Relation of Blood Volume and Hemodynamic Changes During Halothane Anesthesia in Man

H. T. Morse, M.D., H. W. Linde, Ph.D., R. David Mishalove, A.B., H. L. Price, M.D.

DURING halothane anesthesia cardiac output and arterial pressure may increase with time, even though the end-expired concentration of halothane remains constant.[1, 2] A possible explanation for this finding is an increase in blood volume.[3, 4]

In this study changes in blood and plasma volume during halothane anesthesia were determined in human volunteers using a red cell tag (Cr^{51}). Arterial pressure, venous pressure, heart rate and end-expired concentrations of carbon dioxide and halothane were measured concurrently in order to establish whether a relation existed among any of these variables. It was concluded that, while plasma volume and venous pressure were inversely related, there was no relation between blood or plasma volume and the observed changes in arterial pressure.

Methods

Ten healthy male volunteers were studied. Ages ranged from 20 to 28 years.

On the day prior to study blood was withdrawn from the subject and labeled with Cr^{51} according to the method of Gray and Sterling.[5] The subject returned the following morning, having fasted since midnight, and lay on a table in the supine position. Lead 2 of the electrocardiogram was recorded using needle electrodes. An antecubital vein was entered with a 16 gauge thin-walled needle through which a 0.9 mm. bore polyethylene catheter was inserted and advanced until the tip lay within the thorax as judged by the configuration of the pressure tracing. The catheter was connected to a Statham (P23BB) strain gauge for recording of pressure. The tagged red cells were injected through the catheter and flushed in with physiological saline 30 minutes before the control observations of blood volumes were made. Arterial pressure was measured by a transducer (P23D) connected by a stopcock manifold and vinyl tubing to a 21 gauge thin-walled needle placed in a brachial artery. The base line for pressure measurements was a plane 5 cm. dorsal to the angle of Louis. All variables were recorded on a Grass polygraph and mean pressures were obtained by electrical damping.

Following a rest period of fifteen minutes duplicate 10-ml. samples of arterial blood were withdrawn through the manifold into dry syringes and transferred to oxalate tubes. Oxygen was administered by face mask for ten minutes, following which a third blood sample was withdrawn in seven of the ten subjects. Blood, red cell and plasma volume controls were determined from the average of these three samples.

The face mask was provided with an orifice through which respired gases were withdrawn via a malleable lead tube at a rate of 500 ml./minute and continuously analyzed for halothane and carbon dioxide concentrations by a pair of infrared analyzers connected in series. During the period of oxygen breathing the analyzers were calibrated with known concentrations of these gases. When plateaus were not obtained for the carbon dioxide tracing, the chest and abdomen were compressed manually in order to insure more accurate end-expiratory sampling.

Anesthesia was induced using a Fluotec Mark II vaporizer in a nonrebreathing system utilizing a Ruben valve and oxygen flows of 5–12 liters/minute. The inspired concentration of halothane was rapidly increased to 4 per cent and respiration assisted to main-

Accepted for publication June 27, 1963. The authors are in the Department of Anesthesia, University of Pennsylvania Schools of Medicine, Philadelphia, Pennsylvania. The study was supported (in part) by a Grant (RG-9070) from the National Institutes of Health, and Ayerst Laboratories. Dr. Morse, Post-Doctoral Fellow supported by Grant 2G-215.

tain adequate ventilation. A no. 10 Magill endotracheal tube was inserted without the aid of muscle relaxants and the cuff inflated. A maintenance concentration of halothane between 1.5 and 2.0 per cent was selected and spontaneous respiration was permitted to return. The concentration selected was the greatest at which adequate respiration (P_{CO_2} < 50 mm. of mercury) was maintained and where the mean arterial pressure exceeded 50 mm. of mercury. Following intubation of the trachea, a fifteen to twenty minute period elapsed during which arterial pressure, heart rate and end-expired gas concentrations achieved relatively steady values.

Blood samples were withdrawn from the brachial artery approximately 0.5, 1.0 and 1.5 hours after the induction of anesthesia. If two samples were withdrawn during any one time period, the results were averaged as indicated in table 1. Blood loss from sampling amounted to 100–130 ml. and was replaced with an equal volume of physiological saline when the loss occurred. At the conclusion of the study the subjects were observed in the recovery room until normal activity returned.

After blood samples had been hemolyzed with saponin the gamma emission was counted in a well-counter for two minutes or until 10,000 counts were recorded, and the radioactive background was monitored for three minutes. Standard deviations of paired control values were: blood volume, 42 ml. (0.86 per cent); plasma volume, 44 ml. (1.4 per cent). Hematocrit was determined in triplicate in capped Wintrobe tubes centrifuged at 3200 g. (at the tip) for thirty minutes. The hematocrit fraction was corrected to body hematocrit and for trapped plasma by the factor 0.90.[6, 7] Hemoglobin content was measured in duplicate by the cyanmethemoglobin method. Radioactive counts per gram of hemoglobin were determined to check the constancy of red cell tagging during each study.

The red cell volume (RCV) and blood volume (BV) were calculated[5, 8] as:

$$RCV = \frac{\text{total counts injected}}{\text{counts/ml. of blood after circulatory mixing}} \times \frac{\text{peripheral hematocrit}}{100}$$

$$BV = \frac{RCV}{\text{body hematocrit}} \times 100$$

Analyses for statistical significance were made with Student's *t* test. Spearman's rank difference coefficient was used to test for correlation.[9] A *P* value of less than 0.05 was considered significant.

Results

The data obtained from individual subjects are shown in table 1; these results are summarized in table 2. Two of the subjects exhibited apprehension during the control period and three had mild delirium on induction. Apprehension was considered to be present if the subject admitted fright, if the heart rate exceeded 100/minute, if the subject hyperventilated obviously, or if mean arterial pressure exceeded 100 mm. of mercury. There was no consistent difference in the response between apprehensive subjects, those exhibiting induction delirium, and the others.

Total Blood Volume and Plasma Volume. The average total blood volume during the control period was 4.9 liters. Blood volume alterations during anesthesia were not consistent in individual subjects, either in magnitude or direction, when compared with control values. The mean changes for the group studied were an increase in blood volume of 30 ml. (0.61 per cent), 80 ml. (1.66 per cent), and 33 ml. (0.6 per cent), respectively, in the three observation periods. The largest increase in blood volume obtained in any subject was 230 ml. There were no significant differences from control values or variations between time periods for the group. Correlations could not be shown between blood volume and arterial pressure or central venous pressure.

Plasma volume varied directly with blood volume. There was a significant ($P < 0.05$) negative correlation between plasma volume and central venous pressure.

Mean Arterial and Venous Pressures. The average decrease in mean arterial pressure was 22 mm. of mercury ($P < 0.01$) during the inhalation of halothane. This decrease,

TABLE 1. Observations of Blood Volume, Plasma Volume, Mean Arterial and Venous Pressure, Heart Rate, Respiratory Rate, Carbon Dioxide Tension, and Halothane Concentration Before and During Halothane Anesthesia

No., Age, Wt., Ht.	Time in Minutes	% Halo. Insp.	% Halo. End-exp.	Δ% B.V.	Δ% P.V.	M.A.P.	M.V.P.	H.R.	R.R.	P_{CO_2}
(1) 29, 200, 69″	−17					74	7.7	47	15	38
	−7					80	8.1	48	15	38
	35	2.0		−0.8	−1.7	60	11.0	54	41	57
	64	1.8		3.2	2.2	65	8.6	54	34	54
	98	1.8		4.4	4.7	77	9.7	55	35	52
(2) 22, 160, 70″	−21					80	6.0	78		
	−16					80	6.0	68		
	−6					80	5.5	78	17	37
Mild delirium	32	1.5		−2.0	−4.0	59	10.0	68	36	43
	64	1.3		1.9	1.3	63	6.0	68	32	46
	94	1.3		−3.4	−5.0	78	7.5	67	28	35
(3) 27, 165, 75″	−19					87	5.5	68		
	−4					80	5.0	64	16	38
	36	2.0		−0.6	−3.1	70	10.0	70	30	48
	60	1.8		4.3	3.0	65	7.5	66	30	48
	98	2.0		0.3	3.4	80	9.0	75	31	40
(4) 26, 155, 74″	−14					75	6.0	72		
	−10					76	6.0	68	14	36
	−2					85	6.0	64		
	48	2.5	1.5	1.0	−2.0	88	12.0	59	38	
	68	2.3	1.5	3.9	3.1	76	11.0	68	40	49
	100	2.5	1.5	−0.1	−0.3	74	9.5	64	37	43
(5) 21, 155, 70″	−29					90	9.0	52		
	−15					95	9.0	58	12	
	40	2.3	1.4	−2.5	−5.4	74	15.4	56	27	
	67	2.5	1.4	−0.9	−2.6	80	13.0	64	30	
	99	2.4	1.5	−2.3	−7.1	78	13.0	68	35	

Age in years, weight in pounds, height in inches.

Time in minutes from induction: − values are control observations, + values are observations during halothane inhalation.

When two observations were made the results were averaged and marked as $\bar{n}$. Δ%—per cent change; B.V.—blood volume; P.V.—plasma volume; M.A.P.—mean arterial pressure in millimeters of mercury; M.V.P.—mean venous pressure in millimeters of mercury; H.R.—heart rate in beats/minute; R.R.—respiratory rate breaths/minute; P_{CO_2}—end-expired carbon dioxide tension in millimeters of mercury; % Exp. Halo.—volume per cent end-expired vapor concentration of halothane; % Insp. Halo.—volume per cent inspired vapor concentration of halothane.

with small variations, was maintained during the first two observation periods. In the third period the arterial pressure increased 9 mm. of mercury ($P < 0.01$).

The average mean venous pressure exceeded control levels significantly in all periods. An increase averaging 3.2 mm. of mercury was observed in the first observation period. In the second and third periods, venous pressure exceeded the initial level by 1.7 mm. of mercury.

Heart Rate and Rhythm. In general the heart rate remained constant or decreased slightly during induction of anesthesia and the first two observation periods. Heart rate increased on the average by 3 beats/minute ($P < 0.01$) in the last observation period when compared with the first two periods, but there were no significant variations from control values.

Respiratory Rate and End-Expired Carbon Dioxide Tension. With the induction of anes-

TABLE 1. *-Continued*

No., Age, Wt., Ht.	Time in Minutes	% Halo. Insp.	% Halo. End-exp.	Δ% B.V.	Δ% P.V.	M.A.P.	M.V.P.	H.R.	R.R.	P_{CO_2}
(6) 20,	−28					108	5	64		
185, 74″	−25					107	5	76		33
	−8					105	5	76	15	35
Apprehensive	36	2.0	1.1	0.4	−0.3	60	6	60	30	40
	64	2.0	1.2	0.7	0.9	50	5.5	52	35	42
	102	1.9	1.2	1.8	2.0	58	6	60	38	35
(7) 28,	−27					88	10	68		
205, 79″	−17					85	9	68	16	
	−6					89	9	60	15	29
	43	1.5	1.2	−1.1	0.4	70	13	64	23	43
	65	1.4	1.1	−1.1	−2.8	68	10	60	22	46
	110	1.4	1.1	−0.3	−3.3	75	9	64	22	43
(8) 22,	−22					94	8	68		
175, 73″	−16					93	8	64		
	−1					100	7	60	18	34
Mild delirium	44	1.5	0.9	2.2	1.9	65	9	68	34	43
	63	1.5	0.8	−3.2	−0.6	60	9	64	30	46
	110	1.5	1.0	0.8	−6.4	80	10	72	30	39
(9) 21,	−21					85	7	68		
165, 72″	−19					80	4	72		
	−3					80	3	76	14	47
Mild delirium	46	1.5	1.0	5.5	10.7	58	6	68	16	53
	63	1.5	1.0	3.4	7.0	56	6	68	16	50
	108	1.5	1.0	0.2	3.4	70	5	72	18	58
(10) 27,	−60					94	7.0	92		
145, 71″	−13					108	13.0	92	16	37
	−2					105	3.0	80	13	33
Apprehensive	40	1.6	1.3	3.9	9.6	65	5.8	70	38	41
	60	1.6	1.3	4.4	7.5	67	3.6	76	36	45
	106	1.9	1.4	5.2	10.9	70	5.4	80	40	42

thesia the average respiratory rate increased 16 breaths per minute ($P < 0.01$) and remained elevated during the inhalation of halothane. Carbon dioxide tension rose 9–10 mm. of mercury ($P < 0.01$) above control values and showed little variation with time.

Halothane Concentration. The end-expired concentration of halothane following induction varied no more than ± 0.2 per cent in the subjects studied.

Discussion

Blood volume determinations by either the red cell or the plasma tag method depend upon the assumption that the whole body to venous hematocrit ratio remains constant.

It is recognized that the ratio is nearly constant in healthy man, the average value being 0.91.[7] Hope and Verel [10] reported a few discrepancies in the ratio in disease states associated with high or low hematocrit, but Chaplin and associates [7] and Gibson *et al.*[11] reported a remarkably constant ratio over a wide hematocrit range. Actually, "the ratio" itself can be established only by simultaneous measurement of plasma and red cell volumes. Since plasma tagging methods yield erroneously high results due to loss of protein from the circulation [12] "the ratio" must be even closer to unity than is currently estimated.

The relative constancy of the ratio during anesthesia was demonstrated in this laboratory [13] during cyclopropane, ether, thiopental anesthesia, and morphine sulfate narcosis, and plasma volume changes as calculated from hematocrit and dye concentration agreed

TABLE 2. Summary of Blood Volume, Circulatory, and Respiratory Changes During Halothane Anesthesia

Period	Time in Minutes	Δ% B.V.	Δ% P.V.	Δ M.A.P.	Δ M.V.P.	Δ R.R.	Δ H.R.	Δ P_{CO_2}	% Insp. Halo.	% Exp. Halo.
1	40 ± 5.2	0.61	0.62	−21.8*	3.18*	16.1*	−3.7	9.5*	1.8	1.2
2	64 ± 2.6	1.66	1.89	−23.7*	1.60*	15.3*	−3.4	10.8*	1.8	1.2
3	103 ± 5.6	0.67	−0.44	−14.9*	1.70*	16.2*	0.3	6.66*	1.9	1.2

Time in minutes ± standard deviation. Δ—change; Δ% per cent change; B.V.—blood volume; P.V.—plasma volume; M.A.P.—mean arterial pressure in mm. of mercury; M.V.P.—mean venous pressure in mm. of mercury; R.R.—respiratory rate breaths/minute; H.R.—heart rate in beats/minute; P_{CO_2}—end-expired carbon dioxide tension in millimeters of mercury; % Insp. Halo—volumes per cent inspired vapor concentration of halothane; % Exp. Halo.—volumes per cent end-expired vapor concentration of halothane; * significant change from control value ($P < 0.05$).

within the limits of methodological error. Grable and associates showed that the ratio remained constant during anesthesia with halothane–nitrous oxide–oxygen, or cyclopropane.[4] These data demonstrate the constancy of the whole body to venous hematocrit ratio in normal subjects and provide the rationale for blood volume measurement by tagged red cell methods.

Mean capillary pressure is recognized as an important factor in rapid alterations in blood volume. Mean capillary pressure could be affected by changes in arteriolar resistance, in cardiac output, in post-capillary resistance, and in central venous pressure. Decreased arterial pressure during halothane anesthesia is attributed to decreases both in cardiac output and in total peripheral resistance [1, 14, 15]; these changes probably affect capillary pressure in opposite directions. Since alterations in venous pressure have a more profound effect on hydrostatic pressure in the capillaries than does arterial pressure,[16] it is likely that capillary pressure follows the direction of change of central venous pressure. Plasma volume shifts have been observed with other anesthetic agents, as shown by Price and associates,[13] and the direction of change was inversely related to venous pressure, as it was in the present study.

Blood volume changes were estimated during the induction of halothane anesthesia by Payne.[3] Using T-1824 and a two point extrapolation technique, a 0.7 liter increase in blood volume was calculated. No information about carbon dioxide tensions, venous pressures, or methodological error was given. Grable and co-workers[4] investigated blood volume changes during the administration of cyclopropane and halothane–nitrous oxide–oxygen. Although they observed a 10 per cent increase in blood volume after 30 minutes of halothane administration, there was also a 7 per cent increase in red cell volume. This finding is difficult to explain. It could have resulted if tagged cells initially were not evenly distributed among the red cell population, but their own data (complete mixing in ten minutes) rule out this possibility. If a significant increase in hematopoiesis occurring within thirty minutes can be excluded, as seems likely, there remains only the possibility than an increase in red cell size occurred. However, it is difficult to believe that red cell size can increase so markedly under conditions that might be expected to occur during anesthesia.[17] Unfortunately the authors make no statement regarding either hemoglobin concentration or hematocrit. We could confirm neither of the results from the reports cited above. During halothane anesthesia no significant change in red cell volume, hematocrit or hemoglobin concentration was detected.

Although we observed the increase with time in arterial pressure and heart rate and decrease in venous pressure as previously reported by Deutsch[1] and McGregor,[2] these changes could not be attributed to changes in blood volume or to changes in end-expired concentrations of carbon dioxide or halothane,

By exclusion there remains as an explanation an increase in the intensity of external stimulation (for example, owing to discomfort associated with prolonged immobilization or to heat loss) or a decrease in the depth of narcosis. Causes for the latter possibility might include the development of tolerance to the actions of halothane or a change in the ventilation to perfusion ratio that would result in a decrease in arterial halothane tension not reflected in the analysis of end-expired air.

Summary

Blood, red cell and plasma volumes were measured in human volunteers who breathed spontaneously, received no preanesthetic medication or surgical stimulation, and were not hypercarbic.

During the inhalation of 2 per cent halothane in oxygen there was observed a decrease in arterial pressure and heart rate and an increase in venous pressure. Maintenance of a constant end-expired tension of halothane for 1¼ hours resulted in an increase in arterial pressure and heart rate, and a decrease in venous pressure. In contrast, there were no consistent changes in blood, plasma, or red cell volumes. An inverse relationship was established between plasma volume and venous pressure.

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