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ACETATE-FREE BIOFILTRATION FOR THE PREVENTION OF INTRADIALYTIC HYPERCAPNIA IN A PATIENT WITH LIMITED PULMONARY RESERVE

Abstract. *A case of acute hypercapnia occurring during a session of bicarbonate hemodialysis is reported. The 82-year old female patient was affected by cardiac insufficiency, pulmonary hypertension and chronic obstructive lung disease. She developed acute symptomatic respiratory acidosis immediately after the beginning of a bicarbonate hemodialysis session, with arterial pH of 7.25 and $paCO_2$ of 48.1 mmHg. This was related to the well known, but frequently forgotten, CO_2 load from bicarbonate-based dialysate.*
We treated her with acetate-free biofiltration, with stable $paCO_2$ throughout the session. Physiopathology of blood gas dynamics during hemodialysis is reviewed.
Key words: *respiratory acidosis, hypercapnia, bicarbonate hemodialysis, acetate-free biofiltration*

Introduction

Bicarbonate-based hemodialysis (BHD) relies on the on-line preparation of the dialysate from a concentrated acidic electrolyte solution which is diluted and mixed with bicarbonate solution to achieve usual final concentrations dictated by pre-set conductivity and bicarbonate targets. Acidic electrolyte solution contains acetic acid (in most western countries to a final concentration of 3 mM) to stabilize the solution and avoid calcium and magnesium salts precipitation, mostly as carbonates. Despite this, circuit scale remains a problem with dialysis machines, requiring frequent descaling [1]. When mixed with bicarbonate, acetic acid reacts with bicarbonate to give acetate and carbonic acid (i.e. CO_2), to a final partial pressure of about 97 mmHg [2]. Dialysate CO_2 freely diffuses through the filter membrane to the patient blood, resulting in significant load to the patient. Lung ventilation easily removes this CO_2 load preventing pCO_2 to rise in arterial blood. In patients with marginal lung function the BHD-related CO_2 load may result in some degree of CO_2 body retention and clinical consequences.

We describe a case of intradialytic symptomatic hypercapnia in a patient with respiratory insufficiency; acetate-free biofiltration (AFB) allowed successive uneventful dialysis treatments.

Case presentation:

This 82-year old female patient was transferred in our Nephrology Unit because of «acute on chronic» renal failure and anuria. She had known chronic renal insufficiency with a serum creatinine of 2 mg/dL, obesity, hypertension, hypercholesterolemia, gout, diverticulosis, hypokinetic dilated cardiomyopathy with FE 36 % and was in NYHA class 2B classification. She had been admitted to the emergency room several days ago because of acute pulmonary congestion and high ventricular response atrial flutter; she was at first treated with Continuous Positive Airway Pressure (CPAP) and diuretics. She later underwent a coronary angiography and angioplasty with everolimus-medicated stenting of a critical proximal circumflex stenosis. Because of multiple alternating episodes of paroxysmal atrial fibrillation and bradycardia she also had a bicameral pace maker implanted. Lastly she developed severe sepsis, worsening myocardial function and oliguria, and was treated with continuous venous-venous hemofiltration (CVVH).

After patient stabilization, respiratory support changed to O_2 supplementation by open mask and intermittent hemodialysis was then considered. Shortly after the first dialysis treatment start, she developed worsening dyspnea. An arterial blood gas analysis showed respiratory acidosis with a pH of 7,25, pCO_2 48.1 mmHg,

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pO_2 56.2 mmHg, lactate 3.6 mmmol/l and bicarbonate 23.8 mmol/l. Despite high volume O_2 through the mask the patient didn't get better, and the session was stopped with rapid resolution of symptoms.

The day after a new gas analysis (on 4 l/min O_2 through mask) showed arterial pH 7.36, pCO_2 42 mmHg, pO_2 106 mmHg, sO_2 98 %, bicarbonate 24.4 mmol/L, lactate 0.3 mmol/l. A chest radiography showed bilateral pleural effusions and raised diaphragm.

We considered that dialysis-induced CO_2 load was responsible for the acute and reversible episode of respiratory acidosis of the previous day, and decided to treat the patient with AFB, with serial controls of acid-base parameters (Table 2). We used post-dilution bicarbonate infusion with a 145 mM concentration, with infusion rate aimed at a final bicarbonate concentration of 23 mM according to manufacturer's algorithm. The run was conducted uneventfully, as were several additional successive treatments. Lastly she resumed diuresis with stable renal function and serum creatinine at 2.1–2.3 mg/dl. She still needed 2–4 l/min O_2 to keep sO_2 at 96–98 % with a $paCO_2$ of 29 mmHg, with persistent pleural medium-basal effusion on the left.

Discussion

Peculiar changes of acid-base parameters occur during a BHD session, representing instant blood/dialysate equilibration within the dialyzer, intradialytic overall base balance and respiratory accommodation [3–5].

As summarized in Table 1, the dialysate is more acidic than blood, with a pH ranging from 7.1 to 7.3 and a partial pressure of CO_2 approximating 70–100mmHg. H_2CO_3/CO_2 originates in small part from the concentrated bicarbonate solution, and mostly from the chemical reaction between acetic acid (the stabilizing and acidifying agent in the concentrated electrolyte solution, necessary as already said to prevent Ca and Mg salts precipitation) and bicarbonate. In aqueous solution, pCO_2(mmHg) is about $[H_2CO_3]$ (mM)/0.0309; since 3 mmol/l of bicarbonate react with acetic acid, this corresponds to a final concentration in the dialysate of 3 mM acetate (which accounts for a fraction of positive base balance to the patient) and carbonic acid (which dissociates into H_2O and CO_2, resulting in calculated pCO_2 of 97 mmHg [2]; actual measured values are somehow lower, representing escape from the solution through degassing devices in the circuit.

CO_2 has a high solubility and diffusibility, rapidly equilibrating with patient's blood flowing through the dialyzer and increasing pCO_2 in outlet blood to the patient. The increase in pCO_2 is significantly higher than the bicarbonate rise, which is 4 times less diffusible through the membrane than CO_2. A gas analysis carried out in inlet blood (representing patient's arterial systemic blood if an A-V fistula is in use) will show metabolic acidosis, but

Table 1. Representative final mean composition of dialysate from concentrated acidic and alkaline solutions in BHD and AFB. Electrolyte content in concentrated acidic solutions vary according to the final dilution required (1 vol in 35 or 45 final volume); alkaline solution in BHD is saturated sodium-bicarbonate. Concentrate dilution and mixing are targeted to the final pre-set composition by on-line sensors and feedback controlled pumps. In AFB, sodium-bicarbonate is infused post-filter at concentration of 120–167 mM according to manufactor's tables or algorithms of flow, targeted to programmable end-of-treatment «equilibrated» bicarbonate levels

	Acidic electrolyte solution*	Bicarbonate solution BHD**	Bicarbonate solution AFB&	Final dialysate BHD	Final dialysate AFB
Na^+	X	1136.8	145.0	140.0	139.0
K^+	X	–		2.0–3.0	1.0–3.5
Ca^{++}	X	–		1.25–1.75	1.25–2.00
Mg^{++}	X	–		0.5	0.37
Cl^-	X	–		104.0	142.0–145.0
CH_3COOH	X	–		–	–
CH_3COO^-	–	–		3.0	–
HCO_3	–	1136.8	145.0	34.0	< 1.0
pH	2.3	7.80	7.82	7.1–7.3	7,35
pCO_2	< 1.0	96.0	97.0	70.0–100.0	< 1.0
Glucose	X			5.5	5.5

Electrolyte values are in mM, pCO_2 in mmHg, pH in pH units

**** X denotes presence of each compound in the concentrated electrolyte solution; original concentration differs according to the final dilution volume required***

***** Represents saturated sodium-bicarbonate solution (solubility at 20 °C is 95.5 g/l; at the machine temperature of about 36 °C, Na and HCO^{3-} concentrations are about 1200 mM); mixing with electrolyte diluted solution to produce dialysate occurs pre-filter & three concentrations are available, at 120, 145 and 167 mM; this buffer solution does not mix with diluted electrolyte dialysate, but is directly infused into the patient's blood in «post-dilution» (post-filter) mode.***

in the filter bicarbonate, acetate, CO_2 and oxygen are taken up so that outlet blood will show respiratory acidosis without hypoxia [6] Patients with physiological lung function are able to excrete dialysis-related CO_2 load during the first blood pass through the lungs, so that in arterial (pre-filter) blood pCO_2 is no longer increased, or only slightly so [7].

Table 2 summarizes the changes in acid-base parameters occurring in the dialysis circuit (inlet vs outlet, dialysate and blood) in a spot BHD time, as well as the prospective changes in systemic (pre-filter) blood along the dialysis session in a representative patient.

In quantitative terms dialysis-associated CO_2 load to patients amounts to about 60 mmol/hour, about 10% of endogenous metabolic load [8]; accordingly, it is estimated that an increase of about 10% of the pulmonary ventilation is necessary for the disposal of this CO_2 load. In occasional patients with impaired respiratory reserve, CO_2 retention and respiratory acidosis may develop in the course of BHD [3]. Patients with chronic lung disease start BHD with higher levels of pCO_2 and lower pO_2 than healthy controls, and achieve higher pCO_2 and lower pO_2 during the first hour of treatment [7]. With higher dialysate acetate concentration (4 or 5 mM), respiratory difficulties are known to occur even more frequently [1]. While slowly developing hypercapnia is usually well tolerated by the body, acute hypercapnia may have serious adverse consequences on heart function and rhythm, coronary flow past a critical stenosis, mental status (with both agitation and depression of consciousness), pulmonary function (pulmonary vasoconstriction and ventilation/perfusion mismatch) and cell metabolism [9]. It is of note that our patients, as well as a similar case [10], was acutely symptomatic a short time after the beginning of dialysis, indicating that the rapidity in change, rather than absolute pCO_2 level, was responsible for symptoms. Discontinuation of dialysis and associated CO_2 load rapidly restores clinical condition [10, 11].

To overcome the risk of CO_2 overload in patients with reduced respiratory reserve needing dialysis alternative modalities to traditional BHD are to be sought; since dialysate is the source of CO_2 load, one might envisage as a first approach to reduce dialysate flow to less than the traditional 500 ml/min, i.e. to about 200–300 ml/min. No published data concerning gas and pulmonary changes during a low-volume dialysate exist, to our knowledge; reduced efficiency (in terms of quantitative waste solute removal) of such a procedure has to be anticipated, requiring longer or more frequent sessions [12]. An alternative choice might be acetate-based hemodialysis (i.e. without bicarbonate), which is associated with CO_2 loss through the dialyzer [13]. However this technique also induces profound pulmonary hypoventilation with intradialytic hypoxia; additionally, acetate-based dialysate is almost unavailable today from the market. It should be noted that substituting acetic acid with other acidifying compounds (e.g. citric acid, as in current use, at a final 1 mM concentration) in BHD does not result in less CO_2 generation, since the same amount of HCO_3- reacts with the acid (which dissociates 3 protons).

Finally, a different approach to the CO_2 problem is AFB. This type of hemodialysis uses a completely buffer-free dialysate and relies in the direct post-dilution (post-filter) infusion of isotonic bicarbonate for correction of acidosis [14, 15]. It is a diffusion/convection-based methodology, whereby bicarbonate losses and convective fluxes in the dialyzer are matched by post-dilution bicarbonate reinfusion; convection fluxes and reinfusion rates are modeled in order that a progressive rise of positive bicarbonate balance and of systemic bicarbonate blood levels induce a progressive increase of bicarbonate loss in the dialyzer until a pre-defined equilibrium between infusion and losses is reached, with stable bicarbonate systemic blood levels. Table 1 summarizes composition of dialysate in BHD and AFB, and of bicarbonate solution for reinfusion in AFB; it can be seen that almost no

Table 2. Acid-base and electrolyte profile during a representative BHD session
A: Instant evaluation in dialysate and bloo (inlet and outlet), after 60 min from treatment start. B: prospective changes in systemic (inlet filter) blood.
Of note is the CO_2 gain in the outlet blood, with normal pCO_2 and progressive increase of bicarbonate in systemic (inlet) blood throughout the dialysis course.
All data were measured in a STAT PROFILE® pHOx® Plus Analyzer (Nova Biomedical). HCO^{3-} concentration in dialysate was calculated from pH and pCO_2 with Henderson-Hasselbach equation and pK = 6.33 – 0.5 x SQRoot (([Na]/1000) + ([K]/1000)) [16]

A	Dialysate inlet	Dialysate outlet	Blood inlet	Blood outlet
pH	7.28	7.49	7.44	7.29
pCO_2	72.3	34.1	34.8	59.3
pO_2	102.4	114.2	88.8	95.3
HCO^{3-}	34.4	26.3	23.8	28.9
K^+	1.99	2.56	3.71	2.64
Na^+	132.1	132.7	137.7	141.7
Cl^-	97.5	102.5	107.6	108.3

B	Blood inlet Basal	Blood inlet 60 min	Blood inlet 120 min	Blood inlet 180 min	Blood inlet 240 min
pH	7.30	7.44	7.45	7.46	7.45
pCO_2	38.0	34.8	36.1	37.4	39.2
pO_2	102.0	88.8	79.0	98.3	80.2
HCO^{3-}	20.0	23.8	25.4	26.8	27.6
K^+	4.5	3.71	3.60	3.44	3.34
Na^+	138.3	137.7	136.9	135.0	135.1
Cl^-	104.0	107.6	108.5	109.1	108.3

Table 3. Acid-base and electrolyte profile during a representative AFB session
A: instant evaluation of dialysate and blood (inlet and outlet), after 60 min from the start. B: prospective changes in systemic (inlet) blood.
Of note is the CO_2 and bicarbonate gain in outlet dialysate, normal pCO_2 in systemic (inlet) blood throughout the session, and the bicarbonate increase in post-reinfusion blood resulting in progressive increase in systemic levels up to the end of treatment.
All data were measured in a STAT PROFILE® pHOx® Plus Analyzer (Nova Biomedical). HCO^{3-} concentration in dialysate was calculated from pH and pCO_2 with Henderson-Hasselbach equation and pK = 6.33 – 0.5 x SQRoot (([Na]/1000) + ([K]/1000)) [16]

A	Dialysate inlet	Dialysate outlet	Blood inlet («artery» line)	Blood oulet, pre-reinfusion	Blood post-reinfusion («venous» line)
pH	7.36	7.41	7.43	7.38	7.44
pCO_2	5.0	16.9	36.8	7.30	36.9
pO_2	145.8	113.5	67.7	83.2	77.4
HCO^{3-}	2.9	10.9	25.2	4.3	25.6
K	2.08	2.74	3.97	2.73	2.29
Na^+	136.9	133.8	140.9	142.0	139.3
Cl^-	136.1	129.1	105.7	125.0	103.6

B	Blood inlet Basal	Blood inlet 60 min	Blood inlet 120 min	Blood inlet 180 min	Blood inlet 240 min
pH	7.41	7.43	7.41	7.43	7.44
pCO_2	39.0	36.8	41.6	40.8	38.7
pO_2	78.6	67.7	60.1	64.5	69.2
HCO^{3-}	23.5	25.2	26.7	27.5	28.1
K^+	6.61	3.97	3.90	3.66	3.32
Na^+	137.5	140.9	141.1	140.1	139.6
Cl^-	104.9	105.7	105.7	105.9	106.2

CO_2 is present in the AFB dialysate, which in fact takes up CO_2 (and bicarbonate) from the patient (about 15–20 mmol/hour CO_2; see dialysate out, Table 3A). This is much less than CO_2/H_2CO_3 infused with the bicarbonate solution (about 4–6 mmol/hour); since pH of bicarbonate reinfusion solution is higher than in patient's blood, some H_2CO_3/CO_2 may be formed by chemical reaction of bicarbonate with weak acids in blood (e.g. monobasic phosphate), in a quantity hard to calculate, possibly not higher than a few mmoles along the whole treatment time. Thus infused CO_2 remains far less than CO_2 lost through the dialyzer, and actually pCO_2 slightly falls in systemic blood during AFB. Table 3 summarizes the changes in acid-base parameters occurring in dialysate and blood along the dialysis circuit in a «spot» AFB time, as well as the prospective changes in systemic (pre-filter) blood along an AFB session in a representative patient. One should note that in this bicarbonate and acetate-free dialysate electroneutrality is maintained by high Cl^- concentration; this does not result in hyperchloremia because bicarbonate reinfusion (at an almost «physiological» Na^+ concentration) dilutes plasma anions of the same magnitude that it increases bicarbonate concentration. The manufacturer provides a simple electronic program or tables to set reinfusion and convection fluxes according to the bicarbonate bag in use (of 3 available: 120, 145 and 167 mM, the 145 mM being the most used), and pre-set final bicarbonate and Na^+ concentrations.

In our patient we modeled a «safe» final bicarbonate level of 23 mM, but more convenient levels of 28–30 mM are usually chosen in standard patients. Table 4 summarizes acid-base and electrolyte changes in the presented patient's arterial blood at different points of treatment: as can be seen, $paCO_2$ remained stable, target bicarbonate level was achieved, and no hypoxia occurred.

Take home message: BHD is associated with a small, but significant CO_2 load to the patient; in patients with

Table 4. Acid-base and electrolyte parameters during the first AFB treatment in our critical patient

	Arterial blood* Basal	Arterial blood* 90 min	Arterial blood* 240 min
pH	7.37	7.34	7.34
pCO_2	34.7	37.7	39.3
pO_2	65.9	126.7	96.8
HCO^{3-}	20.3	21.5	22.5
K^+	4.06	3.48	3.42
Na^+	135.1	136.4	136.6
Cl^-	105.0	105.4	106.0

****Arterial blood, rather than inlet blood, was used in this patient with a central venous catheter as a dialysis access.***
All data were measured in a STAT PROFILE® pHOx® Plus Analyzer (Nova Biomedical).

reduced pulmonary reserve (for acute or chronic conditions), this load may be associated with acute rise in systemic blood pCO_2 and acute symptoms of respiratory distress. AFB avoids to load patients with CO_2 (actually it removes it) and does not negatively impact on gas blood gases regulation in the course of a dialysis session.

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БЕЗАЦЕТАТНА БІОФІЛЬТРАЦІЯ В ЗАПОБІГАННІ ІНТРАДІАЛІЗНІЙ ГІПЕРКАПНІЇ В ПАЦІЄНТКИ З ОБМЕЖЕНИМ ЛЕГЕНЕВИМ РЕЗЕРВОМ

Резюме. Повідомлення про випадок гострої гіперкапнії, що стався під час сеансу бікарбонатного гемодіалізу. У 82-річної пацієнтки виникла серцева недостатність, легенева гіпертензія та загострилась хронічна обструктивна хвороба легень. У пацієнтки розвинувся гострий симптоматичний дихальний ацидоз відразу після початку сеансу бікарбонатного гемодіалізу з артеріальним pH 7,25 і $paCO_2$ 48,1 мм рт.ст. Це було пов'язано з добре відомим перенасиченням CO_2 з діалізату на основі бікарбонату, про яке часто забувають.

Ми лікували пацієнтку шляхом безацетатної біофільтрації зі стабільним $paCO_2$ протягом усього сеансу. Динаміку газів крові під час гемодіалізу наведено в таблицях.

Ключові слова: респіраторний ацидоз, гіперкапнія, бікарбонатний гемодіаліз, безацетатна біофільтрація.

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БЕЗАЦЕТАТНАЯ БИОФИЛЬТРАЦИЯ В ПРЕДОТВРАЩЕНИИ ИНТРАДИАЛИЗНОЙ ГИПЕРКАПНИИ У ПАЦИЕНТКИ С ОГРАНИЧЕННЫМ ЛЕГОЧНЫМ РЕЗЕРВОМ

Резюме. Сообщение о случае острой гиперкапнии, произошедшем в ходе сеанса бикарбонатного гемодиализа. У 82-летней пациентки возникла сердечная недостаточность, легочная гипертензия и обострение хронического обструктивного заболевания легких. У пациентки развился острый симптоматический дыхательный ацидоз сразу же после начала сеанса бикарбонатного гемодиализа с артериальным pH 7,25 и $paCO_2$ 48,1 мм рт.ст. Это было связано с хорошо известным перенасыщением CO_2 из диализата на основе бикарбоната, о чем часто забывают.

Мы лечили пациентку путем безацетатной биофильтрации со стабильным $paCO_2$ на протяжении всего сеанса. Динамика показателей газов крови во время гемодиализа представлена в таблицах.

Ключевые слова: респираторный ацидоз, гиперкапния, бикарбонатный гемодиализ, безацетатная биофильтрация.