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Original article

The use of elements of the Stewart model (Strong Ion Approach) for the diagnostics of respiratory acidosis on the basis of the calculation of a value of a modified anion gap (AG_m) in brachycephalic dogs

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Abstract

Apart from the HH equation, the acid-base balance of an organism is also described by the Stewart model, which assumes that the proper insight into the ABB of the organism is given by an analysis of: pCO_2, the difference of concentrations of strong cations and anions in the blood serum – SID, and the total concentration of nonvolatile weak acids – Acid total. The notion of an anion gap (AG), or the apparent lack of ions, is closely related to the acid-base balance described according to the HH equation. Its value mainly consists of negatively charged proteins, phosphates, and sulphates in blood. In the human medicine, a modified anion gap is used, which, including the concentration of the protein buffer of blood, is, in fact, the combination of the apparent lack of ions derived from the classic model and the Stewart model. In brachycephalic dogs, respiratory acidosis often occurs, which is caused by an overgrowth of the soft palate, making it impossible for a free air flow and causing an increase in pCO_2 – carbonic acid anhydride The aim of the present paper was an attempt to answer the question whether, in the case of systemic respiratory acidosis, changes in the concentration of buffering ions can also be seen. The study was carried out on 60 adult dogs of boxer breed in which, on the basis of the results of endoscopic examination, a strong overgrowth of the soft palate requiring a surgical correction was found. For each dog, the value of the anion gap before and after the palate correction procedure was calculated according to the following equation: AG = ([Na^+ mmol/l] + [K^+ mmol/l]) – ([Cl^-mmol/l]+[HCO_3^-mmol/l]) as well as the value of the modified AG – according to the following equation: AG_m = calculated AG + 2.5 x (albumins$_r$ – albumins$_d$). The values of AG calculated for the dogs before and after the procedure fell within the limits of the reference values and did not differ significantly whereas the values of AG_m calculated for the dogs before and after the procedure differed from each other significantly. Conclusions: 1) On the basis of the values of AG_m obtained it should be stated that in spite of finding respiratory acidosis in the examined dogs, changes in ion concentration can also be seen, which, according to the Stewart theory, compensate metabolic ABB disorders 2) In spite of the fact that all the values used for calculation of AG_m were within the limits of reference values, the values of AG_m in dogs before and after the soft palate correction procedure differed from each other significantly, which proves high sensitivity and usefulness of the AG_m calculation as a diagnostic method.

Key words: acid-base balance, the Stewart model, brachycephalic syndrome

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Introduction

For describing the acid-base balance of living organisms, the Bronsted theory is used according to which acid is a substance that gives up H^+ ions, whereas base is a chemical that accepts H^+ ions. A pH of a solution is determined by concentration of hydrogen ions which depends on the degree to which an acid dissociates in a solution: the stronger an acid, the higher the degree of dissociation is. Classically, the acid-base balance is described by the Henderson-Hasselbach equation, where the blood pH is the resultant of the metabolic component expressed by concentration of bicarbonates (HCO_3^-) and the respiratory component or the pressure of partial carbon dioxide (pCO_2), which is carbonic acid anhydride (Di Bartola 2006a, Balakrishnan et al 2007, Sławuta et al. 2010).

$$pH = 6.11 + \log \frac{[HCO_3^-]}{pCO_2 \times 0.226}$$

Apart from the HH equation, the acid-base balance of an organism is also described by the Stewart model (Stewart 1978, 1983). According to this theory, which is called the Strong Ion Approach, the ions in the blood serum can be divided into two groups – nonbuffer ions and buffer ions. The first group, which is also called strong ions, is fully dissociated and does not produce the buffering effect. The following cations: Na^+, K^+, Ca^{2+}, and Mg^{2+} and anions: Cl^-, lactate, β-hydroxybutrate, acetoacetate, and SO_4^- are counted as the most important strong ions (Constable 2003). The buffer ions derive from plasma weak acids or those which are not fully dissociated and may give up or accept H^+ ions or those which, according to the Bronsted theory, have a function of an acid or a base (Corey 2005). The level of Atot consists mainly of proteins and phosphates, which practically means that an increase in the total protein concentration causes a decrease in the pH (Figge et al. 1991, 1998, Constable 2003).

In practice, the Stewart model is used to diversify the ABB disorders when their interpretation according to the classic method is doubtful (Sławuta and Glińska-Suchocka 2012, 2013), allows evaluation of chances of the patient survival in the course of the severe metabolic acidosis (Bruegger et al. 2007), and often enables conducting of a more effective treatment (Siegling-Vlitakis et al. 2007).

The notion of an anion gap (AG) is closely related to the acid-base balance described according to the classic model. To maintain electroneutrality of body fluids, cation concentration must be equal to anion concentration. However, in the case of comparison of the concentration of the main cations: Na^+ i K^+ with the concentration of the main anions: Cl^- i HCO_3^- in the blood serum, there will be an apparent lack of the latter or the so-called anion gap: AG = ([Na^+ mmol/l] + [K^+ mmol/l]) – ([Cl^- mmol/l]+ [HCO_3^- mmol/l]) (Constable 2000, Morris and Low 2008). Its value amounts to 12-24 mmol/l in dogs and it mainly consists of negatively charged proteins, phosphates, and sulphates in blood (Di Bartola 2006b). According to the Stewart model, there is the notion of strong ion gap (SIG). Unlike the classic anion gap, the concentration of blood serum buffers i.e. albumins and phosphates is included in its calculation, thus, its diagnostic value is greater compared to the anion gap (Kellum et al. 1995, Wooten 2004). Changes of SIG and their clinical significance in dogs and cats have been already described in detail (Sławuta et al. 2010, Sławuta and Glinska-Suchocka 2012). In the human medicine, especially for patients undergoing intensive therapy, a modified anion gap is used, which is calculated according to the following equation: AG_m = calculated AG + 2.5 x (albumins $_{reference}$ – albumins $_{determined}$) (Figge et al 1998, Oh 2010), which, including the concentration of the protein buffer of blood, is, in fact, the combination of the apparent lack of ions derived from the classic model and the Stewart model.

In brachycephalic dogs, due to the structure of their viscerocranium, the so-called brachycephalic syndrome occurs which is a breathing disorder due to anatomic obstacles in the upper airways, which, making it impossible for a free air flow, cause impaired CO_2 discharge, which, according to the HH equation, causes formation of respiratory acidosis as a result of an increase in pCO_2 – carbonic acid anhydride (Correy 2005, Curley et al. 2010, Sławuta et al. 2010, Hoareau et al. 2012).

The aim of the present paper was an attempt to answer the question whether, in the case of systemic respiratory acidosis, changes in the concentration of ions can also be observed, which, according to the Stewart theory, compensate metabolic disorders of the acid-base balance.

Materials and Methods

The study was carried out on 60 adult dogs of boxer breed (32 males and 28 females) in which, on the basis of the results of endoscopic examination, a strong overgrowth of the soft palate tissue requiring a surgical correction was found. Prior to the surgery and on the 14th day after the surgery, hematologic testing of venous blood was carried out in each dog, including the following: blood cell counts, blood smear, RBC, WBC, and concentration of Na^+, K^+ and Cl^- and albumins. In addition, prior to the surgery and on the 14th day after the surgery, the acid-base balance parameters were determined in a sample of arterial blood in each animal. During surgical correction of the soft palate, swelling of the mucous membrane of the operated area commonly occurs which is caused by the operating surgeon's manipulation and tissue reaction to cutting and laying sutures. The authors of this paper assumed that on the 14th day after the surgery, the surgical wound healing process and potential influence of the drugs used during the surgery would finish, and the ABB data obtained regarding the ABB of the dogs examined would be credible.

For the examination of the ABB parameters, 1 ml of the full blood was drawn from the femoral artery into a heparinized syringe equipped with a needle with an internal diameter of 0.7 mm and was aspirated without access to air. A spot where the needle was injected was pressed for around five minutes after the blood collection to avoid formation of a haematoma. The blood was passed on to the analytical laboratory immediately after its collection. With the use of the Blood Gas Analyzer Osmetech OPTI CCA unit, the following was determined in the drawn sample of arterial blood: the blood pH, HCO_3^-, and pCO_2. As the physiological norm, the following ranges of values of the pH, pCO_2, and HCO_3^- were assumed, provided for the arterial blood of the dogs by Di Bartola (2006a).

On the basis of the data obtained, the value of the anion gap before and after the palate correction procedure was calculated according to the following equation: AG = ([Na^+ mmol/l] + [K^+ mmol/l]) – ([Cl^- mmol/l]+[HCO_3^- mmol/l) (Di Bartola 2006a, Oh 2010) as well as the value of the modified AG – according to the following equation: AG_m = calculated AG + 2.5 x (albumins$_r$ – albumins$_d$) (Oh 2010) where albumins$_d$ are the concentration of albumins determined for the blood serum of the dogs examined, whereas albumins$_r$ are the reference value of their concentration in the blood plasma – in this paper the value of 44.5 g/l was assumed and used in the equation i.e. an average value of the proper range of concentration of albumins in the blood plasma of dogs provided by Winnicka (1997). The results were subject to the statistical analysis. An average value, a standard deviation, and a range of the values obtained were calculated. In order to ascertain significance of the differences, the t-Student test was applied as well as the Wilcoxon matched pair test for related variables.

The endoscopic examination and the surgical procedure were carried out in general anaesthesia. In premedication, the patients received intramuscularly medetomidine at a dose of 30 µg/kg of body mass. After 15 minutes, fentanyl was administered intravenously at a dose of 2 µg/kg of body mass together with atropine at a dose of 40 µg/kg of body mass. The induction was carried out with the use of propophol at a dose of 4mg/kg. Doses of medications and the plan of anaesthesia procedure were in accordance with those described by other researchers (Ambros et al. 2008, Covey-Crump and Murison 2008, Enouri et al. 2008, Grint et al. 2010). Following the insertion of an endotracheal tube and putting in adaptation sutures, surplus tissue in the soft palate was cut off – a place where the incision was performed was located between the upper part of the epiglottis adjacent to the abdominal side of the soft palate and the middle point in pharyngeal tonsils. Then, the surgical anastomosis of the wound was performed with the use of absorbable material with a thickness of 4-0 and continuous suture. After the procedure, general antibiotic cover was applied.

For the performance of the study, consent of the Local Ethics Commission II for Animal Experiments in Wrocław number 07/2008 was received.

Results

The comparison of mean values of the ABB parameters obtained before and after the surgical procedure in the examined boxer dogs is presented in Table 1 – levels of pH of arterial blood and pCO_2 obtained for the examined groups were statistically significantly different. The pH, which was lower before the procedure but still within the normal range, pCO_2 above the normal range, and concentration of HCO_3^- at its upper limit are the signs, according to the interpretation rules of the classic model, of an occurrence of the ABB disorders of the compensated respiratory acidosis type (Kellum 2000, Di Bartola 2006a, Sławuta et al. 2010). An average concentration of ions and albumins in the blood serum before and after the surgical procedure was similar and fell within the physiological norms (Table 2). An average value of AG calculated for the dogs before and after the procedure fell within the limits of the reference values and amounted to 14.49 ± 2.27 and 19.34 ± 1.96 mmol/l, respectively. The results obtained did not differ from each other significantly. The values of AG_m calculated for the dogs before and after the procedure differed from each other significantly ($p \leq 0.01$), and its average value amounted to 35.38 ±2.86 mmol/l and 48.75 ±2.56 mmol/l, respectively (Table 3).

Discussion

As mentioned earlier, according to Peter Stewart's assumptions „purely breathing" disorders should be described as in the classic model i.e. on the basis of

Table 1. Effect of soft palate correction procedure on ABB parameters – mean values and standard deviation, n=60.

Before procedure (37°C)			After procedure (14 th day after procedure, 37°C)		
pH	pCO_2 mmHg	HCO_3^- mmol/l	pH	pCO_2 mmHg	HCO_3^- mmol/l
7.41* ±0.03	44.03* ±3.42	25.80 ±1.00	7.43* ±0.01	32.21* ±1.51	22.01 ±1.31

Explanation: * $p \leq 0.01$

Table 2. Concentration of ions, bicarbonates and albumins in blood serum before and after soft palate correction procedure – mean values and standard deviation, n=60.

Before procedure					After procedure (14 th day after procedure, 37°C)				
Na^+ mmol/l	K^+ mmol/l	Cl^- mmol/l	HCO_3^- mmol/l	albumins g/l	Na^+ mmol/l	K^+ mmol/l	Cl^- mmol/l	HCO_3^- mmol/l	albumins g/l
148.51 ±1.30	4.69 ±0.28	112.76 ±1.90	25.80 ±1.00	36.18 ±1.09	141.05 ±1.13	4.45 ±0.27	104.12 ±1.50	22.01 ±1.31	32.73 ±0.93

Table 3. Values of anion gap (AG) and modified anion gap (AG_m) calculated before and after soft palate correction procedure – mean values and standard deviation, n=60.

Before procedure		After procedure (14 th day after procedure)	
AG mmol/l	AG_m mmol/l	AG mmol/l	AG_m mmol/l
14.59 ± 2.27	35.38* ± 2.86	19.34 ± 1.96	48.75* ± 2.56

Explanation: * $p \leq 0.01$

the analysis of pCO_2 and HCO_3. Setting the research objective, the authors have assumed, however, that a living organism must be understood as a a whole and the ABB regulation through the change of pCO_2 and HCO_3^- or concentration of buffering ions is part of the same process that serves to provide homeostasis of the organism. Thus, if an ABB disorder is of systemic type i.e. concerns the whole organism, then ions which buffer the disorder on an intracellular and pericellular level should also react to it, in spite of the fact that the disorder was of „purely breathing" type. The value of pH in the dogs examined, which was lower before the procedure but still within the normal range, an increase in pCO_2, and concentration of HCO_3^- at the upper limit of a standard (Di Bartola 2006a) prove an occurrence of a compensated respiratory acidosis (Kellum 2000, Di Bartola 2006a, Sławuta et al. 2010). In the case of a respiratory acidosis, an organism, which aims at the pH normalization, stimulates kidneys to regenerate HCO_3^-, which increases concentration of these ions in the blood serum (De Morais and Di Bartola 1991, Constable 2000, Morris and Low 2008). In people with the chronic respiratory acidosis, an increase in pCO_2 by each 1 mmHg is accompanied by an increase in HCO_3^- concentration by 0.51 mmol/l (Martinu et al. 2003), which, as it results from the research conducted by Alfaro et al. (1996), is sufficient for normalization of the blood pH in the course of the disorder. In dogs suffering from an acute respiratory acidosis, an increase in pCO_2 by every 1 mmHg is accompanied by a compensatory increase in HCO_3^- by 0.15 mmol/l, whereas, in a chronic acidosis, by 0.35mmol/l (De Morais and DiBartola 1991) or more (Sławuta et al. 2011). On the basis of the analysis of the results obtained, it was found that in the boxer dogs examined, an increase in pCO_2 by 1 mmHg was accompanied by a compensatory increase in HCO_3^- by 0.58 mmol/l on average – which was sufficient, according to the above-mentioned researchers, for the compensation of the disorder (De Morais and DiBartola 1991). The fact that the respiratory acidosis found in the dogs studied was of a systemic type is proved by a phenomenon of kidney compensation which is shown in the results obtained. This observation is in accordance with an observation carried out in other brachycephalic dogs (Sławuta et al. 2011).

A modified AG, including concentration of the protein buffer of the blood is, in fact, a kind of combination of the classic model concept with the Stewart model (Figge et al. 1998, Oh, 2010). In this paper, the calculated value of AG_m, in the dogs before and after the soft palate correction procedure differed significantly, in spite of the fact that all values used for its calculation fell within the limits of reference values. In addition, a range of the values obtained was very interesting – the highest calculated value of AG_m before the soft palate correction procedure, thus at the time when the dogs suffered from the respiratory acidosis, was lower than the lowest value of AG_m calculated after the procedure – 40.42 mmol/l and 44.47 mmol/l, respectively.

The authors of this paper also wanted to take part in the ongoing discussion on which method that describes the ABB disorders describes them in the most complete way (Russel et al. 1996, Constable 2000, McCullough and Constable 2003, Constable and Stampfli 2005, Siegling-Vlitakis et al. 2007, Sławuta and Glińska-Suchocka 2012) and, what is important, which one can be applied in everyday veterinary practice. From the clinical point of view, the answer to these questions is not simple. An interpretation of the ABB and its disorders which uses the HH equation and the blood gasometry is still the most popular in the diagnostics of the ABB disorders in people and animals, and doctors have the equipment for laboratory diagnostics which automatically determines pH, pCO_2 and HCO_3^- and calculates the anion gap, whereas the application of the Stewart model in the clinical practice is difficult because it requires from a diagnostician his/her own time-consuming calculations (Siggaard-Andersen and Fogh-Andersen 1995, Morris and Low 2008), although Stewart model has already been used in dogs for the diagnostics of the metabolic ABB disorders (Sławuta and Glińska-Suchocka 2012, 2013). The classic method has, however, the essential limitations as it does not include an influence of plasma proteins and phosphates on the blood pH, therefore, it should not be applied for those diseases which cause a decrease in production of albumins and albuminuria (e.g. renal or hepatic failure). Due to the compensation phenomenon, it is essential for the interpretation of the ABB disorders on the basis of the HH equation to decide whether an increase/decrease of pCO_2 or an increase/decrease of HCO_3^- primarily occurred, i.e. whether it is a respiratory or metabolic disorder. In the case of heart beat disorders and hemodynamic disorders that result from the former, it is very difficult to decide whether the increase in pCO_2 primarily occurred and the increase in HCO_3^- results from the compensation phenomenon or whether, as a result of loss of Cl^- resulting from the application of diuretics and/or moving of these ions to the peritoneal fluid, kidneys increased regeneration of HCO_3^-, i.e. the metabolic alkalosis primarily occurred. In this case, the Stewart model, which analyzes concentration of buffer and non-buffer ions, allows one to decide which type of the ABB disorder they deal with (Sławuta and Glińska-Suchocka 2012). The analysis of ion concentration also enables one to conduct a more effective treatment. In dogs, the metabolic acidosis resulting from renal insufficiency and septic shock was diagnosed on the basis of the HH equation and, then, concentration of buffer and non-buffer ions was determined which enabled completion of the conducted treatment with their supplementation (Siegling-Vlitakis et al. 2007). Being part of the Stewart model, SIG or strong ion gap, is considered by some researchers to be the most credible indicator of evaluation of chances of the dog survival in the course of hemorrhagic shock as one can determine how advanced the developing metabolic acidosis is on the basis of the analysis of the difference between concentrations of buffer and non-buffer ions (Bruegger et al. 2007). Constabl (2000) suggested application of the classic method in such cases when concentration of total protein, albumins, and inorganic phosphorus in blood serum of an animal is within the norm.

In the light of the results obtained, considering the above-mentioned Constabl's (2000) proposition and taking into consideration other researchers opinions (Bruegger et al. 2007, Siegling-Vlitakis et al. 2007), it can be assumed that a diagnostic procedure scheme should combine both methods, for example, through the calculation of AG_m, especially as the values needed for its calculation are still normally determined in routine laboratory diagnostics. It ought to be remembered that the notion of anion gap describes an APPARENT lack of negative ions as the total positive and negative charges, according to the electrical neutrality principle, must be the same. If we want to use the value of AG and AG_m in the practice of disease diagnostics, we should assume which ions will be routinely determined and calculate/determine ranges of a norm with the use of them. Development of the rules for the use of the AG_m value and its changes in the course of different diseases which cause ABB disorders also requires further detailed research. The authors of this paper are currently working on the above-mentioned issue.

Conclusions

1) On the basis of the values of AG_m obtained it should be stated that in spite of finding respiratory acidosis in the dogs examined, changes in ion concentration can also be observed, which, according to the Stewart theory, compensate metabolic ABB disorders,

2) In spite of the fact that all the values used for calculation of AG_m were within the limits of reference values, the values of AG_m in dogs before and after the soft palate correction procedure differed from each other significantly, which proves high sensitivity and usefulness of the AG_m calculation as a diagnostic method.

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