

**Original Article**

***Blood Anion Gaps and Venoarterial Carbon Dioxide Gradients as Risk Factors in Long-Term Extracorporeal Support***

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**ABSTRACT**

Increases in the blood anion gap (AG) and venoarterial carbon dioxide gradients [p(V-A)CO<sub>2</sub>] may indicate changes in intracellular acid concentration not demonstrated by blood gas measurements. This prospective study examines these two physiologic markers to determine their relationship to extracorporeal membrane oxygenation (ECMO) survival and duration in 100 patients.

Serum electrolytes were drawn every 6 hours and the AG calculated. Simultaneous arterial blood gases and venous blood gases were drawn every 4 hours and the p(V-A)CO<sub>2</sub> calculated. Cumulative averages were then calculated from all the AG and p(V-A)CO<sub>2</sub> values during each ECMO treatment. The average AG was 11 mEq/L. The average p(V-A)CO<sub>2</sub> was 9 mm of mercury (mmHg).

Patients with an AG of 11 mEq/L or less had a 12% mortality and those with a higher AG had a 43% mortality (p=0.0005). Patients with a p(V-A)CO<sub>2</sub> of less than 9 mmHg had a 13% mortality and those with a 9 mmHg or higher gradient had a 35% mortality (p=0.0126). Patients with both a low AG and a low p(V-A)CO<sub>2</sub> had a 7% mortality and survivors were on ECMO 100 (± 37) hours. Patients with both a high AG and a high p(V-A)CO<sub>2</sub> had a 56% mortality and survivors were on ECMO 190 (± 105) hours.

Both mortality and survivors' ECMO time increase as one or both risk factors increase. Patients with increases in both risk factors have a mortality rate 8 times greater and survivors remain on ECMO almost twice as long as those without increased risk factors. Patients may benefit from a perfusion strategy that seeks to minimize the AG and p(V-A)CO<sub>2</sub>.

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## INTRODUCTION

Perfusionists attempting long-term extracorporeal support rely on clinical parameters such as blood gases, mixed venous saturations, blood pressure measurements and cardiac output to guide them in making adjustments to the support system being used. All too often, however, despite maintaining clinical parameters within the accepted normal ranges, the patient fails to recover or dies on support. This is because the two critical parameters followed by perfusionists, oxygen delivery and mixed venous saturation values, may not be predictive of morbidity and mortality (1). Global measurements often do not help to improve survival (2), because they are too insensitive to detect adequate tissue oxygenation (3). The presence of a normal mixed venous oxygen pressure ( $p_{vO_2}$ ) or a normal mixed venous oxygen saturation ( $SVO_2$ ) does not necessarily predict adequate tissue oxygenation (4-7). Two other clinical measurements that do not involve the measurement of oxygen, blood anion gaps (AG) and venoarterial carbon dioxide gradients [ $p(V-A)CO_2$ ], show promise in predicting morbidity and mortality. Therefore, they may assist the perfusionist in planning a strategy for extracorporeal support.

The AG is a non-specific indicator of metabolic status including the degree of aerobiosis (8,9). A sustained, elevated AG is often indicative of lactic acidosis which, in turn, is highly predictive of mortality (10 - 17). The anion gap is often elevated in severe illness and in addition to metabolic acidosis, it can detect such potentially lethal disturbances as ketoacidosis, uremia, and cyanide poisoning (18 - 25). Cyanide poisoning is a subtle, but potentially deadly complication of extended or excessive nitroprusside administration (26 - 28). Two slightly different abbreviated AG measurements are used clinically and can be calculated from serum electrolytes. One calculation subtracts the total of the chloride (Cl) and bicarbonate ( $HCO_3$ ) ions from the sodium (Na) (21);  $Na - (Cl + HCO_3) = AG$ . If electrolytes are reported with total carbon dioxide ( $TCO_2$ ) a similar formula is used (12):  $Na - (Cl + TCO_2) = AG$ . The results are given in mEq/L. In this study the formula utilizing  $TCO_2$  was used.

An elevated AG may persist even when buffer base is given to correct a base deficit (29) eliminating the false reassurance derived from normalizing the base deficit with sodium bicarbonate. The administration of sodium bicarbonate to correct a base deficit also increases the serum sodium concentration. By increasing the sodium as well as the bicarbonate, the base deficit may be corrected but the elevated AG will persist, indicating an ongoing metabolic acidosis even though blood pH has been normalized.

However, the AG is relatively inaccurate because it requires three other test results for calculation. The Na, Cl and  $TCO_2$  all have a potential laboratory error of as much as 5%. This error is cumulative in the AG calculation (30). To counter this, an accurate AG is best obtained by multiple measurements that are then averaged cumulatively. Because of this requirement, the

AG is most useful during long-term extracorporeal support lasting days or weeks. In addition, the generally accepted normal range for the AG of  $12 (\pm 4)$  mEq/L may have changed to 3 - 11 mEq/L based on the type of testing method used in the laboratory (31). Laboratories using ion selective electrodes should use the lower range over those using traditional flame methods.

The carbon dioxide gradient is the difference between the arterial blood  $pCO_2$  and the mixed venous blood  $pCO_2$ . The normal  $p(V-A)CO_2$  is between 4 mmHg (32) and 11 mmHg (33). The  $p(V-A)CO_2$  can be used to assess the speed of blood flow through the capillaries, because as blood flow slows, the  $p(V-A)CO_2$  increases. Because of this, the cardiac index can be calculated by dividing the constant 12.9 by the  $p(V-A)CO_2$  with a correlation of 0.76 in adults (33). Therefore, the  $p(V-A)CO_2$  is useful in assessing changes in overall perfusion. An increased  $p(V-A)CO_2$  indicates either a decreased cardiac index or an increased metabolic demand without concomitant increase in cardiac index. An increased  $p(V-A)CO_2$  also represents an intracellular retention of  $CO_2$  as volatile acid. For every 1 mmHg increase in the  $p(V-A)CO_2$ , the intracellular  $CO_2$  increases by 2 to 4 mmHg (33). This means that intracellular pH will change 2 to 4 times as much as the mixed venous pH change, making tissue cells very acidotic. Capillary blood flow functions like the sweep gas through an oxygenator. If the sweep gas flow is high, adequate amounts of  $CO_2$  are removed. However, if the sweep gas flow is too slow, the  $CO_2$  is retained in the blood. The difference is that a slow capillary blood flow causes retention of  $CO_2$  in the tissues as indicated by an increased  $p(V-A)CO_2$ .

Hypothetically, an increased AG caused by metabolic acidosis and an increased  $p(V-A)CO_2$  caused by intracellular retention of volatile acid could both represent lethal changes in intracellular pH. If so, patients with elevations in one or both of these markers should have increased morbidity and mortality.

## MATERIALS AND METHODS

This prospective study population consisted of 100 consecutive patients whose ages ranged from newborn to nine months on venoarterial ECMO. There were 24 congenital diaphragmatic hernias (CDH), 9 group B Streptococcus infections (GBS), 25 meconium aspiration syndromes (MAS), 8 respiratory distress syndromes (RDS) and 18 patients with primary pulmonary hypertension (PHTN). There was also a mixed group of 16 other patients whose diagnoses included postcardiotomy support, trauma, adult respiratory distress syndrome, bacterial and viral sepsis and pneumonia.

After the initiation of ECMO, the AG was drawn every 6 hours from the same sample site in the venous return line. The  $p(V-A)CO_2$  was drawn every 4 hours. The arterial blood gas was drawn from an arterial line in the patient (either an umbilical artery line or a left radial line). The venous blood gas was

drawn from the same sample site in the venous return line as the AG. The value for each marker was averaged with all previous values from the initiation of ECMO resulting in a cumulative average for the AG and p(V-A)CO<sub>2</sub> over the entire ECMO treatment of each patient. The median value for each marker was also established. The ECMO blood flow, oxygenator function, and medical management were adjusted to maintain a mixed venous saturation of 70% or greater, venous and arterial blood pH within accepted normal ranges, and hemodynamics within the normal accepted range based on the age and size of the patient. Results were analyzed using simple and multiple column contingency tables, Fisher's Exact test with 2 sided P values and the Chi-squared Test for Independence<sup>a</sup>.

**RESULTS**

Of the 100 patients, there were 75 survivors with the following breakdown by diagnosis (survivors/total = % survival): CDH 13/24 = 54%, GBS 7/9 = 78%, MAS 24/25 = 96%, RDS 7/8 = 88%, PHTN 15/18 = 83%, mixed group 9/16 = 56%. Deaths were the result of multiple organ failure (n=8), failure to improve (n=8), intracranial hemorrhage (n=6) or generalized hemorrhage (n=3). Five of the six deaths from intracranial hemorrhage had a sustained average AG of 16 mEq/L or greater.

The mean and median AG for the entire population was 11 mEq/L (Table 1). Survivors had an average AG of 11 (± 2) mEq/L and non-survivors had an average AG of 15.3 (± 7) mEq/L (p<0.003). These results are very similar to a study (12) of adult patients with abdominal aortic aneurysms and confirm the validity of using the AG to predict mortality in both children and adults with varying diagnoses. The mean and median p(V-A)CO<sub>2</sub> for the entire population were 9 mmHg. Survivors had an average p(V-A)CO<sub>2</sub> of 8.8 (± 2) mmHg and non-survivors had an average p(V-A)CO<sub>2</sub> of 10.3 (± 3) mmHg (p<0.01).

These groups were further divided into four subgroups based on a high or low AG and high or low p(V-A)CO<sub>2</sub> (Table 2). Both mortality and survivors' ECMO time increase as one or both risk factors increase. Patients with increases in both risk factors have a mortality rate 8 times greater and survivors remain on ECMO almost twice as long as those without increased risk factors.

As each marker increases in severity, the mortality rate increases. For example, for the group of patients with an AG over 11 mEq/L the survival is 24/42 = 57%. However, patients with an AG of 18 or greater have a survival of only 1/8 = 13%. For the group of pa-

tients with a p(V-A)CO<sub>2</sub> of 9 mmHg or greater the survival is 36/55 = 65%, but the survival of the group of patients with a p(V-A)CO<sub>2</sub> of 15 mmHg or greater is 0/2 = 0%.

Serum base measurements in most of the patients were usually normal or high, with the bicarbonate often in the upper 20's to upper 30's mEq/L. In the few patients who did develop base deficits, blood pH correction by base infusion failed to halt the increasing AG in the dying patient. The AG increase was more often the result of a decreased Cl ion rather than a decreased HCO<sub>3</sub> ion, which has been reported by others (34).

Multivariate analysis was not performed because other risk factors such as age, weight, and diagnosis are well documented (35) and are independent variables. The dependent variables such as blood pH, buffer base balance and mixed venous saturation values were manipulated into normal ranges and not allowed to remain abnormal for extended periods.

**DISCUSSION**

This study shows a definite positive relationship between an elevation in the AG and p(V-A)CO<sub>2</sub> markers and morbidity and mortality in the long-term extracorporeal support patient. The increased AG most likely reflects the relative change in intracellular pH regardless of the blood pH. The human body's own compensation mechanisms and/or the administration of buffer base give false reassurance of the adequacy of perfusion without actually correcting the problem (36). An increasing p(V-

**Table 1: Anion Gap and Venoarterial Carbon Dioxide Gradient Groups**

Anion Gap		Carbon Dioxide Gradient	
≤ 11 mEq/L	> 11 mEq/L	< 9 mmHg	≥ 9 mmHg
n = 58	n = 42	n = 45	n = 55
51	24	< Survivors >	39
7	18	< Nonsurvivors >	6
12%	43%	< Mortality >	13%
p = 0.0005		Fisher's Exact Test	p = 0.0126

**Table 2: Anion Gap and Venoarterial Carbon Dioxide Subgroups**

	Anion Gap ≤ 11 mEq/L p(V-A)CO <sub>2</sub>		Anion Gap > 11 mEq/L p(V-A)CO <sub>2</sub>	
	< 9 mmHg n = 28	≥ 9 mmHg n = 30	< 9 mmHg n = 17	≥ 9 mmHg n = 25
Survivors	26	25	13	11
Nonsurvivors	2	5	4	14
Mortality	7%	17%	24%	56%
ECMO Hours*	100 (±37)	159 (±98)	127 (±53)	190 (±105)

(Chi-square Test for Independence p = 0.0003) \* Survivors only

<sup>a</sup> InStat 2, GraphPad Software, San Diego, CA

A)CO<sub>2</sub> suggests a relatively slow capillary flow despite clinical indications to the contrary. Poor removal of CO<sub>2</sub> from the capillary beds results in intracellular retention of volatile acid with decreased intracellular pH as the result (32). The combined effects of a high AG and a high p(V-A)CO<sub>2</sub> result in an enhanced detrimental effect on intracellular pH changes that greatly increases mortality in the form of failure to improve, multiple organ failure or intracranial hemorrhage. For survivors, the enhanced detrimental effect greatly increases the ECMO time needed to heal.

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