Anesthesiology
V 42, No 5, May 1975

Sodium Bicarbonate and Systemic Hemodynamics in Volunteers Anesthetized with Halothane

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The cardiovascular effects of acute metabolic alkalosis ($NaHCO_3$) in normal male volunteers anesthetized with halothane were measured. Pure metabolic alkalosis was studied by maintaining the end-tidal carbon dioxide tension at 40 torr. In each subject, cardiac index increased and total peripheral resistance decreased after each dose of $NaHCO_3$. The increased cardiac index was associated with increased central blood volume, left ventricular minute work index, stroke index, and heart rate. Systolic time intervals showed increased myocardial performance. $NaHCO_3$ administered to volunteers whose hearts were depressed by halothane appeared to cause peripheral vasodilation, volume expansion, and myocardial stimulation. The authors conclude that $NaHCO_3$ administered during halothane anesthesia decreases total peripheral resistance and may lead to severe hypotension. (Key words: Acid–base equilibrium, alkalosis, metabolic; Anesthetics, volatile, halothane.)

METABOLIC ALKALOSIS in anesthetized animals has been shown to increase cardiac output and to decrease total peripheral resistance.[1-7] In two of these studies, administration of sodium bicarbonate ($NaHCO_3$) led to increases in myocardial contractile force.[1,5]

Few data describing the effects of acute metabolic alkalosis in anesthetized man are available. Kennel§ showed that $NaHCO_3$ increased cardiac output in man during light general anesthesia with nitrous oxide, oxygen, and *d*-tubocurarine. The purpose of the present study was to quantitate the effects of $NaHCO_3$ administration to anesthetized volunteers with depressed cardiovascular systems. Halothane was selected as the anesthetic agent since it is known to decrease blood pressure, total peripheral resistance, cardiac output, and myocardial contractile force in man.[8-11]

Several doses of $NaHCO_3$ were studied, at two depths of halothane anesthesia, along with the time course of the alkalosis. We found that acute metabolic alkalosis in volunteers at both light and deep levels of halothane anesthesia was associated with increased cardiac output and decreased total peripheral resistance. Measurements of systolic time intervals showed apparent myocardial stimulation. The mechanisms of these cardiovascular effects are not fully known at this time.

Methods

Seven healthy male volunteers, ranging in age from 21 to 29 years, were selected for study during anesthesia without surgery. Informed consent was insured by fully explaining the purposes and procedures of the study in a preliminary interview. Signed consent was obtained at a second interview, when a complete history was taken and a physical examination performed. None of the volunteers had previously been anesthetized with a halogenated hydrocarbon. Each volunteer arrived in the study room on the morning of the experiment after a minimum of eight hours of fasting. No preanesthetic medication

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Received from the Department of Anesthesia, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania. Accepted for publication October 12, 1974. Supported in part by USPHS Research Center Grant, 5-P01-GM-15430-05, from the National Institute of General Medical Sciences, National Institutes of Health. Presented at the Annual Meeting of the American Society of Anesthesiologists, Boston, Massachusetts, October 2, 1972.

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§ Unpublished data. Presented at the annual meeting of the American Society of Anesthesiology, Boston, 1972.

was given. Anesthesia was induced with halothane in oxygen via a Dräger vaporizer, and the trachea was intubated without use of a muscle relaxant. Ventilation was controlled with a volume-limited Bird respirator in a nonrebreathing circuit with a Frumin valve. All subjects were hyperventilated with a minute ventilation of 150 ml/kg, and carbon dioxide was added to maintain the end-tidal carbon dioxide tension ($P_{ET_{CO_2}}$) at 40 torr throughout the study.

An 18-gauge catheter was inserted percutaneously into the left radial artery, and a 16-gauge catheter was inserted percutaneously into the superior vena cava via the right internal jugular vein.[12] A peripheral venous catheter was inserted into the right forearm. Four electrocardiograph electrodes and precordial and carotid microphones were attached. The following variables were measured: 1) Systolic, diastolic, mean arterial, and central venous pressures by model P23Db Statham strain gauges. 2) Heart rate and ECG. 3) Cardiac output by the dye-dilution method using indocyanine green dye. 4) Systolic time intervals, consisting of pre-ejection period (PEP), left ventricular ejection time (LVET), and the total electromechanical systole (QS_2); our technique was similar to that described by Weissler,[13] except that we used Electronics for Medicine phono-pulse transducers (PS-2) for the phonocardiogram and carotid pulse. 5) $P_{a_{O_2}}$, $P_{a_{CO_2}}$, and pH using the Radiometer electrode system maintained at 37 C, and base excess and bicarbonate concentration, calculated with the Severinghaus slide rule.[14] 6) Serum ionized calcium, total calcium, magnesium, sodium, potassium, and hematocrit, immediately before and 30 minutes after each dose of $NaHCO_3$; ionized calcium was analyzed with an Orion Research, Inc., flow-through electrode system (Model 88-20) and a Model 801 digital pH/mv meter. 7) Continuous sampling of end-tidal, mixed-expired and inspired carbon dioxide tensions by a Godard capnograph. 8) Expired minute ventilation by a calibrated dry-gas meter. 9) Inspired and mixed-expired halothane concentrations by intermittent gas chromatography. 10) Mean airway pressure by a model P23BB Statham strain gauge. 11) Body temperature, monitored by a calibrated Yellow Springs rectal thermistor probe, maintained between 36–37 C by means of infrared heat lamps. Blood loss due to sampling did not exceed 500 ml and was replaced with 500 ml Plasmanate in 500 ml physiologic saline solution as samples were drawn.

The following variables were calculated using standard formulas[15,16]: cardiac index (CI), stroke index (SI), left ventricular minute work index (LVMWI), total peripheral resistance (TPR), central blood volume (CBV), and the ratios PEP/LVET, and $1/PEP^2$.

The overall experimental design is summarized in the first column of table 1. The subjects were divided into two groups, one lightly anesthetized and one deeply anesthetized. The lightly anesthetized group of five subjects had a mean inspired halothane concentration of 0.74 per cent and a mean mixed-expired halothane concentration of 0.61 per cent. The deeply anesthetized group (which we limited to two subjects because of unexpectedly profound hypotension) had a mean inspired halothane concentration of 1.0 per cent and a mean mixed-expired halothane concentration of 0.87 per cent.

Control observations were recorded at the end of 1½ hours of a stable depth of halothane anesthesia with the subjects in normal acid–base balance. The volunteers then received three graded doses of 7.5 per cent $NaHCO_3$ via the central venous line at hourly intervals. The deeply anesthetized subjects were the first studied and received the larger doses of $NaHCO_3$. Smaller doses of $NaHCO_3$ were given to the lightly anesthetized group because of the hypotension seen in the first two volunteers with larger doses of $NaHCO_3$. The deeply anesthetized group received 44.6 mEq, 133.8 mEq, and 312.2 mEq; while the lightly anesthetized group received 44.6 mEq, 89.2 mEq, and 178.4 mEq of $NaHCO_3$. Each ampule of 7.5 per cent $NaHCO_3$ (44.6 mEq/50 ml) was injected over 2 minutes while the inspired carbon dioxide concentration was reduced to maintain end-tidal carbon dioxide concentration at 40 torr. Cardiovascular measurements were made before and 5, 15, 30, 45, and 60 minutes after each dose of $NaHCO_3$.

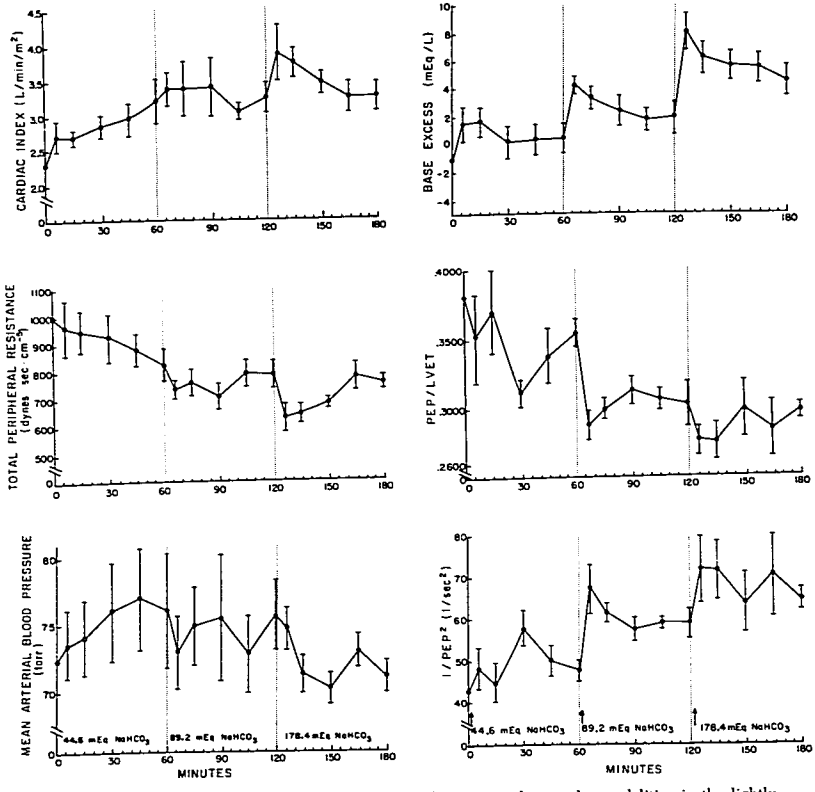

FIG. 1. Time course of the effects of metabolic alkalosis on cardiovascular modalities in the lightly anesthetized group (n = 5; inspired halothane = 0.74 per cent). The vertical axes show the various cardiovascular values. The horizontal axis on each graph shows the three-hour period of study, divided into three one-hour segments. At the start of each one-hour segment, after control measurements, a progressively larger dose of $NaHCO_3$ was given. Mean values ± SEM 5, 15, 30, 45, and 60 minutes after each dose are shown.

Results

The time course of the effects of metabolic alkalosis on cardiovascular values in the lightly anesthetized group is shown in figure 1. Except for starting at more depressed values, the two deeply anesthetized subjects had similar courses. The maximum changes in acid–base values occurred 5 minutes after each dose of $NaHCO_3$, and values gradually returned toward control over one hour. In every subject, cardiac index increased and total peripheral resistance decreased after each dose of $NaHCO_3$. The increased cardiac index was associated with increased left ventricular minute work index, stroke index,

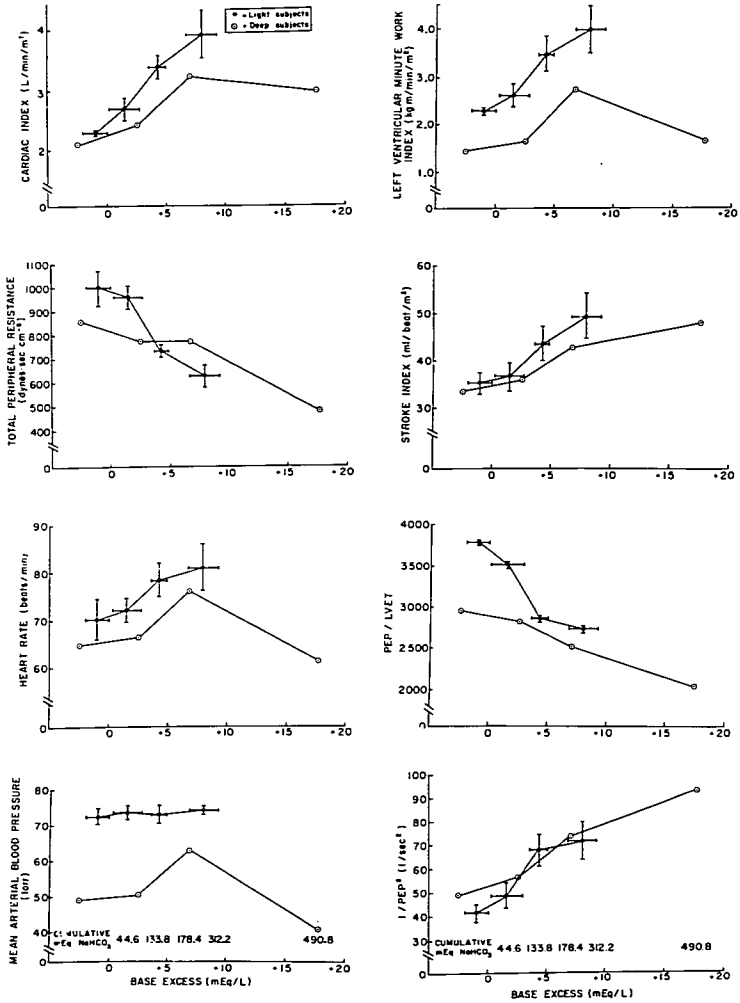

FIG. 2. Dose-related cardiovascular effects 5 minutes after $NaHCO_3$. The vertical axes show the cardiovascular values. Each horizontal axis has two scales—base excess and cumulative $NaHCO_3$ dose in mEq. For lightly anesthetized subjects (n = 5) means ± SEM are shown. For deeply anesthetized subjects (n = 2) only the mean values are shown.

TABLE 1. Dose-related Cardiovascular

Experimental Design	Base Excess (mEq/l)		Mean Arterial Blood Pressure mm Hg			Total Peripheral Resistance (dynes/sec cm^{-5})			Central Venous Pressure (cm H_2O)			Central Blood Volume (liters)		
	Mean	SE	Mean	SE	Per Cent Change	Mean	SE	Per Cent Change	Mean	SE	Per Cent Change	Mean	SE	Per Cent Change
Light halothane anesthesia (n = 5) (mean inspired halothane = 0.7 per cent; SE = 0.05; mean mixed-expired halothane = 0.61 per cent; SE = 0.05)														
Control	−1.06	1.19	72.40	2.16		1,002	76.80		8.92	0.91		2.43	0.08	
44.6 mEq	+1.54*	1.35	73.70	2.59	+1.8	969	96.52	−3.3	9.00	0.77	+1.1	2.40	0.03	−1.2
89.2 mEq	+4.30*	0.62	73.28	2.62	+1.1	731*	39.73	−27.0	8.13	0.49	−8.9	2.56	0.11	+5.3
178.4 mEq	+8.00*	1.31	74.80	1.56	+3.3	628*	47.60	−37.3	9.41	0.61	+5.6	2.86*	0.19	+17.7
Deep halothane anesthesia (n = 2) (mean inspired halothane = 1.0 per cent; mean mixed-expired halothane = 0.87 per cent)														
Control	−2.50		49.00			858			9.00			1.82		
44.6 mEq	+2.50		50.51		+3.0	774		−9.7	8.92		−1.1	1.94		+6.6
133.8 mEq	−6.90		63.83		+30.2	773		−9.8	9.21		+2.2	2.13		+17.0
312.2 mEq	+17.70		40.81		−16.7	478		−44.3	10.73		+19.8	2.02		+11.0

* Significant difference from control, $P < 0.05$, for light-anesthesia group only, by t test for paired data.

heart rate, and 1/PEP[2] and a decreased PEP/LVET ratio.

Dose related cardiovascular effects 5 minutes after each dose of $NaHCO_3$ are shown in figure 2 and table 1. Lightly anesthetized and deeply anesthetized groups had similar dose–response relationships. As the cumulative dose of $NaHCO_3$ increased, cardiac index, heart rate, left ventricular minute work index, stroke index, 1/PEP[2], and central blood volume increased; total peripheral resistance and PEP/LVET ratio decreased; and mean arterial blood pressure and central venous pressure remained stable.

In the lightly anesthetized group, the cumulative dose of $NaHCO_3$ reached 312.2 mEq. At this depth of anesthesia and degree of alkalosis (*p*H 7.51, BE +8 mEq); the volunteers remained in normal sinus rhythm, and blood pressures differed only slightly from control values. When the cumulative dose reached 490.6 mEq $NaHCO_3$ in the deeply anesthetized group (*p*H 7.66, BE +17.7), severe hypotension occurred. This was associated with a significant decrease in total peripheral resistance, slowing of the heart rate, and a nodal or junctional rhythm. These were the only arrhythmias seen during the study. The stroke index increased during hypotension and maintained a relatively constant cardiac index.

The blood–gas and ventilatory conditions are recorded in table 2. In all cases Pa_{O_2} was maintained above 450 torr, with a mean of 558 torr ± SE 9.5 torr. Minute ventilation and mean airway pressure were held constant during each experiment, so as not to affect cardiovascular values.[17,18] There were significant changes in the metabolic values (BE, HCO_3^-), but not in the respiratory values (Pa_{CO_2}, PET_{CO_2}).

Halothane concentration was held constant throughout all seven experiments (Table 3). Hematocrits decreased about 4 per cent. There were progressive decreases in ionized calcium, total calcium, magnesium, and

Effects 5 Minutes after $NaHCO_3$

Heart Rate (Beats/min)			Cardiac Index (l/min/sq m)			Left Ventricular Minute Work Index (kg-meter/min/sq m)			Stroke Index (ml/beat/sq m)			Pre-ejection Period/ Left Ventricular Ejection Time			I/(Pre-ejection Period)^2 (l/sec^4)		
Mean	SE	Per Cent Change	Mean	SE	Per Cent Change	Mean	SE	Per Cent Change	Mean	SE	Per Cent Change	Mean	SE	Per Cent Change	Mean	SE	Per Cent Change
															41.91	3.91	
69.42	4.11		2.32	0.03		2.27	0.06		35.41	2.30		0.38	0.02		48.40	5.84	+15.4
71.80	2.83	+3.4	2.68	0.24	+15.5	2.69	0.23	+18.5	36.58	3.06	+3.3	0.35	0.03	−8.0	67.51	6.00	+61.0
78.41	3.94	+12.9	3.40*	0.24	+46.5	3.38*	0.33	+48.9	43.76*	3.62	+23.5	0.29	0.02	−24.7	71.79*	8.50	+71.3
81.00	5.00	+16.7	3.94*	0.43	+69.8	3.96*	0.39	+74.4	49.03*	5.01	+38.7	0.28*	0.02	−27.8			
64.51			2.12			1.40			33.05			0.30			49.35		
66.00		+2.3	2.44		+15.1	1.67		+19.2	36.95		+11.8	0.29		−3.9	56.40		+14.2
76.00		+17.8	3.26		+53.8	2.76		+97.1	42.80		+29.5	0.26		−14.9	74.20		+50.3
61.53		−4.6	3.00		+41.5	1.67		+19.3	48.80		+47.6	0.20		−31.8	92.13		+86.6

potassium with increasing alkalosis. However, there was a significant increase in serum sodium concentration.

Discussion

This study confirms and extends the previously known information about the cardiovascular effects of metabolic alkalosis. Stoyka's studies in dogs anesthetized with minimum alveolar anesthetic concentrations (1 MAC) of either methoxyflurane or fluroxene showed that cardiac output increased with $NaHCO_3$ infusion up to a pH of 7.48.[2,4] Anderson and Clancy demonstrated increased myocardial contractility in anesthetized dogs after $NaHCO_3$ administration.[1,5] Kennell's study in man anesthetized with nitrous oxide, oxygen, and *d*-tubocurarine showed that cardiac index increased 90 per cent after approximately 350 mEq of $NaHCO_3$, when the pH rose to 7.70. Our study shows that in man either lightly or deeply anesthetized with halothane, there are similar increases in cardiac index and myocardial stimulation. This indicates that $NaHCO_3$ affects the depressed heart as well as the relatively non-depressed heart exposed only to nitrous oxide. Our control values for cardiac index, mean arterial blood pressure, and total peripheral resistance after 1½ hours of halothane anesthesia but before $NaHCO_3$ administration were well below normal awake control values.[19] This justifies our assumption that these volunteers represented a population with depressed cardiovascular systems.

It has been demonstrated by Ostea that $NaHCO_3$ added to a "closed system" may actually decrease pH.[20] This occurs through elevation of Pa_{CO_2} and $P_{ET_{CO_2}}$, as shown by the following reactions:

$$Na^+ + HCO_3 + H\ buf \rightarrow Na^+ + buf^- + H_2CO_3 \quad (1)$$

$$H_2CO_3 \rightarrow H_2O + CO_2\uparrow \quad (2)$$

TABLE 2. Acid–Base and Ventilatory Values 5 Minutes after $NaHCO_3$

Experimental Design	pH		Base Excess (mEq/l)		Serum Bicarbonate (HCO_3^-) (mm/l)		P_{ACO_2} (torr)		P_{ETCO_2} (torr)		P_{ICO_2} (torr)		Minute Ventilation (l/min)		Mean Airway Pressure (cm H_2O)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Light halothane anesthesia																
Control	7.38	0.01	−1.06	1.19	26.31	1.42	40.31	0.99	40.70	0.46	20.82	1.71	12.50	0.56	8.51	0.79
44.6 mEq	7.41*	0.01	+1.54*	1.35	28.86*	1.58	41.00	1.38	41.02	0.36	20.34	1.75	12.50	0.45	8.44	0.56
89.2 mEq	7.47*	0.01	+4.30*	0.62	31.20*	1.70	39.22	0.90	40.51	0.46	16.26*	1.86	12.07	0.49	8.12	0.72
178.4 mEq	7.51*	0.01	+8.00*	1.31	35.14*	1.61	38.81	1.13	40.24	0.59	16.32*	1.51	11.79	0.61	8.01	0.78
Deep halothane anesthesia																
Control	7.40		−2.50		22.71		35.74		41.00		24.65		10.38		5.61	
44.6 mEq	7.45		+2.50		27.11		38.31		40.91		20.50		10.48		5.44	
133.8 mEq	7.53		+6.90		30.62		35.43		39.72		20.00		9.45		5.81	
312.2 mEq	7.66		+17.70		41.24		35.72		42.04		20.65		9.29		5.22	

* Significant difference from control, $P < 0.05$, for light-anesthesia group only, by t test for paired data.

TABLE 3. Laboratory Values 30 Minutes after $NaHCO_3$

Experimental Design	Hematocrit (Per Cent)		Na^+ (mEq/l)		K^+ (mEq/l)		Total Calcium (mg/100 ml)		Ionized Ca^{++} (mg/100 ml)		Mg^{++} (mg/100 ml)		Inspired Halothane (Per Cent)		Mixed Expired Halothane (Per Cent)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Light halothane anesthesia																
Control	36.71	1.30	138.41	0.38	4.29	0.26	9.83	0.07	3.82	0.15	1.77	0.06				
44.6 mEq	35.81	0.82	139.51*	0.47	4.43	0.38	9.63	0.38	3.78	0.14	1.70*	0.07	0.74	0.05	0.62	0.05
89.2 mEq	34.22*	1.19	140.90*	0.52	4.26	0.38	9.37*	0.08	3.68	0.13	1.62*	0.05	0.74	0.07	0.58	0.07
178.4 mEq	32.43*	0.74	144.00*	0.92	3.54*	0.21	9.19*	0.05	3.45*	0.14	1.57*	0.05	0.72	0.05	0.60	0.04
Deep halothane anesthesia																
Control	33.25		138.50		3.94		9.67		3.92		1.73					
44.6 mEq	33.45		139.62		4.03		9.63		3.85		1.71		1.04		0.91	
133.8 mEq	32.75		143.64		3.64		9.36		3.71		1.65		1.05		0.86	
312.2 mEq	29.50		149.40		3.27		8.86		3.28		1.48		1.06		0.91	

* Significant difference from control, $P < 0.05$, for light-anesthesia group only, t test for paired data.

Since it was our desire to study pure metabolic alkalosis, we initially hyperventilated the subjects and added carbon dioxide to produce normal $P_{ET_{CO_2}}$. Hence, during infusion of $NaHCO_3$, we were able to decrease the inspired concentration of carbon dioxide to maintain end-tidal carbon dioxide concentration at 40 torr. In the past, many authors have not controlled $P_{a_{CO_2}}$. Therefore, they were studying an acid–base condition consisting of metabolic alkalosis and respiratory acidosis. This possibly explains the varying results reported after $NaHCO_3$ administration.

The two most likely explanations for the increase in cardiac output seen with $NaHCO_3$ administration are peripheral vasodilation and expansion of circulating blood volume.

$NaHCO_3$ acts as a peripheral vasodilator, with hemodynamic effects similar to those of sodium nitroprusside.[21] The response of total peripheral resistance (fig. 1) suggests persistent and progressive vasodilation associated with the increased cardiac output. This vasodilation reduces the afterload on the heart and places the left ventricle on a higher Frank-Starling curve. As a result of this effect, the increases in stroke volume, cardiac output, and $1/PEP^2$ would be expected.

The vasodilation also explains the profound hypotension seen with large doses of $NaHCO_3$ given to deeply anesthetized volunteers. In this situation, the marked vasodilation could not be compensated for by an increase in flow due to the limitations set by halothane on myocardial contractility. Also, the junctional rhythms seen at the high pH (7.66) limited the cardiac output.

There also appeared to be a hemodynamically significant increase of circulating blood volume in these volunteers. This is reflected in the central blood volume and central venous pressure measurements. If blood volume had stayed the same, central venous pressure should have decreased in association with peripheral vasodilation and increased cardiac output. However, central venous pressure changed little in most of our volunteers. This probably means that hypertonic $NaHCO_3$ caused a progressive increase in intravascular volume.

Three less likely explanations for the increase in cardiac output are: 1) Production of intracellular alkalosis by $NaHCO_3$, which has been demonstrated to increase myocardial contractility in dogs.[1] 2) Beta-adrenergic receptor stimulation by $NaHCO_3$. This appears unlikely since in two previous experiments on intact dogs in our laboratory, blockade with propranolol (0.2–0.4 mg/kg) did not affect the increase in cardiac output associated with $NaHCO_3$ administration. 3) Time compensation to halothane,[22] which appeared to play only a minor role in this study since each dose of $NaHCO_3$ caused acute changes in cardiovascular values.

The use of noninvasive systolic time intervals was popularized by Weissler in 1969.[13] Those most commonly used are the PEP, LVET, and QS_2. These values reflect myocardial performance, but are also markedly affected by changes in preload, afterload, and heart rate. All our measurements were regressed to zero heart rate, to eliminate the effect of changes in heart rate, by using Weissler's formulas.[23] The ratio PEP/LVET has been shown to correlate well with the ejection fraction and dp/dt.[24,25] Reitan has shown that the ratio $1/PEP^2$ correlates with maximal aortic blood flow acceleration.[26] Previously, Noble demonstrated that maximal aortic blood flow acceleration was a good measure of myocardial contractility.[27] Our study showed good correlation between stroke index and $1/PEP^2$.

In the present study, cardiac output determinations were made using indocyanine green, a water-soluble tricarbocyanine dye with a peak spectral absorption at 775 millimicrons in Ringer's lactate solution and 800–810 millimicrons in blood.[28] The effects of pH on the dye have not been studied previously. Solutions of dye in Ringer's lactate solution and $NaHCO_3$ (pH 6.0–7.61) were found to have a peak spectral absorption at 775 millimicrons. Calibration factors were also measured for our densitometer at various pH's and found to be identical. Therefore, we felt that the alkalosis in this study did not affect the properties of the dye.

In conclusion, $NaHCO_3$ appears to have two main circulatory effects: 1) peripheral vasodilation, and 2) volume expansion. Small doses of $NaHCO_3$ given to lightly anesthetized subjects cause a decrease in afterload and an increase in cardiac output and

1/PEP². Large doses of $NaHCO_3$ given to deeply anesthetized subjects produce severe hypotension associated with massive peripheral vasodilation and junctional rhythms. The role of direct myocardial stimulation by $NaHCO_3$ is not clear from this study. If $NaHCO_3$ is needed during halothane anesthesia, moderate doses should be administered slowly intravenously to avoid profound hypotension.

The authors acknowledge the invaluable technical assistance of Mr. Raymond W. Andrews and Mrs. Cheryl McIlvaine.

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