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EDITORIAL

Citrate anticoagulation for continuous renal replacement therapy

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Regional citrate anticoagulation (RCA) is preferred over unfractionated heparin in continuous renal replacement therapy (CRRT) due to benefits like extended filter lifespan (FLS) and reduced bleeding complications [1–4]. RCA works by forming complexes with ionized calcium (iCa2+), inhibiting calcium-dependent coagulation. Citrate is administered pre-filter, and calcium is replenished post-filter. Despite advantages, RCA can cause metabolic side effects like alkalosis, acidosis, hypotension, electrolyte imbalances like hypomagnesemia, hypernatremia, and severe hypocalcemia which can lead to cardiac arrest [1–4].

Optimal anticoagulation requires careful adjustment of citrate infusion based on blood flow rate (BFR). About 50% of calcium-citrate complexes are removed during CRRT, necessitating post-filter calcium infusion [1–4]. Citrate delivery rates typically range from 17 to 45 mmol/h [1].

Citrate accumulation, a significant adverse effect, can occur due to impaired metabolism, leading to acidosis and hypocalcemia, particularly in liver failure, shock, or metformin intoxications [5, 6]. In addition, other intoxications like paracetamol, propofol, linezolid, and tenofovir can cause mitochondrial dysfunction and temporarily decrease citrate metabolism [5, 6]. Hypocalcemia decreases cardiac output and causes hypotension. A total-to-ionized calcium ratio (total Ca/iCa) exceeding 2.3 indicates calcium-citrate complexes accumulation [5, 6]. Indeed, impaired metabolism increases total Ca while reducing systemic iCa due to calcium retention in calcium-citrate complexes. However, diagnostic reliability of total Ca/iCa is debated, with lactate kinetics suggested for improved accuracy [5, 6].

Uncontrolled citrate accumulation requires RCA discontinuation. Metabolic alkalosis from citrate overload needs CRRT adaptation, such as decreasing BFR or citrate concentrations or increasing dialysate or ultrafiltration flow rates [5]. Understanding these metabolic disturbances highlights the complexity of citrate anticoagulation and supports our hypothesis.

Mechanisms contributing to metabolic disturbances

RCA metabolic disturbances related involve mitochondria-rich organs like the liver, muscles, and kidneys, which host the oxygen-dependent citric acid cycle [5, 6]. These disturbances stem from liver injury, shock reducing oxygen perfusion, and metformin intoxication inhibiting the citric acid cycle and oxidative phosphorylation [5–7]. In metformin-associated lactic acidosis (MALA), CRRT is recommended for critically ill patients, especially with acute kidney injury (AKI), with RCA as the first-line anticoagulation strategy [5, 6]. However, metformin's inhibition of citrate metabolism risks citrate accumulation [5, 6]. Given these challenges, we explore strategies to adapt citrate anticoagulation.

Strategies for adapting citrate anticoagulation

In MALA, CRRT can continue with the same citrate dose if metformin is efficiently removed [5, 6]. For liver failure patients, a calcium ratio above 2.3 and increasing lactate contraindicates RCA; stable lactate levels allow cautious RCA use with a higher iCa target of 0.30–0.40 mmol/L, maintaining FLS while reducing citrate exposure [7]. Shock patients with a high calcium ratio and increasing lactate should lead to RCA discontinuation, but stable lactate levels can follow the liver failure approach [5, 6].

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Increasing oxygen perfusion to muscles is vital in managing shock [5, 6].

Hypothesis of an inducible alternative metabolic pathway for citrate metabolization

Clinical observations suggest that liver failure severity does not predict citrate metabolism. We hypothesized an inducible metabolic pathway for citrate outside liver mitochondria. The Cori cycle has been suggested as an alternative citrate metabolism pathway [8, 9].

Klingelé et al. proposed an inducible metabolic pathway for citrate outside liver mitochondria, triggered by the observed discordance between liver failure severity and citrate metabolism capacity. Altered microcirculation can impair hepatic function and cause liver failure and citrate accumulation [8]. RCA is contraindicated in neonates with mitochondrial cytopathy due to impaired citric acid cycle functioning. In two case reports, heparin use led to bleeding complications, and its discontinuation resulted in a reduced FLS of 8 h [9]. Gradual citrate introduction with monitoring revealed citrate metabolization after 96 h, suggesting an inducible pathway activation [9].

The Cori cycle, converting muscle-produced lactate to glucose in the liver and back to muscles, is suggested as an alternative citrate metabolism pathway (Fig. 1) [9–11]. This cycle relies on the liver's ability to metabolize muscle-derived citrate outside mitochondria, within the liver cytosol. While normally slow, this process may be enhanced during liver failure [12]. The Cori cycle can be activated by citrate and epinephrine, with the latter increasing lactate production [12]. A trial on the liver citrate anticoagulation threshold demonstrated RCA safety in continuous veno-venous hemodialysis for patients with severe liver impairment, supporting the Cori cycle's role in citrate metabolism [13].

Establishing thresholds for citrate initiation

Klingelé et al. argue that citrate metabolism is linked to microcirculation rather than hepatic function, with lactate being a critical indicator of liver failure due to altered

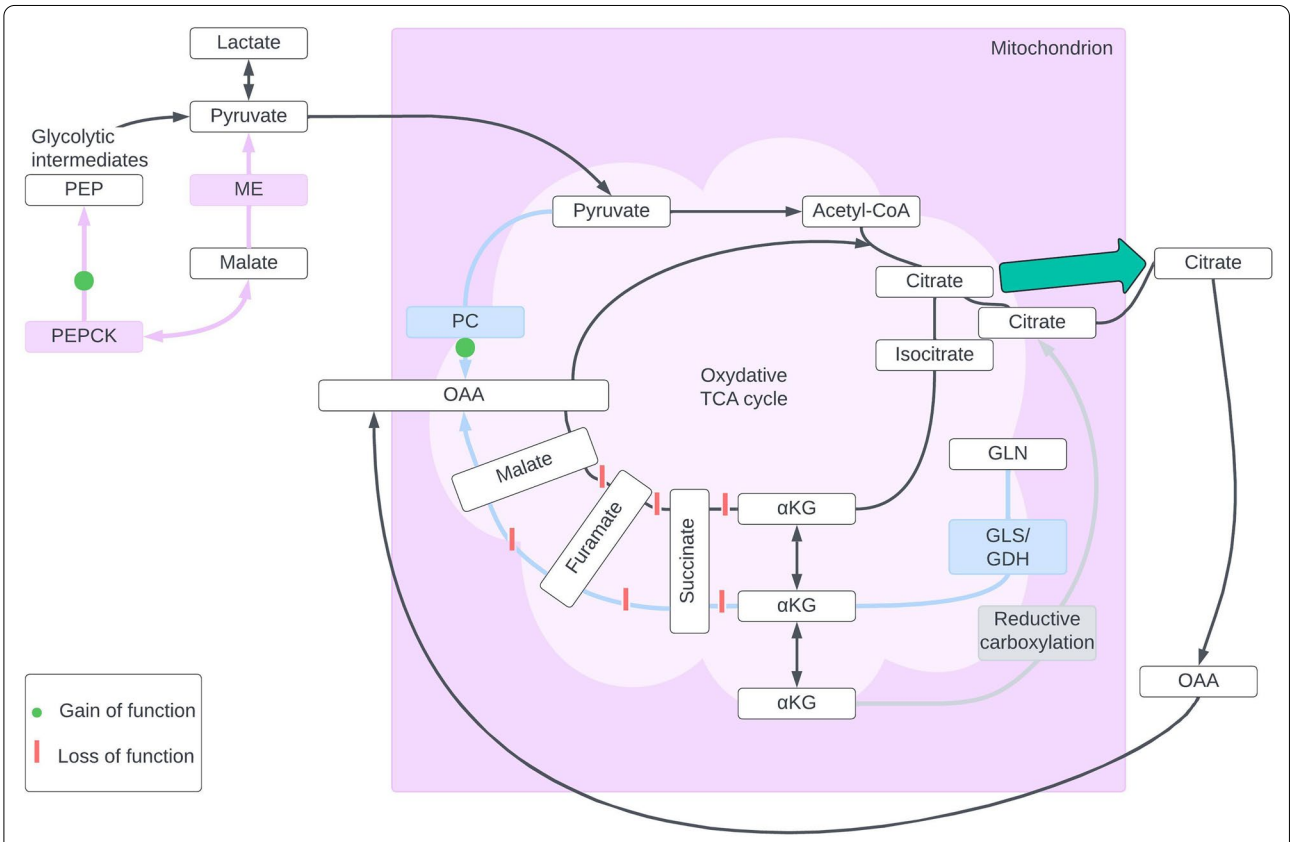

Fig. 1 Link between citric acid cycle in the mitochondria and the Cori cycle inside the liver cell but outside the mitochondria. Adapted and modified from M Inigo, Archives of Revision of nutrition 2021; 41:19–47 Ins and Outs of the TCA Cycle: The Central Role of Anaplerosis. *GDH* glutamate dehydrogenase; *GLS*, glutaminase; *IDH*, isocitrate dehydrogenase; *ME*, malic enzyme; *OAA*, oxaloacetate; *PC*, pyruvate carboxylase; *PEP*, phosphoenolpyruvate; *PEPCK*, phosphoenolpyruvate carboxykinase; *TCA*, tricarboxylic acid; *αKG*, α-ketoglutarate

microcirculation [8]. They propose that citrate accumulation risk during RCA depends on microcirculation [8]. The Cori cycle may substitute for hepatic metabolism in impaired citrate metabolism [6, 9]. Disturbed microcirculation elevates lactate, signaling impaired citrate metabolism [14]. Khadzhynov et al., suggest evaluating lactate kinetics over initial concentration to assess citrate accumulation risk. Intrahepatic, extra-mitochrondrial citrate metabolism may explain why citrate accumulation does not invariably occur in RCA-CRRT patients with liver dysfunction [14]. This challenges the conventional emphasis on hepatic function in RCA-CRRT [6–9], suggesting that microcirculation status and lactate kinetics provide a more comprehensive approach for determining citrate anticoagulation thresholds. Implications for clinical practice include broader citrate use in severe liver failure and better identification of patients who can tolerate citrate, reducing citrate intoxication risk.

The proposed hypothetical mouse model, chosen for its genetic and physiological similarities to humans [15], aims to confirm an alternative inducible citrate metabolism pathway, especially in hyperlactatemia cases. The design involves administering progressive citrate doses, inducing liver failure with high lactate levels via vascular liver exclusion, and identifying the alternative pathway. This approach may provide valuable insights into citrate metabolism and anticoagulation strategies, requiring substantial effort and expertise.

Take-home message

RCA is a viable option for liver failure patients. The proposed inducible metabolic pathway hypothesis challenges the belief in hepatic dominance over citrate metabolism during RCA-CRRT. Additional research, including an animal model, is essential to validate this hypothesis, optimize RCA application for patients previously contraindicated for citrate, and potentially improve anticoagulation strategies in various clinical contexts.

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