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Research Article

THE EFFECT OF HYPERCAPNIA ON ESTIMATED HEPATIC BLOOD FLOW, CIRCULATING SPLANCHNIC BLOOD VOLUME, AND HEPATIC SULFOBROMOPHTHALEIN CLEARANCE DURING GENERAL ANESTHESIA IN MAN *

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Splanchnic circulatory adjustments during general anesthesia in man are difficult to assess in the absence of precise information regarding the depth of anesthesia and the regulation of gas exchange. The vasoconstriction responsible for the fall in hepatic blood flow that has been reported by several investigators (1, 2) may be attributable to the anesthetic agents themselves, to changes in venous return following reduction in activity and tone of skeletal muscles (3), to hypoxia or to hypercapnia. Of all of these the last has been particularly difficult to detect and control (4). Now, however, the availability of satisfactory muscle relaxants (5) and the development of mechanical devices for the maintenance of a suitable respiratory pattern (6) have made it possible to achieve constancy in anesthetic level, oxygenation, and carbon dioxide elimination. Comparable "steady state" measurements of splanchnic hemodynamic parameters can be made before and during hypercapnia, because ventilatory excursion and rate can be fixed by artificial respiration after the administration of neuromuscular blocking agents, and the arterial carbon dioxide content can be altered as desired by appropriate changes in the breathing mixture. Under these circumstances, the volume of blood held within the splanchnic vasculature is determined only by local venomotor activity and by the balance between arteriolar resistances. Interference by variations in intra-abdominal pressure that might otherwise arise from excessive and unpredictable movements of the diaphragm are eliminated. Data of value in elucidating the vascular response to hypercapnia and anesthesia may therefore be obtained from measurements of splanchnic blood volume as well as blood flow (7). In the study reported in this paper, mechanically controlled light anesthesia (thiopental-nitrous oxide) alone appeared to have no effect upon the splanchnic bed, suggesting that extraneous factors may have been influential in producing the changes previously ascribed to anesthesia. In contrast, hypercapnia was associated with splanchnic vasoconstriction and with a reduction in splanchnic blood volume that was consistent with preponderant mesenteric and hepatic arteriolar constriction, splanchnic venoconstriction, or both.

METHODS

The subjects for this study were 19 patients (9 male and 10 female, between 21 and 60 years of age) from the Surgical Service of the Presbyterian Hospital. None presented clinical evidence of cardiovascular, renal, hepatic or biliary tract disease. Each was examined in the fasting state immediately prior to a scheduled operative procedure of relatively short duration such as inguinal herniorrhaphy, excision of pilonidal cyst or biopsy of thyroid nodule. The effects of the preanesthetic medication alone were evaluated in 6. The effects of anesthesia and hypercapnia were studied in 13 subjects who had been given 8 to 15 mg of morphine sulfate and 0.4 to 0.5 mg of scopolamine hydrobromide intravenously, depending upon body weight, approximately 1 hour prior to hepatic venous catheterization.

Following control determinations, light anesthesia was induced by 150 to 400 mg of thiopental sodium given intravenously in divided doses and maintained by the administration of a mixture of 70 per cent nitrous oxide and 30 per cent oxygen, using an endotracheal tube without rebreathing. A 1.0 per cent solution of succinyl-

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choline chloride in 5 per cent dextrose in water was infused intravenously at a rate sufficient to maintain apnea and immobility, permitting mechanical control of respiration.

Ventilation of the apneic patient was controlled by a "servorespirator" in which end-expiratory carbon dioxide tensions ($P_{A_{CO_2}}$) (Liston-Becker infrared analyzer) automatically regulated the inflating pressure (6). This device is capable of maintaining the arterial carbon dioxide tension (Pa_{CO_2}) within ± 3 mm Hg for hours under the conditions employed in this study. After a period of 10 to 20 minutes for stabilization of $P_{A_{CO_2}}$ at approximately 40 mm Hg, all measurements (except total blood volume) were repeated. The $P_{A_{CO_2}}$ was determined with each breath and the Pa_{CO_2} was determined at 9- to 36-minute intervals during multiple sampling periods.

After completion of sampling, the respirator was reset to maintain a $P_{A_{CO_2}}$ of 60 mm Hg. This was accomplished in 4 subjects by reduction of the inspiratory pressures and in 9 subjects by the administration of a mixture of 3 per cent carbon dioxide, 70 per cent nitrous oxide and 27 per cent oxygen at essentially unchanged inspiratory pressures. Approximately 10 minutes was required to attain a new stable carbon dioxide tension. All measurements were repeated after 5 to 15 minutes at the altered $P_{A_{CO_2}}$. In 4 subjects the period prior to anesthesia was omitted and the comparison made only between an initial period of eucapnia and a subsequent period of hypercapnia during anesthesia, while in 3 additional subjects the sequence was reversed.

Hepatic blood flow (EHBF) was estimated by the sulfobromophthalein (BSP) method (8), total blood volume by radioactive iodinated serum albumin dilution, circulating splanchnic blood volume (SBV) by the regional dilution method (9), and arterial pressure by auscultation. Mean arterial blood pressure (MBP) was

TABLE I

Effect of morphine and scopolamine given intravenously on splanchnic hemodynamics and sulfobromophthalein removal *

Subject	Period	Dose	BSP	EHBF	MBP	SVR	SBV	E%	C_{BSP}
		mg	*mg%*	*ml/min*	*mm Hg*	*units*	*ml*		*ml/min*
A	Control		0.94	1,060	92	0.087	490	55.6	350
	Scopol.	0.5	0.92	950	96	0.101	570	62.4	360
	Morph.	10.0	1.01	840	94	0.112	480	62.8	320
B	Control		1.03	1,120	92	0.082	750	53.9	350
	Scopol.	0.5	0.99	1,200	94	0.078	650	52.5	360
	Morph.	7.0	1.01	1,220	82	0.067	730	47.6	340
C	Control		0.79	1,080	93	0.086	910	59.6	380
	Scopol.	0.5	0.97	1,050	92	0.088	1,200	49.9	310
	Morph.	10.0	1.08	910	89	0.098	830	52.9	280
D	Control		0.68	1,560	89	0.057	1,110	56.8	460
	Scopol.	0.5							
	and morph.	10.0	0.71	1,540	92	0.060	1,040	51.7	420
E	Control		0.95	1,030	85	0.083	710	61.0	370
	Scopol.	0.5							
	and morph.	10.0	0.97	1,040	86	0.083	750	62.7	370
F	Control		0.67	1,620	83	0.051	1,130	53.8	510
	Scopol.	0.5							
	and morph.	10.0	0.71	1,350	84	0.062	950	57.7	460
Mean	Control		0.843	1,245	89	0.074	850	56.8	403
± SD			0.370	269	4.2	0.015	250	2.7	66
Mean	Scopol.		0.914	1,150	88	0.080	797	55.9	365
± SD	and morph.		0.399	270	4.6	0.022	196	6.1	66
Mean Δ			+0.072	—95	—1.2	+0.006	—53	—0.9	—38
± SD Δ			0.277	147	4.9	0.013	76	5.9	35
t			0.64	1.6	0.6	1.1	1.7	0.37	2.62
p			>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	<0.05

* After control measurements, Subjects A, B, and C received scopolamine and measurements were repeated within 26 minutes. Morphine was then administered and measurements completed within 24 minutes. Subjects D, E, and F received morphine and scopolamine together and measurements were completed within 25 minutes. Abbreviations: BSP, plasma sulfobromophthalein concentration; EHBF, estimated hepatic blood flow; MBP, mean arterial blood pressure; SVR, splanchnic vascular resistance; SBV, splanchnic blood volume; E%, sulfobromophthalein extraction percentage; C_{BSP}, sulfobromophthalein plasma clearance; SD, standard deviation.

estimated to be the sum of diastolic plus one-third of the pulse pressure. Hepatic BSP clearance (C_{BSP}) was calculated as the BSP removal rate divided by the prevailing plasma concentration and was expressed as milliliters of plasma cleared of BSP per minute. The splanchnic vascular resistance (SVR) was expressed in arbitrary units as the mean arterial blood pressure divided by the hepatic blood flow. Possible changes in the central venous pressure have been neglected in this calculation.

Assiduous attempts were made to maintain a steady state of anesthesia and arterial CO_2 tension. Measurements of hemodynamic variables were discarded when the simultaneous analysis of end-expiratory gas revealed fluctuation of the P_{ACO_2}. In addition, changes in the arterial BSP concentration greater than 0.020 mg per 100 ml per minute were regarded as invalidating a measurement of flow. All values presented in the tables are averages of two or more determinations except in Subjects 1 and 3, in whom only one valid determination of EHBF could be obtained during hypercapnia.

The arterial blood pH was determined anaerobically at 37° C in a modified Cambridge glass electrode pH meter (10) within 1 minute of sampling. Arterial plasma CO_2 content, or in some cases the whole blood CO_2 content, was determined in the Kopp-Natelson microgasometer (11). The Pa_{CO_2} was calculated from the nomogram of Singer and Hastings (12). Arterial oxygen saturations were determined in the microgasometer or by the spectrophotometric method of Nahas (13). The effect of BSP on the Nahas method was investigated and found to be negligible in the concentrations employed (1 to 2 mg per 100 ml).

RESULTS

Effects of scopolamine and morphine (Table I)

Scopolamine alone (Subjects A, B, C) produced no consistent changes. Morphine given after (Subjects A, B, C) or simultaneously with scopolamine (Subjects D, E, F) produced reductions of less than 10 per cent in EHBF and C_{BSP}. Smythe and Gilmore (14), using the same methods, have also reported the absence of an effect of morphine upon the splanchnic circulation in dogs. The mean values for the various splanchnic circulatory parameters (Table I) did not change significantly after administration of scopolamine, with or without morphine. It was concluded, therefore, that the use of premedication would not significantly alter the effects of anesthesia

TABLE II

Effect of nitrous oxide-succinylcholine anesthesia without hypercapnia on splanchnic hemodynamics and sulfobromophthalein removal *

Subject	Period	Pa_{CO_2}	BSP	EHBF	MBP	SVR	SBV	E%	C_{BSP}
		mm Hg	*mg%*	*ml/min*	*mm Hg*	*units*	*ml*		*ml/min*
1	Control	42	1.11	1,070	93	0.087	770	61.7	310
	Anesth.	33	1.39	1,340	91	0.068	1,210	37.1	230
2	Control		0.65	1,640	95	0.058		71.8	660
	Anesth.		0.72	1,640	120	0.073		67.9	600
3	Control	29	1.59	1,000	93	0.093	940	43.1	240
	Anesth.	44	2.28	780	93	0.119	590	36.4	160
4	Control	36	0.91	1,440	93	0.065	1,320	59.5	410
	Anesth.	38	0.63	2,110	103	0.049	1,260	57.5	590
5	Control	39	0.86	1,280	85	0.067	1,150	72.3	480
	Anesth.	41	1.03	1,070	91	0.085	930	70.7	390
6	Control		1.30	820	85	0.104	700	62.1	290
	Anesth.		1.53	1,170	122	0.104	950	44.5	260
Mean	Control	37	1.07	1,208	90.7	0.079	976	61.8	398
± SD		5.6	0.34	303	4.4	0.018	248	10.5	155
Mean	Anesth.	39	1.26	1,351	103.3	0.083	988	52.4	372
± SD		4.6	0.61	469	14.4	0.025	268	15.2	188
Mean Δ		2.5	0.193	143	12.7	0.004	12	—9.4	—26.7
± SD Δ		9.8	0.316	350	15.4	0.019	328	9.6	103.4
t		0.51	1.5	1.0	2.0	0.53	0.08	2.4	0.63
p <		0.7	0.2	0.4	0.1	0.7	0.9	0.1	0.6

* Abbreviations: Pa_{CO_2}, arterial carbon dixoide tension; otherwise as in Table I.

TABLE III

Effect of hypercapnia on splanchnic hemodynamics and sulfobromophthalein removal during nitrous oxide-succinylcholine anesthesia *

Subject	Period	Pa_{CO_2}	BSP	EHBF	MBP	SVR	SBV	E%	C_{BSP}
		mm Hg	*mg%*	*mg/min*	*mm Hg*	*units*	*ml*		*ml/min*
1	E	33	1.39	1,340	91	0.068	1,210	37.1	230
	H	61	1.74	1,200	105	0.088	920	31.2	180
2	E		0.72	1,640	120	0.073		67.9	600
	H		1.17	1,290	107	0.083		53.8	370
3	E	44	2.28	780	93	0.119	590	36.4	160
	H	56	3.31	630	130	0.206	750	30.2	100
4	E	38	0.63	2,110	103	0.049	1,260	57.5	590
	H	50	0.73	1,540	106	0.069	890	43.7	320
5	E	41	1.03	1,070	91	0.085		70.7	390
	H	59	0.96	1,140	120	0.105		56.0	330
6	E	32	1.53	1,170	122	0.104		38.3	250
	H	57	1.54	800	112	0.140		39.6	170
7	E	36	3.13	520	84	0.162	910	40.0	120
	H	61	2.85	550	97	0.176	470	29.1	90
8	E	38	1.43	1,430	98	0.069	560	24.2	220
	H	54	1.36	1,350	96	0.071	600	19.5	170
9	E	36	1.75	470	80	0.170	1,100	65.2	170
	H	51	2.11	490	83	0.167	920	43.1	110
10	E	39	1.14	1,710	77	0.045	1,530	29.6	270
	H	54	0.87	1.030	92	0.089	1,130	50.3	270
11†	E	40	0.83	980	101	0.103	12,90	80.7	450
	H	54	0.70	890	97	0.109	760	78.7	400
12†	E	44	1.09	1,120	80	0.071	660	55.4	350
	H	56	0.87	1,330	102	0.077	740	50.6	370
13†	E	39	2.38	590	89	0.151	570	43.1	150
	H	63	2.24	450	81	0.180	540	63.7	160
Mean	E	38.3	1.486	1,148	94.5	0.098	968	49.7	304
± SD		3.8	0.404	515	14.8	0.043	357	18.4	168
Mean	H	56.3	1.572	976	102.2	0.120	772	45.3	234
± SD		4.2	0.872	382	14.1	0.050	201	16.6	118
Mean Δ		18.0	0.086	—172	—7.6	0.0231	—196	—4.4	—70
± SD		5.9	0.389	256	16.2	0.024	244	13.3	89
t		10.7	0.80	2.42	1.7	3.36	2.54	1.2	2.83
p <		0.001	0.5	0.05	0.2	0.01	0.05	0.3	0.02

* Abbreviations: E, eucapnia; H, hypercapnia. Other abbreviations as in Tables I and II.
† The period of hypercapnia preceded the period of eucapnia in these subjects.

and hypercapnia under the conditions of these studies.

Effect of anesthesia and hypercapnia (Tables II and III)

The arterial carbon dioxide tension was not changed by anesthesia alone in four subjects (Table II). The mean Pa_{CO_2} in 12 subjects during eucapnia (E, Table III) was 38 mm Hg, whereas that during hypercapnia was 56 mm Hg, a change ($p < 0.001$) of + 47 per cent. The relatively constant deviations from the expected values of 40 and 60 mm Hg were largely explicable on the basis of systematic errors in infrared CO_2 monitoring attributable to nitrous oxide (15).

Arterial oxygen saturation during anesthesia

was maintained at or above control values in all cases, with the exception of Subject 5 in whom values of 91 and 89 per cent were obtained by the Nahas method. Subsequently this patient was found to have an arterial oxygen saturation of 93 per cent at rest, as determined by Van Slyke analysis. The data obtained were consistent with those of the 12 other subjects and were included in the final summation.

Mean arterial blood pressure increased 13 mm Hg on the average in 6 subjects (Table II) following the induction of anesthesia, and increased 8 mm Hg on the average in 13 anesthetized subjects (Table III) folowing the elevation of Pa_{CO_2}. Striking rises occurred in isolated instances. However, neither average change was statistically significant.

Estimated hepatic blood flow and the splanchnic vascular resistance did not change significantly with the induction of anesthesia. The estimated hepatic blood flow fell in 9 of the 13 subjects when the arterial P_{CO_2} rose. The mean fall in all 13 was 178 ml per mniute, or 15.4 per cent, a probably significant reduction ($p < 0.05$). The MBP increased in each subject in whom EHBF rose during hypercapnia. For the entire group, SVR in arbitrary units rose 22.4 per cent ($p < 0.01$). This value increased in 8 subjects and was unchanged (less than 10 per cent variation) in 5. It fell in none.

Splanchnic blood volume did not change significantly on the average with anesthesia prior to hypercapnia. Individual changes were erratic in direction and extent. With elevation of Pa_{CO_2} the mean SBV fell from 983 to 772 ml, a change of 211 ml or 21.4 per cent ($p < 0.05$). The SBV fell in 6 patients, rose in 1, and was unchanged (less than 10 per cent variation) in 3.

Sulfobromophthalein clearance was not significantly altered by anesthesia. During hypercapnia, however, the mean C_{BSP} fell from 302 to 234 ml per minute, a reduction of 22 per cent ($p < 0.02$). The data in Table III for Subjects 11, 12 and 13 suggest that the impairment of BSP removal by high carbon dioxide levels is not rapidly reversible.

DISCUSSION

No statistically significant alteration in splanchnic hemodynamics was observed in these subjects during anesthesia with thiopental and nitrous oxide maintained by controlled respiration after intravenous administration of succinylcholine. This finding appears to be at variance with the results of previous studies in which hepatic blood flow was observed to decrease during anesthesia with cyclopropane (1), thiopental-nitrous oxide (1) or thiopental-cyclopropane with *d*-tubocurarine paralysis (2). Superimposition of hypercapnia upon the anesthetic state resulted, however, in a statistically significant increase in splanchnic vascular resistance in association with a reduction in estimated hepatic blood flow except in those instances in which the blood pressure rose. Since hypercapnia is difficult to detect clinically without direct measurement, and since it may have occurred in the previous work owing to the use of larger doses of thiopental or to the combination of curare and cyclopropane, the earlier findings may be attributable—at least in part—to undetected hypercapnia. Hypoxia may have also been present, especially when nitrous oxide was used. This uncertainty points up the need for precise monitoring and control of respiratory homeostasis during physiological investigation in anesthetized animals or man.

In the present study repeated determinations of carbon dioxide and oxygen concentrations in the blood provided a reliable basis for the appraisal of the response to anesthesia and hypercapnia separately, without need to allow for the possibility of hypoxia. Nevertheless, the findings must be interpreted with caution. Narcosis or light anesthesia may interfere with circulatory reactivity without changing the pattern of adjustment at rest. Thus, a striking susceptibility to orthostatic hypotension develops following the intravenous administration of morphine or thiopental in doses too small to affect the arterial pressure in the recumbent position (16, 17). The interference with autonomic regulation implicit in this phenomenon might be expected, on the one hand, to minimize reactions that depend primarily upon normal autonomic mediation, and on the other hand, to predispose to excessive nonspecific responses that may dominate the results. Every precaution was taken throughout the course of this study to avoid shifts in position, vascular compression or environmental factors that might have had a disturbing influence. The character

of the changes in the systemic circulation observed during hypercapnia strongly suggests that the anesthetic state did not, in fact, interfere, and that the data may be assessed in terms of the action of carbon dioxide alone.

Coincident with the rise in average arterial P_{CO_2} from a control level of 38 to 56 mm Hg, the arterial pressure tended to rise, the pulse rate to quicken, and the skin of the face and torso to flush. Anesthesia may have diminished the response, and it is also possible that absence of hyperventilation had a moderating effect. In any case, both vasoconstriction and vasodilation were obviously demonstrable, presumably indicating continued operation of the alleged cerebral and local reactions to carbon dioxide. Within the splanchnic vasculature vasoconstriction predominated. Calculated splanchnic vascular resistance increased in almost every subject even when arterial pressure rose sufficiently to maintain or increase splanchnic blood flow. Under these circumstances, the change in resistance may be construed with some confidence as evidence of active arteriolar constriction. The reduction in circulating splanchnic blood volume could also be attributed to this response.

The pressure responsible for the filling of the splanchnic venous reservoir depends in the first approximation upon the splenic, mesenteric, and hepatic arteriolar resistances. Constriction of mesenteric and splenic arterioles would lower the portal venous pressure with a resultant automatic shift of blood into the systemic circuit. Hypercapnia has been reported, however, to raise portal venous pressure and to increase the intestinal venous tone in the experimental animal (18). It may be inferred, therefore, that a similar change occurs in man and that splanchnic venoconstriction is largely responsible for the decrement in volume.

The vasoconstrictive response to hypercapnia appears to be mediated through the central nervous system. Several investigators (19–21) have shown that an increased tension of carbon dioxide in the blood perfusing splanchnic blood vessels elicits a constrictive response only if the splanchnic nerve supply is intact. Following denervation, an elevated Pa_{CO_2} regularly induces dilatation. Evidently this reflex pathway, unlike those concerned in adjustment to posture and pain, is relatively unaffected by neuromuscular blockade and general anesthesia—at least at the levels that were employed in this study. Whether high concentrations of carbon dioxide could overcome the opposing reflex impulses and dilate the vessels by direct action remains unsettled, although Brickner, Dowds, Willitts and Selkurt (22) have shown that mesenteric vasodilation may occur in the intact animal breathing gas mixtures that contain more than 8 per cent carbon dioxide.

The fall in sulfobromophthalein clearance (often in association with diminished extraction) may have been due to direct action of carbon dioxide upon the hepatic parenchymal cells. More work is required to define this phenomenon in terms of the mechanisms of BSP transfer (23) and to evaluate the role of additional side effects of carbon dioxide. Among these, the release of catecholamines may be particularly important, since epinephrine and norepinephrine may be active both in complicating the hemodynamic changes and in affecting hepatocellular activity. Although thiopental anesthesia alone does not increase the plasma concentration of catecholamines, other agents, such as cyclopropane, do (24). It is possible, therefore, that hypercapnia may elicit a more profound or a totally different reaction during anesthesia by drugs other than thiopental-nitrous oxide. Just as hypercapnia may make it difficult to unravel the changes produced by anesthesia, so anesthesia may complicate the understanding of hypercapnia.

SUMMARY

Estimated hepatic blood flow (sulfobromophthalein method), splanchnic blood volume (regional dilution method), calculated splanchnic vascular resistance, and mean arterial pressure did not change significantly or consistently during light general anesthesia with thiopental and nitrous oxide, maintained by mechanically controlled artificial respiration following neuromuscular blockade with succinylcholine. Hypercapnia (Pa_{CO_2}, 56 mm Hg on the average) under these circumstances resulted in a statistically significant increment in mean calculated splanchnic vascular resistance. Estimated hepatic blood flow decreased, remained unchanged or rose depending upon the behavior of the arterial pressure. The average value for the circulating splanchnic blood

volume also decreased significantly. These changes were ascribed to a combination of arteriolar and venous constriction. Sulfobromophthalein clearance and extraction by the liver, although unaffected by anesthesia, decreased significantly during hypercapnia.

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REFERENCES

1. Habif, D. V., Papper, E. M., Fitzpatrick, H. F., Lowrance, P., Smythe, C. McC., and Bradley, S. E. The renal and hepatic blood flow, glomerular filtration rate, and urinary output of electrolytes during cyclopropane, ether, and thiopental anesthesia, operation, and the immediate postoperative period. Surgery 1951, **30**, 241.
2. Shackman, R., Graber, I. G., and Melrose, D. G. Liver blood flow and general anaesthesia. Clin. Sci. 1953, **12**, 307.
3. Brecher, G. A. Venous Return. New York, Grune and Stratton, 1956.
4. Beecher, H. K., and Ford, C. Anesthesia: Fifty years of progress. Int. Abstr. Surg. 1955, **101**, 105.
5. Cullen, S. C. Clinical practice with muscle relaxants. Anesthesiology 1959, **20**, 530.
6. Frumin, M. J., and Lee, A. S. J. A physiologically oriented artificial respirator which produces N_2O–O_2 anesthesia in man. J. Lab. clin. Med. 1957, **49**, 617.
7. Bradley, S. E. Structural and functional parameters of the normal splanchnic circulation. Proc. Third World Congress of Cardiology, 1958, pp. 239–248.
8. Bradley, S. E., Ingelfinger, F. J., Bradley, G. P., and Curry, J. J. The estimation of hepatic blood flow in man. J. clin. Invest. 1945, **24**, 890.
9. Bradley, S. E., Marks, P. A., Reynell, P. C., and Meltzer, J. The circulating splanchnic blood volume in dog and man. Trans. Ass. Amer. Phycns 1953, **66**, 294.
10. Holaday, D. A. An improved method for multiple rapid determinations of arterial blood pH. J. Lab. clin. Med. 1954, **44**, 149.
11. Holaday, D. A., and Verosky, M. Improved micromanometric methods for the analysis of respiratory gases in plasma and whole blood. J. Lab. clin. Med. 1956, **47**, 634.
12. Singer, R. B., and Hastings, A. B. An improved clinical method for the estimation of disturbances of the acid-base balance of human blood. Medicine (Baltimore) 1948, **27**, 223.
13. Nahas, G. G. Spectrophotometric determination of hemoglobin and oxyhemoglobin in whole hemolyzed blood. Science 1951, **113**, 723.
14. Smythe, C. M., and Gilmore, J. P. The effect of morphine on hepatic blood flow in the normal anesthetized dog. J. Pharmacol. exp. Ther. 1955, **114**, 221.
15. Bergman, N. A., Rackow, H., and Frumin, M. J. The collision broadening effect of nitrous oxide upon infrared analysis of carbon dioxide during anesthesia. Anesthesiology 1958, **19**, 19.
16. Papper, E. M., and Bradley, S. E. The hemodynamic effects of intravenous morphine and pentothal sodium. J. Pharmacol. exp. Ther. 1942, **74**, 319.
17. Drew, J. H., Dripps, R. D., and Comroe, J. H., Jr. Clinical studies on morphine. II. The effect of morphine upon the circulation of man and upon the circulatory and respiratory responses to tilting. Anesthesiology 1946, **7**, 44.
18. Alexander, R. S. The participation of the venomotor system in pressor reflexes. Circulat. Res. 1954, **2**, 405.
19. Mohamed, M. S., and Bean, J. W. Local and general alterations of blood CO_2 and influence of intestinal motility in regulation of intestinal blood flow. Amer. J. Physiol. 1951, **167**, 413.
20. Gollwitzer-Meier, K., and Bohn, H. Über die venoconstrictorische Wirkung der Kohlensäure und ihre Bedeutung für den Kreislauf. Klin. Wschr. 1930, **9**, 872.
21. Fleisch, A. Venomotorenzentrum und Venenreflexe. I. Mitteilung. Pflüg. Arch. ges. Physiol. 1930, **225**, 26.
22. Brickner, E. W., Dowds, E. G., Willitts, B., and Selkurt, E. E. Mesenteric blood flow as influenced by progressive hypercapnia. Amer. J. Physiol. 1956, **184**, 275.
23. Bradley, S. E. The excretory function of the liver. Harvey Lect. 1960, **54**, 131.
24. Price, H. L., Linde, H. W., Jones, R. E., Black, G. W., and Price, M. L. Sympatho-adrenal responses to general anesthesia in man and their relation to hemodynamics. Anesthesiology 1959, **20**, 563.