Hemodynamics, Coronary Blood Flow, and Myocardial Metabolism in Coronary Shock; Response to *l*-Norepinephrine and Isoproterenol

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ABSTRACT Hemodynamics and myocardial metabolism were evaluated in 18 patients in cardiogenic shock following acute myocardial infarction. The response to *l*-norepinephrine was studied in seven cases and the response to isoproterenol in four cases. Cardiac index (CI) was markedly reduced, averaging 1.35 liters/min per m^2. Mean arterial pressure ranged from 40 to 65 mm Hg while systemic vascular resistance varied widely, averaging 1575 dyne-sec-cm^{-5}. Coronary blood flow (CBF) was decreased in all but three patients (range 60–95, mean 71 ml/100 g per min). Myocardial oxygen consumption (MV_{O_2}) was normal or increased ranging from 5.96 to 11.37 ml/100 g per min. Myocardial oxygen extraction was above 70% and coronary sinus oxygen tension was below 22 mm Hg in most of the patients. The detection of the abnormal oxygen pattern in spite of sampling of mixed coronary venous blood indicates the severity of myocardial hypoxia. In 15 studies myocardial lactate production was demonstrated; in the remaining three lactate extraction was below 10%. Excess lactate was present in 12 patients. During *l*-norepinephrine infusion CI increased insignificantly. Increased arterial pressure was associated in all patients by increases in CBF, averaging 28% ($P < 0.01$). Myocardial metabolism improved. Increases in MV_{O_2} mainly paralled increases in CBF. Myocardial lactate production shifted to extraction in three patients and extraction improved in three. During isoproterenol infusion CI increased uniformly, averaging 61%. Mean arterial pressure remained unchanged but diastolic arterial pressure fell. CBF increased in three patients, secondary to decrease in CVR. Myocardial lactate metabolism deteriorated uniformly; lactate production increased or extraction shifted to production. In the acute state of coronary shock the primary therapeutic concern should be directed towards the myocardium and not towards peripheral circulation. Since forward and collateral flow through the severely diseased coronary bed depends mainly on perfusion pressure, *l*-norepinephrine appears to be superior to isoproterenol; phase-shift balloon pumping may be considered early when pharmacologic therapy is unsuccessful.

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INTRODUCTION

Acute pump failure with peripheral circulatory collapse has become one of the major causes of death in acute myocardial infarction. In contrast to the significant improvement in the treatment of cardiac arrhythmias, little change has been made in the mortality of coronary shock. Some investigators have suggested that improved monitoring and treatment techniques may improve immediate survival but increase the incidence of coronary shock; recent reports from coronary care units suggest this to be the case (1).

Systemic hemodynamic measurements have been made in acute shock by a number of investigators (2–9) although coronary shock has not always been clearly separated from other varieties of cardiogenic shock. Isoproterenol (2, 7, 10–12), *l*-norepinephrine (3, 5, 6, 8, 12–14), alpha adrenergic blocking agents (11, 12, 15), intra-aortic phase-shift balloon pumping (16–19), and other techniques have been recommended for coronary shock but evidence of their efficacy has been limited to measurements of cardiac output and peripheral vascular resistance.

We have recently studied myocardial metabolic derangements in a group of patients with shock of varying cause (20) and emphasized that while evidence of anaerobic metabolism is uniformly observed in coronary

TABLE I

Clinical Data in Coronary Shock

Subject	Age	Sex	Infarction (ECG)		Arrhythmia	Pace-maker	Status prior to study			Type of respirator
			Acute	Old			Shock	*l*-NE	Iso.	
	yr						*hr*	*hr*	*hr*	
1	54	F	AWI, RBBB	IWI	AF	No	6		6	Emerson
2	78	M	AWI, IWI, RBBB		AF	Yes	12	10		Emerson
3	47	F	AWI		SVT	"	3	½		Emerson
4	56	M	IWI, PWI, RBBB		VF	"	8	1		Emerson
5	75	F	AWI, IWI, LBBB		SVT, VF	"	6			Emerson
6	60	F	ALWI, IWI, RBBB		VF	"	3			Emerson
7	61	M	IWI, PWI, RBBB		SVT	"	3			Emerson
8	61	M	AWI, RBBB	IWI	AVNR	"	10	2		Mask
9	66	M	ALWI, RBBB, LBBB		VT	"	1			Bird
10	67	M	ASWI, RBBB	IWI	AVB 1°	"	6			Mask
11	60	M	AWI	PWI	Flutter	"	10	3	1	Bird
12	72	M	PWI, LBBB		AVB 3°	"	48		6	Mask
13	62	M	PWI	ASWI	SVT	No	26		2	Emerson
14	58	F	ILWI	ASWI	AF	"	16			Emerson
15	66	M	AWI, RBBB			"	8		2	Emerson
16	67	M	ALWI, RBBB		AVB 1°	Yes	10			Emerson
17	58	M	ALWI		SVT	"	9			Emerson
18	63	M	IPWI		VT, VF	"	3			Emerson

AWI = anterior wall infarction; ALWI = anterior and lateral wall infarction; ASWI = anterior septal wall infarction; PWI = posterior wall infarction; ILWI = inferior and lateral wall infarction; IPWI = inferior and posterior wall infarction; RBBB = right bundle branch block; IWI = inferior wall infarction; LBBB = left bundle branch block; AF = atrial fibrillation; AVNR = AV-nodal rhythm; VT = ventricular tachycardia; AVB = atrioventricular block; Flutter = atrial flutter; SVT = supraventricular tachycardia; VF = ventricular fibrillation; *l*-NE = *l*-norepinephrine; Iso. = isoproterenol.

shock, myocardial metabolism appears to be normal in hemorrhagic, septic, and noncoronary cardiogenic shock. This paper presents myocardial metabolism and systemic hemodynamic data in 18 patients with severe coronary shock. Studies performed during administration of both *l*-norepinephrine and isoproterenol demonstrate the different responses of myocardial perfusion and metabolism to changes in coronary perfusion pressure and vascular resistance.

METHODS

Selection of patients and preliminary therapy

All patients admitted to St. Vincent's Hospital and Medical Center of New York with signs and symptoms suggesting the shock syndrome are transferred to a specially equipped shock unit for continuous electrocardiographic and vascular pressure monitoring. All patients with acute myocardial infarction are admitted to a coronary care unit and transferred to the shock unit if indicated. Details of admission to the coronary care unit together with over-all survival experience have been previously published (21).

Patients were considered for the present study if the following criteria were met: (*a*) systolic blood pressure less than 80 mm Hg or less than 75% of a previously known hypertensive level; (*b*) absent or poorly palpable peripheral pulses; (*c*) cold, clammy extremities with mottled skin; (*d*) changes in mental status with either agitation or lethargy; (*e*) urine output less 20 ml/hr; and (*f*) electrocardiographic findings suggesting acute myocardial infarction. Patients fulfilling these criteria were invariably in severe coronary shock; all but one of the 18 patients died during the current hospitalization although five survived for more than 1 wk.

These 18 patients were studied between October, 1968 and April, 1970. Seven patients died in the emergency room or shock unit before initiation of study and studies in two patients were discontinued for technical reasons. Other patients in shock were evaluated during this period but were rejected for study for a variety of reasons not directly related to the shock state. Drug interventions were based on the over-all clinical status of the patient and reflected our desire to limit the evaluation to one control and one drug study. Isoproterenol was not administered if the control heart rate was above 110 or if the heart was electrically paced. Vasoactive agents were not evaluated in patients 3–8, the most recently studied group, because they were subsequently studied during intra-aortic phase-shift balloon pumping. With these exceptions, no further selection was imposed.

Emergency therapy was instituted and attempts were made to stabilize the patient before performance of studies. Details of preliminary therapy together with a summary of clinical findings are presented in Table I. Ventilatory status was evaluated by measurement of arterial oxygen and carbon dioxide tension (Pa_{O_2} and Pa_{CO_2}) and 15 of the 18 patients were intubated and placed on an appropriate

respirator. Our indications for intubation and selection of respirator have been previously published (22). The remaining three patients were breathing 100% oxygen by face mask. Blood buffer stores were augmented by the infusion of sodium bicarbonate. Volume deficits were corrected and central venous pressure maintained between 10 and 14 mm Hg. Patients were sedated as necessary with Demerol (meperidine) 15–25 mg/hr intravenously and Phenergan (promethazine) 25 mg every 3 hr intravenously. *l*-Norepinephrine was administered in three patients because arterial systolic blood pressure was either unobtainable or below 60 mm Hg. Transvenous pacemakers were inserted in 14 patients.

Experimental procedure

The following protocol was approved by the Research Committee of St. Vincent's Hospital and Medical Center of New York. Specific permission was obtained from responsible family members since the patients were extremely ill and unable to understand the implications of the studies. The family members were told that the situation was extremely grave and the mortality high. It was proposed that the patient be treated on an around-the-clock basis by a specially trained team of attending physicians and nurses. They were specifically informed that many of the procedures were experimental and investigative in nature but that the results might be of direct benefit to the patient under treatment.

A No. 14 polyethylene catheter[1] was inserted by puncture into a surgically exposed radial artery and another No. 14 polyethylene catheter[1] inserted into the right median basilic vein and advanced into the right atrium. A No. 7 Goodale-Lubin catheter was advanced into the middle portion of the coronary sinus via the left median basilic vein. The position of the catheter tip was checked by injection of Hypaque (sodium diatrizoate). A No. 6 USCI bipolar pacemaker catheter was advanced into the right ventricle via the right external jugular vein. Urine output was measured hourly from a Foley catheter. Vascular pressures were measured with P23d Statham strain gauges and recorded by a multichannel oscilloscopic recorder.[2]

Each series of metabolic observations require 20–25 min and approximately 200 ml of blood. Blood required for Indocyanine Green cardiac output determinations could be reduced to 100–120 ml by the reinfusion of part of the withdrawn blood. All volume losses were corrected by either blood or dextran administration; hematocrits were checked before each experimental period. Vasoactive agents were discontinued for 30 min before performance of study. A metabolic series included duplicate determination of cardiac output, coronary blood flow determination, and sampling of arterial and coronary sinus blood. Arterial and central venous pressures and heart rate were recorded during measurement of cardiac output and coronary blood flow. The metabolic series was repeated during the infusion of *l*-norepinephrine, isoproterenol, or both. The vasoactive agent was titrated to maintain a mean aortic pressure of approximately 70 mm Hg.

In addition to these complete studies, serial measurements of arterial lactate and pyruvate, coronary sinus oxygen tension, and extraction ratios for lactate, pyruvate, and oxygen were made in six patients in coronary shock without altering base line conditions.

Methods of analysis

Arterial and coronary sinus blood was collected in heparinized syringes and immediately analyzed in duplicate for oxygen and carbon dioxide tensions and pH using microtip platinum (23), Severinghaus (24), and glass electrodes, respectively (25). Details of tonometry and estimates of reliability have been previously published (26). Oxygen and carbon dioxide content were measured by the Van Slyke manometric method (27).

Additional aliquots of arterial and coronary sinus blood were sampled in dry glass syringes, precipitated within 30 sec in 0.6 M perchloric acid, and analyzed enzymatically for lactate (28) and pyruvate (29). These analyses were begun as soon as the study was completed to prevent in vitro change in lactate and pyruvate concentration (30). The standard deviation of the difference between 106 pairs of bloods analyzed in duplicate for lactate was 0.0578 mmoles/liter (coefficient of variation, 3.35%) while the standard deviation of the differences between 33 lactate determinations compared to a standard solution was 0.0476 mmoles/liter, which gives a coefficient of variation of 4.47%. From these two estimates it may be calculated that the error of dilution and pipetting during the lactate determinations is 3.1%.[3]

The standard deviation of the differences between 90 paired pyruvate duplicate analyses was 0.00358 mmoles/liter (coefficient of variation, 3.0%) with a standard deviation of the differences of 0.0588 mmoles/liter based on comparison with standard solution in 34 analyses (coefficient of variation, 2.7%). These estimates of reliability included all analyses from the shock studies. The average arterial lactate content in 30 normal subjects was 0.916 ±0.0906 mmoles/liter (SD), the average arterial pyruvate content was 0.0896 ±0.0163 mmoles/liter (SD). The myocardial extraction of lactate and pyruvate in 62 patients without evidence of coronary disease was closely related to arterial substrate concentration ($r\,60_{x1}) = 0.885$, $P < 0.001$ for lactate; $r\,60_{x2} = 0.893$, $P < 0.001$ for pyruvate). The linear regression formulas corresponding to these correlations are $y_1 = 0.1981_{x1} - 0.430$ and $y_2 - 0.6361_{x2} - 0.221$, respectively, where y_1 is arterio-coronary sinus lactate difference and x_1 arterial lactate content; where y_2 is arterio-coronary sinus pyruvate difference and x_2 arterial pyruvate content.

Cardiac output was measured by Indocyanine Green dilution techniques (31). Indicator was injected by calibrated observation tube into the right atrium and arterial blood withdrawn through a Gilford densitometer[4] by a Harvard

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[1] Bardic. C. R. Bard, Inc., Murray Hill, N. J.

[2] Electronics for Medicine, Inc., White Plains, N. Y.

[3] $SD_a = \sqrt{(SD_b)^2 \text{ pipetting and dilution} + (SD_c)^2 \text{ other technical errors}}$

where SD_a = standard deviation for check against standard

SD_b = standard deviation due to pipetting and dilution

SD_c = standard deviation for duplicate determination.

[4] Gilford Instrument Labs., Inc., Oberlin, Ohio.

syringe pump.[5] All determinations were performed in duplicate or triplicate. The standard deviation of the difference between 27 duplicate cardiac output determinations performed during acute shock was 0.245 liter/min with a coefficient of variation of 7.35%. Details of methodology including calibration procedures have been previously published (32).

Coronary blood flow was measured by a modification of the ^{131}I-labeled[6] iodoantipyrine method of Krasnow, Levine, Wagman, and Gorlin (33). The method is simplified by providing arterial and coronary sinus catheters of equal volume. Iodoantipyrine-^{131}I is infused at a constant rate into the right atrium and the total amount of isotope delivered during each determination progressively increased in increments of 8 μCi (beginning with 8 μCi) to compensate for increases in isotope background. Arrival time of isotope at the sampling syringes is calculated as the sum of (*a*) arrival time from catheter tip in right atrium to radial artery (derived from Indocyanine Green dilution curve corrected for lag in arterial sampling catheter) and (*b*) the time required for isotope to travel the length of the sampling catheters at the rate of withdrawal used during sampling. Integrated samples are smoothly drawn at a rate of 1 ml/10 sec and syringes changed at intervals of 30 sec. A two-stopcock manifold permits the previous positioning of three sampling syringes and facilitates continuous integrated sampling. 2-ml aliquots from each 30 sec sampling period are counted for 10 min by an auto-gamma counter[7] and arterial and coronary sinus curves plotted for each determination. Coronary blood flow is calculated from the expression of the Kety principle (34) presented by Krasnow et al. (33) with two modifications. The initial 2 min sampling period is disregarded in the calculations and the concentration of isotope in coronary sinus blood at the end of infusion is determined by extrapolation of the coronary sinus saturation curve instead of quickly withdrawing a "spot" sample as recommended by the later group.

Methods of data processing and statistical evaluation

All results of measurements of raw data were entered on a specially prepared coding sheet and punched on standard data cards. Data were analyzed by standard statistical techniques using an IBM 1800 computer. Errors of experimental methods were expressed as the ratio of standard deviations of the differences of duplicate determinations to the average value for all determinations (coefficient of variation). All results were initially evaluated in a multiple regression program for study of interrelationships. Significance of change in any measured or calculated variable following drug administration was tested by variance analysis utilizing each subject as its own control.

Abbreviations and calculations

Directly obtained data. HR = heart rate, S = systolic pressure, D = diastolic pressure, M = mean pressure, CVP = central venous pressure, CBF = coronary blood flow, Pcs_{O_2} = coronary sinus oxygen tension, A_L = arterial lactate content, A_P = arterial pyruvate content.

Derived data. Cardiac index (CI) (liters/min per m^2) = cardiac output divided by body surface area. Systolic ejection period (SEP, sec/beat) = interval between onset of the rise in aortic pressure and the incisura (35). Interval was measured from aortic or radial artery tracing, recorded at 100 mm/sec paper speed. Systolic ejection rate (SER, ml/sec per m^2) = stroke index/systolic ejection period (36). Systemic vascular resistance (SVR, dyne-sec-cm^{-5}) = mean arterial pressure minus mean right atrial pressure times 79.9 (conversion factor for mm Hg to dyne-sec-cm^2)/cardiac output. Tension time index per minute (TTM, mm Hg sec/min) = mean systolic arterial pressure times systolic ejection period times heart rate (37). Left ventricular work index (LV_{WI}, kg-m/min per m^2) = mean systolic arterial pressure times cardiac index times 1.36 (conversion factor for mm Hg to water)/100 (reference 38). Myocardial oxygen consumption (MVo_2, ml/100 g per min) = arterio-coronary sinus oxygen content difference times coronary blood flow (38). Myocardial oxygen extraction ratio (Exo_2, %) = arterio-coronary sinus oxygen difference/arterial oxygen content. Myocardial lactate consumption (MV_L, μmoles/100 g per min) = arterio-coronary sinus lactate difference times coronary blood flow. Myocardial lactate extraction ratio (Ex_L,%) = arterio-coronary sinus lactate difference/arterial lactate content. Myocardial pyruvate consumption (MV_P, μmoles/100 g per min) arterio-coronary sinus pyruvate difference times coronary blood flow. Myocardial pyruvate extraction ratio (Ex_P,%) = arterio-coronary sinus pyruvate difference/arterial pyruvate content. Oxygen utilization coefficient (ml/100 g per SEP) = myocardial oxygen consumption/SEP per minute (38). Lactate utilization coefficient (μmoles/100 g per SEP) = myocardial lactate consumption/SEP per min. Excess lactate (X_L mmoles/liter) = coronary sinus-arterial lactate difference minus coronary sinus-arterial pyruvate difference times arterial lactate to pyruvate ratio (39). Myocardial respiratory quotient (MRQ) = coronary sinus-arterial carbon dioxide difference divided by arterio-coronary sinus oxygen difference.

RESULTS

Clinical course and pathologic findings

Base line arterial blood gas data, vasopressor therapy in the shock unit, and survival and autopsy findings are listed in Table II. Five patients survived for more than 1 wk and one patient was discharged from the hospital. Patients 3–7 and 16–18 were treated with phase-shift balloon pumping (18). Postmortem examinations were performed in 9 of the 17 patients who died and revealed extensive old and recent myocardial infarction associated with severe coronary artery disease.

Temporal variations in myocardial metabolism

Serial measurements of arterial lactate and pyruvate concentrations, coronary sinus oxygen tensions (Pcs_{O_2}), and oxygen extraction ratios for lactate, pyruvate, and oxygen are shown in Table III. The variation among serial measurements for each of the six patients is reflected in the average coefficients of variation. The average coefficient of variation for arterial lactate was 3.9%, for oxygen extraction 3.5%, for lactate extraction 12.8%, and for pyruvate extraction 115%. Lactate extraction never changed to production although frequent

[5] Harvard Apparatus Co., Millis, Mass.
[6] Abbott Laboratories, Chicago, Ill.
[7] Packard Instrument Co., Downers Grove, Ill.

TABLE II

Treatment and Outcome of Coronary Shock

Subject	Base line data				Therapy in unit			Survival	Complications	Autopsy
	pH	HCO_3	Pao_2	Temp.	*l*-NE	Iso.	CP			
	U	*mEq/liter*	*mm Hg*	*°F*	*hr*	*hr*	*hr*			
1	7.46	32	260	99.2	4	20		24 hr	Ocl. of abdominal aorta	Ocl. of RCA and LDCA, recent AWI, old PWI
2	7.49	26	112	98.4	12			12 hr	Mechanical asystole	
3	7.39	25	221	99.8	7		93	4 days	Persistent SVT	Ocl. of LDCA, recent AWI, severe sclerosis of LCCA and RCA
4	7.54	25	255	100.2	72		22	14 days	Kidney failure, pneumonia, ischemia of left leg	Ocl. of RCA and distal LCCA, recent IPWI, sclerosis of LDCA
5	7.40	20	278	97.6	7		72	6½ days	Myxedema, extension of infarction, mechanical asystole	
6	7.35	20	99	98.8	6		17	3½ days	Diabetes mellitus, long-standing hypertension, kidney failure	
7	7.40	24	68	99.6	7		24	38 hr	Mechanical asystole	
8	7.26	18	141	99.8	2			Alive*	Pulmonary edema	
9	7.54	20	70	97.8	12			12 hr	Mechanical asystole	Ocl. of LCA, severe sclerosis of RCA, recent ASLWI
10	7.51	24	55	98.2	12	2		12 hr	Mechanical asystole	
11	7.59	25	58	99.4	46	1		8 days	Kidney failure	Ocl. of LCA, 80% ocl. of RCA, recent ALWI, old PWI, renal tubular necrosis
12	7.49	22	68	100.2	30	10		10 days	Pneumonia	Ocl. of LCCA, recent PWI, moderate sclerosis of LDCA and RCA
13	7.33	26	106	97.6	15			7 days	Persistent SVT	
14	7.34	18	241	98.8	3			3 hr	Mechanical asystole	Ocl. of LCCA, recent IWI, old AWI
15	7.34	20	86	98.7	12	2		72 hr	Pneumonia, kidney failure	Ocl. of LDCA, recent AWI, sclerosis of LCCA and RCA, bronchial carcinoma of left upper lobe, metastases of kidney and liver
16	7.46	27	140	99.2	6		24	30 hr	SVT, VT, mechanical asystole	
17	7.43	25	82	99.8	10		38	3 wk	Extension of infarction	
18	7.34	20	96	98.2	5		36	41 hr	Rupture of balloon	Ocl. of RCA, massive PWI, severe coronary sclerosis of LCA

HCO_3 = bicarbonate, P_aO_2 = arterial oxygen tension, *l*-NE = *l*-norepinephrine; Iso. = isoproterenol; CP = intra-aortic counterpulsation; SVT = supraventricular tachycardia; Ocl. = occlusion; RCA = right coronary artery; LDCA = left descending coronary artery; AWI = anterior wall infarction; PWI = posterior wall infarction; LCA = left coronary artery; ASLWI = anterior septal lateral wall infarction; LCCA = left circumflex coronary artery; IWI = inferior wall infarction.

* Survival at the time of paper submission 8 months.

TABLE III
Temporal Metabolic Variations

Subject	Time	A_L	A_P	Ex_L	Ex_P	Exo_2	$Pcso_2$
	min	*mmoles/liter*		%	%	%	*mmHg*
A	0	4.11	0.278	9	−40		
	10	3.77	0.281	6	−20		
	20	3.70	0.243	8	−33		
B	0	3.72	0.260	16	−12		
	15	3.40	0.217	15	−38		
C	0	1.92	0.219	26	48	86	28
	10	2.01	0.178	22	7	84	20
	20	1.92	0.171	22	41	92	26
D	0	2.17	0.121	13	−3		
	15	2.18	0.159	10	18		
E	0	3.40	0.220	27	2	83	26
	10	2.98	0.219	20	−3	80	27
	20	3.05	0.214	23	−7	86	26
F	0	2.47	0.198	26	12	75	22
	10	2.43	0.161	23	−13	73	20
	20	2.41	0.162	22	−7	76	21
Mean coefficient of variation		3.89	10.54	12.76	115	3.47	8.19
Range		7.15	19.14	19.80	198	4.78	17.33
		0.32	1.37	4.58	31	2.04	2.47

shifts in the direction of net pyruvate flux were observed.

Measurements before administraton of vasoactive agents

Systemic hemodynamics. Cardiac index and stroke index were markedly reduced in all patients ranging from 1.01 to 1.97 liters/min per m^2 and from 7 to 26 ml/beat per m^2, respectively (Table IV). Mean aortic pressure ranged from 40 to 65 mm Hg and systolic aortic pressure was below 90 mm Hg in all but three patients. Systemic vascular resistance ranged from 879 to 2194 dyne-sec-cm^{-5}.

Myocardial energetics. Table IV and Fig. 1 demonstrate that all indices of left ventricular work were markedly reduced. Left ventricular work index ranged from 0.51 to 1.40 kg-m/min per m^2, tension time index per minute from 967 to 1720 mm Hg sec/min, and systolic ejection rate from 40 to 84 ml/sec per m^2 (Table IV). Coronary blood flow averaged 71 ml/100 g per min and was below our normal of 80–95 ml/100 g per min in all but three patients. Myocardial oxygen consumption varied widely; the myocardial oxygen extraction ratio was greater than 70% in all but three patients. The relationship between left ventricular work index and myocardial oxygen utilization coefficient is shown in Fig. 1 together with the regression line for normal energetics from Gorlin (38).

Lactate and pyruvate metabolism (Table V). Arterial lactate ranged from 1.98 to 8.83 mmoles/liter; arterial lactate was 14.61 mmoles/liter in one patients who had been given Ringer's lactate solution. Myocardial lactate production, averaging 49.92 μmoles/100 g per min, was observed in 15 of 18 patients while decreased lactate consumption of 12.71 and 25.11 μmoles/100 g per min was found in two patients. Pyruvate production averaged 2.52 μmoles/100 g per min but varied widely among individual patients. Lactate extraction ratios ranged from + 9 to − 24% and are plotted with pyruvate extraction ratios as a four quadrant diagram in Fig. 2. Included in the diagram are data from patients with other types of shock and from animal experiments exposed to severe hypoxia (40). Excess lactate was present in 12 of the patients with coronary shock.

Homogeneity of groups. Selected parameters of the three control groups (control and drug groups) were compared by analysis of variance. Heart rate, cardiac index, arterial pressure, coronary blood flow, myocardial oxygen consumption and extraction, coronary sinus oxygen tension, arterial lactate content, and myocardial lactate extraction showed no significant differences among the mean values from one group to the other.

Effects of *l*-norepinephrine and isoproterenol (Tables IV–VII)

Isoproterenol, 2.0–3.2 μg/min intravenously, increased cardiac output in all patients from an average of 1.42–2.29 liters/min. Stroke volume did not change in three patients and the increase was primarily due to an increase in heart rate from 89 to 118 beats/min. Mean aortic pressure was essentially unchanged but systolic pressure rose from 71 to 82 mm Hg while diastolic pressure fell from 46 to 43 mm Hg. Systemic vascular resistance fell from 1533 to 968 dyne-sec-cm^{-5} and left ventricular work index increased from 0.91 to 1.74 kg-m/min per m^2.

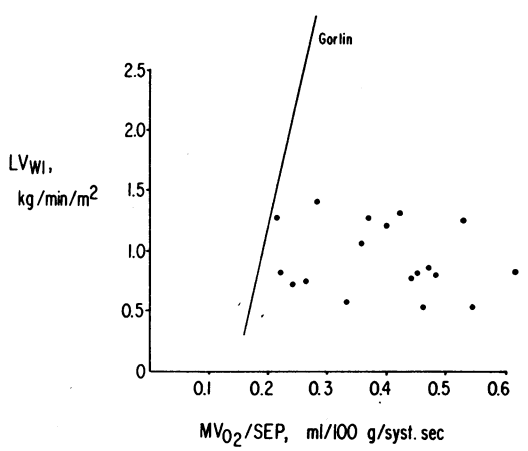

FIGURE 1 Scatter diagram of left ventricular work index (LV_{WI}) and myocardial oxygen consumption per systolic seconds (MVo_2/SEP) in coronary shock. The regression line shows the relationship between these two variables, found by Gorlin, in the metabolic intact heart.

TABLE IV

Hemodynamics and Myocardial Perfusion in Coronary Shock

Subject	Status	HR	CI	SER	Arterial pressure S	Arterial pressure D	Arterial pressure M	CVP	SVR	TTM	MRQ	CBF
		beats/min	*liters/min per m²*	*ml/sec per m²*	*mm Hg*			*mm Hg*	*dyne-sec-cm⁻⁵*	*mm Hg/sec per min*		*ml/100g per min*
1	Control	112	1.23	61	74	36	48	10	1930	1189	0.36	68
2	Control	88	1.13	40	66	30	40	14	1018	1690	0.72	66
3	Control	102	1.14	49	75	40	55	11	1900	1572	1.32	72
4	Control	68	1.12	90	96	57	62	11	2055	967	1.02	85
5	Control	75	1.05	48	79	45	50	8	1962	1281	0.75	66
6	Control	100	1.25	69	90	54	65	15	2080	1529	0.98	68
7	Control	125	1.09	67	82	66	60	9	2194	1105	0.70	62
8	Control	75	1.39	77	81	46	51	13	1393	1404	0.72	65
	Control 24 hr	88	2.00	88	110	69	70	9	1462	2114	0.87	134
9	Control	100	1.22	52	69	45	53	13	1959	1472	0.66	74
	2.6 μg Iso.*	124	2.03	88	75	40	50	11	1273	1517	0.67	83
10	Control	93	1.23	65	65	40	55	15	1521	1134	0.88	74
	2.0 μg Iso.	112	2.23	100	80	35	60	12	1009	1553	0.84	89
11	Control	100	1.57	72	72	48	57	11	1233	1452	0.78	77
	3.0 μg Iso.	125	2.23	94	75	40	55	11	829	1530	0.75	70
12	Control	63	1.64	84	78	50	63	7	1421	1406	0.69	68
	32 μg *l*-NE‡	82	2.19	103	116	72	85	8	1500	2025	0.71	102
	2.0 μg Iso.	110	2.58	109	98	55	67	6	762	1709	0.85	110
13	Control	150	1.97	69	65	42	55	8	1001	1681	0.66	71
	16 μg *l*-NE	146	1.84	65	95	55	68	11	1370	2052	0.68	87
14	Control	133	1.72	66	60	32	46	11	879	1329	0.78	68
	20 μg *l*-NE	125	1.76	78	62	37	49	10	956	1125	0.84	72
15	Control	110	1.95	77	75	48	60	10	1366	1720	1.36	95
	40 μg *l*-NE	119	2.25	90	114	78	92	11	1598	2449	1.09	117
16	Control	140	1.01	56	68	56	58	20	1786	1110	0.85	60
	26 μg *l*-NE	143	1.13	61	102	80	85	19	2776	1710	0.66	84
17	Control *P*§	70	1.44	74	92	55	63	16	1201	1666	0.76	81
	14 μg *l*-NE *P*	70	1.39	71	120	65	75	24	1344	1959	1.02	117
18	Control	136	1.09	54	65	41	50	12	1446	1142	0.53	64
	32 μg *l*-NE‖	130	1.19	58	101	57	66	13	1842	1518	1.67	104
	Control¶	74	1.95	120	90	42	60	10	1065	1107	0.83	84
	16 μg *l*-NE	78	2.17	132	104	59	80	14	1264	1441	0.80	92
	Control n = 18											
	Mean	102	1.35	65	75	46	55	12	1575	1380	0.82	71
	SD	26.0	0.30	13	10.2	9.2	6.6	3.2	416	235	0.22	8.73

Abbreviations, see under Methods.

* Isoproterenol per minute.

‡ *l*-Norepinephrine per minute.

§ Ventricular pacing.

‖ After 8 hr *l*-norephinephrine infusion because of persistent shock.

¶ After 36 hr intra-aortic counterpulsation.

TABLE V

Myocardial Metabolism in Coronary Shock

Subject	Status	MVO_2	E_{XO_2}	$Pcso_2$	A_L	A_P	X_L	Ex_L	Ex_P	MV_L	MV_P
		ml/100 g per min	%	*mm Hg*		*mmoles/liter*		%	%	*μmoles/100 g per min*	
1	Control	9.66	74	24	3.52	0.090	0.2341	−22	−16	−53.01	−1.224
2	Control	6.79	80	24	1.98	0.081	0.8901	−7	37	−99.02	2.010
3	Control	5.96	94	24	8.83	0.289	0.5130	−15	−9	−96.79	−1.958
4	Control	7.11	75	20	5.31	0.254	1.4581	−15	7	−69.88	1.445
5	Control	6.27	73	24	2.81	0.159	−0.8932	−4	−49	−8.07	−5.247
6	Control	9.00	71	13	5.66	0.424	−1.6671	6	−7	27.95	−2.006
7	Control	9.25	82	23	5.83	0.228	1.6570	−11	12	−38.57	1.686
8	Control	7.99	74	21	2.82	0.164	0.0302	−18	−16	−32.50	−1.755
	Control 24 hr	11.53	67	24	1.36	0.131	−0.0901	20	13	36.10	2.278
9	Control	10.76	76	23	3.92	0.207	0.0043	−10	−9	−28.82	−1.332
	2.6 μg Iso.*	10.48	69	25	4.07	0.225	0.5440	−23	−10	−78.81	−1.903
10	Control	10.03	91	17	4.18	0.209	−0.8043	−11	−30	−32.51	−4.662
	2.0 μg Iso.	11.47	86	18	3.49	0.182	0.5601	−24	−8	−72.92	−1.157
11	Control	8.05	69	24	4.80	0.391	0.1181	−7	−5	−27.73	−1.463
	3.0 μg Iso.	6.71	66	18	4.67	0.275	−0.6720	−15	−29	−46.92	−5.530
12	Control	7.19	69	22	4.09	0.275	0.3771	9	18	25.11	3.400
	32 μg *l*-NE‡	11.26	78	20	4.19	0.264	0.4092	15	23	64.22	6.120
	2.0 μg Iso.	8.89	67	26	4.41	0.197	−1.3461	−4	−35	−22.03	−7.700
13	Control	6.08	67	22	3.56	0.191	−0.4110	5	−6	12.71	−0.852
	16 μg *l*-NE	7.72	75	23	3.68	0.241	0.3282	14	23	45.20	4.872
14	Control	11.37	76	25	6.91	0.291	1.8441	−24	4	−112.23	0.748
	20 μg *l*-NE	10.40	68	26	7.11	0.324	1.4431	−18	2	−94.30	0.432
15	Control	7.03	80	25	14.61	0.473	−1.6410	−3	−14	−44.63	−6.460
	40 μg *l*-NE	9.13	73	26	14.44	0.483	−0.6612	2	−2	40.90	−1.170
16	Control	8.46	86	18	5.56	0.370	0.4611	−13	−5	−43.90	−1.629
	26 μg *l*-NE	11.19	81	23	5.63	0.346	−1.1291	14	−6	65.21	−1.806
17	Control *P*§	8.23	77	22	4.04	0.170	−0.7771	−6	−12	−20.62	−1.652
	14 μg *l*-NE *P*	9.24	69	23	4.54	0.129	−1.1712	12	−14	62.43	−2.117
18	Control	6.80	78	23	5.47	0.244	1.0152	−12	7	−40.51	1.088
	32 μg *l*-NE‖	8.15	63	20	6.91	0.307	−1.2590	−11	−28	−73.90	−9.089
	Control¶	7.02	81	27	2.30	0.145	1.1452	7	57	13.93	7.215
	16 μg *l*-NE	8.35	72	28	1.80	0.061	0.6441	12	48	20.42	2.714
	Control n = 18										
	Mean	8.11	77	22	5.217	0.250	0.1821	−9	−5	−34.33	−1.10
	SD	1.62	7.32	3.14	2.850	0.108	1.0250	9.1	18.6	42.74	2.58

Abbreviations, see under Methods.

* Isoproterenol per minute.

‡ *l*-Norepinephrine per minute.

§ Ventricular pacing.

‖ After 8 hr *l*-norepinephrine infusion because of persistent shock.

¶ After 36 hr intra-aortic counterpulsation.

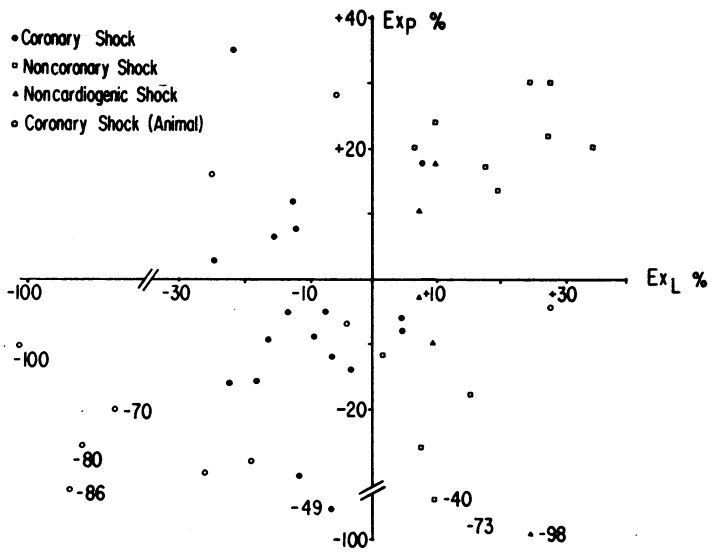

FIGURE 2 Myocardial lactate (Ex_L) and pyruvate (Ex_P) extraction ratios in different kinds of shock. Patients in coronary shock tend to cluster in quadrant three, indicating lactate and pyruvate production. Note that their metabolic behavior differs significantly from patients in noncoronary shock.

Coronary blood flow increased in all but one patient, in average from 73 to 88 ml/100 g per min. Myocardial oxygen consumption increased in two and decreased in two others and myocardial oxygen extraction ratios decreased in all patients. Lactate production increased from an average of 28.12 μmoles/100 g per min to 66.10 μmoles/100 g per min in three patients. Lactate consumption was shifted to production in the fourth patient.

Patient 7 responded differently to isoproterenol. Mean and diastolic arterial pressures did not fall, but increased slightly, associated with a marked rise in coronary blood flow from 68 to 110 ml/100 g per min as well as of myocardial oxygen consumption. Heart rate, cardiac index, and left ventricular work index increased markedly. However, net lactate flux shifted from consumption of 25.11 μmoles/100 g per min to production of 22.03 μmoles/100 g per min.

The hemodynamic and metabolic response to 12–40 μg/min *l*-norepinephrine intravenously showed a uniform trend in all but patient 9, who will be discussed separately. Systolic, diastolic, and mean arterial pressures increased markedly. Cardiac index was not significantly changed but SVR increased from 1307 to 1642 dyne-sec-cm^{-5}. Coronary blood flow improved in all patients from an average of 76–100 ml/100 g per min ($P < 0.01$). Myocardial oxygen consumption increased in all patients, even though myocardial oxygen extraction fell in five out of seven. Lactate fluxes across the myocardium improved uniformly. In three patients lactate production shifted to extraction. Patient 9 was in the irreversible state of coronary shock at the time of evaluation and showed practically no response to *l*-norepinephrine. She died shortly after admission to the shock unit.

The effects of both agents on left ventricular work index and oxygen consumption per systolic seconds are shown in Fig. 3. Both drugs significantly increased left

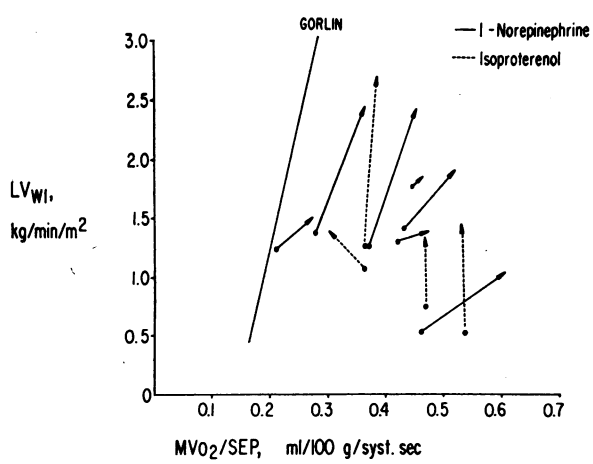

FIGURE 3 Effect of vasoactive agents on left ventricular work index (LV_{WI}) and myocardial oxygen consumption per systolic seconds (MVo_2/SEP). Cardiac work and oxygen consumption appear to increase proportionately by *l*-norepinephrine. Isoproterenol, however, seems to increase cardiac work without improving myocardial oxygen consumption.

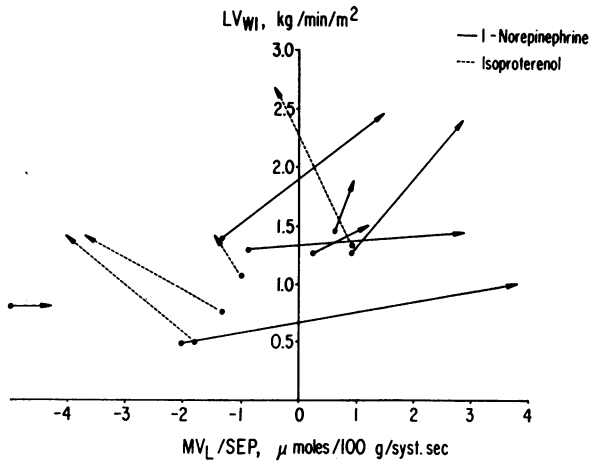

FIGURE 4 Effect of vasoactive agents on left ventricular work index (LV_{WI}) and myocardial lactate consumption per systolic seconds (MV_L/SEP). With increasing left ventricular work, myocardial lactate consumption consistently improved by *l*-norepinephrine, but decreased or shifted to production by isoproterenol.

ventricular work index but *l*-norepinephrine increased oxygen consumption while isoproterenol either did not change or reduced oxygen consumption per systolic second. Fig. 4 expresses the relationship between work and available oxygen by plotting left ventricular work index against lactate fluxes per systolic seconds. The increase in work induced by both agents is associated with increased lactate extraction during *l*-norepinephrine infusion but an increased lactate production when isoproterenol is administered.

Changes caused by *l*-norepinephrine and isoproterenol were significantly different for most of the parameters evaluated (Tables VI, and VII). Coronary blood flow and myocardial oxygen consumption, although not frankly significant, showed differences in the expected direction.

DISCUSSION

Although the factors initiating circulatory collapse in acute myocardial function are not completely understood, certain features appear common to all patients. Pathologic studies have shown that acute coronary occlusion with transmural infarction rather than multicentric nontransmural infarction without coronary occlusion are usually found in the patient with coronary shock (41). The area of transmural infarction has the least blood flow, the greatest muscle fiber destruction, and the poorest contractility. Peripheral to the area of frank infarction is a zone of tissue that presumably could retain its viability if perfusion pressure were adequate to allow collateral flow. Edwards (42) has emphasized that this "twilight zone" is not sharply demarcated from the zone of infarction but scattered within and at the periphery of the area of infarction. A third zone of adequately perfused and normally contracting muscle is peripheral to the infarcted and noninfarcted but ischemic zones.

The unaffected segments of ventricular muscle are subjected to abnormal stresses by the presence of infarcted and noncontractile tissue. If a significant portion of ventricular circumference is rendered noncontractile, surviving viable muscle must increase its extent of shortening and must contract from an increased end-diastolic fiber length in order to maintain systolic emptying.

TABLE VI
Statistical Evaluation of Drug Interventions

Status	HR	CI	SER	Arterial pressure			CVP	SVR	TTM	MRQ	CBF
	beats/min	*liters/min per m²*	*ml/sec per m²*	*mm Hg*			*mm Hg*	*dyne-sec-cm⁻⁵*	*mm Hg sec/min*		*ml/100 g per min*
Isoproterenol, 2.0–3.0 μg/min, n = 4											
Before mean	89	1.42	68	71	46	57	12	1533	1366	0.75	73
SD	17	0.22	11	4.6	3.3	33.6	2.7	266	136	0.099	3.11
During mean	118	2.29	99	82	43	58	10	968	1517	0.78	88
SD	7.84	0.23	8.3	9.4	7.4	66.2	2.1	198	32.25	0.084	14.40
°F	21	128	50	7.81	1.31	0.24	5.4	73	2.79	0.29	2.09
P	<0.05	<0.01	<0.05	NS	NS	NS	NS	<0.01	NS	NS	NS
l-Norepinephrine, 12–40 μg/min, n = 7											
Before mean	105	1.66	78	75	46	58	12	1246	1430	0.85	75
SD	36.5	0.35	20	12	8.4	5.7	4.5	307	264	0.23	12
During mean	109	1.81	86	102	68	76	14	1544	1823	0.83	96
SD	31.8	0.43	25	19.6	15	14	5.6	579	437	0.17	17
°F	0.96	3.01	5.52	26	28	25	2.63	6.03	11.21	0.080	20.06
P	NS	NS	NS	<0.01	<0.01	<0.01	NS	NS	<0.01	NS	<0.05
Differences between drug-induced changes											
°F	32	50	36	8.48	35	28	6.67	51	15	0.51	5.13
P	<0.001	<0.001	<0.001	<0.05	<0.001	<0.001	<0.05	<0.001	<0.01	NS	=0.05

Abbreviations, see under Methods.

TABLE VII

Statistical Evaluation of Drug Interventions

Status	MVo_2	Exo_2	$Pcso_2$	A_L	A_P	X_L	Ex_L	Ex_P	MV_L	MV_P
	ml/100 g per min	%	*mm Hg*		*mmoles/liter*		%	%	*μmoles/100 g per min*	
Isoproterenol, 2.0–3.0 μg/min, n = 4										
Before mean	9.01	76	22	4.247	0.270	−0.0662	−5	−7	−16.01	−1.011
SD	1.04	8.92	2.50	0.943	0.086	0.5121	8.0	17.0	27.64	2.690
During mean	9.34	72	22	4.160	0.220	−0.2285	−17	−20	−55.15	−4.072
SD	1.49	8.09	3.63	0.897	0.041	0.9423	7.9	11.67	26.08	2.471
°F	0.28	14.69	0.01	0.16	3.00	0.05	88	0.76	32	0.97
P	NS	<0.05	NS	NS	NS	NS	<0.01	NS	<0.05	NS
l-Norepinephrine, 12–40 μg/min, n = 7										
Before mean	7.91	76	23	5.867	0.274	0.1435	−4	−13	−24.22	−1.074
SD	1.72	6.70	2.94	4.123	0.118	1.1815	11	22	47.96	3.256
During mean	9.61	74	24	5.913	0.263	−0.0194	7	−5	29.14	1.055
SD	1.37	4.68	2.67	4.102	0.140	0.9856	12	24	56.78	3.572
°F	8.33	0.924	2.20	0.15	0.30	0.254	11.49	3.87	13.13	3.29
P	<0.05	NS	NS	NS	NS	NS	<0.05	NS	<0.01	NS
Differences between drug-induced changes										
°F	4.31	0.23	0.45	1.28	4.16	0.32	52	5.73	0.96	7.95
P	~0.05	NS	NS	NS	<0.05	NS	<0.001	<0.05	NS	<0.05

Abbreviations, see under Methods.

Myocardial oxygen consumption in these viable fibers is increased and coronary vessels in these zones are probably markedly dilated so that blood flow is dependent mainly upon perfusion pressure.

The function of both noninfarcted but ischemic and normally contractile zones are important in the prevention and therapy of circulatory collapse. Maintenance of adequate blood flow and metabolic integrity of these areas might be expected to prevent the development or extension of the shock state. Continued poor perfusion through these critical areas may lead to progressive transmural infarction, decreased ventricular function, and irreversible circulatory collapse.

Critique of experimental methods

These studies were performed on extremely ill patients and precision of data collection had to be secondary to patient safety. The patients were carefully stabilized before study as described in the methods section and are believed to have remained in a relatively "steady state" throughout the period of study. Arterial oxygen and carbon dioxide tensions and hematocrit changed little during the procedure in the majority of the patients.

Validity of coronary sinus sampling techniques in the presence of nonuniform ventricular perfusion. Conclusions based on data presented in this paper are dependent upon the assumption that coronary sinus blood and composition are representative of left ventricular myocardial metabolism. Olson and Gregg (43) and Rayford, Khouri, Lewis, and Gregg (44) have reviewed evidence suggesting that this is the case in the normal experimental animal. In the human heart, however, the venous blood flow of the posterior wall varies, draining directly into the right atrium or into the coronary sinus (45). The problem is additionally complicated in the patient with randomly distributed coronary arterial lesions because of the possibility of both spatial and temporal nonuniformity of ventricular perfusion.

Nonuniform ventricular perfusion is physically analagous to nonuniform alveolar ventilation and perfusion; the problems of using either mixed coronary sinus or mixed arterial blood in the study of over-all gas exchange are obviously similar. Coronary sinus blood in the presence of nonuniform ventricular perfusion is actually a weighted integral of left ventricular events with poorly perfused area contributing relatively less to mixed myocardial venous effluent. Klocke and Wittenberg (46) have emphasized that nonuniform perfusion complicates the estimation of coronary blood flow using inert gas or other diffusable indicators since poorly perfused segments of myocardium may not become saturated during short periods of indicator washin.

The effects of nonuniform distribution on mixed coronary sinus blood may be seen in a two compartment ventricular model presented in Table VIII. The model is based on the known coronary vascular response to occlusion of a branch of the left coronary artery (47) and certain human data obtained from selective myocardial sampling (48). Consider that the left ventricle is totally perfused by the two branches of the left coronary artery and that severe occlusive disease has markedly reduced flow rate through one branch of the main left coronary artery which perfuses precisely one half of the left ventricle. The venous effluent from the noninfarcted compartment is calculated for both normal coronary perfusion and for the diminished coronary perfusion as-

TABLE VIII

Model of a Two-Compartment Left Ventricle

	Compartments			Mean measurements			
	Infarcted	Noninfarcted					
Mass	100 g	100 g	100 g*				
Flow	10 ml/100 g per min	90	50				
Concentration of indicator	40%	98%	88%	92%	(80)	80%	(40)*
A_{O_2}	15 ml/100 ml	15	15				
CS_{O_2}	1 ml/100 ml	5	3	4.6		2.7	
Ex_{O_2}	93%	66%	80%	69%		82%	
A_L	3 mmoles/liter	3	3				
CS_L	6	2.2	2.5	2.6		3.1	
Ex_L	100%	26%	16%	13%		−3%	

Coronary effluent composition for the noninfarcted compartment is shown for two rates of blood flow. The column headed by a value with an asterisk show values for decreased blood flow through the noninfarcted compartment. Concentration of indicator is percentage of equilibrium value at 5 min and is taken from Klocke and Wittenberg (46). Mean measurements are values that would be calculated from mixed coronary sinus blood.

sociated with the shock state. Although half of the left ventricle is infarcted and its venous effluent markedly abnormal, mixed coronary blood is only slightly changed from control levels with extraction ratios of 69% and 13% for oxygen and lactate, respectively. Reduction in perfusion rates of the noninfarcted compartment increases oxygen extraction to 82% and shifts lactate extraction to 3% production. This model demonstrates that mixed coronary sinus composition is influenced mainly by the perfusion characteristics of the noninfarcted segment and that it may remain relatively normal as long as the volume and perfusion rate of those segments are large.

Although the limitations of coronary sinus sampling in the presence of nonuniform blood flow have been stressed, it represents the only technique currently available and reasonable interpretations seem possible provided the basic limitations of the method are understood. Coronary sinus composition suggesting myocardial hypoxia must reflect severe disturbances in myocardial oxygenation while less severe abnormalities cannot be excluded even if coronary sinus blood is normal.

Temporal variations in myocardial metabolism. While spatial variations in myocardial metabolism have been emphasized by selective coronary sinus sampling (48), little attention has been paid to the possibility of temporal variations. A metabolic complex existing at one moment might be quite different from that existing at an earlier or later time and it may be dangerous to assume that myocardial metabolism is unchanged simply because heart rate and blood pressure have not changed. Data presented in Table III shows such temporal variations to vary with the measurement examined. Arterial lactate and oxygen extraction ratios are quite reproducible, coronary sinus oxygen tension and lactate extraction ratios are of intermediate reproducibility, and pyruvate extraction ratios vary widely from moment to moment. These values may be used to estimate the reliability of treatment changes since they include both experimental error and temporal variations. A change in lactate extraction of 25%, for example, would approach two standard deviations and should be significant at the 5% level.

Validity of coronary blood flow measurements. Measurement of coronary blood flow in critically ill patients requires a technique which can be readily performed at the bedside and will not place the patient at additional risk. All currently available techniques including those using precordial scanning as well as those requiring sinus sampling are subject to the problems of spatial variations in coronary blood flow discussed above. The Krasnow (33) modification of the Kety method (34) was chosen. It is relatively simple to perform and coronary sinus sampling was necessary for metabolic studies.

Krasnow, Levine, Wagman, and Gorlin (33) suggested that iodoantipyrine-^{131}I saturation curves could be used to calculate coronary blood flow and Sapirstein and Mellette have shown that the myocardial distribution volumes for antipyrine are identical with tritiated water and that its equilibrium with intracellular water is flow limited (49). Data for partition coefficients between blood and fibrotic areas is not available but conceivably antipyrine distribution might become diffusion limited in severely scarred areas of the myocardium.

A major difference between the nitrous oxide and antipyrine techniques is that arterial antipyrine steadily

rises during indicator infusion. The slopes of arterial and coronary sinus antipyrine are identical at equilibrium and theoretic considerations indicate that the arterio-coronary sinus antipyrine difference must be constant if isotope is added to the coronary arterial blood at a constant rate and if coronary blood flow is unchanged. While Krasnow et al. calculated coronary blood flow from the early segments of the saturation curve, the rapid changes in arterio-coronary sinus isotope difference suggest equilibrium had not been reached in the severely diseased myocardium. Regions of low perfusion would take considerably longer to reach equilibrium than regions of high perfusion suggesting the desirability of limiting sampling to later in the phase of saturation. In our studies, coronary blood flow calculated from the terminal 2 min segment averaged 82 ml/100 g per min and was significantly different from the average value of 87 ml/100 g per min calculated from the initial 2 min of saturation. The standard deviation of the difference was 11.55 ml/100 g per min and the coefficient of variation 14%. Evidence that this modification of the Krasnow method is valid is the mean value of 88 ml/100 g per min for coronary blood flow measurements in 30 patients without significant coronary artery disease. This compares favorably with mean values for the nitrous oxide method reported in the literature. The coefficient of variation of six duplicate determinations averaged 5.79%.

Discussion of results before administration of vasoactive agents

Systemic hemodynamics. Left ventricular output was reduced to 50% of normal in the 18 patients with coronary shock. This striking reduction was due to decrease in stroke output since cardiac rate was either normal or increased. Measurements of ventricular force development and velocity of contraction were not made but the presence of low systolic ejection rates associated with low aortic pressures suggests decreased myocardial contractility. Systemic vascular resistance varied widely and was normal or reduced in nine patients. The failure to increase resistance appropriately may be due to peripheral autoregulatory influences of hypoxia, acidosis, and accumulation of metabolites together with central vascular inhibitory factors (50–53). These findings are similar to previously reported data (2–12, 15, 54–57).

Coronary hemodynamics. Coronary blood flow was reduced in all but three patients due to a reduction in coronary perfusion pressure. Diastolic coronary vascular resistance was not calculated, because of the redistribution of coronary perfusion in severe myocardial failure. Coronary blood flow has been observed to increase during systole due to the decrease in transmural vascular pressure (58) so that calculated diastolic resistance would be falsely low in the shock state. Since coronary perfusion pressure decreased more than blood flow in our patients, however, mean coronary vascular resistance probably was decreased. It seems likely that resistance was increased and flow reduced in the infarcted areas while resistance was markedly decreased and flow maintained or increased in the noninfarcted areas.

This contention is supported by the study of Khouri et al. (47) who produced partial occlusion of the left circumflex artery in dogs and directly measured coronary flow in both the occluded circumflex and the normal anterior descending coronary artery. Flow remained markedly reduced in the occluded vessel at 1 hr and after 7 days. Flow increased in the normal anterior descending artery after 1 hr, compared to control levels, and was steadily increased when measured over 7 days. Since coronary artery perfusion pressure was unchanged, it may be concluded that resistance decreased in the normal vessel while increasing in the occluded vessel.

Myocardial oxygenation. Oxygen consumption ranged from low to high in these patients with coronary shock in contrast to the decrease reported in most animal studies (58–60). The adequacy of oxygen consumption cannot be judged unless mechanical work and oxygen requirements are accurately known. Diastolic fiber length, contractile element work, myocardial wall tension, and velocity of contraction all determine myocardial oxygen consumption (37, 61–63) but could not be measured in these critically ill patients. Two indices of external work, left ventricular work index and time tension index, were measured and did not correlate with oxygen consumption suggesting that external work is only a small part of total ventricular work production in the shock heart. This lack of correlation may be emphasized by plotting left ventricular work index against oxygen consumption per systolic seconds as recommended by Gorlin (38). Fig. 1 shows the lack of correlation between these two variables in the shock state compared to the linear relationship observed by Gorlin for the metabolically intact heart.

The increased myocardial oxygen extraction in most of our patients emphasizes the severity of myocardial hypoxia, since coronary sinus oxygen content is determined by the infarcted as well as by the noninfarcted areas. Previous studies have shown that oxygen extraction ratios vary widely even in severe coronary artery disease (64, 65) and appear to be a poor indicator of myocardial hypoxia (65). Presumably the scattered distribution of myocardial lesions, normal areas masking diseased areas, accounts for this insensitivity.

Myocardial lactate and pyruvate metabolism. Although Fig. 1 might suggest that oxygen consumption was adequate in the shock patient, the inability to estimate total ventricular work together with the finding of

increased oxygen extraction ratios suggest that other indices for measuring oxygen availability are necessary. Considerable work performed over the past decade has attempted to predict the state of intracellular oxygenation from coronary sinus lactate and pyruvate data. Three indices based on these measurements have been recommended. Huckabee and associates suggested that production of lactate in excess of pyruvate, "excess lactate," was a sensitive indicator of myocardial hypoxia (39). Results of animal and clinical research have emphasized that myocardial lactate production alone is a reliable indicator of anaerobic metabolism (65–72) while lactate extraction less than 10% is suggestive of myocardial hypoxia (65). An increased lactate to pyruvate ratio in the coronary sinus compared to arterial blood is believed indicative of inadequate myocardial metabolism (73–75).

The validity of such indices has been questioned, however, and all investigators agree that blood lactate and pyruvate concentrations are at least three stages removed from mitochondrial oxidation. Williamson, for example, using the ratio of beta hydroxybutyrate to acetoacetate has shown that the hepatic mitochondrion is 100 times more reduced than the cytoplasm suggesting that changes in the cytoplasmic NADH/NAD ratio are at best a damped representation of intramitochondrial events (76). An additional reservation lies in observations that the transport of lactate and pyruvate across cellular membranes occur in different speed or may not be due to diffusion alone. Henderson, Craig, Gorlin, and Sonnenblick (77) have demonstrated that lactate lags considerably behind pyruvate in crossing cellular membranes, and Glaviano (78) has shown that myocardial

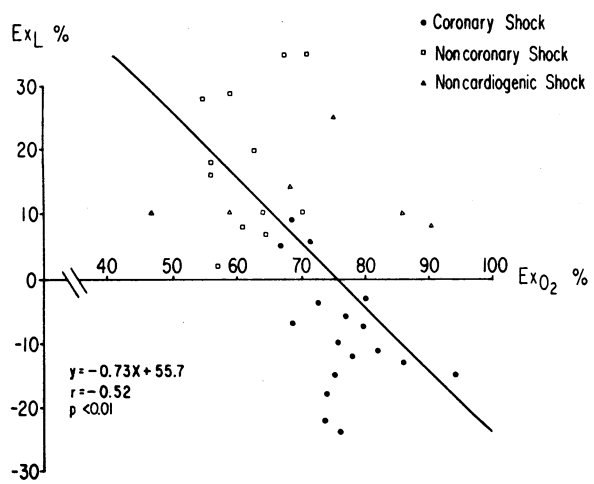

FIGURE 5 Correlation between myocardial oxygen (Ex_{O_2}) and lactate (Ex_L) extraction ratios (see also Fig. 2). The regression line intersects an oxygen extraction ratio of 70% at a lactate extraction ratio of 6%, supporting the use of this level as an indicator of inadequate myocardial oxygenation.

lactate concentration is substantially greater than arterial lactate in the control state and does not change when arterial lactate is increased sixfold by infusion of racemic lactate solution.

Our lactate and pyruvate data, obtained from a group of patients with known severe myocardial hypoxia, may be compared with animal data and studies from other patients in an effort to evaluate the sensitivity of these several indices of hypoxia. Fig. 2 is a four quadrant diagram expressing net myocardial fluxes for lactate and pyruvate. Data from the patients in coronary shock are plotted together with previously reported patients with shock from other causes (18) and animal data from the microembolization studies of Bing and associates (40). Patients with shock from other causes or with low cardiac output tend to cluster in quadrant I and II which represent lactate and pyruvate extraction or lactate extraction and pyruvate production, respectively. Patients with coronary shock tended to cluster in quadrant III which represents lactate and pyruvate production although occasional exceptions were observed. 12 of these patients produced "excess lactate" and fell in quadrant IV or the upper portion of quadrant III. All but three patients with coronary shock demonstrated lactate efflux; these three patients had lactate extraction of less than 10%. Data from the dogs with experimental coronary shock fall predominantly in quadrant III.

These studies presented in the four quadrant diagram indicate that lactate and pyruvate metabolism differ markedly in patients with known myocardial hypoxia compared to other patients in shock or under stress. All would be considered to demonstrate anaerobic metabolism using the criteria of Cohen, Elliot, Klein, and Gorlin (65) while only 12 would fulfill the excess lactate criteria of Huckabee. Further evidence that lactate production indicates myocardial hypoxia is found in Fig. 5 which relates oxygen and lactate extraction data from the patients shown in the four quadrant diagram. In general, lactate extraction decreases or shifts to production as oxygen extraction increases indicating the close interrelationship between these two measurements. Of interest, the regression line relating these two variables intersects an oxygen extraction ratio of 70% at a lactate extraction of 6% supporting the use of that level as an indicator of inadequate myocardial oxygenation. Similar findings in Bing's canine model also support the validity of location in quadrant III as evidence of myocardial hypoxia.

Discussion of effects of *l*-norepinephrine and isoproterenol

The systemic hemodynamic effects of *l*-norepinephrine (3–6, 9, 12, 14) and isoproterenol (7, 10–12, 15, 79–82) were similar to those reported by other investigators.

Peripheral vascular resistance and aortic pressure rose during *l*-norepinephrine infusion. Stroke index did not change, the heart rate response was variable, and neither cardiac index nor systolic ejection rate was significantly changed for the group. In contrast, isoproterenol decreased peripheral vascular resistance, increased cardiac output and systolic ejection rate, and decreased aortic pressure. These differences were statistically significant.

Coronary blood flow increased with both agents but for different reasons. An increase in aortic diastolic pressure from 46 to 68 mm Hg during *l*-norepinephrine infusion increased coronary blood flow an average of 28%. Aortic diastolic pressure fell from 46 to 42 mm Hg during isoproterenol infusion so that the increase in coronary blood flow in three of four patients was due to a decrease in coronary vascular resistance. In the fourth patient, diastolic pressure fell more than resistance producing a decrease in coronary blood flow. Disregarding patient 9 in the irreversible state of shock, myocardial oxygen consumption uniformly rose during *l*-norepinephrine infusion predominantly due to an increase in coronary blood flow. Oxygen extraction decreased with isoproterenol, similarly to the decrease reported by other investigators, so that changes in oxygen consumption were variable and related to changes in blood flow.

Ventricular work, estimated by either time-tension index, left ventricular work index, or mean systolic ejection rate increased with both drugs. The time-tension index was increased but slightly with isoproterenol while the mean systolic ejection rate was only minimally increased by *l*-norepinephrine. The net effects of catecholamine infusion in coronary shock must be related to the relationship between changes in ventricular work and oxygen availability. Fig. 3 is similar to Fig. 1 and relates left ventricular work index to oxygen consumption per systolic seconds. Work and oxygen consumption appear to increase proportionately during *l*-norepinephrine but inadequate increases in oxygen consumption are observed during isoproterenol infusion in the face of increased ventricular work. Isoproterenol appears to increase ventricular work and systemic hemodynamics without improving myocardial oxygenation.

Myocardial lactate fluxes confirm the impression that oxygen requirements exceed oxygen availability during isoproterenol infusion. Fig. 4 is similar to Fig. 3 with left ventricular work index on the ordinate but net lactate flux per systolic seconds replaces oxygen consumption per systolic seconds. Myocardial lactate extraction consistently improved during *l*-norepinephrine infusion, but decreased or shifted to production during isoproterenol infusion.

Our conclusion that *l*-norepinephrine is superior to isoproterenol in coronary shock is based on consideration of both hemodynamic and lactate flux data. Although the number of patients studied was relatively small, statistically significant differences in drug action were observed. The relationship shown in Fig. 3 may be statistically evaluated by computing the left ventricular work index per oxygen consumption per systolic seconds as suggested by Gorlin. This index increased with isoproterenol and decreased with *l*-norepinephrine; the difference was statistically significant ($P < 0.05$).

While shift from lactate extraction to production suggests increased myocardial hypoxia with isoproterenol, an alternate explanation is possible. Catecholamine infusion is known to stimulate both glycolysis and metabolism of fatty acids. Increased pyruvate loads produced by glycolysis might compete with increased amounts of fatty acid 2-carbon fragments for entrance into the Krebs cycle leading to increased cytoplasmic pyruvate with subsequent reduction to lactate. Myocardial respiratory quotients did not change significantly during infusion of isoproterenol suggesting that the pattern of substrate metabolism was not altered. In addition, Cohen et al. (65) state they have not seen isoproterenol stimulate lactate production in patients with normal coronary arteries and presumably normal oxygen delivery systems. We have administered isoproterenol to patients with low cardiac output following open heart surgery and to patients in shock due to other causes and have not observed a shift from lactate extraction to lactate production.[8] These observations support our contention that lactate production with isoproterenol infusion in coronary shock reflects an unfavorable balance between ventricular work and oxygen availability.

The pharmacologic studies emphasize the importance of maintenance of coronary perfusion pressure in the patient with coronary shock. Isoproterenol improves the peripheral circulation but extracts an hypoxic price from the myocardium. *l*-Norepinephrine improves myocardial oxygenation but may actually decrease regional blood flow by increasing the resistance of critical peripheral vascular beds. Since an adequate peripheral circulation is worthless in the face of a deteriorating cardiac pump, the latter drug appears to be the best compromise in most situations. Clinical experiences and animal experiments confirm these observations. The ineffectiveness of isoproterenol in coronary shock was suggested by several groups based on hemodynamic data and clinical course (79–83). After an initial "improvement" during isoproterenol infusion hemodynamics tended to deteriorate. On the other hand the dependency of forward and collateral blood flow upon coronary perfusion pressure in experimental myocardial infarction was demonstrated by Corday, Williams, de Vera, and Gold (59). Later Kuhn et al. showed the obvious improvement of myocardial perfusion and metabolism following experimental

[8] Unpublished observation.

coronary embolization by rising aortic coronary perfusion pressure (60, 84).

Although our data strongly suggest the superiority of *l*-norepinephrine to isoproterenol for the treatment of coronary shock, all but one of the patients studied ultimately died. Our experience is similar during intra-aortic phase shift balloon pumping.[9] Coronary blood flow and myocardial metabolism improved in 9 of 10 patients during balloon pumping but 8 of the 9 patients showing initial improvement died. It appears that the myocardium in patients with coronary shock is so damaged that even agents which can be demonstrated to improve myocardial metabolism are unable to improve cardiac function sufficiently to reverse the generalized system failure characteristic of the shock syndrome.

Perhaps the most important conclusion from this study is the need for early recognition of the "preshock" state and the prompt institution of measures designed to maintain aortic perfusion pressure. It is likely that lactate production exists for many hours prior to the onset of clinically recognizable shock. Early administration of dilute solution of *l*-norepinephrine, carefully regulated by intra-arterial pressure monitoring to prevent excessive increases in ventricular work, might well preserve the integrity of noninfarcted regions of the myocardium and prevent the development of circulatory collapse.

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