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A very simple formula to compute pCO_2 in hemodialysis patients

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Abstract
Purpose To identify mixed acid–base disorders, clinicians must estimate the value of partial pressure of carbonic dioxide (pCO_2), complying with the reduced plasma bicarbonate concentration (HCO_3). What is the most appropriate equation relating the two quantities in chronic hemodialysis patients remains unknown. Chronic hemodialysis patients remains unknown, which motivates our study.
Methods Among a large database of blood gas analysis from chronic hemodialysis patients, we selected 291 blood samples showing $HCO_3 < 24$ mmol/L and, among these, we further selected a subset of samples claimed for pure metabolic acidosis. A linear approximation based upon the least-square criterion was adopted to derive the best-fit equation. The differences between this and other commonly used formulas were computed in terms of root mean square (RMS) errors.
Results In chronic hemodialysis patients, the reduction in pCO_2 due to metabolic acidosis is better predicted multiplying by 1.2 the reduction in HCO_3, or by using the expression $pCO_2 = HCO_3 + 15$; the two approaches lead to almost the same results. In contrast, the equation $pCO_2 = 1.5 \times HCO_3 + 8$, known as Winters' formula, exhibits larger errors.
Conclusions The easy-to-use expression $pCO_2 = HCO_3 + 15$ seems suitable for the daily clinical practice in hemodialysis patients. However, if HCO_3 value is lower than 12 mmol/L, a threshold at which different formulas return almost the same value, also Winters' formula, derived in the 60's from patients with low values of HCO_3, could be used.

Keywords Bicarbonate · Carbon dioxide · Metabolic acidosis · Respiratory compensation · Winters' formula

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Introduction

Metabolic acidosis is the more frequent acid–base derangement in hemodialysis patients as a consequence of kidney failure [1, 2]. However, mixed acid–base disorders are not a rare occurrence because respiratory diseases can complicate the clinical picture of this frail population. To identify the presence of additional acid–base disorder, clinicians must evaluate the physiologic respiratory response to metabolic acidosis or, in other words, they must estimate the value of partial pressure of carbonic dioxide (pCO_2) complying with the reduced plasma bicarbonate concentration (HCO_3). If the measured pCO_2 value is larger or smaller than the "expected" one, then mixed disorder occurs. Incorrect calculations could lead to wrong diagnosis and inappropriate treatment, but a single and widely accepted formula to compute the pCO_2 in the presence of metabolic acidosis seems not available in the literature. The most frequently used are: $pCO_2 = 1.5 \times HCO_3 + 8$—known as Winters' formula [3–5]—and the common practical rule that reads "the reduction in pCO_2 with respect to its normal value equals 1.2 multiplied by the reduction in HCO_3 with respect to its normal value" [6–9]. A rarely used alternative expression is $pCO_2 = HCO_3 + 15$ [4, 5, 9]. These formulas have been validated in simple acid–base disorders, but not in double and triple disorders [8] that often occur in hemodialysis patients featured by various comorbidities. Moreover, in this scenario, a specific HCO_3 value may be due to more than one simple acid–base disorder, i.e., metabolic acidosis or respiratory alkalosis, as well as by several disorders simultaneously occurring. This notwithstanding, in daily clinical practice, clinicians have to predict the expected value of CO_2 in order to identify acute illness overlapping chronic kidney disease. What is the most appropriate equation to be applied to chronic hemodialysis patients is unknown, and this motivates our analysis.

Materials and methods

Patients and data collection

The present study is based on the database of arterial blood gas analysis samples (henceforth, simply "samples") collected at the hemodialysis unit of "Maria Rosaria" Clinic, Pompeii, Italy, over the period from January 2008 to December 2012. In this database, samples were labeled as "arterial" if the oxyhemoglobin saturation was equal to that displayed by a digital pulse oximeter placed on the hand without vascular access, or if the oxyhemoglobin saturation was larger than or equal to 97 %.

We have selected the samples drawn by the arteriovenous fistula needle, just before the treatment of patients on bicarbonate hemodialysis scheduled at rate of three sessions per week, and only patients with at least one available sample per year have been included in the analysis. To avoid the inclusion of patients with acute illness, samples withdrawn during the first six months of dialysis vintage, and those ones obtained during hospital admission, have been discarded, thus yielding a dataset of 339 samples taken from 30 patients, see Table 1. From each sample the values of pH, HCO_3 and pCO_2, were obtained. Note that the gas analyzer computes the value of the HCO_3 by the measured values of pCO_2 and pH. Among this dataset, we selected 291 blood samples showing $HCO_3 < 24$ mmol/L. This cutoff value was chosen to compare our results with those reported in the literature [6, 7]. A further analysis was carried out in the subgroup of blood samples featuring pH < 7.38, $HCO_3 < 22$ mmol/L and $pCO_2 < 38$ mmHg, claimed for pure metabolic acidosis according to widely accepted criteria [10]. It is worth mentioning that the availability of a gas analyzer (OMNI S-4, Roche Diagnostic) at the hemodialysis unit made it possible to process the collected samples within few minutes from the withdrawn, thus ensuring the reliability of the measured values.

Table 1 Main characteristics of the patients involved in the present study

Number of patients (male/female)	30 (14/16)
Number of samples (1st/2nd/3rd dialysis of the week)	339 (129/109/101)
Number of samples per patient, mean (±SD)	11.3 (±4.3)
Age in years, median, 1st–3rd quartile	70.9 (65.5–79.2)
Vintage in months, median, 1st–3rd quartile	40.2 (21.8–100.85)
Interdialytic weight gain (%), mean (±SD)	2.8 (±1.6)
Diabetes mellitus	36.7 %
Ischemic heart disease	30 %
Chronic pulmonary disease	20 %

Table 2 Main blood gas analysis statistics (339 samples)

	Mean ± SD	1st–3rd quartile	2.5th–97.5th percentile
pH	7.389 ± 0.043	7.360–7.420	7.303–7.447
HCO_3 (mmol/L)	21.6 ± 2.4	20–23.1	17.2–26.3
pCO_2 (mmHg)	36.6 ± 4.5	34–39	28.3–45.5

Statistical analysis

Preliminary, we check the Gaussianity of the datasets by resorting to a standard Chi-square goodness-of-fit test. Then, we focus on the following quantities: mean value, standard deviation (SD), median value, quartiles and percentiles. To obtain mathematical models relating sets of data, we adopt the linear approximation method based upon the least-square criterion. Accordingly, the differences between the prediction of the model and the data are computed in terms of root mean square (RMS) errors.

Results

As shown in Table 1, our dataset consists of aged patients. Thanks to the aforementioned criteria for selecting the samples, our study involves patients with less severe comorbidities and, as a consequence, with long staying in dialysis. Acid–base parameters (see Table 2) showed numbers consistent with compensated mild metabolic acidosis. HCO_3 values are typical of modern dialysis population with mean value not so far from the *normal* value. Values of pCO_2 are slightly reduced as a result of respiratory compensation. These values agree with compensated mild metabolic acidosis and, alone or superimposed, respiratory alkalosis. However, inspection of individual data suggests that all the four acid–base disorders could be present.

In this dataset, the relationship between pCO_2 and HCO_3 as linear best-fit equation was found in the form:

Table 3 Expected pCO_2 in chronic hemodialysis patients

	Blood samples featuring $HCO_3 < 24$ mmol/L	Blood samples claimed for metabolic acidosis
Number of samples	291	65
Best-fit equation	$pCO_2 = 1.13 \times HCO_3 + 11.96$	$pCO_2 = 1.28 \times HCO_3 + 10.57$
Root mean square error (mmHg)	3.07	1.20

Table 4 Root mean square errors pertaining to other formulas applied to our dataset

	Blood samples featuring $HCO_3 < 24$ mmol/L	Blood samples claimed for metabolic acidosis (mmHg)
"Winters' formula" $pCO_2 = 1.5\ HCO_3 + 8$	4.85	2.06
"Practical rule" $pCO_2 = 1.2 \times HCO_3 + 11.2$	3.14	1.50
"Alternative formula" $pCO_2 = HCO_3 + 15$	3.09	1.56

$pCO_2 = 1.13 \times HCO_3 + 11.96$, with RMS error amounting to 3.07 mmHg (see Table 3, left column). As shown in Table 4 (left column), Winters' formula applied to these data yields an RMS error of 4.85 mmHg. With regard to the common practical rule, if 40 mmHg and 24 mmol/L are the normal values of pCO_2 and of HCO_3, respectively, then such practical rule reads: $pCO_2 = 40 - [24 - HCO_3] \times 1.2$, which can be equivalently rewritten as $pCO_2 = 1.2 \times HCO_3 + 11.2$. The RMS error pertaining to this expression is 3.14 mmHg. Finally, if we use the expression $pCO_2 = HCO_3 + 15$, then the RMS error amounts to 3.09 mmHg.

At this point, we focus our analysis to the narrowed dataset consisting of samples for which pH < 7.38, $HCO_3 < 22$ mmol/L and $pCO_2 < 38$ mmHg, which is the typical picture of metabolic acidosis. We found 65 samples from 21 patients matching these criteria. In this group of samples, the mean value (±SD) of pH is 7.353 (±0.02), that of HCO_3 is 19.1 (±1.3) mmol/L, with values ranging from 15.1 to 21.2 mmol/L. Finally, the mean value of the pCO_2 value is 35.0 ± 2.1 mmHg. The statistical correlation between HCO_3 and pCO_2 is relevant (Pearson's *r* coefficient is 0.82), and the best-fit linear equation is found as: $pCO_2 = 1.28\ HCO_3 + 10.57$ mmHg (see Table 3, right column, and Fig. 1). The RMS error pertaining to this formula is 1.20 mmHg. By applying Winters' formula, the "common practical rule" and the "alternative formula" yield RMS errors amounting to 2.06, 1.50 and 1.56 mmHg, respectively (see Table 4, right column).

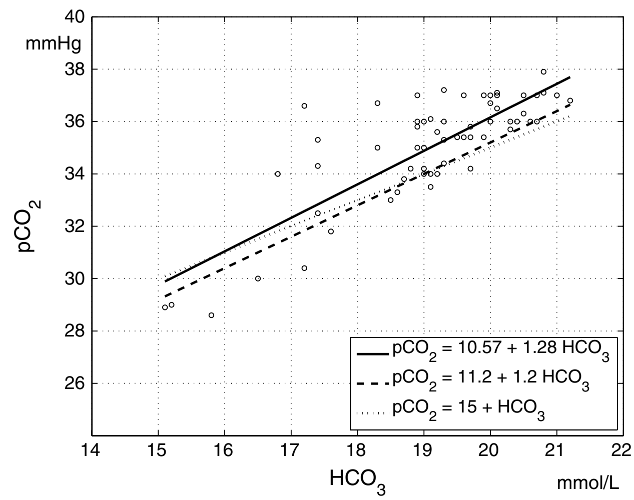

Fig. 1 Blood samples claimed for metabolic acidosis. The linear approximations represent the best fit (*solid line*), the "practical rule" (*dashed*) and a simpler, yet accurate, expression (*dotted*)

Discussion

Metabolic acidosis is the most common acid–base disorder in hemodialysis patients, due to kidney failure. Secondary ventilatory response occurs to compensate reduction in HCO_3 yielding a reduction in pCO_2 [8]. However, in this population, different acid–base disorders can arise as isolated disturbance or as mixed disorders, thus affecting the pCO_2 value. This notwithstanding, in the complex and heterogeneous scenario of daily clinical practice, clinicians, facing with low HCO_3 value, try to predict the expected value of CO_2 in order to identify acute illness overlapping chronic kidney disease. Acute respiratory disorders can be life threatening and could require rapid actions, often bedside. Therefore, the availability of reliable and easy-to-use equations is essential. However, a single and widely accepted formula seems not available in the literature. Despite its popularity, Winters' formula [3–5] seems not suitable to infer mixed acid–base disorders in the clinical context of hemodialysis units because of large RMS error (see Table 4, left column) even in the case of pure metabolic acidosis (see Table 4, right column). This is not an unexpected finding since Winters' formula was derived by a patient population of the 60's, with a mean value of HCO_3 of 9.9 mmol/L, while *modern* hemodialysis population [2], and also the patients under investigation (see Table 2), show a mean value of HCO_3 which is approximately the double of that.

The common practical rule "the reduction in pCO_2 equals 1.2 multiplied by the reduction in HCO_3" and its equivalent form $pCO_2 = 40 - [24 - HCO_3] \times 1.2$ are widely used [6–9]. However, we would like to stress that, despite labeled as *practical*, it requires some calculation and, above all, while there is general agreement on the normal value of pCO_2, the same is not true for that of HCO_3. At any rate, the common practical rule always exhibits a smaller RMS error than that obtained with Winters' formula (see Table 4) and therefore should be preferred in this population. The aforementioned formulas might seem conflicting with each other, but it is not necessarily so. In fact, as pointed out by Bushinsky et al. [6], the relationship between pCO_2 and HCO_3 is curvilinear with a slope of 1.5 (the same of Winters' formula) up to a value of HCO_3 of 10 mmol/L, and with a slope close to 1.2 (which resembles both the practical rule and our best-fit equations) for larger values of HCO_3. Accordingly, the appropriateness of the formulas depends upon the range which the value of HCO_3 belongs to, or in other words, no linear approximation may be appropriate for all possible values of HCO_3.

Surprisingly, the little-known and rarely used equation $pCO_2 = HCO_3 + 15$, also found in some textbook, applied to our data showed almost the same (low) error of the common practical rule (see Table 4). It also has the evident advantage of simplicity, and hence has to be preferred in modern chronic hemodialysis patients.

However, also in this population a quarter of samples exhibits HCO_3 values <20 mmol/L (see Table 2), and in daily clinical practice more severe metabolic acidosis can also occur. By setting $HCO_3 = 12$ mmol/L, all formulas yield almost the same value of pCO_2. Thus, a possible recommendation for bedside acid–base interpretation could be to use the simpler expression $pCO_2 = HCO_3 + 15$ when the value of HCO_3 is above 12 mmol/L, and to resort to Winters' formula for lower values of HCO_3, as already suggested elsewhere [11]. The results of the present study are certainly biased by the retrospective and single-center nature of the investigation, implying that a validation in terms of a larger, prospective, and multi-center data collection would be certainly desirable. This represents part of our ongoing research.

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Conflict of interest The authors declare that they have no conflict of interest.

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