STUDIES ON MYOCARDIAL METABOLISM. III. CORONARY BLOOD FLOW, MYOCARDIAL OXYGEN CONSUMPTION AND CARBOHYDRATE METABOLISM IN EXPERIMENTAL HEMORRHAGIC SHOCK [1, 2]

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A series of reports have been published on the cause of irreversibility from hemorrhagic shock (1–5). Wiggers and Werle (2, 3), on the basis of pressure and volume curves obtained from dogs during various phases of hemorrhagic shock, suggested the possibility that the deterioration of myocardial expulsive power contributed to circulatory failure and that this myocardial depression contributed to the reappearance of circulatory failure during the normovolemic phase. It was assumed that the trigger mechanism for myocardial depression was a decrease in the coronary flow with resulting myocardial ischemia. Opdyke and Foreman (6) indicated that during the period of hypotension, the actual coronary flow was seriously curtailed, providing ample opportunity for myocardial changes. Immediately following reinfusion, however, the coronary flow appeared adequate.

Several studies have indicated the existence of general tissue anoxia in shock (7, 8). Thus, anoxia manifests itself in shock in a state of metabolic acidosis, which is at least partially the result of an increase in blood lactate (9, 10). Simultaneously, the blood levels of pyruvate and glucose increase (11, 12). A shift toward anaerobic metabolism in impending or progressive shock is further suggested by an increase in the ratio of lactate to pyruvate in the blood (11). The studies of McShan, Potter, Goldman, Shipley, and Meyer (11) suggested that a steady progressive depletion of high energy phosphate compounds and of glycogen occurs during the impending stage of traumatic shock. Greig and Govier in studying the changes in intermediary metabolism in hemorrhagic shock found a decrease in the cocarboxylase content of tissues of dogs in shock and in anoxic anoxia (13). These authors believed that under these conditions cocarboxylase is dephosphorylated, resulting in a breakdown of cocarboxylase into thiamin and phosphate. This appears to be in line with the work of Ochoa who found in *in vitro* work that in many tissues under anaerobic conditions cocarboxylase is enzymatically destroyed (14). Greig also found changes in cozymase (D.P.N.) in muscle liver and brains after hemorrhage and De Turk and Greig reported diminished ability of tissues to metabolize amino acids (15, 16).

This report deals with a study of changes in coronary flow and myocardial oxygen consumption in experimental hemorrhagic shock and with the effect of these changes on the myocardial metabolism of glucose, pyruvate, and lactate.

MATERIAL AND METHODS

The experiments were carried out on a total of 28 dogs anesthetized intravenously with sodium pentobarbital (30 mg. per Kg. weight). A tracheotomy tube was inserted for collection of expired air and to permit the animal to inhale nitrous oxide. A femoral artery was cannulated for withdrawal of arterial blood samples and for the measurement of mean arterial pressures with a mercury manometer. In experiments in which cardiac output as well as coronary flow were determined, two No. 7 birdseye cardiac catheters were inserted into the heart through a single jugular vein. Under fluoroscopic guidance, one was then placed in the pulmonary artery, the other in the coronary sinus. In experiments in which the cardiac output was not determined, a single catheter was introduced in the coronary sinus. All animals were heparinized with 400 units of heparin per Kg. weight, intravenously, with an additional 500 units being given every 30 minutes.

During the control period the dog's mean arterial pressure and the pulse rate were recorded and simultaneous

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samples of coronary vein and femoral arterial blood were collected for the determination of blood concentrations of oxygen, pyruvate, glucose, and lactate. Following this, expired air was collected in a Douglas bag over a time interval of from 3 to 6 minutes. During the collection of expired air, arterial and pulmonary arterial blood were collected. This was followed by determination of coronary blood flow using the nitrous oxide desaturation method previously described (17, 18).

Irreversible hemorrhagic shock was produced by a modification of the method of Wiggers (1). The main difference between the procedure of Wiggers and that employed in this study was to extend the critical period of lowest blood pressure (30 mm. Hg) to 60 minutes. In line with the procedure of Wiggers, oligemic shock was produced as follows: Blood was withdrawn from the femoral artery at the rate of approximately 50 cc. per minute until mean systemic arterial pressures had fallen to 50 mm. Hg. Arterial pressures were then maintained at this level for 90 minutes by withdrawal of small quantities of blood at varying intervals. Following this, the pressure was further lowered to 30 mm. Hg and maintained for 60 minutes at this level by small extractions or infusions of blood.

At the end of the critical period (60 minutes) samples of arterial and coronary vein blood were drawn for analysis of metabolites and the coronary blood flow was again determined. Following this, the normovolemic phase of shock was produced by reinfusing the filtered blood withdrawn previously. In addition, 200 cc. of blood were infused as replacement of blood removed for analytical purposes. After from 15 to 20 minutes to allow equilibration, blood samples were again drawn and the coronary flow was determined. It was assumed that these animals were in the compensatory stage of normovolemic shock.

In order to follow changes in cardiac metabolism at more frequent intervals, three experiments were performed in which blood samples were drawn at 30-minute intervals. Only glucose, lactate, pyruvate, and ketone bodies were determined in these samples and the coronary flow was not measured.

Blood was collected in lightly oiled syringes to which 8 drops of heparin had been added to prevent clotting. Samples were analyzed for oxygen and nitrous oxide on the manometric apparatus of Van Slyke and Neill (19). Carbon dioxide and oxygen in expired air were measured in the Haldane apparatus (20). Blood glucose was determined with the method of Hagedorn and Jensen, using the method of Somogyi to prepare the blood filtrates (21, 22). Pyruvate was determined according to the method of Friedemann and Haugen, using a trichloracetic acid filtrate (23). Lactate was measured with the method of Barker and Summerson (24). Ketones were determined with a modification of the micromethod of Greenberg and Lester (25).

The coronary blood flow per 100 gm. was calculated according to the method previously described (17, 26). Blood flow through the left ventricular muscle was obtained by multiplying blood flow per 100 gm. times left ventricular weight. This was determined by the formula of Herrmann (27) (body weight in Kg. $\times$ 0.0037). Myocardial usage of oxygen and of various foodstuffs was obtained as the product of coronary flow per 100 gm. or per left ventricular weight times the respective myocardial oxygen, glucose, lactate or pyruvate extractions. Cardiac work and mechanical efficiency of the left ventricle were calculated as previously described (17).

For the statistical work-up of the data, paired algebraic differences were recorded for each animal and in each classification for which usable data were available. In each case the "student" t test was applied to test the null hypothesis that the mean difference was zero

$$\frac{(t = (\text{mean } \sqrt{n-1})}{\text{std. deviation}} \quad (28).$$

The probability value "p" was obtained from tables printed elsewhere (28). Sigma expresses the standard deviation and p the probability value.

RESULTS

Hemodynamic studies during oligemic shock

Table I illustrates that the cardiac output declined during the oligemic phase. The average fall was 3443 cc. with a standard deviation of 2311.2 cc. The fall was significant at the 5 per cent level (p of 0.025). The stroke volume also diminished an average of 22 cc. per beat with a standard deviation of 16.69 cc. and a p of 0.025. Both these changes were statistically significant. The large variations of the cardiac output during the control period are probably the result of anesthesia. The fall in cardiac output and stroke volume was primarily a reflection of increased systemic oxygen extraction since the oxygen consumption was not altered. This "stagnant anoxemia" has been repeatedly observed by a series of investigators (29, 30). The rise in systemic arteriovenous oxygen difference was statistically highly significant (p value of 0.005). No significant alterations occurred in the heart rate during hemorrhagic shock (p value of 0.2).

In contrast to the systemic oxygen extraction, the myocardial oxygen extraction showed no significant change during oligemic shock (mean fall of 1.00 vol. per cent sigma of 1.81 and a probability of 0.15). This is in line with the previous observation that changes in myocardial oxygen consumption are brought about by variations in coronary flow and not by alterations in myocardial oxygen extraction (31, 32). The coronary flow

TABLE I

No.	Weight	Card. output *cc.*	Heart rate/ min.	St. vol./cc.	Mean B.P. *mm./Hg*	Systemic O_2 ext. *vol. %*	Cor. O_2 ext. *vol. %*	L.V. work *Kg./met.*	L.V. wt. *gm.*	Cor. resist. *mm. Hg/ 100 gm./ min.*	Hema-tocrit %	Cor. flow *cc./100 gm./min.*	Cor. flow L.V. *cc./min.*	Myoc. O_2. us. *cc./min./ 100 gm.*	L.V. O_2 usage *cc./min.*	En. cost *Kg./met.*	Effi-ciency %
S1A*	13.6	4,860	180	27.0	140	1.7	12.1	9.24	50	.85	—	165	82	20.0	9.9	19.8	46.5
B		760	160	4.8	50	11.1	11.4	.52	50	.41	—	121	60.5	13.8	6.9	13.8	3.7
S2A	19.9	7,090	160	44.3	138	2.6	9.2	13.3	74	.70	—	196	145	18.0	13.3	26.6	50.0
B		860	212	4.1	50	12.0	12.2	.58	74	.83	—	60	44	7.3	5.4	10.8	5.3
S3A	12.8	7,200	140	51.4	140	1.1	9.8	13.7	47	1.1	—	138	60.5	13.7	5.9	11.8	—
B		682	212	3.2	50	9.7	10.8	.46	47	.71	—	70	33	7.6	3.5	7.0	6.6
S4A	15.8	2,110	172	12.3	115	3.5	11.0	3.30	58	.91	—	127	74	14.0	8.1	16.2	20.3
B		428	160	2.7	50	10.3	10.6	.29	58	.60	—	84	49	8.9	5.2	10.4	2.8
S5A	12.6	2,145	160	13.4	170	7.9	12.6	4.96	46	1.15	—	148	68	18.7	8.6	17.2	28.7
C		1,940	130	14.9	90	4.7	10.5	2.40	46	.64	—	142	65	14.9	6.8	13.6	17.7
S7A	16.2	4,270	192	22.2	160	3.5	12.6	9.28	60	.62	—	259	155	32.7	19.5	39.0	23.8
C		3,250	200	16.2	160	6.3	14.6	7.08	60	.71	—	226	136	33.0	19.8	39.6	21.5
S8A	22.0	2,340	148	15.8	140	5.0	14.1	4.46	81	1.19	—	118	96	16.6	13.5	27.0	26.7
C		1,430	104	13.8	115	7.7	10.3	2.24	81	1.35	—	85	69	8.8	7.1	14.2	25.4
S9A	14.6	1,662	140	11.9	110	6.7	15.9	2.49	54	2.20	—	50	27	7.95	4.3	8.6	34.5
C		703	160	4.4	85	13.0	15.3	.81	54	1.55	—	54.5	29	8.30	4.4	8.8	9.8
S12A	16.1	2,500	168	14.9	135	3.4	11.4	4.59	59	.98	44	137	81	15.6	9.2	18.4	25.0
B	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
S12C		1,340	140	9.6	145	5.9	14.3	2.69	59	1.78	48	82	48	11.6	6.9	13.8	19.2
S13A	18.3	4,300	144	29.8	140	2.15	10.25	8.20	68	.85	38	165	112	16.9	11.5	23.0	35.6
B	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
C		1,580	144	11.0	120	4.6	10.5	2.58	68	.81	38	148	101	15.6	10.6	21.2	12.1
S14A	13.6	2,700	126	21.4	125	4.0	12.4	4.59	50	1.10	41	108	54	13.4	6.7	13.4	34.2
B	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
C		800	138	5.8	105	10.9	12.1	1.14	50	1.48	49	71	35	8.6	4.24	8.48	13.5

* A = Control
B = Oligemic shock
C = Normovolemic shock

TABLE I—*Continued*

No.	Weight	Card. output *cc.*	Heart rate/ min.	St. vol./cc.	Mean B.P. *mm./Hg*	Systemic O_2 ext. *vol. %*	Cor. O_2 ext. *vol. %*	L.V. work *Kg./met.*	L.V. wt. *gm.*	Cor. resist. *mm. Hg/ 100 gm./ min.*	Hema- tocrit %	Cor. flow *cc./100 gm./min.*	Cor. flow L.V. *cc./min.*	Myoc. O_2 us. *cc./min./ 100 gm.*	L.V. O_2 usage *cc./min.*	En. cost *Kg./met.*	Effi- ciency %
S15A	14.2	1,810	144	12.6	120	4.6	10.7	2.95	52	.81	32	149	78	15.9	8.3	16.6	17.8
B	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
C		1,450	104	17.8	120	5.9	11.7	2.37	52	1.05	45	114	59	13.3	6.9	13.8	17.2
S16A	13.6	2,420	174	13.9	140	3.7	10.7	4.61	50	.58	35	240	120	25.7	12.8	25.7	14.0
B	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
C		2,310	132	17.5	140	4.7	10.2	4.40	50	1.27	45	111	55	11.3	5.6	11.2	39.2
S17A	13.5	1,935	12.8	15.1	125	4.2	10.9	3.37	50	1.04	38	120	60	13.1	6.5	13.1	25.7
B	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
C		1,325	9.6	13.8	136	5.3	9.1	2.46	50	1.27	51	107	53	9.7	4.8	9.6	39.2
S19A	13.0	2,100	180	11.7	145	4.3	7.2	4.15	48	.67	42	215	103	15.50	7.4	14.8	35.7
B	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
C		970	164	5.9	130	7.7	8.5	2.17	48	2.28	57	57	27	4.85	2.3	46	4.72
S20A	13.0	1,435	180	8.0	140	4.8	9.8	2.73	48	.98	—	142	68	13.9	6.6	13.2	20.7
B		306	160	1.9	35	13.6	13.6	.15	48	.55	—	64	31	8.7	4.2	8.4	1.8
S21A	13.9	1,430	160	8.9	140	6.8	14.5	2.72	52	1.01	—	138	72	20.7	10.4	20.8	12.5
B		427	160	2.6	35	14.1	13.8	.21	52	.64	—	55	29	7.5	4.0	8.0	3.8
S22A	18.0	3,750	168	22.3	125	2.9	10.2	6.39	67	1.04	43	120	80	12.2	8.2	16.4	39.0
B	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
C		1,170	148	7.9	120	9.5	15.9	1.91	67	1.58	53	76	51	120	8.1	16.2	11.8
S23A	20.8	2,060	160	12.9	145	5.3	13.5	4.06	77	1.36	40	107	82	14.5	11.1	22.2	18.3
B	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
C		1,320	160	8.3	155	6.8	15.7	2.79	77	1.81	55	86	66	13.5	10.4	20.8	13.4
S24A	13.7	1,250	140	8.9	155	5.5	13.3	2.64	51	.74	41	210	108	28.0	14.4	28.8	9.2
B	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
C		1,210	134	9.0	80	5.4	10.1	1.32	51	.71	52	112	57	11.3	5.8	11.6	8.8
S25A	14.8	1,210	200	6.1	135	6.2	14.8	2.22	55	1.06	43	127	70	18.8	10.4	20.8	10.7
B	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
C		750	180	4.2	120	11.4	15.8	1.22	55	1.79	60	67	37	10.6	5.9	11.8	10.3

and, therefore, myocardial oxygen usage decreased significantly during oligemic shock (mean fall in oxygen usage of 7.75 cc. with a sigma of 3.08 and a probability of 0.005). In contrast to the systemic circulation, a decrease in coronary flow produced no change in myocardial oxygen extraction.

Changes in left ventricular work and myocardial efficiency observed during oligemic shock are illustrated in Table I and Figure 1. As left ventricular work decreased proportionally more than myocardial oxygen usage, the myocardial efficiency declined. The mean percentage fall in efficiency was − 26.5 per cent with a sigma of 14.5.

The coronary resistance declined during oligemic shock (mean of − 0.302 with a probability of 0.01). This was probably the result of myocardial anoxia which is known to be an effective coronary vasodilator.

Hemodynamic changes during normovolemic shock

Many of the changes observed during the oligemic phase persisted after reinfusion of blood. For example, both cardiac output and stroke volume remained considerably below their control values (decrease in the mean of − 993 cc. and − 4.85 and a sigma of 798.8 and of 6.72, respectively). The probability values were 0.005 and 0.01, respectively. The systemic arteriovenous oxygen difference remained elevated (Table I) (mean of 3.12 with probability of 0.005 and a sigma of 2.11). Although there was considerable rise in systemic blood pressure from levels recorded during oligemia, both coronary flow and myocardial oxygen consumption were still significantly below their control levels (mean difference of − 49 cc. of − 4.9 cc. and sigma of 44.3 and 5.93, respectively) (Table I). This differ-

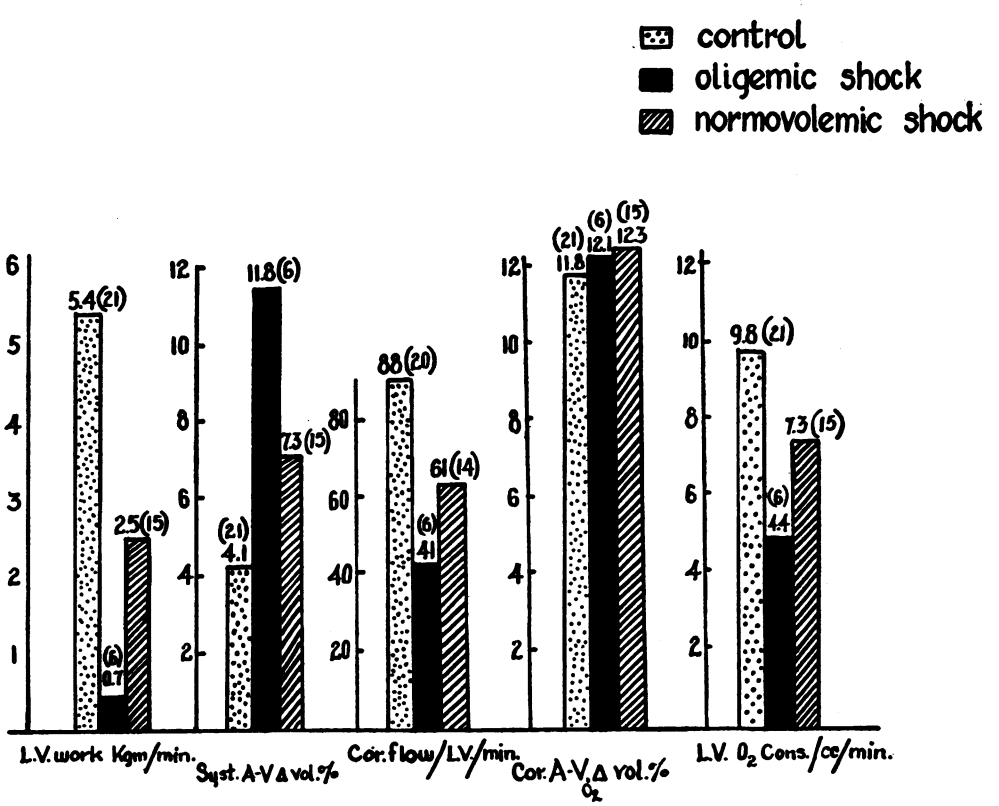

FIG. 1. THE HEMODYNAMIC CHANGES OCCURRING DURING NORMOVOLEMIC AND OLIGEMIC SHOCK

It may be seen that with exception of the coronary arteriovenous oxygen extraction which remains unchanged during the oligemic and normovolemic phase, the left ventricular work, systemic oxygen content, the coronary flow, and the left ventricular oxygen consumption remain below control values during the normovolemic phase.

TABLE II

No.	Glucose			Lactate			Pyruvate		
	Art. concen. *Mgm. %*	Myoc. extra. *Mgm. %*	L.V. usage *Mgm./min.*	Art. concen. *Mgm. %*	Myoc. extra. *Mgm. %*	L.V. usage *Mgm./min.*	Art. concen. *Mgm. %*	Myoc. extra. *Mgm. %*	L.V. usage *Mgm./min.*
S1A	94.3	3.7	3.07	12.9	4.6	3.77	2.1	.85	.70
B	153.0	2.8	1.69	108.0	3.2	1.94	4.2	−.5	−.31
S2A	93.8	0	0	20.0	7.4	10.7	2.5	1.10	1.60
B	206	0	0	38.6	4.9	2.2	5.1	−.69	−.31
S3A	86.1	5.6	3.39	12.2	5.1	3.01	2.3	.96	.59
B	543.0	5.0	1.65	81.3	18.3	6.04	3.4	−.48	−.15
S4A	87.3	2.3	1.70	7.3	1.4	1.04	1.4	.2	.15
B	131.0	13.5	6.62	97.0	6.0	2.94	6.0	−.8	−.24
S5A	94.0	3.5	2.38	10.9	3.7	2.52	1.9	.49	.33
C	83.4	5.0	3.25	113.7	2.1	1.37	4.1	−.49	−.32
S7A	91.5	.5	.78	21.6	9.0	14.0	.12	.06	.09
C	110.1	3.2	4.35	89.5	11.5	15.6	.09	.01	.01
S8A	94.6	1.9	1.82	6.9	2.1	2.01	.16	.02	.02
C	46.7	6.5	4.48	127.5	6.5	4.48	.97	.19	.13
S9A	85.7	1.7	.46	28.1	15.8	4.27	.35	.17	.05
C	213.2	.5	.15	86.4	19.9	5.77	1.10	.26	.07
S12A	92.1	1.6	1.30	5.3	2.5	2.05	.34	.02	.02
B	175.1	7.6	—	132.0	15.5	—	1.8	−.68	—
C	93.6	—	—	125.0	13.5	6.48	2.18	−.41	−.20
S13A	98.0	1.7	1.91	15.9	6.0	6.72	.15	.12	.13
B	411.0	1.0	—	110.0	7.0	—	.35	−.05	—
C	150.1	−2.7	−2.73	83.5	6.5	6.57	.42	.06	.06
S14A	92.7	9.0	4.86	18.2	8.2	4.43	.42	.12	.06
B	97.6	−4.0	—	132.2	10.0	—	1.64	−.60	—
C	177.5	−1.5	−5.25	137.2	14.7	5.14	2.16	−.49	−.17
S15A	96.1	1.8	1.40	12.8	3.4	2.65	.33	.05	.04
B	347.0	10.0	—	106.0	11.0	—	1.5	−.85	—
C	145.0	−3.5	−2.06	106.8	15.1	8.90	1.34	−.13	−.07
S16A	75.1	.8	.96	19.4	4.1	4.92	.53	.04	.05
B	203.9	.3	—	136.5	5.0	—	1.5	−.70	—
C	105.0	−.8	−.44	115.0	1.0	.55	1.7	−.05	−.03
S17A	107.8	1.0	.60	12.5	6.3	3.78	.53	.10	.06
B	73.0	1.8	—	117.0	7.5	—	1.30	−.40	—
C	49.8	2.4	1.27	96.5	11.5	6.10	1.20	−.18	−.09
S19A	101.5	3.1	3.2	10.7	2.0	2.06	.47	.03	.03
B	80.8	3.8	—	85.0	14.1	—	1.0	−.10	—
C	—	—	—	58.9	3.2	.85	1.0	−.35	−.09
S20A	2.0	2.0	1.36	17.2	3.7	2.52	.5	.0	—
B	324	11.0	3.41	178.0	12.5	3.88	1.4	−.85	−.26
S21A	130.8	7.0	5.04	23.0	7.4	5.33	.58	.05	.04
B	343.5	3.5	1.02	182.0	12.5	3.63	2.4	−.63	−.18
S22A	102.0	4.0	3.20	13.9	7.1	5.68	.42	—	—
B	226.2	—	—	73.0	11.7	—	1.5	.22	—
C	109.5	2.5	2.81	53.0	11.0	5.62	1.5	.55	.26
S23A	96.3	1.5	1.23	18.9	3.9	3.20	.55	—	—
B	203	2.0	—	115.0	25.0	—	.96	−.25	—
C	94.0	1.8	1.19	107.5	18.0	11.9	1.4	−.56	−.37
S24A	79.0	3.6	3.89	16.0	5.5	5.94	.44	.05	.05
B	—	—	—	—	—	—	—	—	—
C	30.4	−1.6	−.91	110.2	11.5	6.55	1.20	−.25	−.14
S25A	84.3	6.7	4.69	16.7	6.2	4.34	.65	.07	.05
B	181.5	14.5	—	117.5	34.0	—	.88	.13	—
C	123.5	—	—	88.5	26.0	9.63	.57	—	—

ence was statistically significant (p values of 0.005). The effect of retransfusion of blood on myocardial efficiency was not as uniform. Table I illustrates that left ventricular efficiency fell significantly in eight animals, rose in two and showed only a slight change in the remainder of the animals. Because of this wide scatter there was no significant statistical change (p value of 0.050).

Changes in coronary resistance during normovolemic shock were not uniform. Table I illustrates that the coronary resistance rose above control levels in ten experiments, fell in four and showed no significant change in the remainder. Because of the wide scatter the increase in algebraic difference from the control value was just significant at the 5 per cent level (p of 0.025).

RESULTS OF METABOLIC STUDIES

Oligemic shock

The experimental results are summarized in Table II. There was a statistically highly significant increase in the arterial concentrations of glucose, lactate, and pyruvate during oligemic shock (mean rise of 141, 98 and 1.31 mg. per cent respectively with a sigma of 132, 34 and 1.06, respectively and a probability of 0.005 for all three foodstuffs). Similar observations were made by previous investigators (9–12). It is likely that the metabolic acidosis produced by the increase in arterial lactate was the result of tissue hypoxia.

It has been previously demonstrated that the extraction of glucose by the heart muscle depends on its arterial concentration (33, 34). The data in Table II illustrate that although the rise in arterial glucose concentration often exceeded 300 per cent, the rise in myocardial glucose extraction was small and statistically not significant (mean rise of 1.67, sigma of 5.85, and probability of 0.15) (Figure 2). There was even a slight fall in the mean average value for myocardial glucose usage during oligemic shock (mean fall of −0.028, sigma of 2.87, and probability of .05) (Table II). In five experiments the glucose concentration in coronary vein blood exceeded that of arterial blood, the difference ranging from + .8 to 4.0 mg. per cent of glucose (Table II and Figure 2). These results suggested that the heart in oligemic shock has partially lost its ability to utilize glucose.

In contrast, a rise in arterial lactate concentration was accompanied by a statistically significant increase in myocardial lactate extraction (mean rise of 7.43, sigma of 8.07, and a probability of 0.005 [Table II, Figure 3]). However, because of the accompanying fall in coronary flow, the

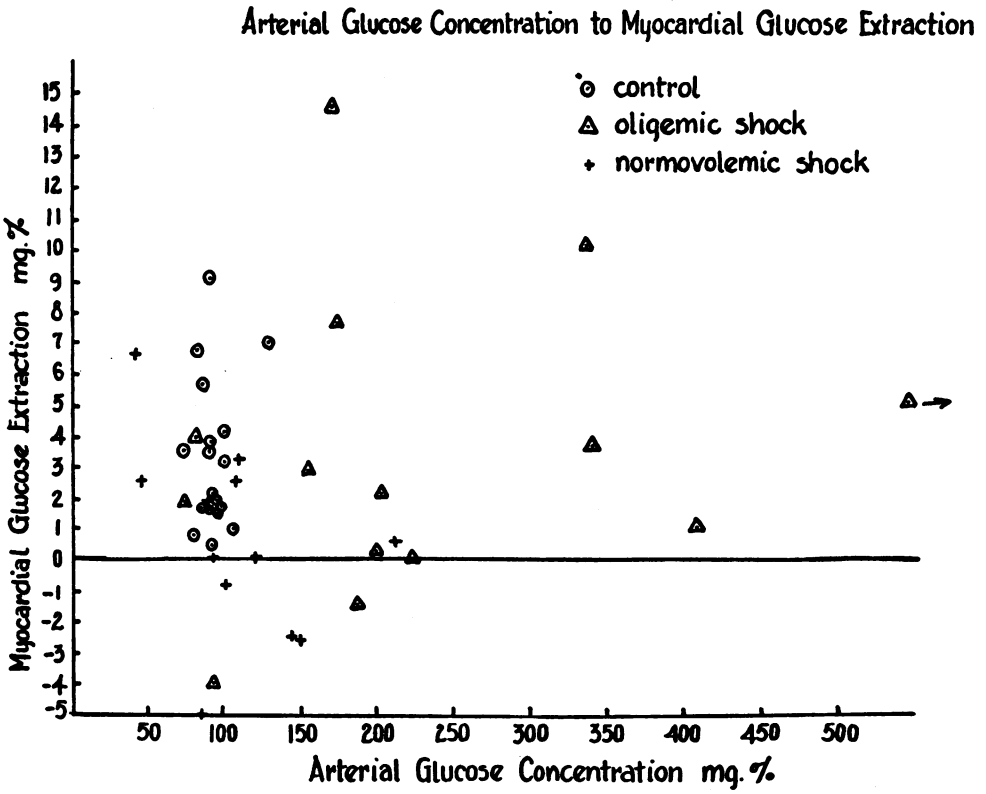

FIG. 2. CHANGES IN ARTERIAL GLUCOSE CONCENTRATION AND MYOCARDIAL GLUCOSE EXTRACTION DURING OLIGEMIC AND NORMOVOLEMIC SHOCK

During oligemic shock the arterial glucose concentration is elevated returning to almost control values during normovolemia. Despite elevated arterial glucose concentration the myocardial glucose extraction is not significantly increased; in some instances glucose concentrations in coronary vein blood even exceed those in arterial blood.

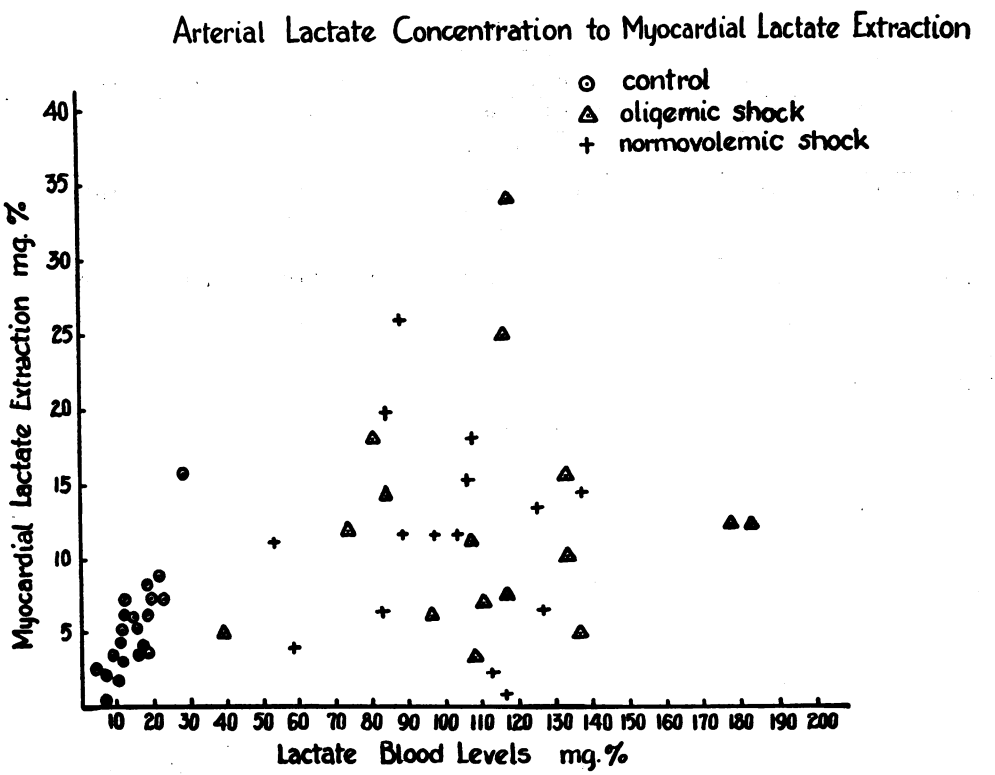

FIG. 3. THE RELATIONSHIP OF ARTERIAL CONCENTRATIONS OF LACTATE TO MYOCARDIAL LACTATE EXTRACTION

Marked elevations in blood lactic acid levels are found in oligemic and normovolemic shock and myocardial lactate extractions are elevated. The lactate concentrations in coronary vein blood never exceed those in arterial blood.

myocardial usage of lactate was not increased (mean fall of -0.39, sigma of 3.92, probability of $\pm .4$). In no instance did the lactate concentration in coronary vein blood exceed that in arterial blood (Table II, Figure 3).

The changes in myocardial pyruvate extraction during oligemic shock are illustrated in Table II and Figure 4. The trend toward a negative myocardial balance of pyruvate is even more conspicuous than in the case of glucose. The pyruvate level in coronary vein blood exceeded that of arterial blood in most instances (Table II and Figure 4). The results were statistically highly significant (the mean fall from the control value was -0.799 mg. per cent with a standard deviation of 0.495 and a probability of 0.005). In contrast to the results of Govier and Greer (35) who found very little change in pyruvate level of arterial blood during oligemic shock, the rise of pyruvate concentration in arterial blood was highly significant (mean rise of 1.32, sigma of 1.06, and a probability value of 0.005). As a result of the negative pyruvate extraction, myocardial usage of pyruvate also became negative (Table II). The difference from the control level was statistically significant at the 5 per cent level (p of 0.025).

Metabolic changes during normovolemic shock

In some instances the trend of metabolic changes, apparent during the oligemic phase, persisted during normovolemic shock. The blood levels of pyruvate and lactate remained significantly elevated above control values (Table II, Figures 3 and 4). (In case of pyruvate a rise of the mean pyruvate level above control of .915 mg. per cent, a probability of 0.005, and a sigma of .602; in the case of lactate, a rise of mean arterial concentration of 84.7 mg. per cent, with a sigma of 24.7, and a probability of 0.005.) In contrast, arterial glucose concentration returned to almost

TABLE III

No.	Time	B.P.	Glucose A. level	Glucose Ext.	Pyruvate A. level	Pyruvate Ext.	Lactate A. level	Lactate Ext.	Ketone bodies A. level	Ketone bodies Ext.	L/P ratio	% Change
						Control						
26	10:15	146	93.4	1.3	.912	.304	9.35	3.42	0.742	−0.074	10.2	0
						Oligemic						
	10:45	50	174	8.8	.589	−.72	35.4	10.00	1.038	0.098	59.6	49.4 *+485*
	11:15	50	198	1.8	1.632	1.005	39.22	10.04	—	—	24.5	14.3 *+140*
	11:45	50	—	—	2.210	0.05	—	—	—	—	—	
	12:15	30	344.2	3.2	2.440	−0.01	82.0	8.8	1.924	0	33.6	23.4 *+228*
	12:45	30	—	—	2.730	0.22	—	—	—	—	—	
						Normovolemic						
	1:30	120	160.8	2.7	2.410	0.39	53.6	9.36	—	—	22.4	12.2 *+220*
	2:00	120	—	—	1.362	0.15	—	—	—	—	—	
	2:30	114	120	1.9	1.511	0.419	—	—	0.092	0.077	—	
	3:00	117	—	—	1.026	0	—	—	—	—	—	
						Control						
27	10:15	125	83.6	1.2	0.269	0.054	5.70	0.97	0.936	0.102	21.2	0
						Oligemic						
	11:10	50	163.6	−1.9	1.612	0.392	52.55	12.70	1.146	.00	32.6	11.4 *+54*
	11:40	50	106.2	0.2	1.200	0	—	—	—	—	—	
	12:10	50	71.1	1.6	1.705	−0.09	—	—	—	—	—	
	12:40	30	34.	0.2	1.720	−0.310	88.35	10.35	1.288	0.676	51.4	30.2 *+143*
	1:10	30	21.5	1.9	1.775	−0.585	—	—	—	—	—	
						Normovolemic						
	1:30	50	25.	1.99	2.280	−0.410	99.5	8.0	0.919	0.184	43.5	22.3 *+105*
						Control						
28	10:45	140	83.7	3.7	0.905	0.40	15.8	6.72	.33	0.094	17.6	0
						Oligemic						
	11:30	50	115.2	6.2	1.701	0.431	—	—	—	—	—	
	12:00	50	138	3.4	2.465	0.535	47.6	16.2	0.613	±0	19.4	1.8 *+10.2*
	12:30	50	126.3	5.3	2.435	0.594	63.2	22.2	0.800	.235	26.0	8.4 *+19.4*
	1:00	30	77.0	−14.	2.200	− .0	—	—	—	—	—	
	1:30	30	56.9	1.5	2.650	−0.340	—	—	0.877	0.219	36.0	18.4 *+104*
						Normovolemic						
	2:00	110	46.0	−3.1	2.505	−.325	109.0	15.5	1.042	0.275	43.5	25.9 *+148*
	2:30	105	40.8	0.2	2.505	−.290	92.	12.0	0.603	−0.164	37.0	19.4 *+11*
	3:00	50	43.4	0.9	3.400	0.120	—	—	—	—	—	
	3:30	80	37.5	−0.1	2.280	0.811	68.7	23.4	1.042	0.329	30.1	12.5 *+7.1*
	4:00	70	40.6	3.6	2.521	0.126	—	—	—	—	—	
	4:30	58	—	—	2.921	0.146	49.6	10.8	0.823	0.056	17.0	.6 *−.3*

control values (p value of 0.15) making the change from control figures statistically insignificant. Similar observations have been made by other investigators (36). It seemed likely that hyperglycemia during oligemic shock was the result of glycogenolysis with depletion of liver glycogen while the fall in blood glucose during the impending or progressive stages was caused by depletion of liver glycogen (36).

The myocardial extraction of pyruvate remained reduced (Table II and Figure 4) (mean of − 0.258, sigma of 0.303, probability of 0.01). This decline in pyruvate extraction from control level during normovolemia was statistically significant at the 5 per cent level. In some experiments, the pyruvate concentration of coronary vein blood still exceeded that in arterial blood (Table II). Apparently, the infusion of blood had in some instances, failed to correct the metabolic disturbance, initiated during the oligemic phase.

The myocardial extraction of lactate which had risen during the oligemic phase remained significantly elevated after retransfusion of blood (mean rise of 5.75 mg. per cent of lactate with a sigma of 5.94 and a probability value of 0.005). As during the oligemic phase, myocardial lactate usage showed no significant deviation from the control (Table II).

Although myocardial glucose extraction and usage during normovolemic shock showed statistically no significant deviation from the control, it is apparent from Table II and Figure 2 that in a number of experiments, the glucose concentration of coronary vein blood still exceeded that of arterial blood (13–16, 24 and Table II).

In three experiments in which metabolic changes were observed at frequent (30-minute)

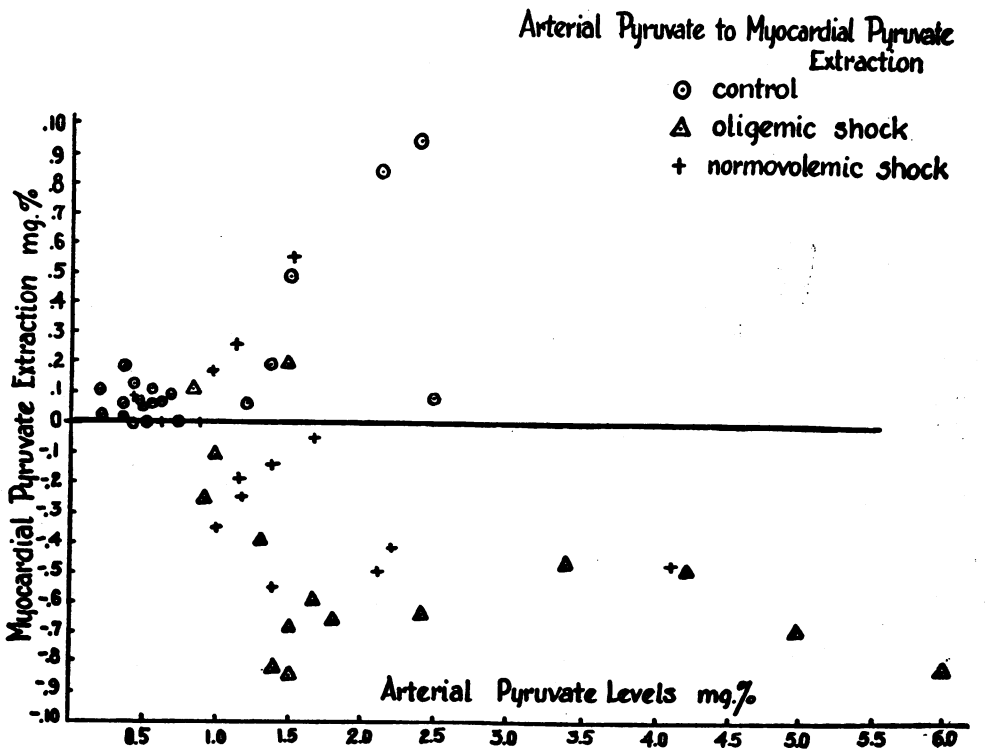

FIG. 4. THE RELATIONSHIP OF ARTERIAL CONCENTRATIONS OF PYRUVATE TO MYOCARDIAL PYRUVATE EXTRACTION

The arterial concentrations of pyruvate are elevated during both oligemic and normovolemic shock. Many of the points fall below the zero line, illustrating that pyruvate concentration in coronary vein blood exceed those in coronary arterial blood in many instances. This "pyruvate reversal" is present during both phases of shock.

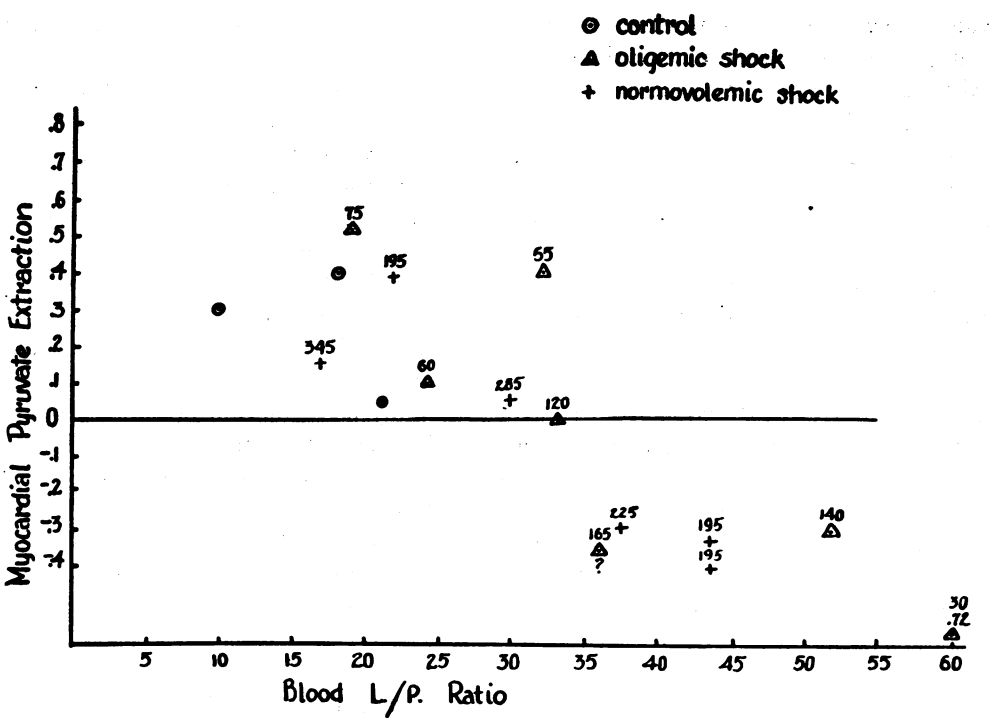

FIG. 5. ILLUSTRATION OF AN INVERSE RELATIONSHIP BETWEEN THE RATIO OF ARTERIAL LACTATE TO PYRUVATE AND THE MYOCARDIAL PYRUVATE EXTRACTION

An increase in the ratio of blood lactate to pyruvate is accompanied by a negative pyruvate extraction (coronary pyruvate concentrations in coronary vein blood exceed those in arterial blood).

intervals, the findings described above could be confirmed. Table III illustrates a rise in arterial glucose, pyruvate and lactate concentration during the oligemic phase, which is partially maintained during normovolemia. The pyruvate concentration in coronary vein blood exceeded that of arterial blood in many instances. Figure 5 illustrates that an inverse relationship existed between the lactate to pyruvate ratio in arterial blood and the myocardial pyruvate extraction. This suggested that the change in myocardial pyruvate metabolism was associated with a shift toward anaerobic metabolism of the organism.

There was also a rise in the arterial concentration of ketone bodies during oligemic and normovolemic shock (Table III). Myocardial extraction of ketones, however, was not greatly altered (Table III).

DISCUSSION

Results on the dynamic changes of hemorrhagic shock confirm the results of previous investigators. A fall in cardiac output and stroke volume observed during the oligemic and normovolemic phase has been noted in experimental hemorrhagic shock by Wiggers and Werle (3) and in clinical shock by Richards (37). The resulting "stagnant anoxemia" also has been repeatedly described (29, 30). The data reported in this paper are in partial agreement with those of Opdyke and Foreman (6). Their experiments indicated that during the period of hypotension, the actual coronary flow was seriously curtailed; immediately following infusion, however, the coronary flow appeared adequate. The results reported in this report illustrate that the coronary flow remains below control levels during the normovolemic phase contributing to the persistence of myocardial ischemia.

It must be stressed that the degree of myocardial anoxia is less severe than that encountered in ventricular fibrillation where the cardiac output is below 10 per cent of normal (38). It is likely that the metabolic response of the myo-

cardium varies with the degree of ischemia. In complete myocardial ischemia, glycolysis occurs and lactate is produced by the muscle. Glucose and potassium levels of coronary vein blood are also higher than those in arterial blood (39). Furthermore, in complete anoxia, the coronary arteriovenous oxygen difference is significantly reduced (39). A reduction in oxygen consumption of the heart is not synonymous with myocardial anoxia. However, it is likely that the metabolic changes in the myocardium can result from myocardial ischemia alone. An important factor in determining the metabolic response of the myocardium in the presence of reduced coronary flow is the ratio of oxygen demand of the heart muscle to its oxygen supply. If oxygen demand and supply are proportionally diminished, the metabolic effect of myocardial ischemia is slight. Within the conditions of these experiments, the metabolic requirements of the myocardium are probably not reduced; furthermore, although under normal conditions the energy liberation of the heart appears to vary directly with energy utilization, this relationship is broken in certain pathologic conditions such as myocardial failure (32). It is unlikely that in the hearts of animals suffering from hemorrhagic shock, supply and demand for oxygen are in equilibrium. This is in contrast to the effect of a reduction in body temperature (hypothermia). There, metabolic disturbances do not develop because the reduction in body temperature lessens oxygen demands and supply in the same proportion (31).

Myocardial ischemia is, therefore, present throughout the various phases of shock and might well show its result in irreversible myocardial failure. Similar conclusions have been reached by Wiggers (1) and by Case and Sarnoff (40). The latter workers showed that left atrial pressure fell to normal if the left descending coronary artery was perfused at normal arterial pressure in the presence of low systemic arterial pressure (40). Characteristic deviations of S-T segment and T wave in the electrocardiogram during oligemic shock and irreversible normovolemic shock are further support of the presence of myocardial ischemia (41).

In contrast, myocardial oxygen extraction showed no significant change during the oligemic and normovolemic phase of shock (Table I, Figure 1). It had been shown in previous studies that the changes in coronary blood flow and not the myocardial oxygen extraction are responsible for alterations in myocardial oxygen consumption (31, 32). In most organs, a reduction of blood flow is at least partially compensated for by increased oxygen extraction. This appears not to be the case for the heart.

The coronary vascular resistance falls during the oligemic phase and increases during normovolemia (Table I). The mechanism of increased coronary vascular resistance during normovolemia is difficult to understand. Such a decrease in coronary vascular resistance would not seem fortuitous in replenishing the ischemic myocardium. In contrast, Opdyke and Foreman, using a coronary artery perfusion set in open chest dogs, observed a marked decrease in coronary resistance following reinfusion (6).

Since left ventricular work falls proportionally more than left ventricular oxygen consumption, the cardiac efficiency declines during oligemic shock (Table I). Retransfusion does not result in any uniform change in myocardial efficiency (Table I). It is likely that the persistence of low myocardial efficiency in some of the animals indicates the presence of myocardial failure. The observation that not all hearts show this decline in their mechanical efficiency is in line with the findings of Wiggers who detected evidence of myocardial failure as demonstrated by rising effective filling pressure in a majority but not all dogs in normovolemic failure (1).

Metabolic studies demonstrate a significant rise in the arterial concentration of glucose, lactate, and pyruvate during oligemic shock (Table II, Figures 2–4). During the normovolemic phase the blood concentration of glucose falls, while those of pyruvate and lactate remain elevated (Table II, Figures 2–4). These findings are in line with those of other investigators (9–12). It is likely that hyperglycemia is the result of glycogenolysis with depletion of liver glycogen (1). Glycogenolysis is also accelerated by the acidosis. The role played by epinephrine in this mechanism is not yet clear (42). The rise in arterial lactate concentration is probably the result of a shift toward anaerobic metabolism (1). Acceleration of lactate production by the muscle and gradual failure of the liver to remove lactate may

play a role in elevating blood lactate. If the heart responded to anoxia as other organs by an increased production of lactate *via* the usual glycolytic scheme, one might expect little lactate utilization and even an increased concentration of lactate in the coronary venous blood as compared to the arterial blood. From results obtained in this paper, it would seem that myocardial extraction of lactate is greatly increased during both oligemic and normovolemic shock, although its myocardial usage is not altered because of the fall in coronary blood flow. Lactate is utilized by the isolated heart and by the human and dog's heart *in situ* (31, 33, 43). Increased extraction by the heart in shock indicates that the enzymatic pathways through which lactate is channeled are not interfered with by the myocardial ischemia in hemorrhagic shock. On the basis of results discussed below, an increased breakdown of lactate through the tricarboxylic acid cycle seems unlikely, because decarboxylation of pyruvate is blocked. A conversion of lactate through reversal of the glycolytic reaction remains, therefore, a possibility although Greig had demonstrated disappearance of cozymase following hemorrhagic shock (15).

The other possibility is that lactate is oxidized during enzymatic action of lactic acid oxidase I which has recently been isolated from mycobacterium tuberculosis avium (44). Only molecular oxygen is required for the action of this enzyme and addition of cytochrome c, cytochrome oxidase is not necessary. Furthermore, the enzyme is not dependent upon the addition of A.T.P., D.P.N., or cocarboxylase.

The trend toward a negative myocardial balance of pyruvate during both phases of shock could conceivably result from destruction of the coenzyme cocarboxylase. Ochoa first observed that in experiments with liver, kidney, muscle and brain, cocarboxylase is destroyed under anaerobic conditions, by an enzyme, probably a phosphatase (14). Greig and Govier demonstrated in dogs in hemorrhagic shock that the cocarboxylase content of muscle, liver and duodenum decreased (13). The disappearance of the coenzyme was thought to result from its dephosphorylation, which occurred most frequently in muscle. Similar results were obtained, when the animals were made anoxic by inhalation of 10 per cent oxygen mixtures (13). It thus appears that anaerobiasis, as a common factor in both shock and anoxic anoxia, is responsible for dephosphorylation of cocarboxylase. Although direct determinations of cocarboxylase in heart muscle have not been made in this investigation, the findings of negative myocardial pyruvate balance are consistent with a destruction of this coenzyme in heart muscle. This destruction, resulting from increased dephosphorylation of the coenzyme, is possibly the result of a diminution in coronary blood flow. The importance of anaerobiasis in the production of this metabolic disturbance is illustrated in Figure 5 in which it may be seen that an inverse relationship exists

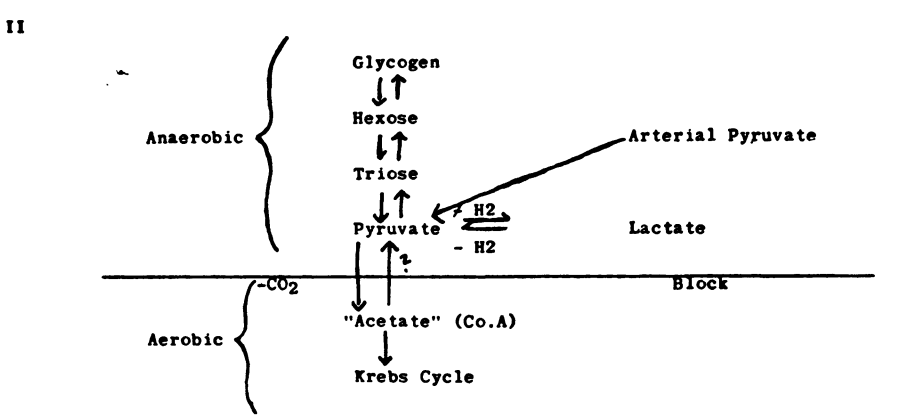

FIG. 6. METABOLIC SCHEME ILLUSTRATING THE METABOLIC BLOCK WHICH RESULTS FROM INHIBITION OF COCARBOXYLASE

The metabolic break occurs between pyruvate and "acetate," thus eliminating the aerobic Krebs cycle.

between the lactate to pyruvate ratio and the myocardial pyruvate extraction.

Changes in glucose metabolism are more difficult to interpret. The most conspicuous finding is that of reduced myocardial extraction and usage of glucose in the presence of increased arterial glucose concentration (Table II, Figure 2). In several instances there is also a negative myocardial glucose balance. These findings might be interpreted as suggesting either diminished myocardial glucose utilization, or gluconeogenesis by the heart muscle with glucose escaping into the coronary venous blood. Any conclusions are at the moment not possible.

The results reported in this paper illustrate the metabolic response of the intact heart to hemorrhagic shock and in a more specific sense to myocardial ischemia. The data suggest that moderate ischemia, resulting from a diminution in coronary blood flow, can bring about specific metabolic changes in the myocardium. Figure 6 illustrates that, assuming partial or complete inhibition of cocarboxylase, the metabolic break occurs between pyruvate and "acetate." This does not mean that other aerobic metabolic processes not connected with the action of cocarboxylase are interfered with. Thus, oxidation of fatty acids and the attachment of fatty acids to coenzyme A may proceed in a normal fashion, furnishing the high energy phosphate needed in the glycolytic cycle. However, this possibility is unlikely because the flavin cofactor (F.A.D.) required for the first step in fatty acid catabolism cannot be reoxidized under anaerobic conditions as is the case for the pyridine cofactor (D.P.N.) involved in glycolysis.

SUMMARY

Cardiac output, stroke volume and coronary blood flow were diminished during oligemic and normovolemic phase of hemorrhagic shock.

As a result of diminished coronary flow, the myocardial oxygen usage was significantly reduced during both phases of shock.

The myocardial oxygen extraction showed no significant change during the oligemic and normovolemic phase of shock.

The coronary vascular resistance fell during the oligemic phase and increased during normovolemia.

Cardiac efficiency declined during oligemia; there was no uniform change in cardiac efficiency after retransfusion of blood.

Arterial concentrations of pyruvate and lactate were elevated during oligemic and normovolemic shock. The arterial glucose concentration which had risen during oligemia, declined during normovolemia.

The myocardial extraction of lactate was increased during hemorrhagic shock. In contrast, elevation of arterial blood glucose concentration did not result in an increase in myocardial glucose extraction. In some instances, glucose concentration in coronary venous blood exceeded that in arterial blood.

Myocardial pyruvate extraction was diminished, and frequently the pyruvate concentration in coronary vein blood exceeded that in arterial blood.

These data suggest that myocardial ischemia, resulting from a diminution in coronary flow can bring about specific metabolic changes in the heart muscle, as for example, destruction of cocarboxylase.

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