Can General Anesthetics Produce Splanchnic Visceral Hypoxia by Reducing Regional Blood Flow?

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Thirty-five normal adult males were studied before and during either cyclopropane or halothane anesthesia in an effort to learn whether these agents cause a critical reduction in the availability of oxygen to the splanchnic viscera. Although hepatic blood flow was markedly reduced during the inhalation of either agent, splanchnic oxygen utilization was not consistently affected, and restoration of blood flow to the initial level gave no clear evidence that an oxygen debt has been incurred during the period of reduced flow. Clearance of indocyanine green dye was reduced in proportion to blood flow when either cyclopropane or halothane was inhaled, but restoration of flow rate to normal did not correct the deficiency in clearance. "Excess" lactate was produced by the splanchnic viscera during cyclopropane but not during halothane anesthesia. This effect could be abolished by a beta adrenergic blocking drug. Therefore, "excess" lactate apparently resulted not from splanchnic ischemia but from metabolic action associated with increased sympathetic nervous activity in these viscera.

It has been suggested [1] that splanchnic ischemia occurring during anesthesia may result in regional hypoxia. Since both cyclopropane [2] and halothane [3] have recently been shown to cause substantial reductions in hepatic blood flow, we considered it important to determine whether the administration of either anesthetic could reduce oxygenation to the point of cellular functional deterioration. For this purpose healthy young men were studied before and during anesthesia. The results are reported and discussed below.

Methods

The subjects were 36 normal male volunteers who reported in the early morning following a twelve hour fast. Under local anesthesia a Cournand needle was inserted in the right femoral artery, a Rochester needle into a forearm vein, and a no. 7 Lehman catheter into an antecubital vein. The Lehman catheter was inserted into a right hepatic vein under fluoroscopic guidance. The ECG was recorded from 24 gauge needle electrodes.

For measurement of splanchnic blood flow, a 15 mg. dose of indocyanine green (ICG) was injected through the Rochester needle, followed by a twenty minute priming infusion containing the dye (stabilized with human albumin), at a constant rate approximating 4 mg./minute. The concentration of ICG in arterial plasma averaged 1 mg./liter during infusion. Preanesthetic medication, 0.1 mg. atropine sulfate/25 pounds body weight, was administered intravenously during the priming period and oxygen inhalation was begun; sampling of femoral arterial and hepatic venous blood followed. In a typical experiment three observations of flow were made during a 30 minute period in each of three study phases (control, anesthesia, and anesthesia with augmented blood flow). Flow was increased dur-

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ing cyclopropane anesthesia by the slow (10 minutes) intravenous administration of a small dose of hexamethonium (10–12 mg.), of phentolamine (15 mg.), or of dibenzylene (20 mg.). During halothane inhalation flow was increased either by head-down tilt or by adding carbon dioxide to the inspired mixture. The calculations involved in estimating flow are detailed by Bradley and his co-workers [4] and Caesar and his associates.[5] Corrections for blank density were made when necessary.[6] Following the induction of anesthesia the rate of ICG infusion was reduced by ½ in order to compensate for reduced ability of the liver to extract the dye during the administration of cyclopropane or halothane. No subject at any time extracted less than 45 per cent of arterial ICG in a single hepatic passage. The mean extraction during anesthesia was 69 per cent and the maximum 82 per cent.

Femoral arterial and hepatic venous pressures were sensed by Statham strain gauges and recorded on a Grass polygraph. Vascular resistance was calculated as perfusion pressure (mean arterial minus mean venous) divided by blood flow rate. Hematocrit was determined in capped Wintrobe tubes spun at 2,300 g. (at the tip) for 30 minutes. P_{CO_2} and P_{O_2} of arterial and venous blood were measured by means of an Instrumentation Laboratories electrode assembly Model no. 102. End-expired P_{CO_2} was estimated using a Beckman LB-1 microcatheter cell gas analyzer. The oxygen content of arterial and hepatic venous blood samples containing cyclopropane was determined by the method of Orcutt and Waters; [7] otherwise, that of van Slyke and Neill [8] was employed. Arterial and hepatic venous lactate, pyruvate, and glucose concentrations were determined by enzymatic methods.[9, 10, 11] "Excess" lactate (XL) was estimated according to the formulae of Huckabee.[12, 13]

Upon completion of the control measurements, anesthesia was induced in the 35 subjects with either cyclopropane or halothane in oxygen. Intubation of the trachea was accomplished with the aid of succinyldicholine (60–80 mg. intravenously). A thermistor probe was inserted in the esophagus. Following this, the inspired tension of cyclopropane was adjusted to produce an end-expired concentration of 16–20 per cent as determined by the method of Linde and Price; [14] inspired halothane tension was fixed at a level ranging from 1.3 to 1.9 per cent in various subjects (with a median value of 1.5 per cent) by means of a calibrated Fluotec vaporizer. When adequate respiration ($P_{A_{CO_2}} < 45$ mm. of mercury) obtained during anesthesia, it was allowed to continue; otherwise reoperation was controlled or assisted by intermittent inflation of the lungs under positive pressure. Following the establishment of a steady state of anesthesia with respect to $P_{A_{CO_2}}$, anesthetic concentration, heart rate, and systemic arterial pressure, the measurements made during the control period were repeated. The first study period during anesthesia began 40 to 60 minutes following induction. In all subjects the esophageal temperature was maintained at the normal level (±0.5° C.), external heat being supplied when necessary by means of a thermostatically controlled electric blanket which covered the subject's body.

Further treatment of the subjects differed as follows: In nine subjects, after a 30 minute interval, a third 30 minute period of study served to check the stability of the changes observed. In sixteen subjects the measurements already detailed were performed for a third time following restoration of the hepatic blood flow rate to normal. Unsuccessful attempts to restore flow were encountered in four additional subjects. In six subjects anesthetized with cyclopropane, the effects of the beta adrenergic blocking drug 1-isopropylamino-3-(1-naphthyl-oxy) 2-propanol hydrochloride (ICI 45,520) * were ascertained. This agent was given intravenously in a dose ranging from eight to ten milligrams over a period of ten minutes. Finally, in one additional conscious subject, 500 ml. of 10 per cent glucose in water were infused intravenously.

The data were analyzed for statistical significance by means of paired Student's t test.[12]

Results

The effects of anesthesia in individual subjects are given in table 1. Summaries and the results of special maneuvers are contained in tables 2–5.

* Supplied by Ayerst Laboratories.

TABLE 1. Effects of Cyclopropane and Halothane on Splanchnic Blood Flow and Metabolism

Cyclopropane

Subject	Arterial L/P		Venous L/P		A-V XL		P_{VO_2}		Q_{O_2}		CICG		$\dot{Q}H$		SVR	
	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E
02	15.2	16.9	14.3	19.9	−0.033	0.127	87	75	63	69	650	458	1,570	1,570	46	62
03	17.6	15.0	14.3	10.4	−0.194	−0.255	42	40	92	65	655	423	1,990	1,080	40	92
04	14.2	12.7	10.1	10.9	−0.197	0.151	61	64	61	49	516	363	1,380	940	64	120
05	15.7	15.8	14.7	23.9	−0.051	0.238	55	40	66	63	615	406	1,540	1,180	54	78
06	14.6	13.0	15.0	18.9	0.012	0.157	54	48	63	49	762	384	1,480	870	49	107
07	11.7	11.2	12.0	8.2	−0.067	−0.328	47	41	75	72	759	341	1,610	780	46	101
08	11.4	12.6	8.5	12.3	−0.341	−0.028	86	93	46	48	843	615	1,490	1,380	37	33
09	11.0	10.6	10.5	14.5	−0.035	0.178	45	53	91	61	785	595	1,950	2,040	32	42
11	11.7	11.6	6.3	15.7	−0.757	0.497	56	45	49	55	772	386	1,540	750	51	129
14	10.5	13.4	9.4	19.0	−0.206	0.488	52	52	48	44	525	348	1,150	805	75	135
19	11.4	12.2	10.2	13.1	−0.036	0.031	46	42	42	57	560	384	1,170	850	71	126
25	11.0	11.5	11.0	12.8	−0.006	0.172	43	50	72	83	724	534	2,030	1,460	45	71
26	8.8	9.8	8.4	10.8	−0.012	0.036	49	42	69	100	840	536	1,920	1,240	44	75
28	9.3	10.1	13.1	18.0	0.091	0.357	40	47	64	61	522	342	1,070	1,380	68	56
30	17.6	17.8	(12.00)	25.0	(−0.082)	0.231	79	66	74	34	696	492	2,690	1,840	40	40
31	7.9	9.2	8.3	15.2	0.013	0.230	67	52	70	98	940	638	2,040	1,780	40	40
33	10.9	11.0	12.9	12.9	0.040	0.091	55	41	75	56	645	380	1,540	1,200	56	79
34	13.5	12.7	11.3	13.2	−0.064	0.013	50	37	91	62	720	395	1,640	1,050	54	104
35	19.3	15.8	17.8	22.8	−0.045	0.159	95	51	49	60	763	656	2,450	1,440	35	58
36	10.0	7.0	9.9	9.8	−0.002	0.116	68	39	50	57	913	453	2,080	970	41	92

Halothane

Subject	Arterial L/P		Venous L/P		A-V XL		P_{VO_2}		Q_{O_2}		CICG		$\dot{Q}H$		SVR	
	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E
12	10.0	12.3	11.2	9.4	0.036	−0.220	60	63	68	53	755	395	1,620	1,130	54	47
13	11.9	15.6	9.5	19.5	−0.159	0.114	57	46	100	55	842	455	2,120	1,030	45	68
16	16.5	13.6	15.5	16.8	−0.030	0.082	54	43	72	79	816	572	1,740	1,280	56	38
17	15.5	14.9	10.9	11.0	−0.235	−0.215	58	40	58	39	785	460	1,770	1,380	51	48
18	8.6	12.4	10.6	14.6	0.242	0.298	52	38	60	69	769	492	1,580	1,060	62	58
20	10.2	11.5	10.4	14.0	0.006	0.088	40	45	67	75	562	515	(1,760)	1,830	46	29
21	10.0	12.8	11.0	12.2	0.041	−0.022	50	47	67	71	733	532	1,720	1,250	47	43
22	8.6	11.1	8.0	9.2	−0.022	−0.062	47	42	81	72	740	490	1,640	1,180	46	51
23	11.5	12.2	10.1	11.3	−0.074	−0.071	52	46	73	79	945	740	2,420	2,240	35	29
24	10.9	10.6	8.2	11.4	−0.086	0.030	58	55	114	63	946	580	2,320	1,740	36	30

Means and Significance

	Arterial L/P		Venous L/P		A-V XL		P_{VO_2}		Q_{O_2}		CICG		$\dot{Q}H$		SVR	
Cyclopropane:	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E
Means	12.66	12.49	11.50	15.66	−0.099	0.133	59	51	66	62	711	457	1,717	1,232	50	83
Sig.		Ins.		<0.001		<0.01		<0.02		Ins.		<0.001		<0.001		<0.001
Halothane:																
Means	11.38	12.80	10.53	12.93	−0.028	0.002	53	47	76	66	789	523	1,869	1,412	48	44
Sig.		<0.10		<0.05		Ins.		<0.05		Ins.		<0.001		<0.01		Ins.

Effects of Anesthesia. In brief, the administration of cyclopropane was accompanied by a statistically significant increase in venous lactate/pyruvate (L/P) ratio and arterio-venous (A-V) "excess" lactate, while venous oxygen tension, ICG clearance and blood flow were diminished. The reduction in blood flow was attributable to a marked increase in splanchnic vascular resistance. Oxygen consumption (flow rate times arteriovenous oxygen content difference) was not affected. Arterial L/P ratios and arterial "excess" lactate were unchanged.

The findings during halothane inhalation were qualitatively and quantitatively similar, with two exceptions. First, the reduction in flow was caused not by increased vascular resistance, but by arterial hypotension. Second, venous L/P ratio and A-V excess lactate were markedly elevated in only one case (13), and

for a group as a whole these two quantities were, respectively, slightly elevated and unaltered (table 1).

Effects of Increased Duration of Anesthesia. In order to determine the effects of various maneuvers (*e.g.*, ganglionic blockade) upon blood flow and metabolism, it was necessary to establish those changes that would occur in the absence of any intervention. In a series of nine subjects the mere passage of time (½–¾ of an hour) had no consistent effect upon any of the measured variables. Data are given in detail for venous L/P ratios and A-V "excess" lactate during cyclopropane anesthesia (table 2).

Effects of Increased Blood Flow. The administration of hexamethonium, phentolamine, or dibenzylene to subjects anesthetized with cyclopropane without exception diminished splanchnic vascular resistance. Provided that no marked decrease in mean arterial blood pressure occurred simultaneously, splanchnic blood flow, therefore, was elevated. Increased flow occurred in eight of 10 subjects to whom these drugs were given. Pertinent results are shown in the first half of table 3. The effect of restoring blood flow to normal was to increase oxygen consumption by ten per cent and ICG clearance by 15 per cent. Dye clearance was not restored to the control level. Venous L/P ratio, A-V excess lactate, and venous oxygen tension were inconsistently affected. In six subjects the rate of oxygen con-

TABLE 2. Effect of Time Alone on Arterio-Venous XL and Venous L/P Ratio

No.	A-V XL		Lv/Pv	
	1	2	1	2
36	0.118	0.113	9.8	11.2
35	0.204	0.269	22.8	25.5
34	0.077	±0.000	13.2	9.4
33	0.051	0.221	12.9	16.2
32	0.230	0.146	16.9	18.0
30	0.311	0.189	25.0	16.1
Means	0.165	0.156	16.75	16.04
Sig.		Ins.		Ins.

TABLE 3. Effects of Increased Splanchnic Blood Flow on Metabolism During Anesthesia

Cyclopropane

Subject	Lv/Pv			A-V XL			Q̇H			Q̇o₂			CICG		
	C	E	↑F	C	E	↑F	C	E	↑F	C	E	↑F	C	E	↑F
7	12.0	8.2	12.8	0.015	−0.339	−0.100	1,610	789	1,460	74	72	75	759	341	493
9	10.5	14.5	16.0	−0.035	0.178	0.108	1,950	2,040	2,300	91	61	71	785	595	600
11	6.3	15.7	7.8	−0.757	0.497	−0.716	1,540	750	1,350	49	55	61	772	386	459
19	10.2	13.1	14.5	−0.036	0.031	0.020	1,180	850	1,070	42	57	70	750	384	495
26	8.4	10.8	9.2	−0.012	0.036	−0.005	1,920	1,280	1,750	69	100	105	840	536	594
28	13.1	18.0	14.8	0.091	0.357	0.122	1,080	1,380	2,350	64	61	56	522	342	461
29	(12.0)	23.6	21.1	(−0.082)	0.262	0.142	1,650	1,180	1,340	93	54	56	675	456	482
30	(12.0)	25.0	16.1	(−0.082)	0.231	0.109	2,690	1,840	2,500	74	34	51	696	492	532
Mean	10.56	16.11	14.0	−0.112	0.169	−0.018	1,703	1,263	1,765	70	62	68	701	442	511
Sig.			Ins.			Ins.			$P<0.01$			$P<0.05$			$P<0.05$

Halothane

Subject	Q̇H			Q̇o₂			CICG		
	C	E	↑F	C	E	↑F	C	E	↑F
18	1,580	1,060	1,740	60	69	101	769	492	644
21	1,720	1,250	1,510	67	57	64	733	532	525
22	1,610	1,180	1,630	81	72	78	740	490	533
23	2,420	2,240	2,790	73	79	79	945	740	735
24	2,320	1,740	1,510	114	65	90	946	580	742
15	2,120	1,030	1,180	100	55	70	812	455	486
23	2,420	2,240	2,680	73	79	80	945	740	770
24	2,320	1,740	1,880	114	65	66	946	565	580
Mean	2,068	1,560	2,210	85	68	79	858	574	627
Sig.			$P=0.05$			$P<0.05$			$P=0.05$

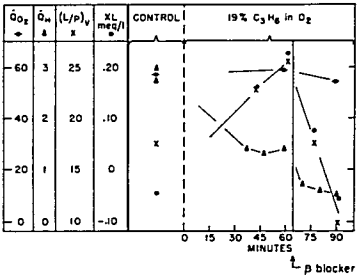

FIG. 1. Effects of beta blockade on splanchnic metabolism. (See text for explanation.)

sumption was measured both at five to ten and at twenty to twenty-five minutes following administration of the blocking drug. Although the rate of oxygen consumption diminished with time in three subjects, it increased in one and remained the same in two, and the effect of time upon this measurement in the group as a whole was statistically insignificant.

In the subjects anesthetized with halothane the effects of increasing blood flow were indistinguishable from those reported above. The data are shown in the lower half of table 3. Since carbon dioxide inhalation was usually employed to augment flow in these subjects, it was necessary to assume that the changes observed were caused by the increase in flow and not directly by the increase in P_{CO_2}. The correctness of this assumption was supported by the observation that, irrespective of the level of P_{CO_2}, neither oxygen consumption nor ICG clearance increased unless accompanied by increase in flow.

Effects of Beta Adrenergic Blockade. In six subjects anesthetized with cyclopropane the effects of the beta blocking drug 1-isopropyl-amino-3-(1-naphthyl oxy)-2-propanol hydrochloride (ICI 45,520) were observed. This administration of this agent was followed by a marked reduction in splanchnic blood flow, venous oxygen tension and venous L/P ratio and the disappearance of A-V "excess" lactate. Oxygen consumption and arterial L/P ratio were unaffected. A representative example of the results is shown in figure 1 and the individual measurements are reproduced in table 4.

The Calculation of "Excess" Lactate. Table 5 gives mean values for the measured concentrations from which L/P ratios and A-V "excess" lactate were calculated. The formula for the latter is shown at the bottom. It can be seen that, of the three terms used to compute A-V "excess" lactate, only the arterio-venous differences in pyruvate concentration contributed to the result observed during cyclopropane anesthesia. Thus, the term Lv L_A averaged −0.128 mEq./liter during the control period and −0.135 mEq./liter during anesthesia; the L_A/P_A ratios were essentially equal before and during anesthesia (12.7 and 12.4); but the quantity $-(Pv - P_A)$ increased from +0.004 when oxygen alone was

TABLE 4. Circulatory and Metabolic Effects of I.C.I. 45,520 During Cyclopropane Anesthesia

Subject	L_A/P_A		Lv/Pv		A-V XL		$\dot{Q}H$		$\dot{Q}_{O_2}$		P_{VO_2}	
	Δ	Δ & B	Δ	Δ & B	Δ	Δ & B	Δ	Δ & B	Δ	Δ & B	Δ	Δ & B
31	9.2	11.4	15.2	9.8	0.230	−0.060	1,780	660	98	79	52	27
32*	17.5	17.5	18.0	17.3	0.066	−0.039	2,550	1,810	45	30	117	78
33	9.6	11.0	16.2	14.8	0.261	0.179	1,290	730	56	51	41	30
34	12.7	10.3	13.2	10.6	0.013	0.012	1,050	530	62	64	37	27
35	14.2	14.2	25.5	17.3	0.224	0.075	1,440	610	60	54	51	28
36	8.7	8.8	11.2	7.3	0.111	−0.110	970	520	57	64	39	27
Means	11.98	12.20	16.55	12.85	0.150	0.057	1,498	810	63	57	56	36
Sig.		Ins.		$P<0.05$		$P=0.02$		$P<0.01$		Ins.		$P<0.01$

* This individual was febrile following termination of the study, and was probably undergoing a "tubing reaction" during the measurements reported. His data are included for the sake of completeness. Eliminating them does not affect the statistical significance of the results.

TABLE 5. Effects of Anesthetics on L/P Ratio and Excess Lactate

Agent	Lactate		Pyruvate		L/P Ratio		A-V XL
	Arterial	Venous	Arterial	Venous	Arterial	Venous	
Control	0.734	0.616	0.060	0.056	12.66	11.50	−0.099
Cyclopropane	0.961	0.826	0.079	0.054	12.49	15.66	0.133
Control	0.651	0.504	0.059	0.048	11.38	10.53	−0.028
Halothane	0.787	0.644	0.066	0.051	12.80	12.93	0.002

Arterio-venous $XL = (L_V - L_A) - (P_V - P_A)\frac{L_A}{P_A}$.

Concentrations of lactate and pyruvate are expressed in millimoles per liter.

breathed to +0.025 during cyclopropane and oxygen inhalation. In other words, the 0.23 mEq./liter increase in "excess" lactate observed during anesthesia was caused entirely by the increase in the pyruvate extraction ratio. The increase in venous L/P ratio observed during cyclopropane anesthesia occurred for the same reason. Finally, when the rates of uptake of pyruvate and lactate were computed (by multiplying A-V concentration difference and flow rate) it was found that the rate of pyruvate extraction was significantly increased ($P < 0.02$) while that of lactate was unchanged. In contrast, the administration of halothane did not significantly alter the value of any of the three terms used to calculate A-V "excess" lactate.

Effects of Infusion of Glucose. In considering possible explanations for the increase in uptake of pyruvate, it was noted that cyclopropane anesthesia was associated with a 30 per cent increase in the concentrations of both pyruvate and lactate in arterial blood. Administration of halothane had much less effect, particularly upon the pyruvate concentration. It was reasoned, therefore, that the cause of the increase in pyruvate extraction (and thus of the appearance of "excess" lactate and augmented venous L/P ratio) during cyclopropane anesthesia could represent nothing more than differing rates of approach to diffusion equilibrium during the transient of change to a new arterial concentration of both substances. Although *a priori* this explanation seemed unlikely, particularly in view of the persistence of the changes (table 2), a direct test was deemed desirable.

Accordingly, in one conscious subject the arterial concentrations of lactate and pyruvate were increased by the intravenous administration of 500 ml. of 10 per cent glucose in water. The results, which are graphed in figure 2, indicate that the procedure had an effect upon the calculations of A-V "excess" lactate, venous L/P ratio, lactate uptake and pyruvate uptake which were all directionally opposite from those observed during cyclopropane administration.

LEGENDS FOR TABLES AND FIGURES

L/P	Lactate-pyruvate ratio.
A-V XL	Splanchnic arterio-venous "excess" lactate (mEq./liter).
P_{VO_2}	Oxygen tension of hepatic venous blood (mm. of mercury).
$\dot{Q}_{O_2}$	Oxygen consumption (ml./minute).
CICG	ICG clearance from plasma (ml./minute).
$\dot{Q}H$	Hepatic blood flow (ml./minute).
SVR	Splanchnic vascular resistance (mm. of mercury/liter of flow/minute).
Sig.	Significance of difference from control (expressed as probability).
C	During control period.
E	During experimental (anesthesia) period.
↑F	During increased blood flow and anesthesia.
Δ	During cyclopropane anesthesia.
Δ + B	During cyclopropane anesthesia and beta blockade.
( )	Median control value used because the measured value was significantly beyond the normal range.

Splanchnic Glucose Production. Since increased glucose liberation is one of the signs of hepatic anoxia,[16] the rate of production of this substance was estimated in two subjects before and during the administration of cyclo-

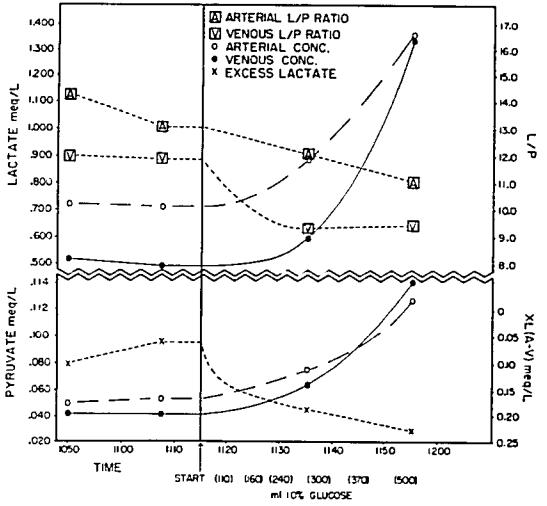

FIG. 2. Effects of glucose infusion on L/P ratios and excess lactate. The numerals are negative in the lower right-hand ordinates. (See text for explanation.)

propane. Although both exhibited a marked increase in splanchnic vascular resistance and an increase in the glucose concentration in arterial blood, the rate of splanchnic glucose liberation was reduced during anesthesia (from 300 to 165 mg./minute in subject 6 and from 120 to zero mg./minute in subject 35).

Discussion

"Excess" Lactate and Lactate/Pyruvate Ratios. The findings reported here raise more questions than they answer. As noted, the increase in arterio-venous "excess" lactate and venous L/P ratio during cyclopropane anesthesia were both caused by increased extraction of pyruvate and not by an accelerated release of lactate. It could be supposed that the increase in splanchnic extraction of pyruvate (and not that of lactate) represented only a passive consequence of changed arterial concentrations of these substances. This possibility was tested by infusing glucose, thereby increasing concentrations both of lactate and pyruvate. No evidence in support of this supposition was obtained.

Ganglionic and alpha blocking drugs were incapable, in the subjects studied, of consistently decreasing either "excess" lactate or elevated venous L/P ratios, while a beta-blocker reduced both. Further, the former group increased blood flow while the latter decreased it, thus divorcing the metabolic changes from any dependence upon blood flow. Finally, the administration of the beta-blocker did not, despite its effects upon vascular resistance and blood flow, cause a consistent reduction in splanchnic oxygen consumption. This observation apparently rules out the possibility that the reduction in "excess" lactate production caused by beta blockade depends upon shunting of blood flow away from areas of marginal circulatory adequacy, thereby diminishing the liberation of lactic acid into, or the uptake of pyruvate from the blood stream. Any such shunting should have reduced oxygen consumption as well.

Oxygen Consumption. This was not consistently reduced by either anesthetic (table 1). However, the ability of increases in blood flow to elevate calculated oxygen consumption during both cyclopropane and halothane anesthesia apparently means either that a systematic error was present (*i.e.*, that arterio-venous oxygen differences or flow rates were over-

estimated) or that the delivery of oxygen to the respiring tissues was flow-limited. Since the agency used to increase the rate of splanchnic blood flow caused no consistent change in the blood oxygen content, it is unlikely that a systematic error in this measurement was introduced. On the other hand, the increase in flow rate was associated with a small but consistent reduction in the concentration of ICG in arterial blood which averaged ten per cent. Since the estimation of hepatic blood flow by the Fick principle is subject to greater uncertainties during changing plasma concentrations of the dye, it is possible that some of the alteration of flow, and hence of calculated oxygen consumption, may be an artifact of the method. Assuming that the splanchnic viscera were in or near diffusion equilibrium with the previously maintained arterial level of ICG, a sudden reduction in that level would have the effect of causing these tissues to release ICG until a new equilibrium was established. Such transient desaturation could lead to an underestimation of the equilibrium A-V concentration difference and a corresponding overestimation of the increase in flow rate. Thus the apparent increase in oxygen consumption might not be real; it is definitely within the error of the methods employed.[5]

Assuming that an increase in oxygen consumption actually did occur, the fact that consumption remained constantly elevated over a thirty minute period following the injection of sympatholytic drugs does not support the notion that this increase in metabolic rate represented the repayment of an oxygen debt. Presumably, such repayment would begin as soon as flow was restored and would soon be completed, after which oxygen consumption would decline. Moreover, the decrease in blood flow caused by the beta blocker was far greater than that produced by cyclopropane alone, yet it did not consistently reduce oxygen consumption. This observation makes it difficult to argue that the relatively modest reduction in flow caused by the anesthetics could have interfered seriously with oxygenation.

A final possibility is that increased blood flow caused an increment in metabolic demand by delivering more substrate.

ICG Clearance. This was markedly and equally reduced both by cyclopropane and by halothane, to a level approximating 65 per cent of the control value. Although increased flow caused a significant increment in clearance during the administration of both anesthetics, clearance was restored only to 72 per cent of the initial level on the average. Since flow rate may have been overestimated (as discussed above), some of this increase in clearance may be spurious. In any case, most of the reduction in clearance during anesthesia was apparently caused by metabolic actions of cyclopropane and halothane, and not by ischemia.

These various observations can be reconciled only when it is admitted that the calculation of either L/P ratios or excess lactate can be a fallible tool in the diagnosis of hypoxia. There is extensive evidence for this: only a few notes need be included here. It has previously been pointed out that the blood L/P ratio, which is believed by some [12] to reflect the intracellular DPN/DPNH ratio, differs from the predicted value by three orders of magnitude, that there are at least two intracellular pools of DPN which are not in diffusion equilibrium with each other, and that the entire reaction is *p*H dependent.[17] This last fact may explain our observation that respiratory acidosis can produce an increase in arterial "excess" lactate when the change in *p*H is not taken into account. Other recent observations show that either acidosis or alkalosis can increase the L/P ratio.[18] Whether this dependence on *p*H explains the difference between our results and those of Greene,[19] who found increased arterial "excess" lactate during cyclopropane anesthesia, but who did not monitor P_{CO_2}, cannot be answered at this time.

We are not suggesting that the metabolic changes occasioned by cyclopropane inhalation are either nonexistent or meaningless. The immediate point is that the present findings probably do *not* represent what they seem to, namely anaerobic metabolism caused by splanchnic ischemia. Instead, they suggest that administration of cyclopropane increases splanchnic pyruvate consumption via some mechanism which can be interrupted by beta adrenergic blockade.

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Summary and Conclusions

(1) In a series of normal human volunteers the inhalation of either cyclopropane (18 per cent) or halothane (1.5 per cent) diminished hepatic blood flow, indocyanine green dye clearance and venous oxygen tension without affecting splanchnic oxygen consumption. Cyclopropane reduced blood flow by increasing regional vascular resistance; halothane did so by reducing systemic arterial pressure.

(2) Cyclopropane, but not halothane, caused an increase in calculated arterio-venous "excess" lactate production despite the fact that the splanchnic viscera were net consumers of lactate throughout the entire course of study. The increase in arterio-venous "excess" lactate was not accompanied by an increase in glucose output, was not duplicated by an infusion of glucose (which raised arterial lactate and pyruvate concentrations), and was not the result of ischemia. It apparently represented a metabolic consequence of increased sympathetic nervous activity.

(3) Restoration of hepatic blood flow to the control level did not restore dye clearance to normal and did not consistently eliminate the production of "excess" lactate. It was attended by a small increase in the apparent rate of oxygen consumption during either cyclopropane or halothane anesthesia.

(4) Convincing evidence that a critical reduction in the oxygen supply to the splanchnic viscera was caused by either anesthetic was not obtained by the procedures and methods used in this study.

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