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Cardiovascular Effects of Carbon Dioxide in Man

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Circulatory responses to administration of carbon dioxide were determined in 41 awake human volunteers during controlled or spontaneous respiration. Compared with spontaneous respiration (Pa_{CO_2} 37 torr), controlled respiration (Pa_{CO_2} 36 torr) was associated with a significantly lower cardiac index and stroke index but with an increased total peripheral resistance which maintained constant arterial blood pressure. When exogenous CO_2 was administered during either controlled or spontaneous respiration (range 39 → 50 torr), cardiac index, heart rate, stroke index, indices of myocardial contractility, and forearm blood flow all increased significantly, while total peripheral resistance decreased significantly. These data serve as reference points for measurements of cardiovascular function in normal man, and for studying the modification of the circulatory response to CO_2. Anesthetic agents, drugs, and disease states which alter autonomic tone in either direction may modify the response. (Key words: Carbon dioxide: cardiovascular response; Heart: carbon dioxide; Arteries: carbon dioxide; Blood pressure: carbon dioxide.)

CARBON DIOXIDE induces direct and indirect circulatory effects in man and experimental animals. Acting directly, CO_2 dilates peripheral arterioles and depresses myocardial contractility.[1-5] It also stimulates the central nervous system at several levels directly and at the vasomotor level indirectly by initiating afferent impulses from the peripheral chemoreceptors. Activation of the central nervous system evokes sympathoadrenal responses, resulting in increased myocardial contractility, tachycardia, and hypertension.[2,5,6,7] This paper reports the sum of these effects by detailing the circulatory responses of 41 awake human volunteers to administration of CO_2 under carefully controlled circumstances. Control measurements (without added CO_2) during both controlled and spontaneous respiration also serve as reference data for circulatory measurements in man.

Methods

Forty-one healthy, young, adult, male volunteers were interviewed and informed consent was obtained. The procedures and consent form had been approved by the University of California and Stanford University Committees on Human Experimentation. All subjects fasted overnight and the studies were conducted the following morning.

Using local anesthesia, an arterial catheter was inserted percutaneously into the brachial or radial artery and a right atrial catheter was inserted through a 14-gauge needle into the basilic vein. In most cases, the catheter was advanced until a right ventricular pressure trace appeared and was then withdrawn until an atrial pressure wave was observed. A peripheral venous catheter was inserted in the forearm. Whitney strain gauges (mercury-filled plastic tubing) were placed about the fleshy portion of the forearm. Venous occlusion cuffs were placed at the base of the wrist and on the arm. A lead II electrocardiogram was used for recording heart rate. In 34 subjects, a precordial phonocardiogram and carotid pulse monitor were attached for determining intervals of electrical and mechanical systole. Each subject lay on an inflated air mattress which rested on an ultra-low-frequency air-bearing ballistocardiogram bed. The air mat-

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TABLE 1. Control Values (Means ± 1 SE)

	Controlled Respiration (n = 15)	Spontaneous Respiration (n = 26)
Age (years)	24.2 ± 0.8	24 ± 0.6
Height (cm)	175 ± 2	174 ± 1.4
Weight (kg)	70 ± 2.2	70.4 ± 1.4
$P_{a_{O_2}}$ (torr)	492* ± 13.6	525 ± 8.1
$P_{a_{CO_2}}$ (torr)	35.7 ± 1	37 ± 0.8
pH	7.39 ± 0.01	7.40 ± 0.001
Base excess (mEq/l)	−3.1* ± 0.5	−1.6 ± 0.3
Cardiac output (l/min)	4.64* ± 0.2	5.91 ± 0.2
Cardiac index (l/min/m²)	2.48* ± 0.1	3.15 ± 0.1
Stroke volume (ml)	78.7* ± 4	95.3 ± 3.6
Stroke index (ml/m²)	42.1* ± 1.6	51.1 ± 1.8
Heart rate (beats/min)	60 ± 1.7	62 ± 1.5
Mean arterial pressure (torr)	90 ± 2.6	88.2 ± 1.6
Mean right atrial pressure (torr)	3.6 ± 0.8	4.4 ± 0.5
Total peripheral resistance (dynes/sec/cm⁻⁵)	1,530* ± 78	1,174 ± 52
Ejection time (msec)	300 ± 7	289 ± 9
Mean rate ventricular ejection (ml/sec)	0.28 ± 0.01	0.32 ± 0.01
Left ventricular stroke work (kg-m)	0.10 ± 0.007	0.11 ± 0.005
Left ventricular work (kg-m/min)	6.04 ± 0.4	7.07 ± 0.4
Tension-time Index†	26.9 ± 0.1	24.9 ± 1.2
Ballistocardiogram IJ-wave amplitude	21.2 ± 2.9	14.6 ± 1.4
Forearm blood flow (ml/100 g tissue/min)	3.1 ± 0.3	3.0 ± 0.3
Forearm vascular resistance (dynes/sec/cm⁻⁵)	30.9 ± 3	34.3 ± 4
Forearm venous compliance (ml/torr)	0.16 ± 0.03	0.13 ± 0.02

* $P < 0.05$, controlled respiration cs. spontaneous respiration.
† AP × ET × 0.001.

tress was deflated during ballistocardiographic and other cardiovascular measurements.

Mean arterial pressure (MAP), mean right atrial pressure (MRAP), and peripheral venous pressure (PVP) were transduced with Statham strain gauges. Duplicate cardiac outputs were obtained by dye dilution with indocyanine green using a Beckman Cardiodensitometer. Arterial P_{O_2}, P_{CO_2}, and pH were measured with blood–gas electrodes. Forearm blood flow was obtained by venous occlusion plethysmography with the Whitney strain gauge.[8] The amplitude of the IJ wave of the ballistocardiogram was recorded. Oral and skin temperatures were measured with thermistors.

Calculated variables included stroke volume (SV), stroke index (SI), cardiac index (CI), total peripheral resistance (TPR), ejection time (ET), mean rate of left ventricular ejection (MRLVE), left ventricular stroke work (LVSW), left ventricular work (LVW), forearm venous compliance (FVC), forearm vascular resistance (FVR), and base excess (BE).

Control measurements were obtained with the subject breathing oxygen from an anesthetic circle system via a mouthpiece. The nose was occluded by nose clips. After the subjects had become accustomed to the breathing system, ventilation of 15 of the 41 was changed from spontaneous to controlled with a volume-limited ventilator. There was no sign that the subjects resisted ventilation over the range of CO_2 studied. End-tidal P_{CO_2} was monitored with an infrared CO_2 analyzer and maintained at normal levels. The control (no added CO_2) data for the 15 subjects whose ventilation was controlled were compared with the data from the 26 subjects whose ventilation was spontaneous at the same Pa_{CO_2}, using unpaired t tests. $P < 0.05$ was accepted as statistically significant.

After control measurements had been obtained, CO_2 was added in incremental amounts to the breathing system to produce 2–4-torr stepwise increases in Pa_{CO_2}. All measurements were repeated after equilibrating for 6 minutes at each level of Pa_{CO_2}. At the end of 6 minutes, an arterial sample was

TABLE 2. Circulatory Responses to CO_2 (Means ± 1 SE)*

	Controlled Respiration		Spontaneous Respiration	
	Regression Equation	Per Cent Change with 10-torr Increase in Pa_{CO_2}	Regression Equation	Per Cent Change with 10-torr Increase in Pa_{CO_2}
Cardiac output (l/min)	$y = 0.17x - 2.2$	39 ± 5	$y = 0.17x - 1.3$	32 ± 4
Cardiac index (l/min/m²)	$y = 0.09x - 0.8$	39 ± 5	$y = 0.10x - 0.6$	32 ± 4
Stroke volume (ml)	$y = 0.62x + 55.6$	10 ± 2	$y = 0.34x + 83.3$	11 ± 2
Stroke index (ml/m²)	$y = 0.34x + 29.7$	11 ± 2	$y = 0.23x + 44.4$	11 ± 2
Heart rate (beats/min)	$y = 1.74x - 4.8$	28 ± 4	$y = 1.7x - 1.8$	26 ± 3
Mean arterial pressure (torr)	$y = 0.82x + 60.9$	9 ± 1	$y = 0.89x + 50.4$	10 ± 2
Mean right atrial pressure (torr)	$y = -0.05x + 5.3$	0	$y = -0.05x + 7.4$	0
Total peripheral resistance (dynes/sec/cm⁻⁵)	$y = -28.7x + 2,580$	−17 ± 4	$y = -16.7x + 1,800$	−14 ± 3
Ejection time (msec)	$y = -0.25x + 309.1$	−0.544 ± 0.77	$y = -1.16x + 336$	−3 ± 2
Mean rate ventricular ejection (ml/sec)	$y = 0.0008x + 0.3$	3 ± 4	$y = 0.0028x + 0.2$	8 ± 3
Left ventricular stroke work (kg-m)	$y = 0.001x + 0.06$	12 ± 3	$y = 0.002x + 0.04$	25 ± 10
Left ventricular work (kg-m/min)	$y = 0.33x - 6.4$	54 ± 11	$y = 0.31x - 4$	46 ± 5
Tension–time index	$y = 0.25x + 18$	10 ± 2	$y = 0.11x + 22$	65 ± 2
Forearm blood flow (ml/100 g tissue/min)	$y = 0.1x - 0.4$	30 ± 11	$y = 0.12x - 1.1$	44 ± 10
Forearm vascular resistance (dynes/sec/cm⁻⁵)	$y = -0.13x + 37.5$	−6 ± 9	$y = -0.71x + 64$	−10 ± 10
Forearm venous compliance (ml/torr)	$y = 0.00009x + 0.14$	0	$y = 0.0014x + 0.08$	0

* There was no significant difference comparing the circulatory responses to CO_2 during spontaneous respiration with those during controlled respiration.

obtained and the Pa_{CO_2} value was used in the regression analyses described below. Measurements at three separate levels of Pa_{CO_2} were obtained for each subject. The cardiovascular response to CO_2 was analyzed by linear regression, again comparing the 15 subjects during controlled respiration with the 26 subjects during spontaneous respiration. A regression line was calculated for each individual subject, with Pa_{CO_2} always serving as the independent variable. The individual slopes and y intercepts were combined into two groups, controlled respiration and spontaneous respiration. The mean and standard error were calculated for the slope and y intercept for each group. The mean slope values for controlled respirations were compared statistically with the mean slope values for spontaneous respiration by unpaired t tests. Additionally, for each individual subject, the percentage change (mean and standard error) for each measured value in response to a 10-torr increase in Pa_{CO_2} was calculated (table 2). The initial value measured prior to CO_2 challenge served as the baseline value.

Results

CONTROL DATA (TABLE 1)

The control measurements during both controlled respiration (n = 15) and spontaneous respiration (n = 26) showed that the subjects were equivalent with respect to age, height, weight, Pa_{CO_2}, and *p*H. However, cardiac output and index, stroke volume and index, and Pa_{O_2} were significantly lower, while TPR was significantly higher, during controlled respiration than during spontaneous respiration. A slight but statistically significant metabolic acidosis was present during controlled respiration.

CIRCULATORY RESPONSES TO CO_2 (TABLE 2)

The mean Pa_{CO_2} at which the regression lines began was 38.7 ± 0.3 torr (1 SE). The mean Pa_{CO_2} at which the last measurement was obtained was 50.2 ± 0.9 torr. The mean increase in Pa_{CO_2} was 11.5 ± 0.9 torr. Given this hypercarbia, several circulatory variables (cardiac output, cardiac index, stroke volume,

TABLE 3. Effects of anesthetics on the Cardiac-index Response to CO_2 in Man*

	Response (Δ ml/torr Increase in P_{aCO_2})
Conscious	95
Cyclopropane, 15–20 per cent (alveolar)[16]	76
Cyclopropane, 25–30 per cent (alveolar)[16]	51
Halothane, 0.8 per cent (alveolar)[17]	34
Halothane, 1 per cent (inspired)[18]	23
N_2O–meperidine–*d*-tubocurarine[19]	22
Fluroxene, 5 per cent (alveolar)[20]	59
Fluroxene, 9 per cent (alveolar)[20]	65
Isoflurane, 1.2 per cent (alveolar)[21]	75
Isoflurane, 1.8 per cent (alveolar)[21]	48
Enflurane, 1.9 per cent (alveolar)[22]	104
Spinal anesthesia (T1 level)†	24

* Calculated milliliter increase in cardiac index per torr increase in P_{aCO_2}.

† Bonica, J. J.: Personal communication.

stroke index, mean arterial pressure, left ventricular stroke work, left ventricular work, forearm blood flow and heart rate) were significantly increased, while one (peripheral resistance) decreased.

The slopes of the various CO_2 response curves were similar during controlled and spontaneous respiration. For example, although the control cardiac output was lower during controlled respiration, the responsiveness of cardiac output to CO_2 administration was not different.

Discussion

Administration of CO_2 during either controlled or spontaneous respiration significantly increased cardiact output and indices of myocardial contractility, while peripheral vascular resistance decreased. Hypercarbia acts through central nervous system stimulation to increase sympathetic tone, thereby increasing myocardial contractility and vascular tone.[3,5,6,7,9,10] Peripherally, however, the indirect effects of vasoconstriction are overcome by the direct peripheral vasodilating effect of CO_2, so that total peripheral resistance decreases. Our data quantitate these well-known effects of CO_2 in young healthy human subjects.

Just as anesthetics, narcotics, and disease states may modify the ventilatory response to CO_2, so also may the circulatory responses to CO_2 be modified. For example, anesthetics depress the normal increase in cardiac index produced by elevation of Pa_{CO_2} (table 3). The ability of various anesthetics to modify this response probably relates to suppression of sympathetic activity imposed by the anesthetics. For example, halothane[11] reduces preganglionic sympathetic activity in the intact cat and greatly attenuates the circulatory response to CO_2. Conversely, cyclopropane,[12] and fluroxene[13] induce central sympathetic activity, and both agents are associated with a vigorous, albeit slightly blunted, cardiovascular response to increased CO_2 levels. Where the other anesthetics fit into this scheme is not well established.

Sympathetic blockade should reduce the circulatory response to CO_2. During total spinal anesthesia in volunteers, the cardiac index response to exogenously administered CO_2 was markedly diminished, although a slight response did occur,† possibly through inhibition of vagal activity. Undoubtedly, as other drugs and disease states are studied, further interference with normal circulatory responses to CO_2 will be demonstrated.

The differences between controlled respiration and spontaneous respiration for the control baseline data support previous findings.[14,15] Impedence of venous return during controlled respiration results in increased peripheral vascular tone and maintenance of blood pressure in the face of reduced cardiac output.

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Drugs and Their Actions

SCOPOLAMINE DELIRIUM The effects of intravenously administered physostigmine on scopolamine-induced confusion and amnesia were studied in the parturient patient. Physostigmine completely reversed the central depression and amnesia produced by scopolamine. All patients became cooperative and oriented within 3 to 5 minutes and had good antegrade memory after administration of the drug. The effectiveness of physostigmine in this preliminary study warrants more definitive studies of the maternal and fetal effects of the drug. *(Smiler, B., Bartholomew, E.G., Sivak, B.J., and others: Physostigmine Reversal of Scopolamine Delirium in Obstetric Patients. Am J Obstet Gynecol 115: 326–329, 1973.)*