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A Mathematical Model of Regional Citrate Anticoagulation in Hemodialysis

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Key Words
Regional citrate anticoagulation · Citrate dialysis · Calcium · Solute kinetics

Abstract
Background/Aims: Regional citrate anticoagulation (RCA) during hemodialysis (HD) has several advantages over heparin anticoagulation, but calcium (Ca) derangements are a major concern necessitating repeated monitoring of systemic ionized Ca (Ca^{2+}). We developed a mathematical model of Ca and citrate (Ci) kinetics during RCA. ***Methods:*** Using patient- and treatment-related parameters, including pre-HD serum Ca and protein concentrations, hematocrit, blood and dialysate flow rates, dialysate composition and access recirculation, the model computes all relevant aspects of RCA based on physicochemical, biochemical and physiological principles such as chemical Ca and Ci equilibria, transmembrane solute fluxes and Ci metabolic rate. The model was validated in 17 treatments using arterial Ci infusion, Citrasate® dialysate, and no postdialyzer Ca substitution. ***Results:*** Measured and predicted systemic Ca^{2+} before HD was 1.08 ± 0.06 and 1.05 ± 0.05 mmol/l, respectively (difference –0.03 ± 0.046, 95% confidence interval, CI, –0.055 to –0.007), and at 15 min into the treatment 1.01 ± 0.05 and 1.02 ± 0.05 mmol/l, respectively (difference 0.012 ± 0.054, 95% CI –0.015 to 0.04). At 15 min, the measured and predicted predialyzer Ca^{2+} was 0.33 ± 0.06 and 0.39 ± 0.05 mmol/l, respectively (difference 0.06 ± 0.03; 95% CI 0.044–0.077), and the measured and predicted postdialyzer Ca^{2+} was 0.7 ± 0.05 and 0.61 ± 0.05 mmol/l, respectively (difference –0.09 ± 0.04; 95% CI –0.11 to –0.07). Bland-Altman analysis showed no systematic bias in these predictions. ***Conclusion:*** This novel model of RCA shows excellent accuracy in predicting systemic, pre- and postdialyzer Ca^{2+} concentrations and may prove valuable in both research and clinical applications of RCA. Copyright © 2010 S. Karger AG, Basel

Introduction

Renal replacement therapy generally requires anticoagulation of the blood to prevent clotting in the extracorporeal circuit. For this purpose, systemic anticoagulation using heparin is the method most frequently applied in clinical practice. This is associated, however, with a long list of potential complications, side effects and contraindications. Most obviously, systemic anticoagulation is not desirable in patients with active bleeding or even increased bleeding risk, such as trauma patients dialyzed after major surgery. Additionally, chronic heparinization

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may lead to side effects such as osteoporosis, hyperlipidemia and hair loss. Heparin-induced thrombocytopenia type II, although rare in chronic hemodialysis (HD) patients, is a potentially life-threatening condition that can develop after exposure to heparin.

Regional citrate (Ci) anticoagulation (RCA), meaning anticoagulation strictly confined to the extracorporeal circuit, is achieved by infusion of Ci into the arterial line. Traditionally, a calcium (Ca)-free dialysate is used, and Ca losses across the dialyzer membrane are countered by postdialyzer Ca infusion. The infused Ci forms stable complexes with ionized Ca (Ca^{2+}), which is thereby markedly decreased. Since Ca^{2+} is an indispensable cofactor in the coagulation cascade, its depletion mediates the desired anticoagulative effect. This is not a new concept. In the setting of renal replacement therapy, it was already described in the early 1960s [1]. Some of its benefits are immediately apparent: it does not increase bleeding risk and also spares the patient the other potential complications and side effects of heparin therapy. Of note, RCA confers advantages that go beyond the benefits of simply avoiding heparin administration: RCA has been shown to reduce complement activation, degranulation of granulocytes and platelets and the release of interleukin 1β, thus improving biocompatibility of the extracorporeal circuit [2–4]. The actual anticoagulative effect of RCA in the dialyzer has also been demonstrated to be superior to both unfractionated and low-molecular-weight heparin [5]. More recently, the sharp rise of heparin costs has further spurred interest in RCA as an alternative mode of anticoagulation.

The reasons that RCA, despite its advantages, does not dominate the chronic HD landscape fall into two broad categories: laboriousness and safety concerns. These are partly interrelated. Methodologically, traditional RCA requires a more complex setup involving two additional pumps (one for the arterial Ci infusion, one for the postdialyzer Ca substitution to replenish Ca losses) as well as the corresponding lines and connections to the extracorporeal circuit, which adds to the time required to set up the machine. The primary concern during RCA is an acute Ca derangement, which can potentially be life-threatening. Therefore, patients require close clinical observation and repeated measurements of systemic Ca^{2+}, again adding to the laboriousness and costs of this treatment modality. The initial flow rates of Ci and Ca infusions as well as subsequent adjustments to Ca substitution during the treatment in response to untoward shifts in systemic Ca^{2+} are guided by more or less complex algorithms, and a physician should be present in case decisions have to be made that are not covered by these algorithms. Due to this complexity, the routine administration of RCA to a large fraction of chronic HD patients has so far not been feasible.

Our goal was to develop a mathematical model of RCA that would broaden our understanding of the solute kinetics and mass balances involved in RCA, increase the comfort level of RCA administration by individualization, and guide the development of Ci anticoagulation regimens other than traditional RCA that provide benefits to the patients while maintaining feasibility for broad-scale clinical application.

Methods

Mathematical Model

The model is an extension of work done by Kozik-Jaromin [6]. Our model comprises the following 7 main components (fig. 1).

(1) Calculation of systemic Ci generation, Ci metabolism and resulting solute equilibria:
   (a) Ci generation is calculated assuming an average generation rate of 240 mg/24 h
   (b) Ci metabolism: $C_{Ci}(t) = C_0 \cdot e^{-k \cdot t}$ with k = 0.0145 min^{-1}
   (c) Solute equilibria (Ca^{2+}, protein-bound Ca, free Ci, CaCi complexes) are calculated assuming a mono-ionic milieu, using the following dissociation constants: K_{CaCi} (for CaCi complexes) = 0.776 mmol/l; K_{CaP} (for Ca-protein binding) = 11 mmol/l
(2) Calculation of solute concentration changes caused by access recirculation
(3) Calculation of required predialyzer Ci concentration and resulting solute concentrations and equilibria:
   (a) Concentration of protein-binding sites for Ca (C_B) according to protein concentration and 12 binding sites per molecule of albumin
   (b) $C_{CiT} = [-(C_{Ca^{2+}})^3 - (C_{Ca^{2+}})^2 \cdot K_{CaCi} - (C_{Ca^{2+}})^2 \cdot K_{CaP} - (C_{Ca^{2+}})^2 \cdot C_B + (C_{Ca^{2+}})^2 \cdot C_{CaT} - C_{Ca^{2+}} \cdot K_{CaCi} \cdot K_{CaP} - K_{CaCi} \cdot C_B + C_{Ca^{2+}} \cdot K_{CaCi} \cdot C_{CaT} + C_{Ca^{2+}} \cdot K_{CaP} \cdot C_{CaT} + K_{CaCi} \cdot K_{CaP} \cdot C_{CaT}]/[(C_{Ca^{2+}})^2 + C_{Ca^{2+}} \cdot K_{CaP}]$
(4) Calculation of dialysate composition with respect to free Ci, Ca^{2+}, CaCi complexes:
   (a)

$$C_{Ci\_free} = -0.5 \cdot \sqrt{0.5 \cdot \left(C_{CaT} - C_{CiT} + K_{CaCi}\right)^2 + K_{CaCi} \cdot C_{CiT}}$$

   (b)

$$C_{Ca\_free} = C_{CaT} \quad OR \quad \frac{K_{CaCi} \cdot \left(C_{CiT} - C_{Ci\_free}\right)}{C_{Ci\_free}}$$

$$\left(\textit{if citrate-containing dialysate}\right)$$

   (c)

$$C_{CaCi} = \frac{C_{Ca\_free} \cdot C_{Ci\_free}}{K_{CaCi}}$$

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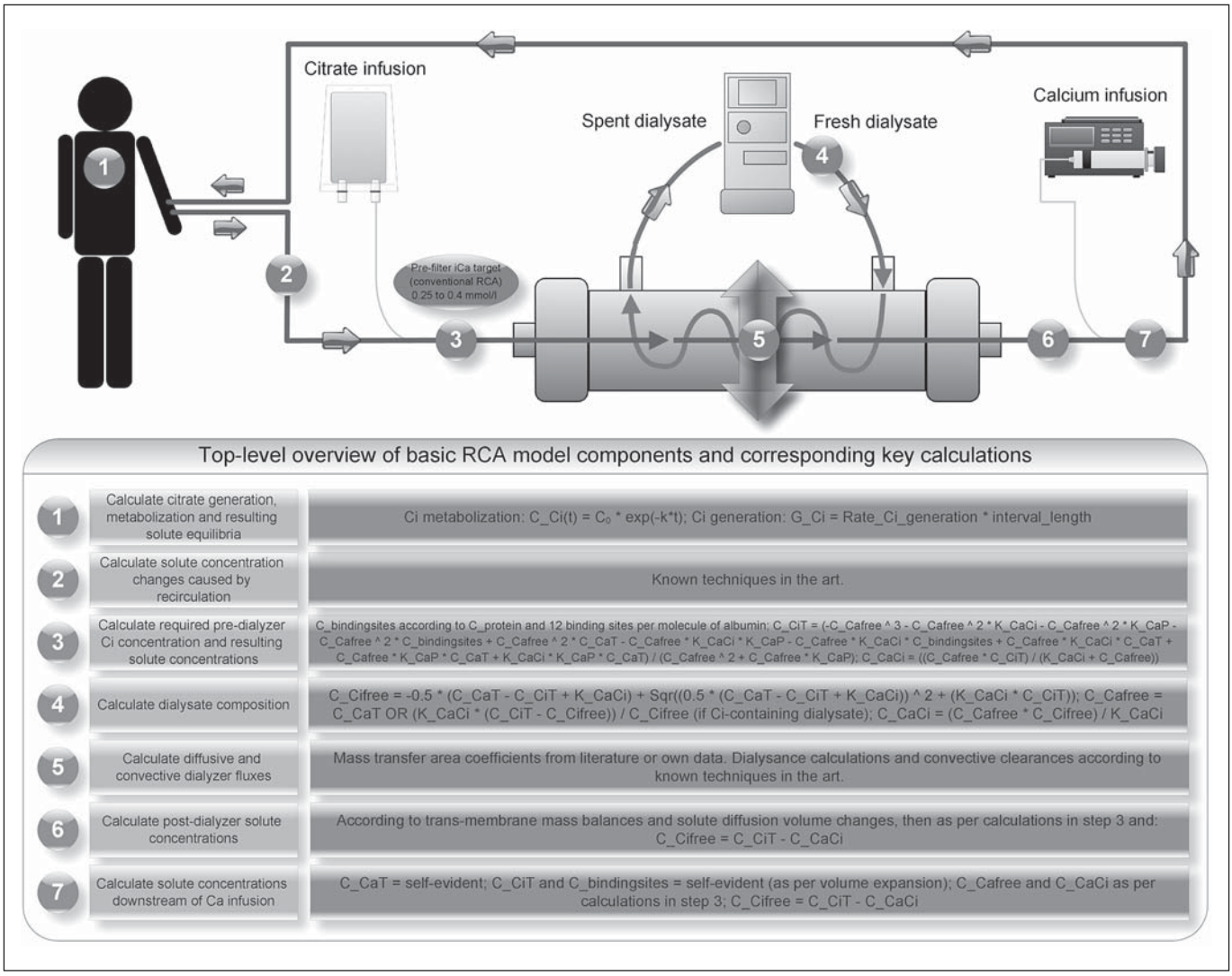

Top-level overview of basic RCA model components and corresponding key calculations

1	Calculate citrate generation, metabolization and resulting solute equilibria	Ci metabolization: C_Ci(t) = C_0 * exp(-k*t); Ci generation: G_Ci = Rate_Ci_generation * interval_length
2	Calculate solute concentration changes caused by recirculation	Known techniques in the art.
3	Calculate required pre-dialyzer Ci concentration and resulting solute concentrations	C_bindingsites according to C_protein and 12 binding sites per molecule of albumin; C_CiT = (-C_Cafree ^ 3 - C_Cafree ^ 2 * K_CaCi - C_Cafree ^ 2 * K_CaP - C_Cafree ^ 2 * C_bindingsites + C_Cafree ^ 2 * C_CaT - C_Cafree * K_CaCi * K_CaP - C_Cafree * K_CaCi * C_bindingsites + C_Cafree * K_CaCi * C_CaT + C_Cafree * K_CaP * C_CaT + K_CaCi * K_CaP * C_CaT) / (C_Cafree ^ 2 + C_Cafree * K_CaP); C_CaCi = ((C_Cafree * C_CiT) / (K_CaCi + C_Cafree))
4	Calculate dialysate composition	C_Cifree = -0.5 * (C_CaT - C_CiT + K_CaCi) + Sqr((0.5 * (C_CaT - C_CiT + K_CaCi)) ^ 2 + (K_CaCi * C_CiT)); C_Cafree = C_CaT OR (K_CaCi * (C_CiT - C_Cifree)) / C_Cifree (if Ci-containing dialysate); C_CaCi = (C_Cafree * C_Cifree) / K_CaCi
5	Calculate diffusive and convective dialyzer fluxes	Mass transfer area coefficients from literature or own data. Dialysance calculations and convective clearances according to known techniques in the art.
6	Calculate post-dialyzer solute concentrations	According to trans-membrane mass balances and solute diffusion volume changes, then as per calculations in step 3 and: C_Cifree = C_CiT - C_CaCi
7	Calculate solute concentrations downstream of Ca infusion	C_CaT = self-evident; C_CiT and C_bindingsites = self-evident (as per volume expansion); C_Cafree and C_CaCi as per calculations in step 3; C_Cifree = C_CiT - C_CaCi

Fig. 1. Top level model overview illustrating the fundamental components of the mathematical model and the corresponding key calculations. C_bindingsites = Concentration of protein binding sites for Ca; C_CaCi = concentration of CaCi complex; C_Cafree = Ca^{2+} concentration; C_CaT = total Ca concentration; C_Ci(t) = Ci concentration at time point t; C_Cifree = free Ci concentration; C_CiT = total Ci concentration; C_protein = protein concentration; C_0 = Ci concentration at time point zero; K_CaCi = dissociation constant for CaCi complex; K_CaP = dissociation constant for Ca protein complex; see text for further details.

(5) Calculation of diffusive and convective dialyzer solute fluxes, assuming KoA_{Ca_free} = 603 ml/min; KoA_{Ci_free} = 337 ml/min; KoA_{CaCi} = 337 ml/min [6]
(6) Calculation of postdialyzer solute concentrations according to transmembrane mass balances and solute diffusion volume changes. Calculation of solute equilibria as in step 3, and $C_{Ci\_free} = C_{Ci\_total} - C_{CaCi}$
(7) Calculation of solute concentrations after Ca substitution:
  (a) Total Ca, total Ci, Ca-binding sites: self-evident (as per volume expansion)
  (b) Ca^{2+} and CaCi as per calculations in step 3
  (c) $C_{Ci\_free} = C_{CiT} - C_{CaCi}$

The entire HD treatment is modeled iteratively by performing these calculations for consecutive intervals of user-definable duration.

Model Validation

The study was approved by the Beth Israel Medical Center Institutional Review Board, and written informed consent was obtained from each subject before enrollment. Seventeen HD treatments were conducted in 8 maintenance HD patients using Ci bicarbonate dialysate (Citrasate®; Advanced Renal Technologies, Bellevue, Wash., USA; 3 mEq/l calcium, 2.4 mEq/l Ci). For one treatment only, Citrasate with 2.5 mEq/l Ca was used. No post-

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dialyzer Ca substitution was performed. Total Ca, Ca^{2+} and total Ci were measured systemically, before and after dialyzer at the following time points: before HD (systemically only), at several time points throughout the treatment, and at the end of HD. Total protein and albumin were measured before dialysis. The most recent alkaline phosphatase (AP) and total parathyroid hormone (tPTH; Scantibodies Laboratory Inc., Santee, Calif., USA) were recorded. Trisodium Ci (136 mmol/l; 4%) was infused into the arterial line at various rates to result in predialyzer Ca^{2+} values of approximately 0.25–0.65 mmol/l. Blood flow rate was 350 ml/min in 4 treatments and 400 ml/min in 13 treatments; the dialysate flow rate was fixed at 500 ml/min. All subjects used Optiflux F180NR dialyzers (Fresenius Medical Care, Waltham, Mass., USA).

Measured and model-predicted systemic Ca^{2+} concentrations were compared before HD and at 15 min into the treatment. For the latter, pre-HD model predictions were adjusted to measured values. Pre- and postdialyzer comparisons between measured and predicted Ca^{2+} were performed at 15 min into the treatment.

Deviations between model-predicted and measured systemic Ca^{2+} over the entire treatment were compared for tertiles of AP and tPTH.

Statistical Analysis

Results are presented as mean ± standard deviation, unless otherwise noted. Differences between predicted and measured values were calculated as predicted – measured and were tested for significant deviation from zero by means of a 2-tailed 1-sample t test. Bland-Altman plots were generated and the underlying data analyzed for systematic bias by means of linear regression. Statistical significance was accepted for an α-level of <0.05.

Results

The study cohort consisted of 8 subjects (aged 63 ± 13.6 years, 4 males). Measured and predicted systemic Ca^{2+} at baseline (before HD) was 1.08 ± 0.06 and 1.05 ± 0.05 mmol/l, respectively (difference –0.03 ± 0.046, 95% confidence interval, CI, –0.055 to –0.007; fig. 2a), and at 15 min into the treatment 1.01 ± 0.05 and 1.02 ± 0.05 mmol/l, respectively (difference 0.012 ± 0.054, 95% CI –0.015 to 0.04; fig. 2b). At 15 min, the measured and predicted predialyzer Ca^{2+} was 0.33 ± 0.06 and 0.39 ± 0.05 mmol/l, respectively (difference 0.06 ± 0.03, 95% CI 0.044–0.077; fig. 2c). At the same time point, corresponding postdialyzer Ca^{2+} was 0.7 ± 0.05 and 0.61 ± 0.05 mmol/l, respectively (difference –0.09 ± 0.04, 95% CI –0.11 to –0.07; fig. 2d). Neither visual inspection of Bland-Altman plots nor formal analysis of the underlying data revealed any systematic bias in any of these predictions.

The tertile ranges for AP were 85–106 U/l (low AP), 112–143 U/l (medium AP) and 154–592 U/l (high AP). For tPTH, the tertile ranges were 258–627 pg/ml (low tPTH), 636–856 pg/ml (medium tPTH) and 916–1,287 pg/ml (high tPTH). Figure 3 shows the difference between predicted and measured systemic Ca^{2+} plotted against treatment time. Figure 3a is stratified by AP tertiles; figure 3b is stratified by tPTH tertiles. While the curves for the low and medium tertiles show no clear separation, the curves corresponding to the high-AP tertile as well as the high-tPTH tertile cluster toward the bottom of the plots, indicating that the most pronounced differences between model prediction and measured values occur in these tertiles.

Discussion

The presented model of RCA, validated here in treatments employing Ca- and Ci-containing dialysate and no venous Ca substitution, shows good accuracy in estimating serum Ca^{2+} concentrations. The predialysis Ca^{2+} is underestimated by only 0.03 mmol/l (with the 95% CI ranging from –0.055 to –0.007), which is clinically negligible. At 15 min into the treatment, serum Ca^{2+} is overestimated by merely 0.012 mmol/l. It is worth noting that this time point covers a period of pronounced solute flux across the membrane, and it is reassuring that the model predicts these complex events and their corresponding influences on serum Ca^{2+} levels adequately. Currently, the model assumes a baseline systemic Ci concentration of 0.1 mmol/l for all treatments. It stands to reason that individualization of predialysis Ci level input will further improve model accuracy. Ci measurements are currently under way to test this hypothesis.

The pre- and postdialyzer Ca^{2+} predictions, while statistically differing from the measured values, show relatively little scatter (standard deviation of the difference 0.03 and 0.04, respectively). More importantly, however, both appear to follow almost a parallel shift from the identity line (fig. 2c, d). This underscores the validity of the underlying calculations, and it would appear that the model may readily be adjusted to correct for this shift.

Fig. 2. Comparison of predicted and measured Ca^{2+} systemically before dialysis (**a**), systemically at 15 min into the treatment (**b**), before the dialyzer (**c**) and after the dialyzer (**d**) at 15 min into the treatment. The left panel shows correlations (dotted line = line of identity), the right panel shows the corresponding Bland-Altman plots.

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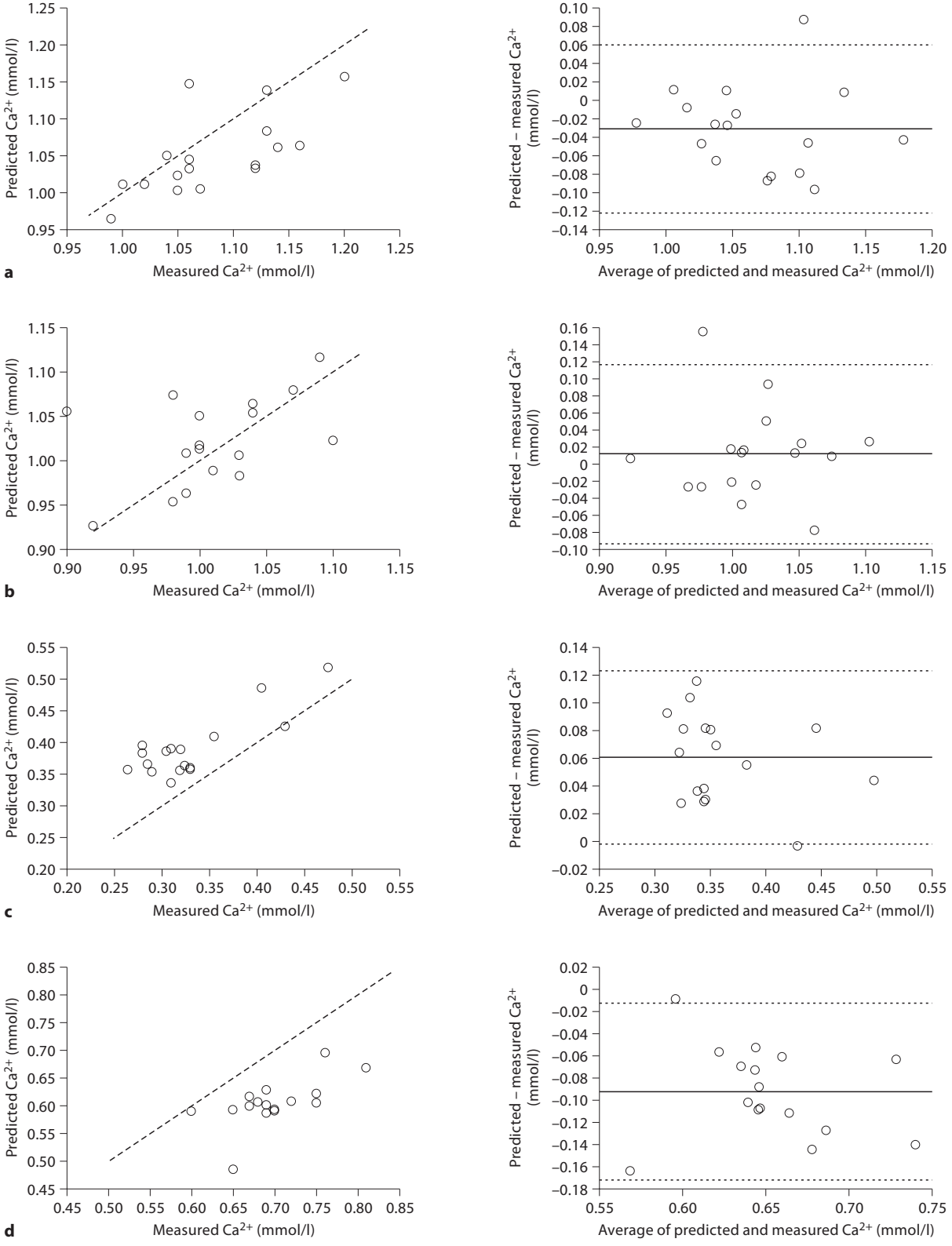

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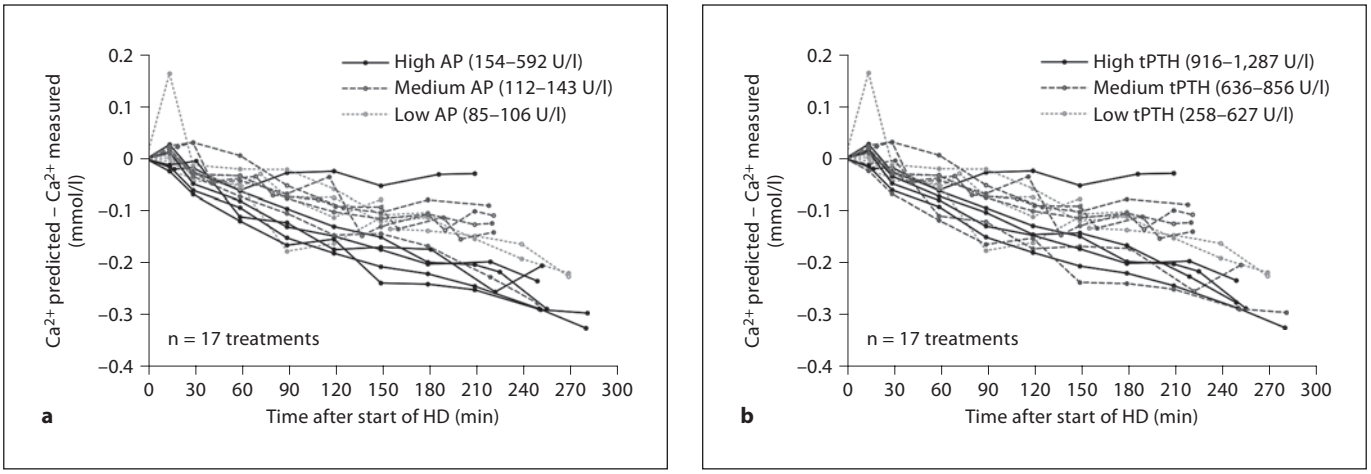

Fig. 3. Model performance over the entire course of the treatments. The difference between measured and predicted systemic Ca^{2+} (predicted – measured) is plotted on the y-axis. Results are stratified by tertiles of AP (**a**) and tPTH (**b**). See text for tertile limits. Of note, the one treatment in the high-AP and high-tPTH tertiles that does not cluster with the rest of the group is the one treatment using a dialysate with 2.5 mEq/l Ca as opposed to 3.0 mEq/l for all other treatments.

It must be noted that for the comparison at 15 min into the treatment, the baseline model predictions were adjusted to measured values in order to avoid carry-over errors and to assess how the model handles a period of pronounced Ci and Ca flux. When simulating an entire treatment en bloc, even slight deviations may add up, as can be seen in figure 3. It is also apparent that the predictions are more accurate for some treatments than for others. One major contributor to this is certainly the individual subject's capacity to buffer changes in serum Ca^{2+}. Currently, this factor is implemented in the model in the form of a term that eliminates a user-specified fraction (from 0 to 100%) of the diffusive Ca flux that occurs per iteration interval, thereby treating it as being buffered by the subject's bone. This concept has limitations primarily insofar as it does not account for changes in serum Ca^{2+} concentration that occur as a consequence of the metabolism of CaCi complexes in the liver and, hence, are not immediately related to diffusive Ca transfer across the membrane. Secondly, it is conceivable that Ca buffer capacity is not constant throughout the treatment but rather is a function of the absolute Ca^{2+} level, the rate of its change and its direction of change, as evidenced by PTH secretion being related to those factors [7]. That aside, since we do not currently have a way of estimating a subject's Ca buffer capacity, all treatments presented here were modeled using an identical buffering factor of 80%, which derives from Ca kinetic studies we are conducting at our institute [8]. The model, in its current implementation, will tend to err on the safe side, meaning it will generally predict a greater decline in serum Ca^{2+} than observed. One would expect that improved Ca buffer capacity would go along with less pronounced drops of systemic Ca^{2+} over the course of the treatment, which, in turn, would result in greater discrepancies between modeled and measured values, since for the simulations at hand, individual differences in Ca buffer capacity were not taken into account. It is conceivable that AP and tPTH, as biochemical markers of bone turnover, may provide some indication of Ca buffer capacity. As can be seen in figure 3a and b, the results in the highest tertiles of AP and tPTH, respectively, cluster toward the bottom of the plots. Following the above reasoning, this is exactly what one would expect to find, assuming that these patients are better capable of buffering changes in serum Ca^{2+} concentration than those in the middle or low tertiles. This observation leads us to believe that it will be possible to further improve the model's prediction qualities by accounting for differences in surrogates of bone turnover. A more dynamic modeling of such parameters, rather than simply applying the monthly snapshot measurements of these surrogate markers, is conceivable. Furthermore, we are currently working on a more refined approach to the general concept of implementing Ca buffer capacity that is suited for the setting of RCA and will address the shortcomings mentioned above. One limita-

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tion of the current model is that only Ca is considered for forming complexes with Ci, neglecting other cations in solution. The multi-ionic milieu will be considered in a future iteration of the model.

The presented implementation of the model is very versatile in that it not only allows the simulation of traditional RCA (with arterial Ci infusion, venous Ca substitution, and Ca-free dialysate), but also grants complete freedom in the choice of dialysate composition with respect to both Ca and Ci content. Therefore, as an example, treatments without venous Ca substitution and using Ci bicarbonate dialysate containing various Ca contents may be simulated. Such regimens are of interest because they appear to increase dialyzer performance [9] and may even permit significant reductions in heparin use. Before switching an entire dialysis unit to such a regimen, the patients may be screened with the presented model for risk of developing hypocalcemia in order to identify subgroups who deserve closer monitoring or in whom the switch may not be advisable. The ultimate goal of these efforts is to devise RCA strategies that are effective in terms of anticoagulation but at the same time reduce or eliminate heparin exposure (and associated side effects), laboriousness of RCA (setup and frequent systemic Ca^{2+} monitoring) and risk for acute hypocalcemia.

We believe the presented model will be a valuable tool in research (i.e., for exploring in silico the impact of various RCA settings on solute kinetics and mass balances, and in guiding clinical research studies on RCA) as well as in actual clinical application, be it using conventional RCA or modified regimens.

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