

Optimizing the dialysate calcium concentration in bicarbonate haemodialysis

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Abstract

Background. There is no consensus regarding the optimal dialysate calcium concentration (DCa) during haemodialysis (HD). Low DCa may predispose to acute arrhythmias, whereas high DCa increases the long-term risk of soft tissue calcifications.

Methods. Twenty-two HD patients treated in four dialysis centres underwent two HD sessions, respectively, with 1.5 and 1.25 mmol/L total DCa. Calcium mass balance (CMB) was calculated from ionized calcium (iCa) in the dialysate and blood at the start and end of each run, using a kinetic formula to define the mean concentrations in the blood and dialysate and then estimating CMBs over the entire treatments.

Results. Mean blood iCa levels increased using 1.5 DCa, whereas they remained unchanged using 1.25 DCa. Diffusive CMB positively correlated with the dialysate/blood iCa gradient. With 1.5 DCa, diffusive CMBs were strongly positive at the blood side and negative at the dialysate side, indicating transfer from dialysate to blood. With 1.25 DCa, despite a negative dialysate/blood iCa gradient, diffusive CMB was slightly positive in blood and negative in dialysate. The global balances based on both the convective and diffusive components showed a positive net transfer of Ca from dialysate to blood with 1.5 DCa and an approximately neutral Ca flux with 1.25 DCa.

Conclusions. While CMB is nearly neutral when using 1.25 DCa, the use of 1.5 DCa results in a gain of Ca during HD. The risks associated with Ca load should be considered in the choice of DCa prescription for HD but need also be weighed against the risk of worse haemodynamic dialysis tolerance.

Keywords: calcium mass balance; CKD-MBD; dialysate calcium; Gibbs-Donnan factor; ionized calcium

Introduction

Disturbances in mineral and bone metabolism are highly prevalent and cause significant morbidity among chronic kidney disease patients [1–3]. Patients undergoing haemodialysis (HD) frequently develop widespread arterial calcification, which is strongly associated with calcium (Ca) and phosphorus (P) overload, dialysis vintage and adverse cardiovascular outcomes [1, 4–8]. Current guidelines recommend various strategies to control the derangements of mineral metabolism, including P binders, vitamin D analogues or calcimimetics [9]. However, little attention is paid, in current clinical practice, to the choice of the dialysate Ca concentration (DCa). There is controversy in the literature about the optimal DCa, and strong arguments are reported as being either in favour of the use of a low DCa [10–13], mainly to avoid the long-term risk of vascular calcifications, or against the use of low DCa, which has been reported to be associated with more frequent episodes of hypotension and cardiac arrhythmias during HD and long-term risk of secondary hyperparathyroidism (SHPT) [14–18]. Recently, Basile *et al.* [19] reported data on measured ionized calcium (iCa) concentration in the fresh dialysis fluid, which resulted in it being lower than the label value. As the dialysable Ca is mainly represented by the ionized fraction, and the pre-dialysis diffusion gradient of iCa between dialysate and plasma water is the main driving force of Ca mass transfer during HD, theoretically the use of 1.25 mmol/L DCa may lead to either neutral or largely negative calcium mass balance (CMB) depending on pre-dialysis plasma water iCa levels [15, 19–22]. Therefore, diffusive CMB may remain neutral using 1.25 DCa, despite an apparent negative dialysate/blood iCa gradient, and positive when using 1.5 DCa [22]. We tested this hypothesis in a multicentre study comparing the effects of 1.25 and 1.5 DCa on CMB.

Materials and methods

Twenty-two stable prevalent uraemic patients (16 males and 6 females, mean age 63.6 ± 14.2 years, vintage 48.7 ± 42.7 months) receiving chronic bicarbonate HD treatment in four dialysis centres were enrolled. Ca-based and non-Ca-based phosphate binders were employed, respectively, in 14 and 11 patients; vitamin D or Vitamin D analogues in 15 and calcimimetics in 5. Each patient underwent two HD sessions, respectively, using 1.5 and 1.25 mmol/L total DCa to evaluate CMB. Blood and dialysate samples were drawn before and after the dialyser from dialysate and blood ports, soon after the start and before the end of the session, and hourly from the pre-filter blood port for the determination of ionized calcium concentration (iCa). iCa was measured by means of an ion-selective electrode (Nova Biomedical Corporation—Waltham, MA—Stat Profile® PhOx® in Biella Laboratory and Stat Profile® Plus-B® in Vercelli Laboratory, Radiometer® ABL 800, Kobenhavn, Denmark in Cremona and Acquaviva delle Fonti Laboratories). Plasma and plasma water flow were obtained from the blood flow by measuring haematocrit (Ht) and total protein (TP) concentration at the start and end of all dialysis sessions.

CMB was determined at the dialysate and blood side by means of a formula [23], which allows the calculation of solute integral concentration ($_{\text{int}}C$) from the initial and final dialysis values. The integral concentration indicates the mean concentrations in the blood and dialysate over the entire treatments. Thus, CMB was determined according to the following equations:

$$\varepsilon = t / \text{Ln} ({}_{\text{int}}C / {}_{\text{fin}}C), \quad (1)$$

$${}_{\text{int}}C = \varepsilon \times {}_{\text{init}}C \times (1 - \exp(-t / \varepsilon)) / t, \quad (2)$$

where ε is an exponential coefficient, ${}_{\text{init}}C$ and ${}_{\text{fin}}C$ are, respectively, the initial and final solute concentrations.

Plasma water flow rate is given as follows:

$$Q_{\text{pw}} = Q_{\text{b}} \times ((100 - \text{Ht}) / 100) \times ((100 - \text{TP}) / 100), \quad (3)$$

where it is assumed that 1 g of TPs occupies an equivalent volume of 1 mL of fluid, and:

$$Q_{\text{b}} = \text{blood flow rate (L/min)}; Q_{\text{pw}} = \text{plasma water flow rate (L/min)}.$$

The Gibbs–Donnan coefficient value for iCa was assumed to be 1.12 [13], corresponding to normal plasma TP concentration of ~ 7 g/dL. Therefore, the CMB general equation may be written as follows:

$$\begin{aligned} & [Q_{\text{pw-IN}} \times t \times \text{pwCa-IN} / 1.12] + [Q_{\text{d-IN}} \times t \times \text{dCa-IN}] \\ &= [Q_{\text{pw-OUT}} \times t \times \text{pwCa-OUT} / 1.12] \\ &+ [Q_{\text{d-OUT}} \times t \times \text{dCa-OUT}], \end{aligned} \quad (4)$$

where: IN-OUT = inlet and outlet port, respectively; pwCa and dCa = plasma water and dialysate calcium concentration, respectively, expressed as their integral value, obtained by Equations (1) and (2).

$$Q_{\text{d}} = \text{dialysate flow rate (L/min)}; Q_{\text{f}} = \text{ultrafiltration rate (L/min)}.$$

Considering separately the dialyser blood side, and assuming $[Q_{\text{pw-OUT}} = (Q_{\text{pw-IN}} - Q_{\text{f}})]$, blood-side diffusive CMB ($\text{diff}_{\text{B}}\text{CMB}$), convective ($\text{conv}_{\text{B}}\text{CMB}$) and global ($\text{global}_{\text{B}}\text{CMB}$) CMB equations may be obtained by means of simple steps as follows:

$$\text{diff}_{\text{B}}\text{CMB} = ({}_{\text{int}_{\text{pw}}}i\text{Ca}_{\text{OUT}} / 1.12 - {}_{\text{int}_{\text{pw}}}i\text{Ca}_{\text{IN}} / 1.12) \times Q_{\text{pwIN}} \times t, \quad (5)$$

$$\text{conv}_{\text{B}}\text{CMB} = ({}_{\text{int}_{\text{pw}}}i\text{Ca}_{\text{OUT}} / 1.12) \times Q_{\text{f}} \times t, \quad (6)$$

$$\text{global}_{\text{B}}\text{CMB} = \text{diff}_{\text{B}}\text{CMB} + \text{conv}_{\text{B}}\text{CMB}. \quad (7)$$

Conversely, at the dialysate side where minimal or no protein effect is expected, the Gibbs–Donnan coefficient must be omitted; assuming $[Q_{\text{D-OUT}} = (Q_{\text{D-IN}} + Q_{\text{f}})]$, the dialysate-side diffusive CMB ($\text{diff}_{\text{D}}\text{CMB}$), convective ($\text{conv}_{\text{D}}\text{CMB}$) and global ($\text{global}_{\text{D}}\text{CMB}$) CMBs equations are obtained as follows:

$$\text{diff}_{\text{D}}\text{CMB} = ({}_{\text{int}}\text{D}i\text{Ca}_{\text{OUT}} - {}_{\text{int}}\text{D}i\text{Ca}_{\text{IN}}) \times Q_{\text{dIN}} \times t, \quad (8)$$

$$\text{conv}_{\text{D}}\text{CMB} = {}_{\text{int}}\text{D}i\text{Ca}_{\text{OUT}} \times Q_{\text{f}} \times t, \quad (9)$$

$$\text{global}_{\text{D}}\text{CMB} = \text{diff}_{\text{D}}\text{CMB} + \text{conv}_{\text{D}}\text{CMB}. \quad (10)$$

The results are expressed as means \pm SD. Statistical analysis was performed using parametric Student's *t*-test for paired data and linear regression modelling with two-sided $P < 0.05$ as statistical significant level.

Results

Change in iCa concentrations

Treatment time, blood and dialysate flow rates and the variations of haematocrit and total plasma protein concentrations were comparable during the dialysis sessions performed using the two different DCa concentrations (Table 1). Pre-dialysis blood iCa levels were 1.16 ± 0.08 mmol/L (range 1.0–1.29) and 1.15 ± 0.08 (range 1.01–1.30) mmol/L during dialysis with 1.50 and 1.25 DCa, respectively. Blood iCa levels did not change significantly during treatments with 1.25 DCa. However, in 5 of 22 patients in this group, who had pre-dialysis blood iCa > 1.25 mmol/L, there was a decrease of blood iCa throughout the dialysis session. On the contrary, blood iCa levels increased significantly with 1.50 DCa from the first hour of treatment (Table 2). Ca levels were significantly higher in the blood leaving the dialyser than in the blood entering the dialyser both at the start and end of treatment, suggesting a diffusive transfer of Ca to the patient during the session with 1.5 DCa (Table 3). Accordingly, the iCa concentration in the dialysate leaving the dialyser was significantly lower in comparison with the iCa concentration in the inflow dialysate both at the start and at the end of the dialysis session, confirming a significant diffusive transfer of Ca to the patient during treatment with 1.5 DCa (Table 4). During treatments with 1.25 DCa, the difference in iCa concentrations both between the inflow and outflow blood and the inflow and outflow dialysate, either at the start or at the end of treatments, suggested a diffusive transfer of Ca to the patient, although smaller compared to dialysis treatments with higher DCa (Tables 3 and 4). Table 5 shows the CMBs calculated at both the blood and dialysate side. The diffusive CMB was strongly positive with 1.5 DCa and slightly positive with 1.25 DCa.

Regression analysis showed that diffusive CMBs, measured at the dialysate side, were positively correlated with the iCa gradient between the inflow dialysate and pre-dialysis blood iCa concentrations ($y = 1110.9x + 168$, $r^2 = 0.6819$, $P < 0.001$). Interestingly, there was a mean positive diffusive CMB of 168 mg (transfer from dialysate to blood) for a null gradient (Figure 1). When blood iCa values are corrected for the Gibbs–Donnan factor, the diffusive CMB tends to become neutral for a null gradient (Figure 2). Diffusive CMBs calculated at the blood and dialysate side were significantly correlated (Figure 3); however, the values obtained at the blood side were significantly lower (Figure 3, Table 5). The convective loss of Ca was similar using 1.5 and 1.25 DCa, both at the blood and dialysate side (Table 5). The global balances, resulting from the algebraic sum of the convective and diffusive components, showed a net positive transfer of Ca from

Table 1. Main dialysis parameters at the start and the end of the dialysis sessions using a dialysate calcium (DCa) concentration of either 1.50 or 1.25 mmol/L^a

	Treatment time min	Q_b mL/min	Q_{pw} mL/min	Q_d mL/min	Q_f mL/min	Ht (%) Start	Ht (%) End	TP (g/dL) Start	TP (g/dL) End
DCa 1.50 ($n = 22$)									
Mean \pm SD	229 \pm 27	300 \pm 21	176 \pm 15	502 \pm 13	12.19 \pm 44.42	36.8 \pm 4.0	39.8* \pm 5.3	6.94 \pm 0.63	7.86* \pm 0.87
DCa 1.25 ($n = 22$)									
Mean \pm SD	229 \pm 28	299 \pm 17	175 \pm 12	503 \pm 16	11.88 \pm 27.15	36.9 \pm 3.7	40.2* \pm 4.7	6.97 \pm 0.69	7.93* \pm 0.75

^a Q_b , blood flow rate; Q_d , dialysate flow rate; Q_f , ultrafiltration rate; Ht, haematocrit; TP, total protein.

*P < 0.001 versus start of dialysis.

Table 2. Blood ionized calcium concentrations during dialysis using a dialysate calcium (DCa) concentration of either 1.50 or 1.25 mmol/L

	Start	1 h	2 h	3 h	End
DCa 1.50					
Mean \pm SD	1.165 \pm 0.08	1.206* \pm 0.05	1.221* \pm 0.04	1.242* \pm 0.04	1.246* \pm 0.05
DCa 1.25					
Mean \pm SD	1.149 \pm 0.08	1.157** \pm 0.06	1.151** \pm 0.05	1.146** \pm 0.04	1.141** \pm 0.04

*P < 0.001 versus start of dialysis.

**P < 0.001 versus 1.50 mmol/L.

Table 3. Plasma water ionized calcium concentrations (pw iCa) at the inlet (IN) and outlet (OUT) port of the dialyser, at the start and at the end of dialysis session and their integral values

	Plasma water iCa-IN			Plasma water iCa-OUT		
	Start	Integral	End	Start	Integral	End
DCa 1.5 ($n = 22$)						
Mean \pm SD	1.165 \pm 0.08	1.204* \pm 0.055	1.246* \pm 0.05	1.340*** \pm 0.05	1.364*** \pm 0.052	1.390*** \pm 0.07
DCa 1.25 ($n = 22$)						
Mean \pm SD	1.149 \pm 0.08	1.145** \pm 0.056	1.141** \pm 0.04	1.163** \pm 0.11	1.184*** \pm 0.059	1.208*** \pm 0.05

*P < 0.001 versus start of dialysis.

**P < 0.001 versus 1.50 mmol/L.

***P < 0.001 versus IN.

Table 4. Ionized Ca concentrations in the dialysis fluid at the inlet (IN) and outlet (OUT) port of the dialyser, at the start and at the end of dialysis and their integral values

	Dialysate iCa-IN			Dialysate iCa-OUT		
	Start	Integral	End	Start	Integral	End
DCa 1.5 ($n = 22$)						
Mean \pm SD	1.336 \pm 0.07	1.329 \pm 0.068	1.322 \pm 0.07	1.215* \pm 0.07	1.240* \pm 0.063	1.267* \pm 0.06
DCa 1.25 ($n = 22$)						
Mean \pm SD	1.130*** \pm 0.11	1.127*** \pm 0.073	1.126*** \pm 0.06	1.107*** \pm 0.09	1.104*** \pm 0.059	1.103*** \pm 0.06

*P < 0.001 versus IN.

**P < 0.05 versus IN.

***P < 0.001 versus 1.50 mmol/L.

dialysate to blood with 1.5 DCa and an approximately neutral Ca flux with 1.25 DCa.

Global calcium balances

All patients treated with 1.50 DCa showed a positive global Ca transfer from dialysate to blood. Also, patients with high

convective Ca losses (range 15–232 mg) or high pre-dialysis blood iCa levels (range 1.00–1.29 mmol/L) did not show Ca losses over the dialysis session. Global Ca balances were negative in 12 of 22 patients treated with 1.25 DCa and blood iCa levels decreased during the session in 5 patients using 1.25 DCa. All these five patients had a marked negative pre-dialysis iCa gradient (difference between

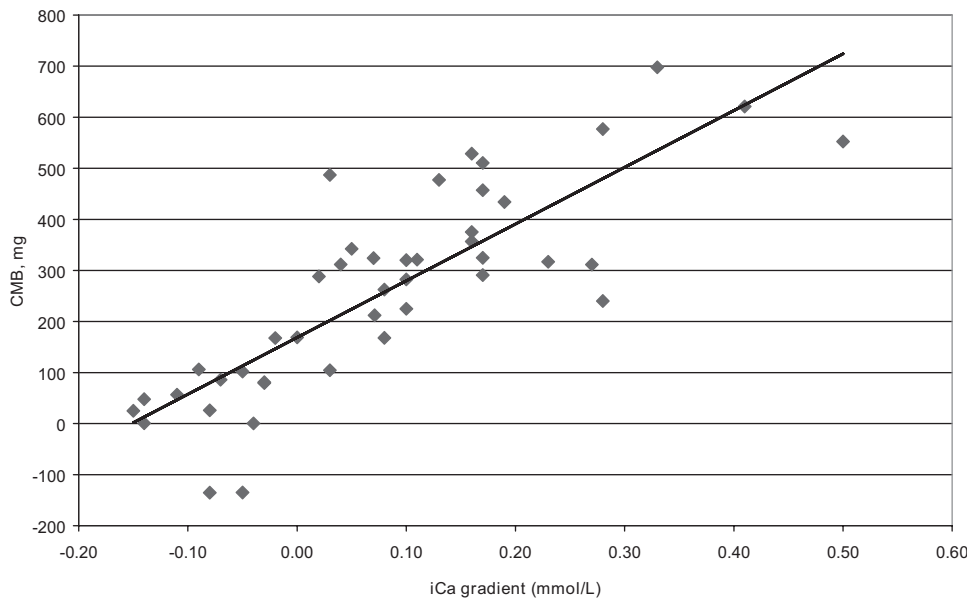
Table 5. CMB (mg) calculated at the blood side (B-side) and at the dialysate side (D-side)

	B-side			D-side		
	Diffusive	Convective	Global	Diffusive	Convective	Global
DCa 1.5 (<i>n</i> = 22)						
Mean ± SD	229 ± 103	-137 ± 60	93 ± 112	-404** ± 130	138 ± 60	-266** ± 116
Range	+71/+519	-14/-222	-108/+337	-212/-620	+15/+232	-76/-490
DCa 1.25 (<i>n</i> = 22)						
Mean ± SD	58* ± 81	-115 ± 32	-57* ± 82	-101**** ± 170	119 ± 33	18* ± 179
Range	-157/+189	-35/-186	-288/+110	-477/+135	+36/+191	-385/+326

*P < 0.001 versus DCa 1.5.

**P < 0.001 versus B-side.

***P < 0.01 versus B-side.

**Fig. 1.** Dialysate-side diffusive CMB as a function of the iCa gradient between the inflow dialysate and pre-dialysis blood iCa. Model: $y = 1110.9x + 168$, $r^2 = 0.6819$, $P < 0.001$.

dialysate and pre-dialysis blood levels ranging from -0.09 to -0.15 mmol/L). Two of these five patients had higher convective Ca losses: ultrafiltration rate of 3.6 and 4.3 L/session. They also had a negative diffusive Ca transfer from blood to dialysate. The remaining three patients had a neutral diffusive mass transfer (0–1 mg/session) and lower convective Ca losses (ultrafiltration volume of 0.8, 1.7 and 1.8 L/session). The behaviour observed in these five patients is well explained by multivariate analysis. The main predictor of the global mass transfer was the iCa gradient between dialysate and blood. However, when the ultrafiltration rate was included in the model, taking into account the effect modification induced by DCa (1.5 versus 1.25) for both ultrafiltration rate and iCa gradient, the global mass transfer during dialysis resulted in a direct correlation to the iCa gradient using both DCa solution types {85 mg [95% confidence interval (95% CI) 43–127] for 0.1 unit of gradient for DCa 1.25 and 66 mg (95% CI 26–106) for DCa 1.5} and inversely correlated to the ultrafiltration rate (lesser Ca gain with higher ultrafiltration rate) only when DCa was 1.25 [7.7

mg per session lower mass transfer per 100 mL of ultrafiltration (95% CI 3.5–11.9)]. The effect of ultrafiltration on global mass transfer of Ca was non-significant when DCa was 1.5 (model $r^2 = 0.732$, $P < 0.001$). Results were similar when the response variable was the change in blood iCa levels during treatment (the difference between end of dialysis and pre-dialysis levels) (model $r^2 = 0.748$, $P < 0.001$).

Discussion

There is controversy in literature about the prescription of DCa. Some authors recommend the use of low DCa to limit the risk of vascular and soft tissue calcifications secondary to a positive CMB [12, 13]. Others suggest the use of 1.5 DCa to minimize the risk of cardiac arrhythmias, haemodynamic instability or long-term worsening of SHPT due to the negative Ca balances induced by lower DCa [14–18]. In the present work, we evaluated the effect of the two DCa concentrations (1.25 and 1.50 mmol/L) recommended by

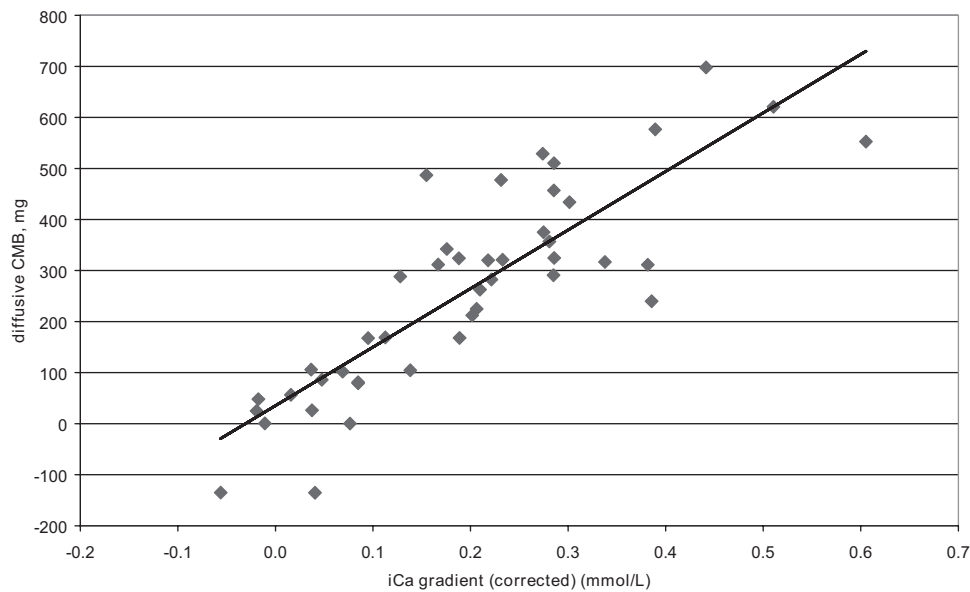


Fig. 2. Dialysate-side diffusive CMB as a function of the iCa gradient between the inflow dialysate and pre-dialysis pw iCa corrected for Gibbs–Donnan factor. Model: $y = 1147.5x + 35$, $r^2 = 0.719$, $P < 0.001$.

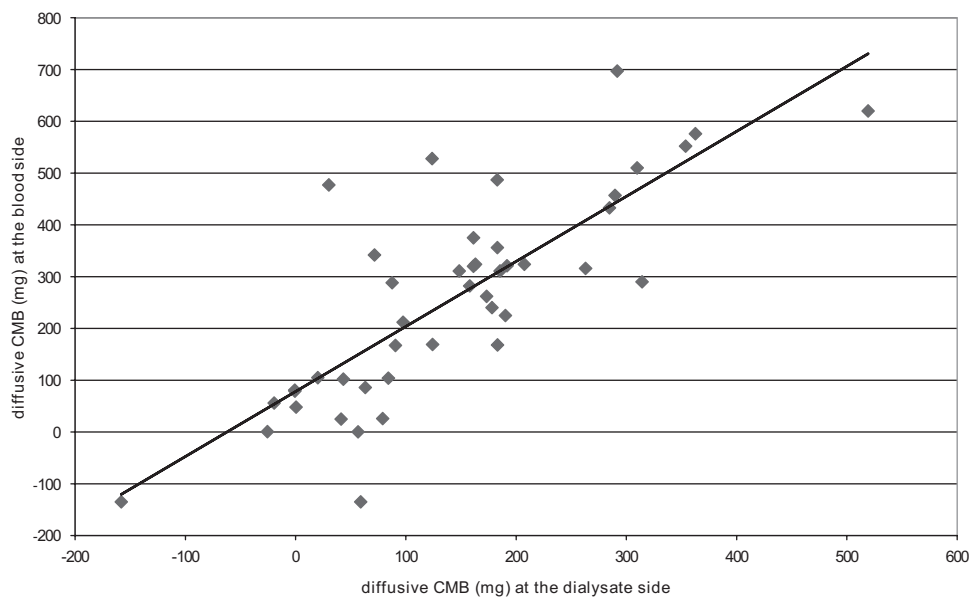


Fig. 3. Dialysate-side diffusive CMB as a function of blood-side CMB. Model: $y = 1.256x + 78$, $r^2 = 0.6353$, $P < 0.001$.

the recent K-DIGO guidelines [9] on diffusive and global CMB in bicarbonate HD. CMB was determined at both the dialysate and blood side by measuring iCa concentrations at the start and end of each session and calculating the mean concentrations over the entire treatments by means of a kinetic method [23]. This method allows the calculation of CMB without the need for total [24] or partial [25] dialysate collection and the separate contribution of diffusive and convective mass transfer to global CMB.

CMB equations were derived from the principle of mass conservation, assuming that in the case of instantaneous mass balance, the total iCa mass entering the dialyser must equal the Ca mass leaving the dialyser. Conversely, if the

whole CMB session is considered, the CMB during treatment may be obtained from the $i_{int}C$, dialysis session length (t) and blood and dialysate flow rates. Furthermore, in the CMB calculation based on pw iCa, the plasma water flow and the Gibbs–Donnan coefficient due to plasma proteins have to be taken into account. The convective CMBs showed a satisfactory correspondence at the blood and dialysate side (the mass-balance ‘closed’). On the contrary, the diffusive CMBs showed a difference when comparing the blood with dialysate side. This may be explained by the rapid diffusion of calcium from the extracellular fluid into the exchangeable calcium pool [11]. For this reason, the correlation between blood-side and dialysate-side CMBs

was poor. Therefore, the CMBs calculated at the blood side underestimate the real balance (lower diffusive transfer of Ca to the patient), whereas the dialysate-side values must be considered more reliable. Thus, the assessment of CMB in clinical practice could be simply performed at the dialysate side, sampling dialysis fluid IN and dialysate OUT, 2–3 min after dialysis commences and before the session end, and applying Equations (1) and (2) to calculate respective dialysate IN and OUT integral values and Equations (8–10) for CMB. We documented that the ionized DCa concentrations were ~10–15% lower than the value reported on the label (on average 1.33 mmol/L, corresponding to 88.6% of label value with 1.5 DCa and 1.13 mmol/L, corresponding to 90.1% of label value with 1.25 DCa). Similar results were reported in other studies [17, 19, 26].

Pre-dialysis blood iCa concentrations in our patients were on average 1.15 mmol/L. Such levels correspond approximately to a serum total calcium concentration of 9.2 mg/dL and are within the normal range, as recommended by the K-DIGO guidelines [9]. Blood iCa levels significantly increased during treatment with 1.5 DCa in our patients, whereas they did not change significantly with 1.25 DCa. Our results confirm the findings of previous studies using either 1.5 DCa [15, 19, 27] or 1.25 DCa [20, 21]. In other studies, a significant decrease of blood iCa levels was observed during treatment with 1.25 DCa; however, these patients had higher pre-dialysis iCa levels than those reported in the present study [15, 27]. A marked diffusive Ca transfer from dialysate to the patient was observed using 1.5 DCa, as iCa levels were significantly higher in the blood leaving rather than in the blood entering the dialyser, and concomitantly, iCa levels were significantly lower in the outflow rather than in the inflow dialysate, both at the start and end of dialysis sessions. The behaviour of iCa was similar during treatment with 1.25 DCa. However, the concentration differences between the inlet and outlet fluids were smaller than those with 1.50 DCa, suggesting a diffusive transfer of Ca from the dialysate to the patients also with the lower DCa, despite the fact that the iCa gradient between dialysate and blood was negative. This observation may be explained by the effect of the negatively charged plasma proteins, which tend to retain Ca cations in the blood compartment despite the presence of a diffusive gradient. The diffusive CMB analysis is fundamental in the evaluation of the safety of DCa considering the potential risks of cardiac arrhythmias or parathyroid hormone (PTH) stimulation. An excessive diffusive gradient might lead to dangerous hypocalcaemia, whereas calcium removal by convection does not reduce blood calcium levels. This is the result of the relative greater removal of water than of calcium due to the lower concentration of Ca in the ultrafiltrate than in the plasma water (Gibbs–Donnan effect).

The diffusive CMBs calculated at the dialysate side documented a marked diffusive Ca gain (on average 404 mg) using 1.5 DCa and moderate gain (on average 101 mg) using 1.25 DCa. When single individuals were considered, only 2 of 22 patients showed a negative diffusive CMB using 1.25 DCa. Diffusive CMB was positively correlated with the iCa gradient between the inflow dialysate and pre-dialysis blood iCa concentrations, as reported by other studies [15, 19, 21]. Regression analysis showed a mean diffusive

transfer of Ca from dialysate to blood of 168 mg with null diffusive gradient. This apparently unexpected result was due to the Gibbs–Donnan effect. In fact, the diffusive CMB tended to become neutral for a null gradient when the pre-dialysis pw iCa values corrected for the Gibbs–Donnan factor were used in the regression analysis. Global CMB in our patients was positive (266 mg on average) using 1.5 DCa and nearly neutral using 1.25 DCa. Our results on CMB using 1.5 DCa are comparable to those reported recently by Basile *et al.* [19]. Less positive CMBs were reported in other studies. In a previous study, Malberti *et al.* [15] documented a Ca removal of ~200 mg using 1.50 DCa. However, average pre-dialysis serum iCa levels (1.27 mmol/L) in those patients were markedly higher than those reported in the present study and therefore, the diffusive iCa gradient was not comparable in the two studies. Karohl C *et al.* [27] reported an average influx of 46 mg of Ca using 1.50 DCa with large inter-individual variations (25–75% range: +142 to –231 mg). Pre-dialysis serum iCa levels in Karohl's study were higher (1.27 mmol/L) than in the present study. Using 1.25 DCa, we observed a nearly neutral global CMB. The results are comparable to those reported by Fabrizi *et al.* [20]. On the contrary, others reported mean losses ranging from 188 to 468 mg [15, 21, 27]. However, pre-dialysis serum iCa levels were markedly higher in such studies [15, 27]. A decrease of serum total calcium levels over a period of time has been documented in all countries participating in the three phases of DOPPS (1996–2007) [28]. This trend is likely the result of the implementation of the recommendations of the K-DOQI guidelines to maintain serum calcium concentrations in the lower normal range [29]. Many years ago, when cinacalcet and less hypercalcaemic vitamin D metabolites, such as paricalcitol, were not available, the maintenance of mild hypercalcaemia was a common strategy to better control PTH levels. Now, the observation that total serum Ca levels >10 mg/dL are associated with higher relative risk of mortality [9, 28, 29] suggests targeting serum Ca levels within the normal range and early prescription of cinacalcet and/or less hypercalcaemic vitamin D metabolites to control PTH levels.

The present study documents how the use of 1.25 DCa in patients with pre-dialysis blood iCa in the normal range allows stable blood iCa levels over the dialysis sessions and approximately neutral dialysis CMBs. On the contrary, the use of 1.5 DCa significantly increases blood iCa levels during the session and induces a marked Ca gain. As dialysis patients are at increased risk of developing over suppression of PTH and adynamic bone disease, hypercalcaemia and soft tissue and vascular calcification [1–8], we think that 1.5 DCa should be used with caution. This is particularly true for those patients who are receiving oral Ca salts and/or active vitamin D compounds, which tend to enhance intestinal Ca absorption [10–13, 30]. On the other hand, excessive lowering of blood iCa levels during a dialysis session by low DCa may be associated with more frequent episodes of hypotension and cardiac arrhythmias during the session and a long-term risk of worsening of SHPT [14–18]. Recently, Pun *et al.* [31] documented that sudden death among dialysis patients was associated to exposure to a DCa <1.25 mmol/L, but use of 1.25 DCa was not different between cases of

sudden death and controls (74.6 versus 74.7%). Our results suggest that the decrease of blood iCa during dialysis session with 1.25 DCa is negligible or absent when pre-dialysis blood iCa are <1.25 mmol/L. Thus, the risk of adverse hypocalcaemia-mediated events using 1.25 DCa is minimal when pre-dialysis blood iCa levels are within the normal range. However, in patients prone to cardiac arrhythmias, special caution is warranted when considering a move from 1.50 DCa to 1.25 DCa. Nevertheless, as potentially dangerous calcium removal during dialysis should be avoided, DCa in our opinion should be targeted to obtain a neutral diffusive CMB and a slightly negative convective CMB. Therefore, the results of the present study support the choice of 1.25 DCa; as a strongly positive Ca load could worsen the vascular calcification rate in HD patients, 1.5 DCa should be discouraged or employed with caution in selected cases. Alternatively, new solutions may be considered. A recent study found that a dialysate Ca concentration of 1.375 mmol/L is associated with mildly positive CMB, normal blood water iCa levels and stable PTH levels during dialysis [32].

Some limitations of the study must be acknowledged. Firstly, our model ignores other existing Ca pools. In fact, iCa is in equilibrium between iCa, protein-bound Ca and bone-sequestered Ca [11, 32]. Our model assumes that there is no flux between these 'compartments'. Since albumin binding of Ca is related to pH and bicarbonate concentration, Ca equilibrium does change during dialysis. However, we do not believe that this factor affects substantially our results. Secondly, dialysis with 1.5 DCa may suppress PTH levels and rapidly reduce osteoclastic bone resorption, thus affecting the Ca equilibrium [32]. The lack of agreement between diffusive flux from the perspective of the blood and dialyser sides may be evidence of this phenomenon. Furthermore, the lack of agreement suggests that dissociation of Ca from albumin occurs rapidly, so that the driving force for diffusion could be the total Ca rather than simply the iCa [32]. Finally, failure to close mass balances might reflect errors in the measurement of fluxes in the two streams. Consequently, it may be argued that the algorithm used to estimate the time average (integral) Ca concentrations, based on urea kinetics [23], is the most likely source of error. However, the algorithm is based on assumptions, which may be applicable to many solutes other than the urea.

In conclusion, while CMB is nearly neutral using 1.25 DCa, the use of 1.5 DCa results in a gain of Ca during HD. The risks associated with Ca load should be considered when choosing the DCa for HD; however, particularly in patients prone to cardiac arrhythmias, special caution is warranted when considering a move from 1.5 DCa to 1.25 DCa. The optimal strategy includes tailoring DCa concentration for each patient's individual condition, taking into account pre-dialysis iCa levels, ultrafiltration rate and medications (Ca salts and active vitamin D metabolites). Our method to measure CMB at the dialysate side may be a helpful tool in daily practice to personalize the prescription of DCa concentration.

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