The Circulatory Response to Hypercapnia during Fluoroxyne Anesthesia in Man

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The circulatory response to hypercapnia was studied in nine volunteers. The inhalation of carbon dioxide by conscious subjects led to increases in cardiac output, heart rate, mean arterial pressure, and myocardial function (measured indirectly by ballistocardiography). Central venous pressure and total peripheral resistance decreased. During anesthesia at both 5 and 9 per cent alveolar fluoroxyne concentrations, responses of cardiac output to CO₂ were attenuated by 40 per cent, primarily because of depression of the heart rate and the myocardial contractile response to hypercapnia. The effects of CO₂ on other cardiovascular variables were similarly attenuated. The data suggest that fluoroxyne attenuates the sympathetic response to hypercapnia. The depression of the response of cardiac output to hypercapnia was less with fluoroxyne than with halothane or deep cyclopropane anesthesia. (Key words: Fluoroxyne; Carbon dioxide; Circulation.)

In conscious man the inhalation of carbon dioxide increases cardiac output, blood pressure, and heart rate, and lowers total peripheral resistance. This response results from central sympathetic stimulation, which opposes a direct depressant effect of carbon dioxide on the myocardium and peripheral circulation.¹⁻² Halothane,³⁻⁴ cyclopropane,⁵⁻⁶ and nitrous oxide ⁷ depress the circulatory stimulation produced by hypercapnia. That fluoroxyne (Fluoromar) increases sympathetic activity at normocapnia ⁸ interested us in studying the effects of fluoroxyne on the circulatory response to hypercapnia. The results of the study are reported below.

Methods

Nine healthy, unmedicated, male volunteers served as subjects. Prior to induction of anesthesia, arterial and right atrial catheters were inserted under local anesthesia to permit measurement of cardiac output (dye dilution), blood pressure, and blood gases. All subjects lay supine, and six lay on an ultralow-frequency ballistocardiogram bed. The IJ wave of the ballistocardiogram was recorded and served as an indirect measure of myocardial contractility.⁹⁻¹⁰ Infrared analyzers permitted measurement of end-tidal fluoroxyne and carbon dioxide concentrations. Body temperature was held constant by adjustment of room temperature. Additional details regarding techniques of measurement can be found in a prior publication.¹²

Before induction of anesthesia, and again at 5 and 9 per cent alveolar fluoroxyne concentrations in oxygen, the circulatory responses to hypercapnia were determined by increasing the inspired concentration of carbon dioxide progressively in three or four steps from zero to a level sufficient to produce a PaCO₂ of 50 to 60 torr. Measurements were obtained after end-tidal carbon dioxide had been held constant for ten minutes at each level. Two subjects needed ventilatory support to maintain normal PaCO₂'s at 9 per cent fluoroxyne; otherwise, all measurements were obtained while the subjects breathed spontaneously. At 9 per cent fluoroxyne, five subjects were studied two
| Table 1. Mean Slopes (±1 SD) of Carbon Dioxide Response Curves during Fluoxetine Anesthesia |
|---------------------------------------------|---------------------------------|-----------------------------|-----------------------------|----------------------------|-------------------------------|-----------------------------|
|                                      | Cardiac Output                  | Mean Arterial Pressure      | Heart Rate                  | Stroke Volume               | [2] Wave of HCO₃⁻ (Per Cent of Control) | Total Peripheral Resistance |
|                                      | (/min)                          | (torr)                      | (beats/min)                 | (ml)                        |                                | (dynes/sec/cm²)             |
| Conscious                             | 0.191 ± 0.028                   | 0.900 ± 0.156               | 1.580 ± 0.250               | 0.408 ± 0.507               | 0.032 ± 0.006                  | -0.144 ± 0.077               | -16.5 ± 3.53                |
| Fluoxetine, 5 per cent               | 0.112 ± 0.013†                  | 0.530 ± 0.096†              | 0.878 ± 0.119†              | 0.874 ± 0.152               | 0.015 ± 0.010†                 | -0.006 ± 0.005               | -3.13 ± 1.25†               |
| Fluoxetine, 9 per cent               | 0.119 ± 0.009†                  | 0.621 ± 0.096†              | 0.643 ± 0.109†              | 0.800 ± 0.129               | 0.010 ± 0.002†                 | 0.062 ± 0.083†               | -3.45 ± 0.60†               |

* Six subjects only.
† Significantly different from conscious value (P < 0.05).
‡ Significantly different from conscious value (P < 0.10).

Results
At 9 per cent fluoxetine, there was no significant difference in the responses of cardiac output to changes in arterial pressure. The slope of the response curve was 0.012 (mmHg/min), which is comparable to that in the conscious state. There was also no difference between the responses of cardiac output to changes in arterial pressure during (+0.13 ± 0.010 (mmHg/min) and those in subjects studied early in the anesthetic period (0.11 ± 0.005 (mmHg/min)). There was also no difference between the responses of cardiac output to changes in arterial pressure during (+0.13 ± 0.010 (mmHg/min) and those in subjects studied late in the anesthetic period (0.11 ± 0.005 (mmHg/min)).
1.58 bpm/torr to 0.39 and 0.44 bpm/torr during anesthesia. It is noteworthy that no arrhythmias were observed during hypercapnia at either fluroxene concentration.

Although fluroxene significantly reduced the slopes of the response curves for cardiac output and heart rate, there was no significant change in slope of the stroke volume response curves (Fig. 4), despite what appeared to be a considerable increase during anesthesia. The slopes of the stroke volume response curves were 0.47 ml/torr awake and 0.87 and 0.80 ml/torr at 5 and 9 per cent fluroxene. Scatter in the data precluded any significance in these changes.

As evidenced by IIJ-wave amplitude increases (Fig. 5), progressive hypercapnia produced marked increases in myocardial contractility in conscious subjects. During anesthesia the slope of the ballistocardiogram response curve was significantly reduced from the value for conscious subjects, but there was no significant difference between slopes at the two fluroxene concentrations.

In conscious subjects progressive hypercapnia decreased venous pressure, producing a response curve slope of $-0.14$ torr/torr (Fig. 6). At 5 per cent fluroxene the slope was nearly horizontal, but this change was not significant. At 9 per cent fluroxene the slope was positive,
with a value of 0.09 torr/torr (significantly different from control) and the entire curve was elevated approximately 4 torr above the conscious and 5 per cent fluoroxene curves.

In conscious subjects, total peripheral resistance (fig. 7) fell with increased PaCO₂. During anesthesia the slopes of the response curves were roughly a third of the awake values.

**Discussion**

We have shown in nine unmedicated volunteers that fluoroxene alters the circulatory response to hypercapnia. By diminishing the heart rate response to hypercapnia to 25 per cent of the awake value, 5 or 9 per cent fluoroxene reduced the slope of the cardiac output—carbon dioxide response curve to 60 per cent of the conscious value. Associated with the weaker heart rate response was attenuation of the myocardial contractile and total peripheral resistance responses to hypercapnia. Attenuation of the circulatory response to hypercapnia during anesthesia may result from blockade of the stimulation of central sympathetic activity usually produced by carbon dioxide. That is, although fluoroxene itself stimulates sympathetic activity,

9, 12 it appears to hinder another sympathetic stimulant (carbon dioxide) in its action.

There were no significant differences between the responses of most variables to carbon dioxide at the two fluoroxene concentrations. An exception was the response curve of central venous pressure at 9 per cent fluoroxene, which was elevated 4 torr above the curve at 5 per cent fluoroxene. The increased central venous pressure at the deeper level of anesthesia probably signifies greater myocardial depression by fluoroxene, although this was not apparent in the ballistocardiogram. The lack of difference between circulatory responses to carbon dioxide at the two depths of anesthesia is consistent with data published previously. 12

In that report we found no significant differences between cardiac outputs, mean arterial pressures, total peripheral resistances, or myocardial contractilities at 5 and 9 per cent fluoroxene at normal Pao₂'s.

At 9 per cent fluoroxene the responses of cardiac output to carbon dioxide did not change
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at constant alveolar concentrations during normocapnia. If sympathetic activity increased with time one might also expect an increasing response to sympathetic stimulation with time. The failure to observe this time-related response may have been due to the small number of subjects in each subgroup. Attenuation of the circulatory response to hypercapnia observed with fluoxetine appears to be less than that observed with other anesthetics. Cardiac output—carbon dioxide response curves for fluoxetine, cyclopropane, and halothane are shown in figure 8. The cyclopropane and halothane data also were obtained during studies of unpremedicated volunteers. The fluoxetine and halothane data came from subjects breathing spontaneously and the cyclopropane data from subjects whose respiration was controlled. The responses of cardiac output to carbon dioxide at 5 and 9 per cent fluoxetine were similar to that found with 15–20 per cent cyclopropane. Both fluoxetine and cyclopropane depressed the slopes of the cardiac output curves from the conscious values, but neither agent depressed the response to the extent observed with halothane. The mechanisms which account for this variation in the responses to hypercapnia are not known, but we may speculate that these agents differ in the extent to which they depress the central sympathetic sensitivity to carbon dioxide.

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Drugs

DIAZEPAM Dizepam was used to treat 17 patients who had tetanus, ten of whom survived. Nine survivors showed psychic changes after diazepam had been discontinued. There was slowness of thinking, restlessness, disorientation, confusion, tremor and rigidity. Such symptoms had not been seen in patients recovering from tetanus prior to the use of diazepam. There was no correlation with the severity of the disease nor with the doses given. All symptoms subsided after a few days of treatment with diazepam and sedation. A marked reduction in mortality from tetanus was found when diazepam was used. The dosage of diazepam should be decreased slowly; it should not be suddenly withdrawn. (Haider, W., and Tscha-
kaloff, Ch.: Temporary Psychic After-effects of Long-term Treatment of Tetanus with Dizepam, Der Anaesthetist 19: 165 (May) 1970.)

AMPHETAMINE POISONING The ingestion of two grams of amphetamine sulfate by a 21-year-old man resulted in delirium with temperatures above 108 F. Acute self-limited renal failure developed. A coagulopathy with intramuscular hemorhages produced entrapment neuropathies. A striking resemblance to heatstroke suggests a similar pathophysiology. (Ginsberg, M. D., Hertzman, M., and Schmidt-

ASTHMATIC PATIENTS If an operation on a patient known to have asthmatic attacks is to begin later than 10 AM, an intravenous infusion of dextrose and water should be started early in the morning to inhibit inspissation of bronchial secretions. The preoperative dose of atropine and scopolamine should be kept to the lowest effective dose. Patients who have been taking corticosteroids for asthma within a year of operation should receive intramuscular doses of cortisone acetate preoperatively. General anesthesia for asthmatic patients usually is preferred. Bronchospasm during operation can be controlled by addition of aminophylline to intravenous infusion, but too-rapid administration may cause nausea and retching in the recovery room. Morphine, codeine, suxamethonium and tubocurarine liberate histamine, which may cause bronchospasm. (Valentine, M. D.: The Asthmatic Patient as a Surgical Risk, Surg. Clin. N. Amer. 50: 631 (June) 1970.)