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Research Article

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Lactate and Pyruvate Metabolism in the Exercising Ischemic Limb *

B. L. PENTECOST,† J. A. REID, AND D. REID

(From the Medical Research Council Cardiovascular Research Group, Department of Medicine, Postgraduate Medical School, London, England)

It has long been appreciated that contraction of skeletal muscle results in the production of lactic acid. Fletcher and Hopkins (1) demonstrated that stimulation and contraction of an isolated muscle preparation led to the accumulation of lactic acid and eventual fatigue. This process was accelerated by anaerobic conditions and delayed in an oxygen-enriched atmosphere. Much of the lactate derived from muscle glycogen appeared to be resynthesized to glycogen during the recovery period (2). In man total body oxygen uptake after exercise was found to be inadequate to permit oxidation of all the lactate formed during the exercise period, implying that a similar resynthesis was occurring (3). There remains some controversy over the site of glycogen resynthesis, but attention has been drawn to the important part played by the liver during muscular activity (4), lactate being taken up by the liver and glucose released. The ability of mammalian skeletal muscle to resynthesize glycogen from lactate is less certain. More recently the expected increase in lactate production by the limb during exercise has been demonstrated by measuring arteriovenous differences in lactate concentration across the limb before and during the period of activity (5–7). Possibly because of difficulties encountered in measurement of blood flow through exercising limbs, the time course of lactate has not been determined during exercise in man. It might be expected that, since in a limb with major arterial occlusion oxygen consumption is continued into the recovery period (8), there would be evidence of sustained lactate production. This study was designed to investigate the production of lactate during and after exercise by measuring limb blood flow and arteriovenous difference of lactic acid in a group of patients with occlusive arterial disease. Huckabee (9) has shown that a rising lactate concentration is not specifically indicative of anaerobic conditions and that it is necessary to take account of the concentration of pyruvate in the blood if a true indication of the anaerobic state of the tissues is sought. Simultaneous observations have, therefore, been made on pyruvate metabolism.

Methods

Ten male subjects, average age 58 (range 51 to 68), were studied. Nine subjects had bilateral occlusive arterial disease of the lower limbs. All experienced the symptom of intermittent claudication, pain in the calf, thigh, or buttocks being experienced when walking between 25 and 100 yards at a slow pace. No evidence of cardiopulmonary disease was detected in any patient by clinical examination, chest X ray, or electrocardiogram. In these nine men, arteriograms revealed a complete occlusion of one or more main arteries in both limbs. In six patients the artery affected was the superficial femoral or one of its branches, but in subjects J.R., J.Mc., and H.L. the common iliac vessel was obstructed. One 51-year-old subject, T.C., had normal vasculature on arteriography, and his leg pain was due to mild degenerative arthritis of the hip.

The subjects were fasted overnight and mildly sedated with 75 mg pethidine and 25 mg phenergan administered intramuscularly 1 hour before the study. The procedure was carried out at a room temperature of 21 to 23° C, with the patients wearing loosely fitting clothing. The brachial artery was catheterized by the Seldinger technique (10). PE 60 polythene tubing (i.d. 0.76 mm) was left indwelling for blood sampling. Catheterization was performed from an antecubital vein with a specially adapted no. 9 U.S. double lumen cardiac catheter with a three-hole spray tip and a sampling orifice 15 mm proximal to the tip. The tip of the catheter was advanced under fluoroscopic control into the external iliac vein of the more severely affected leg, 4 to 6 cm distal to its junction with the internal iliac vein. In each instance the catheter position was confirmed by venous angiography. Heparin (60 mg) was administered intravenously to prevent clotting of the sampling orifice.

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† Address requests for reprints to Dr. B. L. Pentecost, Dept. of Medicine, Queen Elizabeth Hospital, Edgbaston, Birmingham 15, England.

TABLE 1

Blood flow ($\dot{Q}$) and arterial (A) and venous (V) lactate

Subject	Work load		Rest			Exercise						Recovery					
						2 minutes			4 minutes			2 minutes			5 minutes		
			$\dot{Q}$	La	Py	$\dot{Q}$	La	Py	$\dot{Q}$	La	Py	$\dot{Q}$	La	Py	$\dot{Q}$	La	Py
	kg-m/min		*ml/min*	*mmoles/L*		*ml/min*	*mmoles/L*		*ml/min*	*mmoles/L*		*ml/min*	*mmoles/L*		*ml/min*	*mmoles/L*	
J.R.	150	A		0.60	0.030		1.82	0.076	Exercise discontinued at 3 min				3.92	0.136		3.68	0.180
		V	390	0.80	0.046	610	4.62	0.200				1,590	6.70	0.143	2,620	6.37	0.197
J.Mc.	150	A		0.63	0.022		1.84	0.102	Exercise discontinued at 3 min				2.85	0.145		3.54	0.227
		V	210	0.88	0.053	370	3.54	0.220				400	6.08	0.138	410	5.15	0.194
H.L.	150	A		0.83	0.073		1.34	0.100		2.50	0.108		3.27	0.165		2.97	0.211
		V	360	0.90	0.068	930	2.62	0.177	900	3.97	0.159	500	7.06	0.161	610	5.59	0.255
D.Le.	150	A		0.38	0.023		0.98	0.057		2.05	0.083		2.44	0.109		1.88	0.115
		V	230	0.40	0.027	750	1.48	0.053	810	3.73	0.117	900	3.96	0.111	430	2.93	0.110
A.D.	150	A		0.69	0.036		1.35	0.095		1.87	0.120		1.73	0.137		1.72	0.132
		V	190	0.94	0.042	710	1.89	0.106	920	2.24	0.123	630	1.87	0.143	220	1.79	0.128
L.O.	50	A		0.91	0.036		1.13	0.053		1.58	0.069		1.40	0.104		1.54	0.106
		V	290	1.01	0.058	700	2.06	0.099	850	2.38	0.107	340	2.95	0.135	350	2.10	0.133
D.R.	50	A		0.87	0.047		1.09	0.057		1.58	0.077		1.95	0.124		1.86	0.136
		V	420	1.08	0.052	1,700	1.38	0.063	2,350	2.46	0.076	1,010	2.54	0.094	570	2.45	0.103
H.L.C.	150	A		0.64	0.056		1.73	0.065		2.44	0.091		2.57	0.155		2.16	0.163
		V	160	0.80	0.065	1,490	2.97	0.089	1,670	3.39	0.105	680	3.41	0.194	510	2.87	0.163
E.J.	150	A		0.62	0.037		1.52	0.088		2.57	0.108		2.66	0.217		2.47	0.213
		V	240	0.88	0.052	1,670	2.58	0.147	2,150	3.70	0.140	1,490	3.90	0.266	860	2.92	0.252
T.C.	150	A		0.43	0.030		1.03	0.059		1.13	0.063		0.98	0.068		0.81	0.059
		V	440	0.62	0.030	1,300	1.42	0.077	2,000	1.86	0.085	710	1.21	0.098	640	1.02	0.066

The subjects were allowed a further 30 minutes' rest after positioning of the catheters before observations were begun.

External iliac venous flow measurement was made utilizing a continuous injection dilution technique (11) that has been further verified in animal experiments (12) and used extensively in man (8, 13, 14). The indicator, albumin-^{131}I diluted in physiological saline, was injected through the spray tip at a constant rate of approximately 130 ml per minute. In vessels 1 cm in diameter this gives uniform mixing at flow rates of up to 2.7 L per minute (13). Injection of indicator has been demonstrated not to diminish the venous return or to produce changes in local venous pressure. Two or three measurements were made at rest over a 15-minute period, and single estimations were made during the second and fourth minutes of exercise and the second, fifth, tenth, fifteenth, twenty-fifth, and fiftieth minutes during the recovery period.

A bicycle ergometer, set at a constant load, was operated by the supine subject during the exercise period, which lasted 4 minutes, except for subjects J.R. and J.Mc., who were prevented from completing the exercise by severe leg pain during exercise. The rate of work performed was 150 kg-m per minute in all but two subjects, who could achieve only 50 kg-m per minute. External iliac venous blood samples for oxygen analysis were collected 20 seconds before flow measurements. Arterial blood samples were obtained at rest, during exercise, and in the recovery period. Blood oxygen saturation analyses were performed in duplicate on the Kipp hemoreflector oximeter.

Arterial and external iliac venous blood samples for pyruvic and lactic acid determinations were collected simultaneously 20 to 45 seconds after each blood flow measurement. The blood was immediately transferred from the collecting syringe to a chilled, weighed tube containing 10% trichloroacetic acid in 0.5 N hydrochloric acid packed about with ice until centrifugation at the end of the study. Trichloroacetic acid was used in preference to perchloric acid because the former has been demonstrated to yield 97% recovery of pyruvate standards from whole blood, whereas perchloric acid, although efficient in the case of plasma, yielded only 60% from whole blood (15), possibly due to failure to inhibit lactic dehydrogenase in the red cells. Some preliminary experiments in this laboratory confirmed these observations. Lithium pyruvate standards were used; comparison with a sodium pyruvate standard revealed no difference between the two. The pyruvate and lactic acid concentration in the supernatant was determined in duplicate by a modification of the enzymatic spectrophotometric method[1] (15). Recovery of lactic acid added to blood supernatant averaged 96% with linearity of recovery from 0.5 mmole per L up to 8 mmoles per L. Recovery of pyruvic acid averaged 106% with linearity of recovery from 0.05 mmole per L to 0.40 mmole per L. The mean difference between duplicate lactic acid determinations (181 pairs) was 0.049 mmole per L (SD 0.0813). The mean difference between pyruvic acid duplicate determinations ($n = 171$ pairs) was 0.003 mmole per L). The lactic acid values were calculated as millimoles per liter of blood water (measured by desiccation). Arteriovenous differences were then multiplied by the corresponding flow measurement to calculate lactate and

[1] Boehringer and Sons, Mannheim, Germany.

TABLE I
(La) and Pyruvate (Py) concentrations during the study

Recovery														
10 minutes			15 minutes			25 minutes			35 minutes			50 minutes		
Q̇	La	Py	Q̇	La	Py	Q̇	La	Py	Q	La	Py	Q̇	La	Py
ml/min	*mmoles/L*		*ml/min*	*mmoles/L*		*ml/min*	*mmoles/L*		*ml/min*	*mmoles/L*		*ml/min*	*mmoles/L*	
	3.48	0.186		2.86	0.165		1.96	0.128		1.43	0.090		0.88	0.060
2,620	5.39	0.203	2,160	4.06	0.173	810	2.70	0.134	810	1.78	0.110	380	1.30	0.069
	2.96	0.236		2.11	0.209		1.44	0.150		1.03	0.119		1.10	0.148
440	4.11	0.250	370	2.96	0.185	230	1.77	0.125	230	1.35	0.104	240	1.03	0.099
	2.42	0.167		2.15	0.150		1.33	0.121		0.95	0.092		0.60	0.077
530	4.28	0.231	490	3.64	0.168	500	2.01	0.116	360	1.36	0.101	310	0.98	0.083
	1.43	0.093		1.08	0.078		0.72	0.058		0.65	0.043		0.54	0.046
160	1.94	0.089	150	1.56	0.067	110	0.90	0.049	150	0.62	0.040	180	0.51	0.041
	1.46	0.116					1.52	0.098		1.23	0.094			
290	1.69	0.106				200	1.53	0.092	140	1.44	0.074			
	1.47	0.089		1.31	0.082		1.24	0.081					0.92	0.080
530	1.87	0.113	460	1.69	0.094	350	1.29	0.077				310	1.09	0.070
	1.54	0.112		1.29	0.100		1.28	0.078					0.90	0.064
460	2.09	0.085	480	1.67	0.082	400	1.44	0.074				420	1.11	0.054
	1.68	0.138		1.25	0.110		1.00	0.088		0.79	0.061		0.63	0.057
240	1.74	0.102	210	1.57	0.104	190	1.12	0.090	170	1.03	0.064	210	0.80	0.064
				1.77	0.172		1.32	0.125		1.18	0.131			
			310	2.28	0.136	250	1.65	0.143	200	1.40	0.102			
	0.59	0.048		0.44	0.044		0.46	0.041		0.35	0.047		0.32	0.034
530	0.78	0.047		0.71	0.049	450	0.53	0.048	440	0.45	0.047	340	0.40	0.039

pyruvate production or oxygen consumption of the limb. Excess lactate production by the leg was calculated with the instantaneous arteriovenous lactate-pyruvate ratio after the manner of Huckabee (1959) (16).

Results

Blood flow and lactate and pyruvate concentrations are shown in Table I and the calculated oxygen consumption and lactate and pyruvate release in Table II. Excess lactate production and the local oxygen debt are also tabulated in Table II.

Blood flow. Resting lower limb blood flow ranged from 160 to 440 ml per minute (mean 290 ml per minute). On exercise the blood flow always increased at the first estimation made at 2 minutes, and a similar value was usually recorded at 4 minutes. Two blood flow patterns emerged. In one there was a brisk rise in flow during activity to several times the resting value; on cessation of exercise the blood flow fell to near resting values in a short period of time (Figures 1 and 2). This response was seen in patients T.C., H.L.C., A.D., and D.R. The second pattern comprised a moderate increase in flow during exercise that was either continued long into the recovery period or actually increased in the latter period. This response is well illustrated by subjects J.R., J.Mc., D.Le., and H.L. (Figures 3 and 4).

Oxygen consumption. At rest the lower limb consumed oxygen at from 7 to 21 ml per minute (mean 13.7 ml per minute). During exercise oxygen consumption always increased above resting values, the uptake being mainly during the active period in those patients with a brisk flow response, but was greatly prolonged into the recovery period in patients with a protracted post-exercise hyperemia.

Lactate and excess lactate release. The mean concentration of lactate in arterial blood at rest

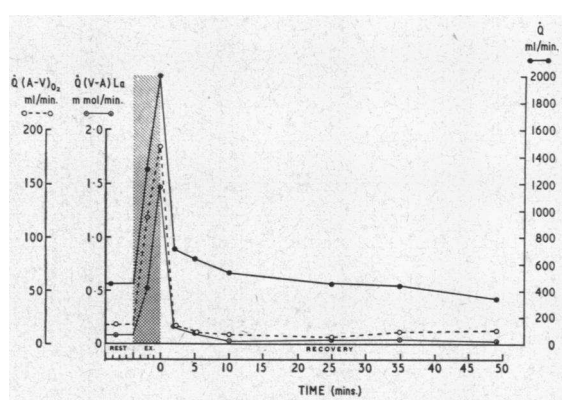

FIG. 1. BLOOD FLOW (Q), OXYGEN CONSUMPTION [$\dot{Q}(A - V)O_2$], AND LACTATE RELEASE [$\dot{Q}(V - A)La$] IN THE LOWER LIMB BEFORE, DURING, AND AFTER EXERCISE IN NORMAL SUBJECT T.C.

was 0.66 mmole per L (SD 0.16, n = 10) and in the venous blood 0.83 mmole per L (SD 0.18). In all patients there was a negative arteriovenous difference at rest (average 0.17 mmole per L) that was significant (SE 0.075, p 0.025), indicating production of small quantities of lactate by the inactive limb. During exercise the quantity of lactate leaving the leg increased and in the recovery period returned towards resting values. In those subjects showing a prolonged hyperemia and oxygen consumption into the recovery period, the washout of lactate was similarly prolonged (Figures 3 and 4). This extended production of lactate was observed only in those subjects who failed to reach a peak blood flow of 900 ml per minute. In the later stages of the 50-minute recovery period the local blood flow and lactate release always returned to resting values, although the arterial and venous concentrations of lactate were still elevated. At no time was there apparent uptake of lactate by the recovering limb even in the presence of a raised arterial concentration.

Total lactate and excess lactate production were

TABLE II

Oxygen consumption $\dot{Q}(A - V)O_2$, lactate release $\dot{Q}(V - A)La$, and pyruvate release $\dot{Q}(V - A)Py$ during the study period

	Exercise								
	Rest			2 minutes			4 minutes		
Subject	$\dot{Q}(A-V)O_2$	$\dot{Q}(V-A)La$	$\dot{Q}(V-A)Py$	$\dot{Q}(A-V)O_2$	$\dot{Q}(V-A)La$	$\dot{Q}(V-A)Py$	$\dot{Q}(A-V)O_2$	$\dot{Q}(V-A)La$	$\dot{Q}(V-A)Py$
	ml/min	*mmole/min*		*ml/min*	*mmoles/min*		*ml/min*	*mmoles/min*	
J.R.	21	0.08	0.006	55	1.71	0.076			
J.Mc.	9	0.05	0.007	36	0.62	0.044			
H.L.	20	0.03	−0.002	79	1.19	0.069	83	1.32	0.045
D.Le.	17	0.00	0.000	60	0.37	−0.003	72	1.36	0.024
A.D.	7	0.04	0.001	60	0.38	0.007	80	0.34	0.005
L.O.	11	0.03	0.007	51	0.65	0.032	59	0.68	0.030
D.R.	16	0.09	0.002	127	0.49	0.017	186	2.06	0.000
H.L.C.	8	0.03	0.002	138	1.88	0.037	175	1.59	0.023
E.J.	10	0.07	0.004	174	1.77	0.092	209	2.43	0.065
T.C.	18	0.08	0.000	118	0.52	0.020	184	1.47	0.040

	Recovery								
	2 minutes			5 minutes			10 minutes		
Subject	$\dot{Q}(A-V)O_2$	$\dot{Q}(V-A)La$	$\dot{Q}(V-A)Py$	$\dot{Q}(A-V)O_2$	$\dot{Q}(V-A)La$	$\dot{Q}(V-A)Py$	$\dot{Q}(A-V)O_2$	$\dot{Q}(V-A)La$	$\dot{Q}(V-A)Py$
	ml/min	*mmoles/min*		*ml/min*	*mmoles/min*		*ml/min*	*mmoles/min*	
J.R.	137	4.42	0.016	152	7.05	0.039	121	5.00	0.052
J.Mc.	38	1.28	−0.002	27	0.63	−0.012	16	0.50	0.007
H.L.	47	1.90	−0.003	37	1.61	0.028	24	0.98	0.034
D.Le.	52	1.36	0.000	21	0.45	−0.002	9	0.09	−0.001
A.D.	30	0.14	0.006	13	0.02	0.000	14	0.07	−0.003
L.O.	21	0.52	0.010	10	0.19	0.010	17	0.22	0.013
D.R.	51	0.60	−0.030	25	0.34	0.017	17	0.26	−0.012
H.L.C.	18	0.57	0.027	11	0.36	0.000	9	0.01	−0.008
E.J.	51	1.85	0.075	27	0.39	0.030			
T.C.	16	0.17	0.021	11	0.13	0.003	9	0.10	−0.003

	Recovery								
	15 minutes			25 minutes			35 minutes		
Subject	$\dot{Q}(A-V)O_2$	$\dot{Q}(V-A)La$	$\dot{Q}(V-A)Py$	$\dot{Q}(A-V)O_2$	$\dot{Q}(V-A)La$	$\dot{Q}(V-A)Py$	$\dot{Q}(A-V)O_2$	$\dot{Q}(V-A)La$	$\dot{Q}(V-A)Py$
	ml/min	*mmoles/min*		*ml/min*	*mmole/min*		*ml/min*	*mmole/min*	
J.R.	89	2.59	0.022	38	0.60	0.004	39	0.29	0.016
J.Mc.	17	0.32	−0.009	13	0.07	−0.006	14	0.08	−0.003
H.L.	22	0.72	0.010	22	0.34	−0.002	17	0.15	0.004
D.Le.	11	0.08	−0.002	8	0.02	−0.001	11	0.01	−0.001
A.D.				8	0.00	−0.002	9	0.03	−0.003
L.O.	16	0.17	0.007	14	0.02	−0.002			
D.R.	17	0.18	−0.010	18	0.06	−0.002			
H.L.C.	7	0.07	−0.001	6	0.02	0.000	5	0.04	0.001
E.J.	16	0.16	−0.020		0.08	0.005		0.04	−0.006
T.C.				7	0.03	0.005	11	0.04	0.000

TABLE II—(*Continued*)

Subject	Recovery 50 minutes $\dot{Q}(A-V)O_2$	$\dot{Q}(V-A)La$	$\dot{Q}(V-A)Py$
	ml/min	*mmole/min*	
J.R.	16	0.16	0.004
J.Mc.	10	−0.02	−0.012
H.L.	20	0.11	0.003
D.Le.	15	0.01	−0.001
A.D.			
L.O.	13	0.05	−0.003
D.R.	17	0.08	−0.004
H.L.C.	7	0.03	0.002
E.J.			
T.C.	13	0.03	0.002

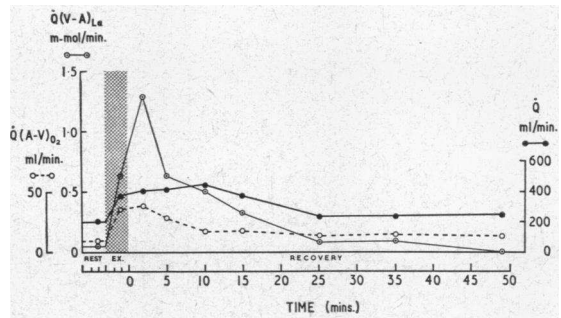

FIG. 3. $\dot{Q}$, $\dot{Q}(A-V)O_2$, AND $\dot{Q}(V-A)La$ IN THE LOWER LIMB BEFORE, DURING, AND AFTER EXERCISE IN PATIENT J.Mc. (OCCLUSION OF COMMON ILIAC ARTERY).

estimated by calculating the area under time-lactate production curves constructed from the data in Tables II and III. Table III shows that among patients with severe occlusive arterial disease, as suggested by failure to complete the exercise or a peak lower limb blood flow of less than 1 L per minute, the excess lactate produced accounts for most of the total lactate production. In contrast, in the lower half of the Table, which contains the patients with higher peak flows and the normal subject T.C., excess lactate accounts for a smaller fraction of total lactate production. Local oxygen debt, i.e., the volume of oxygen consumed by the limb during the recovery period in excess of resting requirements, was directly related to the total excess lactate production over the same period ($r = +0.97$) when calculated from all the data in Table III and to total lactate production ($r = +0.94$), but this calculation is greatly influenced by the extremely high values in patient J.R. A more reliable correlation coefficient may be calculated from the data excluding patient J.R. The local oxygen debt then appears more closely related to excess lactate production ($r = +0.77$) than to total lactate production ($r = +0.64$).

Pyruvate release. The mean arterial concentration of pyruvate at rest was 0.039 mmole per L (SD 0.015, $n = 10$), and in venous blood, 0.049 mmole per L (SD 0.013). There was a small negative arteriovenous difference (average 0.010 mmole per L) in all but one subject, but this was not significant. On exercise the arteriovenous difference became consistently negative, and there was an increased washout of pyruvate from the limb, which declined rapidly in the recovery period. Only in subjects J.R., H.L., and E.J. were appreciable quantities of pyruvate released from the limb after 4 minutes of the recovery period. Although systemic concentration of pyruvate always rose during exercise, frequently reaching

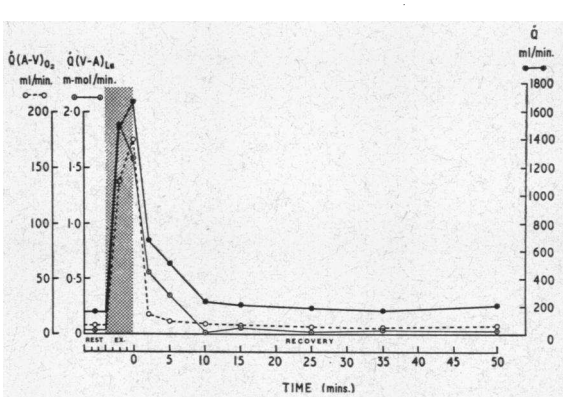

FIG. 2. $\dot{Q}$, $\dot{Q}(A-V)O_2$, AND $\dot{Q}(V-A)La$ IN THE LOWER LIMB BEFORE, DURING, AND AFTER EXERCISE IN PATIENT H.L.C. (OCCLUSION OF SUPERFICIAL FEMORAL ARTERY).

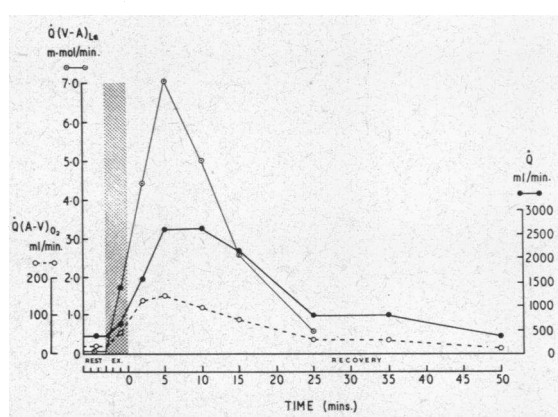

FIG. 4. $\dot{Q}$, $\dot{Q}(A-V)O_2$, AND $\dot{Q}(V-A)La$ IN THE LOWER LIMB BEFORE, DURING, AND AFTER EXERCISE IN PATIENT J.R. (OCCLUSION OF COMMON ILIAC ARTERY).

TABLE III

*Lactate release $\dot{Q}(V-A)La$ and excess lactate release $\dot{Q}(V-A)XLa$ during the study period**

Subject		Rest	Exercise		Recovery							Total lactate	Total X lactate	Oxygen debt
			2 min	4 min	2 min	5 min	10 min	15 min	25 min	35 min	50 min			
		mmole/min	*mmoles/min*		*mmoles/min*							*mmoles*		*ml*
J.R.	$\dot{Q}(V-A)$ La	0.08	1.71		4.42	7.05	5.00	2.59	0.60	0.29	0.16	79.0	73.5	2,230
	$\dot{Q}(V-A)$XLa	0.05	0.11		4.19	5.87	4.17	2.30	0.53	0.26	0.94			
J.Mc.	$\dot{Q}(V-A)$ La	0.05	0.62		1.28	0.63	0.50	0.32	0.07	0.08	0.02	12.3	15.6	288
	$\dot{Q}(V-A)$XLa	0.13	0.16		1.47	1.13	0.43	0.39	0.13	0.11	0.10			
H.L.	$\dot{Q}(V-A)$ La	0.03	1.19	1.32	1.90	1.01	0.98	0.72	0.34	0.15	0.11	22.9	15.8	244
	$\dot{Q}(V-A)$XLa	0.05	0.23	0.26	1.94	1.22	0.49	0.60	0.37	0.11	0.10			
D.Le.	$\dot{Q}(V-A)$ La	0.00	0.37	1.36	1.36	0.45	0.09	0.06	0.02	0.01	0.01	9.7	9.2	143
	$\dot{Q}(V-A)$XLa	0.01	0.43	1.30	1.33	0.49	0.09	0.10	0.03					
A.D.	$\dot{Q}(V-A)$ La	0.04	0.38	0.34	0.14	0.02	0.07		0.00	0.03		2.6	2.8	186
	$\dot{Q}(V-A)$XLa	0.02	0.27	0.30	0.14	0.03	0.10		0.02	0.07				
L.O.	$\dot{Q}(V-A)$ La	0.03	0.65	0.68	0.52	0.19	0.22	0.17	0.02		0.05	6.5	2.9	116
	$\dot{Q}(V-A)$XLa	0.13	0.04	0.07	0.38	0.24	0.00	0.22	0.04		0.09			
D.R.	$\dot{Q}(V-A)$ La	0.09	0.49	2.06	0.60	0.34	0.26	0.18	0.06		0.08	10.9	11.8	305
	$\dot{Q}(V-A)$XLa	0.05	0.30	2.12	1.07	0.59	0.42	0.29	0.09		0.09			
H.L.C.	$\dot{Q}(V-A)$ La	0.03	1.88	1.59	0.57	0.36	0.01	0.07	0.02	0.04	0.03	10.6	6.9	206
	$\dot{Q}(V-A)$XLa	0.01	0.90	1.14	0.11	0.36	0.09	0.08	0.02	0.03	0.02			
E.J.	$\dot{Q}(V-A)$ La	0.07	1.77	2.43	1.85	0.39		0.16	0.08	0.04		18.6	7.6	405
	$\dot{Q}(V-A)$XLa	0.02	0.07	0.79	0.99	0.00		0.26	0.03	0.08				
T.C.	$\dot{Q}(V-A)$ La	0.08	0.52	1.47	0.17	0.13	0.10		0.03	0.04	0.03	5.9	2.9	160
	$\dot{Q}(V-A)$XLa	0.08	0.10	0.67	0.14	0.07	0.11		0.00	0.04	0.01			

* Calculated total lactate and excess lactate production for the whole period of study up to 25 minutes of the recovery period.

TABLE IV

Arterial and venous lactate-pyruvate ratios at rest, on exercise, and in the recovery period

Subject		Rest	Exercise		Recovery						
			2 min	4 min	2 min	5 min	10 min	15 min	25 min	35 min	50 min
J.R.	A	20.0	24.0		28.8	20.4	18.7	17.3	15.3	15.9	14.7
	V	17.4	23.1		46.9	32.3	27	23.5	20.1	16.2	18.8
J.Mc.	A	28.6	18.1		19.7	15.6	12.5	10.1	9.6	8.7	7.4
	V	16.6	16.1		44.1	26.5	16.4	16.0	14.2	13.0	10.4
H.L.	A	11.4	13.4	23.1	19.8	14.1	14.5	14.3	11.0	10.3	7.8
	V	13.2	14.8	25.0	43.9	21.9	18.5	21.7	17.3	13.5	11.8
D.Le.	A	16.5	17.2	24.7	22.4	16.3	15.4	13.8	12.4	15.1	11.7
	V	14.8	27.9	31.9	35.7	26.6	21.8	9.3	18.4	15.5	12.4
A.D.	A	19.2	14.2	12.6	13.0	13.0	12.6		15.1	13.1	
	V	22.4	17.8	18.2	13.1	14.0	15.9		16.6	19.5	
L.O.	A	25.3	21.3	22.9	13.5	14.5	16.5	16.0	15.3		11.5
	V	19.1	20.8	22.2	21.9	15.8	16.5	18.0	16.8		15.6
D.R.	A	18.5	19.1	20.5	15.7	13.7	13.8	12.9	16.4		14.1
	V	20.8	21.6	32.4	27.0	23.8	24.6	20.4	19.5		20.6
H.L.C.	A	11.4	26.6	26.8	16.6	13.3	12.2	11.4	11.4	13.0	11.1
	V	12.3	33.3	29.4	17.6	17.6	17.1	15.1	12.4	16.1	12.5
E.J.	A	16.8	17.3	23.8	12.3	11.6		10.3	10.6	9.0	
	V	16.9	17.6	26.4	14.7	11.6		16.8	11.5	13.7	
T.C.	A	14.3	17.5	17.9	14.4	13.7	12.3	10.0	11.2	7.4	9.4
	V	20.7	18.7	21.9	12.3	21.5	16.6	14.5	10.9	9.6	10.0

peak concentration in the early recovery period, the net release of pyruvate by the limb was frequently small.

Not infrequently the arteriovenous difference of pyruvate concentration became positive in the recovery period, suggesting an uptake of pyruvate by the recovering limb. The small number of observations limits statistical analysis, but in several patients (J.Mc., D.Le., A.D., D.R., and H.L.C.) the positive arteriovenous difference at some time exceeded twice the standard deviation (0.004) from the mean of the duplicate pyruvate estimations. In addition, in subjects J.Mc., D.Le., and D.R. the positive arteriovenous difference was observed over at least four sequential measurements, which is further evidence of true pyruvate uptake. This uptake usually occurred late in the recovery period when blood flow was steady and near resting levels; the quantities of pyruvate consumed were, therefore, extremely small in most cases.

Lactate-pyruvate ratio. In all subjects the resting lactate-pyruvate ratio, both venous and arterial, was greater than that observed at some stage of the recovery period (Table IV) with the exception of the venous ratio in H.L.C. During exercise the ratio increased in eight subjects in venous blood and in seven subjects in arterial blood.

Discussion

Blood flow. It has previously been shown that occlusive arterial disease results in the reduction of peak blood flow through the limb during exercise and a prolongation of hyperemia into the recovery period (8). This is in agreement with earlier plethysmographic observations on reactive and postexercise hyperemia in normal subjects and patients with major artery obstruction (17–19). In this study, the pattern of blood flow response varied from normal as seen in patient T.C. through varying degrees of reduced peak flow and prolonged hyperemia. Three subjects showed an increase in blood flow on passing from the period of activity to that of recovery. Two of these patients had common iliac artery obstruction, and one had occlusion of the common femoral artery at its origin. This flow pattern resembles that sometimes seen in the calf in the presence of proximal arterial disease in the lower limb (17). Similarly, hyperemia in the foot may be shown to follow that in the calf in the presence of obstruction of major limb arteries (20, 21). Whereas in the normal limb the main artery acts as a supply line with a low internal resistance, in the presence of occlusive arterial disease the resistance of the collateral vessels may limit arterial inflow. When inflow is limited and perfusion

pressure reduced as beyond a common iliac artery obstruction, blood flow to the thigh and calf may not rise until the flow requirements of the more proximal regions have been fulfilled. In addition, there is evidence that arteries with reduced intraluminal pressure may be compressed by contracting skeletal muscle (22).

Lactate and excess lactate production and oxygen consumption. Although the measurement of external iliac venous blood flow does not account for total limb perfusion, the flow measurements are appropriate to the arteriovenous differences measured. The limitations imposed upon studies of regional metabolism by techniques that involve the measurement of arteriovenous differences have been analyzed by Zierler (23). Arteriovenous differences can only be equated with tissue metabolism when blood flow is constant and known and may only be used if arterial concentration and tissue uptake of the metabolite are also constant. In this study, blood flow is known and appears to have changed rapidly only in the first minute of exercise or recovery, as might be expected from the results of other workers (24–26), and measurements in these periods have been avoided. Whereas the calculated total quantity of lactate leaving the limb during the entire period of observation should be an accurate reflection of total lactate production, the apparent rate of production is likely to be distorted. In ischemic regions of the exercising limb volume blood flow is inappropriate to the mass of metabolizing tissue, and the capillary supply will be sparse. The transit time from cell to capillary will therefore be greatly increased. This phenomenon in addition to the delayed hyperemia in distal parts of the ischemic limb may partially explain the apparently prolonged lactate production by some subjects. It is, however, apparent that increased oxygen consumption was continued into the recovery period in a similar manner to the delayed washout or release of lactate. This observation suggests that oxygen lack was still present at that time unless there existed a considerable tissue oxygen store that had been depleted during exercise, and therefore lactate formation might reasonably be expected to continue. Lactate production occurs for a brief period into the recovery state to restore the content of adenosine triphosphate and creatine phosphate in muscle by further glycolysis. In addition, in the absence of an adequate oxygen supply, the conversion of pyruvate to lactate may release a further supply of DPN required in the tricarboxylic acid cycle. As oxygen consumption by the limb returned to near resting levels, it was noted that lactate production was in a similar state. Excess lactate accounted for the majority of lactate produced in the limb in those patients with the most severe limitation of arterial inflow; this is in keeping with the biological concept of excess lactate as is the positive correlation between total excess lactate and local oxygen debt.

Controversy exists concerning the ability of skeletal muscle to resynthesize glycogen from lactate. Peters and Van Slyke (27) doubt whether skeletal muscle is capable of handling lactate at all. Harris, Bateman, and Gloster (7) demonstrated uptake of lactate by resting skeletal muscle during leg exercise, and under certain circumstances, skeletal muscle does appear to be capable of using lactate as a fuel. Thus, in the eviscerated rabbit, Drury, Wick, and Morita (28) demonstrated that muscle oxidized large amounts of lactate. This achievement was attributed to the high tissue concentrations present in the preparation, lactate replacing glucose as tissue fuel. Other workers have failed to show synthesis of glycogen from isotopic lactate by perfused muscle unless insulin and glucose were administered simultaneously (29). In the present study, the failure of the limbs to take up lactate in the later recovery period, when the blood flow and oxygen consumption of the limb had returned to normal but while the lactate concentration in arterial blood was still elevated, suggests that there is little metabolism of lactate by the limb musculature, although some degree of glycogen synthesis cannot be excluded.

Pyruvate production and the lactate-pyruvate ratio. In this study the resting lactate-pyruvate ratio, in both arterial and venous blood, was with one exception always higher than in the late recovery period. The explanation of the high ratio in the present study is to be found in the low resting concentration of pyruvate. Gloster and Harris (15) have demonstrated that the enzymatic method used here gives significantly lower readings than the phenylhydrazine method of Friedemann and Haugen (30), which was the technique most frequently used by the earlier investigators. Slight variations in pyruvate concentration, there-

fore, result in large changes in lactate-pyruvate ratio. Delay in denaturation of blood results in loss of pyruvate (31, 32), but this error was avoided, and technical errors do not explain the systematic finding of a lower lactate-pyruvate ratio in the recovery period than in the pre-exercise period. It is pertinent to consider some of the resting blood pyruvate determinations, enzymatically determined, that have appeared in the literature in recent years. Landon, Fawcett, and Wynn (33) found a mean value of 0.05 mmole per L and Gloster and Harris (15) a mean value of 0.055 mmole per L. Two other groups of investigators found concentrations of 0.08 to 0.09 mmole per L (34, 35), but in both cases the subjects were postabsorptive and ambulatory, and the results of this study indicate a prolonged elevation of pyruvate levels after even mild degrees of exercise. Krasnow, Neill, Messer, and Gorlin (36) found a wide range of lactate-pyruvate ratios in arterial blood among a group of six resting normal subjects; the ratio varied from 3:1 to 13:1. In the present study, the average resting lactate-pyruvate ratio was 18:1. The observation that the lactate-pyruvate ratio is not at its lowest in the resting and fasting state suggests that it is either a less direct reflection of the reduction oxygenation potential than previously supposed, or that this potential is improved by a short period of light exercise. The latter possibility is worthy of consideration, since the circulatory and respiratory status of a subject is frequently more stable after a short period of light exercise than in the pre-exercising resting phase (37). It is possible that the prolonged period of rest and fasting for several hours, often overnight, was responsible for the low pyruvate concentrations. Finally, the degree of exercise by the patients was extremely light in this study, and the elevated blood pyruvate concentrations at 50 minutes after exercise emphasize the necessity to define carefully what is meant by the resting state for each study.

Summary

The external iliac venous blood flow was measured in nine patients with occlusive arterial disease and one with a normal lower limb vasculature. Changes in venous return during and after exercise have been monitored together with arteriovenous differences in oxygen, lactate, and pyruvate concentrations across the limb. The following conclusions were reached:

1. High peak blood flows during exercise with rapid return to resting values after exercise were seen in the normal subjects and patients with superficial femoral artery obstruction. Delayed hyperemia with peak flow in the recovery period was observed among subjects with more proximal arterial block.

2. Oxygen consumption and lactate release were continued long into the recovery period in patients with delayed hyperemia. This finding could be partly explained by a delayed hyperemia in distal parts of the limb, but probably represents some continuing anoxic state.

3. Total excess lactate accounted for a greater part of total lactate production in the patients with severe reduction of blood flow than in those with relatively high peak blood flow. There was a positive correlation between local oxygen debt and excess lactate production.

4. Blood flow returned to resting values before the arterial lactate concentration, and there was no evidence of lactate uptake by the limb.

5. Pyruvate release by the limb was slight, and there was occasionally evidence of pyruvate uptake by the limb in the recovery period.

6. The lactate-pyruvate ratio in both arterial and regional venous blood was usually higher in the pre-exercise period than that at some stage of the recovery period.

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