Splanchnic Circulation During Nitrous Oxide Anesthesia and Hypocarbia in Normal Man

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Circulatory effects of nitrous oxide-*d*-tubocurarine anesthesia with hyperventilation were studied in healthy, young men. Cardiac output, mean arterial blood pressure, and splanchnic blood flow were measured. During anesthesia and hyperventilation with normal P_{CO_2} (CO_2 added to the inspired gases), splanchnic vascular resistance was elevated significantly and the blood flow reduced, but oxygen consumption was unaltered from control values. Cardiac output and total peripheral resistance were unchanged. When P_{aCO_2} was not maintained at the normal level, total peripheral resistance and splanchnic vascular resistance were reduced and the respective blood flows augmented compared with the normocarbic period. However, the demand of the splanchnic viscera for oxygen was increased out of proportion to the increase in flow. It is suggested that the nitrous oxide-curare-hyperventilation technique may be a poor choice for patients with marginal levels of splanchnic blood flow.

CARBON DIOXIDE TENSION profoundly affects vascular tone in both conscious and anesthetized individuals. Controlled studies of the splanchnic circulation made during halothane anesthesia and during nitrous oxide anesthesia have demonstrated that hypercarbia has marked effects on blood flow.[1,2] However, hypocarbia produced by artificial hyperventilation of the lungs is a more frequent accompaniment of many techniques of general anesthesia. In particular, the nitrous oxide-relaxant technique commonly utilizes hyperventilation and predictably causes respiratory alkalosis. Since hypocarbia can increase vascular resistance and decrease blood flow in other vascular beds, *e.g.*, cerebral, it seemed important to ascertain the effect of hypocarbia on the splanchnic circulation in man during nitrous oxide anesthesia.

Methods

Six healthy male volunteers to whom the procedures had been explained thoroughly on two prior visits to the laboratory were studied. Their ages ranged from 21 to 30 years. Each reported in the early morning following a 12-hour fast. Under local anesthesia a 100 cm. No. 7 Lehman catheter was introduced into an antecubital vein, and with the aid of image intensification fluoroscopy, advanced into a right hepatic vein. In addition, a Cournand needle was placed into a femoral artery and a 60 cm. radiopaque polyethylene catheter was inserted into an antecubital vein and advanced into the superior vena cava (SVC). The electrocardiogram was recorded from plate electrodes on the skin, using a Grass recorder.

The splanchnic blood flow was measured by the Fick principle using indocyanine green dye (ICG).[3,4] A 20 mg. priming dose, also used for cardiac output determination, was followed by a sustaining infusion of dye (stabilized with human albumin) from a constant infusion pump through the SVC catheter. The infusion rate was approximately 1 mg./minute and the concentration of ICG in the arterial plasma averaged 1 mg./liter. Twenty minutes were allowed for stabilization of arterial ICG concentration; sampling of arterial and hepatic venous blood then began. Three observations of flow were made during a 30-minute period in each of three study phases (control, nitrous oxide anesthesia with normal P_{aCO_2}, and ni-

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trous oxide anesthesia with reduced Pa_{CO_2}). Following induction of anesthesia the rate of ICG infusion was decreased by one-third to compensate for reduced dye clearance by the liver.

Femoral arterial and hepatic venous pressures were monitored with Statham strain gauges and the Grass recorder. Splanchnic vascular resistance was calculated as perfusion pressure (mean arterial minus mean venous) divided by blood flow rate. Hematocrit was determined in capped hematocrit tubes spun at 2,300 *g* for 30 minutes. Arterial P_{O_2}, P_{CO_2}, and *p*H were measured using an IL electrode assembly. Cardiac outputs were determined in duplicate using a 5 or 10 mg. injection of ICG, a Waters' cuvette densitometer, and a Harvard constant withdrawal pump.

When control measurements were completed, anesthesia was induced with thiopental (2 mg./kg. body weight) given intravenously, followed by N_2O–O_2 in a 2:1 ratio from a nonrebreathing circuit. *d*-tubocurarine (0.7 mg./kg.) was given intravenously and the trachea was intubated with a cuffed Magill tube. Additional *d*-tubocurarine was given as needed, the total dose ranging from 61 to 72 mg. in the six subjects. Mechanical ventilation was maintained using a Bird Mark IV assistor controller. Respiratory rate and tidal volume were kept constant throughout the anesthetic period. Tidal volume was monitored with a Wright respirometer. Esophageal temperature was measured with a thermistor and body temperature was maintained at the initial level (±0.5° C.) with an electric heating blanket. End tidal P_{CO_2} was measured using a L-B-1 CO_2 analyzer, pressurized with nitrous oxide to eliminate the crossover effect.

A delay of 30 to 45 minutes (average 39) ensued before establishment of a steady state of anesthesia with respect to end-tidal P_{CO_2}, pulse rate, and arterial pressure, following which the measurements made during the control period were repeated twice more. The two study periods during anesthesia were comparable except for levels of end-tidal and arterial P_{CO_2}. During one period, hypocarbia was produced by hyperventilation, whereas during the other CO_2 was added to the inspired gas mixture to produce normocarbia. The order in which the normocarbic and hypocarbic periods were studied was randomized.

The results were analyzed statistically using Student's *t* test.

Results

Results are summarized in tables 1 and 2. Table 1 lists the general conditions and findings; table 2 lists the data pertaining to the splanchnic circulation. The three observations of splanchnic blood flow made at ten-minute intervals in each of the three study periods have been averaged. In brief, the administration of nitrous oxide-oxygen-curare with intermittent positive-pressure ventilation and normocarbia was accompanied by significantly increased splanchnic vascular resistance and perfusion pressure. Splanchnic blood flow and clearance of ICG diminished. There was no significant change in oxygen consumption or P_{CO_2} in hepatic venous blood. Cardiac output, heart rate, and total peripheral resistance were unaltered.

When CO_2 was not added to the inspired nitrous oxide-oxygen mixture, hypocarbia (mean $Pa_{CO_2} = 18$ mm. Hg) developed. However, there was no significant change in perfusion pressure, clearance of ICG, or splanchnic blood flow when compared with the normocarbic period. Splanchnic vascular resistance was decreased ($P < 0.05$) though still elevated when compared with the control period, and the P_{O_2} of hepatic venous blood also was reduced ($P < 0.01$). Oxygen consumption was increased in five of six cases, but the change for the group was only of borderline significance statistically ($P < 0.08$). Total peripheral resistance was reduced, and cardiac output increased, in three of the four individuals for whom these data were obtained.

Discussion

The marked increase in splanchnic vascular resistance observed in the present study was unexpected, since Epstein and his co-workers [1] previously had examined the splanchnic circulation during nitrous oxide anesthesia and found no change provided that Pa_{CO_2} remained normal. Differences between their study and ours with respect to the initial conditions and to anesthetic technique might account for the discrepancy. The earlier workers gave mor-

TABLE 1. Respiratory and Circulatory Effects of Nitrous Oxide-curare-hyperventilation Anesthesia

Subject	Heart Rate			Cardiac Output			TPR			Pa_{CO_2}			$\dot{V}_E$	
	C	N	H	C	N	H	C	N	H	C	N	H	N	H
1	76	67	68							39	41	29	9.2	9.2
2	70	68	71							40	36	16	15.6	15.6
3	73	81	88	6.24	5.76	8.16	13.6	14.8	9.8	40	34	14	18.9	18.9
4	77	99	95	5.86	8.52	8.73	17.0	11.7	12.0	39	36	16	18.2	17.5
5	76	90	92	4.68	5.86	6.73	19.2	17.0	12.2	38	38	17	16.5	17.3
6	54	64	54	6.12	5.96	5.88	11.4	14.3	15.3	34	37	18	16.9	16.8
Mean	71	78	78	5.73	6.53	7.38	15.3	14.5	12.3	38	37	18	15.9	15.9
Sign.		No	No		No	No		No	No		No	***	No	No

C = during control period; N = during anesthesia and normocarbia; H = during anesthesia and hypocarbia.

Heart rate = beats per minute; cardiac output = liters per minute; TPR = total peripheral persistence, mm Hg/liter per minute; Pa_{CO_2} = mm Hg; $\dot{V}_E$ = respiratory minute volume during anesthesia in liters per minute.

Perfusion pressure = mean arterial minus mean hepatic venous pressure; SVR = splanchnic vascular resistance (splanchnic perfusion pressure in mm Hg/splanchnic blood flow in liters per minute); SBF = splanchnic blood flow in liters per minute; $\dot{Q}_{O_2}$ = Splanchnic oxygen consumption in ml per minute; CICG = ICG clearance of plasma in ml per minute; Pv_{O_2} = oxygen tension of hepatic venous blood in mm Hg.

* P 0.05.

** P 0.01.

*** P 0.001.

Sign. = Significance referred to column at left.

phine and scopolamine for preanesthetic medication, used succinyldicholine instead of *d*-tubocurarine to produce muscular flaccidity, and studied male and female patients rather than healthy, young men. In addition, the initial level of splanchnic blood flow was significantly higher in our subjects than in theirs. However, the most important difference between their study and ours is the manner in which the subjects' lungs were ventilated. Epstein *et al.* maintained a normal Pa_{CO_2} with a "servorespirator" in which end-expired carbon dioxide tension automatically regulated the inflating pressure. We, on the other hand, intentionally hyperventilated our subjects, producing tidal volumes which averaged 1.3 l. and minute volume approximating 15 l./minute. It is well recognized that the motions of the diaphragm have important effects upon the hepatic circulation.[5] In addition, the peripheral pooling of blood caused by elevated airway pressure is capable of inducing vasoconstriction reflexly by way of the barostatic mechanisms[6,7] and this could further increase splanchnic vascular resistance.

Another possible cause for splanchnic vasoconstriction observed during anesthesia and normocarbia in the present study is that oxygen consumption was diminished. Since the tissues (except muscle) have no significant capacity for storing oxygen, the steady-state oxygen consumption is identical with oxygen demand. It is well recognized that local metabolic demand regulates vascular resistance in many areas. However, the change in oxygen requirement (about 20 per cent) is far too small to account for either the increase in resistance or the reduction in blood flow.

Therefore, the question arises whether hyperventilation of the magnitude employed in this study can reduce splanchnic blood flow sufficiently to interfere with tissue oxygenation. We have no direct information on this point; however, the oxygen tension in hepatic venous blood was unaffected by hyperventilation at normal Pa_{CO_2}.

The same cannot be said for the situation during hypocapnea, for the shift from normal to reduced Pa_{CO_2} increased splanchnic oxygen demand by 50 per cent while increasing splanchnic blood flow only half as much. From the standpoint of availability of oxygen in rela-

TABLE 2. Splanchnic Circulation and Metabolism Before and During Nitrous Oxide Anesthesia

Subject	Perf. Pres.			SVR			SBF			Q_{O_2}			CICG			Pv_{O_2}		
	C	N	H	C	N	H	C	N	H	C	N	H	C	N	H	C	N	H
1	81	88	88	37	103	87	2.17	0.86	1.01	76	70	103	0.97	0.45	0.52	41	24	22
2	89	96	78	65	104	82	1.38	0.92	1.04	73	59	59	0.57	0.40	0.45	41	40	29
3	79	85	83	33	82	35	2.52	1.06	2.41	58	49	134	0.70	0.40	0.52	46	49	38
4	99	109	98	34	44	41	2.93	2.46	2.40	144	75	112	0.96	0.91	0.81	35	51	38
5	88	91	84	54	117	103	1.63	0.78	0.84	43	40	47	0.62	0.34	0.38	49	40	32
6	73	80	81	43	125	112	1.71	0.65	0.73	59	59	70	0.63	0.34	0.36	45	32	28
Mean	85	92	85	44	96	77	2.06	1.12	1.40	76	59	88	0.74	0.47	0.51	43	39	31
Sign.		**	No		**	*		**	No ($P=0.09$)		No	No ($P=0.08$)		**	No		No	**

See footnotes to Table 1 for explanation of symbols.

tion to demand, this situation is the least favorable of those studied by us though there still was no evidence for splanchnic hypoxia. The measured reduction in hepatic venous oxygen tension (table 2) merely reflected the Bohr effect, and the oxygen content of the hepatic venous blood was not reduced during hypocarbia. The increase in oxygen demand during hypocarbia probably underlies the increase in splanchnic blood flow which was observed. However, the effect itself is inexplicable in terms of mechanism and, to our knowledge, has not been reported previously.

The general circulatory changes induced by hypocarbia—that is, increased cardiac output and reduced peripheral resistance—have been reported previously[8, 9] and are well documented. Our findings, however, are dissimilar to those of Prys-Roberts and his coworkers[10] who found that cardiac output and Pa_{CO_2} were correlated directly. We have no explanation for this discrepancy; however, we consider their "eucapnic" level (48 mm. Hg) to be hypercarbic.

We can now compare the effects of seven different anesthetic techniques in relation to splanchnic oxygen uptake and blood flow. Table 3 summarizes the results which have been obtained previously by ourselves and others.[2, 11, 12] It can be seen that spinal anesthesia resembles halothane anesthesia in its action on the splanchnic circulation whereas the nitrous oxide-curare-hyperventilation technique resembles cyclopropane anesthesia. Although there is a similar change in splanchnic blood flow in all cases, splanchnic vascular resistance is little changed in the former group and greatly increased in the latter. In addition, the variations in oxygen consumption are not nearly as marked as are the changes in splanchnic blood flow, implying that even a reduced blood flow will provide adequate oxygenation. However, these studies were conducted in healthy, young individuals. It might well be that in the patient with marginal circulatory adequacy in the splanchnic viscera, an anesthetic technique which does not increase vascular resistance would be preferable.

TABLE 3. Comparison of Effects of Anesthetic Techniques on Splanchnic Circulation and Oxygen Consumption

Anesthetic Technique	Ventilation	Pa_{CO_2}	Percentage Change in			Reference
			SVR	SBF	Q_{O_2}	
High spinal	Spontaneous	Normal	+ 7	−29	− 2	11
Halothane	Spontaneous	Normal	−11	−23	−10	2
	Controlled	Normal	+ 9	−33	−18	2
Cyclopropane	Spontaneous	Normal	+72	−30	− 5	12
	Controlled	Normal	+61	−27	− 6	12
Nitrous oxide-curare-hyperventilation	Controlled	Decreased	+74	−32	+16	Present study
Nitrous oxide-succinylcholine	Controlled	Normal	+ 5	+11		1

Summary

1. The splanchnic circulation and metabolism were studied in six normal male volunteers during anesthesia with nitrous oxide, *d*-tubocurarine, and hyperventilation. Pa_{CO_2} was controlled by adding CO_2 to the inspired gases.

2. During hyperventilation with normal Pa_{CO_2} splanchnic vascular resistance more than doubled and blood flow was reduced by a corresponding amount; however, the demand of the splanchnic viscera for oxygen was unaltered.

3. When Pa_{CO_2} was permitted to fall (CO_2 not added) there was a marked increase in oxygen demand but only a small increase in blood flow, and the splanchnic vascular resistance remained significantly elevated above normal.

4. With respect to its effects on the splanchnic circulation, the nitrous oxide hypocarbic technique resembles cyclopropane, whereas halothane resembles spinal anesthesia.

5. It is concluded that the nitrous-oxide-*d*-tubocurarine-hyperventilation technique may be a poor choice for clinical use in patients with marginal levels of splanchnic circulation.

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Anesthesia

INTRAUTERINE HEPATITIS Fetal erythroblastosis frequently is treated by intrauterine transfusion. Donor cells are injected into the peritoneal cavity of the unborn, where they are absorbed. Probably it was inevitable that serum hepatitis would be transmitted in this way. A case is presented in which a fetus, transfused on four occasions, was delivered by cesarean section after meconium was found in amniotic fluid. The infant, jaundiced at birth, was given four exchange transfusions in the first four days of life, but died on the 16th day of life. Autopsy revealed active hepatitis. Neither the mother nor other recipients of the donor blood developed hepatitis. (*Mandelbaum, B., and Brough, J. A.: Hepatitis Following Multiple Intrauterine Transfusions, Obstet. Gynec. 30: 188 (Aug.) 1967.*)