FRESENIUS MEDICAL CARE

Principles and Benefits of Citrate Anticoagulation

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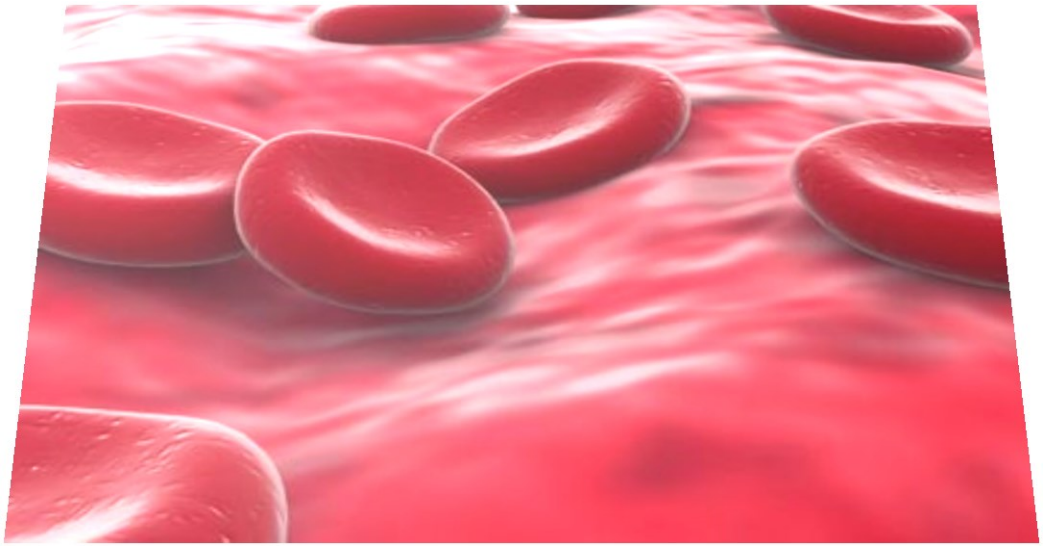
What's new in ICU

The Use of Citrate

- Citrate has been used for many years across a variety of medical applications, for example, it is widely used for the storage of red blood cells [22]
- As early as 1990, clinicians began to see the possibilities for utilising citrate as a regional anticoagulant in CRRT [1]
- Fresenius has extensive experience with regional citrate anticoagulation, with the commercial launch of Ci-Ca® in February 2006 after many years of research and development



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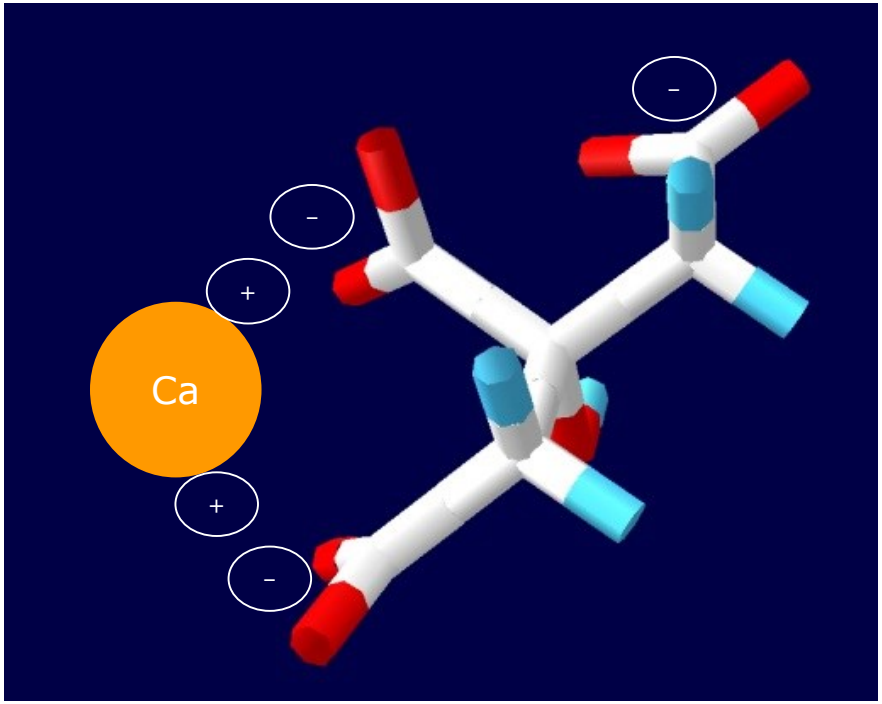
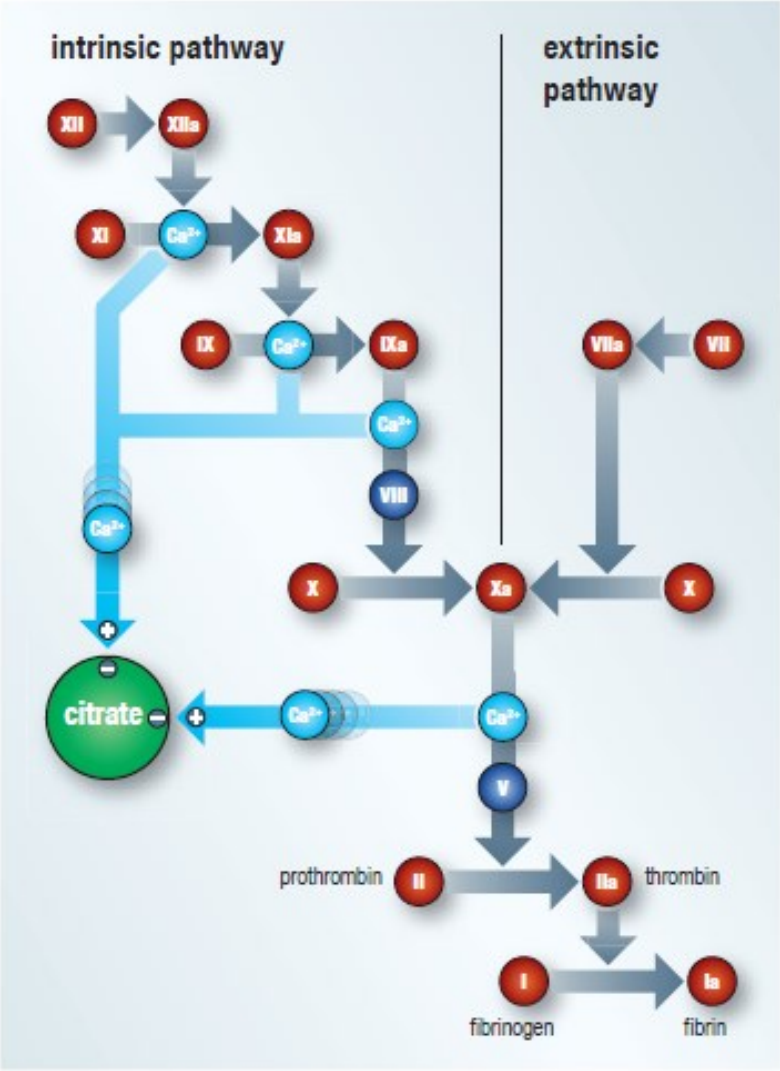
The Citrate-Calcium Complex

Anticoagulation with citrate utilises a process called **'chelation'**

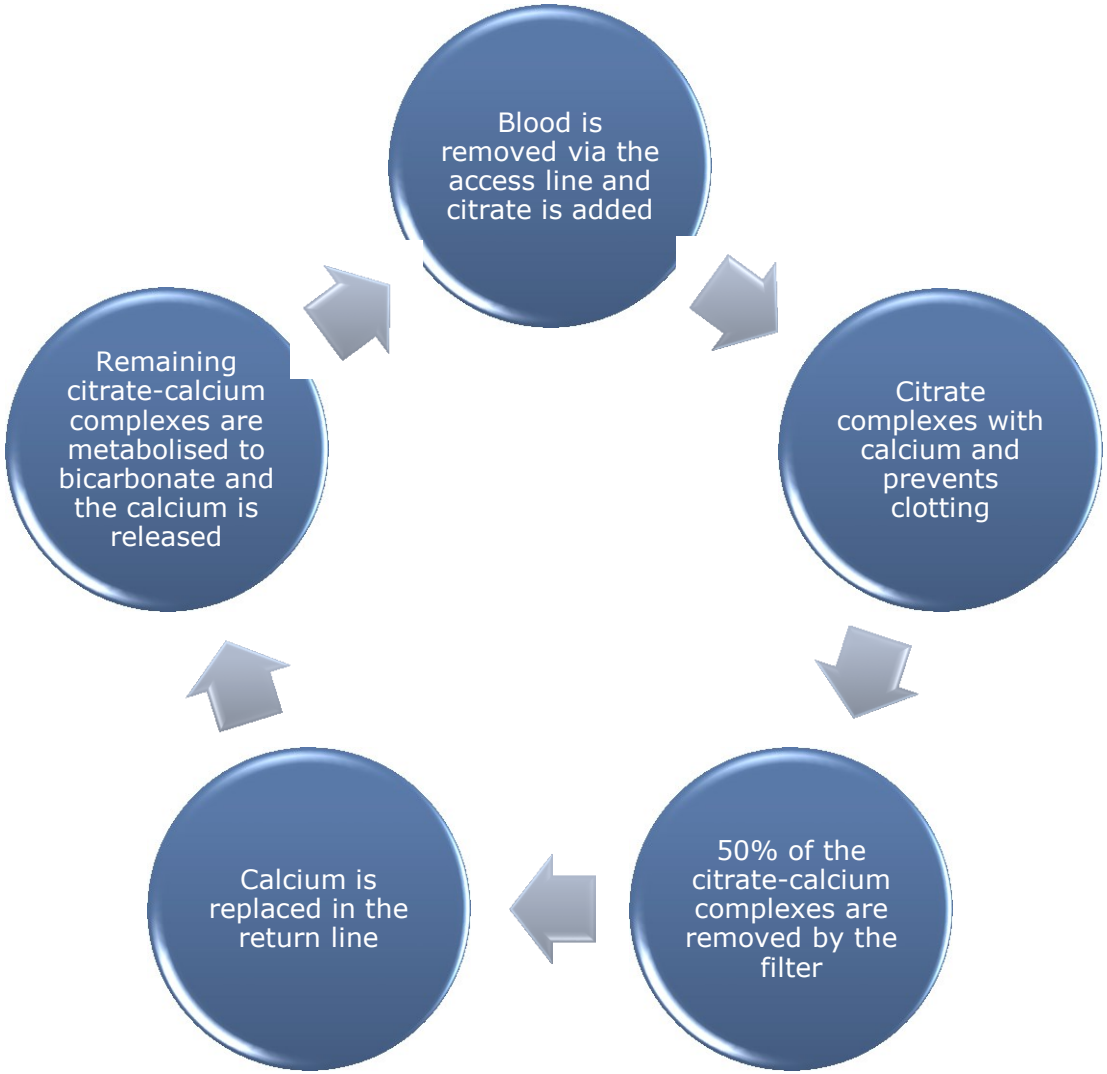


Citrate forms a complex with the Ca^{2+} ions, making them unavailable as a co-factor within the clotting cascade

Calcium and the Clotting Cascade

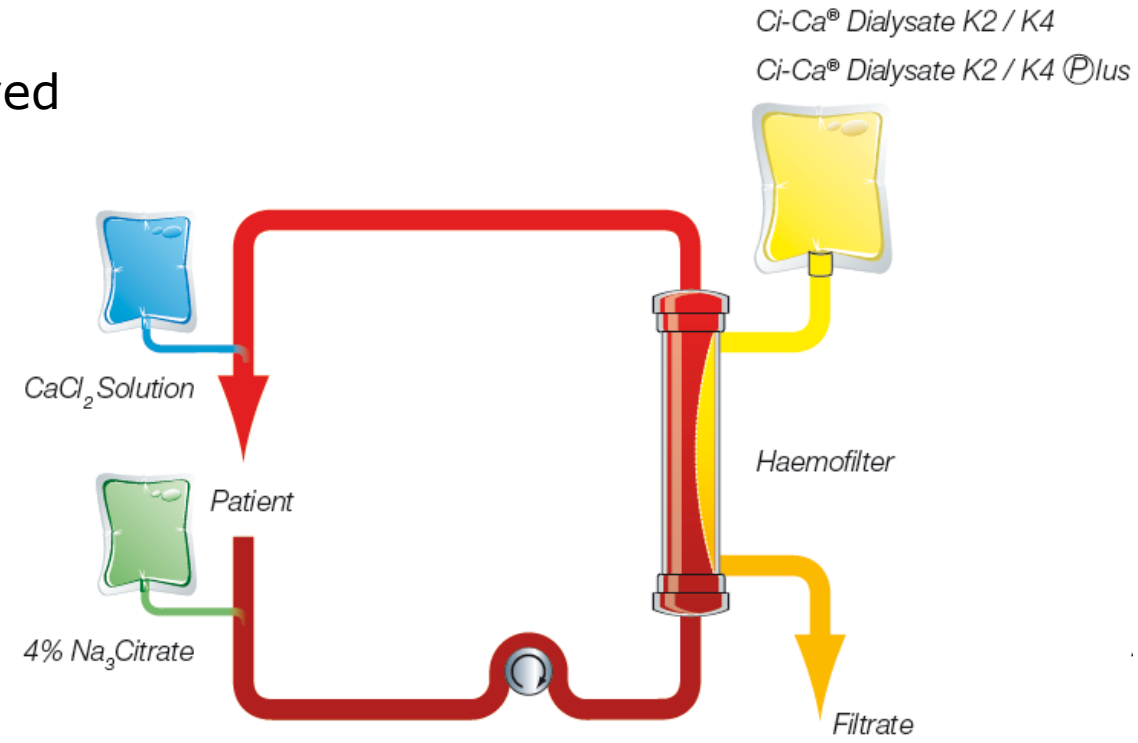


What Are We Doing in Citrate Anticoagulation?



Fresenius Ci-Ca® CVVHD Circuit

- Citrate solution is introduced after the access connection
- Calcium solution is infused just prior to the return connection
- Anticoagulation is achieved in the circuit, but the patient's clotting status is unaffected



Fluids for Ci-Ca® Therapy

Ci-Ca Dialysates
calcium free, 4 types

4% Sodium Citrate
Contains 136 mmol/L citrate

Calcium Chloride
100 mmol/L

Fluids for Citrate Therapy

Name	Language/Art. No. D/GB/F/I/E/P/NL/ DK/S/N/FIN/CZ/ SRB/SK/TR	Language/Art. No. RUS/EST/LT/LV/ GR/H	Na^+ mmol/L	K^+ mmol/L	Ca^{++} mmol/L	Mg^{++} mmol/L	Cl^- mmol/L	HCO_3^- mmol/L	Glucose g/L
Ci-Ca® Dialysate K2	9689201	F00003194	133	2	0	0.75	116.5	20	1
Ci-Ca® Dialysate K4	F00000431	F00003195	133	4	0	0.75	118.5	20	1

Name	Language/Art. No. D/GB/F/I/E/P/NL/ DK/S/N/FIN/CZ/ SRB/SK/TR	Language/Art. No. RUS/EST/LT/LV/ GR/H/SLO	Na^+ mmol/L	K^+ mmol/L	Ca^{++} mmol/L	Mg^{++} mmol/L	Cl^- mmol/L	HCO_3^- mmol/L	inorganic Phosphate mmol/L	Glucose g/L
Ci-Ca® Dialysate K2 *Plus*	F00001624	F00003579	133	2	0	1	115.75	20	1.25	1
Ci-Ca® Dialysate K4 *Plus*	F00001625	F00003580	133	4	0	1	117.75	20	1.25	1

- Sodium and bicarbonate are reduced to compensate for the systemic infusion of sodium citrate
- Calcium-free to minimise the citrate requirement
- Slightly increased magnesium as citrate also chelates with magnesium

Backed by Experts

- KDIGO AKI Guideline [2], 2012: 'We suggest using CRRT, rather than standard intermittent RRT, for hemodynamically unstable patients.'
- Oudemans-van Straaten *et al*. [3], 2011: 'The full advantage of citrate anticoagulation can only be realized, however, if its risks are well controlled by means of a sound protocol, well-trained staff, and the incorporation of a citrate module in the CRRT device.'
- Zhang & Hongying [4], 2012: 'Regional citrate anticoagulation is superior to systemic heparin concerning circuit life and risk of bleeding.'
- Link *et al*. [6], 2012: 'Regional citrate anticoagulation is an effective and safe alternative to heparin.'
- Morgera *et al*. [7], 2009: '[The Ci-Ca CVVHD protocol] enabled an effective treatment of acute renal failure and excellent control of acid-base status as well on the systemic ionized calcium in combination with negligible clotting issues.'

Backed by Experts

- Kalb *et al*. [8], 2013: 'In conclusion, the [Ci-Ca CVVHD] protocol is effective to guarantee very long filter running times enabling the delivery of high dialysis doses.'
- Schultheiß *et al*. [9], 2012: 'The sodium balance was stable during [Ci-Ca] CVVHD treatment, with sodium values being within the reference range […] in 91 % of runs after 72 hours.'
- Schmidt *et al*. [10], 2012: 'The EMiC2 provides superior middle molecule elimination compared to the AV 1000S dialyzer without significant difference in albumin elimination.'
- Raimundo *et al*. [11], 2013: 'In conclusion, [the Ci-Ca CVVHD] protocol with target systemic ionised calcium concentration in the physiologic range maintains stable PTH levels.'
- Rimmele *et al*. [12], 2012: 'The removal of middle molecular weight molecules is higher with SHF-HD [i.e. CVVHD using EMiC2]. Albumin loss was limited in both groups, even with SHF-HD.'

Benefits of Regional Citrate Anticoagulation

- **Delivery of prescribed dialysis dose** – through long and reliable filter running times [8]
- **Continuous uninterrupted treatment** – through minimised clotting events and fewer treatment interruptions [4, 13, 18]
- **Reduced risk of bleeding** - compared to systemic anticoagulation with heparin, allowing treatment even where heparin is contraindicated e.g. HIT [4, 15, 16, 17, 18]
- **Fewer blood transfusions** - related to less bleeding incidents and re-priming of circuits) compared to heparin [15, 16, 17, 18]
- **Nursing time released for patient care** – through reduction in machine interactions when compared with heparin [8, 19]
- **Prolonged lifespan of the extracorporeal circuit reducing circuit usage** – compared to heparin [4, 13, 18]
- **Lower blood flow rates with CVVHD compared to CVVH** - smaller access catheter to be used

Patient Selection

All patients .. but especially

- Patient's pre- or postoperatively where systemic anticoagulation may be contraindicated
- Patients with significant coagulopathy – related to sepsis, large volume transfusion etc.
- Trauma patients with potentially undiagnosed bleeding points
- Patients where surgical wound healing may be compromised by systemic anticoagulation
- Patients with profound cardiovascular instability – for whom high blood flows would be detrimental

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Regional Citrate Anticoagulation in CRRT

Management of Citrate Anticoagulation with multiFiltrate Ci-Ca®



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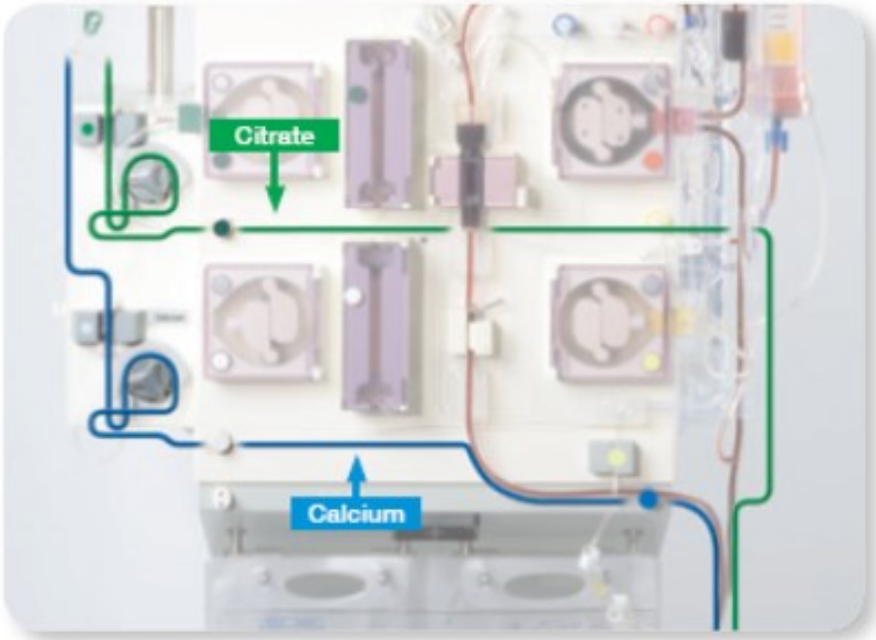
Fully Integrated Citrate & Calcium Pumps to Safeguard

Integrated Citrate & Calcium Lines to Safeguard



Mechanically Different Citrate & Calcium Connectors to Safeguard

Citrate connector

Calcium connector

Colour Coded Connectors to Safeguard

Maintaining Dialysis and Blood Flow Rates

Overall dose ≈ Dialysate flow	Blood flow	Citrate dose	Calcium dose
1600 mL/h	80 mL/min	4.0 mmol/L	1.7 mmol/L
2000 mL/h	100 mL/min	4.0 mmol/L	1.7 mmol/L
2200 mL/h	110 mL/min	4.0 mmol/L	1.7 mmol/L
2600 mL/h	130 mL/min	4.0 mmol/L	1.7 mmol/L
3000 mL/h	150 mL/min	4.0 mmol/L	1.7 mmol/L
3200 mL/h	160 mL/min	4.0 mmol/L	1.7 mmol/L
3600 mL/h	180 mL/min	4.0 mmol/L	1.7 mmol/L

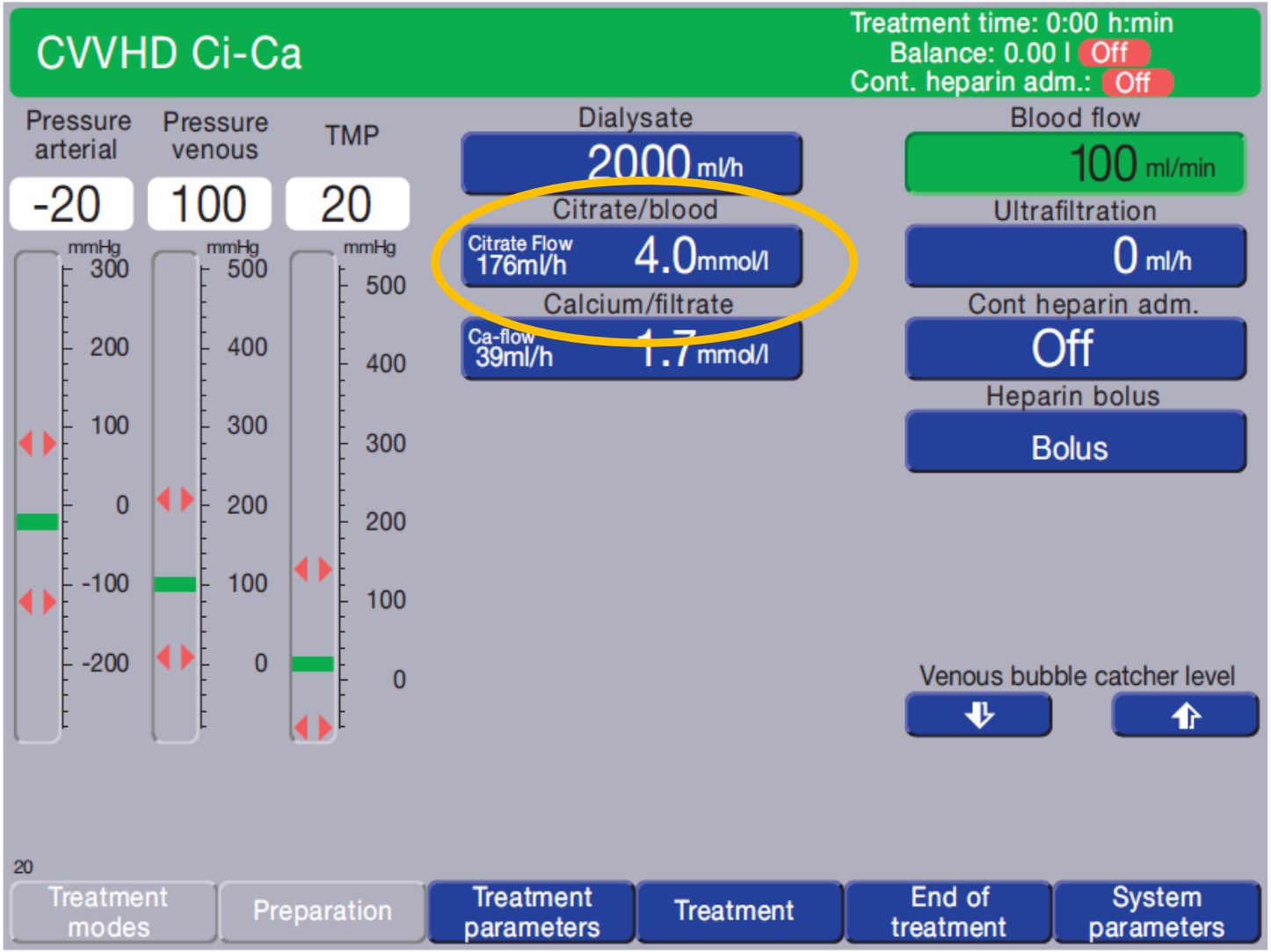
- The dialysate to blood flow ratio should be at a constant numerical ratio of 20:1 (corresponding to a physical flow ratio of 1.3)
- If the patient's acid-base balance is deranged this ratio can be adjusted

Display During Citrate Anticoagulation

Post-Filter Ionised Calcium

Postfilter *ionised* calcium [mmol/L]	Change of the citrate dose (citrate/blood)
>0.40	Increase by 0.2 mmol/L and inform physician
0.35–0.40	Increase by 0.1 mmol/L
0.25–0.34	No change (typical target range)
0.20–0.24	Decrease by 0.1 mmol/L
<0.20	Decrease by 0.2 mmol/L and inform physician

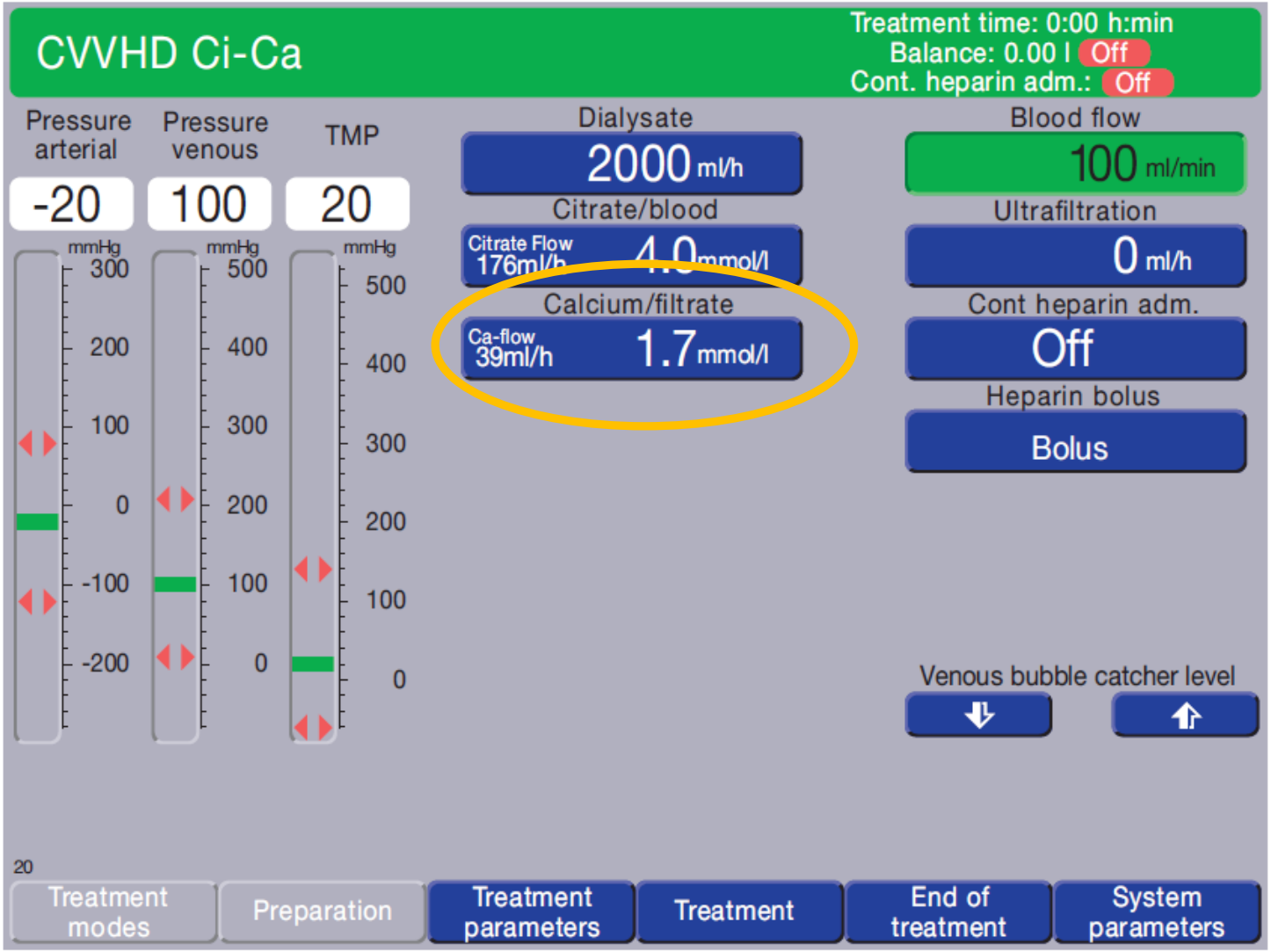
Adjust the Citrate Flow



Systemic Ionised Calcium

Systemic *ionised* calcium [mmol/L]	Change of the calcium dose (calcium/filtrate)
>1.35	Decrease by 0.4 mmol/L and inform physician
1.21–1.35	Decrease by 0.2 mmol/L
1.12–1.20	No change (typical target range)
1.00–1.11	Increase by 0.2 mmol/L
<1.00	Increase by 0.4 mmol/L and inform physician

Adjust the Calcium Flow



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Regional Citrate Anticoagulation in CRRT

Clinical Signs of Poor Citrate Metabolism and the Management Strategy With multiFiltrate Ci-Ca®



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Potential Complications of Citrate Anticoagulation

- Heparin Induced Thrombocytopenia occurs in 3 – 5% of patients receiving standard heparin therapy [20]

- Reduced citrate metabolism occurs in 3.6% of patients [21]

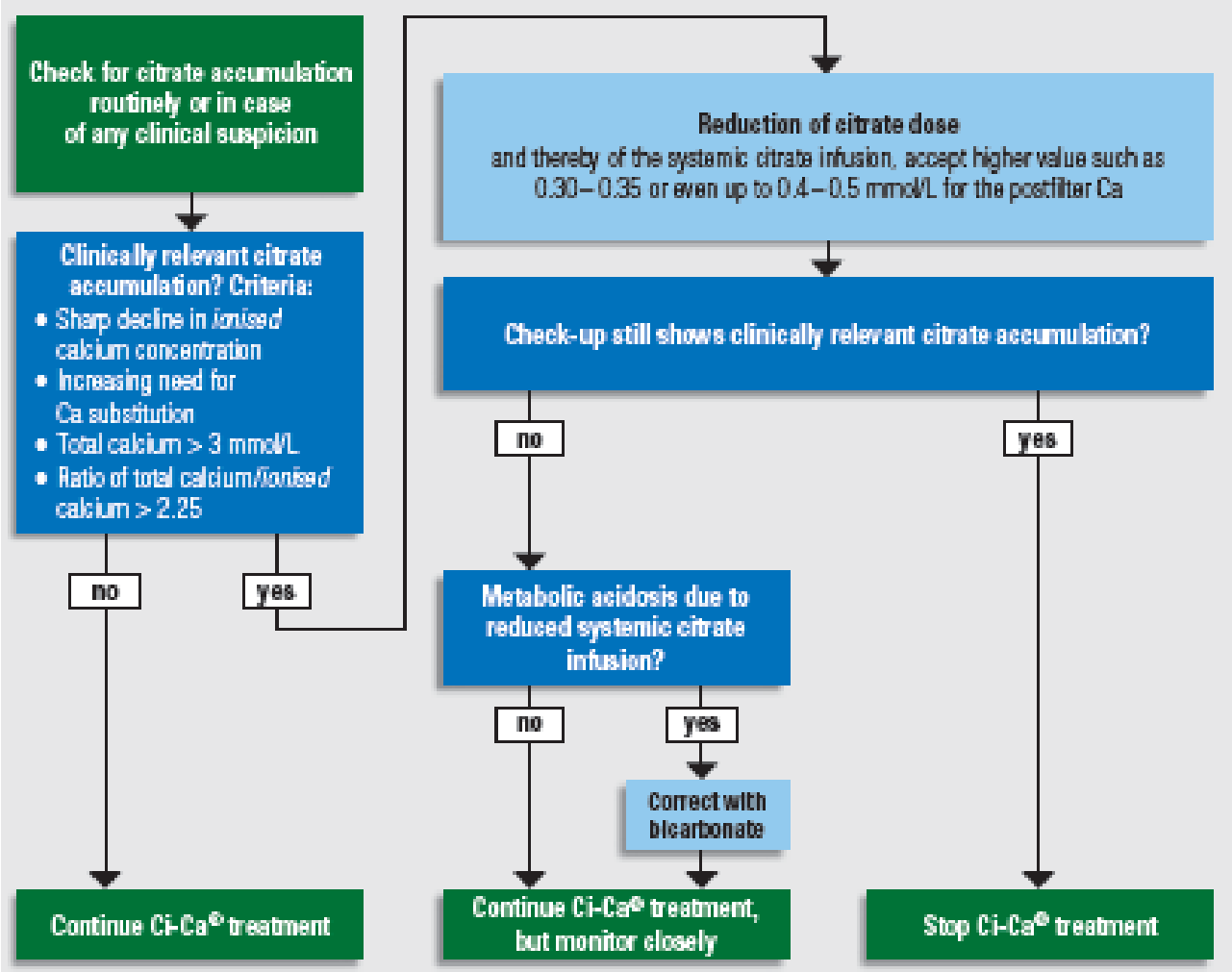
Poor Citrate Metabolism

The clinically diagnosable parameters that indicate impaired citrate metabolism are:

- Decreasing systemic ionised calcium level despite increasing calcium supplementation as per protocol
- Increased systemic total calcium
- A total calcium to ionised calcium ratio above 2.25 (this will be checked by the renal team / consultant)
- Increasing metabolic acidosis

If the patient demonstrates any of the above clinical signs, or the calcium infusion rate is running at greater than 2.1mmol/L, this could be indicative of poor citrate metabolism

Possible Strategy for Poor Citrate Metabolism



Revised Sliding Scale for Poor Citrate Metabolism

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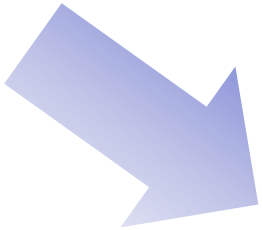

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Regional Citrate Anticoagulation in CRRT

Using Citrate to Manipulate Acid-Base Balance



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Maintaining Dialysis and Blood Flow Rates

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Managing an Acidosis

- First review the patient, treat any underlying condition and ensure dialysate dose is appropriate
- Check that the dialysate and blood flow rates are set according to the protocol

To correct an acidosis *either:*

- Decrease the dialysate flow (a decrease of 20% will increase the serum bicarbonate level by approximately 4mmol/L)

or

- Increase the blood flow rate (an increase of 20% to the blood flow rate will increase the serum bicarbonate level by approximately 4mmol/L)

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Thank You

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