

# The Cardiovascular Effects of Compound 469 (Forane\*) during Spontaneous Ventilation and CO<sub>2</sub> Challenge in Man

Thomas H. Cromwell, M.D.,† Wendell C. Stevens, M.D.,‡ Edmond J. Eger, II, M.D.,§  
Thomas F. Shakespeare, M.D.,¶ Michael J. Halsey, Ph.D.,\*\*  
Steven H. Bahlman, M.D.,† Henry E. Fourcade, M.D.††

The new inhalation anesthetic, Forane, has been shown to produce only minimal depression of cardiac output during controlled ventilation, but a significant decrease in arterial pressure and profound respiratory depression. This study was undertaken to determine whether spontaneous ventilation, with the consequent elevations in CO<sub>2</sub>, would alter the cardiovascular responses to Forane, and whether Forane alters the cardiovascular response to imposed increases in CO<sub>2</sub> (CO<sub>2</sub> challenge). During controlled ventilation Forane maintains cardiac output, primarily through an increase in heart rate at the expense of stroke volume. Spontaneous ventilation alters the cardiovascular response to Forane, in that heart rate and cardiac output are further increased. These changes can be explained by the increase in PaCO<sub>2</sub> secondary to spontaneous ventilation. Cardiovascular CO<sub>2</sub> response slopes reveal that Forane decreases the response of the cardiovascular system to increases in P<sub>CO<sub>2</sub></sub>. As in previous studies with Forane, the authors did not find any stimulation of the cardiovascular system with time. (Key words: Forane; Carbon Dioxide; Circulation.)

AS REPORTED PREVIOUSLY,<sup>1</sup> a new inhalation anesthetic, Forane, has several advantages

\* Trademark, Ohio Medical Products, Division of Air Reduction Company, Inc.

† Research Trainee, University of California.

‡ Assistant Professor of Anesthesia, University of California.

§ Professor of Anesthesia, University of California.

¶ Acting Assistant Professor of Anesthesia, Stanford University Hospital, Stanford, California.

\*\* Postgraduate Research Chemist, University of California.

†† Assistant Professor in Residence, University of California.

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over the potent anesthetic most commonly used, halothane. Studies by Stevens *et al.* of the cardiovascular effects in man at constant normal PaCO<sub>2</sub> suggested minimal depression of cardiac output but a significant decrease in arterial pressure.<sup>1</sup> Initial studies of Forane in man suggested that this agent was a profound respiratory depressant.<sup>2</sup> We asked if spontaneous ventilation and the consequent elevation in CO<sub>2</sub> would alter these cardiovascular effects. We also asked whether Forane would alter the cardiovascular response to imposed increases in CO<sub>2</sub> (CO<sub>2</sub> challenge).

## Methods

Nine unpremedicated, healthy male volunteers 23 ± 6 (SE) years old were apprised of the nature and risks of the study and an informed consent was obtained from each. The procedure and consent forms were approved by the Committees on Human Experimentation at the University of California, San Francisco, and Stanford University. The subjects weighed 71.2 ± 2.8 kg and were 183.4 ± 3.9 cm tall. The awake subjects were prepared as previously reported.<sup>1</sup> We measured arterial, right atrial, and peripheral venous pressures through indwelling catheters. Cardiac output was determined by dye dilution, and arterial and right atrial P<sub>O<sub>2</sub></sub>, P<sub>CO<sub>2</sub></sub>, and pH were measured by electrodes. We also measured forearm and finger blood flows, end-tidal CO<sub>2</sub>, oral (awake) or esophageal (anesthetized) temperature and skin temperature, cardiac cycle intervals, I-J waves of the ballistocardiogram, and the electrocardiogram. Blood volumes and microhematocrits were measured with the subjects awake and at the beginning and end of anesthesia. During anesthesia, end-tidal Forane was measured by

TABLE 1. Changes in Blood Volume, Blood Components, and Glucose with Forane Anesthesia (Mean  $\pm$  SE)

|                                 | Number of Subjects | Awake Control   | Early Anesthesia (First Hour), Per Cent of Awake Value | Late Anesthesia (Fifth Hour), Per Cent of Awake Value |
|---------------------------------|--------------------|-----------------|--|---|
| Time from induction (min)       | 9                  | -38.3 $\pm$ 9.8 | 88.1 $\pm$ 4.2   | 262.4 $\pm$ 8.2                                       |
| Hematocrit (per cent)           | 9                  | 45.9 $\pm$ 0.57 | 97.4 $\pm$ 1.03*                                       | 94.8 $\pm$ 1.37*†                                     |
| Blood volume (liters)           | 9                  | 5.93 $\pm$ 0.36 | 95.7 $\pm$ 4.7   | 83.4 $\pm$ 4.4*                                       |
| Plasma volume (liters)          | 9                  | 3.21 $\pm$ 0.19 | 97.4 $\pm$ 5.0   | 94.1 $\pm$ 5.3  |
| Erythrocyte volume (liters)     | 9                  | 2.73 $\pm$ 0.18 | 93.4 $\pm$ 4.5   | 84.0 $\pm$ 3.9*                                       |
| Total serum protein (mg/100 ml) | 9                  | 7.52 $\pm$ 0.16 | 89.4 $\pm$ 1.7*  | 85.3 $\pm$ 2.5*†                                      |
| Blood glucose (mg/100 ml)       | 9                  | 82.4 $\pm$ 3.6  | 152 $\pm$ 16.1   | 164.5 $\pm$ 17.5                                      |

\* Significantly different from awake control value ( $p < 0.05$ ).† Significantly different from "early" value ( $P < 0.05$ ).

infrared analysis. At the beginning and end of anesthesia, end-tidal and arterial blood levels of Forane were measured by gas chromatography. Blood glucose levels were measured before and one hour after induction of anesthesia and near the end of the study.

Blood withdrawn for analysis (total approximately 300 ml) was replaced with 1,890  $\pm$  134 ml of Ringers' lactate solution. In addition, after an hour of anesthesia (after the first blood glucose sample under anesthesia had been obtained), we infused 209  $\pm$  23 ml of dextrose, 5 per cent in water, including 22 mEq/l of sodium bicarbonate, during the remainder of each study.

The awake subject breathed 100 per cent oxygen through a mouthpiece from an Ohio circle absorption system. A noseclip prevented breathing through the nose. Control measurements listed previously were then obtained and repeated until cardiac output determinations varied less than 5 per cent. The two lowest cardiac outputs and their associated values were selected as the control values. CO<sub>2</sub> was then added to the respired gases to raise end-tidal CO<sub>2</sub> in steps of approximately 5 torr for a total of three steps above control. Each elevated level was held for six minutes, after which cardiovascular measurements were repeated (CO<sub>2</sub> response).

Induction was achieved with Forane and subjects were intubated 13.8  $\pm$  0.98 minutes after induction without muscle relaxants or topical anesthesia. Subjects breathed 1.2 per cent alveolar Forane spontaneously, allowing ten minutes for equilibration. Measurements made when awake were repeated, and the anesthetic dose was increased to 1.5 per cent and

subsequently to 1.8 per cent. Following this, CO<sub>2</sub> responses were measured in one of two sequences.

In each of five subjects the anesthetic dose was returned to 1.2 per cent. A reduction in PaCO<sub>2</sub> was achieved by controlled ventilation for a 20-minute period, after which spontaneous ventilation was resumed. A ten-minute period was allowed for stabilization of PaCO<sub>2</sub>, after which a CO<sub>2</sub> response test similar to the awake test was performed. Anesthetic dose was then increased to 1.8 per cent and another CO<sub>2</sub> response test undertaken. The Forane concentration was then decreased to 1.2 per cent and ventilation controlled for 20 minutes to reduce CO<sub>2</sub> to awake values. To assess the effect of duration of anesthesia on cardiovascular function, measurements were again carried out at 1.2, 1.5, and 1.8 per cent alveolar Forane with spontaneous ventilation as originally.

In the other four subjects the sequence of CO<sub>2</sub> response tests was reversed, the initial CO<sub>2</sub> response test being done at 1.8 per cent alveolar Forane, followed by a CO<sub>2</sub> response test at 1.2 per cent Forane. Ventilation was then controlled for 20 minutes so as to reduce PaCO<sub>2</sub> to awake values. Spontaneous ventilation was resumed and measurements were made at 1.2, 1.5, and 1.8 per cent alveolar Forane. CO<sub>2</sub> response tests were analyzed by the method of least squares. Statistical analysis was carried out by paired *t* tests.

## Results

Changes in blood volume, proteins, and glucose are described in table 1. Significant de-

TABLE 2 Pooled Results (Mean  $\pm$  SE)

|   | No. Subjects | Awake Control     | Early (First Hour)           |                              |                              | Late (Fifth Hour)            |                              |                              |
|---|--------------|-------------------|------------------------------|------------------------------|------------------------------|------------------------------|------------------------------|------------------------------|
|   |              |                   | Alveolar Forane 1.2 Per Cent | Alveolar Forane 1.5 Per Cent | Alveolar Forane 1.8 Per Cent | Alveolar Forane 1.2 Per Cent | Alveolar Forane 1.5 Per Cent | Alveolar Forane 1.8 Per Cent |
| Time from induction (min)*                                | 9            |                   |                              |                              |                              |                              |                              |                              |
| Cardiac output (l/min)†                                   | 9            | 5.9 $\pm$ 0.27    | 34.4 $\pm$ 1.6               | 55.4 $\pm$ 1.5               | 69.9 $\pm$ 4.1               | 283 $\pm$ 9.9                | 302 $\pm$ 12                 | 320 $\pm$ 11                 |
| Mean right atrial pressure (torr)†                        | 9            | 2.7 $\pm$ 0.73    | -0.42 $\pm$ 0.46             | 0.51 $\pm$ 0.75              | 0.83 $\pm$ 0.45              | -0.36 $\pm$ 0.58             | -0.03 $\pm$ 0.62‡            | 0.26 $\pm$ 0.63              |
| Mean arterial pressure (torr)†                            | 9            | 89.3 $\pm$ 2.6    | 78.9 $\pm$ 3.6‡              | 78.9 $\pm$ 3.6‡              | 67.6 $\pm$ 2.5‡              | 69.9 $\pm$ 2.2‡              | 72.1 $\pm$ 4.0‡              | 67.9 $\pm$ 2.9‡              |
| Heart rate (beats/min)†                                   | 9            | 62.4 $\pm$ 3.5    | 126.7 $\pm$ 5.8‡             | 122.6 $\pm$ 6.5‡             | 123.7 $\pm$ 5.8‡             | 146 $\pm$ 5.4‡§              | 148 $\pm$ 10.2‡§             | 150.0 $\pm$ 8.9‡§            |
| Left ventricular stroke work (joules)†                    | 9            | 0.11 $\pm$ 0.0052 | 78.0 $\pm$ 4.0‡              | 70.6 $\pm$ 3.0‡              | 66.2 $\pm$ 8.2‡              | 59.6 $\pm$ 4.6‡              | 62.4 $\pm$ 6.1‡              | 64.3 $\pm$ 4.9‡              |
| Left ventricular stroke volume (ml)†                      | 9            | 97.2 $\pm$ 5.0    | 101.9 $\pm$ 4.2              | 103.5 $\pm$ 3.5              | 103.5 $\pm$ 7.5              | 81.7 $\pm$ 4.0‡              | 83.5 $\pm$ 6.9               | 91.8 $\pm$ 6.0               |
| I-J wave amplitude†                                       | 5            | 14.9 $\pm$ 1.5    | 96.4 $\pm$ 1.3               | 92.7 $\pm$ 8.4               | 93.4 $\pm$ 8.9               | 74.8 $\pm$ 7.6‡              | 83.4 $\pm$ 5.1‡              | 91.5 $\pm$ 7.8               |
| Cardiac output/minute oxygen consumption†                 | 9            | 25.7 $\pm$ 1.8    | 159 $\pm$ 11‡                | 173 $\pm$ 13‡                | 193 $\pm$ 13‡                | 158 $\pm$ 17                 | 132 $\pm$ 11.8‡§             | 173 $\pm$ 13‡                |
| Prejection period (msec)†                                 | 5            | 118.6             | 82.4 $\pm$ 6.2‡              | 79.8 $\pm$ 4.1               | 74.2 $\pm$ 5.2‡              | 90.2 $\pm$ 6.8               | 78.9 $\pm$ 11.4‡             | 77.1 $\pm$ 13.3‡             |
| Total peripheral resistance (dynes/sec/cm <sup>2</sup> )† | 9            | 1,189 $\pm$ 48    | 59 $\pm$ 4.6‡                | 51.6 $\pm$ 3.9‡              | 47.8 $\pm$ 3.5‡              | 60.4 $\pm$ 3.3‡              | 60.5 $\pm$ 3.4‡§             | 49.6 $\pm$ 1.9‡              |
| Minute oxygen consumption (ml/min)†                       | 9            | 242.6 $\pm$ 16.0  | 91.6 $\pm$ 8.4               | 75.9 $\pm$ 8.2‡              | 70.11 $\pm$ 7.9‡             | 77.3 $\pm$ 1.8‡              | 83.0 $\pm$ 10.8              | 82.4 $\pm$ 9.8               |
| Forearm blood flow (ml/min/100 ml)†                       | 9            | 2.43 $\pm$ 0.24   | 228.8 $\pm$ 21.4‡            | 303.6 $\pm$ 36.9‡            | 341.1 $\pm$ 38.7‡            | 400 $\pm$ 75.5‡              | 416.8 $\pm$ 74.3‡            | 425.6 $\pm$ 45.2‡            |
| Forearm vascular resistance (dynes/sec/cm <sup>2</sup> )† | 9            | 42.4 $\pm$ 3.04   | 33.6 $\pm$ 4.9‡              | 23.3 $\pm$ 5.0‡              | 19.71 $\pm$ 3.6‡             | 19.2 $\pm$ 2.5‡§             | 17.8 $\pm$ 2.3‡              | 15.9 $\pm$ 2.1‡              |
| Forearm venous compliance (ml/torr)†                      | 8            | 0.18 $\pm$ 0.08   | 92.3 $\pm$ 26                | 102.7 $\pm$ 18.9             | 71.7 $\pm$ 21.3              | 100.6 $\pm$ 27.8             | 105.0 $\pm$ 21.2             | 112.4 $\pm$ 33.7             |
| Finger blood flow (ml/min/100 ml)†                        | 9            | 10.92 $\pm$ 1.97  | 470.6 $\pm$ 98.8‡            | 470.6 $\pm$ 98.8‡            | 334.4 $\pm$ 52.9‡            | 351.7 $\pm$ 120.7‡           | 423.4 $\pm$ 157.7‡           | 397.1 $\pm$ 97.5‡            |
| Skin temperature (C)*                                     | 9            | 32.1 $\pm$ 0.5    | 2.02 $\pm$ 0.44              | 2.59 $\pm$ 0.48              | 2.53 $\pm$ 0.45              | 2.52 $\pm$ 0.50              | 2.84 $\pm$ 0.38              | 2.61 $\pm$ 0.48              |
| Esophageal temperature (C)*                               | 9            | 36.8 $\pm$ 0.1    | -0.3 $\pm$ 0.08              | -0.35 $\pm$ 0.10             | -0.34 $\pm$ 0.09             | 0.04 $\pm$ 0.13              | 0.07 $\pm$ 0.13              | 0.10 $\pm$ 0.10              |
| Paco <sub>2</sub> (torr)*                                 | 9            | 38.4 $\pm$ 1.2    | 8.62 $\pm$ 1.5               | 14.7 $\pm$ 2.0               | 22.6 $\pm$ 2.2               | 8.34 $\pm$ 1.4               | 13.8 $\pm$ 2.1               | 20.1 $\pm$ 3.0               |
| Pao <sub>2</sub> (torr)*                                  | 9            | 533 $\pm$ 7.9     | -20.6 $\pm$ 9.1              | 31.9 $\pm$ 9.5               | -34.5 $\pm$ 9.1              | -18.4 $\pm$ 6.6              | -21.6 $\pm$ 6.5              | -32.6 $\pm$ 10.2             |
| pH*   | 9            | 7.39 $\pm$ 0.0091 | -0.07 $\pm$ 0.01             | -0.08 $\pm$ 0.03             | -0.14 $\pm$ 0.02             | -0.06 $\pm$ 0.01             | -0.05 $\pm$ 0.03             | -0.12 $\pm$ 0.02             |
| $\Delta$ base excess*                                     | 9            | -0.62 $\pm$ 0.42  | -0.83 $\pm$ 0.58             | -1.15 $\pm$ 0.46             | -1.33 $\pm$ 0.46             | -0.27 $\pm$ 0.48             | 0.60 $\pm$ 0.76              | 0.096 $\pm$ 0.73             |

\* Absolute change.

† Per cent of control values.

‡ Significantly different from awake control ( $P < 0.05$ ).§ Significantly different from first hour value at the same concentration ( $P < 0.05$ ).

creases in blood volume, hematocrit, erythrocyte volume, and total serum protein occurred. Induction of Forane anesthesia, with spontaneous ventilation, caused an increase in cardiac output to above control values, while mean arterial pressure decreased and mean right atrial pressure remained unchanged (table 2; fig. 1).

Cardiac output was elevated to 130 per cent of control at the light levels of anesthesia and was not significantly affected by further increases in anesthetic concentration or

duration of anesthesia. Mean arterial pressure decreased significantly to 80 per cent of control and decreased further as anesthetic concentration was increased. This effect also was not influenced by duration of anesthesia. Mean right atrial pressure was unaffected by anesthetic depth both early and late in anesthesia. Total peripheral resistance fell to below control at every anesthetic concentration. Heart rate increased upon induction and, in contrast to other variables, was further increased with

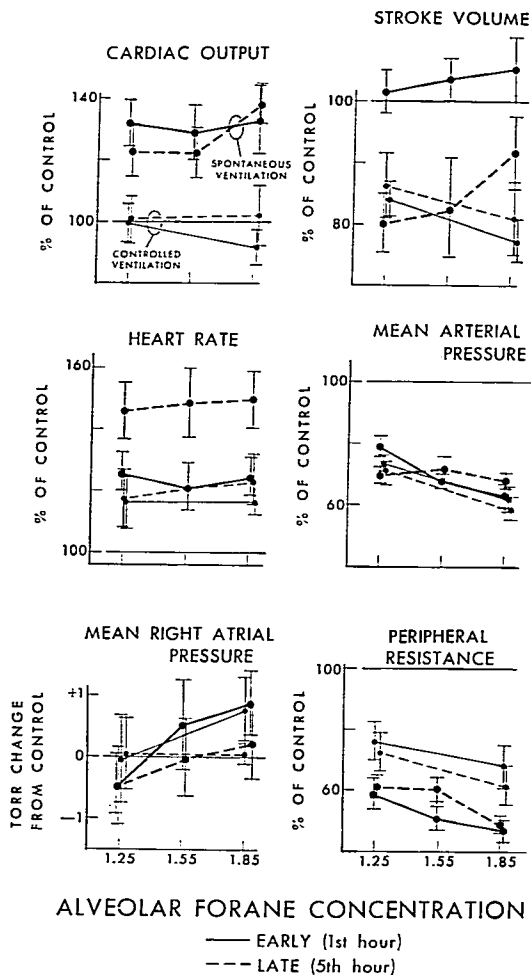


FIG. 1 (left) and FIG. 2 (right). Graphs of information from table 2 with data from controlled ventilation study<sup>1</sup> for comparison. The vertical axis in each case is per cent of awake control except that mean right atrial pressure is torr change from control and base excess is mEq change from control. The horizontal axis is alveolar Forane concentration. Heavy lines represent values obtained during spontaneous ventilation; light lines represent values obtained during controlled ventilation<sup>1</sup> ( $P_{aCO_2}$  maintained at awake control value). Solid lines represent early anesthesia (first hour); dashed lines, late anesthesia (fifth hour). The horizontal line at 100 per cent represents awake control value. The vertical bars represent  $\pm$ SE. Note that for controlled ventilation only two anesthetic concentrations are available for comparison.

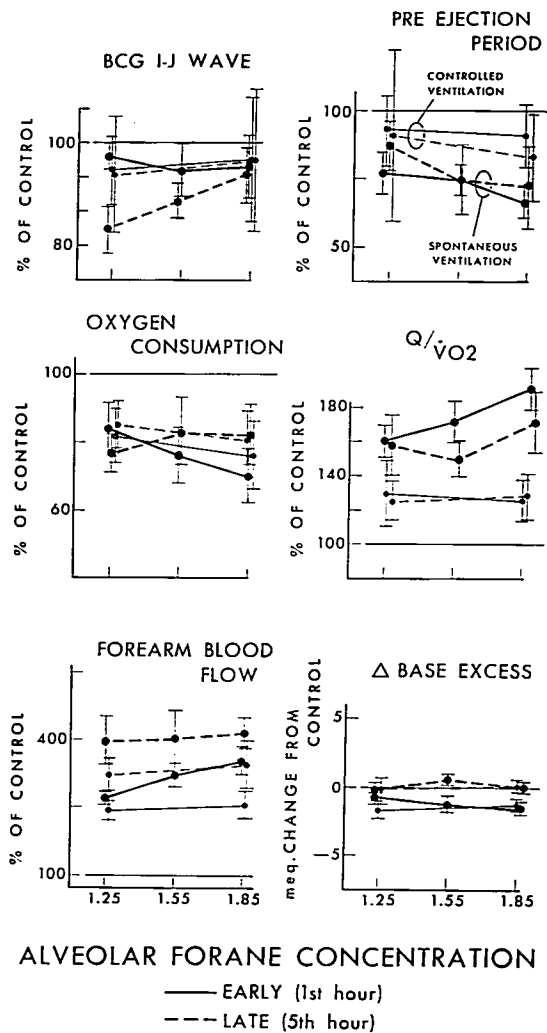


FIG. 2.

TABLE 3. Cardiovascular CO<sub>2</sub> Response Slopes (Mean ± SE)

|                              | Number of Subjects | Awake           | 1.2 Per Cent Forane | 1.8 Per Cent Forane |
|------------------------------|--------------------|-----------------|---------------------|---------------------|
| Time from induction          | 9                  |                 | 174.4 ± 8.6         | 160.2 ± 8.5         |
| Cardiac output               | 9                  | 0.1822 ± 0.026  | 0.1427 ± 0.018      | 0.0909 ± 0.024*†    |
| Heart rate                   | 9                  | 1.438 ± 0.17    | 0.5935 ± 0.25*      | 0.300 ± 0.16*       |
| Mean right atrial pressure   | 9                  | -0.088 ± 0.04   | 0.0508 ± 0.03*      | 0.009 ± 0.02        |
| Mean arterial pressure       | 9                  | 0.727 ± 0.19    | 0.474 ± 0.26        | -0.202 ± 0.9*       |
| Left ventricular stroke work | 9                  | 0.0016 ± 0.0004 | 0.0014 ± 0.0002     | 0.0114 ± 0.0111     |
| Stroke volume                | 9                  | 0.4914 ± 0.36   | 1.1345 ± 0.2813     | 0.6985 ± 0.3049     |
| I-J wave amplitude           | 9                  | 0.356 ± 0.04    | 0.247 ± 0.04        | 0.257 ± 0.03        |
| Total peripheral resistance  | 9                  | -14.8 ± 3.9     | -7.6 ± 2.7          | -7.2 ± 2.4          |

\* Significantly different from awake control,  $P < 0.05$ .

† Significantly different from 1.2 per cent value,  $P < 0.05$ .

duration of anesthesia. Stroke volume and I-J wave amplitude (table 2; fig. 2), a measure of myocardial contractility,<sup>2-6</sup> remained at control values at each anesthetic concentration early in anesthesia. Both decreased significantly late in anesthesia at the light and moderate levels and then returned toward normal at the deep levels of anesthesia. With the concomitant increase in heart rate late in anesthesia, the net result was no change in cardiac output. The pre-ejection period was reduced to 80 per cent of control with induction but was not affected by time or depth of anesthesia (table 2; fig. 2). There were marked increases in blood flow to skin and muscle with induction of anesthesia to account for the decrease in total peripheral resistance. Muscle blood flow increased to 200 per cent of control and skin blood flow to 500 per cent of control. Neither changed significantly with increasing anesthetic concentration or duration of anesthesia. Oxygen consumption values were less than control values at the moderate and deep levels early in anesthesia, and at the light level late in anesthesia. At these times cardiac output was increased above control, so that the ratio of cardiac output to oxygen consumption was also increased. We take this to mean that the oxygen supply was adequate to meet the metabolic demands of the body as a whole. This was corroborated by the finding that base excess did not change significantly from control throughout anesthesia (table 2; fig. 2). Arterial oxygen partial pressure did

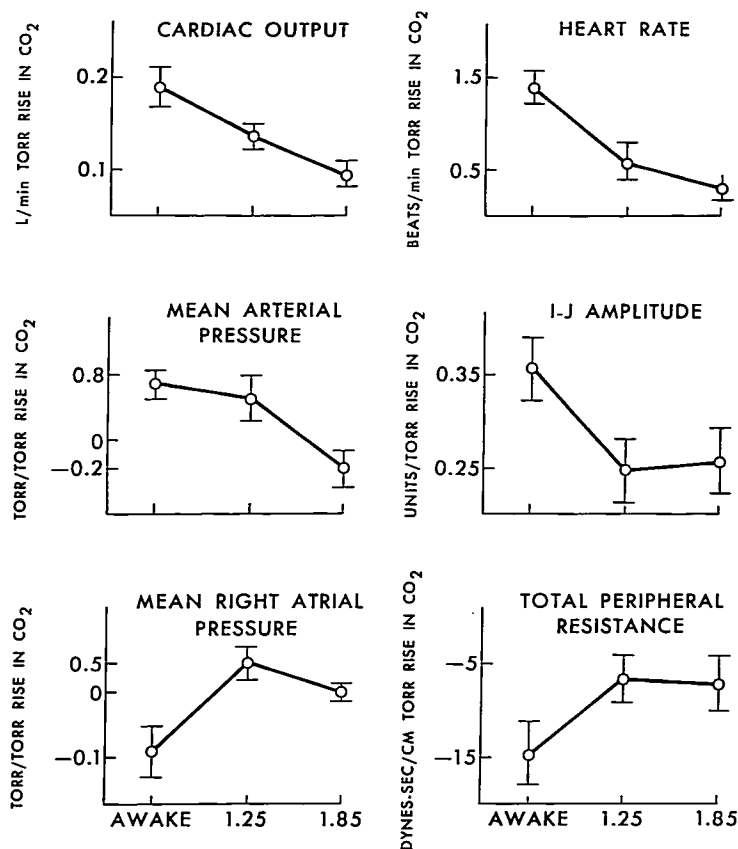
not change significantly with anesthesia. Arterial CO<sub>2</sub> partial pressures increased upon induction and further increased with deepening anesthesia, both early and late (table 2).

When these data were compared with the results of earlier studies of Forane with ventilation controlled to maintain PaCO<sub>2</sub> at awake levels,<sup>1</sup> the only significant differences produced by controlled ventilation were that cardiac output remained at control early and late in anesthesia, heart rate showed no further increase late in anesthesia, and stroke volume was not maintained early in anesthesia (figs. 1 and 2). The increased cardiac output and heart rate occurring with spontaneous ventilation can be explained by the direct and reflex effects of increased PaCO<sub>2</sub> secondary to spontaneous ventilation (table 2).

With spontaneous ventilation, as anesthetic concentration increased the responses of cardiac output, heart rate, mean arterial pressure, I-J wave amplitude, mean right atrial pressure, and total peripheral resistance to imposed increases in PaCO<sub>2</sub> (CO<sub>2</sub> challenge) were attenuated (table 3, fig. 3).

### Discussion

During controlled ventilation Forane maintains cardiac output primarily through an increase in heart rate at the expense of stroke volume.<sup>1</sup> Spontaneous ventilation alters these cardiovascular effects of Forane, in that cardiac output and heart rate are increased and stroke volume is maintained early in anesthe-



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FIG. 3. Slopes of cardiovascular responses to CO<sub>2</sub>. Graph of information from table 3. The vertical axis represents the absolute value of the slope of the cardiovascular response to increase in CO<sub>2</sub>. The horizontal axis represents the awake control value, and two alveolar anesthetic concentrations. Anesthesia decreased the responses of cardiac output, heart rate, mean arterial pressure, and I-J wave amplitude to CO<sub>2</sub>. Slopes of mean right atrial pressure and peripheral resistance responses to CO<sub>2</sub> were negative in the awake subject, meaning that they decreased in response to increased PaCO<sub>2</sub>. During anesthesia, the slopes increased toward zero, meaning that the decrease in response to PaCO<sub>2</sub> became less during anesthesia. Thus, with all variables measured, anesthesia reduced the response to increase in PaCO<sub>2</sub>.

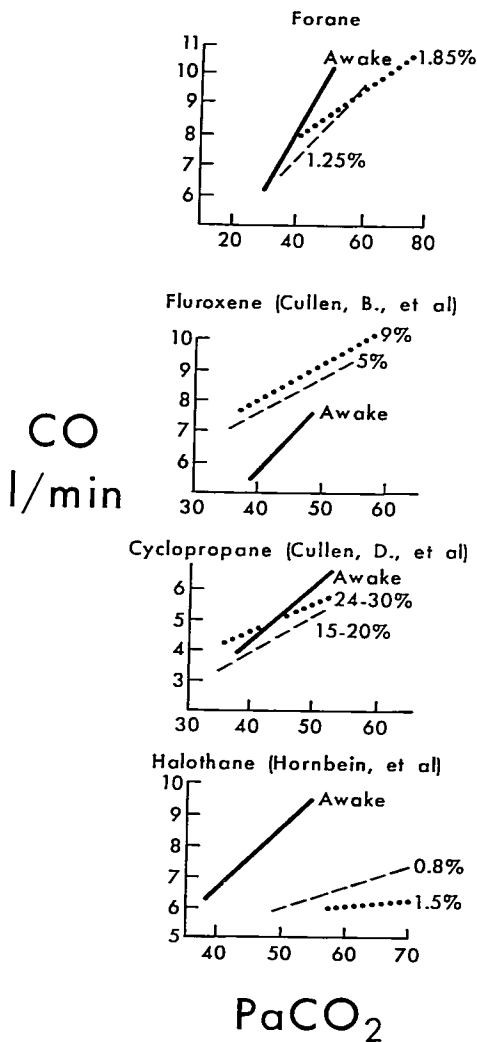


FIG. 4. Responses of cardiac output to increases in  $P_{aCO_2}$  with four anesthetic agents. The vertical axis is cardiac output in l/min; the horizontal axis is  $P_{aCO_2}$ . The solid line represents awake control; the dashed and dotted lines represent two alveolar anesthetic concentrations.



sia. These changes from effects seen with controlled respiration can be explained by the increase in  $P_{aCO_2}$  secondary to spontaneous ventilation and the avoidance of increased intrathoracic pressure<sup>7</sup> with spontaneous ventilation. As in previous studies with Forane,<sup>1</sup> we failed to show any stimulation of the cardiovascular system with time.

Cardiovascular  $CO_2$  response slopes reveal that Forane decreases the response of the cardiovascular system to imposed increases in  $CO_2$ . This apparent sympathetic depression is interesting in view of the apparent beta sympathetic effects seen with Forane (increases in heart rate, myocardial contractility, and muscle blood flow, and elevated blood glucose levels). The depression of the response of cardiac output to  $CO_2$  by Forane is similar to the depressions produced by fluroxene and cyclopropane and less than that produced by halothane (fig. 4). At alveolar concentrations approximating  $1\frac{1}{2}$  MAC of Forane,<sup>9</sup> fluroxene, or cyclopropane, the response of cardiac output to increasing  $CO_2$  is approximately half the awake slope (fluroxene 5 per cent = 58.9 per cent of awake slope<sup>9</sup>; cyclopropane 15–20 per cent = 51.0 per cent of awake slope<sup>9</sup>; Forane 1.85 per cent = 50.0 per cent of awake slope). Halothane appears to have a greater depressant effect: 0.8 per cent, or 1 MAC = 35 per cent of awake slope.<sup>10</sup>

Decreases in blood volume appear to be primarily losses of erythrocyte volume and can be explained by the loss of whole blood through sampling. Decreases in total serum protein can be explained similarly. Increases in blood glucose probably result from glycolysis secondary to increased sympathetic activity.

In view of the dose-related decrease in arterial pressure early in anesthesia, one could assume that blood pressure could be used in clinical assessment of anesthetic depth. However, with spontaneous ventilation this dose-related decrease is attenuated (although not significantly) with duration of anesthesia, which

suggests that blood pressure is an unreliable indicator of depth late in anesthesia. Tidal volume, which demonstrates dose-related depression both early and late in anesthesia,<sup>2</sup> appears to be a more reliable indicator of depth of anesthesia with Forane.

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<sup>9</sup> Clinical studies with Forane in this age group indicate that MAC is 1.2 per cent alveolar concentration.