Antikoagulation bei kontinuierlicher Nierenersatztherapie

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Interessenkonflikte

Erklärung zu finanziellen Interessen

- Forschungsförderung
  - Fresenius Medical Care
- Honorare (Beratung; Vorträge)
  - Ablynx; Alexion; Astute; Baxter; Cytosorbents; Fresenius Medical Care, Mitsubishi; Sanofi-Aventis

Erklärung zu nichtfinanziellen Interessen

- Mitgliedschaften und Ämter
  - DGfN, DGIM, DGIIN, DIVI, ERA-EDTA, ASN, ISN, ISPD
  - Stellv. Vorsitzender und Schatzmeister, EuroPD e.V.

Antikoagulation bei kontinuierlicher Nierenersatztherapie

- Kontakt von Blut mit künstlichen Oberflächen führt zur Aktivierung des Gerinnungssystems.
- Alle Blutzellen, einschließlich der Thrombozyten, Erythrozyten und Leukozyten können letztlich in die Thrombusbildung einbezogen werden.
- Das Ziel einer Antikoagulation bei der Nierenersatztherapie ist die Reduktion der Gerinnungsaktivierung (“Clotting”) im Extrakorporalsystem und damit die Vermeidung von
  - Blutverlust des Patienten
  - Ungewollten Therapieunterbrechungen (mit der Folge einer substantiellen Reduktion der Behandlungszeit und -effektivität)
- Hauptrisiko: Blutungskomplikationen

Kontinuierlicher Nierenersatztherapie
Antikoagulationsstrategien

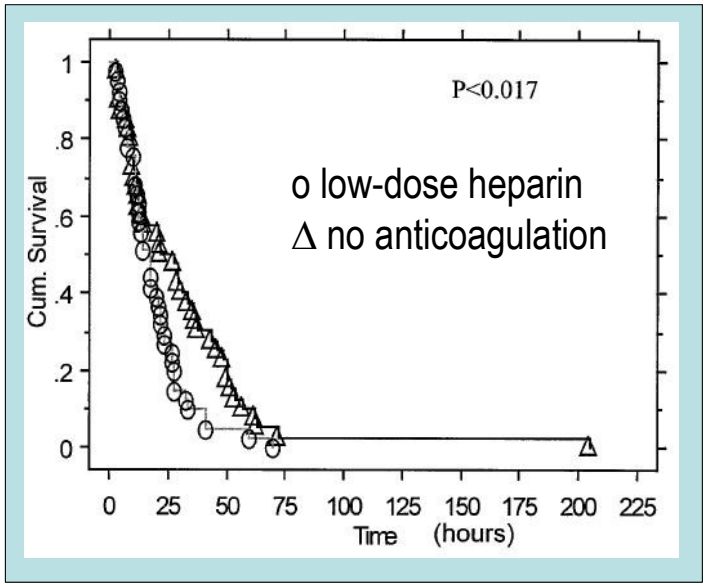
- Ohne Antikoagulation

Continuous veno-venous hemofiltration without anticoagulation in high-risk patients

- 40 CVVH circuits in 12 patients with high risk of bleeding run without anti-coagulation or compared to 40 control CVVH circuits in 12 patients with low-dose pre-filter heparin (mean 716 IU), 2 L/h or filtration rate.

- Mean circuit life without anti-coagulation 32 h (95% CI 20-44.4)

- 43% of filters lasted >30h

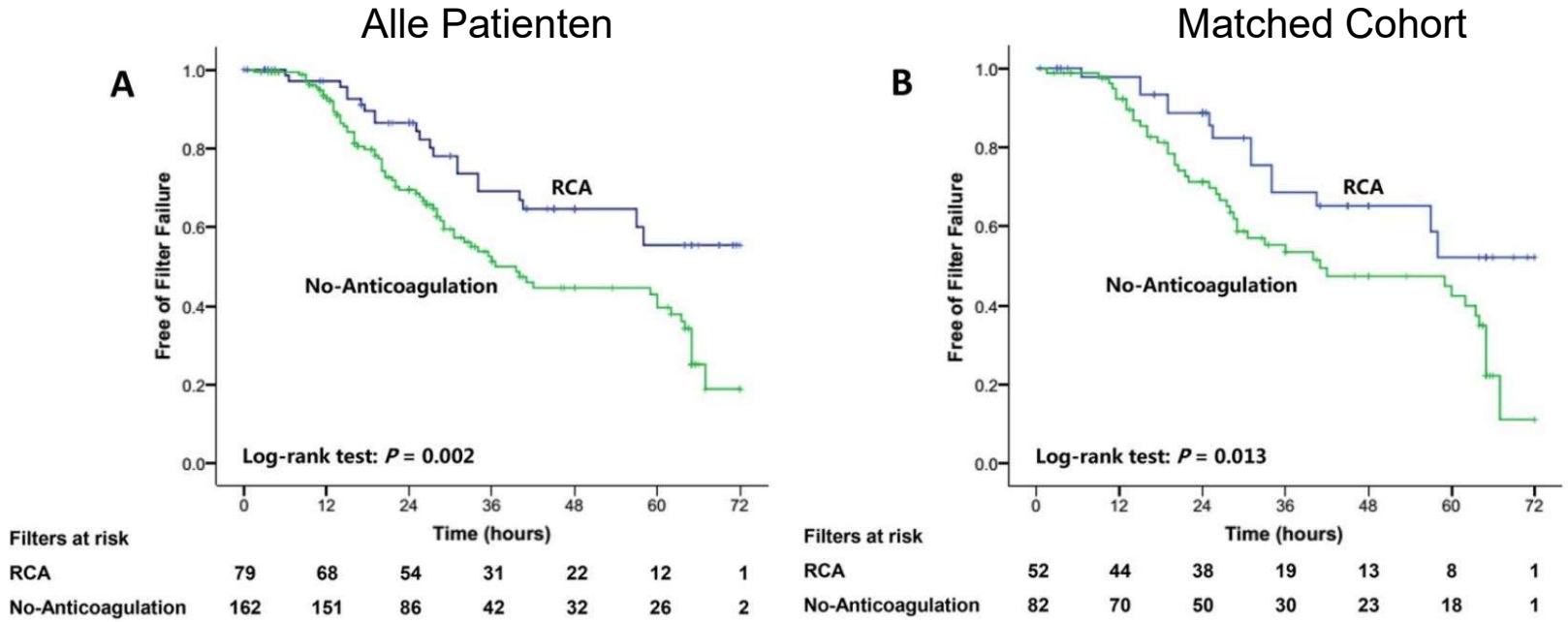


Tan HK *Int. Care Med*. 2000; 26: 1652-7

Regional citrate anticoagulation versus no-anticoagulation for continuous venovenous hemofiltration in patients with liver failure and increased bleeding risk: A retrospective case-control study

Yan Yu[☯], Ming Bai*[☯], Feng Ma[☯], Wei Zhang, Yangping Li, Lijuan Zhao, Li Li, Meilan Zhou, Lu Li, Shiren Sun*

Department of Nephrology, Xijing Hospital, The Fourth Military Medical University, Shaanxi, China



PLOS one 2020; 15(5): e0232516

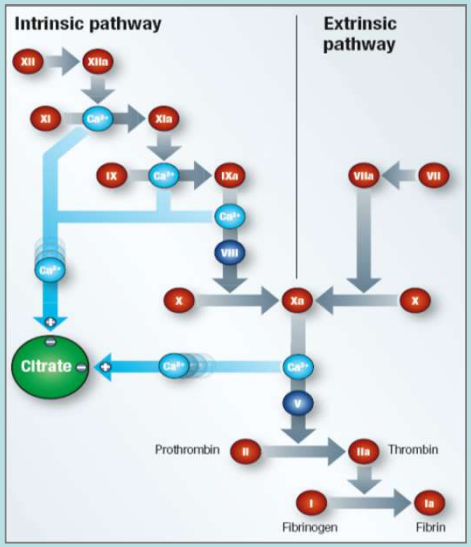
Kontinuierlicher Nierenersatztherapie
Antikoagulationsstrategien

- Ohne Antikoagulation
- Unfraktioniertes Heparin
- Niedermolekulares Heparin
- Prostacyclin
- Direkte Thrombininhibitoren
  - Bivalirudin
  - Argatroban

Kontinuierlicher Nierenersatztherapie
Antikoagulationsstrategien

- Ohne Antikoagulation
- Unfraktioniertes Heparin
- Niedermolekulares Heparin
- Prostacyclin
- Direkte Thrombininhibitoren
  - Bivalirudin
  - Argatroban
- **Regionale Antikoagulation**
  - Heparin / Protamin
  - **Zitrat**

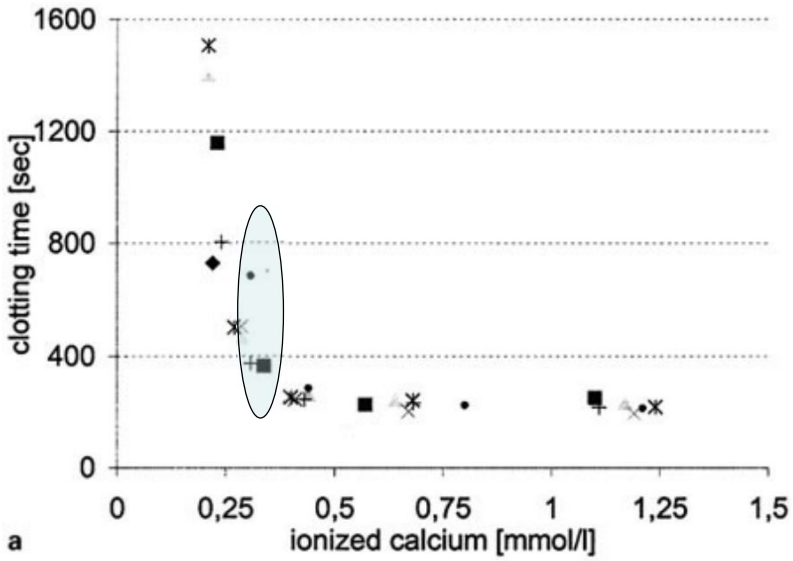
- Zitrat bindet Kalziumionen
- Ionisiertes Ca^{++} ist bei mehreren Schritten der plasmatischen Gerinnungskaskade notwendig
- Die plasmatische Gerinnung wird bei iCa^{++} ~0.3 mval/L gehemmt



Effekt von Zitrat auf ionisiertes Kalzium und Blutgerinnung

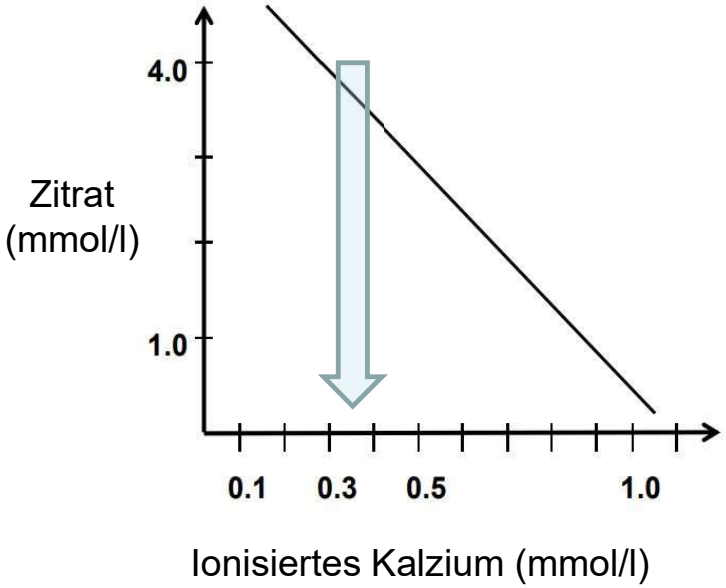
Citrate Anticoagulation for Extracorporeal Circuits: Effects on Whole Blood Coagulation Activation and Clot Formation

A. Calatzis[a] M. Toepfer[b] W. Schramm[a] M. Spannagl[a] H. Schiffl[b]

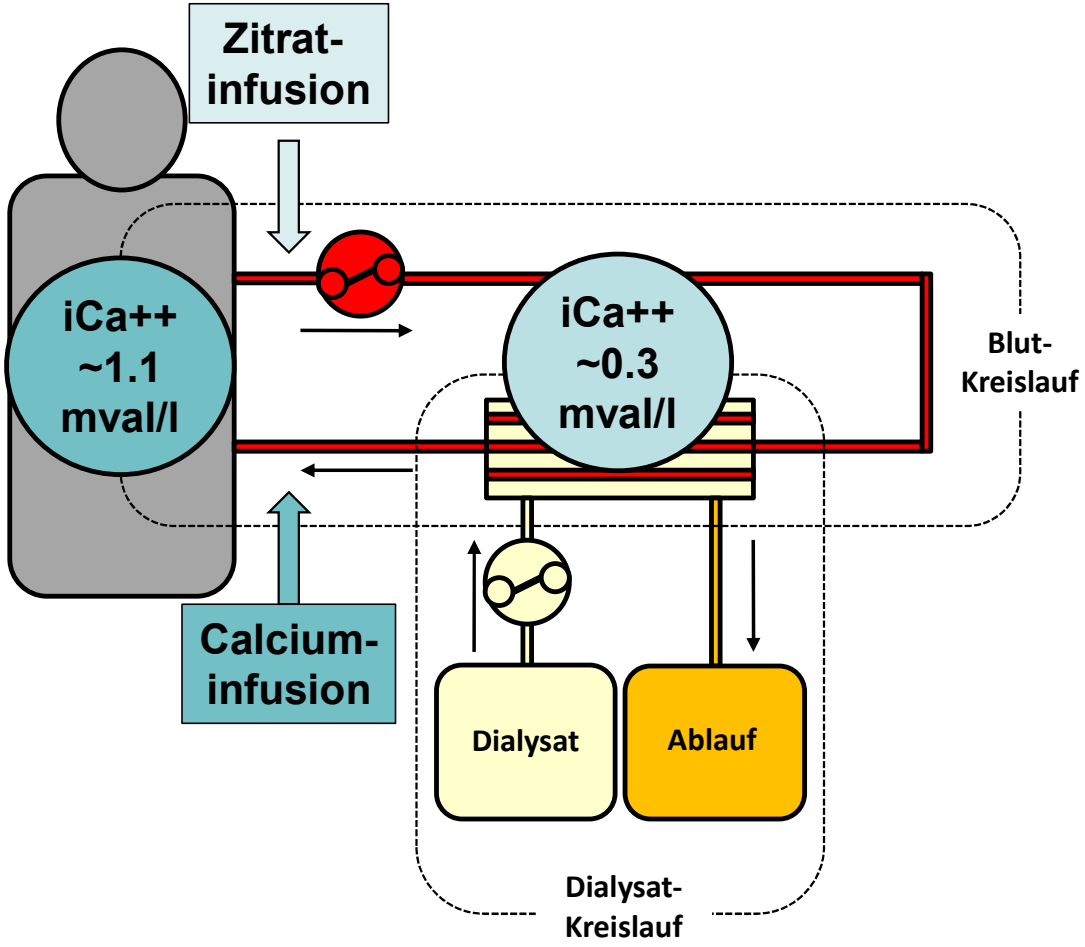


Nephron 2001;89:233–236

Lineare Beziehung zwischen Zitrat und ionisiertem Kalzium im Plasma



Regionale Zitratantikoagulation



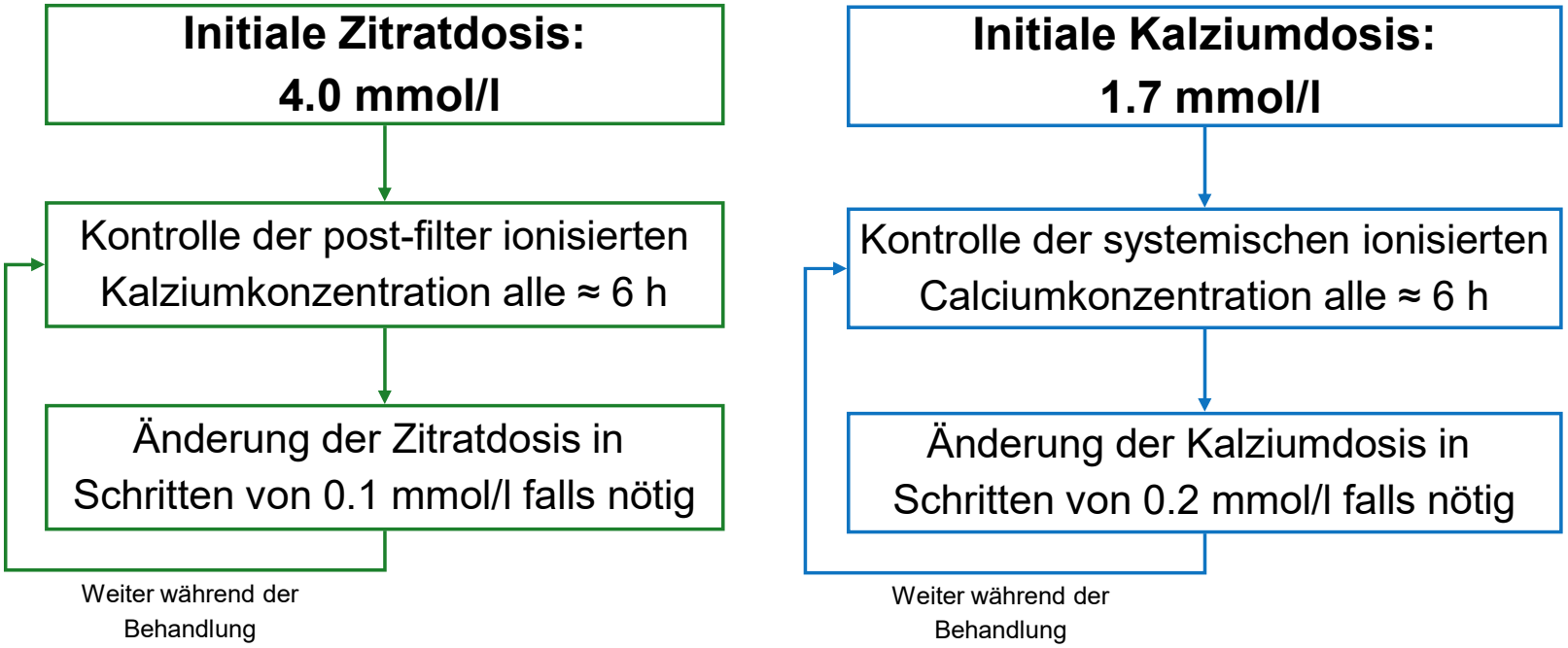
Regionale Zitratantikoagulation

- Ein Mol Zitrat wird zu 3 Mol Bicarbonat konvertiert
- Ein Mol Trinatriumzitrat ergibt 3 Mol Natrium
  - Angepaßtes Dialysat: reduziertes Natrium und Bikarbonat, Kalziumfrei

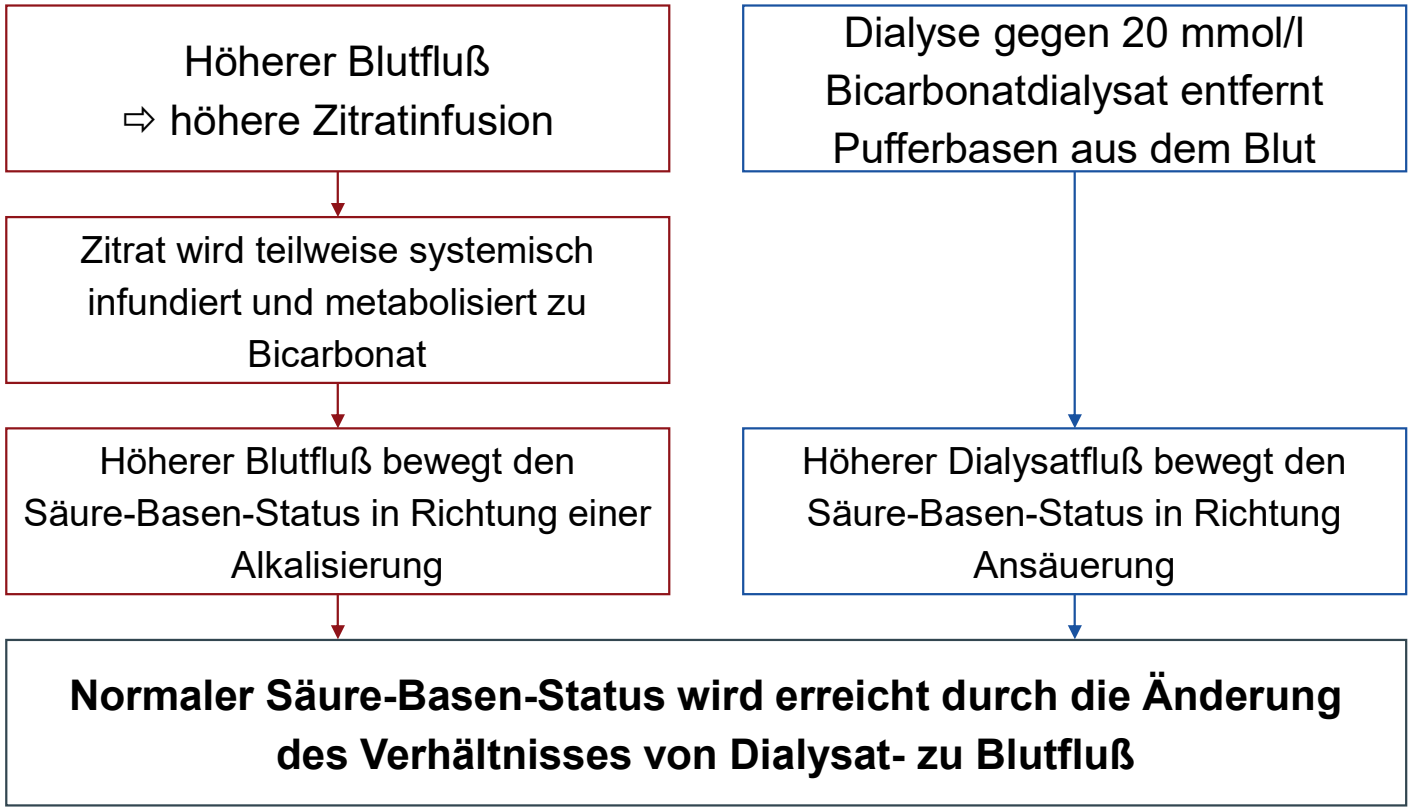
- Potentielle Komplikationen:
  - Hypokalzämie, Hypomagnesiämie
  - Metabolische Alkalose
  - Hypernatriämie

Na^{+}	133	mmol/l
K^{+}	2	mmol/l
Mg^{++}	0.75	mmol/l
Ca^{++}	0	mmol/l
HCO_3^{-}	20	mmol/l
Cl	116.5	mmol/l
Glucose	1	g/l

Anpassung von Zitrat- und Kalziumdosis



Management des Säure-Basen-Status



Regional citrate versus heparin anticoagulation for continuous renal replacement therapy in critically ill patients: a meta-analysis with trial sequential analysis of randomized controlled trials

Chao Liu[†], Zhi Mao[†], Hongjun Kang, Jie Hu and Feihu Zhou[*]

- Systematischer Review und Metaanalyse von 14 RCTs / 1.133 Patienten zum Vergleich von regionaler Zitratantikoagulation vs. Heparin bei CRRT
- Vergleichbare Überlebensraten, mit Zitrat weniger Blutungskomplikationen und längere Filterlaufzeiten

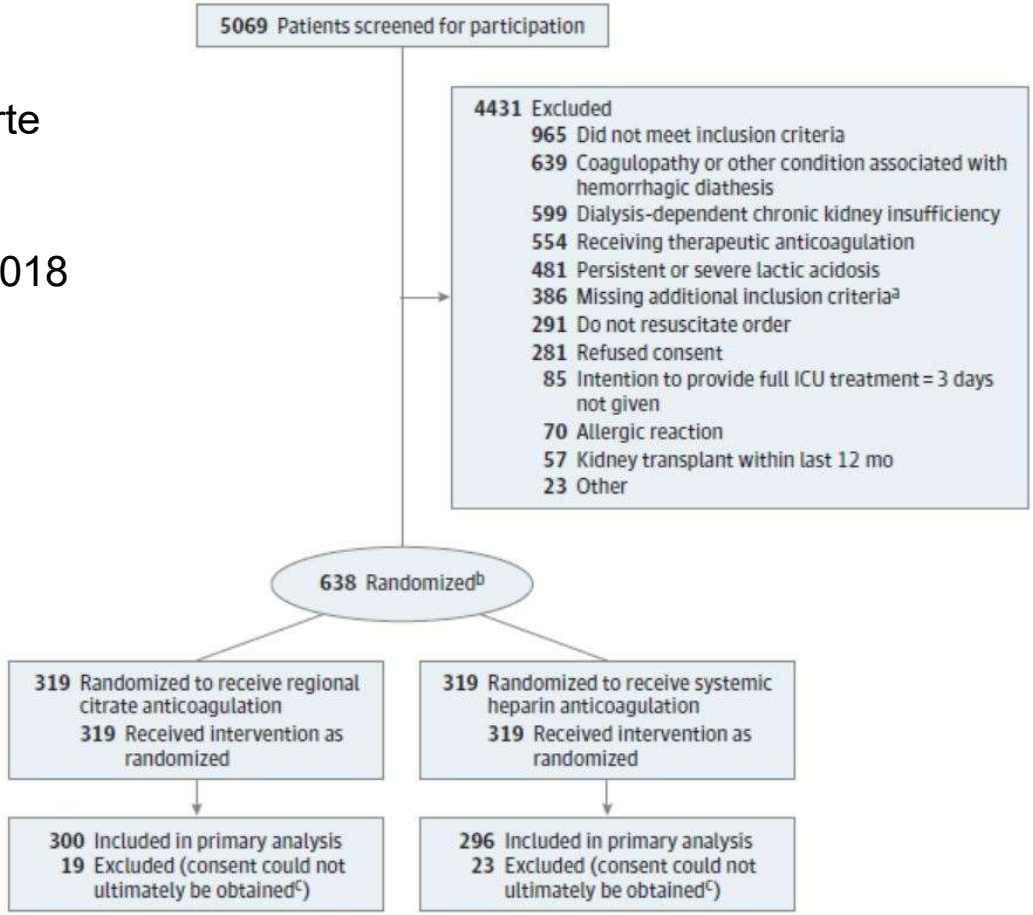
Liu C et al, *Crit Care* 2016; 20: 144

Effect of Regional Citrate Anticoagulation vs Systemic Heparin Anticoagulation During Continuous Kidney Replacement Therapy on Dialysis Filter Life Span and Mortality Among Critically Ill Patients With Acute Kidney Injury

A Randomized Clinical Trial

Prospektive randomisierte Multicenterstudie

28 Zentren in D, 2016-2018



638 Patients randomisiert, 596 (93.4%) ausgewertet

Ursprünglich geplant: 1450

A. Jörres 12-2020

Zarbock et al, *JAMA* 2020 (Oct 23): 144

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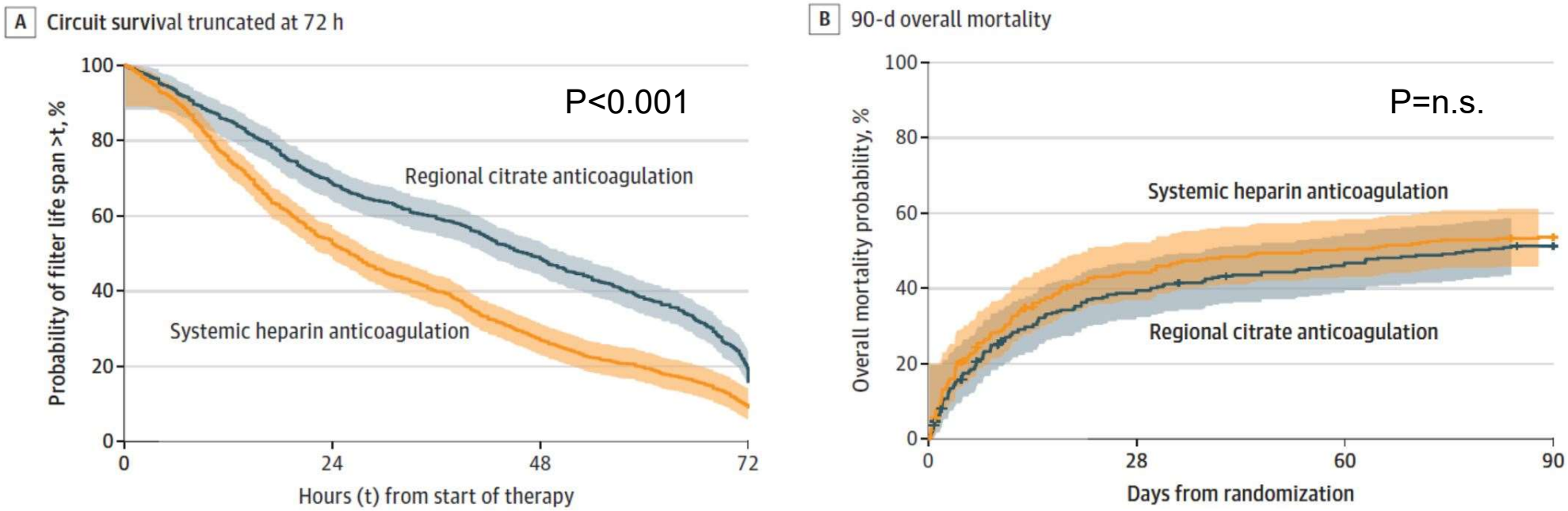

A. Jörres 12-2020

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Effect of Regional Citrate Anticoagulation vs Systemic Heparin Anticoagulation During Continuous Kidney Replacement Therapy on Dialysis Filter Life Span and Mortality Among Critically Ill Patients With Acute Kidney Injury

A Randomized Clinical Trial

	Regional citrate anticoagulation (n = 300)	Systemic heparin anticoagulation (n = 296)	Absolute difference (95% CI)	OR or HR (95% CI)	*P* value
Primary outcome					
Filter life span, h					
Mean (SD)	44.9 (26.9)	33.3 (25.1)	11.2 (8.2 to 14.3) [adjusted][a]		<.001
Median (IQR)	46.5 (18.8-70.3)	26.0 (12.0-50.6)	15.4 (11.3 to 19.5)[b]		
90-d all-cause mortality					
Unadjusted, No. (%)	150 (51.2)[c]	156 (53.6)[c]	−2.4 (−10.5 to 5.8)[d]	HR, 0.91 (0.72 to 1.13)	.38
Adjusted[a]			−6.1 (−12.6 to 0.4)[d,e]	HR, 0.79 (0.63 to 1.004)	.054
Secondary outcomes					
Dialysis- and kidney-associated outcomes, median (IQR)					
Total filter downtime, min	120 (0-720)	300 (0-930)	−30 (−120 to 0)[b]		.011
Duration of CKRT, d[f]	9.6 (3.9-57.0)	8.4 (3.6-45.0)	1.2 (−5.8 to 4.7)	HR, 0.89 (0.72 to 1.09)	.24
Bleeding and transfusion, No./ total No. patients who started CKRT (%)					
Bleeding[g]	15/293 (5.1)	49/290 (16.9)	−11.8 (−16.8 to 6.8)[d]	OR, 0.27 (0.15 to 0.49)	<.001
Received RBC transfusion	197/293 (67.2)	184/290 (63.4)	3.8 (−3.9 to 11.5)[d]	OR, 1.18 (0.84 to 1.66)	.34
RBC transfusion volume, median (IQR), mL	500 (0-1085) [n = 293]	560 (0-1200) [n = 290]	0 (0 to 0)[b]		.85
Infection, No. (%)					
New culture-proven infection since start of dialysis	204 (68.0)	164 (55.4)	12.6 (4.9 to 20.3)[d]	OR, 1.71 (1.23 to 2.39)	.002

A. Jörres 12-2020

Zarbock et al, *JAMA* 2020 (Oct 23): 144

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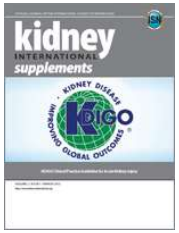
AKI Guideline 5.3.



2. For patients **without an increased bleeding risk or impaired coagulation** and not already receiving effective systemic anticoagulation, we suggest the following:

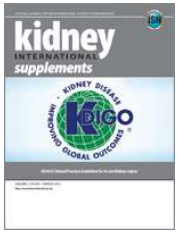
    1. For anticoagulation in intermittent RRT, we recommend using either unfractionated or low-molecular weight heparin, rather than other anticoagulants. (1C)

    2. For anticoagulation in CRRT, we suggest using regional citrate anticoagulation rather than heparin in patients who do not have contraindications for citrate. (2B)

    3. For anticoagulation during CRRT in patients who have contraindications for citrate, we suggest using either unfractionated or low-molecular-weight heparin, rather than other anticoagulants. (2C)

Kidney Int. Suppl. Volume 2, No 1 (March 2012)

AKI Guideline 5.3.



3. For patients **with an increased bleeding risk** who are not receiving anticoagulation, we suggest the following for anticoagulation during RRT:

   3. We suggest using regional citrate anticoagulation, rather than no anticoagulation, during CRRT in a patient without contraindications for citrate. (2C)
   4. We suggest avoiding regional heparinization during CRRT in a patient with increased risk of bleeding. (2C)

4. In a patient with HIT who does not have severe liver failure, we suggest using argatroban rather than other thrombin or Factor Xa inhibitors during RRT. (2C)

Kidney Int. Suppl. Volume 2, No 1 (March 2012)

Kontraindikationen für Zitrat ?

- Zitratakkumulation kann bei Patienten mir reduzierter Metabolisierung auftreten
  - Persistierendem Schock mit reduzierter Muskelperfusion

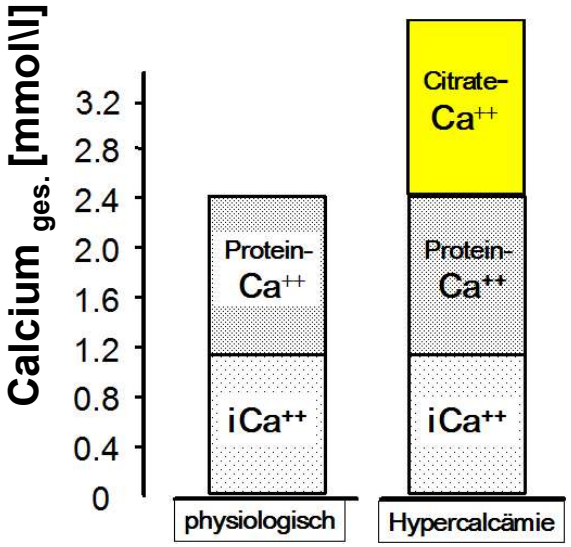
Cave: Patienten mit erhöhtem Serumlaktat !

Kontraindikationen für Zitrat ?

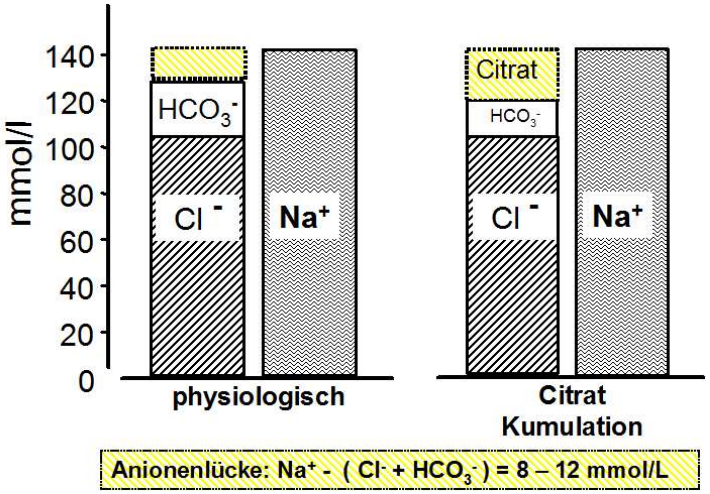
- Zitratakkumulation kann bei Patienten mir reduzierter Metabolisierung auftreten
  - Persistierendem Schock mit reduzierter Muskelperfusion
  - Schwerem Leberversagen

Mögliche Zeichen der eingeschränkten Zitratmetabolisierung bei Leberinsuffizienz

Kumulation von Kalziumzitrat-Komplexen



Anion Gap Azidose



H. Peters, in: ANV auf der Intensivstation
A Jörres (Hrsg.) Dt. Ärzteverlag 2009

Safety and efficacy of regional citrate anticoagulation in continuous venovenous hemodialysis in the presence of liver failure: the Liver Citrate Anticoagulation Threshold (L-CAT) observational study

- 133 consecutive adult ICU patients prospectively observed for 72 hours of citrate-CVVHD.
- Patients were stratified into 3 groups of liver function impairment according to their serum bilirubin (mg/dl)
  - normal: ≤2, *n* = 48
  - mild: >2 to ≤7, *n* = 43
  - severe: >7, *n* = 42
- End-points for safety were: severe acidosis or alkalosis (pH ≤7.2; ≥7.55) and severe hypocalcemia or hypercalcemia (≤0.9; ≥1.5 mmol/l) of any cause.
- End-point for efficacy was the filter lifetime.

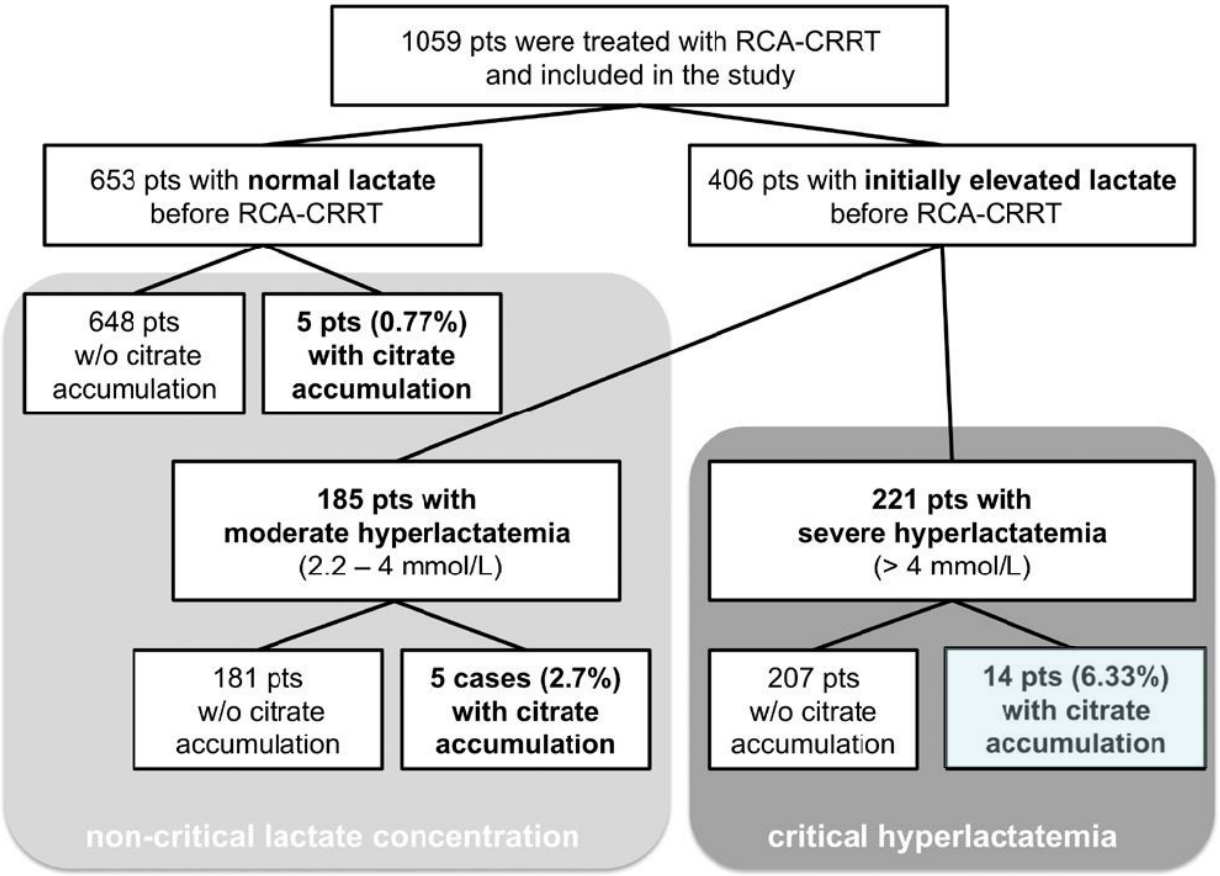
Slowinski T. et al, *Crit. Care* 2015, 19: 349

Safety and efficacy of regional citrate anticoagulation in continuous venovenous hemodialysis in the presence of liver failure: the Liver Citrate Anticoagulation Threshold (L-CAT) observational study

- The frequency of safety end-points of any cause did not differ between the three patient strata:
  - severe alkalosis (normal: 2%, mild: 0%, severe: 5%; $P = 0.41$);
  - severe acidosis (normal: 13%, mild: 16%, severe: 14%; $P = 0.95$);
  - severe hypocalcemia (normal: 8%, mild: 14%, severe: 12%; $P = 0.57$);
  - severe hypercalcemia (0% in all strata).
- Only in 3/133 patients an increased ratio of total to ionized calcium (≥2.5) was detected (2%).
- Overall filter lifetime was 49% after 72 hours; however, after censoring for discontinuation due to non-clotting causes (for example, renal recovery, death) 96% of all filters were running after 72 hours.

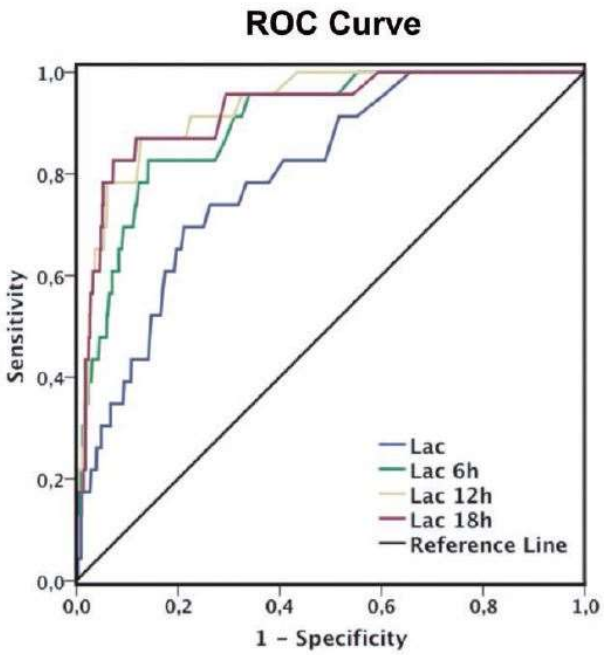
Slowinski T. et al, *Crit. Care* 2015, 19: 349

Hyperlactatemia, Lactate Kinetics and Prediction of Citrate Accumulation in Critically Ill Patients Undergoing Continuous Renal Replacement Therapy With Regional Citrate Anticoagulation



Khadzhynov D. et al, *Crit Care Med* 2017; 45:e941–e946

Hyperlactatemia, Lactate Kinetics and Prediction of Citrate Accumulation in Critically Ill Patients Undergoing Continuous Renal Replacement Therapy With Regional Citrate Anticoagulation



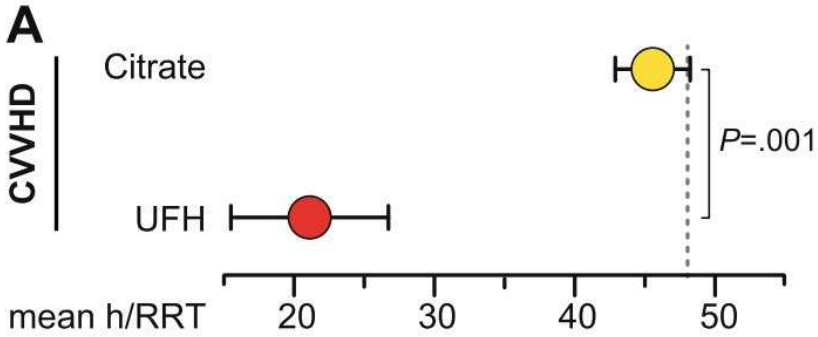
	AUC	95% CI	p - Value
Lac	0.789	0.714 - 0.864	<0.001
Lac 6h	0,898	0,842 - 0,953	<0.001
Lac 12h	0,930	0,886 - 0,974	<0.001
Lac 18h	0,925	0,870 - 0,978	<0.001

Variable	Threshlod Values (mmol/L)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive Predictive Value (%)	Negative Predictive Value (%)
Lactate before regional citrate anticoagulation	2.29	79.2 (57.9–92.9)	66.7 (63.7– 69.5)	5.2	99.3
Lactate at 6 hr	4.16	83.3 (62.6–95.3)	85.9 (83.7–88.0)	12.1	99.6
Lactate at 12 hr	3.94	87.5 (67.6–97.3)	88.4 (86.3–90.3)	14.9	99.7
Lactate at 18 hr	3.72	83.3 (62.6–95.2)	89.9 (87.9–91.7)	16.0	99.6

Khadzhynov D. et al, *Crit Care Med* 2017; 45:e941–e946

Comparison of different anticoagulation strategies for renal replacement therapy in critically ill patients with COVID-19: a cohort study

	CVVHD	
	UFH	Citrate
No. of RRT treatments	13	92
No. of patients	7	18
Total RRT duration, h	274.7	4192.6
Mean duration per RRT, h (SD)	21.1 (20.2)	45.6 (25.6)
Early RRT termination, %	92	55
Therapeutic range, %	81	98



Arnold F . et al, *BMC Nephrol* 2020; 21: 486

Zusammenfassung

- Die regionale Zitratantikoagulation hat sich zunehmend zum Standard für die kontinuierliche Nierenersatztherapie entwickelt.
- Sie ermöglicht signifikant längere Filterstandzeiten als die Heparinantikoagulation und geht mit weniger Blutungskomplikationen einher.
- Auch bei Patienten mit schwerer COVID-19 Infektion konnten längere Filterstandzeiten als mit Heparin erzielt werden.
- Insbesondere bei Patienten mit Schock und steigendem Serumlaktat kann es zu einer Zitratakkumulation kommen.
- Dieses Risiko scheint eher gering zu sein bei Patienten mit Leberfunktionsstörungen.
- Bei Risikopatienten sollten regelmäßige Kontrollen erfolgen, um indirekte Hinweise auf eine Zitratakkumulation zu detektieren:
  - Abfall des systemischen iCa <1.1 mmol/L bei gleichzeitigem Anstieg des Gesamtkalziums
  - Anstieg des Quotienten aus Gesamtkalzium und iCa (> 2.25)
  - eine anderweitig unerklärte metabolische Azidose (pH < 7.2 und/oder base excess < –5 mmol/L)
  - vergrößertes Anion gap (> 12 mmol/L).