

# Pulmonary Hemodynamics during General Anesthesia in Man

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Pulmonary hemodynamic effects of halothane, halothane-nitrous oxide, and cyclopropane anesthesia were studied in healthy young men. Cardiac output, pulmonary artery and wedge pressures, and arterial and venous oxygen contents were measured. During halothane and halothane-N<sub>2</sub>O anesthesia there were no significant changes in pulmonary arterial and wedge pressures or in pulmonary vascular resistance. A marked decrease in left ventricular stroke work during halothane anesthesia, with unchanged wedge pressure, suggested myocardial depression. Administration of cyclopropane caused a marked increase in pulmonary arterial and wedge pressures and in pulmonary vascular resistance. The increase in wedge pressure reflected an increase in cardiac work. Increased physiologic shunting occurred with all anesthetic mixtures, but the contribution of maldistribution to the shunt was greater during spontaneous than during controlled respiration. Neither halothane nor cyclopropane prevented changes in pulmonary vascular resistance associated with altered inspired oxygen tension.

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THE PULMONARY VASCULAR RESISTANCE during general anesthesia in man has not previously been reported. Instead, inferences have been drawn from measurements of pulmonary arterial pressure and cardiac output, neglecting the fact that the level of pulmonary venous pressure cannot be assumed to remain constant during anesthesia. Because of this lack of information, the effects of general anesthesia with cyclopropane, halothane and halothane-nitrous oxide on pulmonary hemodynamics were determined in man. Two different inspired oxygen concentrations were used during the cyclopropane and halothane studies, in light of the known alterations in circulation attending changed oxygen tension. We elected to compare spontaneous and controlled respiration, choosing a level of arterial P<sub>CO<sub>2</sub></sub> consistent with spontaneous respiration to avoid including CO<sub>2</sub> effects in this comparison.

## Methods

Twelve subjects, healthy male volunteers between the ages of 21 and 27 years, reported to the laboratory in the early morning after an overnight fast. Under local anesthesia a Courmand needle was placed in a femoral artery and a #7 Lehman catheter advanced through an antecubital vein into the main pulmonary artery with the aid of an image-intensification fluoroscope.

The subjects breathed various gas mixtures from a one-way circuit consisting of a reservoir bag and a lightly-loaded overflow valve, corrugated inspiratory tubing to a Frumin valve and corrugated expiratory tubing to collecting bags or a gas meter. During awake control studies each subject breathed through a standard rubber metabolism mouthpiece. The nostrils were occluded with a clamp. During an-

TABLE 1. Systemic Circulatory and Metabolic Measurements before and during Anesthesia

Anesthetic Respiration	None Spontaneous	Halothane + O <sub>2</sub> Spontaneous	Halothane + O <sub>2</sub> Controlled	None Spontaneous	Cyclopropane Spontaneous + Controlled	Halothane + N <sub>2</sub> O Spontaneous + Controlled
Inspired O <sub>2</sub> concentration (atmospheres) (F <sub>I</sub> O <sub>2</sub> )	.25 1.00	.25 .985	.25 .985	.25 .80	.25 .80	.28
Heart rate (beats/min) S.E.M.	77.9 72.6 3.6 5.2	87.3 80.8 2.7 3.1 ††	85.7 83.8 2.9 2.1	79.0 69.7 7.1 6.2	77.3 79.5 10.2 8.3	85.4 10.8
Mean systemic arterial pressure (mm Hg) S.E.M.	83.6 86.4 2.8 3.3	64.1 67.0* 2.9 3.0 ††	68.0 68.8 5.2 5.2	83.2 84.0 4.7 4.7	90.2 95.8 5.8 5.2	71.8 3.6 ††
Total peripheral resistance (mm Hg/l/min) S.E.M.	11.2 12.6** 0.3 0.4	8.7 10.2 0.5 0.6 †	9.6 9.9 0.5 0.6	12.0 13.8 0.5 1.1	14.5 15.0 1.2 1.2	11.8 1.1
Oxygen consumption (ml/min) S.E.M.	272 254 17 12	224 208 14 10 †	206 231 14 11	256 253 11 17	249 254 16 4	213 30
P <sub>a</sub> O <sub>2</sub> S.E.M.	110 579 6 16	85 536 6 15 †	86 464 5 38 †	126 487 4 13	94 423 8 46 †	124 11
P <sub>a</sub> CO <sub>2</sub> S.E.M.	37.2 35.5 2.2 1.9	47.8 47.3 1.1 1.4 ††	44.6 46.7 1.3 1.0	36.7 38.1 2.0 1.8	46.9 44.7 3.0 2.6	45.1 3.0
Arterial pH S.E.M.	7.45 7.47 0.02 0.02	7.35 7.37 0.01 0.01 ††	7.37 7.35 0.01 0.01	7.44 7.43 0.02 0.01	7.35 7.36 0.01 0.01 †	7.35 0.01

\* Significant difference due to change in F<sub>I</sub>O<sub>2</sub>, P < 0.05.\*\* Significant difference due to change in F<sub>I</sub>O<sub>2</sub>, P < 0.01.

† Significant difference due to anesthetic or type of respiration (compared with comparable column immediately to the left), P &lt; 0.05.

†† Significant difference due to anesthetic or type of respiration, P &lt; 0.01.

TABLE 2. Pulmonary Circulation and Ventilation Measurements before and during Anesthesia

Anesthetic Respiration	None Spontaneous	Halothane + O <sub>2</sub> Spontaneous	Halothane + O <sub>2</sub> Controlled	None Spontaneous	Cyclopropane Spontaneous + Controlled	Halothane + N <sub>2</sub> O Spontaneous + Controlled
Inspired O <sub>2</sub> concentration (atmospheres) (F <sub>I</sub> O <sub>2</sub> )	.25 1.00	.25 .985	.25 .985	.25 .80	.25 .80	.28
Mean pulmonary artery pressure (mm Hg)	12.2 11.2	12.1 10.5	12.5 10.7	10.1 9.6	18.2 15.8	12.5
S.E.M.	1.0 0.9	1.6 1.5	1.8 1.7	0.9 0.9	0.8 1.9	1.6
					†† †	
Mean pulmonary artery wedge pressure (mm Hg)	7.1 7.7	7.2 6.7	6.8 6.4	5.4 6.3	10.2 10.1	7.4
S.E.M.	0.9 0.9	1.3 1.3	1.3 1.5	0.6 0.8	0.5 1.8	1.4
					†† †	
Cardiac output (l/min) (Q <sub>T</sub> )	7.54 6.90*	7.58 6.77*	7.23 7.06	6.97 6.41	6.66 6.73	6.55
S.E.M.	0.28 0.41	0.58 0.57	0.68 0.54	0.16 0.43	0.59 0.41	0.57
Pulmonary vascular resistance (mm Hg/l/min)	0.69 0.52*	0.68 0.57	0.75 0.63	0.68 0.53	1.25 0.86*	0.80
S.E.M.	0.11 0.08	0.13 0.07	0.10 0.19	0.09 0.04	0.12 0.09	0.11
					† †	
Q <sub>s</sub> /Q <sub>r</sub>	5.9 3.1	18.9 6.1**	15.1 11.1	2.5 2.0	11.3 7.9	10.0
S.E.M.	1.4 0.9	2.9 1.2	3.6 2.5	0.8 0.4	3.3 1.9	6.7
		† †	†		†	
Alveolar ventilation (l/min) (V <sub>A</sub> )	5.05 5.24	3.45 3.30	4.53 4.59	5.87 5.34	4.44 4.99	4.59
S.E.M.	0.49 0.32	0.34 0.20	0.74 0.98	0.58 0.35	0.52 0.59	0.52
		† ††				

\* Significant difference due to change in F<sub>I</sub>O<sub>2</sub>, P < 0.05.

\*\* Significant difference due to change in F<sub>I</sub>O<sub>2</sub>, P < 0.01.

† Significant difference due to anesthetic or type of respiration (compared with comparable column immediately to the left), P < 0.05.

†† Significant difference due to anesthetic or type of respiration, P < 0.01.

esthesia the subject breathed through an endotracheal tube. End-tidal carbon dioxide was measured at the mouthpiece or tracheal tube with an LB-1 infrared analyzer, using a flow of 500 ml per minute. This sampled gas was returned to the chamber of the Frumin valve so that measurements of the expired air were not in error.

During anesthesia esophageal temperature was measured with a thermister probe and maintained at  $37\text{ C} \pm 0.5$  with the help of an electrically heated blanket.

#### ANALYTICAL TECHNIQUES

The vascular and airway pressures were measured with Statham strain gauges and recorded on a Grass model 5 polygraph. The reference level for circulatory pressures was the plane 5 cm dorsal to the angle of Louis. Cardiac output was measured with the Stewart-Hamilton technique, using 5 mg of indocyanine green dye per determination. This was injected in the pulmonary artery; sampling was via the femoral artery using a Waters densitometer. Pulmonary vascular resistance was calculated as mean pulmonary arterial pressure minus mean pulmonary wedge pressure, divided by cardiac output. The sequence of measurements was pulmonary wedge pressure, pulmonary artery pressure, and cardiac output, in duplicate, all within a five-minute period.

Blood samples from the arterial needle and pulmonary artery catheter were drawn into heparinized syringes and immediately iced. The oxygen and carbon dioxide contents of these blood samples were determined by the manometric method of Van Slyke and Neill.<sup>1, 2</sup> The pH,  $P_{\text{CO}_2}$  and  $P_{\text{O}_2}$  of blood were determined at 37 C with an Instrumentation Laboratories electrode assembly. Oxygen consumption was calculated from the arterial-venous oxygen content differences and the cardiac output.

The physiologic shunt, calculated as shown in the appendix, was determined at two different oxygen tensions. Physiologic shunt is a sum of venous admixture, atelectasis and a contribution due to ventilation/perfusion maldistribution. The latter contribution varies with alveolar oxygen tension, being insignifi-

cant at high concentrations (when  $FI_{\text{O}_2}$  is 0.8 or greater), and increasing toward a maximum when  $FI_{\text{O}_2}$  approaches 0.2. End-expired concentrations of cyclopropane were measured by the method of Linde and Price.<sup>3</sup> End-tidal carbon dioxide and halothane concentrations were measured using a Liston-Becker infrared gas analyzer.

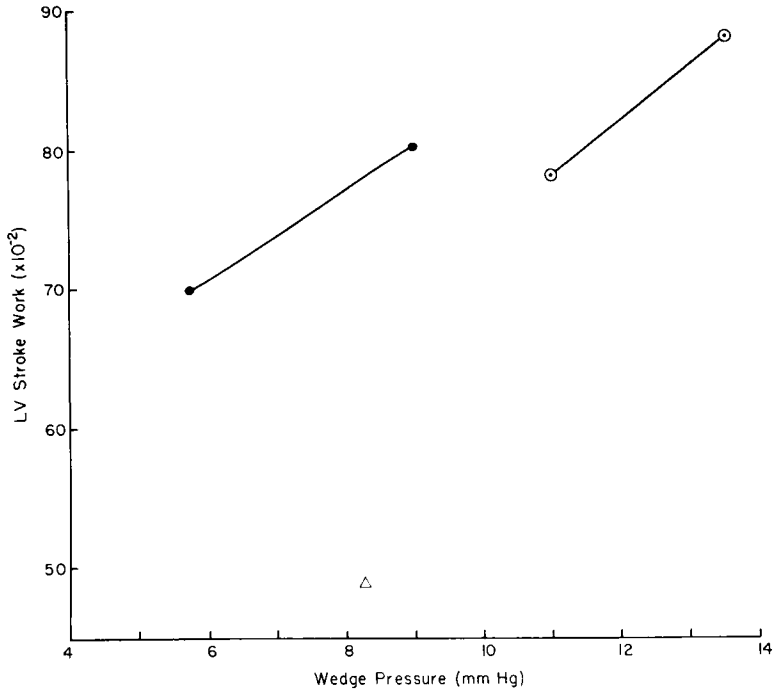
The data were analyzed statistically by Student's *t* test. *P* values of 0.05 or less were considered significant.

*Halothane Anesthesia.* Measurements during halothane anesthesia with controlled respiration and with spontaneous respiration were compared with control values in six subjects. Cardiac output, vascular pressures, and blood gas contents and tensions were measured six times in each subject in order to study the effects of the two different inspired oxygen concentrations in the three different states (one awake and two anesthetized). The control studies always preceded the induction of anesthesia, but the order of alteration of oxygen tension was reversed from one subject to the next, as was the order of the respiratory states (spontaneous or controlled) during anesthesia.

The inspired oxygen concentrations were 25 per cent and 98½ per cent in the control study; the balance of the gas was nitrogen. During anesthesia 1½ per cent halothane was included, nitrogen again making up the balance. When the inspired gas was changed from one oxygen concentration to another, sufficient time was allowed to achieve a calculated 99 per cent washout of the previous mixture.

*Cyclopropane Anesthesia.* In the study of cyclopropane anesthesia five similar sets of experimental observations were made in each of six subjects. In two control studies inspired oxygen concentrations were alternately 25 per cent oxygen, 20 per cent cyclopropane with the balance nitrogen, or 20 per cent cyclopropane in oxygen. The inspired anesthetic mixture was then changed to nitrous oxide-halothane, and 40 minutes later a study of 70 per cent nitrous oxide, 1 per cent halothane, the balance oxygen, completed this protocol. Three of these six subjects were allowed to breathe spontaneously throughout the studies, while in the other three respiration was controlled

FIG. 1. Effects of anesthesia on the relationship between left ventricular stroke work and pulmonary wedge pressure. Different work levels during consciousness and cyclopropane anesthesia were produced by varying  $FI_{O_2}$  from 0.25 to 0.80 atmospheres. Units of stroke work = ml  $\times$  mm Hg mean arterial pressure. ● = control; ○ = cyclopropane anesthesia;  $\Delta$  = halothane anesthesia.



using minute volumes chosen to maintain arterial carbon dioxide tensions similar to those in the three who were breathing spontaneously. Since there were no clear differences between values in controlled and spontaneously-ventilating subjects, their data were combined.

### Results

The principal findings are summarized in tables 1 and 2. General findings appear in table 1; those related to the pulmonary circulation are entered in table 2. General anesthesia was associated with slightly increased  $Pa_{CO_2}$  and reduced  $Pa_{O_2}$  and  $pH$ . These changes are attributed to hypoventilation and increased pulmonary shunting.

#### EFFECTS ON THE SYSTEMIC CIRCULATION

Halothane in oxygen (1 per cent end-tidal) reduced mean arterial blood pressure and total peripheral resistance to equal extents, leaving cardiac output unaltered. It did not prevent the further reduction in peripheral resistance or the increase in cardiac output which had occurred when the lower tension of oxygen was inspired before the induction of anesthesia.

One per cent halothane with 70 per cent nitrous oxide produced essentially no effect on general hemodynamics other than a decrease in arterial pressure.

Cyclopropane (16 per cent end-tidal) had no consistent effect on the systemic circulation, although there were increases in arterial blood pressure and total peripheral resistance in most individuals. The increase in cardiac output and decrease in total peripheral resistance which occurred on exposure to the lower oxygen tension in the first group of subjects did not occur in the individuals given cyclopropane, either before or during anesthesia.

#### EFFECTS ON THE PULMONARY CIRCULATION

Changes in pulmonary hemodynamics during anesthesia were of considerably greater interest. Cyclopropane administration not only increased the pulmonary vascular resistance, it also appeared to enhance the response to decreased oxygen tension. It distinctly elevated not only the pulmonary arterial and perfusion pressures, but also the wedge pressure. Of the total increase in pulmonary arterial pressure, roughly 60 per cent was estimated to be

caused by actions distal to the pulmonary capillaries. Halothane, in contrast, had no conspicuous effect on these measurements.

Both halothane (with either oxygen or 70 per cent nitrous oxide) and cyclopropane anesthesia increased the physiologic shunt through the lung. The sum of venous admixture and atelectasis (measured at high inspired oxygen concentrations) was greater during anesthesia than during consciousness. When 25 per cent oxygen was inspired the calculated physiologic shunt increased further during both halothane and cyclopropane anesthesia. Such a change indicates a significant increase in ventilation/perfusion maldistribution during anesthesia. It was most evident during halothane anesthesia with spontaneous respiration.

#### EFFECTS ON THE HEART

The 4-mm Hg increase in wedge pressure during cyclopropane anesthesia suggested that left atrial pressure was elevated and raised the question whether myocardial incompetence was present. To answer this we calculated left ventricular stroke work and plotted it against wedge pressure. An illustrative result, shown in figure 1, indicates that the increase in wedge pressure was accompanied by an increase in stroke work. In contrast, the unchanged wedge pressure during halothane administration was accompanied by a substantial reduction in stroke work.

#### EFFECTS ON OXYGEN UPTAKE

Cyclopropane had an inconsistent effect on oxygen consumption. In the 12 instances where paired comparisons were made, there were increases in  $\dot{V}O_2$  in six and decreases in six. Halothane was associated more frequently with diminished  $\dot{V}O_2$ . There were small increases in  $\dot{V}O_2$  with halothane in three subjects and decreases in nine. There were also reductions in oxygen consumption following the change from cyclopropane to nitrous-oxide-halothane anesthesia.

#### Discussion

We became interested in the reactions of the pulmonary circulation during anesthesia not simply because of the absence of published measurements but because of a num-

ber of previous observations which suggested that important changes take place in this area. An effect of general anesthesia on pulmonary physiologic shunting is now well recognized.<sup>4, 5</sup> Still earlier work suggested that some of the elevation in central venous pressure during cyclopropane anesthesia reflected an increase in right ventricular stroke work.<sup>6</sup> Finally, the observation that pulmonary arterial pressure can be increased both by cyclopropane<sup>7</sup> and by halothane<sup>8</sup> raised the question whether these agents acted upon the pulmonary vasculature or whether their effects were secondary to changes in cardiac performance.

Our data are consistent with the view that cyclopropane causes pulmonary arteriolar constriction, either by a direct action or via sympathetic nerves supplying the lung.<sup>9</sup> An alternative possibility—that the mild respiratory acidosis encountered may have been responsible (table 1)—apparently can be discarded both on the basis of earlier work<sup>10</sup> and because no such changes were observed during halothane or halothane-nitrous oxide anesthesia when similar degrees of acidosis were present.

Our findings are thus in basic agreement with those of Etsten *et al.*,<sup>7</sup> although it should be pointed out that most of the elevation in pulmonary artery pressure in our subjects was caused by changes *beyond* the pulmonary capillaries. Inferences drawn from the measurement of pulmonary arterial pressure alone, as in the previous study,<sup>7</sup> would *seriously overestimate* the degree of pulmonary vasoconstriction. Similarly, we detected no change in pulmonary resistance attributable either to halothane or to halothane-nitrous oxide, despite the fact that pulmonary arterial pressure occasionally was elevated during anesthesia in this study and was increased consistently in an earlier investigation.<sup>8</sup>

Increased postcapillary pressure during anesthesia could result from depressed myocardial contractility (caused by the anesthetic), from a higher (more positive) level of intrapleural pressure (caused by respiratory depression and/or positive-pressure lung inflation), or from an increased level of cardiac work. In the case of halothane, the first two factors appeared important in some subjects. Cyclo-

propane produced no clear evidence of impaired cardiac performance, but did elevate left ventricular stroke work. Increased intrapleural pressure presumably also occurred, as can be inferred from figure 1, which shows parallel lines (before and during anesthesia) separated by a distance equivalent to a 2-mm Hg increase in intrathoracic pressure.

The inverse relation between  $P_{aO_2}$  and pulmonary arteriolar resistance at tensions above the ambient level has not previously been shown, to our knowledge. It is possible that this response could be valuable clinically in the treatment of incipient right heart failure. The response of the pulmonary arterioles to altered oxygen tension appeared uninfluenced by halothane and may have been augmented by cyclopropane. It is conceivably of clinical importance that in the presence of nearly-normal inspired oxygen tension (*i.e.*, 25 per cent) cyclopropane can approximately double pulmonary vascular resistance. Such conditions could be encountered initially upon discontinuation of cyclopropane administration and substitution of either room air or a nitrous oxide-oxygen mixture. A large increase in the work of the right ventricle, which might precipitate failure in a patient with marginal right heart function, could be expected at this time.

Anatomic pulmonary shunting was increased more consistently during controlled than during spontaneous ventilation, largely due to an increase in fixed shunt and/or atelectasis. However, there was no statistically significant difference between the degrees of this shunting observed with the three different anesthetic mixtures. The increase in  $Q_s/Q_T$  attending lowered inspired oxygen tension is due to maldistribution of blood and gas in the lung. This effect was most marked during spontaneous ventilation with halothane, where the V/Q component contributed twice as much to physiologic shunting as fixed admixture. During controlled respiration with halothane, or during both types with cyclopropane, V/Q abnormalities were only half as important as fixed venous admixture in producing physiologic shunting at 25 per cent inspired oxygen, and would be even less important at higher concentrations.

The changes in  $VO_2$  associated with halothane are in agreement with the earlier findings of Severinghaus and Cullen<sup>11</sup> and Theye,<sup>12</sup> and those with cyclopropane are similar to the data of Underwood *et al.*<sup>13</sup> *In vitro* studies of brain, heart and liver slices have shown that halothane causes a decrease in oxygen consumption,<sup>14</sup> and our findings may reflect similar *in vivo* actions.

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$P_{aO_2}$  was calculated as  $P_B - P_{H_2O} - P_{aCO_2} - P_i$  anesth.  $P_{aO_2}$  was measured by polarographic analysis of an iced arterial sample corrected for the cooling time by the average change of Fletcher and Barber.<sup>15</sup>  $CaO_2 - C_{vO_2}$  was measured by the Van Slyke manometric method.

During the inhalation of low oxygen mixtures ( $F_{IO_2} = 0.25$ ), physiologic shunt was calculated by:

$$\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{(0.0032 \times P_{aO_2}) + (Sc \times 1.34 \times Hb) - CaO_2}{(0.0032 \times P_{aO_2}) + (Sc \times 1.34 \times Hb) - C_{vO_2}}$$

$P_a$  was obtained by the physiologic deadspace method of Filley<sup>16</sup>:

$$P_a = (P_B - 47) \times F_{IO_2} - P_{aCO_2}/P_{ECO_2}(F_{IO_2} - F_{EO_2})$$

#### APPENDIX

During inspiration of the high oxygen mixtures ( $F_{IO_2} = 0.80$  to  $0.90$ ) the physiologic shunt was calculated by:

$$\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{(A - aDO_2) \times \lambda \text{ body temp.}}{(A - aDO_2) \times \lambda + CaO_2 - C_{vO_2}}$$

$$Hb \text{ was calculated from } \frac{[CaO_2 - P_{aO_2} \times 0.0031]}{1.34 \times SaO_2}$$

$ScO_2$  and  $SaO_2$  were taken from the Severinghaus slide rule, knowing  $P_{aO_2}$ ,  $P_{aCO_2}$ ,  $pH_a$  and body temperature.

## Drugs

**ISOPROTERENOL** The effect of intravenous isoproterenol upon cardiorenal hemodynamics was studied in ten patients with, and three patients without, heart disease. Although cardiac output was increased in every patient in response to the drug, no significant change in glomerular filtration rate or renal blood flow was seen, and the percentage of cardiac output delivered to the kidney decreased. The data suggest that there is either a weak beta receptor response in the kidney or none. (*Rosenblum, R., and others: Effect of Acute Intravenous Administration of Isoproterenol on Cardiorenal Hemodynamics in Man, Circulation* 38: 158 (July) 1968.)

**IRREVERSIBLE HYPOGLYCEMIA** The glucose-lowering action of alcohol augments that of other hypoglycemic agents and may induce severe hypoglycemia with irreversible neurologic changes. In six healthy subjects infusion of alcohol during a standard insulin-tolerance test inhibited the usual rebound of glucose after hypoglycemia. Alcohol interferes with hepatic glycogenesis and induces hypoglycemia whenever glycogenesis is required to maintain normal glucose levels. Diabetics receiving other hypoglycemic agents should be warned about the blood-glucose-lowering action of alcohol. (*Arky, R. A., and others: Irreversible Hypoglycemia: A Complication of Alcohol and Insulin, J.A.M.A.* 206: 575 (Oct.) 1968.)