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MYOCARDIAL LACTATE AND PYRUVATE METABOLISM *

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Although the heart has been considered primarily an aerobic organ, recent work (1) has reemphasized the possibility that measurement of oxygen consumption alone may not be adequate to define the total energy utilization under all conditions. The role of anaerobic metabolism must be reviewed.

Methods of defining as well as quantifying anaerobiosis are currently in dispute. When oxidation and glycolysis proceed at the same rate, carbohydrate is oxidized to CO_2 and H_2O. Lactate arises whenever the rate of glycolysis exceeds the rate of oxidation. Net production of lactate by an organ, as evidenced for example by venous concentration greater than arterial, has been considered to represent anaerobic metabolism due to cellular hypoxia (2). More recent work (3) has demonstrated that large changes in lactate production can occur unassociated with hypoxia, but related instead to increased pyruvate production. Huckabee introduced the concept of "excess lactate" in order to distinguish between pyruvate-induced changes in lactate and those related solely to a shift in DPN : DPNH redox potential. This was inferred from alterations in arterial lactate-pyruvate ratio and the relative arteriovenous differences of the two substrates. "Excess lactate," so defined, was considered an indicator of cellular oxygenation and was used quantitatively as a measure of anaerobic metabolic rate.

Anaerobic metabolism in cardiac muscle has been considered to occur only under extreme conditions. Whereas earlier work (4–9) showed lactate production only sporadically with stresses of hypoxia, shock, or myocardial emboli, Huckabee (1) found that in dogs the stress of either 10 per cent oxygen breathing or leg exercise would result in myocardial excess lactate despite positive myocardial lactate extraction. Excess lactate has not been found in normal or diseased human subjects (10–15) at rest except in a few patients with progressive muscular dystrophy (16). None has been subjected to exercise.

The purposes of this report are to describe *1*) the effects of the stresses of physical exercise and ischemia on myocardial lactate and pyruvate metabolism in man and dogs and *2*) the role of anaerobiosis during these stresses.

MATERIALS AND METHODS

Thirty-four fasting subjects were studied by cardiac and coronary sinus catheterization. Diagnoses are listed in Table I. Left ventricular failure was defined as an end-diastolic pressure greater than 10 mm Hg at rest, or a pulmonary wedge pressure greater than 12 mm Hg at rest or 17 on exercise. Coronary insufficiency (including angina pectoris alone) was defined as described elsewhere (17). No patients had diabetes mellitus, elevated fasting blood sugar,[1] or severe nutritional deprivation. Cardiac medications included digitalis and thiazides; the latter have been reported to raise blood pyruvate levels (18). Blain, Eddleman, Siegel, and Bing (19) indicated that digitalization had no effect on lactate and pyruvate metabolism. In most cases no premedication was necessary; in a few, 1 ml of a mixture of meperidine (25 mg per ml), Phenergan (6.25 mg per ml), and chlorpromazine (6.25 mg per ml) was given intramuscularly. Special care was taken to place the catheter deep in the proximal coronary sinus where homogeneity of sampling has been observed (17), and maximal representation of left ventricular events may be expected (20). Measurements of blood oxygen content were made immediately prior to and at least 3 minutes after onset of supine leg-raising; exercise was sufficient to raise mean myocardial oxygen consumption by 42 per cent (11.2 to 15.9 ml per 100 g per minute) and total body oxygen consumption by 112 per cent (145 to 307 ml per minute per m^2). Samples for lactate and pyruvate were taken simultaneously from systemic artery and coronary vein immediately prior to and between the fifth and sixth minutes of exercise, when a steady state of hemodynamics (21) and arterial blood lactate (22) has been observed. Samples were taken in dry syringes and transferred

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[1] One patient had an abnormal glucose tolerance test.

TABLE I

Myocardial lactate-pyruvate

Patient no.	Patient initials	Age	Sex	Diagnosis: Etiologic	Diagnosis: Physiologic: Coronary insufficiency	Diagnosis: Physiologic: Congestive heart failure	Rest: Arterial lactate mmoles/L	Rest: Arteriovenous lactate mmoles/L	Rest: Arterial pyruvate mmoles/L	Rest: Arteriovenous pyruvate mmoles/L	Rest: Lactate:pyruvate ratio (arterial)	Exercise: Arterial lactate mmoles/L	Exercise: Arteriovenous lactate mmoles/L	Exercise: Arterial pyruvate mmoles/L
Control—normal left ventricle														
1	GW	31	F	HB	0	0	.59	+.04	.06	−.02	10.6	1.95	+.21	.07
2	CC	64	F	N, small ASD	0	0	.92	+.59	.07	0	12.8	1.78	+.72	.11
3	DB	18	M	N	0	0	.53	+.20	.06	−.01	9.3	.90	+.44	.07
4	JLy	43	M	N	0	0	.35	+.11	.11	+.03	3.2	1.21	+.46	.17
5	RA	41	M	N	0	0	.59	+.03	.09	+.01	6.6	1.45	+.31	.15
6	AH	47	M	MS	0	0	.59	+.13	.05	+.01	13.1	2.5	+.60	.05
Control—diseases involving LV without CI or CHF														
7	LT	20	M	Myocard	0	0	.63	+.26	.07	−.02	8.6	1.35	+.64	.07
8	RG	25	M	Hypervent, AI	0	0	1.06	+.43	.07	−.01	14.9	2.06	+.70	.06
9	WG†	39	M	AI	0	0	2.85	+.90	.10	−.04	28.5	3.63	+.88	.13
10	RD†	20	M	AI	0	0	.59	+.02	.10	+.05	5.8	.93	+.37	.08
11	JDe†	32	M	AI	0	0	.54	+.14	.06	+.03	9.1	.65	+.32	.07
12	JW†	26	M	AI	0	0	.52	+.29	.11	+.04	4.7	1.03	+.47	13
13	FB†	18	M	AI	0	0	.36	+.14	.09	+.03	4.2	.45	+.05	.10
Coronary insufficiency														
14	PM	33	F	AI, mild		0	.59	+.11	.10	+.01	5.8	.77	+.16	.12
15	LY	37	F	LVH, CAD (uncertain)	+	0	.81	+.37	.06	−.01	14.0	.71	+.35	.08
16	EE	38	M	CAD	+	0	.85	+.41	.12	+.04	7.2			
							.99	+.52	.13	+.05	7.9	1.26	+.54	.13
17	JL	53	M	CAD	+	0	.37	+.20	.09	+.03	4.2	.49	+.27	.09
												.59	+.32	.11
18	RC	58	M	CAD	+	0	.63	−.15	.08	+.03	8.0	1.06	+.68	.09
19	JK	29	M	AS, AI	+	0	.52	+.07	.08	+.01	6.4			
20	SB†	36	F	CAD	+	0	.55	−.06	.07	−.02	8.2	1.15	−.22	.10
21	MC	38	F	CAD, MS, old my	+	0	.50	+.13	.08	−.01	6.3	1.29	+.29	.11
22	JT	54	M	CAD, old my	+	0	.52	+.07	.06	0	8.1	.90	+.25	.09
23	VW	51	F	Hypervent, CAD (uncertain)	+	0	.49	−.03	.12	+.02	4.2	.98	−.26	.15
24	AS	36	M	AI, CAD, old my	+	0	.43	+.12	.05	0	9.0	1.96	+.60	.14
Congestive heart failure														
25	JD	57	M	AI, AS, MI	0	+	.50	+.16	.09	+.02	5.7	.94	+.33	.11
26	HJ	53	M	AI, MI	0	+	.47	+.12	.08	+.02	6.3	1.54	+.37	.12
27	MCi	46	M	AI, AS, MS, MI	0	+	.75	+.22	.07	−.06	10.3	1.29	+.34	.07
Coronary insufficiency and congestive heart failure														
28	CM	45	M	AS, AI, MI	+	+	1.01	+.16	.14	+.01	7.5	2.77	+.73	.19
29	JA	56	M	AI	+	+	.67	+.20	.09	−.04	7.8	.99	+.40	.11
30	LR	53	M	AS	+	+	.81	−.14	.11	+.01	7.2	2.56	+.43	.19
31	JO	36	M	AI	+	+	.52	+.26	.12	+.03	4.5	.67	+.21	.13
32	ED	47	M	HCVD, old my	+	+	.38	+.03	.09	0	4.2	.82	+.25	.11
33	LM	51	M	AI, MI, AS, MS	+	+	1.06	+.47	.12	+.03	8.9	1.78	+.86	.12
Miscellaneous														
34	JM	20	F	Tetralogy	0	0	.81	+.15	.21	+.04	3.8			
							.99	+.40	.20	−.03	5.0			
Mean							.70	.20	.10	.01	8.1	1.36	.40	.11
Standard deviation							.43	.17	.04	.03	4.6	.69	.22	.035
p value												p .001		

* Abbreviations: HB = heart block; N = normal; ASD = atrial septal defect; MS = mitral stenosis; LV = left ventricle; CI = coronary insufficiency (including angina pectoris); CHF = congestive heart failure; myocard = myocardopathy; hypervent = hyperventilation; AI = aortic insufficiency; LVH = left ventricular hypertrophy; CAD = coronary artery disease; AS = aortic stenosis; old my = old myocardial infarction; MI = mitral insufficiency; HCVD = hypertensive cardiovascular disease; PTM = pressure time per minute; Q_{O_2} = oxygen consumption.

† Rest samples taken 16 to 20 minutes after exercise.

within 30 seconds to test tubes containing 3 cc of ice-cold 10 per cent perchloric acid. This was done to approximate as closely as possible the *in vivo* lactate and pyruvate concentrations that change rapidly *in vitro* (23). A constant time interval for transferring samples was maintained.

Twenty dogs, weighing 17 to 24 kg, anesthetized intravenously with morphine, chloralose, and urethane, or with pentobarbital, were studied. They were ventilated through a cuffed endotracheal tube via a Harvard respiration pump. Catheters were placed in the coronary sinus and femoral artery. Control samples were taken preceding each experimental procedure. Six dogs were made hypoxic by clamping the trachea or by making

metabolism in humans *

		Extraction coefficient				Myocardial				Total body				
		Lactate		Pyruvate		Excess lactate		Qo_2		Excess lactate	Qo_2		PTM	
Arteriovenous pyruvate *mmoles/L*	Lactate:pyruvate ratio (arterial)	A-V/A rest	A-V/A exercise	A-V/A rest	A-V/A exercise	Rest *mmoles/L*	Exercise *mmoles/L*	Rest *ml/100g/min*	Exercise *ml/100 g/min*	Rest-exercise *mmoles/L/5 min*	Rest *ml/min/m²*	Exercise *ml/min/m²*	Rest *mm Hg sec/min*	Exercise *mm Hg sec/min*
−.02	28.7	.07	.11	−.41	−.25	−.28	−.70	10.9	18.9	+1.23	153	316	1490	2660
−.01	16.2	.64	.41	0	+.05	−.59	−.64	10.8	16.6	+.37	152	237	2710	4410
0	12.7	.38	.49	−.16	0	−.28	−.44	11.0	21.0	+.24	128	361	2240	2760
+.06	7.0	.30	.38	+.25	−.37	−.02	−.02	12.7	14.8	+.75	120	279	2590	4010
+.04	9.6	.05	.22	+.11	+.29	+.04	+.11	9.7	11.9	+.46	145	416	2360	2080
+.01	55.8	.22	.24	+.27	+.16	+.03	−.21	8.6	11.7	+1.91	163	290	1830	2470
−.01	19.0	.42	.47	−.30	−.18	−.45	−.88			+.74	151	326	1640	2750
−.04	37.5	.40	.34	−.10	−.66	−.53	−2.79	13.3	13.8	+1.24	131	324	3370	3230
0	29.0	.32	.24	−.44	+.02	−2.15	−.82	8.1	16.5	+.07	116	305	2390	3880
+.07	10.1	.03	.39	+.52	+.85	+.29	+.34	11.4	18.0	+.45	141	288	1950	2620
+.04	9.5	.25	.48	+.47	+.57	+.12	+.06	19.8	18.0	+.19	148	187	3600	3710
+.03	7.8	.55	.46	+.35	+.22	−.11	−.25	12.1	17.0	+.41	155	485	2540	3380
+.03	7.5	.38	.14	+.33	+.30	−.05	−.10	10.5	14.2	+.33	147	364	3100	3540
+.02	6.6	.18	.20	+.11	+.17	−.04	−.03	12.9	11.6	+.10	144	216	2330	2700
+.03	9.3	.45	.50	+.01	+.40	−.43	−.07	6.1	10.5	−.36	105	230	1690	2150
		.48		+.37		−.10				+.32				
+.05	9.6	.52	.43	+.43	+.38	−.10	−.06	11.5	30.0	+.23	127		3640	4750
+.01	5.7	.56	.55	+.29	+.16	−.10	−.19	7.7	9.7	+.13	151	219	3770	3450
+.03	5.6		.55		+.24		−.18		9.7	+.14		232		3710
+.02	11.3	−.23	.64	+.33	+.23	+.35	−.43	7.2	9.5	+.30	132	247	3240	4790
		.14		+.16		+.01		8.4	13.5		185	334	3360	5040
−.02	11.9	−.11	−.19	−.31	−.17	−.11	+.03	7.2	14.3	+.36	138	386	2080	2800
0	12.5	.26	.22	−.15	−.04	−.22	−.38	9.0	10.5	+.62	129	317	1980	2470
−.07	10.2	.14	.28	+.02	−.81	−.07	−.98	8.1	18.1	+.19	115	190	3880	4180
+.01	6.7	−.06	−.27	+.13	−.05	+.08	+.36	8.3		+.36	123	223	2840	3550
+.09	14.5	.27	.31	0	+.66	−.12	+.69	9.9	19.8	+.75	129	447	2110	3240
+.04	8.5	.32	.35	+.17	+.34	−.07	−.01			+.31			3220	4000
+.05	12.9	.25	.24	+.29	+.40	+.02	+.24	11.9	12.9	+.69	136	356	4020	5700
−.06	17.7	.29	.26	−.80	−.80	−.82	−1.37	15.8	20.6	+.54	145	305	3950	6660
+.07	14.6	.16	.26	+.04	+.38	−.12	+.33	9.5	13.4	+1.35	174	368	3120	3940
−.03	9.3	.30	.40	−.42	−.24	−.48	−.64	9.3	13.9	+.15	189	342	3680	4860
+.02	13.4	−.18	.17	+.09	+.11	+.22	−.15	21.1	22.5	+1.18	148	230	5350	7820
+.04	7.5	.49	.31	+.29	+.30	−.11	+.08	11.8	14.3	+.27	122	240	2400	3240
+.02	7.5	.07	.30	+.02	+.16	−.02	−.12	9.5	15.9	+.36	158	332	4100	6900
+.01	14.5	.44	.48	+.26	+.11	−.19	−.66	13.3	17.2	+.68	168	422	1880	3450
		.18		+.20		+.02							2450	3470
		.40		+.38		−.27								
.02	14.1	.26	.31	.06	.15	.18	.29	11.2	15.9	.50	145	307		
.03	9.8	.21	.19	.32	.81	.45	.62	3.5	4.4	.45	20	67		
	p.001		.100 < p < .200	p < .500										

them breath 100 per cent nitrogen for varying periods of time; seven dogs were given KCN intravenously (3.3 mg per kg) as a single rapid injection, and serial spot samples were taken at timed intervals (Table II). Two dogs were given atropine to produce tachycardia; four dogs were bled progressively with dextran replacement to produce anemia without hypovolemia; in one dog the effects of anesthesia alone were studied during the experimental time period.

Coronary blood flow was measured by nitrous oxide desaturation (24); oxygen consumption was calculated as the product of flow and coronary arteriovenous oxygen difference, as determined manometrically in duplicate. Pressure-time per minute [tension-time index (25)] was

TABLE II

*The effect of stress of myocardial lactate and pyruvate metabolism in the dog**

Dog no.	State	Myocardial						Total body "excess lactate"
		Arterial lactate	Arterial pyruvate	Arterio-venous lactate	Arterio-venous pyruvate	Lactate-pyruvate ratio (arterial)	"Excess" lactate	
		mmoles/L	*mmoles/L*	*mmoles/L*	*mmoles/L*		*mmoles/L*	*mmoles/L/5 min*
1	Control	.86	.08	+.53	+.02	10.46	−.35	
	2 hrs	1.56	.17	+1.16	+.05	9.40	−.74	−.18
	3 hrs	1.08	.12	+.75	−.05	9.15	−1.21	−.241
2	Control (HR 37)	.99	.09	+.10	−.01	11.12	−.19	
	Atropine (HR 120)	1.01	.10	+.50	+.00	10.10	−.47	−.10
3	Control (HR 102)	1.12	.05	+.22	−.03	20.74	−.93	
	Atropine (HR 150)	1.72	.09	+.24	−.11	19.55	−2.53	−.11
4	Control (CA O_2 22.9)	1.03	.08	+.34	+.01	12.56	−.22	
	Anemia							
	no. 1 (CA O_2 20.8)	.90	.12	+.24	+.02	7.68	−.05	−.57
	no. 2 (CA O_2 17.6)	1.85	.19	+.40	+.05	9.84	+.11	−.52
5	Control (CA O_2 20.7)	.20	.05	±0	−.08	4.40	−.37	
	Anemia							
	no. 1 (CA O_2 9.3)	1.58	.23	+.37	+.02	6.87	−.24	+.57
	no. 2 (CA O_2 4.0)	1.65	.25	+.20	−.01	6.65	−.29	+.56
6	Control (CA O_2 21.7)	.71	.09	+.17	−.01	7.67	−.23	
	Anemia							
	no. 1 (CA O_2 7.9)	.72	.08	+.06	−.04	8.56	−.41	+.07
	no. 2	.50	.08	+.01	−.04	5.98	−.25	−.14
7	Control (CA O_2 16.8)	1.25	.13	−.66	−.03	9.54	+.41	
	Anemia (CA O_2 5.7)	5.21	.29	−.33	+.02	18.15	+.62	+2.47
8	Control (CA O_2 18.5)	1.19	.08	+.73	−.00	14.51	−.77	
	Hypoxia (CA O_2 10.3)	1.47	.18	+.22	+.01	8.26	−.15	−1.12
	Hypoxia + methoxamine (CA O_2 11.9)	2.97	.23	−.33	+.01	13.20	+.40	−0.30
9	Control (CA O_2 18.7)	1.64	.17	+.99	+.11	9.45	+.04	
	Hypoxia (CA O_2 9.0)	2.32	.17	+.16	+.01	14.03	−.09	+.76
	10′ recovery	3.53	.26	+.68	−.03	13.48	−1.13	+1.06
10	Control (CA O_2 18.4)	.35	.10	−.15	+.01	3.43	+.18	
	Hypoxia (CA O_2 6.1)	.50	.16	−.15	+.00	3.08	+.15	−.06
	10′ recovery (CA O_2 21.0)	.65	.14	−.30	+.02	4.69	+.41	+.17
11	Control (CA O_2 24.0)	1.83		+.82				
	Hypoxia (CA O_2 1.5)	1.67		−.30				
	10′ recovery	4.40		−.08				
12	Control (CA O_2 17.1)	3.35		+.64				
	Hypoxia (CA O_2 0.6)	5.03	.15	−1.47	+.03	33.76	+2.31	
	10′ recovery		.18		+.05			
13	Control (CA O_2 19.4)	1.99	.22	+.98	+.12	8.91	+.12	
	Hypoxia (CA O_2 0.1)	5.01	.17	−1.69	+.02	30.55	+2.36	+3.55
14	Control	1.69	.19	+.64	+.09	8.83	+.13	
	1.5′ after KCN	3.32	.15	−.82	−.01	22.15	+.71	+2.00
	3.5′ after KCN	5.60	.15	−.39	+.01	38.08	+.58	+4.30
	4.5′ after KCN	7.70	.14	+.26	−.01	56.23	−.71	+6.49
15	Control	1.20	.14	+.22	−.01	8.72	−.26	
	1.5′ after KCN	3.00	.14	−1.20	+.01	22.07	+1.45	+1.85
	4.5′ after KCN	5.74	.11	−.13	−.02	53.10	−1.05	+4.79
16	Control	.89	.11	+.30	+.02	8.30	−.15	
	1.5′ after KCN	2.03	.13	−1.69	+.00	15.60	+1.74	+0.95
	3.5′ after KCN	3.13	.11	−.94	±0	27.95	+.94	+2.20
	4.5′ after KCN	4.04	.13	−.51	−.01	30.60	+.36	+2.95
17	Control	3.90	.31	+1.35	+.10	12.81	−.12	
	4.5′ after KCN	8.37	.20	−.27	−.03	42.72	−.83	+5.86
18	Control	1.07	.13	+.01	+.00	8.45	+.00	
	1.5′ after KCN	2.89	.15	−1.06	−.02	19.68	+.61	+1.65
	3.5′ after KCN	4.38	.12	−1.27	−.03	36.80	+.05	+3.38
	4.5′ after KCN	5.48	.13	−.56	−.05	41.50	−1.56	+4.37
	6.5′ after KCN	7.05	.15	−.56	−.04	46.45	−1.34	+5.77
19	Control	4.13	.35	+1.57	+.16	11.71	+.33	
	1.5′ after KCN	4.85	.24	−1.02	+.05	20.02	+2.10	+2.01
	4.5′ after KCN	7.86	.15	−.41	+.01	53.89	+.99	+4.89
	Recovery	6.91	.51	+.76	−.01	13.68	−.91	+.99
20	Control	6.66	.35	+1.37	+.09	18.91	+.35	
	5.5′ after KCN	9.64	.19	−1.22	+.02	50.70	+2.08	+6.05

* Abbreviations: HR = heart rate; CA O_2 = coronary artery O_2 content.

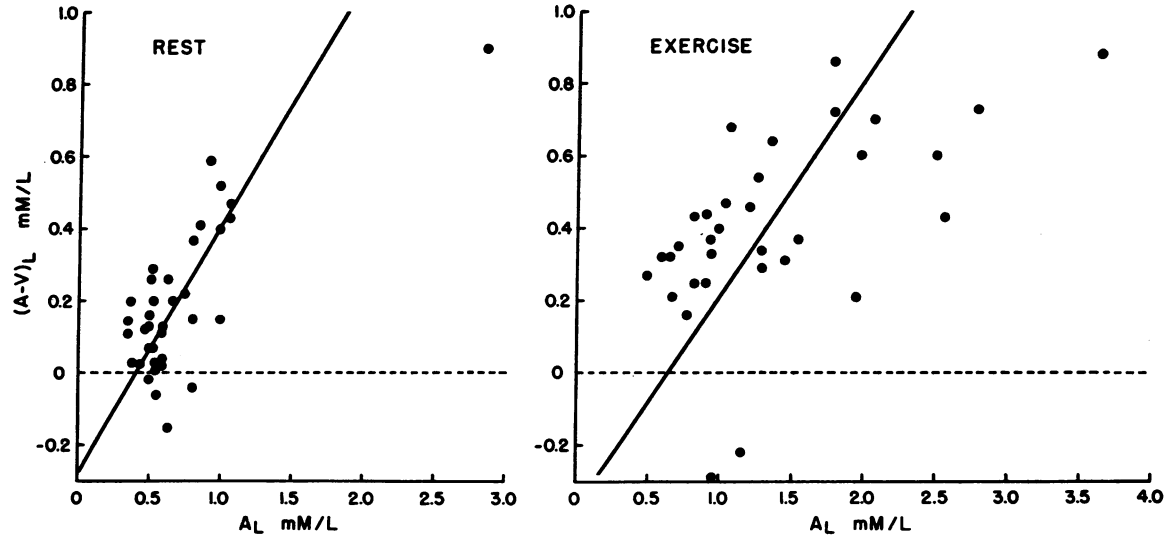

FIG. 1. MYOCARDIAL LACTATE EXTRACTION $(A\text{-}V)_L$ PLOTTED AGAINST ARTERIAL LACTATE CONCENTRATION (A_L) IN MAN. Rest: $r = 0.70$, σ_m 0.18; regression equation: $y = 0.70x - .28$. Exercise: $r = 0.57$, σ_m 0.19; regression equation: $y = 0.58x - .34$. The slopes are similar.

calculated as the product of arterial mean systolic pressure, and the total seconds of systole per minute derived from the directly recorded systemic pressure with a Statham P-23D strain gauge. Total body oxygen consumption was measured with a Pauling oxygen analyzer and Tissot spirometer.

Lactate was measured by a slight modification of the enzymatic method of Horn and Bruns (26). Lactic dehydrogenase and trapping pyruvate formed with semicarbazide was used, and DPNH generation was read at 340 mμ on a Beckman DU spectrophotometer. Pyruvate was determined by a modification of the method of

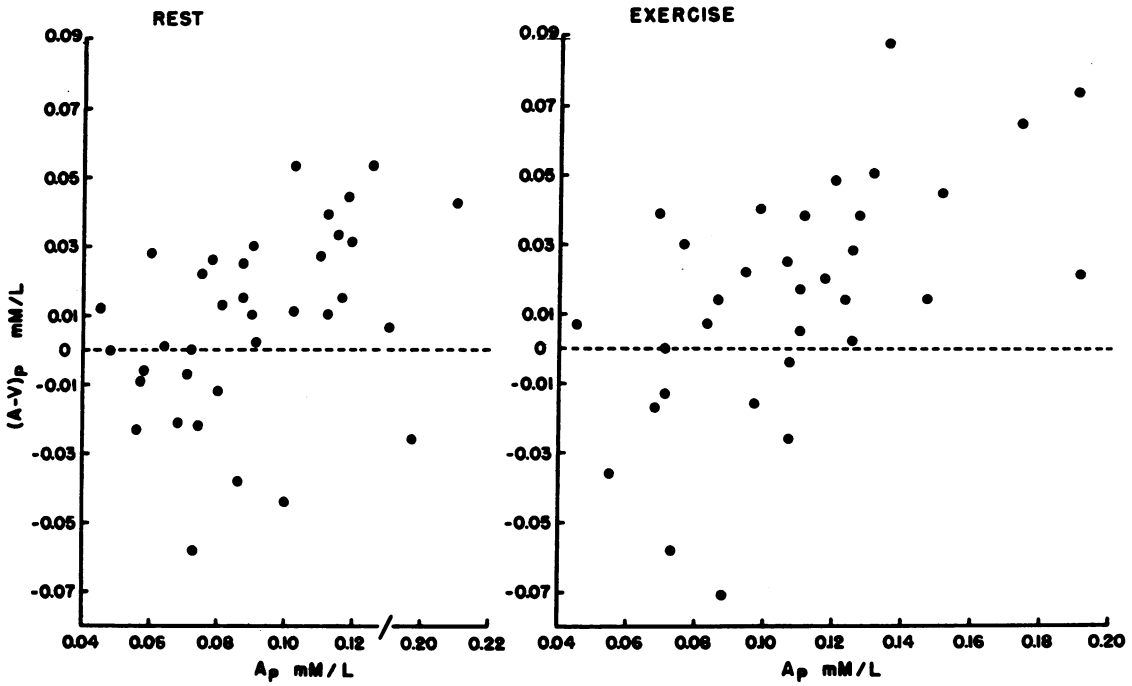

FIG. 2. MYOCARDIAL PYRUVATE EXTRACTION $(A\text{-}V)_P$ PLOTTED AGAINST ARTERIAL PYRUVATE CONCENTRATION (A_P) IN MAN. On exercise a trend toward increasing extraction with increasing arterial concentration is seen ($r = 0.43$, σ_m .19).

Redetzki, Blaedon, and Bansi (27), by the addition of lactic dehydrogenase and DPNH to the sample in phosphate buffer. Filtrates were stored at 5° C until analyzed. Standards were run with each set of determinations and averaged 98 per cent recovery for lactate and 107 per cent for pyruvate with linearity of recovery over a range of standard concentrations. Duplicate lactate and pyruvate determinations agreed within an average of .03 mmoles per L and .004 mmoles per L, respectively. In some instances, lactate was measured by the same method (26) in the laboratory of Dr. Albert Renold and pyruvate by the colorimetric method of Bueding and Wortis (28). There were some minor quantitative differences in results from the two laboratories when the results were run in duplicate, but these were random and the data, therefore, will be treated as homogeneous.

Myocardial excess lactate (XL) in millimoles per liter of whole blood was calculated with the Huckabee equation (3): *myocardial* $XL = (CV - A)_L - (CV - A)_P (A_L/A_P)$, where CV_L = coronary venous lactate, mmoles per L; A_L = arterial lactate, mmoles per L; CV_P = coronary venous pyruvate, mmoles per L; and A_P = arterial pyruvate, mmoles per L.

Total body excess lactate production during 5 minutes of exercise was calculated from the shift in arterial values from rest to exercise: $TBXL = (A_{es} - A_r)_L - (A_{es} - A_r)_P (A_{r_L}/A_{r_P})$, where A_{es_L} = arterial lactate during exercise, mmoles per L; A_{r_L} = arterial lactate at rest, mmoles per L; A_{es_P} = arterial pyruvate during exercise, mmoles per L; and A_{r_P} = arterial pyruvate at rest, mmoles per L.

A positive excess lactate refers to that amount of lactate produced in excess of that related to pyruvate consumption. A negative excess lactate implies consumption of lactate by the organ in excess of that related to pyruvate consumption.

RESULTS

Human observations

Myocardial lactate-pyruvate extraction. There was no pattern of lactate and pyruvate extraction

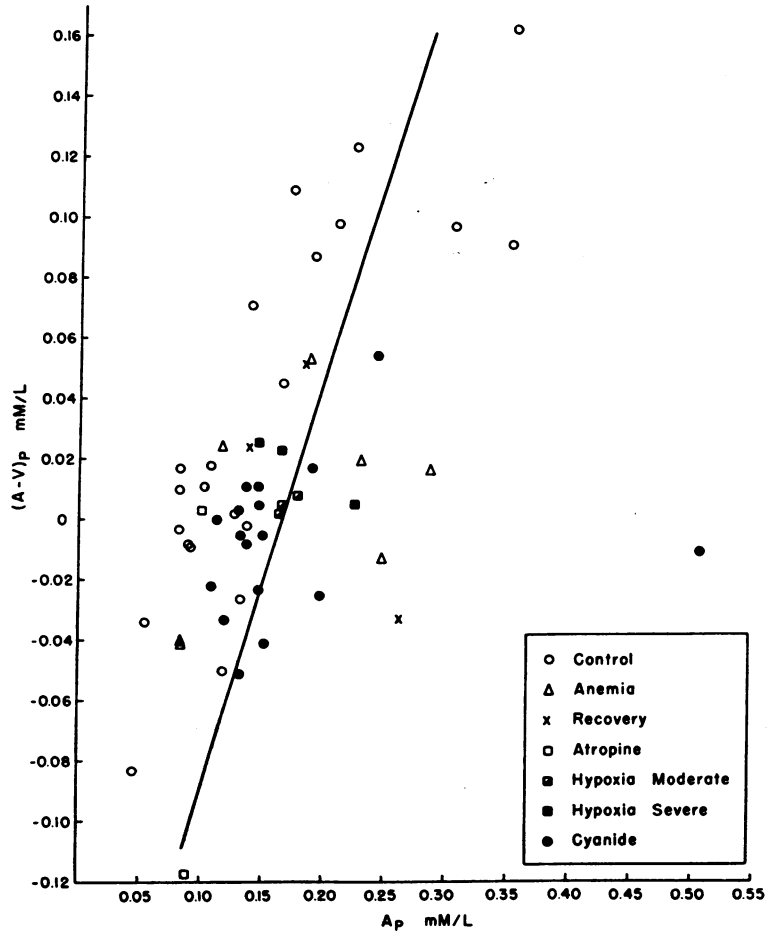

FIG. 3. MYOCARDIAL PYRUVATE EXTRACTION $(A\text{-}V)_P$ PLOTTED AGAINST ARTERIAL PYRUVATE CONCENTRATION (A_P) IN DOGS. $r = 0.52$, σ_m 0.13; regression equation: $y = 1.37x - .23$.

characteristic of any clinical group. These data will, therefore, be considered as from a homogeneous sample. The differences in hemodynamics and myocardial oxygen supply among these groups have been discussed elsewhere (17, 29). Both at rest and on exercise, there was a linear correlation between arteriovenous extraction of lactate and arterial concentrations ($r = 0.70$, σ_m 0.18 at rest; and $r = 0.57$, σ_m 0.19 on exercise) (Figure 1). At the lower ranges of arterial concentration, a few negative differences were seen. Although there was a trend for pyruvate extraction to follow arterial concentration, because of the scatter, a low correlation was seen (Figure 2).

The mean coefficients of extraction (A-V/A) for lactate and pyruvate at rest were 0.26, $\sigma = .21$, and 0.06, $\sigma = .32$, respectively. With exercise, the mean arterial pyruvate, arteriovenous difference, and extraction ratio did not change significantly. On the other hand, the mean arterial lactate level and arteriovenous difference increased significantly, but the extraction coefficient did not (0.31, $\sigma = .19$) ($0.1 < p < 0.2$).

Myocardial excess lactate. The mean resting myocardial excess lactate was -0.18, $\sigma = .45$ mmoles per L. Only three subjects, two with a history of angina pectoris (LR, RC), produced excess lactate at rest. During exercise excess lactate remained the same [2] or became more negative in 26 of 32 subjects (including LR and RC). Five subjects produced excess lactate during effort; three of these had coronary insufficiency (VW, AS, CM). Four of these five subjects extracted lactate (positive arteriovenous difference), but to a lesser degree relative to pyruvate extraction. There was no quantitative correlation of lactate utilization with the degree of stress as defined by individual changes in pressure-time per minute or myocardial oxygen consumption. There was no correlation of excess lactate with the level of coronary venous oxygen saturation at rest or change on exercise. Net changes in lactate-pyruvate ratio from arterial to coronary venous blood were similar in direction to changes in excess lactate.

Systemic excess lactate. There was a rise in arterial lactate from rest (.070, $\sigma = .43$ mmoles per L) to exercise (1.36, $\sigma = .69$ mmoles per L), and since arterial pyruvate did not increase proportionately, calculated total body excess lactate was positive in all patients (except one) after 5 min-

[2] Less than 0.2 mmoles per L. This approximated the potential error if each figure in the excess lactate equation varied by the mean error of the determination, but in the opposite direction to maximize or minimize the calculated excess lactate.

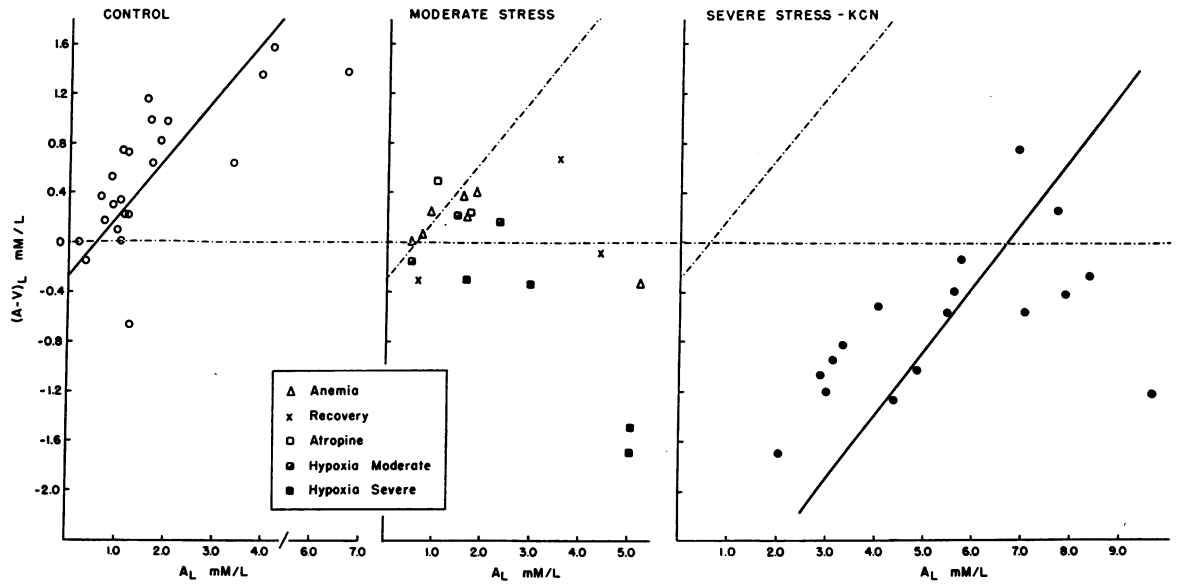

FIG. 4 (A, B, AND C). MYOCARDIAL LACTATE EXTRACTION $(A-V)_L$ PLOTTED AGAINST ARTERIAL LACTATE CONCENTRATION (A_L) IN DOGS. Control: $r = 0.76$, σ_m .21; $y = .48x - .29$. Cyanide: $r = 0.53$, σ_m .25; $y = .52x - 3.44$ (dashed line represents control). Note parallel slopes.

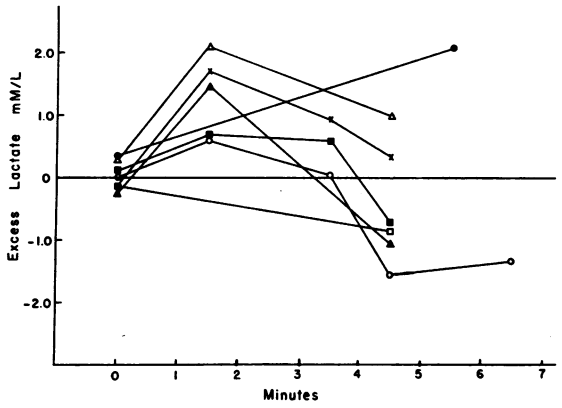

FIG. 5. EXCESS LACTATE PRODUCTION AFTER A SINGLE INTRAVENOUS INJECTION OF CYANIDE GIVEN IMMEDIATELY AFTER CONTROL OBSERVATIONS (TIME ZERO). Note the initial rise, then decline, and finally reversal to negative excess lactate.

utes of exercise. This rise in total body excess lactate correlated well in most cases with the increment of total body oxygen consumption, although in four (LR, GW, AH, RG), there was considerably greater total body excess lactate produced relative to oxygen consumption (30). Only two of these latter had congestive heart failure.

Animal observations

In control observations myocardial lactate and pyruvate extractions were proportional to their respective arterial concentrations (Figures 3 and 4). Myocardial excess lactate was less than 0.2 mmoles per L in 15 of 18 control observations.

The stress of mild tachycardia (heart rate, 109 to 150), anemia (arterial oxygen, 4.0 to 17.6 vol per cent [3]), or moderate hypoxia (arterial oxygen, 6.1 to 10.3 vol per cent) depressed lactate extraction (Figure 4B), but excess lactate was seen in only three experiments.

Cyanide and severe hypoxia decreased the absolute extraction of lactate at any given arterial level (Figure 4C). Successive increases in arterial lactate in each dog, however, were associated with a slope of progressively increased extraction (or decreased production), but transposed to the right of the control slope. Extraction was depressed or reversed, but at sufficiently high arterial concentrations did become positive. Myocardial excess lactate was observed consistently during the first 2 minutes after cyanide injection. However, after 2 minutes, while arterial lactate rose progressively, myocardial excess lactate decreased or even became negative (Figure 5).

[3] Initial capacity, 22.9 vol per cent.

DISCUSSION

Lactate and pyruvate are of interest in myocardial metabolism for two reasons: *1*) myocardium, liver, and renal cortex are the major mammalian tissues known to utilize lactate as substrate for energy production; *2*) lactate and pyruvate hold a central position in relation to anaerobic metabolism.

Substrate utilization. Utilization of lactate has usually been expressed as an extraction ratio, i.e., uptake relative to arterial level. Extraction ratios for lactate and pyruvate have been shown to be decreased in a variety of human disease states (10–12, 14–16) and animal experiments (4–7, 31–34). In the current study, no differences were found in mean extraction of lactate and pyruvate between patients in failure and other patient groups at rest. The stress of mild physical exercise in these subjects did not significantly alter extraction. The variation in data preclude drawing any inference from changes in extraction ratios in a given patient.

Extraction is not a problem of "threshold," as was previously maintained (12, 13), but rather one of net balance. The regression lines for pyruvate and lactate extraction in man and dogs do not pass through the origin (Figures 1–4). At low arterial levels the effects of endogenous lactate production may be observed as a negative arteriovenous difference. Conversely, in cyanide anaerobiosis a linear relation between arterial level and extraction was maintained, with a slope similar to the controls, but transposed to the right (Figure 4C). The negative arteriovenous difference actually became positive when the arterial level was sufficiently elevated.

Myocardial lactate uptake for any given arterial concentration will be decreased if intracellular glycolysis increases or if increased free fatty acid uptake inhibits pyruvate entry into the tricarboxylic acid cycle through competition for available coenzyme A (35). In either circumstance, increased intracellular lactate and pyruvate concentrations will prevent further ingress from the

blood. The low extraction ratio observed during cyanide poisoning may result from either or both possibilities.

Anaerobic metabolism. Although open to certain objections (see below), the calculation of excess lactate permits analysis of one aspect of myocardial redox potential under physiologic conditions. In the human study, the fact that excess lactate at rest was usually negative and tended to become more negative on exercise would suggest that the myocardium was deriving energy through oxidative pathways. Although Huckabee (1) found myocardial excess lactate in the anesthetized dog exercised by electrical stimulation of leg muscles, this was demonstrated only rarely in the exercising human subject, or with mild stress in the dog. The discrepancy in results may be related in part to different experimental conditions, including duration and degree of physical stress.

Of five patients who did develop excess lactate on exercise, three had clinical coronary insufficiency. Only two of these showed a fall in coronary venous oxygen saturation (17) during exercise, but none had chest pain at the time of study. In three patients not in this series, angina pectoris precipitated by exertion was associated with excess lactate production. There is no explanation for the occurrence of resting excess lactate in three patients discussed earlier.

Myocardial excess lactate has not occurred thus far in normal subjects. It is possible that with further refinement of technic and by prolonged or more severe stress, excess lactate may be seen more frequently. At present, however, these results militate against the concept of myocardial anaerobiosis as a physiologic process in normal man. Anaerobiosis in subjects with coronary insufficiency may represent a biochemical expression of the basic pathologic defect. Excess lactate may derive solely from localized portions of ischemic myocardium. With both normal and ischemic muscle draining into the coronary sinus, sampling of such mixed venous blood may not always reveal excess lactate even when it is generated locally.

That anaerobiosis remains primarily a late phase of defense against deprivation of oxygen supply is evident from these and other animal studies. Moderate hypoxia or anemia comparable to the hypoxic stress applied by Huckabee (1) was usually met by increased oxygen extraction and coronary flow alone. Only when severe hypoxemia was produced, or when cyanide was used to inhibit tissue respiration did anaerobic metabolism become uniformly apparent.

Energy availability. The total energy derived from anaerobiosis poses a different phase of the problem. In the human subjects and mildly stressed animals, the calculated contribution (1) of excess lactate to total energy utilization comprised less than 5 per cent of the total. During the early phase of cyanide intoxication, however, calculated excess lactate became significant in amount but rapidly decreased by 4.5 minutes after injection. The reasons for this are unclear. Although the pattern of change was uniform, these results may have been due to an unsteady state (36) or to the unusually high coronary flow rates (37), either of which might have rendered blood concentrations of one or both substances nonrepresentative of tissue. The cyanide experiments of Lochner, Mercker, and Nasseri (38) would suggest that the declining excess lactate seen in the present study is not due to inhibition of glycolysis by increased lactate or hydrogen ion concentration or to depletion of tissue glycogen. These problems prevent calculation of the precise energy balance. Furthermore, although excess lactate may serve as an indicator of anaerobiosis, energy in the form of phosphate bonds may be generated from glycolysis per se even when excess lactate is zero.

There are other problems associated with the excess lactate concept in addition to difficulties with steady state and heterogeneous tissue perfusion mentioned above. *1*) The quantities of pyruvate involved are small and, accordingly, difficult to measure. Moreover, the influence of these low values for pyruvate on the lactate-pyruvate ratio, and thereby on the entire calculated excess lactate, may be considerable. *2*) The assumption that lactate is a dead-end of metabolism has recently been questioned (39) with *in vitro* evidence suggesting that lactate may react directly with cytochrome b and thus bypass the DPN : DPNH ratio as the sole arbiter of its oxidation-reduction shifts with pyruvate. The quantitative importance, however, of this pathway has not been measured. *3*) The DPN : DPNH re-

dox potential is the lowest of the electron transport system and, presumably, the most sensitive to hypoxia. This represents the intramitochondrial DPN : DPNH. The DPN : DPNH system regulating the lactate-pyruvate ratio, however, is extramitochondrial and dependent on a "shuttle" system for transporting intracellular hydrogen across the mitochondrial membrane (40). The full details and significance of this "shuttle" system for normal mammalian tissue and its role in DPN : DPNH control as opposed to the lactic dehydrogenase system as an indicator of anaerobiosis remain to be elucidated. In any case, it is clear that blood lactate and pyruvate, and blood redox potential (16) are several stages removed from the locus of cellular oxygenation, and represent only an approximation of intracellular events.

SUMMARY

Lactate and pyruvate metabolism was studied in 34 patients with varying forms of heart disease, at rest and during mild leg-exercise, and in 20 intact anesthetized dogs subjected to varying stress. Lactate and pyruvate extraction was a function of arterial concentration, with uptake at the higher ranges and production at lower arterial concentrations. Exercise did not alter the mean extraction ratio of lactate or pyruvate from the resting value. Myocardial excess lactate was negative at rest in the majority of subjects, and did not change or became more negative (i.e., increased utilization) on exercise in the majority, irrespective of the type of heart disease. In some subjects, however, primarily those with coronary insufficiency, positive excess lactate was seen at rest, or on exercise, or both, suggesting that anaerobic metabolism may sporadically contribute small amounts of energy to the heart.

Control myocardial excess lactate in dogs was negative and became more negative with moderate stress. Lactate production and positive excess lactate were consistently seen only with severe hypoxia and cyanide intoxication.

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