EXACERBATION OF HYPERCAPNIA AND ACIDOSIS OF CENTRAL VENOUS BLOOD AND TISSUE FOLLOWING ADMINISTRATION OF SODIUM BICARBONATE DURING CARDIOPULMONARY RESUSCITATION

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Administration of sodium bicarbonate during cardiopulmonary resuscitation (CPR) is controversial, and our aim was to elucidate whether or not its administration is beneficial by analyzing the acid-base status and the level of carbon dioxide in central venous blood during CPR, and their changes following administration of sodium bicarbonate. Six patients were studied. They had all been admitted to the intensive care unit (ICU), had already had pulmonary arterial or central venous catheters inserted, and had acute episodes of circulatory collapse during their stay in the ICU. The following phenomena were observed: 1) hypercapnia and acidosis of central venous blood were prominent during both cardiogenic shock and CPR, although arterial hypocapnia was maintained by hyperventilation; 2) administration of sodium bicarbonate during cardiogenic shock and CPR induced exacerbation of hypercapnia and acidosis of central venous blood; 3) when arterial hypercapnia was present due to disturbed ventilation, administration of sodium bicarbonate exacerbated hypercapnia and acidosis of both arterial and central venous blood; 4) administration of sodium bicarbonate did not induce hypercapnia of central venous blood in a septic shock patient in whom the septic hyperdynamic state was prevalent in spite of low systemic perfusion pressure. It was concluded that hypercapnia and acidosis of the central venous blood and tissues were exacerbated by administration of sodium bicarbonate during CPR, and that such an effect might be dependent on the severity of the decrease in tissue perfusion.

IT has been widely believed that administration of sodium bicarbonate during cardiopulmonary resuscitation (CPR) is effective in reversing acidosis, improving myocardial contrac-

tility, and increasing the threshold for ventricular fibrillation.¹ Bishop and others² however, first rated that administration of bicarbonate during CPR induces arterial hypercapnia and might be deleterious to CPR. Although a number of studies have since conducted, a definite conclusion about the role of sodium bicarbonate during CPR has yet to be established.^{3,4} Weil and others⁵⁻⁷ identified significant hypercapnia of mixed venous blood and possible acidosis of

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Fig.1. Serial changes in pHs (upper half) and actual bicarbonate levels (lower half) in arterial and inferior caval venous blood in patient 1. Cardiac arrest is indicated by the closed arrows, and bolus administrations of sodium bicarbonate are shown by open arrows. pHs decreased gradually and differences between arterial and venous blood pHs increased with time.

Fig.2. Serial changes in carbon dioxide levels (the upper half) and oxygen saturation of arterial and inferior caval venous blood in patient 1. A sharp rise in the carbon dioxide level in venous blood occurred after the second cardiac arrest, and after the second and third administrations of sodium bicarbonate. Oxygen saturation of arterial blood was maintained above 90% but that of venous blood decreased with time.

tissues during CPR, and they stressed the importance of monitoring the acid-base status of central venous blood during CPR. It is difficult, however, to secure the central venous line in such an emergency situation, so there has been only a limited number of reports about acid-base status of mixed venous blood during CPR.⁵⁻⁷

We have observed a few patients in whom the central venous lines had already been secured and in whom cardiac arrest took place while in the intensive care unit (ICU). Central venous blood samples were serially examined during the resuscitative efforts, and the effects of administration of sodium bicarbonate were evaluated. The purpose of this study was to elucidate from clinical observations the way in which the

acid-base status of the central venous blood changes during circulatory failure, and how the administration of sodium bicarbonate affects it during CPR.

CASE PRESENTATION AND RESULTS

Data were obtained from 6 patients who had been admitted to the intensive care unit of Gunma University Hospital, and who had episodes of cardiac arrest during their stay in the ICU. In every patient arterial blood pressure was observed directly by radial or dorsal pedal arterial cannulation with a pressure transducer (Gould P50, USA) and a critical care information system (DMP-6000, Nihon Kohden, Tokyo,

Fig.3. Serial changes in the difference in carbon dioxide tensions between arterial and venous blood (the upper half) and lactate levels in arterial and venous blood (the lower half) in patient 1. Three sharp peaks in the difference in carbon dioxide tension between arterial and venous blood were apparent during the second episode of cardiac arrest, and after the second and third administrations of sodium bicarbonate. The closed and open arrows denote the same as in Figs. 1 and 2.

Japan). Balloon-tipped pulmonary arterial catheters with a quadrilumen or central venous catheters were inserted and mixed or central venous blood was obtained serially. Blood gas measurements were made using ABLII (Radiometer, Copenhagen, Denmark) and lactate concentrations were determined using Lactate Analyzer 640 (Roche, Switzerland).

Case 1

A female patient of 50 years of age uneventfully underwent graft replacement for a thoracoabdominal aortic aneurysm which had occurred about a month before. Postoperatively she had a slightly impaired renal function. One month

later she reported a sharp pain in her back, and then developed cardiac arrest when she arrived at the hospital. Emergency echocardiography revealed an enlarged ascending aorta and distended mediastinum; a dissecting aneurysm and cardiac tamponade were diagnosed. An emergency epicardial centesis successfully saved her. The therapeutic principle in her treatment was to strictly control her blood pressure at a low level until a radical operation for her dissecting aneurysm could be conducted. On the eighth day in the ICU sudden hypotension, massive bleeding from the pericardial drainage tube, and cardiac arrest attacked her but she was successfully resuscitated by cardiac massage, blood transfusion, artificial ventilation, and administration of epinephrine (the first arrow in Figs. 1, 2, and 3). An emergency operation was planned but she was reattacked by a second episode of cardiac arrest following massive bleeding from the pericardial drainage tube (the second arrow in Figs. 1, 2, and 3). She was resuscitated again from this second cardiac arrest but her general condition was so severely aggravated that she was no longer fit enough for an emergency operation. She expired seven hours after her first cardiac arrest.

A central venous catheter had been secured near her right atrium through the inferior caval vein for monitoring of central venous blood pressure and as a route for hyperalimentation. Changes in the acid-base status of the central venous blood and responses to repetitive administration of sodium bicarbonate (the open arrows in Figs. 1, 2, and 3) were observable during her two episodes of cardiac arrest and her seven-hour cardiogenic shock. Although arterial blood pH was maintained above 7.2 by hyperventilation, that of the central venous blood could not; it had never rose above 7.1 after the second episode of cardiac arrest (the upper half of Fig. 1). The difference in pHs between the arterial and central venous blood increased gradually, and then greatly increased after the second administration of sodium bicarbonate (the upper half of Fig. 1). The concentration of bicarbonate in the arterial blood decreased progressively due to arterial blood hypocapnia and metabolic acidosis, and the difference in the bicarbonate concentrations between the arterial and central venous blood increased progressively (the lower part of Fig. 1). Although carbon dioxide levels in the arterial blood were maintained close to 20 mmHg throughout the course of resuscitation by

TABLE I EFFECT OF NaHCO_3 ON ARTERIAL AND CENTRAL VENOUS BLOOD ACID-BASE STATUS DURING CARDIOPULMONARY RESUSCITATION

Case No		1			2	3	4	5	6		
A	pH _a	7.202	7.186	6.936	7.006		7.214	7.195	7.291	7.195	7.243
	P _a CO ₂	18.2	15.4	16.0	27.2		53.6	42.2	32.3	29.5	41.5
	pH _v	7.037	7.025	6.794	6.833				7.187	7.144	7.204
	P _v CO ₂	52.5	50.1	74.4	86.6				39.3	35.6	53.0
	a-vD _p H	0.165	0.161	0.142	0.234				0.104	0.051	0.039
	a-vD _{CO2}	34.3	34.7	58.4	59.4				7.6	6.1	11.5
	BE	-19.5	-20.9	-29.5	-21.5		-6.2	-11.2	-9.7	-15.0	-9.2
	Lactate	13.62	15.47	17.78	15.95				6.8	7.81	17.53
Dose of NaHCO ₃		60	60	60	60	100	20	100	83	83	83
Patient's Status		Cardiogenic Shock			Cardiac Massage				Septic Shock		
B	pH _a	7.335	7.236	7.109	7.206	7.390	6.993	7.197	7.375	7.232	7.260
	P _a CO ₂	15.0	16.4	21.5	33.3	23.2	88.0	69.6	35.2	29.4	46.1
	pH _v	7.155	6.608	6.755		6.895	6.888	7.111	7.329		
	P _v CO ₂	44.2	122.4	120.2		107.5	129.4	84.3	45.0		
	a-vD _p H	0.18	0.628	0.354		0.505	0.105	0.086	0.046		
	a-vD _{CO2}	29.2	106	98.7		84.3	31.4	14.4	9.8		
	BE	-15.5	-18.8	-22.0	-13.9		-11.8	-2.2	-4.1	-13.5	-6.6
	Lactate	13.38	16.09	15.96	17.68		13.71		6.29	7.74	18.03

A: Before administration of sodium bicarbonate, B: After administration of sodium bicarbonate,

$a-v\text{DpH}$: arteriovenous difference in pH, $a-v\text{DCO}_2$: arteriovenous difference in CO_2

Units: BE mEq/l, Lactate mmol/l, NaHCO_3 mEq

hyperventilation, those of the central venous blood were consistently above 60 mmHg, and finally reached almost 100 mmHg after the second episode of cardiac arrest and after the second and third administrations of sodium bicarbonate (the upper part of Fig. 2). As a result, the difference in carbon dioxide tension between the arterial and central venous blood was always greater than 20 mmHg, a difference which might have been caused by insufficient washout of carbon dioxide from the tissues due to poor tissue perfusion (the upper half of Fig. 3).

Although oxygen saturation of the arterial blood was maintained above 90%, that of the central venous blood was strikingly low, reflecting poor tissue perfusion (the lower part of Fig. 2). The level of lactate increased progressively, probably due to enhanced anaerobic metabolism resulting from low tissue perfusion. Lactate levels were the same in both the arterial and central venous blood, except after the second administration of sodium bicarbonate during which the level in the inferior caval venous blood

increased greatly. This suggested a massive and abrupt inflow of lactate from the splanchnic region (Fig. 3, lower half).

Case 2

A male patient of 51 years of age suffered from mitral stenosis complicated by severe infection, and finally developed adult respiratory distress syndrome. Continuous positive airway pressure was applied to relieve his respiratory distress, but he had sporadic ventricular arrhythmia and finally he suffered ventricular tachycardia and fibrillation. Closed chest cardiac massage and ordinary resuscitative maneuvers could not restore his cardiac rhythm. A central venous catheter inserted with its tip secured near his right atrium, enabled serial central venous blood sampling and hence analysis of the central venous blood acid-base status during the one-hour resuscitative maneuver. Differences in pHs and carbon dioxide levels between arterial and central venous blood after 10 min of closed chest cardiac massage were 0.21 pH units and 68 mmHg, respectively; closed chest cardiac massage could not

Fig.4. Effect of administration of sodium bicarbonate (83 mEq) in a bolus to patient 6. The status of catecholamine support is shown in the bottom of the Figure.

improve these differences. This meant that the closed chest cardiac massage was not able to induce sufficient cardiac output to remove the carbon dioxide produced in the tissues. At the terminal state, 60 mEq of sodium bicarbonate were administered slowly, but unfortunately central venous blood samples could not be obtained (Case 2 in Table I).

Case 3

A male patient of 66 years of age, who had suffered tetanus and was paralyzed by a muscle relaxant, was ventilated mechanically, and had his sympathetic nervous overactivity controlled by administration of labetalol. (Paroxysmal hypertension and tachycardia accompanied by a massive release of catecholamines is frequently experienced in severe tetanus and that is one of its characteristics⁸.) Although his condition seemed to be stable, sudden cardiovascular collapse of unknown etiology occurred. Ordinary resuscitative maneuvers, closed chest cardiac massage, administration of sodium bicarbonate (about 2 mEq/kg), bolus administration of epinephrine, and a few attempts at counter-shock could not restore his spontaneous rhythm. A pulmonary arterial catheter had previously been

inserted to monitor his circulatory status, and mixed venous blood could be analyzed. Ten minutes after administration of sodium bicarbonate during cardiac massage, the values for carbon dioxide levels and pH in the arterial and mixed venous blood were 23 and 107 mmHg, and 7.38 and 6.89, respectively. Thus the carbon dioxide and pH differences between the arterial and mixed venous blood were 84 mmHg and 0.49, respectively, differences which were excessively large. These results showed that removal of carbon dioxide from the tissues was severely impaired, that cardiac massage was insufficient for tissue respiration, and that administration of sodium bicarbonate when tissue perfusion was impaired resulted in exacerbation of the tissue acidosis (Case 3 in Table I).

Case 4

A male patient of 54 years of age suffered from sepsis of unknown etiology and developed severe respiratory distress. After he had been treated with high oxygen concentrations (90–100%) for one week, he was transferred to our ICU. He was diagnosed to be suffering from ARDS complicated with suspected oxygen toxicity. He was initially treated with CPAP to control the concentration of oxygen inhaled, but gradual retention of carbon dioxide was observed, with his arterial carbon dioxide tension rising to 59 mmHg, and his arterial oxygen tension at 60 mmHg. Due to progressive respiratory acidosis, mechanical ventilatory support was added. However, barotrauma and tension pneumothorax followed, and cardiac arrest developed. Prompt cardiac massage was started and insertion of an intrathoracic catheter was tried. During this procedure 20 mEq of sodium bicarbonate were slowly administered intravenously, and as a result carbon dioxide levels of the arterial and central venous blood reached 88 and 129 mmHg respectively, while the corresponding pHs fell to 6.99 and 6.88 respectively. After the establishment of chest drainage on both sides of the pleural space, the patient's circulatory status recovered rapidly, and the differences in carbon dioxide levels and pHs between the arterial and central venous blood improved rapidly. Although the dose of bicarbonate was as small as 20 mEq, prominent arterial and central venous hypercapnia and acidosis resulted because adequate ventilation could not be performed and tissue perfusion was insufficient (Case 4, in Table I).

Fig. 5. Effect of sodium bicarbonate or carbicarb on the acid-base status in the closed system. Twenty ml of HCl-acidified blood was mixed with sodium bicarbonate or carbicarb and significant hypercapnia was subsequently noticed. The Figure is based on the data described in Filley GF & Kinding NB.²⁰

Case 5

A male patient of 77 years of age had been treated for ARDS complicated with pulmonary hypertension and sepsis. During his stay in the ICU he suffered cardiac arrest of an unspecified cause, and closed chest cardiac massage was started at once. Sodium bicarbonate (100 mEq) was administered during the cardiac massage, and carbon dioxide levels in his arterial and mixed venous blood increased to 70 and 84 mmHg, respectively, after 10 min. His spontaneous rhythm was restored within a few minutes and his mixed venous blood hypercapnia and acidosis improved gradually (Case 5 in Table I).

Case 6

A female patient of 46 years of age underwent an uneventful hysterectomy. However, 5 days later acute abdominal distension and abdominal pain ensued. Emergency laparotomy revealed that she was suffering from thrombosis of the superior mesenteric artery, and extensive resection of the small intestine and partial resection of the colon was performed. Postoperatively severe septic syndrome and multiple organ failure (MOF) followed, and finally a massive dose of catecholamine was necessary to maintain her systolic arterial blood pressure above 120 mmHg (0.4 $\mu\text{g/kg/min}$ of norepinephrine, 10.0 $\mu\text{g/kg/min}$ of dopamine and 8.0 $\mu\text{g/kg/min}$ of dobutamine; Fig. 4). Hyperventilation could only partially compensate for her acidosis, as her arterial blood pH was 7.29, base excess was -9.7 mEq/l and

pHv	7.37	7.03	6.61
PvCO ₂	46	50	122
PvO ₂	40	18	11
Venous Blood	↑	↑	↑
Capillary Blood	↑	↑	↑
Arterial Blood	↑	↑	↑
pHa	7.40	7.19	7.24
PaCO ₂	40	15	16
PaO ₂	95	94	91

Fig. 6. Relationships of pH and carbon dioxide tension between arterial and venous blood in normal, low perfusion, and low perfusion status patients receiving sodium bicarbonate.

A: The normal state

B: Low perfusion state, before administration of sodium bicarbonate to patient 1 (see details in the text)

C: Low perfusion state after administration of sodium bicarbonate (the second administration of sodium bicarbonate to patient 1, see details in the text)

blood lactate level was 6.8 mmol/l. Sodium bicarbonate (83 mEq) was administered for 20 min (Fig. 4). The difference in carbon dioxide levels between the arterial and central venous blood increased only from 7.0 to 9.8 mmHg and the acidemia of both improved. Next day, her MOF was further aggravated and an increase in norepinephrine dosage to 1.5 $\mu\text{g/kg/min}$ was necessary to maintain her systolic arterial blood pressure near 90 mmHg, while the same doses of dopamine and dobutamine as had previously been given were used. Under hyperventilation her arterial pH was 7.19; 83 mEq of sodium bicarbonate were administered for 20 min, and thereafter 83 mEq/h were infused continuously. The difference in carbon dioxide tensions between the arterial and central venous blood was 6 mmHg before administration of sodium bicarbonate and was near 10 mmHg during its continuous infusion (Case 6 in Table I). Her blood lactate level was 7.8 mmol/l before and after administration of sodium bicarbonate. A few hours before her expiration, 2.5 $\mu\text{g/kg/min}$

of norepinephrine were necessary to maintain her blood pressure near 60 mmHg, and continuous infusion of sodium bicarbonate at 83 mEq/h was necessary to maintain her arterial pH above 7.25. The difference in carbon dioxide tensions between the arterial and central venous blood was near 10 mmHg, although her circulatory condition became worse.

DISCUSSION

From the present clinical observations, we concluded that severe hypercapnia of central venous blood was evident during CPR, that the difference in carbon dioxide tensions between the arterial and central venous blood increased during CPR, that administration of sodium bicarbonate aggravated the central venous hypercapnia and acidosis, and that these phenomena might correlate with low tissue perfusion. In case 1, these phenomena increased after the cardiogenic shock worsened, and in cases 2 and 3, they were serious during unsuccessful cardiac massage. However, during hyperdynamic septic shock case 6 did not experience these phenomena in spite of severe acidosis and circulatory failure.

Undoubtedly closed chest cardiac massage has saved a lot of lives since the rediscovery of external cardiac compressions by Kouwenhoven.⁹ However, it is also apparent that this technique cannot induce sufficient blood flow to the tissues.^{10,11} Attempts to change the mode and frequency of compressions have all failed to improve cardiac output.^{12,13}

If ventilation is maintained at normal levels in the low cardiac output state, the ventilation perfusion ratio in the lung increases due to low pulmonary blood flow. As a result arterial hypocapnia and normoxia are common, although mixed venous hypercapnia and hypoxemia are apparent. The carbon dioxide levels of the central venous blood occurring in emergency situations like CPR have not been described in detail, but recently Weil and others⁵⁻⁷ found that patients undergoing CPR suffered from severe hypercapnia. Our data support their findings, and especially the increased differences in carbon dioxide levels between the arterial and central venous blood were characteristic. During CPR the patients of Weil and his colleagues showed arterial blood pHs averaging 7.41, whereas the average mixed venous blood pH was 7.15, pHs caused by mixed venous hypercapnia (arterial vs mixed venous blood carbon dioxide

levels were 32 vs 74 mmHg;⁷). Such a central venous blood hypercapnia is apparently due to insufficient tissue perfusion; tissue metabolism continues to produce carbon dioxide but there is not sufficient tissue perfusion to keep tissue carbon dioxide levels down to normal. During CPR the exhaled volume of carbon dioxide is proportional to the cardiac output, and endtidal carbon dioxide monitoring is a good indicator of pulmonary blood flow, something that is equal to cardiac output.¹⁴⁻¹⁹

Our clinical observations clearly demonstrated what happened if sodium bicarbonate is administered to patients with severely disturbed perfusion (Table I). In case 1 suffering severe cardiogenic shock, central venous hypercapnia was aggravated by administration of sodium bicarbonate. In cases 3, 4 and 5, each patient suffering very low tissue perfusion while under cardiac massage, tremendous hypercapnia of central venous blood was apparent after administration of sodium bicarbonate. In case 6, a patient possibly suffering a septic hyperdynamic state, venous hypercapnia was not induced in spite of administration of sodium bicarbonate. All these findings support the hypothesis that venous hypercapnia is inversely related to the level of tissue perfusion. This phenomenon could explain how sodium bicarbonate works as buffer. Filley and Kinding²⁰ showed that when 20 ml of acidified blood (pH 6.98 and carbon dioxide 82 mmHg) were mixed in a closed space with 2 mEq of sodium bicarbonate, the pH rose to 7.17 and the carbon dioxide tension rose to as high as 133 mmHg (Fig. 5). In the normal circulatory state, the difference in the carbon dioxide tension between the arterial and mixed venous blood is 6 mmHg; this small difference is sufficient to carry the carbon dioxide produced during tissue metabolism as bicarbonate ions and carbamino compounds (A in Fig. 6). In the low flow state, however, arterial carbon dioxide tension rapidly decreases due to the rising ventilation/perfusion ratio in the lung, while the low flow through the tissues ensures the continuous accumulation of carbon dioxide in the tissues (B in Fig. 6 shows the state just before the second administration of bicarbonate to Case 1). When sodium bicarbonate is administered intravenously, it reacts with the venous blood, produces carbon dioxide, and reaches a new $[\text{HCO}_3^-]/[\text{H}_2\text{CO}_3]$ equilibrium (C in Fig. 6 shows the acid-base status after the second administration of sodium bicarbonate to Case 1).

This slightly increased $[\text{HCO}_3^-]/[\text{H}_2\text{CO}_3]$ ratio will react with the very low pH extracellular fluid of the tissues, absorb H^+ , produce carbon dioxide, and reach a new $[\text{HCO}_3^-]/[\text{H}_2\text{CO}_3]$ equilibrium. During CPR, cardiac output will be minimal, tissue perfusion will be at its worst, and the situation described in Fig. 6 will be very close to the one described in Fig. 5. The elevated carbon dioxide level induced by addition of bicarbonate ions will probably diffuse intracellularly and rapidly induce intracellular hypercapnic acidosis.

From the factors described above, administration of sodium bicarbonate might be expected to be effective under conditions in which sufficient tissue perfusion could be maintained. Arieff and others administered sodium bicarbonate to their metabolic acidosis models induced by phenformin²¹ or hypoxic gas exposure^{22,23} and found that lactic acidosis was aggravated after administration of sodium bicarbonate. Could not be explained why this metabolic acidosis worsened in their hypoxia-induced acidosis models since they might be expected to have been able to retain sufficient tissue perfusion and to maintain normal tissue carbon dioxide tension. The harmful effect of sodium bicarbonate may have been due to some factor other than the production of carbon dioxide, but this remains obscure.

During CPR, metabolic acidosis would be expected to worsen progressively because of low tissue perfusion. Metabolic acidosis might suppress myocardial contractility and lower the myocardial threshold for fibrillation^{24,25}. Thus, administration of suitable alkalizing agents to correct extracellular as well as intracellular acidosis ought to be recommended, but of course administration of sodium bicarbonate might induce tissue hypercapnia and possibly intracellular acidosis, due to the carbon dioxide ability to easily diffuse through the cell membrane. To overcome these problems the first recommended step is hyperventilation. At the early stages of CPR hyperventilation should maintain arterial pH within a reasonable range for a considerable period²⁶. However, hyperventilation will not reverse venous acidosis. In the next step, alkalizing agents other than sodium bicarbonate should be used. In this context carbicarb (Fig. 5)^{27,28} and trihydroxymethyl aminomethan^{29,30} will need to be investigated further for clinical consideration. Lastly, we consider it most important that artificial methods of

increasing cardiac output be explored. Cardiac massage is not sufficient to maintain cardiac output during CPR, but emergency partial cardiopulmonary bypass might be expected to compensate for the deficient tissue flow and hence improve tissue metabolism, including, that of the heart.^{31,32} It is expected that emergency cardiopulmonary bypass surgery, such as extracorporeal membrane oxygenator, will be established and developed for acute circulatory failure.

In conclusion, administration of sodium bicarbonate during CPR might be harmful because it increases tissue hypercapnia and acidosis. This effect might be inversely related to the rate of tissue perfusion. It is expected that other alkalizing agents will be developed and/or techniques to improve tissue perfusion during CPR will be established.

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