight heparin in CRRT in those with contraindication to citrate; no role for prostacyclins	2C
Regional citrate in CRRT for those with at increased bleeding risk – avoid regional heparinisation	2C
Stop all heparin and use direct thrombin inhibitors (argatroban) or factor Xa inhibitors (danaparoid or fondaparinux) in heparin-induced thrombocytopenia – argatroban preferred if severe liver failure	1A
Access	
Choice of vein as follows: (1) Right Jugular (2) Femoral (3) Left jugular (4) Subclavian – dominant side	ungraded
Ultrasound-guided insertion	1A
No use for topical antibiotics or antibiotic locks	2C
Modality	
CRRT preferred to intermittent haemodialysis for those with: (1) Cardiovascular instability (2) Acute brain injury or cerebral oedema or raised intracranial pressure	2B
Buffer	
Use of bicarbonate rather than lactate as a buffer in those with associated circulatory shock/liver failure/lactic acidosis	1B–2B
Dose	
Kt/V of 3.9 per week for those on intermittent or extended RRT	1A
Effluent volume of 20–25 ml/kg/h for CRRT	1A

Table 3. Key recommendations for dialysis interventions for treatment of AKI

Recommendation	Evidence level
Anticoagulation	
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CRRT preferred to intermittent haemodialysis for those with: (1) Cardiovascular instability (2) Acute brain injury or cerebral oedema or raised intracranial pressure	2B
Buffer	
Use of bicarbonate rather than lactate as a buffer in those with associated circulatory shock/liver failure/lactic acidosis	1B–2B
Dose	
Kt/V of 3.9 per week for those on intermittent or extended RRT	1A
Effluent volume of 20–25 ml/kg/h for CRRT	1A

Table 3. Key recommendations for dialysis interventions for treatment of AKI

Recommendation	Evidence level
Anticoagulation	
Use anticoagulation in RRT as long as no impaired coagulation/bleeding risk	1B
Unfractionated or low-molecular-weight heparin for intermittent RRT	1C
Regional citrate preferred for CRRT	2B
Unfractionated or low-molecular-weight heparin in CRRT in those with contraindication to citrate; no role for prostacyclins	2C
Regional citrate in CRRT for those with at increased bleeding risk – avoid regional heparinisation	2C
Stop all heparin and use direct thrombin inhibitors (argatroban) or factor Xa inhibitors (danaparoid or fondaparinux) in heparin-induced thrombocytopenia – argatroban preferred if severe liver failure	1A
Access	
Choice of vein as follows: (1) Right Jugular (2) Femoral (3) Left jugular (4) Subclavian – dominant side	ungraded
Ultrasound-guided insertion	1A
No use for topical antibiotics or antibiotic locks	2C
Modality	
CRRT preferred to intermittent haemodialysis for those with: (1) Cardiovascular instability (2) Acute brain injury or cerebral oedema or raised intracranial pressure	2B
Buffer	
Use of bicarbonate rather than lactate as a buffer in those with associated circulatory shock/liver failure/lactic acidosis	1B–2B
Dose	
Kt/V of 3.9 per week for those on intermittent or extended RRT	1A
Effluent volume of 20–25 ml/kg/h for CRRT	1A

Vinsonneau *et al. Ann. Intensive Care (2015) 5:58*
DOI 10.1186/s13613-015-0093-5

Annals of Intensive Care
a SpringerOpen Journal

REVIEW Open Access

Renal replacement therapy in adult and pediatric intensive care

Recommendations by an expert panel from the French Intensive Care Society (SRLF) with the French Society of Anesthesia Intensive Care (SFAR) French Group for Pediatric Intensive Care Emergencies (GFRUP) the French Dialysis Society (SFD)

Christophe Vinsonneau[1*], Emma Allain-Launay[2], Clarisse Blayau[3], Michael Darmon[4], Damien Ducheyron[5], Theophile Gaillot[6], Patrick M. Honore[7], Etienne Javouhey[8], Thierry Krummel[9], Annie Lahoche[10], Serge Letacon[11], Matthieu Legrand[12], Mehran Monchi[1], Christophe Ridel[3], René Robert[13], Frederique Schortgen[14], Bertrand Souweine[15], Patrick Vaillant[16], Lionel Velly[17], David Osman[18] and Ly Van Vong[1]

Littérature sur l’EER-Ci…

1961

Première description d'une hémodialyse au Citrate

Morita Y. et al. - Regional anticoagulation during hemodialysis using citrate. Am. J. Med. Sci., 1961; 242: 32-43.

Progrès technologiques

Machines - Asservissement

Surveillance Biologique

Fiabilité - Biologie délocalisée

2012

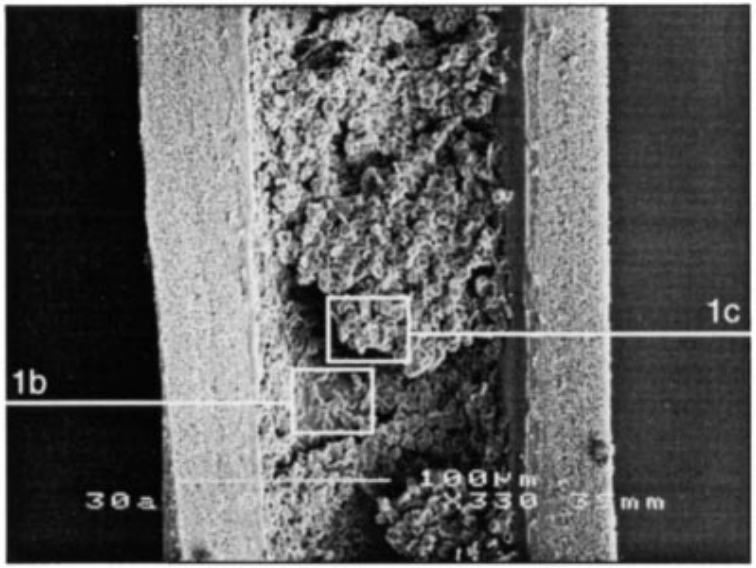
Recommandations KDIGO

1999

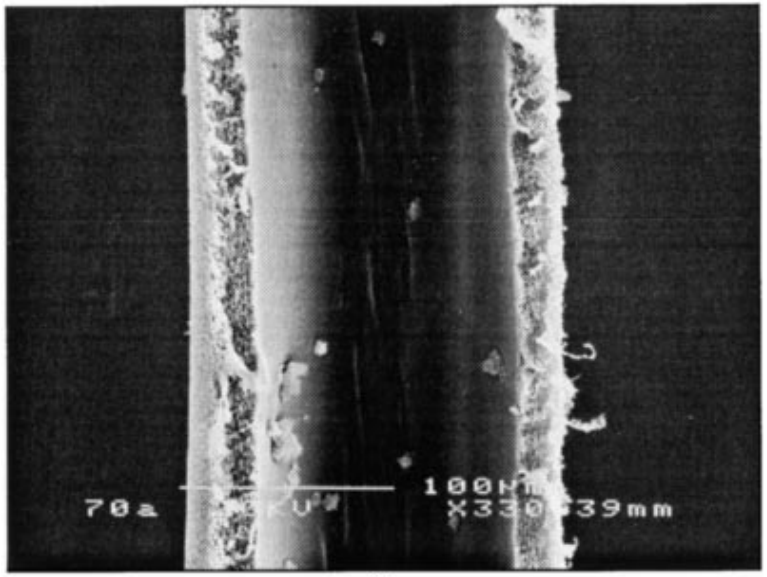
Effect of anticoagulation on blood membrane interactions during hemodialysis

Roland Hofbauer, Doris Moser, Michael Frass, Rainer Oberbauer, Alan D. Kaye, O. Wagner, Stylianos Kapiotis, and Wilfred Druml

Department of Medical and Chemical Laboratory Diagnostics, Department of Oral and Maxillofacial Surgery, Department of Internal Medicine I (MICU), and Department of Internal Medicine III, Nephrology and Dialysis, University of Vienna, Austria, and Department of Anesthesiology and Intensive Care Medicine, Texas Tech University, Health Science Center, Lubbock, Texas, USA



Héparine



Citrate

Hofbauer R. *et al.* - Effect of anticoagulation on blood membrane interactions during hemodialysis. *Kidney Int*., 1999*; 56(4):* 1578-1583.

1999

Effect of anticoagulation on blood membrane interactions during hemodialysis

Roland Hofbauer, Doris Moser, Michael Frass, Rainer Oberbauer, Alan D. Kaye, O. Wagner, Stylianos Kapiotis, and Wilfred Druml

Department of Medical and Chemical Laboratory Diagnostics, Department of Oral and Maxillofacial Surgery, Department of Internal Medicine I (MICU), and Department of Internal Medicine III, Nephrology and Dialysis, University of Vienna, Austria, and Department of Anesthesiology and Intensive Care Medicine, Texas Tech University, Health Science Center, Lubbock, Texas, USA

Table 2. Dialyzer clotting score (DCS) of a polysulfone hollow fiber dialysis membrane during three types of anticoagulation during hemodialysis therapy: unfractionated heparin (UFH), low molecular weight heparin (LMWH), and sodium citrate anticoagulation (SCA)

	UFH	LMWH	SCA
Surface area involved	3.2 ± 0.4	2.4 ± 0.2	0.8 ± 0.2[a]
Fibrin net formation	1 ± 0.3	2.4 ± 0.4	0 ± 0[a]
Involvement of erythrocytes	3.6 ± 0.2	2.4 ± 0.2	0.8 ± 0.4[a]
Involvement of platelets	0.8 ± 0.2	1.6 ± 0.2	0 ± 0[a]
Obstruction of fiber lumen	3.8 ± 0.2	1.6 ± 0.2	0 ± 0[a]
Total "DCS"	11.5 ± 1.3	10.4 ± 1.2	1.6 ± 0.6[a]

[a] $P < 0.05$

Hofbauer R. *et al.* - Effect of anticoagulation on blood membrane interactions during hemodialysis. *Kidney Int*., 1999*; 56(4):* 1578-1583.

EER-Ci, oui mais pour quels bénéfices ?

2004

Intensive Care Med (2004) 30:260–265
DOI 10.1007/s00134-003-2047-x

ORIGINAL

Mehran Monchi
Denis Berghmans
Didier Ledoux
Jean-Luc Canivet
Bernard Dubois
Pierre Damas

Citrate vs. heparin for anticoagulation in continuous venovenous hemofiltration: a prospective randomized study

Réanimation
Médico-Chirurgicale

Randomisée

EERC

CVVH (post-dilution)

Héparine (n=26) *vs* Citrate (n = 23)

2004
Intensive Care Med (2004) 30:260–265
DOI 10.1007/s00134-003-2047-x
ORIGINAL

Mehran Monchi
Denis Berghmans
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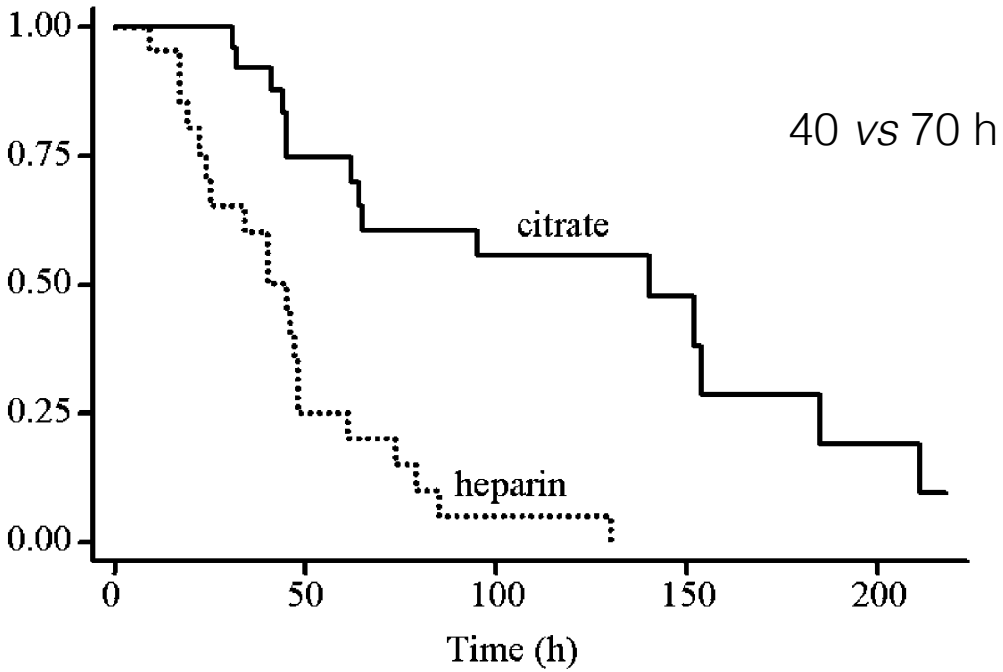

Fig. 1 Kaplan-Meier curves of time to spontaneous failure of the hemofilters, according to the anticoagulation used ($p<0.0001$)

2004
Intensive Care Med (2004) 30:260–265
DOI 10.1007/s00134-003-2047-x
ORIGINAL

Mehran Monchi
Denis Berghmans
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Citrate vs. heparin for anticoagulation in continuous venovenous hemofiltration: a prospective randomized study

Table 5 Red cells transfusion rates

	Heparin (*n*=23)	Citrate (*n*=26)	*p*
Patients transfused	15 (63%)	9 (38%)	0.03
Patients transfused after circuit clotting	10 (44%)	5 (19%)	0.06
Number of units transfused per day of CVVH, median (interquartile range)	1.0 (0–2.0)	0.2 (0–0.4)	0.0008

2005

Regional citrate versus systemic heparin anticoagulation for continuous renal replacement in critically ill patients

DEMETRIOS J. KUTSOGIANNIS, R.T. NOEL GIBNEY, DANIEL STOLLERY, and JUN GAO

Division of Critical Care Medicine, Department of Public Health Sciences; and Department of Mathematical and Statistical Sciences, The University of Alberta, Edmonton, Alberta, Canada

Kidney International, Vol. 67 (2005), pp. 2361–2367

Réanimation
Médico-Chirurgicale

Randomisée

EERC

CVVHDF (pré-dilution)

Risque hémorragique faible

Héparine (n=36) *vs* Citrate (n = 43)

2005

Regional citrate versus systemic heparin anticoagulation for continuous renal replacement in critically ill patients

DEMETRIOS J. KUTSOGIANNIS, R.T. NOEL GIBNEY, DANIEL STOLLERY, and JUN GAO

Division of Critical Care Medicine, Department of Public Health Sciences; and Department of Mathematical and Statistical Sciences, The University of Alberta, Edmonton, Alberta, Canada

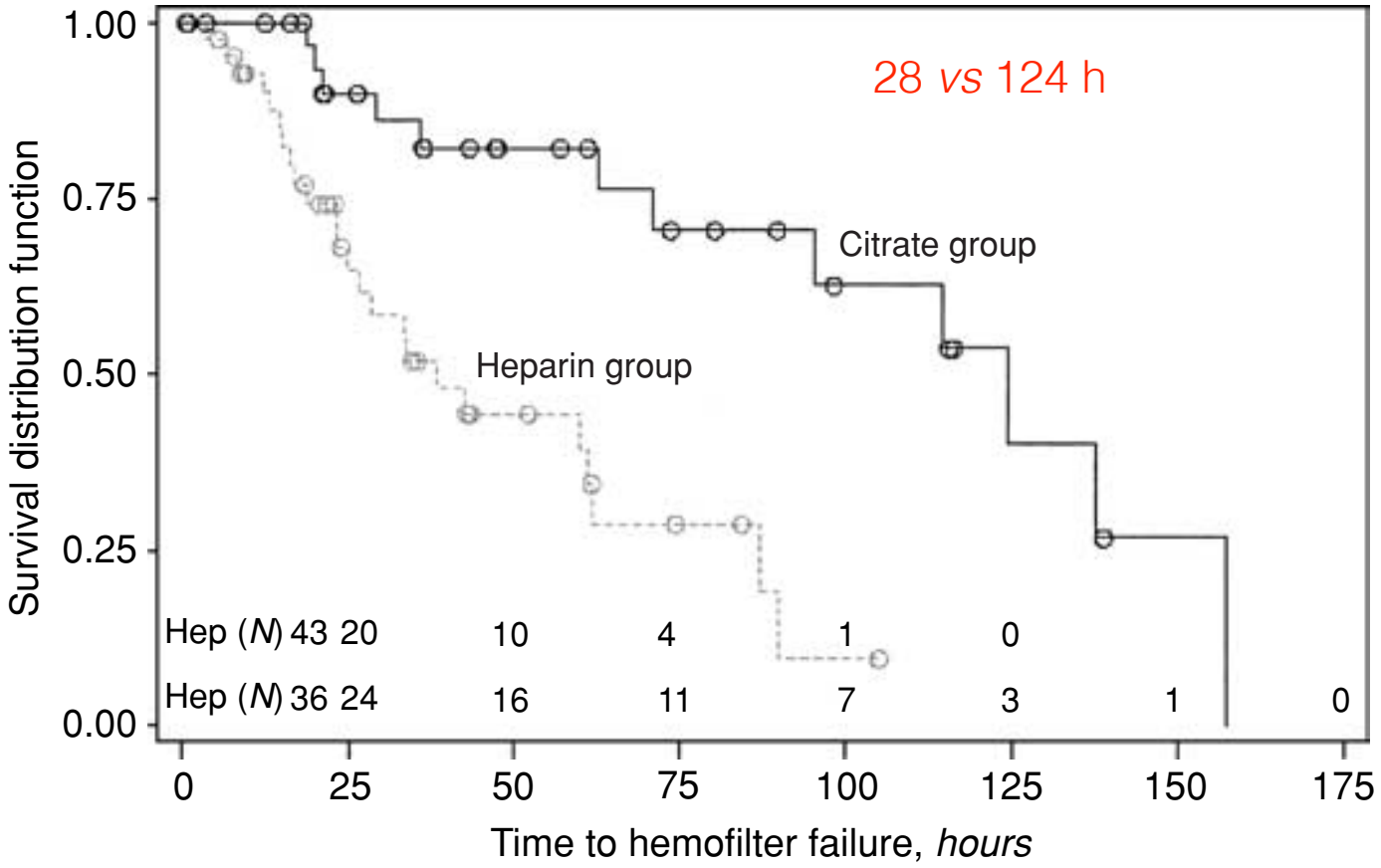

Table 1 Comparison between three large randomized controlled trials comparing citrate to heparin anticoagulation for continuous venovenous hemofiltration

	CASH trial 2014 [1] (multicenter)		OLVG trial 2009 [2] (single center)		Hetzel trial 2011 [3] (multicenter)	
Excluded (percentage of patients needing CRRT)	1,297/2,300 (94%)		170/385 (44%)		Not reported	
Modality	Predilution CVVH		Postdilution CVVH		Predilution CVVH	
Groups	**Citrate**	**Heparin**	**Citrate**	**LMWH**	**Citrate**	**Heparin**

Table 1 Comparison between three large randomized controlled trials comparing citrate to heparin anticoagulation for continuous venovenous hemofiltration

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Modality	Predilution CVVH		Postdilution CVVH		Predilution CVVH	
Groups	**Citrate**	**Heparin**	**Citrate**	**LMWH**	**Citrate**	**Heparin**

2009 Citrate anticoagulation for continuous venovenous hemofiltration*

Heleen M. Oudemans-van Straaten, MD, PhD; Rob J. Bosman, MD; Matty Koopmans, RN; Peter H. J. van der Voort, MD, PhD, MSc; Jos P. J. Wester, MD, PhD; Johan I. van der Spoel, MD; Lea M. Dijksman, MSc; Durk F. Zandstra, MD, PhD

Réanimation Médico-Chirurgicale

Monocentrique (Pays-Bas)

Randomisée

Nadroparin 500 UI/h

Citrate concentré

CVVH (postdilution)

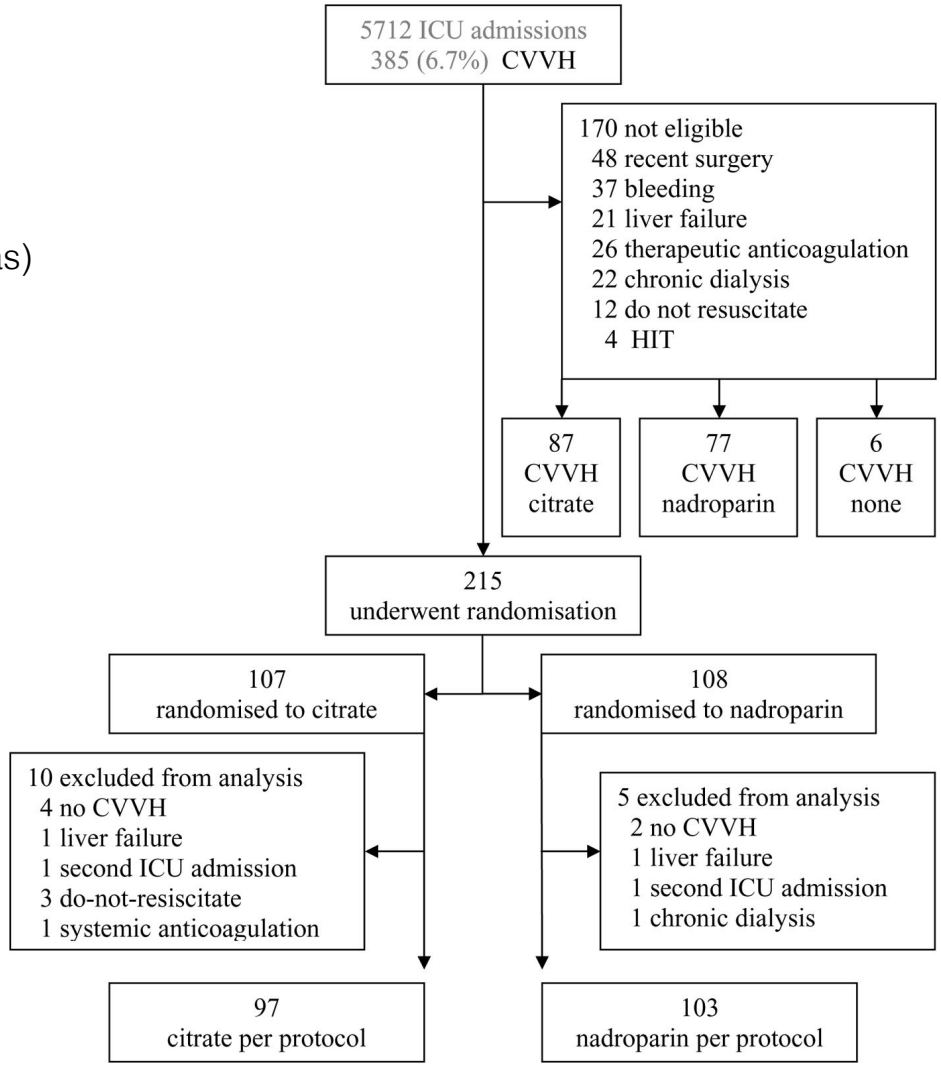

Figure 1. Enrollment, exclusion, and randomization of study patients. *ICU*, intensive care unit; *CVVH*, continuous venovenous hemofiltration; *HIT*, heparin-induced thrombocytopenia.

Citrate anticoagulation for continuous venovenous hemofiltration*

Heleen M. Oudemans-van Straaten, MD, PhD; Rob J. Bosman, MD; Matty Koopmans, RN;
Peter H. J. van der Voort, MD, PhD, MSc; Jos P. J. Wester, MD, PhD; Johan I. van der Spoel, MD;
Lea M. Dijksman, MSc; Durk F. Zandstra, MD, PhD

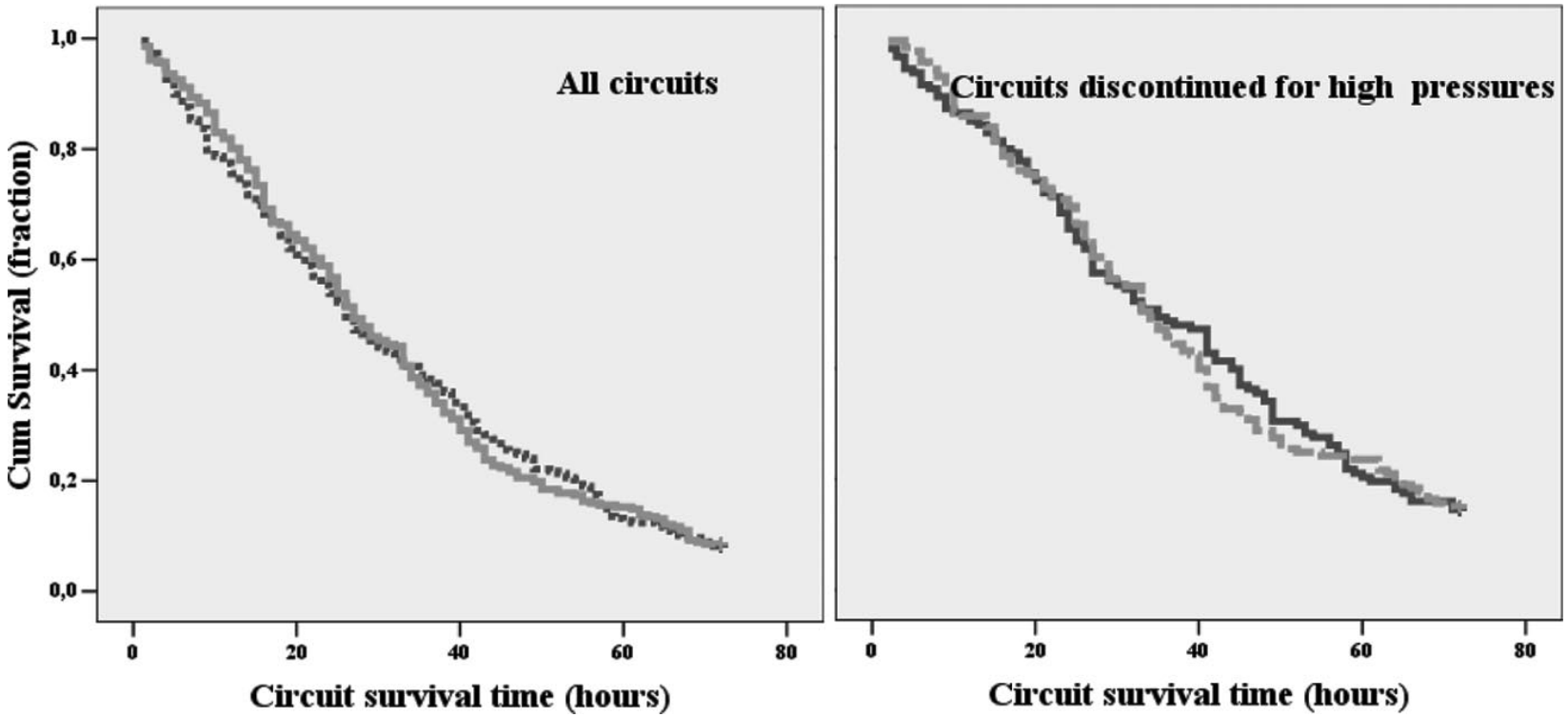

Figure 2. Graphs represent circuit survival. *Dotted lines* represent the citrate patients; *continuous lines* represent the nadroparin patients. In the right graph, circuits disconnected for catheter failure, recovery of renal function, (impending) death or logistic reasons are censored. *p* values (log rank) for both populations are 0.92.

2009 Citrate anticoagulation for continuous venovenous hemofiltration*

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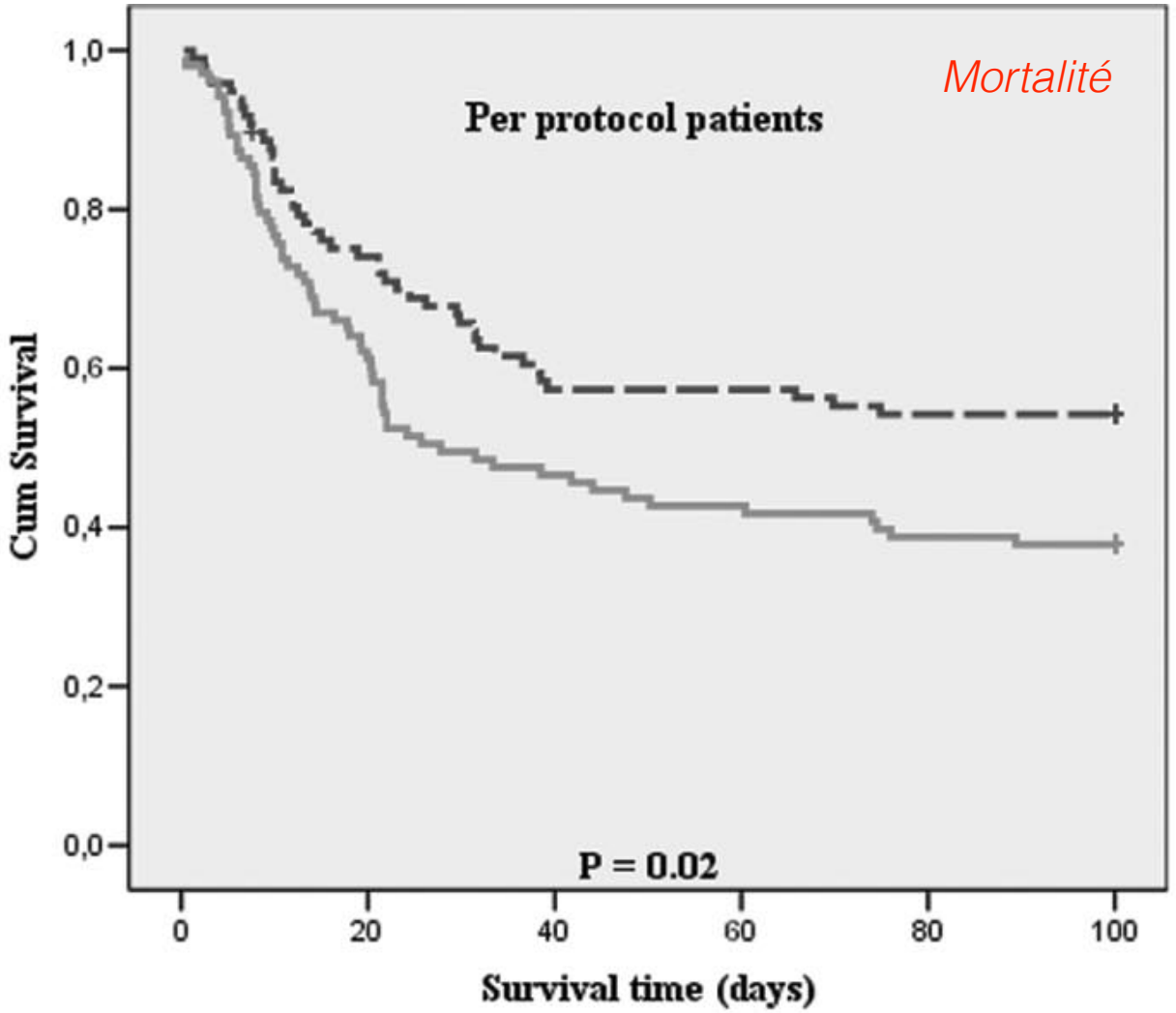

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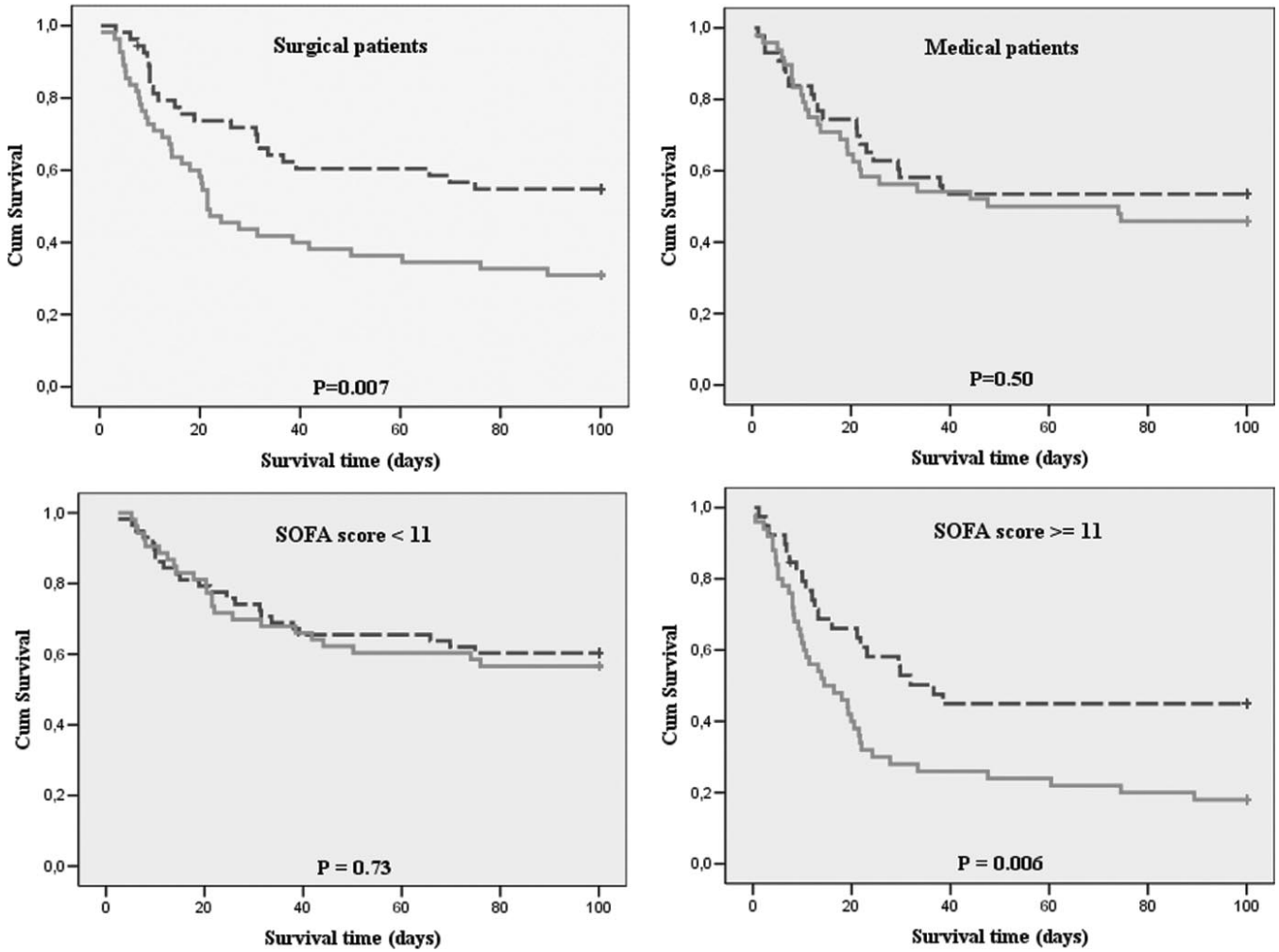

Citrate anticoagulation for continuous venovenous hemofiltration*

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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
Transfusion			
Red blood cells			
During CVVH period, number of patients (%)	56 (58)	62 (60)	0.89
Per CVVH day, number of units (IQR)	0.27 (0.0–0.63)	0.36 (0.0–0.83)	0.31
Quarantaine plasma, number of patients (%)	8 (8)	11 (11)	0.63
Platelets, number of patients (%)	6 (6)	9 (9)	0.59
Hemoglobin start-end CVVH (mmol/L) (IQR)	−0.10 (−0.06 to 0.05)[a]	0.20 (−0.07 to 0.07)[b]	0.36
Platelet count start-end CVVH (10^9/L) (IQR)	−6 (−32 to +13)	−8 (−32 to +9)	0.46

Table 1 Comparison between three large randomized controlled trials comparing citrate to heparin anticoagulation for continuous venovenous hemofiltration

	CASH trial 2014 [1] (multicenter)		OLVG trial 2009 [2] (single center)		Hetzel trial 2011 [3] (multicenter)	
Excluded (percentage of patients needing CRRT)	1,297/2,300 (94%)		170/385 (44%)		Not reported	
Modality	Predilution CVVH		Postdilution CVVH		Predilution CVVH	
Groups	**Citrate**	**Heparin**	**Citrate**	**LMWH**	**Citrate**	**Heparin**

Nephrol Dial Transplant (2011) 26: 232–239
doi: 10.1093/ndt/gfq575
Advance Access publication 27 September 2010

2011

Réanimation
Médico-Chirurgicale

Multicentrique (9 sites)
Allemagne

Randomisée

HNF (n = 47)

Citrate (n = 62)

CVVH (prédilution)

Regional citrate versus systemic heparin for anticoagulation in critically ill patients on continuous venovenous haemofiltration: a prospective randomized multicentre trial

Gerd R. Hetzel[1,*], Michael Schmitz[1,*], Heimo Wissing[2], Wolfgang Ries[3], Gabriele Schott[4], Peter J. Heering[5], Frank Isgro[6], Andreas Kribben[7], Rainer Himmele[8], Bernd Grabensee[1] and Lars C. Rump[1]

Table 4. Comparison of the mean morning standard bicarbonate as the primary parameter of efficacy

Visit	*n* HF-Citrate/ HF-Bicarbonate	HF Citrate mean (SD) (mmol/L)	HF Bicarbonate mean (SD) (mmol/L)	Difference	95% CI
Day 0 morning	61/47	22.2 (4.7)	22.9 (4.6)	–	–
Day 1 morning	62/47	23.1 (3.3)	24.1 (4.0)	–	–
Day 2 morning	62/47	24.0 (2.8)	24.6 (2.5)	–	–
Day 3 morning	62/47	24.2 (3.1)	25.1 (2.7)	−0.827	(−1.948–0.294)
Day 4 morning	55/39	24.3 (2.6)	25.2 (2.5)	−0.850	(−1.927–0.228)
Day 5 morning	50/34	24.7 (3.4)	25.0 (2.6)	−0.317	(−1.703–1.069)
Day 6 morning	43/28	24.9 (2.9)	24.2 (2.3)	0.645	(−0.672–1.961)
Day 7 morning	33/22	24.8 (3.1)	24.3 (2.9)	0.489	(−1.182–2.160)
Day 8 morning	29/19	24.7 (3.1)	24.4 (2.6)	0.307	(−1.422–2.036)
Day 9 morning	27/17	24.7 (3.5)	24.8 (2.3)	−0.013	(−1.947–1.921)
Day 10 morning	20/15	24.4 (2.7)	24.0 (2.8)	0.392	(−1.501–2.286)
Day 11 morning	20/12	24.6 (2.9)	24.2 (2.5)	0.393	(−1.669–2.456)
Day 11 noon	20/12	24.7 (2.8)	23.3 (2.8)	1.397	(−0.682–3.475)

An overview of the morning standard bicarbonate values. The hierarchical test procedure started on Day 3 and ended at noon on Day 11 when the confirmatory test procedure for equivalence was no longer statistically significant.

Nephrol Dial Transplant (2011) 26: 232–239
doi: 10.1093/ndt/gfq575
Advance Access publication 27 September 2010

2011

Regional citrate versus systemic heparin for anticoagulation in critically ill patients on continuous venovenous haemofiltration: a prospective randomized multicentre trial

Gerd R. Hetzel[1,*], Michael Schmitz[1,*], Heimo Wissing[2], Wolfgang Ries[3], Gabriele Schott[4], Peter J. Heering[5], Frank Isgro[6], Andreas Kribben[7], Rainer Himmele[8], Bernd Grabensee[1] and Lars C. Rump[1]

Haemofilter patency. Mean haemofilter patency as a parameter of technical safety was significantly longer in the HF-Citrate group compared with the HF-Bicarbonate group (37.5 ± 23 h versus 26.1 ± 19 h, $P < 0.001$, $n = 87/81$). The mean duration of interruption of CVVH was 1.7 h per day in the HF-Citrate group compared with 2.8 h per day in the HF-Bicarbonate group, a difference that was not statistically significant.

Nephrol Dial Transplant (2011) 26: 232–239
doi: 10.1093/ndt/gfq575
Advance Access publication 27 September 2010

Regional citrate versus systemic heparin for anticoagulation in critically ill patients on continuous venovenous haemofiltration: a prospective randomized multicentre trial

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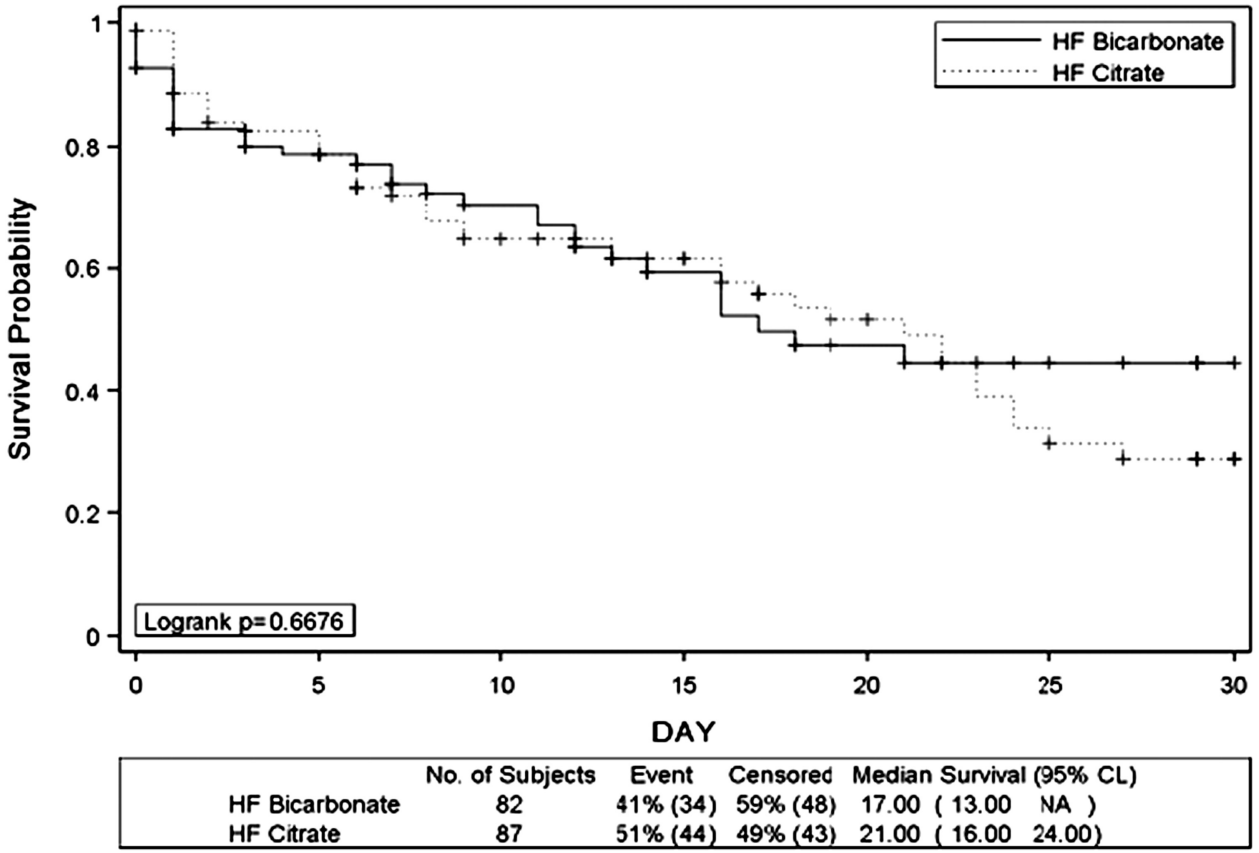

Fig. 3. Kaplan–Meier survival analysis up to Day 30.

Table 1 Comparison between three large randomized controlled trials comparing citrate to heparin anticoagulation for continuous venovenous hemofiltration

	CASH trial 2014 [1] (multicenter)		OLVG trial 2009 [2] (single center)		Hetzel trial 2011 [3] (multicenter)	
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Modality	Predilution CVVH		Postdilution CVVH		Predilution CVVH	
Groups	**Citrate**	**Heparin**	**Citrate**	**LMWH**	**Citrate**	**Heparin**

Réanimation
Médico-Chirurgicale

Multicentrique
(Pays-Bas)

Randomisée

HNF (n = 73)

Citrate (n = 66)

CVVH (prédilution)

Schilder *et al. Critical Care* 2014, **18**:472
http://ccforum.com/content/18/4/472

CRITICAL CARE

RESEARCH Open Access

Citrate anticoagulation versus systemic heparinisation in continuous venovenous hemofiltration in critically ill patients with acute kidney injury: a multi-center randomized clinical trial

Louise Schilder[1*], S Azam Nurmohamed[1], Frank H Bosch[2], Ilse M Purmer[3], Sylvia S den Boer[4], Cynthia G Kleppe[5], Marc G Vervloet[1], Albertus Beishuizen[6], Armand RJ Girbes[6], Pieter M ter Wee[1], AB Johan Groeneveld[7] and for the CASH study group

2014

CRITICAL CARE

RESEARCH Open Access

Citrate anticoagulation versus systemic heparinisation in continuous venovenous hemofiltration in critically ill patients with acute kidney injury: a multi-center randomized clinical trial

Louise Schilder[1*], S Azam Nurmohamed[1], Frank H Bosch[2], Ilse M Purmer[3], Sylvia S den Boer[4], Cynthia G Kleppe[5], Marc G Vervloet[1], Albertus Beishuizen[6], Armand RJ Girbes[6], Pieter M ter Wee[1], AB Johan Groeneveld[7] and for the CASH study group

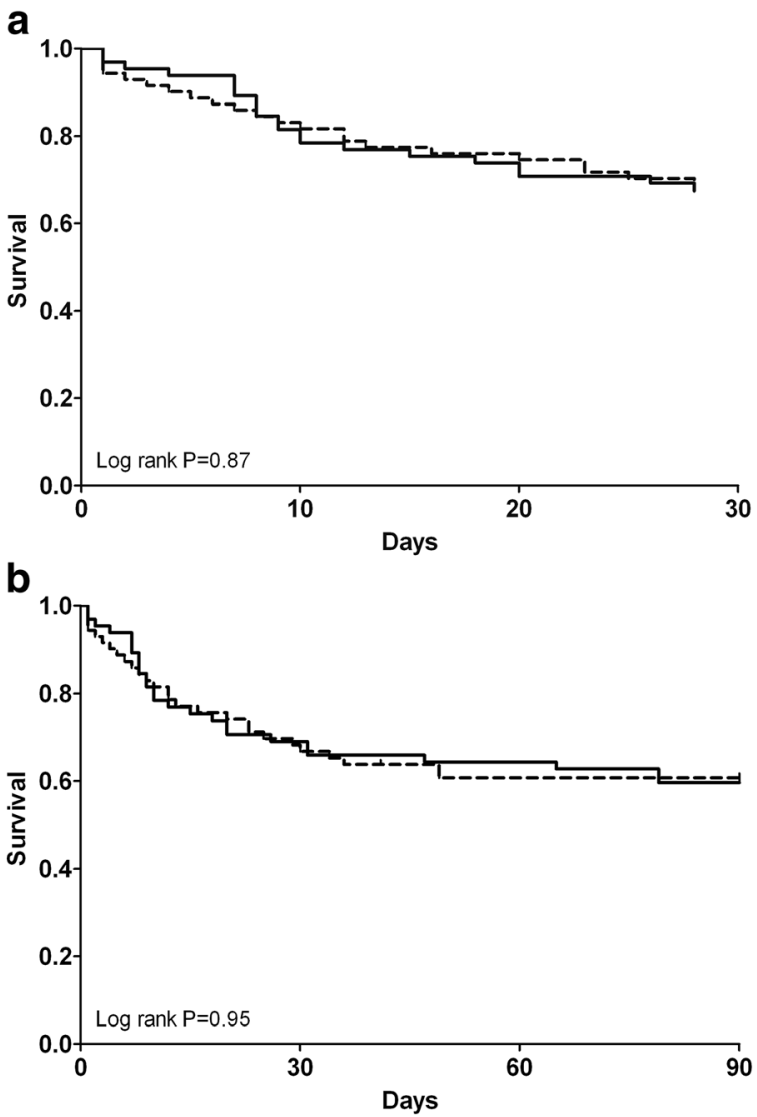


Figure 1 Patient survival. (a) Survival 28 days after initiation of continuous venovenous haemofiltration (CVVH). **(b)** Survival 90 days after initiation of CVVH. Continuous line represents citrate, dotted line represents heparin.

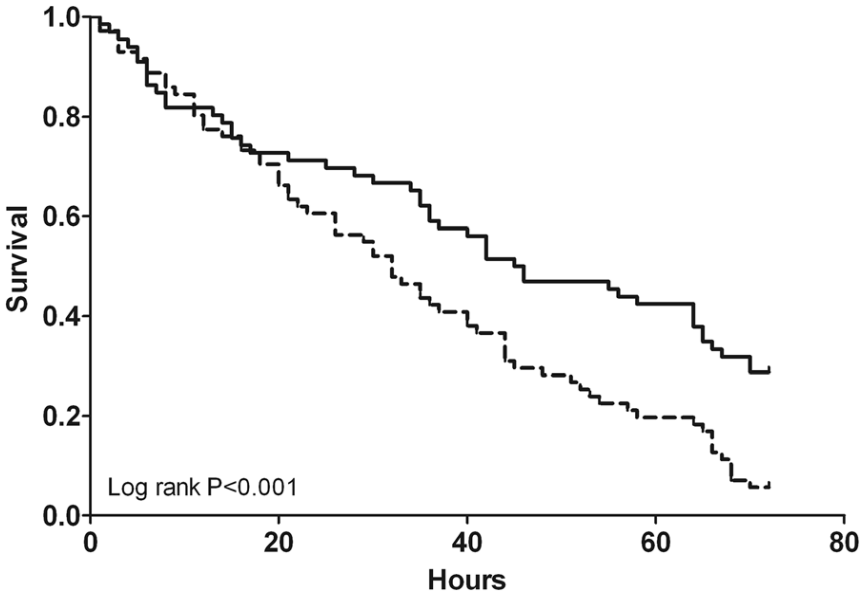


Figure 2 Survival times for the first filter. Continuous line represents citrate, dotted line represents heparin.

CRITICAL CARE

RESEARCH Open Access

Citrate anticoagulation versus systemic heparinisation in continuous venovenous hemofiltration in critically ill patients with acute kidney injury: a multi-center randomized clinical trial

Louise Schilder[1*], S Azam Nurmohamed[1], Frank H Bosch[2], Ilse M Purmer[3], Sylvia S den Boer[4], Cynthia G Kleppe[5], Marc G Vervloet[1], Albertus Beishuizen[6], Armand RJ Girbes[6], Pieter M ter Wee[1], AB Johan Groeneveld[7] and for the CASH study group

Table 2 Secondary outcomes

	Citrate (n = 66)	Heparin (n = 73)	*P*-value
Costs			
Total cost of first 72 h of CVVH, €	553 (436 to 872)	663 (320 to 1,319)	<0.001
Replacement fluid, €	316 (225 to 366)	429 (119 to 736)	<0.001
Wage nursing staff for filter change, €	19 (19 to 95)	38 (19 to 171)	0.02

Oudemans-van Straaten *Critical Care* 2014, **18**:661
http://ccforum.com/content/18/6/661

COMMENTARY

Citrate for continuous renal replacement therapy: safer, better and cheaper

Heleen M Oudemans-van Straaten

Conclusion

The CASH trial confirms the superiority of citrate in patients without an increased risk of bleeding in terms of safety and efficacy, while the intervention is less costly. Citrate confers an even greater benefit when the risk of bleeding is increased, because CRRT without anticoagulation is really problematic. Randomized studies in this population will, however, never be available. Thus, stubborn objectors: surrender! Citrate is the first choice.

Stucker et al. Critical Care (2015) 19:91
DOI 10.1186/s13054-015-0822-z

CRITICAL CARE

RESEARCH Open Access

Efficacy and safety of citrate-based anticoagulation compared to heparin in patients with acute kidney injury requiring continuous renal replacement therapy: a randomized controlled trial

Fabien Stucker[1†], Belen Ponte[1†], James Tataw[1], Pierre-Yves Martin[1], Hannah Wozniak[2], Jérome Pugin[2] and Patrick Saudan[1*]

Réanimation
Médico-Chirurgicale

Monocentrique
(Suisse)

Randomisée

HNF (n = 49)

Citrate (n = 54)

CVVHDF (prédilution)
Filtration 30 ml/kg/h
Dialysat 10 ml/kg/h

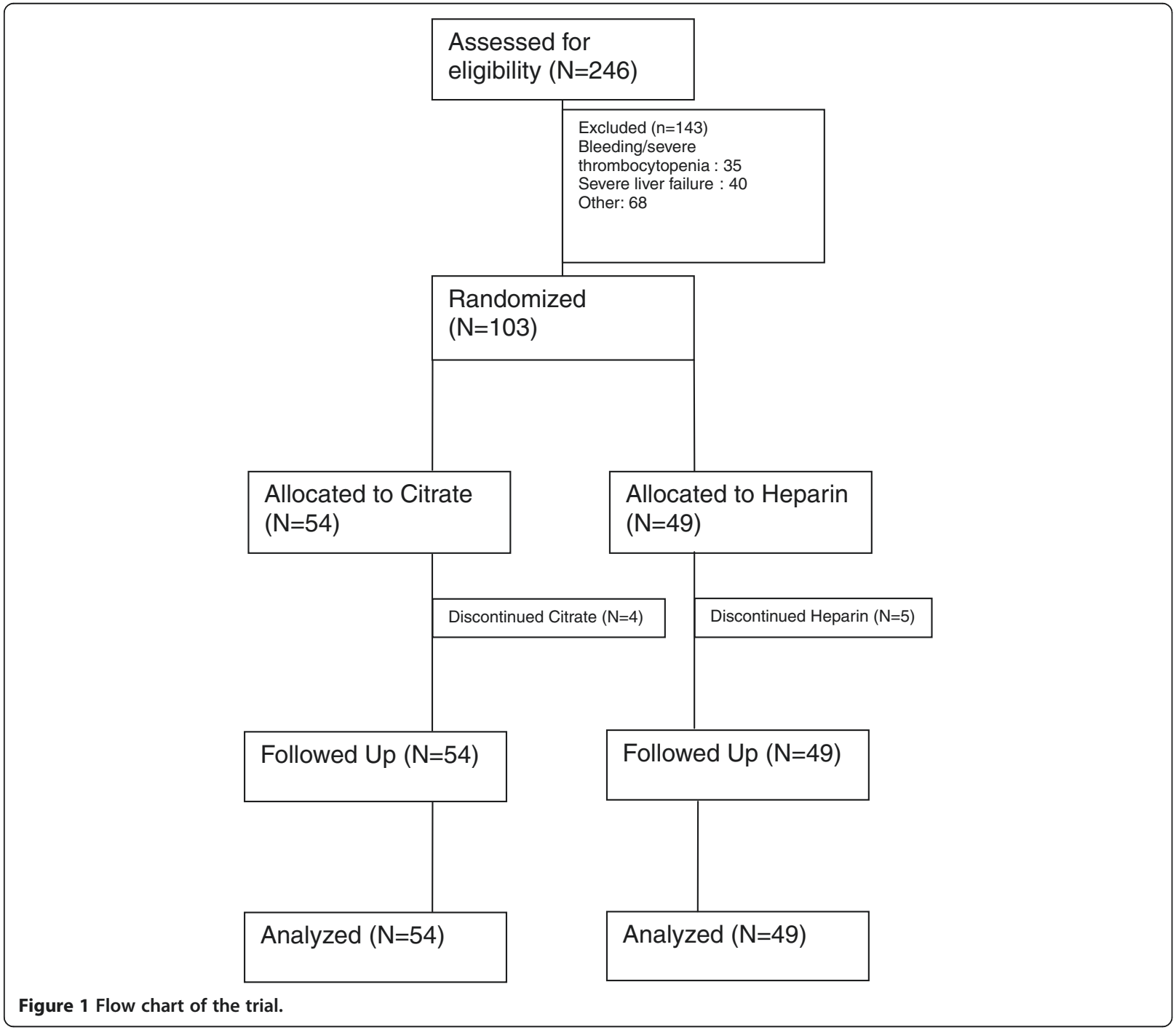


Figure 1 Flow chart of the trial.

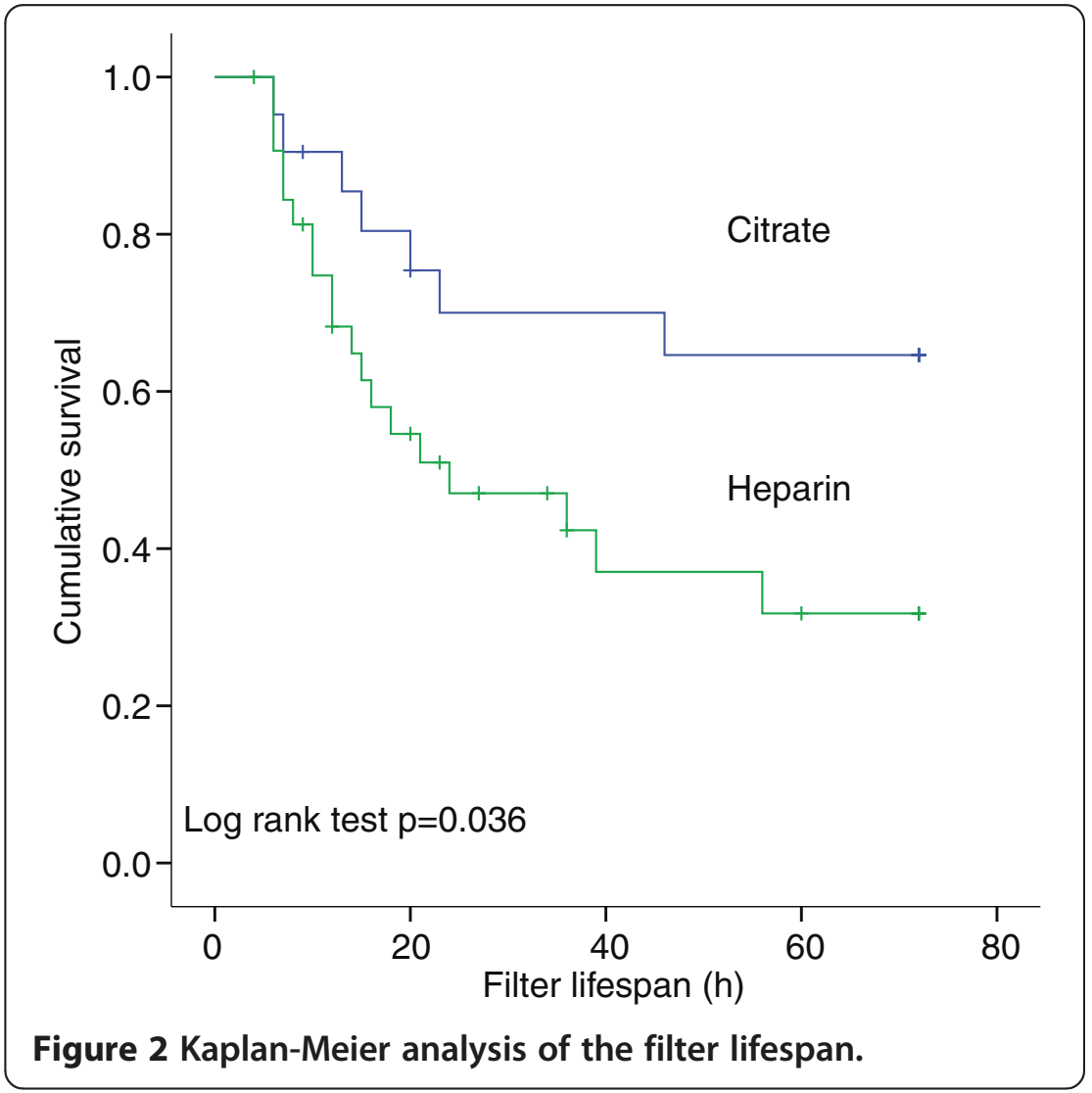


Figure 2 Kaplan-Meier analysis of the filter lifespan.

RRT long-term dependence

Nine patients remain RRT-dependent, five in the heparin group, and four in the citrate group at 90-day follow up.

Table 2 Intervention data

Variables	Citrate (n = 54)	Heparin (n = 49)	*p*
Delivered RRT dose, ml/kg/h	29 (3)	27 (5)	**0.005**
Effective delivered RRT dose*, ml/kg/h	28 (5)	26 (4)	0.15
Filter lifespan, h	49 (29)	28 (23)	**0.004**
Mean heparin, IU/ml dose	6,757 (5,455)	10,567 (7,760)	0.005
CRRT, days	3 (2 to 6)	3 (2 to 5)	0.30
ICU, days	7 (4 to 15)	7 (4 to 12)	0.79
Hospital, days	22 (6 to 35)	16 (9 to 30)	0.45
Survival at 28 days	43 (80)	36 (74)	0.46
Survival at 90 days	40 (74)	35 (73)	0.90

Conclusion

Technique recommandée depuis 2012

Amélioration de la durée de vie des hémofiltres

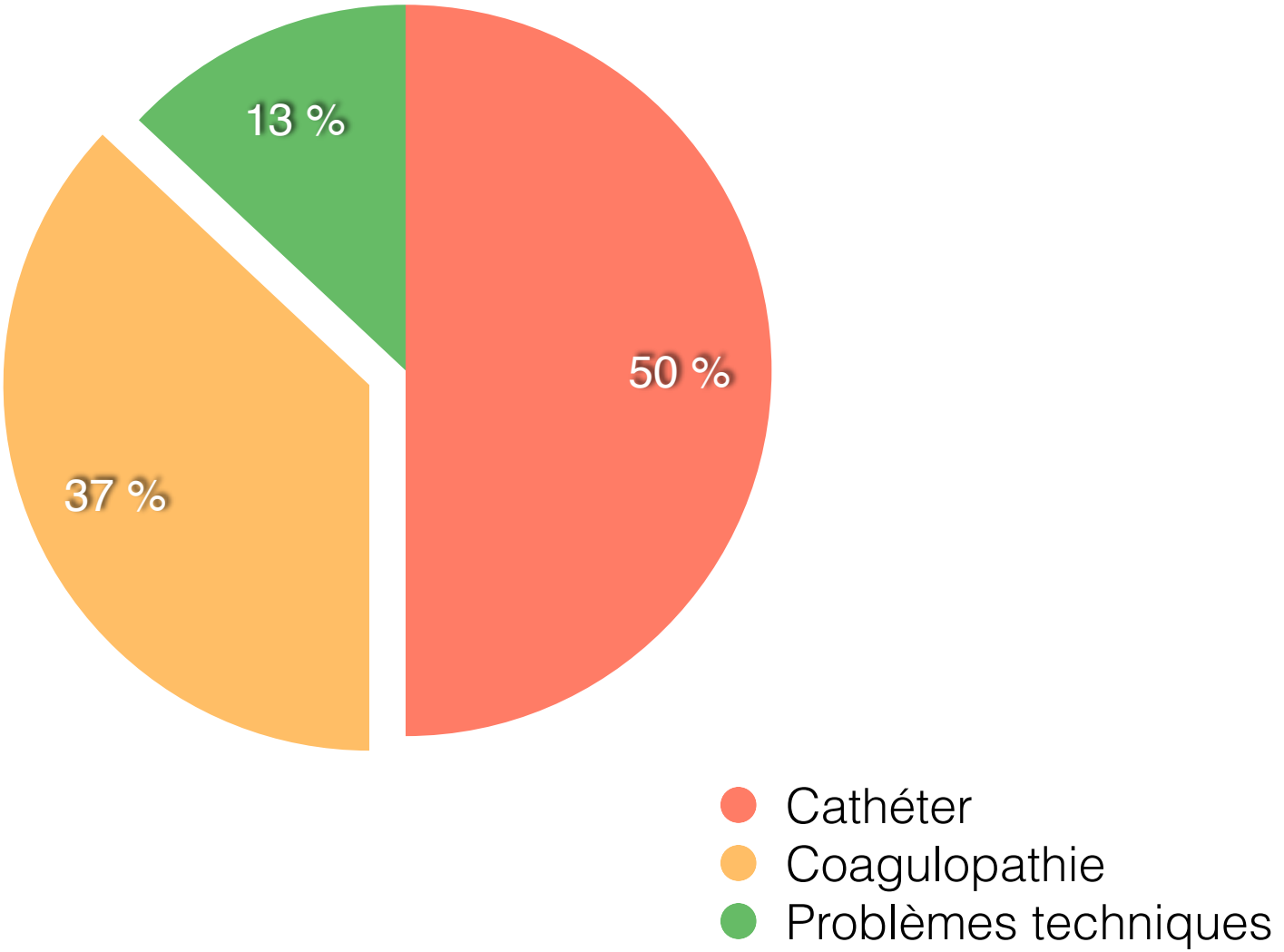
Baisse du risque hémorragique

Survie ?
Soyons modeste…

Coordination médicale/paramédicale +++

Surveillance rigoureuse

Causes des thromboses de Filtres



Citrate, un rôle sur la mortalité ?

1 - Effet anti-inflammatoire du citrate

Baisse de l'activation du complément

Baisse de la dégranulation des neutrophiles

Baisse de l'activation endothéliale induite par l'hémofiltre

Schilder L. *et al.* -. *BMC Nephrol.,* 2014 *; 15 :* 19

2 - L'hypocalcémie locale diminuerait l'inflammation locale in fine systémique…

Berridge M.J., Bootman M.D., Roderick H.L. - Calcium signalling: dynamics, homeostasis and remodelling. *Nat. Rev. Mol. Cell. Biol.,* 2003 *; 4(7) :* 517-529.

3 - Citrate serait un substrat énergétique directement disponible

Amélioration ainsi la balance énergétique

Perfusé (jusqu'à 20 g/j)

Owen O.E., Kalhan S.C., Hanson R.W. - The key role of anaplerosis and cataplerosis for citric acid cycle function. *J. Biol. Chem.,* 2002*; 277(34):* 30409-30412.

4 - S'affranchir de l'héparine c'est s'affranchir de l'inhibition de l'ATIII

Hors l'ATIII qui a un rôle anti-Inflammatoire

Warren B.L. *et al.* - Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA,* 2001 *; 286(15) :* 1869-1878.

Quid des patients en défaillance hépatique aiguë ou chronique ?

Plusieurs études ont montré l'efficacité et la sécurité d'une EER-Ci en situation de dysfonction hépatique

Morath C. et al. *- Nephrol. Dial. Transplant., 2008; 23(1): 421-422*
Balogun R.A. et al. *-. J. Nephrol., 2012 ; 25(1) : 113-119*

Deux critères apparaissent cependant prédictifs d'un risque élevé d'accumulation de citrate :
TP ≤ 26 %
Lactate ≥ 3,4 mM

Schultheiss C. et al. *Crit. Care, 2012; 16(4): R162.*

L'initiation d'une EER-Ci en situation de défaillance hépatique **est possible**
MAIS
pour des **équipes entraînées** qui surveilleront de façon étroite l'évolution du ratio « **CaT/Ca^{2+}** » dès la mise en route du traitement !