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Relationship between cardiac output and mixed venous-arterial P_{CO_2} gradient in sodium bicarbonate-treated dogs

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Abstract: We examined the relationship between cardiac output (CO) and mixed venous-arterial P_{CO_2} gradient ($\bar{v}$-aP_{CO_2}) along with the other variables derived from arterial and/or mixed venous blood gases in sodium bicarbonate-treated dogs. Six dogs with low cardiac output following cardiopulmonary resuscitation were used. CO, blood gases, and hemoglobin measurements were repeated every 20–30 min after administration of sodium bicarbonate or normal saline. All measurements were performed after the confirmation of a steady state of CO_2 elimination by end-tidal CO_2 monitoring. Arteriovenous oxygen content difference (Cao_2-$C\bar{v}o_2$), mixed venous oxygen saturation ($S\bar{v}o_2$), and $\bar{v}$-aP_{CO_2} were highly correlated with CO. The correlation coefficients between Cao_2-$C\bar{v}o_2$, $S\bar{v}o_2$, and $\bar{v}$-aP_{CO_2} were $r = -0.81$ ($P < 0.001$), $r = 0.70$ ($P < 0.001$), and $r = -0.77$ ($P < 0.001$), respectively. The results suggest that, if $\bar{v}$-aP_{CO_2} is measured during the steady state, except for the period during the transient increase in CO_2 elimination just after the administration of sodium bicarbonate, $\bar{v}$-aP_{CO_2} can be used as an index of systemic perfusion even after the administration of sodium bicarbonate.

Key words: Cardiac output, Mixed venous-arterial carbon dioxide gradient, Arteriovenous oxygen content, Mixed venous oxygen saturation

Introduction

There has been increasing evidence of venous hypercarbia and of increases in mixed venous-arterial P_{CO_2} gradient ($\bar{v}$-aP_{CO_2}) in animals and humans during cardiopulmonary resuscitation (CPR) [1–3]. In a porcine preparation of cardiac arrest, Grundler et al. [1] demonstrated that there was a marked disparity between arterial and mixed-venous P_{CO_2}. Weil et al. [2] confirmed this disparity in humans during CPR.

Recently, this disparity was observed not only during CPR but in a variety of other low perfusion states, such as acute cardiac tamponade, hypovolemic shock, cardiogenic shock, and septic shock [3–6]. However, it is not clear whether, similar to mixed venous oxygen saturation ($S\bar{v}o_2$) and arteriovenous oxygen content difference (Cao_2-$C\bar{v}o_2$), $\bar{v}$-aP_{CO_2} can be used as an index of systemic perfusion even after sodium bicarbonate is administered for the correction of metabolic acidosis. Although the effectiveness of sodium bicarbonate during low cardiac output (CO) state is controversial [7], it is often used to correct metabolic acidosis when the use of catecholamines fails to improve CO. The purpose of this study was to determine the relationship between CO and $\bar{v}$-aP_{CO_2} along with the other variables derived from arterial and/or mixed venous blood gases in sodium bicarbonate-treated dogs with low CO after CPR.

Materials and methods

This study was performed in accordance with the guidelines of the institutional committee for the care and use of animals. Six mongrel dogs resuscitated (9.4 to 15.0 kg) following ventricular fibrillation (Vf) were used in this study. Before the induction of Vf, the animals were anesthetized with ketamine (10 mg·kg^{-1} i.m.) and diazepam (3 mg·kg^{-1} i.v.), followed by a constant i.v. infusion of 40 mg·h^{-1} ketamine and 1.6 mg·h^{-1} pancuronium throughout the experiment. The animals were restrained in the supine position on a V-shaped board. An endotracheal tube with an inflatable cuff was inserted and the animals were ventilated by a volume-limited ventilator (KMA-1300, Acoma Medical, Tokyo, Japan).

A left femoral vein cannula for i.v. drug administration, and a left femoral artery cannula were inserted for

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arterial blood pressure monitoring and arterial blood sampling. A Swan-Ganz thermodilution catheter (93A-131F-7F, American Edwards, Irvine, Calif.) was inserted via the right femoral vein for monitoring pulmonary arterial pressure and pulmonary arterial blood sampling. The femoral and pulmonary arterial lines were connected to pressure transducers (P23ID, Gould Stathan, Oxnard, Calif.) and were continuously recorded on a polygraph (RM-6200, Nihon Kohden, Tokyo, Japan). The left jugular vein was surgically prepared to insert a wire electrode to induce Vf. Heparin (1 mg·kg^{-1} i.v.) was administered to prevent clot formation in the catheters and to reduce intravascular coagulation during circulatory arrest. Electrocardiogram (lead II) was continuously monitored.

Vf was induced by applying an alternating current to the right ventricular endocardium. After 1 min of Vf, a bolus injection of epinephrine (0.5 mg i.v.) was given, and the combination of intermittent positive pressure ventilation (IPPV) and external cardiac compressions at a rate of 92/min were started. The timing of cardiac compression was synchronized with the sound of a metronome and the sternum was depressed about 3 to 5 cm. After 15 min of CPR, a nonsynchronized 100-J defibrillation shock was administered to the anterior chest using a direct-current defibrillator (MDV-2, Nihon Kohden). A bolus of 0.5 mg of intravenous epinephrine was administered before each defibrillation shock. If no viable cardiac rhythm was produced, 200-J and 300-J defibrillation shocks were given as needed. Sodium bicarbonate and calcium chloride were not administered at any time during CPR.

The resuscitated animals were ventilated by IPPV with 100% oxygen and a tidal volume of 200 ml at a rate sufficient to maintain $Paco_2$ between 35 and 45 mmHg. End-tidal CO_2 concentration was monitored continuously. Blood temperature was monitored with a Swan-Ganz thermodilution catheter and maintained within the normal range using a fluid-filled heating pad.

Thirty min after resuscitation, femoral and pulmonary arterial blood samplings for both blood gases and hemoglobin analyses were performed along with hemodynamic measurements. Then the sampling and measurements were repeated every 20–30 min after administration of sodium bicarbonate 5–20 mEq or normal saline 20 ml. All the sampling and measurements were performed after the confirmation of a steady state of CO_2 elimination by end-tidal CO_2 monitoring.

CO was measured in triplicate using 10-ml injections of 5% dextrose in water at room temperature and a CO computer (SAT-1, American Edwards). To avoid variations in injection temperature, both the injection solution and plastic syringes were stored in the laboratory for at least 24 h before use. The dextrose solution was smoothly injected over an approximately 3-s period. Each CO measurement was considered accurate if its thermodilution waveform showed a normal curve. The triplicate measurements were averaged to calculate the mean value.

Arterial and mixed venous blood gases and pH were measured with a Corning 170 pH/blood gas analyzer. The blood gas analyzer was recalibrated immediately prior to each determination. All blood gas values were corrected for body temperature. Hemoglobin was measured with a hemoglobin meter (Hb-350, Erma, Tokyo, Japan). Cao_2-$C\bar{v}o_2$ was calculated using the standard formula.

Data were analyzed using Pearson correlation coefficient with linear regression techniques for computing the correlation between CO and variables derived from blood gases.

Results

Ninety-two simultaneous measurements of CO, blood gases, and hemoglobin were performed in the six resuscitated dogs. Of these measurements, 60 were performed after the administration of sodium bicarbonate. Of all measurements, the minimum CO value was 0.2 L·min^{-1} and the maximum was 1.3 L·min^{-1}. The minimum CO value of each animal ranged from 10% to 48% of the prearrest level and the maximum CO value ranged from 28% to 102%.

Table 1 summarizes the correlations between CO and variables derived from blood gases and hemoglobin. Cao_2-$C\bar{v}o_2$ and $\bar{v}$-aPco_2 were inversely correlated with CO. The reduction of Cao_2-$C\bar{v}o_2$ and $\bar{v}$-aPco_2 was almost proportional to the increase of CO (Fig. 1), expressed as: Cao_2-$C\bar{v}o_2$ (ml·dl^{-1}) = 13.8 − 7.8 CO (L·min^{-1}), $\bar{v}$-aPco_2 (mmHg) = 39.0 − 27.2 CO (L·min^{-1}),

Table 1. Relationship between cardiac output and variables derived from arterial and/or mixed venous blood gases along with hemoglobin

	r	r^2	P value
Cao_2-$C\bar{v}o_2$	−0.81	0.65	<0.001
$\bar{v}$-aPco_2	−0.77	0.60	<0.001
$S\bar{v}o_2$	0.70	0.48	<0.001
$P\bar{v}co_2$	−0.68	0.46	<0.001
$\bar{v}$pH	0.60	0.36	<0.001
apH	0.52	0.27	<0.001
a-$\bar{v}$pH	−0.41	0.17	<0.001
$P\bar{v}o_2$	0.14	0.02	N.S.
$Paco_2$	0.03	0.00	N.S.

r, correlation coefficient; r^2, coefficient of determination; Cao_2-$C\bar{v}o_2$, arteriovenous oxygen content difference; $\bar{v}$-aPco_2, mixed venous-arterial Pco_2 gradient; $S\bar{v}o_2$, mixed venous oxygen saturation; $P\bar{v}co_2$, mixed venous Pco_2; $\bar{v}$pH, mixed venous pH; apH, arterial pH, a-$\bar{v}$pH, arterial-mixed venous pH difference; $P\bar{v}o_2$, mixed venous Po_2; $Paco_2$, arterial Pco_2; N.S., not significant.

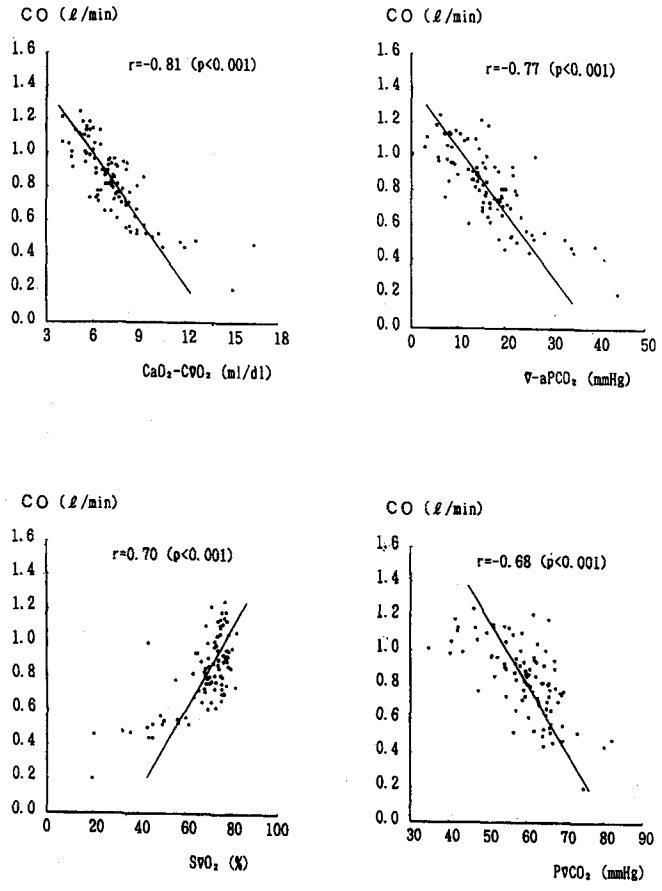

Fig. 1. Relationship between cardiac output (CO) and arteriovenous oxygen content difference (Cao_2–$C\bar{v}o_2$), mixed venous-arterial Pco_2 gradient ($\bar{v}$-$aPco_2$), mixed venous oxygen saturation ($S\bar{v}o_2$), and mixed venous Pco_2 ($P\bar{v}co_2$)

respectively. $S\bar{v}o_2$ was also highly correlated with CO. The increase of $S\bar{v}o_2$ was almost proportional to the increase of CO (Fig. 1), expressed as: $S\bar{v}o_2$ (%) = 34.6 + 40.9 CO ($L \cdot min^{-1}$). $P\bar{v}co_2$ was also correlated with CO. The reduction of $P\bar{v}co_2$ was proportional to the increase of CO (Fig. 1), expressed as: $P\bar{v}co_2$ (mmHg) = 81.9 − 26.6 CO ($L \cdot min^{-1}$).

Mixed venous pH and arterial pH tended to increase when CO increased, but the correlation coefficients with CO were lower ($r = 0.60$ and $r = 0.52$, respectively). Arterial-mixed venous pH difference (a-$\bar{v}$pH) showed a poor correlation with CO. $P\bar{v}o_2$ and $Paco_2$ did not show any correlation with CO.

Discussion

Systemic perfusion monitoring is essential for the appropriate hemodynamic therapy and the subsequent response to intervention in a variety of low perfusion states. CO measurements are usually used to assess the general status of systemic perfusion. $S\bar{v}o_2$ and Cao_2-$C\bar{v}o_2$ are also established indices to assess systemic perfusion [8].

Based on the Hindman's hypothesis derived from the Fick principle [7], the following equation holds: ($P\bar{v}co_2$-$Paco_2$) = $k \cdot (\dot{V}co_2/\dot{Q})$, where k is a constant, $\dot{V}co_2$ is defined as the net CO_2 production by the whole body, and $\dot{Q}$ is cardiac output. This equation implies that, if CO_2 production remains constant, CO may influence $P\bar{v}co_2$-$Paco_2$, namely $\bar{v}$-$aPco_2$.

The administration of sodium bicarbonate produces a transient increase in CO_2 production in the presence of adequate ventilation and CO [7]. However, in the low CO states, the increased CO_2 in the central veins that is formed from sodium bicarbonate administration would not be eliminated efficiently due to the low pulmonary perfusion [1–6]. Thus, the administration of sodium bicarbonate during the low CO states may produce a prolonged enlargement of $\bar{v}$-$aPco_2$ which is not based on changes in CO.

In addition, since CO_2 may enter cells freely, the administration of sodium bicarbonate during the low CO states may produce a drop in intracellular pH (paradoxical intracellular acidosis) and thereby further depress cellular function [9]. Thus the administration of sodium bicarbonate may change CO_2 production in the tissue level.

However, we found a high correlation between $\bar{v}$-$aPco_2$ and CO after bicarbonate administration. This relationship is consistent with the other low CO states without bicarbonate administration [3,4–6]. This suggests that, if measurements are performed after the confirmation of a steady state of CO_2 elimination by end-tidal CO_2 monitoring, $\bar{v}$-$aPco_2$ can be used as an index of systemic perfusion, even in a patient who has received sodium bicarbonate after CPR to correct extreme metabolic acidosis.

$P\bar{v}co_2$ was also correlated with CO. Based on the Fick equation, if CO_2 production and $Paco_2$ remain constant, a reduction in CO may result in an increase in $P\bar{v}co_2$. Conversely, this implies that, if $Paco_2$ does not remain constant during alveolar hypoventilation and/or bicarbonate administration, $P\bar{v}co_2$ will not be proportional to CO.

An increase in $P\bar{v}co_2$ may produce a decrease in mixed-venous pH. Adrogue et al. [3] have showed that a decrease in mixed-venous pH and an increase in a-$\bar{v}$pH occur during systemic hypoperfusion in humans. Our findings are consistent with those of Androgue et al. [3]. However, the correlation between CO and mixed-venous pH as well as a-$\bar{v}$pH were low.

$S\bar{v}o_2$ has been generally advocated as a sensitive indicator for the assessment of systemic perfusion [8,10]. However, some investigators have questioned the value of $S\bar{v}o_2$ in CO monitoring [11]. The present study has shown that there is a close relationship between $S\bar{v}o_2$

and CO. The findings suggest that $S\bar{v}o_2$ can be used as an index of systemic perfusion.

The present study demonstrated that, if the measurement of $\bar{v}$-aPco_2 was performed during the steady state, except for the period during the transient increase in CO_2 elimination just after the administration of sodium bicarbonate, $\bar{v}$-aPco_2 correlated well with CO even after the administration of sodium bicarbonate. Profound increases in $\bar{v}$-aPco_2 are quantitatively related to the severity of perfusion failure. The calculation of $\bar{v}$-aPco_2 is very easy and does not require hemoglobin measurements. We believe that the concept of $\bar{v}$-aPco_2 may be useful in the diagnosis and estimation of perfusion failure.

In conclusion, the results of the present study suggest that, similar to Cao_2-$C\bar{v}o_2$ and $S\bar{v}o_2$, $\bar{v}$-aPco_2 can be used as an index of systemic perfusion even after the administration of sodium bicarbonate.

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