The Effects of Intra-Aortic Counterpulsation on Cardiac Performance and Metabolism in Shock Associated with Acute Myocardial Infarction

HILTRUD MUELLER, STEPHEN M. AYRES, E. FOSTER CONKLIN, STANLEY GIANNELLI, JR., JAMES T. MAZZARA, WILLIAM T. GRACE, and THOMAS F. NEALON, JR.

From the Departments of Medicine and Surgery of St. Vincent's Hospital and Medical Center of New York, New York 10011, and the New York University Medical School, New York 10016

ABSTRACT The effect of intra-aortic counterpulsation (IACP, 22–94 hr) on hemodynamics and cardiac energetics was evaluated in 10 patients in shock after acute myocardial infarction. The data clearly indicate that IACP improves myocardial oxygenation, enhances peripheral perfusion, and probably improves myocardial contractility in the severely diseased heart.

Before treatment, decreases in cardiac index (mean value, 1.22 liter/min per m^2), systolic ejection rate (67 ml/sec), and time-tension index per minute (1280 mm Hg·sec/min) were observed. Systemic vascular resistance varied widely. Low coronary blood flow (68 ml/min per 100 g) was associated with increased myocardial oxygen extraction (79%), low coronary sinus oxygen tension (20 mm Hg), and abnormal myocardial lactate-pyruvate metabolism.

During 4–6 hr of IACP, systolic pressure and left ventricular outflow resistance decreased by 18% and 24%, respectively, while cardiac index improved by 38%. Diastolic arterial pressure rose 98%. Increase in coronary blood flow from an average of 68 to 91 ml/100 g per min ($P < 0.001$) was significantly correlated with rise in mean arterial pressure ($r = 0.685$). This correlation was best expressed in a third-order curve, which intercepts the point of no flow at a mean aortic pressure of 30 mm Hg. The flow-pressure curve is relatively flat above 65–70 mm Hg, but becomes steeper as mean aortic pressure falls below this point. Myocardial oxygen consumption remained essentially unchanged during early IACP and tended to rise during the later stages. However, the relationship of cardiac work performed to oxygen availability was markedly improved. Myocardial lactate production of 6% shifted to 15% extraction ($P < 0.001$).

After termination of IACP, hemodynamics and myocardial perfusion and metabolism remained improved in the four patients who could be reevaluated. Although the acute shock state was reversed in all patients, only one left the hospital. Extensive myocardial damage limits the long-term survival of such patients. Therefore early IACP seems desirable, when subtle evidence of pump failure after acute myocardial infarction occurs. Early use of IACP may prevent the development of severe coronary shock or may stabilize cardiac energetics in severe shock facilitating subsequent surgical intervention.

Received for publication 23 December 1970 and in revised form 7 April 1971.

INTRODUCTION

Pump failure is the most common cause of death in patients with acute myocardial infarction, who do not succumb to fatal cardiac arrhythmias. The functional integrity of tissues in the hours after an acute decrease in coronary perfusion depends upon the delicate balance between oxygen need and availability. Changes in the amount and distribution of coronary blood flow determine oxygen delivery to the myocardium while changes in heart rate, ventricular wall tension, and the contractile state of cardiac muscle determine the oxygen requirement (1–10). Tachycardia and ventricular dilatation may well increase oxygen need and, together with decreased oxygen availability, initiate a vicious cycle terminating in irreversible ventricular failure.

In theory, at least three compartments exist after local decrease or cessation of blood flow: a central dead or infarcted segment, a peripheral ischemic segment, and

adjacent or remote areas of functionally normal myocardium (11). The relative size of these segments presumably depends upon surviving areas of myocardium. Periods of hypotension lead to extension of the central necrotic areas decreasing ventricular function, while producing ventricular dilatation which may increase oxygen requirements. Further extension of infarcted and ischemic areas may so impair ventricular function that circulatory collapse or acute mechanical asystole result.

Recent studies have suggested that intra-aortic counterpulsation (IACP) may decrease ventricular work and increase oxygen delivery in coronary shock (10, 12–29). Detailed studies of myocardial metabolism with IACP have not been reported, however.

This paper presents hemodynamic and metabolic data before, during, and after IACP in human coronary shock. These studies confirm earlier work and demonstrate that IACP both decreases ventricular work and increases oxygen delivery in the infarcted heart.

METHODS

Selection of patients and preliminary therapy

All patients admitted to the hospital 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 overall survival experience have been previously published (30).

Patients were considered for the present study if all of the following criteria were met: (*a*) absent or poorly palpable peripheral pulses, (*b*) cold, clammy extremities with mottled skin, (*c*) changes in mental status with either agitation or lethargy, (*d*) urine output less than 25 ml/hr, and (*e*) electrocardiographic findings suggesting acute myocardial infarction. While most patients had a systolic blood pressure less than 80 mm Hg, four patients had peak systolic pressures in excess of this level even though they were in profound shock.

The first 12 patients, treated with IACP from March 1969 through May 1970 in this institution, were selected from a group of approximately 45 patients in coronary shock. 10 of the 12 patients had special hemodynamic and metabolic evaluation. Our objective was to initiate IACP when the shock state persisted after correction of oxygenation, acid-base balance, and intravascular volume, and when the patient was dependent on *l*-norepinephrine for more than 4 hr. However, most of the patients received *l*-norepinephrine longer than 4 hr before initiation of IACP for a variety of reasons not directly related to the shock state.

Emergency therapy was instituted, and the patient was stabilized before and during the time of evaluation and balloon insertion. Details of preliminary use of vasoactive agents together with a brief summary of the clinical data and of the outcome are presented in Table I. The ventilatory status was evaluated by measurement of arterial oxygen and carbon dioxide tension. All 12 patients were intubated and placed on a volume cycled respirator (Emerson). Our indication for intubation and selection of respirators have been previously published (31). Acid-base balance was achieved by infusion of sodium bicarbonate. Volume deficits were corrected, and central venous pressure was maintained between 10 and 14 mm Hg. Patients were sedated as necessary with meperdine (Demerol; Winthrop Laboratories) 15–25 mg/hr i.v. and promethazine (Phenergan; Wyeth Laboratories) 25 mg every hr i.v. *l*-Norepinephrine was administered in all patients before IACP (see Table I). Transvenous pacemakers were inserted in 11 patients.

Experimental protocol

The polyurethane balloon catheter[1] was inserted via cutdown of the right femoral artery. The tip of the catheter was placed approximately ½ in. distal to the left subclavian artery. The position of the balloon was determined by fluoroscopy with a portable image intensifier[2] before the catheter was secured in the artery using the method described by Kantrowitz et al. (18). Balloons of either 33 or 27 ml were used depending upon the size of the patient. All patients were heparinized after the balloon was inserted.

The following protocol for hemodynamic and metabolic evaluation was approved by the Hospital Research Committee. Written permission for both IACP and hemodynamic and metabolic studies was obtained from responsible family members since the patients were extremely ill. 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.

Vasoactive agents were discontinued for approximately 20 min before the procedure. Arterial and central venous pressures, arterial pH, oxygen, and carbon dioxide tensions were monitored. Studies were not performed when these measurements could not be stabilized. Temporal variations of myocardial metabolism in coronary shock were presented previously, demonstrating that a relatively steady state had been achieved and confidence limits had been established, to judge the effect of therapeutic interventions (32). The patients treated with IACP were similar to those previously reported. Statistical evaluation indicated that the two groups of patients were clinically and hemodynamically similar. An attempt was made to utilize IACP in all patients meeting the criteria listed under Methods so that the group reported represents an essentially unselected series of patients with severe coronary shock. Studies reported after the initial period of IACP are highly selective, however, since certain patients died before repeat observations could be made. In spite of these limitations, we believe that the data reported demonstrate the effect of IACP in a representative series of patients with severe coronary shock.

A metabolic evaluation included duplicate determinations of cardiac output, a single measurement of coronary blood flow, 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 hemodynamic and metabolic studies were repeated in all patients 4–6 hr during IACP. Sequential studies were performed at intervals of approximately 24 hr up to 94 hr. Four patients were evaluated 4–6 hr after discontinuation of IACP (subjects 3, 6, 7, 9), and two of them were reevaluated 14-18 hr later.

A No. 14 polyethylene catheter was inserted by puncture into a surgically exposed radial or brachial artery and ad-

[1] Plastron Medical Devices, Inc., Brooklyn, N. Y.
[2] Westinghouse Electric Corp., Pittsburgh, Pa.

TABLE I

Clinical Data, Treatment, and Outcome of Coronary Shock

Case	Age	Sex	Infarction and ECG		Status before IACP		Duration of IACP	Survival after IACP	Complications	Autopsy
			Acute	Old	Shock	*l*-NE				
	yr				*hr*		*hr*	*days*		
1	58	M	AWI, ALWI, SVT*		19	10	38 6	21 None	Extension of infarction, SVT	
2	67	M	ALWI, RBBB, AVB 1°		16	6	24	None	SVT, VT, mechanical asystole	
3	63	M	IPWI		8	5	36	None	Rupture of balloon	Ocl. of RCA, massive PWI, severe sclerosis of LCA
4	56	M	IPWI, RBBB, VF		8	72	22	10	Kidney failure, pneumonia, ischemic left leg	Ocl. of RCA and distal LCCA, recent IPWI, sclerosis of LDCA
5	54	M	IWI, LBBB, SVT, VT	ASWI	16	6	35	None	Persistent SVT, VT, mechanical asystole	Ocl. of LDCA, severe diffuse sclerosis of LCCA and RCA, recent ASWI and PWI
6	47	F	AWI, SVT		13	10	93	None	Previous hypertension, persistent SVT	Ocl. of LDCA, recent AWI, severe sclerosis of LCCA and RCA
7	75	F	AWI, IWI, LBBB, SVT, VF		10	7	72	3	Extension of infarction, mechanical asystole	
8	61	M	ALWI, IWI		8	4	52	None	Extension of infarction, mechanical asystole	Ocl. of LDCA, diffuse coronary sclerosis, recent ALWI, PWI
9	60	F	ALWI, IWI RBBB, VF		5	6	17	3	Diabetes mellitus, long-standing hypertension, kidney failure	
10	61	M	IPWI, RBBB, SVT		10	7	24	None	Mechanical asystole	
11	68	M	IWI, AVB 3°, VF		4	10	35	Alive	Upper gastrointestinal bleeding	
12	61	M	ASWI, LBBB, AVB 1°		6	12	140	None	Acute respiratory stress syndrome, diabetes mellitus, pulmonary edema, acute stress ulcer	Ocl. of LDCA, marked sclerosis of LCCA, recent AWI, IWI, diffuse pneumonitis

Abbreviations: *l*-NE, *l*-norepinephrine; IACP, intra-aortic counterpulsation; AWI, anterior wall infarction; ASWI, anterior and septal wall infarction; ALWI, anterior and lateral wall infarction; IWI, inferior wall infarction; IPWI, inferior and posterior wall infarction; SVT, supraventricular tachycardia; VT, ventricular tachycardia; VF, ventricular fibrillation; AVB, atrioventricular block; RBBB, right bundle branch block; LBBB, left bundle branch block; PWI, posterior wall infarction; LCA, left coronary artery; LCCA, left circumflex coronary artery; LDCA, left descending coronary artery; RCA, right coronary artery; Ocl., occlusion.

* 3 wk later.

vanced into the axillary artery. A No. 14 polyethylene catheter was inserted into the right median basilic vein and positioned into the right atrium. A No. 7 Goodale-Lubin catheter [3] 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 sodium diatrizoate (Hypaque; Winthrop Laboratories). A No. 6 bipolar pacemaker catheter was advanced into the right ventricle via the right external jugular vein. Urine output was measured hourly by Foley catheter. Vascular pressures were measured with P23d strain gauges [4] and recorded by a multichannel oscilloscopic recorder.

Each series of metabolic observations required 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 reinfusion of part of the withdrawn blood. All volume losses were corrected by either blood or low molecular dextran administration; hematocrits were checked before each experimental period.

Methods of analysis

Arterial and coronary sinus blood were collected in heparinized syringes and immediately analyzed in duplicate for oxygen and carbon dioxide tensions and pH using a microtip platinum (33), Severinghaus (34), and glass electrodes, respectively (35). Details of tonometry and estimates of reliability have been previously published (36). Oxygen and carbon dioxide contents were measured by the Van Slyke manometric method (37).

Additional portions 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 (38) and pyruvate (39). Details and reliability of analysis have been reported previously (32).

Cardiac output was measured by an Indocyanine Green dilution technique (40). Indicator was injected by calibrated observation tube into the right atrium, and arterial blood was withdrawn through a Gilford densitometer by a Harvard syringe pump. All determinations were performed in duplicate. The standard deviation of the difference between 27 duplicate cardiac output determinations, performed during acute coronary shock, was 0.245 liter/min with a coefficient of variation of 7.35%. Details of methodology including calibration procedures, have been previously published (41).

Coronary blood flow was measured by a modification of the iodoantipyrine-^{131}I method of Kransnow, Levine, Nagman, and Gorlin (42). The method is simplified by providing arterial and coronary sinus catheters of equal volume. Iodoantipyrine-^{131}I was 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, to compensate for increase in isotope background. Details of methodology, critique of the method at the presence of unequal regional blood flow have been previously published (32). Plasma hemoglobin was measured spectrometrically (43).

Technique of intra-aortic counterpulsation

Counterpulsation was performed with a balloon-driving unit triggered by a precordial electrocardiogram. The balloon was inflated with helium gas, and the peak pressure varied from 110 to 160 mm Hg. The balloon was inflated immediately after the dicrotic notch of the arterial tracing, and deflated immediately before the following QRS complex. The balloon inflation time varied from 220 to 480 msec. Premature balloon inflation was carefully avoided to prevent interference with systolic blood ejection.

Fig. 1A shows initiation of IACP. Peak systolic pressure fell after initiation of counterpulsation, which was related to the "unloading effect" of sudden balloon deflation, and systolic ejection period became considerably shorter. The proper sequence of balloon inflation is confirmed by gradually lengthening the delay of inflation. Fig. 1B demonstrates that such delayed inflation caused a loss of approximately 0.04 sec of early diastole for counterpulsation. Fig. 1C shows a tracing with a broad diastolic peak approaching a plateau and with a diastolic pressure slightly lower than systolic, suggestive of occlusion of the aorta by the inflated balloon.

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 after drug administration was tested by variance analysis using each subject as his own control.

Abbreviations and calculations

Directly obtained data. Heart rate, HR (beats/min); systolic arterial pressure, S (mm Hg); diastolic arterial pressure, D (mm Hg); mean arterial pressure, M (mm Hg); central venous pressure, CVP (mm Hg); coronary blood flow, CBF (ml/100 g per min); coronary sinus oxygen tension, P_{CSO_2} (mm Hg); arterial lactate content, A_L (mmoles/liter); arterial pyruvate content, A_P (mmoles/liter).

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 (44). Interval was measured from aortic or axillary artery tracing, recorded at 100 mm/sec paper speed. Systolic ejection rate, SER (ml/sec per m^2) = stroke index/systolic ejection period (45). Systemic vascular resistance, SVR (dynes-sec-cm^{-5}) = mean arterial pressure minus mean right atrial pressure times 79.9 (conversion factor for mm Hg to dynes-sec-cm^{-5}) cardiac output. Time-tension index per minute, TTM (mm Hg·sec/min) = mean systolic arterial pressure times systolic ejection period times heart rate (2). 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 cm water)/100 (reference 46). Myocardial oxygen consumption, MV_{O_2} (ml/100 g per min) = arteriocoronary sinus oxygen difference times coronary blood flow (46). Myocardial oxygen extraction ratio, Ex_{O_2}, % = arteriocoronary sinus oxygen difference/arterial oxygen content. Myocardial lactate consumption, MV_L (μmoles/100 g per min) = arteriocoronary sinus lactate difference times coronary blood flow. Myocardial lactate extraction ratio

[3] U. S. Catheter & Instrument Corp., Glenn Falls, N. Y.
[4] Statham Instruments, Inc., Los Angeles, Calif.

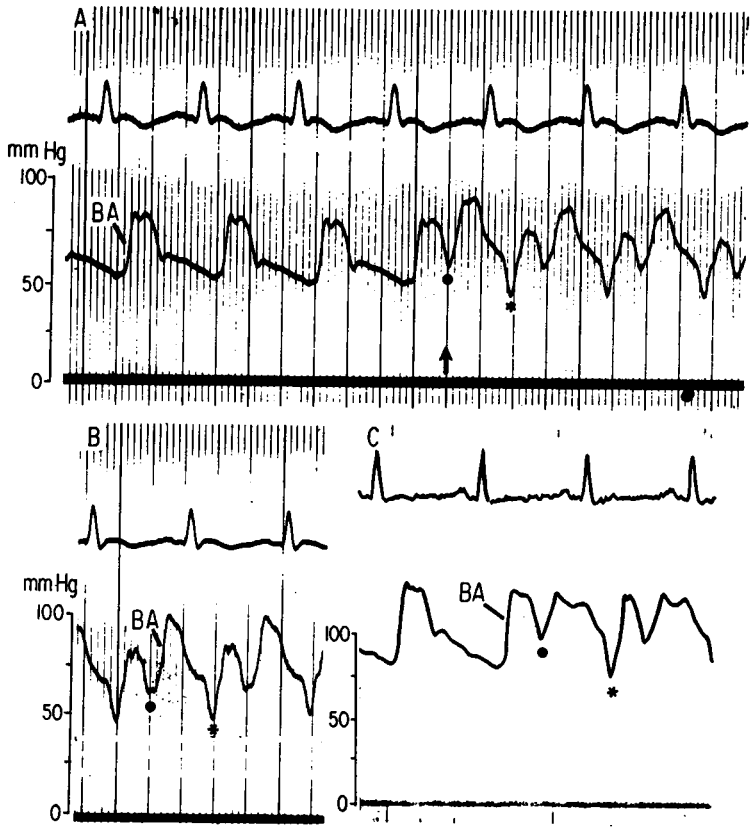

FIGURE 1 (A) Initiation of IACP (↑). Duration of balloon inflation is indicated by dot and star. During IACP, peak systolic pressure decreased, and systolic ejection period became considerably shorter. (B) Balloon inflation occurred too late and caused a loss of 0.04 sec of early diastole for counterpulsation. (C) The diastolic peak is relatively broad approaching a plateau. Diastolic pressure is slightly lower than systolic, suggestive of occlusion of the aorta by the inflated balloon.

Ex_L, % = arteriocoronary sinus lactate difference/arterial lactate content. Myocardial pyruvate extraction ratio, Ex_P, % = arteriocoronary sinus pyruvate difference/arterial pyruvate content. Excess lactate, X_L (mmoles/liter) = coronary sinus-arterial lactate difference minus coronary sinus-arterial pyruvate difference times arterial lactate to pyruvate ratio (47). Left ventricular mean outflow resistance, LVOR (mm Hg/ml per sec) = systolic aortic mean pressure times SEP per beat/stroke volume (48, 49).

RESULTS

Clinical course and pathologic findings. 11 of the 12 patients, who underwent IACP, died during the same hospitalization. The survival of time of the 12th patient is 21 months at the time of submission of the paper. 4 of the 11 patients, who died, lived for 3–21 days after discontinuation of IACP. One patient (No. 1) did well for 21 days after IACP, he then apparently extended his infarction and developed coronary shock. A second attempt of IACP was unsuccessful, and the patient died after 12 hr of IACP in untractable supraventricular arrhythmias. Patient 3 maintained adequate hemodynamics for 3 days after IACP but extended the infarction and died in coronary shock. Two patients (Nos. 5 and 8) had stable hemodynamics for 10 and 3 days after IACP. Their deaths were not directly related to circulatory collapse, but to kidney failure. One patient had good hemodynamics after 36 hr IACP. During the attempt to discontinue IACP, the balloon ruptured, and the patient died.

Postmortem examinations were performed in 6 of the 11 patients who died and revealed extensive old and recent myocardial infarctions associated with severe coronary artery disease.

Problems associated with IACP. One patient (No. 4) with known diabetes mellitus developed severe ischemia of the lower extremity distal to the site of balloon insertion. The severity of his peripheral vascular insufficiency was evidenced by the occurrence of ischemia at

TABLE II

Hemodynamics before, during, and after Intra-Aortic Counterpulsation

	Control		Hours on intra-aortic counterpulsation (IACP) 4–6		12–20		24–36		40–72		Hours off IACP, 4–24	
Case	HR CI	S/D M	HR CI	S/D M	HR CI	S/D M	HR CI	S/D M	HR CI	S/D M	HR CI	S/D M
1	70[P] 1.44	92/50 60	70[P] 2.30	56/95 70								
2	140 1.01	68/56 58	122 1.29	52/103 60								
3	136 1.10	69/41 50	81 1.42	60/99 65	73 2.03	80/105 79	74 2.00	85/100 65			78 2.21	104/59 80
4	68 1.10	96/57 65	63 1.82	83/102 75	64 2.23	90/120 85						
5	80 1.50	80/45 50	88 2.30	72/113 85			96 1.01	75/90 70				
6	102 1.14	75/40 55	88 1.78	65/100 75	76 1.96	85/130 100	80 1.59	75/114 90	86 1.85 86* 1.87	85/115 95 98/140 100	86 1.53	109/63 90
7	75 1.01	79/45 50	62 1.70	70/100 75			69 1.73	85/94 75	68* 1.40 69 1.38	81/114 85 131/130 93	80 1.20 63 1.53‡	140/65 80 118/47 68
8	140 1.11	72/51 55	122 1.32	65/99 70	122 1.22	63/86 68						
9	100 1.35	94/64 68	97 1.92	83/121 80	87 2.29	71/96 65					90 2.10 110 1.57‡	128/60 85 110/60 78
10	125 1.45	82/66 64	102 1.09	75/97 65	125 1.39	79/100 75			140 0.96	66/83 58		
Mean	104 1.22	79/52 58	90 1.69	68/103 72	91 1.85	78/106 79	74 1.77	82/103 75	90 1.49	92/116 86	84 1.69	118/59 80
SD	30 0.19	10/9.11 6.63	22 0.41	10/8.21 7.50	26 0.44	9.7/1.6 12	5.51 0.20	5.71/10 11	29 0.37	24/9.65 12	15 0.38	13/6.29 7.38
F_1§	6.7 16.5	23/23 20										
P_1	<0.05 <0.01	<0.001/ <0.001 <0.01										
Mean	103 1.15	82/48 56									79 1.84	115/63 81
SD	25 0.14	15/11 8.5									12 0.36	11/2.75 9.4
F_2‖	4·4 19.2	107/5.33 32										
P_2	NS <0.05	<0.01/NS <0.05										

Abbreviations: HR, heart rate (beats/min); CI, cardiac index (liters/min per m²); S, systolic; D, diastolic; M, mean arterial pressure (mm Hg); [P], ventricular paced rhythm.

* 62–72 hr during IACP.

‡ 20–24 hr off IACP.

§ F_1, variance ratio between data before and 4–6 hr during IACP.

‖ F_2, variance ratio between data before and after discontinuation of IACP (cases 3, 6, 7, 9).

the sites of arterial monitoring catheters. In one patient, the balloon could not be inserted because both exposed femoral arteries were small and revealed severe occlusive disease.

One death was directly attributable to balloon pumping. The balloon ruptured during the 36th hr of counterpulsation because of a horizontal tear close to the base of the balloon assembly. Examination of the balloon suggested that the tear was produced by change in position of the metal stylette carrier, probably due to a loose stylette during balloon insertion.

The plasma hemoglobin increased from 0 to an average

of 7 mg/100 ml during IACP. In two of six patients in whom the coagulation status was studied, platelets fell below 100,000. However, similar changes were observed in patients with coronary shock who were not treated with IACP. Serum fibrinogen remained within normal limits.

Observations during early hours of IACP. Studies were made in 10 patients after 4–6 hr of continuous IACP. Table II demonstrates that peak systolic pressure fell from an average of 79 to 68 mm Hg while both diastolic and mean arterial pressure rose from 52 and 58 to 103 and 72 mm Hg during IACP. Heart rate decreased from an average of 104 to 90 beats/min, and stroke index rose from 13 to 20 ml/min per m^2. Cardiac index increased from 1.22 to 1.69 liters/min per m^2. All of these changes were statistically significant.

Systemic vascular resistance dropped in five patients, remained unchanged in two, and rose in three. The relationship between mean aortic pressure and cardiac index during all periods of study is shown in Fig. 2. Mean left ventricular outflow resistance decreased in all patients. Increases in systolic ejection rate and decreases in time-tension index/min were statistically significant (Table III). Left ventricular work index was low before IACP, 0.86 kg-m/min per m^2, and remained essentially unchanged during IACP.

Arterial lactate content decreased from a mean of 5.08 to 2.98 mmoles/liter ($P < 0.001$), and the hourly rate of urine increased from an average of 18–60 cc. Mental status changed towards normal, peripheral pulses improved in quality, and the skin became warmer and dry.

Table IV demonstrates that coronary blood flow increased in all patients from a mean of 68–91 ml/100 g per min and that myocardial oxygen extraction decreased from 79 to 61% while coronary sinus oxygen tension increased from 20 to 26 mm Hg. Myocardial oxygen consumption did not change significantly with IACP.

In 7 of 10 patients, lactate was produced by the myocardium before IACP, and lactate extraction was reduced to 3, 6, and 11% in the 3 others (Table V). During IACP, all patients extracted lactate, an average of 15%. Seven patients demonstrated myocardial excess lactate before treatment, two during IACP.

Serial changes during IACP. Additional observations were made on six patients during the 12–20th hr, on four patients during the 24–36th hr, and on three patients during the 40–72nd hr of IACP. Two of the latter three patients were studied twice during the 40–72 hr period. Technical problems prevented a complete study series in four patients (cases 1, 5, 7, 8); additional studies were also impossible in patient 2, who developed intractable arrhythmias and deteriorated sharply.

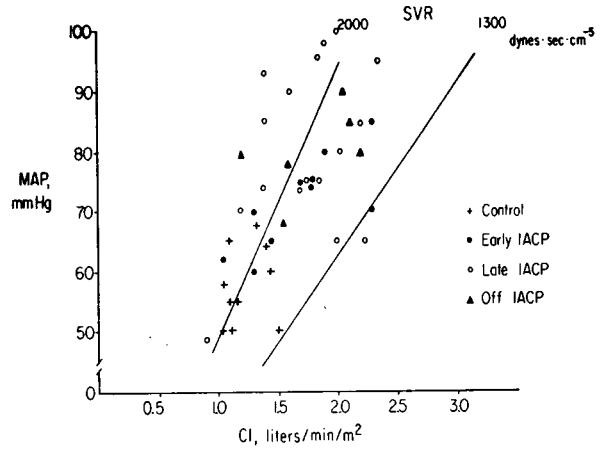

FIGURE 2 Relationship between cardiac index (CI) and mean arterial pressure (MAP) in different stages of coronary shock. Isopleths are drawn for systemic vascular resistances of 1300 and 2000 dynes-sec-cm^{-5}. Points to the left of the 1300 line indicate elevated resistances. There was little consistent shift in flow-pressure relationships during the entire period of observation.

Systolic and mean arterial pressures tended to rise, while systolic ejection rate fell. Stroke index continued to rise in seven of the nine patients who demonstrated further decreases in mean left ventricular outflow resistance. In four patients, stroke index decreased and left ventricular outflow resistance increased in the late hours of IACP (Fig. 3). Coronary blood flow tended to fall after the initial increase associated with a decrease in diastolic arterial pressure. Myocardial oxygen extraction steadily increased leading to a fall in coronary sinus oxygen tension. All but two of the patients continued to extract lactate although the percentage of lactate exracted decreased throughout IACP.

Performance after discontinuation of IACP. Studies were performed in four out of six patients in whom IACP could be discontinued. The data were obtained 4–6 hr after termination of IACP; two of these were again studied 14 and 18 hr later.

The following measurements changed significantly from data obtained before initiation of IACP. Cardiac index increased from 1.15 to 1.84 liters/min per m^2, mean and systolic arterial pressures rise from 56 and 82 to 81 and 115 mm Hg, respectively. Left ventricular work index increased from 0.86 to 2.07 kg·m/min per m^2, and systolic ejection rate rose from 58 to 98 ml/sec per m^2. Arterial lactate fell from 6.02 to 2.36 mmoles/liter.

Statistically significant increases in coronary blood flow (67–91 ml/min per 100 g) and in myocardial oxygen consumption (7.34–9.66 ml/min per 100 g) were observed. Oxygen extraction decreased in all patients, but the difference was not statistically significant. The

TABLE III

Cardiac Energetics before, during, and after Intra-Aortic Counterpulsation

Case	Control		Hours on intra-aortic counterpulsation (IACP) 4–6		12–20		24–36		40–72		Hours off IACP, 4–24	
	LVOR SER	SVR TTM	LVOR SER	SVR TTM	LVOR SER	SVR TTM	LVOR SER	SVR TTM	LVOR SER	SVR TTM	LVOR SER	SVR TTM
1	0.42 74	1.1 1352	0.13 117	0.8 686								
2	0.66 56	1.8 1110	0.23 81	1.8 714								
3	0.59 54	1.4 1142	0.23 124	1.6 703	0.20 198	1.4 644	0.25 120	1.2 1123			0.34 133	1.3 1441
4	0.47 92	2.0 967	0.32 178	1.6 685	0.18 218	1.5 778						
5	0.41 82	1.1 1269	0.24 60	1.8 1355			0.64 53	2.6 1228				
6	0.85 49	1.9 1571	0.43 63	1.8 1214	0.42 108	2.2 1368	0.51 82	2.5 1305	0.43 103 0.36* 135	2.2 1336 2.4 1128	0.62 89	2.3 1548
7	0.77 48	2.0 1281	0.36 66	1.2 1116			0.55 81	1.8 1368	0.70 66 0.97* 63	2.6 1632 2.8 2296	0.94 50 0.76‡ 68	2.6 2256 1.7 1950
8	0.72 46	1.9 1428	0.41 72	1.4 1079	0.42 68	2.1 933						
9	0.59 80	2.1 1529	0.37 94	1.6 1224	0.31 114	1.1 1240					0.50 102 0.55‡ 79	1.4 1987 1.6 1762
10	0.49 90	1.6 1150	0.44 97	2.3 913	0.37 93	2.0 929			0.35 38	2.7 1001		
Mean	0.60 67	1.70 1280	0.32 95	1.56 977	0.32 133	1.71 982	0.49 94	2.02 1256	0.56 92	2.54 1479	0.62 86	1.82 1824
SD	0.15 18	0.39 193	0.09 34	0.42 272	0.10 60	0.44 274	0.16 21	0.65 100	0.26 34	0.10 314	0.20 28	0.21 302
F_1§	50.3 5.21	0.80 23.3										
P_1	<0.001 =0.05	NS <0.001										
Mean	0.70 58	1.80 1380									0.59 98	1.89 1731
SD	0.13 15	0.31 204									0.25 27	0.64 277
F_2‖	1.10 10.33	0.03 5.78										
P_2	NS <0.05	NS NS										

Abbreviations: LVOR, mean left ventricular outflow resistance (mm Hg/ml per systolic sec); SER, systolic ejection rate (ml/sec per m^2); TTM, time-tension index per minute (mm Hg·sec/min); SVR, systematic vascular resistance (dynes-sec-cm^{-5} × 10^3).

* 62–72 hr during IACP.

‡ 20–24 hr off IACP.

§ F_1, variance ratio between data before and 4–6 hr during IACP.

‖ F_2, variance ratio between data before and after discontinuation of IACP (cases 3, 6, 7, 9).

myocardium produced 48.83 μmoles/min per 100 g (extraction ratio − 10%) of lactate before IACP and extracted 30.93 μmoles/min per 100 g (extraction ratio 16%) after IACP.

Interrelationships between certain variables in severe coronary shock. Changes in stroke index during IACP were significantly correlated with changes in tension time index per beat ($r = -0.61$, $P < 0.05$) and closely related with changes in left ventricular outflow resistance ($r = -0.81$, $P < 0.001$). Fig. 3 shows that IACP almost always decreased outflow resistance and increased stroke index. In four instances, left ventricular outflow resistance increased, and stroke index decreased.

Fig. 4 emphasizes the dependency of coronary blood

TABLE IV

Myocardial Perfusion and Oxygenation before, during, and after Intra-Aortic Counterpulsation

	Control		Hours on intra-aortic counterpulsation (IACP) 4–6		12–20		24–36		40–72		Hours off IACP, 4–24	
Case	CBF MVO_2	Exo_2 $Pcso_2$	CBF MVO_2	Exo_2 $Pcso_2$	CBF MVO_2	Exo_2 $Pcso_2$	CBF MVO_2	Exo_2 $Pcso_2$	CBF MVO_2	Exo_2 $Pcso_2$	CBF MVO_2	Exo_2 $Pcso_2$
1	81	75	100	70								
	7.42	22	8.44	27								
2	60	86	88	67								
	8.46	18	8.43	30								
3	64	77	87	68	100	55	83	81			92	73
	6.80	23	7.24	23	8.05	23	7.02	27			8.35	28
4	81	75	97	64	107	76						
	7.11	20	6.31	27	8.28	24						
5	54	73	94	61			67	71				
	6.80	22	7.89	26			6.01	22				
6	72	94	112	52	92	71	88	69	86	71	84	76
	5.96	20	5.48	26	9.31	26	6.97	24	7.92	22	8.51	24
									127*	66		
									12.25	25		
7	67	73	76	50			78	52	57	67	86	68
	6.27	26	4.64	32			4.96	29	4.90	24	8.69	20
									77*	66	97†	72
									7.45	20	8.64	19
8	70	76	93	62	80	61						
	10.71	24	9.08	29	7.12	26						
9	68	78	77	53	104	58					101	74
	10.50	11	7.44	19	9.83	18					13.15	18
											98†	85
											13.20	18
10	62	84	86	66	81	72			92	82		
	9.43	22	10.76	24	9.97	23			10.60	29		
Mean	68	79	91	61	94	65	83	67	90	70	93	74
	7.95	20	7.57	26	8.76	23	6.32	27	9.00	24	10.08	21
SD	8.6	6.8	11	7.2	11	8.6	5.0	10	18	6.8	6.8	5.6
	1.74	4.1	1.78	3.7	1.12	2.9	1.07	2.4	2.71	3.3	2.39	4.4
F_1§	58.9	28										
	0.71	28										
P_1	<0.001	<0.001										
	NS	<0.001										
Mean	67	81									91	72
	7.34	20									9.66	22
SD	3.30	9.25									7.31	3.40
	2.13	6.48									2.32	5.16
F_2‖	30.1	5.12										
	86.8	0.55										
P_2	<0.05	NS										
	<0.01	NS										

Abbreviations: CBF, coronary blood flow (ml/100g per min); MVO_2, myocardial oxygen consumption (ml/100 g per min); Exo_2, myocardial oxygen extraction ratio (%); $Pcso_2$, coronary sinus oxygen tension (mm Hg).

* 62–72 hr during IACP.

† 20–24 hr off IACP.

§ F_1, variance ratio between data before and 4–6 hr during IACP.

‖ F_2, variance ratio between data before and after discontinuation of IACP (cases 3, 6, 7, 9)

TABLE V

Myocardial Lactate-Pyruvate Metabolism before, during, and after Intra-Aortic Counterpulsation

	Control		Hours on intra-aortic counterpulsation (IACP) 4–6		12–20		24–36		40–72		Hours off IACP, 4–24	
Case	Ex_L Ex_P	MV_L A_L	Ex_L Ex_P	MV_L A_L	Ex_L Ex_P	MV_L A_L	Ex_L Ex_P	MV_L A_L	Ex_L Ex_P	MV_L A_L	Ex_L Ex_P	MV_L A_L
1	6	20.6	16	74.4								
	−12	4.30	−6	3.53								
2	−13	−43.9	19	41.1								
	−5	5.56	54	2.47								
3	−12	−40.5	11	35.6	33	109	7	13.8			12	20.4
	7	5.47	−40	4.12	10	3.36	57	2.99			51	1.79
4	−15	−66.6	23	58.2	16	33.3						
	7	5.31	14	2.60	48	1.92						
5	3	4.79	24	38.6			−25	−138				
	27	2.74	33	1.70			9*	8.01				
6	−15	−96.8	12	53.5	9	16.4	42	99.7	2	2.86	16	45.2
	−9	8.83	−10	3.90	49	1.99	24	2.68	−8	1.89	20	3.30
									10†	36.7		
									7	2.81		
7	−4	−8.19	14	14.3			34	33.8	−5	−3.23	23	20.0
	−49	3.81	−20	1.37			22	1.25	4	1.11	68	1.02
									28†	29.9	28§	30.1
									56	1.31	85	1.11
8	11	23.3	16	45.5	12	19.5			10	136		
	10	3.00	−16	2.09	46	2.03			20	14.7		
9	−10	−49.8	5	17.9	12	24.3					9	28.05
	−2	6.97	−13	4.08	18	2.66					6	3.22
											2§	7.54
											−15	4.02
10	−14	−38.6	12	15.3	14	44.1						
	−7	5.80	−5	4.28	20	3.83						
Mean	−6	−29.6	15	39.4	16	41.2	28	49.1	9	40.5	15	25.1
	−3	5.08	−9	2.98	32	2.63	34	2.30	16	4.34	36	2.42
SD	9.6	38.9	5.83	19.7	8.64	35.1	18	44.2	12	56.1	9.4	5.14
	19.7	1.95	27	1.08	17.6	0.81	19	0.93	24	5.80	38	1.27
F_1‖	46.2	26.7										
	0.07	26.4										
P_1	<0.001	<0.001										
	NS	<0.001										
Mean	−10	−48.8									16	30.9
	−13	6.02									36	2.36
SD	4.64	36.6									6.05	10.4
	24	2.54									28	1.08
F_2¶	75	12.8										
	4.36	21.9										
P_2	<0.01	<0.05										
	NS	<0.05										

Abbreviations: Ex_L, myocardial lactate extraction ratio (%); Ex_P, myocardial pyruvate extraction ratio (%); MV_L, myocardial lactate consumption (μmoles/100g per min); A_L, arterial lactate content (mmoles/liters).

* Case 5 not included in mean statistics because of rapid deterioration.

† 62–72 hr during IACP.

§ 20–24 hr off IACP.

‖ F_1, variance ratio between data before and 4–6 hr during IACP.

¶ F_2, variance ratio between data before and after discontinuation of IACP (cases 3, 6, 7, 9).

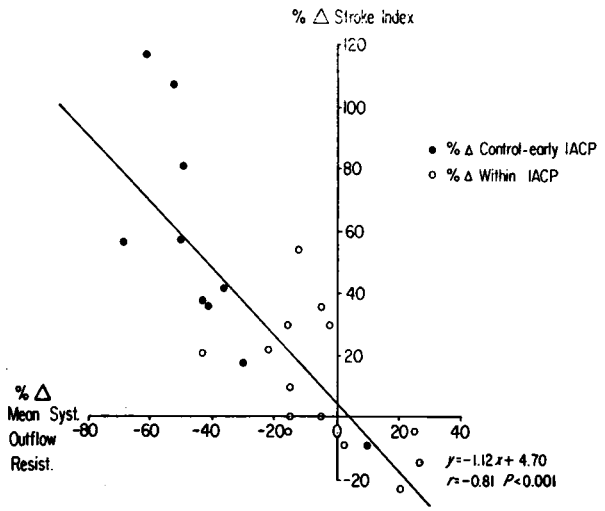

FIGURE 3 Correlation between changes in left ventricular mean outflow resistance and stroke index; $y = -1.12x + 4.70$; $r = -0.81$; $P < 0.001$. During the early stage of IACP, left ventricular outflow resistance decreased and stroke index increased in all but one patient (dots). In the later stages of IACP, outflow resistance tended to rise and stroke index to fall (circles).

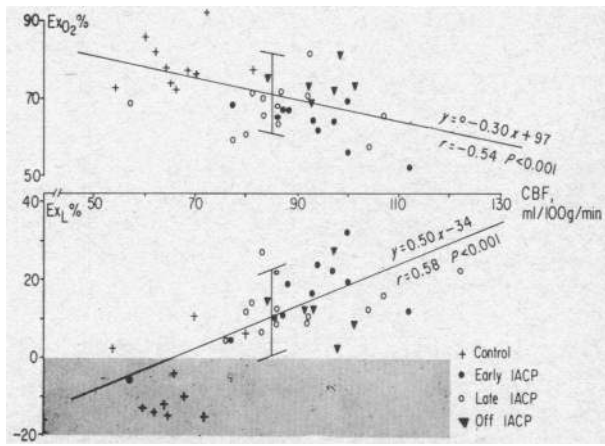

FIGURE 5 Interrelationship between coronary blood flow (CBF) and myocardial oxygen (Ex_{O_2}) and lactate (Ex_L) extraction in different stages of coronary shock. Before treatment, myocardial lactate production occurred together with oxygen extractions above 78% and coronary blood flows below 65 ml/100 g per min. During IACP, increase in coronary blood flow above 100 ml/100 g per min was associated with improvement of both, oxygen and lactate extractions, towards normal.

flow on mean aortic pressure in coronary shock. Included are observations of patients in coronary shock before treatment (11) and during *l*-norepinephrine infusion (8), previously reported (32). All data have been plotted together and are shown as a nonlinear relationship, derived by a third-order equation. Although the correlations, obtained by linear and third-order equation,

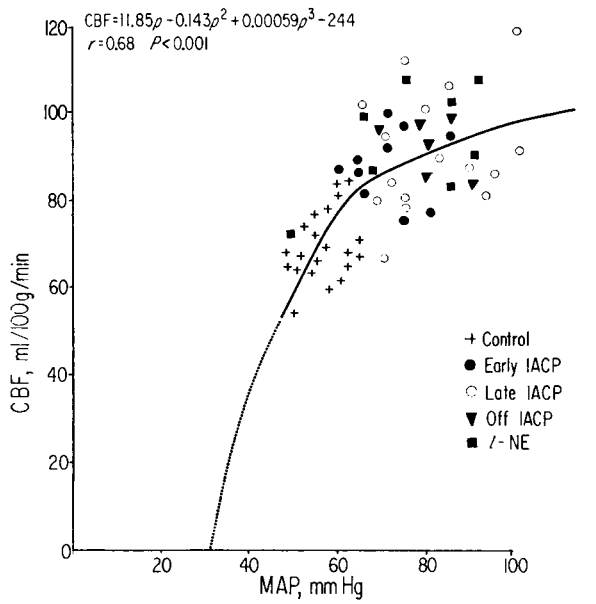

FIGURE 4 Correlation between coronary blood flow (CBF) and mean aortic pressure (MAP) before treatment, during, and after IACP and during *l*-norepinephrine infusion. The points are best described by a third-order equation; $CBF = 11.85\ p - 0.143\ p^2 + 0.00059\ p^3 - 244$; $r = 0.683$; $P < 0.001$. CBF decreased sharply when MAP fell below 65–70 mm Hg. Extrapolation of the third-order curve reveals a critical closing pressure of 30 mm Hg.

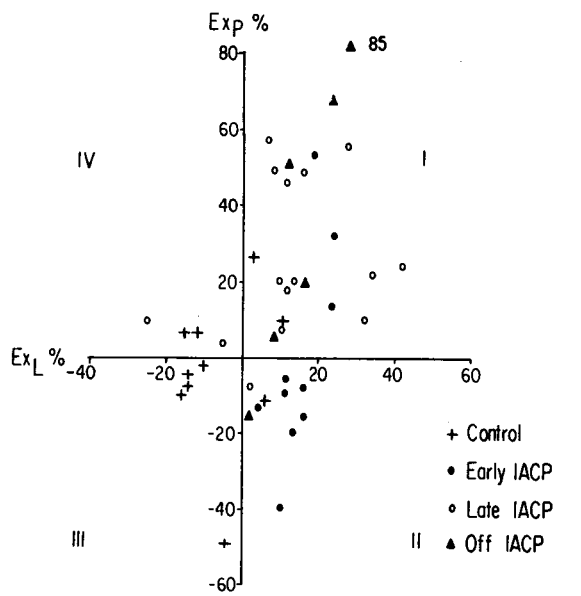

FIGURE 6 Myocardial lactate (Ex_L) and pyruvate (Ex_P) extraction ratios in different stages of coronary shock. Before treatment, production of lactate occurred together with production or extraction of pyruvate, suggesting anaerobic metabolism. During early IACP, the extraction ratios tended to cluster in quadrant II, and then during the later stages and after discontinuation of IACP in quadrant I, indicating significant improvement of myocardial metabolism.

were not significantly different ($r = 0.640$ and $r = 0.683$, respectively), the nonlinear relation was preferred, because it is similar to that shown by others in the passive vascular bed (50). The extrapolation of the curve beyond the observed data intersects the x axis at a mean pressure of approximately 30 mm Hg.

Both oxygen and lactate extraction were related to coronary blood flow during all periods of observation. Fig. 5 shows that lactate extraction decreased to 11% and oxygen extraction increased to 71% as coronary blood flow decreased to 85 ml/100 g per min. Lactate production was observed with oxygen extractions above 78% and coronary blood flows below 65 ml/100 g per min.

Myocardial lactate and pyruvate extractions in all stages of study are shown as cartesian coordinates in the four-quadrant diagram presented in Fig. 6. Before treatment, all but three patients produced lactate. During early IACP, the extraction ratios tended to cluster in quadrant II and during the later stages of IACP and after discontinuation in quadrant I suggesting progressive improvement in myocardial metabolism.

Serial changes during and after IACP in two patients. Fig. 7 shows the course of a patient (No. 7) who did relatively well during IACP. Mean arterial pressure increased markedly during counterpulsation while cardiac index fell gradually after an initial rise. During the 48th hr of IACP, the systolic and diastolic pressures rose to approximately the same levels, 118/114 mm Hg, and the patient appeared to deteriorate. The arterial tracing suggested that the balloon pump was occlusive during diastole. Cardiac output and coronary blood flow were decreased, and the myocardium produced lactate again. After 5 mg chlorpromazine (Thorazine; Smith Kline & French Laboratories) i.v., the arterial pressures changed without additional volume replacement to 81 mm Hg systolic and 102 mm Hg diastolic. Later, measurements showed improvement of hemodynamics and myocardial oxygenation. Studies performed after discontinuation of IACP showed significant improvement compared with initial results before circulatory assist. 3 days after discontinuation of IACP the infarction extended; the patient developed signs of left ventricular failure, rapidly deteriorated, and died. Fig. 8 demonstrates the course of one patient (No. 5) who deteriorated during IACP after an initial period of improvement. An evaluation performed during infusion of *l*-norepinephrine before IACP is also shown. *l*-Norepinephrine increased mean arterial pressure, coronary blood flow, and cardiac in-

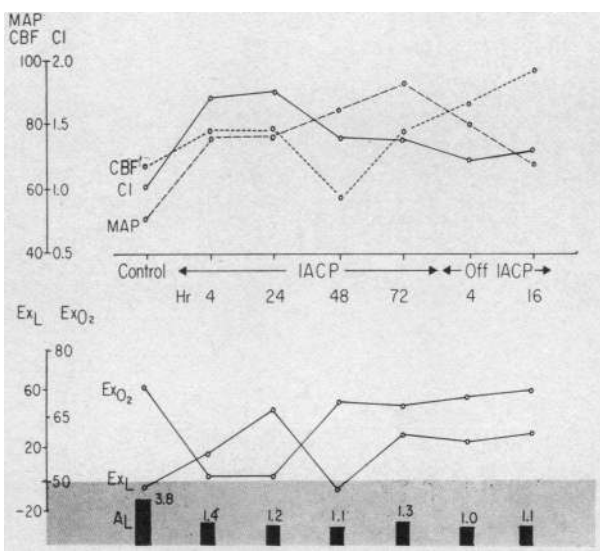

FIGURE 7 Serial changes of cardiac energetics in a patient, who did relatively well during IACP (No. 7). Mean arterial pressure (MAP) increased markedly while cardiac index (CI) fell gradually after an initial rise. Coronary blood flow (CBF), myocardial oxygen (Ex_{O_2}), and lactate (Ex_L) extraction and arterial lactate content (A_L) improved. During the 48th hr of IACP, the arterial tracing suggested occlusion of the aorta by the inflated balloon. Coronary blood flow (CBF) was decreased, and myocardial oxygen and lactate metabolism was abnormal. Chlorpromazine, 5 mg i.v., was administered. Subsequent studies showed improvement of all measurements.

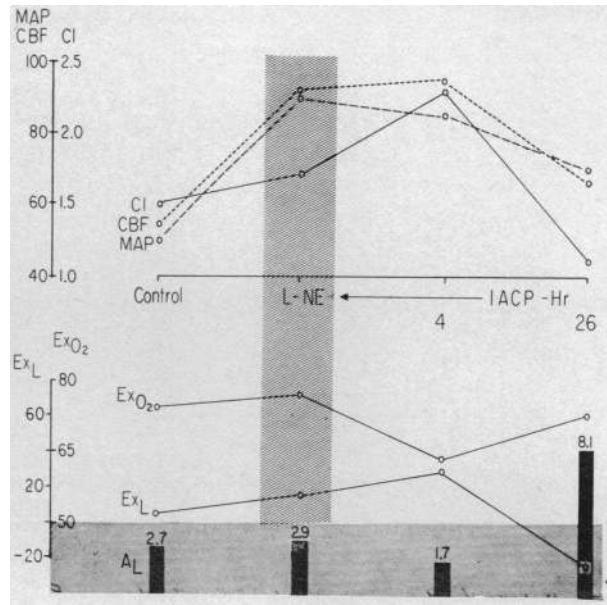

FIGURE 8 Serial changes of cardiac energetics during *l*-norepinephrine infusion and IACP (No. 5). *l*-Norepinephrine increased mean arterial pressure (MAP), coronary blood flow (CBF), and myocardial lactate extraction (Ex_L). Arterial lactate content (A_L) remained essentially unchanged and cardiac index (CI) increased only slightly. During early IACP, all measurements improved strikingly but deteriorated over the subsequent 22 hr. The patient died with intractable supraventricular arrhythmias.

dex. Myocardial lactate evtraction rose, but arterial lactate content was essentially unchanged; myocardial oxygen extraction increased slightly. Cardiac index and extraction of oxygen and lactate improved strikingly during IACP. However, over the subsequent 12 hr arterial pressures and coronary blood flow fell, oxygen extraction increased, and myocardial lactate production developed. Shortly thereafter, the patient developed intractable supraventricular arrhythmias leading to ventricular asystole and death.

DISCUSSION

Patients with severe coronary shock appear to fall into two general groups. Some respond promptly to small amounts of *l*-norepinephrine with improved arterial pressure and peripheral perfusion. Within several hours, blood pressure may be maintained without vasoactive agents. This group probably represents those patients with relatively small amounts of myocardial damage and inappropriate systemic arteriolar dilatation. The failure to adequately increase peripheral resistance may be related to decreased sympathetic activity demonstrated during acute left ventricular dilatation (51–54). This group has a relatively good prognosis and will not be further considered here.

The majority of patients with coronary shock, however, are similar to those presented in this study; peripheral perfusion is not improved by *l*-norepinephrine, and they usually die. Pathologic studies have shown that an average of 47% of myocardial tissue is infarcted in patients with fatal coronary shock and have suggested that part of the necrosis may be associated with hypotension occurring after the initial infarction (55). Treatment for this group of patients must be directed towards salvaging as much myocardium as possible by reducing myocardial oxygen demands and increasing myocardial oxygen delivery.

Three therapeutic interventions have been extensively studied in both human and experimental coronary shock: *l*-norepinephrine, isoproterenol, and IACP. Isoproterenol improves myocardial contractility and stroke output (10, 56). This increase in cardiac work, however, is not accompanied by adequate rise in coronary blood flow because of decrease in aortic diastolic pressure. Myocardial metabolism deteriorates (32). Therefore, isoproterenol appears to be harmful in the treatment of coronary shock (57–61).

l-Norepinephrine restores myocardial lactate metabolism towards normal by raising coronary perfusion pressure and blood flow; myocardial oxygen extraction remains elevated, however, indicating that ventricular work still exceeds oxygen availability (32). Nevertheless, we believe *l*-norepinephrine is the drug of choice in the initial treatment of coronary shock (32, 62–68) although increased peripheral resistance may diminish blood flow to critical organ systems.

IACP appears to combine the advantages of isoproterenol and *l*-norepinephrine. In this study, IACP improved perfusion of the myocardium as well as of the periphery. Improved peripheral perfusion was evidenced by increases in cardiac output and urine flow and striking decreases in arterial lactate concentration. Improved oxygen delivery to the myocardium was demonstrated by significant increases in coronary blood flow in every patient. Under the different conditions of the study (before, during, and after termination of IACP), changes in coronary blood flow were correlated with changes in coronary perfusion pressure (Fig. 4). The increased oxygen delivery to the heart was associated with decreased oxygen extraction across the coronary bed, and thus with only little changes in myocardial oxygen consumption. That this decrease in myocardial oxygen extraction was an adequate response was evidenced by the associated improvement of myocardial lactate fluxes. The importance of coronary blood flow for myocardial metabolism is shown in Fig. 5. It demonstrates that both oxygen and lactate extraction were significantly correlated with coronary blood flow during the entire period of observations.

It is difficult to relate our data to other clinical and experimental observations because of differences in protocol and in the preexisting state of the coronary vascular bed. In animal experiments, the response of coronary blood flow and myocardial metabolism to IACP varied, depending upon the condition of the myocardium. IACP decreased cardiac work and oxygen consumption in normal hearts while coronary blood flow remained essentially unchanged and oxygen extraction decreased (16, 24, 69, 70). In contrast, in the ischemic and dilated heart, IACP increased coronary blood flow and oxygen consumption (16, 24, 25). In human coronary shock, Leinbach et al. reported varying responses of myocardial perfusion and metabolism to IACP (71). Coronary blood flow and oxygen consumption did not change or actually decreased with IACP in most of their patients. This discrepancy with our findings may be related to differing protocols. We compared measurements before treatment with those during IACP while Leinbach et al. compared changes after the patients had been treated with IACP for an average of 17 hr.

IACP must have diminished myocardial oxygen requirements in our patients, since myocardial oxygen consumption remained essentially unchanged, but lactate and oxygen extractions had improved. Cardiac work was diminished during IACP by decrease in left ventricular outflow resistance in every patient. Urschel et al. (26) and Matloff et al. (23) studied changes in left ventricular afterload during IACP by continuous recording of

aortic flow and left ventricular pressure. Both peak and mean integrated wall tension decreased. Force-velocity curves derived by Matloff et al. for one experimental study failed to reveal changes in V_{max} leading those investigators to conclude that myocardial contractility was unchanged during IACP (23). We studied six patients after successful termination of IACP. For comparable levels of left ventricular outflow resistance, stroke volume was significantly greater than that measured before IACP, suggesting that myocardial contractility had improved.

Our studies clearly indicate that IACP improves myocardial oxygenation and probably myocardial contractility in the severely diseased human heart. In addition, significant decreases in arterial lactate, increased cardiac output, and increased urine flow were evidence of improved peripheral perfusion. Although the actue shock state was successfully reversed in 5 of 12 patients, who survived from 3 to 21 days after IACP, extensive myocardial destruction appears to limit long-term survival. For this reason, it seems desirable to focus attention on those patients showing subtle evidence of early pump failure after acute myocardial infarction. IACP may well augment coronary perfusion in this group, salvaging viable myocardium and interrupting the vicious cycle of events leading to coronary shock. The ability of IACP to stabilize hemodynamics in severe coronary shock suggests that its major role in that syndrome may be to facilitate subsequent diagnostic and surgical intervention.

ACKNOWLEDGMENTS

We wish to thank Doctors Darline Smith and Alfred Lowenstein who participated in the evaluation and management of patients in coronary shock, and Dr. Leonard Stutman, who performed coagulation studies in these patients. We would like to thank Miss Meta Buehler who prepared the illustrations.

This work was supported in part by U. S. Public Health Service National Heart Institute Research Grant HE-12323 and Training Grant 5-T01-HE-05686-5, the John A. Hartford Foundation, Inc., and the Council for Tobacco Research, U. S. A.

REFERENCES

1. Braunwald, E. 1969. Bowditch lecture: the determinants of myocardial oxygen consumption. *Physiologist.* **12**: 65.
2. Sarnoff, S. J., E. Braunwald, G. H. Welch, Jr., R. B. Case, W. N. Stanisby, and R. Macruz. 1958. Hemodynamic determinations of oxygen consumption of the heart with special reference to the tension time index. *Amer. J. Physiol.* **192**: 148.
3. Monroe, R. G., and G. N. French. 1961. Left ventricular pressure volume relationship and myocardial oxygen consumption in isolated heart. *Circ. Res.* **9**: 362.
4. Sonnenblick, E. H., J. Ross, Jr., J. W. Covell, G. A. Kaiser, and E. Braunwald. 1965. Velocity of contraction as a determinant of myocardial oxygen consumption. *Amer. J. Physiol.* **209**: 919.
5. Graham, T. P., Jr., J. W. Covell, E. H. Sonnenblick, J. Ross, Jr., and E. Braunwald. 1968. Control of myocardial oxygen consumption: relative influence of contractile state and tension development. *J. Clin. Invest.* **47**: 375.
6. Ross, J., Jr., E. H. Sonnenblick, G. A. Kaiser, P. L. Frommer, and E. Braunwald. 1965. Electroaugmentation of ventricular performance and oxygen consumption by repetitive application of paired electrical stimuli. *Circ. Res.* **16**: 332.
7. Coleman, H. N., III. 1968. Effect of alteration in shortening and external work on oxygen consumption of cat papillary muscle. *Amer. J. Physiol.* **214**: 100.
8. Coleman, H. N., III. 1967. Role of acetylstrophanthidin in augmenting myocardial oxygen consumption: relation of increased O_2 consumption to change in velocity of contraction. *Circ. Res.* **21**: 487.
9. Braunwald, E., J. Ross, and E. H. Sonnenblick. 1968. Relation between utilization and contraction mechanics. *In* Mechanism of Contraction of the Normal and Failing Heart. Little, Brown and Company, Boston. 91.
10. Braunwald, E., J. W. Corell, P. R. Maroko, and J. Ross, Jr. 1969. Effects of drugs and of counterpulsation on myocardial oxygen consumption. Observation on the ischemic heart. *Circulation.* **40** (Suppl. 4): 220.
11. Edwards, J. E. 1969. What is myocardial infarction? *Circulation.* **11**: 5.
12. Birtwell, W. C., H. S. Soroff, M. Wall, A. Bisberg, H. J. Levine, and R. A. Deterling, Jr. 1962. Assisted circulation: improved method for counterpulsation. *Trans. Amer. Soc. Artif. Intern. Organs.* **8**: 35.
13. Ellis, P. R., Jr., C. Lee, S. Wong, V. C. Del Rosario, T. W. Hyland, and G. Prator. 1965. Assisted circulation in treatment of experimental heart failure. *Arch. Surg.* **90**: 879.
14. Gallo, E., P. Eichelter, and W. G. Schenk, Jr. 1966. Influence of counterpulsation on experimental acute cardiac failure. *J. Thorac. Cardiovasc. Surg.* **52**: 745.
15. Hahnloser, P., E. Gallo, and W. G. Schenk, Jr. 1966. Hemodynamics of counterpulsation. *J. Thorac. Cardiovasc. Surg.* **51**: 366.
16. Hirsch, L. J., S. Lluch, and L. N. Katz. 1966. Counterpulsation effects of coronary blood flow and cardiac oxygen utilization. *Circ. Res.* **19**: 1031.
17. Goldfarb, D., B. G. Brown, C. R. Conti, and V. L. Gott. 1968. Cardiovascular responses to diastolic augmentation in the intact canine circulation and after ligation of the anterior descending coronary artery. *J. Thorac. Cardiovasc. Surg.* **55**: 243.
18. Kantrowitz, A., S. Tjonneland, J. S. Krakauer, S. J. Phillips, P. S. Freed, and A. N. Butner. 1968. Mechanical intra-aortic cardiac assistance in cardiogenic shock. Hemodynamic effects. *Arch. Surg.* **97**: 1000.
19. Spotnitz, H. M., and J. W. Covell. 1968. Effects of counterpulsation on the mechanics of left ventricular contraction and myocardial oxygen consumption (MVO_2). *Fed. Proc.* **27**: 318.
20. Birtwell, W. C., H. S. Soroff, and U. Ruiz. 1969. Synchronous pressure assist counterpulsation. *Progr. Cardiovasc. Dis.* **11**: 323.
21. Buckley, J. J., R. C. Leinbach, J. A. Kastor, A. R. Kantrowitz, J. D. Laird, and W. G. Austen. 1969. Hemodynamic evaluation of intra-aortic balloon pumping (IAP) in man. *Circulation.* **40** (Suppl. 3): 52.
22. Kuhn, L. A., A. H. Unger, S. A. Novick, A. J. Marano, and A. S. Rosenberg. 1970. Hemodynamics and cardiac

metabolic effects of diastolic intraaortic balloon obstruction combined with distal aortic "booster" occlusion in experimental acute myocardial infarction. *Amer. J. Cardiol.* **25**: 111.
23. Matloff, J. M., W. W. Parmley, J. H. Manchester, B. Berkovits, E. H. Sonnenblick, and D. E. Harken. 1970. Hemodynamic effects of glucagon and intraaortic balloon counterpulsation in canine myocardial infarction. *Amer. J. Cardiol.* **25**: 675.
24. Powell, W. J., Jr., W. M. Daggett, A. E. Margo, J. A. Bianco, M. J. Buckley, C. A. Sanders, A. R. Kantrowitz, and W. G. Austen. 1970. Effects of intra-aortic balloon counterpulsation on cardiac performance, oxygen consumption and coronary blood flow in dogs. *Circ. Res.* **36**: 753.
25. Summers, D. N., J. Norris, A. I. Arieff, R. I. Nacht, B. M. Wechsler, P. N. Sawyer, M. J. Kaplitt, R. Rubin, and C. Dennis. 1970. Hemodynamic, metabolic and angiographic studies during circulatory assist in cardiogenic shock. *Amer. J. Cardiol.* **25**: 131.
26. Urschel, C. W., L. Eber, J. Forrester, J. Matloff, R. Carpenter, and E. H. Sonnenblick. 1970. Alteration of mechanical performance of the ventricle by intraaortic balloon counterpulsation. *Amer. J. Cardiol.* **25**: 546.
27. Krakauer, J. S., A. Rosenbaum, P. Freed, D. Jaron, and A. Kantrowitz. 1971. Clinical management ancillary to phase-shift balloon pumping in cardiogenic shock. Preliminary comments. *Amer. J. Cardiol.* **27**: 123.
28. Feola, M., M. Adachi, W. W. Akers, J. N. Ross, Jr., D. W. Wieting, and J. H. Kennedy. 1971. Intraaortic balloon pumping in the experimental animal. Effects and problems. *Amer. J. Cardiol.* **27**: 129.
29. Jacobey, J. A. 1971. Results of counterpulsation in patients with coronary artery disease. *Amer. J. Cardiol.* **27**: 137.
30. Grace, W. J. 1969. The use of monitoring devices in acute myocardial infarction. *In* Advances of Cardiopulmonary Diseases. Year Book Medical Publishers, Inc., Chicago. **4**: 91.
31. Mueller, H., S. Ayres, J. Gregory, S. Giannelli, and W. Grace. 1970. Evaluation and treatment of cardiogenic shock. *Med. Times (Port Wash. N. Y.)*. **98**: 137.
32. Mueller, H., S. M. Ayres. J. Gregory, S. Giannelli, Jr., and W. Grace. 1970. Hemodynamics, coronary blood flow and myocardial metabolism in coronary shock. *J. Clin. Invest.* **49**: 1885.
33. Staub, N. C. 1961. Simple small oxygen electrode. *J. Appl. Physiol.* **16**: 192.
34. Severinghaus, J. W., and A. F. Bradley. 1958. Electrodes for blood P_{O_2} and P_{CO_2} determinations. *J. Appl. Physiol.* **13**: 515.
35. Malcolm, D. 1941. The glass electrode. John Wiley & Sons, Inc., New York.
36. Ayres, S. M., A. Criscitiello, and E. Grabovsky. 1964. Components of alveolar arterial O_2 difference in normal man. *J. Appl. Physiol.* **19**: 43.
37. Van Slyke, D. D., and J. M. Neill. 1924. The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. *J. Biol. Chem.* **61**: 523.
38. Scholz, H. S., T. Buecher, and J. O. Lampen. 1959. Ueber die Wirkung von Nystatin auf Baeckerhefe. *Biochem. Z.* **331**: 71.
39. Buecher, T., R. Chak, W. Lamprecht, and E. Letzko. 1965. Methods of Enzymatic Analysis. Academic Press Inc., New York. 2nd edition. 253.
40. Hamilton, W. F., J. W. Moore, J. M. Kinsman, and R. S. Spurling. 1932. Studies in circulation: IV: Further analysis of injection method, and of changes in hemodynamics under physiological and pathological conditions. *Amer. J. Physiol.* **99**: 534.
41. Giannelli, S., Jr., S. M. Ayres, J. W. Vastor, R. A. Goldstone, and M. S. Buehler. 1965. Indicator in dilution curves obtained across the systemic circulation during cardiopulmonary bypass perfusion. *Surgery.* **57**: 423.
42. Krasnow, N., H. J. Levine, R. J. Wagman, and R. Gorlin. 1963. Coronary blood flow measured by I^{131} iodoantipyrine. *Circ. Res.* **12**: 58.
43. Stutman, L. J., and G. Y. Shinowara. 1965. Plasma tetrapyrrole pigments in sickle cell anemia. *Amer. J. Clin. Pathol.* **43**: 94.
44. Remington, J. W., W. F. Hamilton, and R. P. Ahlquist. 1948. Interrelationship between length of systole, stroke volume and left ventricular work in the dog. *Amer. J. Physiol.* **154**: 6.
45. Krasnow, N., E. L. Roleff, P. M. Yurchak, W. B. Hood, Jr., and R. Gorlin. 1964. Isoproterenol and cardiovascular performance. *Amer. J. Med.* **37**: 514.
46. Gorlin, R. 1960. Measurement of coronary blood flow in health and disease. *In* Modern Trends in Cardiology. P. B. Hoeber, Inc., New York. 191.
47. Huckabee, W. E. 1961. Relationship of pyruvate and lactate during anaerobic metabolism. V. Coronary adequacy. *Amer. J. Physiol.* **200**: 1169.
48. Urschel, C. W., J. W. Covell, E. H. Sonnenblick, J. Ross, Jr., and E. Braunwald. 1968. Myocardial mechanics in aortic and mitral valvular regurgitation: the concept of instantaneous impedence as a determinant of the performance of the intact heart. *J. Clin. Invest.* **47**: 867.
49. Wilcken, D. E. L., A. A. Charlier, J. I. E. Hoffman, and A. Grutz. 1964. Effects of alteration in aortic impedence on the performance of the ventricles. *Circ. Res.* **14**: 283.
50. Braunwald, E. 1967. The pathogenesis and treatment of shock in myocardial infarction. *John Hopkins Med. J.* **121**: 421.
51. Agress, C. M., H. F. Glassher, M. J. Binder, and J. Fields. 1957. Hemodynamic measurements in experimental coronary shock. *J. Appl. Physiol.* **10**: 469.
52. Constantin, L. 1963. Extracardiac factors contributing to hypotension during coronary occlusion. *Amer. J. Cardiol.* **11**: 205.
53. Sleight, P., and J. G. Widdicombe. 1966. Action potentials in fibers from receptors in the epicardium and myocardium of the dog's left ventricle. *J. Physiol. (London).* **181**: 235.
54. Kezdi, P., S. N. Misra, R. K. Kordenat, J. W. Spickler, and E. L. Stanley. 1970. The role of vagal afferents in acute myocardial infarction. *Amer. J. Cardiol.* **26**: 642.
55. Harnarayan, C., M. A. Bennett, B. L. Pentecost, and D. B. Brewer. 1970. Quantitative study of infarcted myocardium in cardiogenic shock. *Brit. Heart J.* **32**: 728.
56. Dodge, H. T., J. D. Lord, and H. Sandler. 1960. Cardiovascular effects of isoproterenol in normal subjects and subjects with congestive heart failure. *Amer. Heart J.* **60**: 94.
57. Raab, W., P. Van Lith, E. Lepeschkin, and H. C. Herrlich. 1962. Catecholamine induced myocardial hypoxia in the presence of impaired coronary dilatability independent of external cardiac work. *Amer. J. Cardiol.* **9**: 455.

58. Gunnar, R. M., H. S. Loeb, R. J. Pietras, and T. R. Tobin, Jr. 1967. Ineffectiveness of isoproterenol in shock due to acute myocardial infarction. *J. Amer. Med. Ass.* **202**: 64.
59. Eichna, L. W. 1967. The treatment of cardiogenic shock. III. Use of isoproterenol in cardiogenic shock. *Amer. Heart J.* **74**: 848.
60. Goldberg, L. I. 1968. The treatment of cardiogenic shock. IV. The search for an ideal drug. *Amer. Heart J.* **75**: 416.
61. Kuhn, L. A., H. J. Kline, P. Goodman, and C. D. Johnson. 1967. Effects of isoproterenol on hemodynamic alterations, myocardial metabolism and coronary flow in experimental acute myocardial infarction with shock. *Amer. J. Cardiol.* **19**: 137.
62. Udoji, V. N., and M. H. Weil. 1964. Circulatory effects of angiotensin, levarterenol and metaraminol in the treatment of shock. *N. Engl. J. Med.* **270**: 501.
63. Gunnar, R. M., A. Cruz, J. Boswell, B. S. Co, R. J. Pietras, and I. R. Tobin, Jr. 1966. Myocardial infarction with shock. Hemodynamic studies and results of therapy. *Circulation.* **33**: 753.
64. Gunnar, R. M., R. J. Pietras, C. Stavrakos, H. S. Loeb, and J. R. Tobin, Jr. 1967. The physiologic basis for treatment of shock associated with myocardial infarction. *Med. Clin. N. Amer.* **51**: 69.
65. Ross, J. 1967. Left ventricular contraction and the therapy of cardiogenic shock. *Circulation.* **35**: 611.
66. Corday, E. (Part I), and R. C. Lillehei (Part II). 1969. Pressure agents in cardiogenic shock. *Amer. J. Cardiol.* **23**: 900.
67. Kuhn, L. A. 1967. The treatment of cardiogenic shock. Part I. The nature of cardiogenic shock. *Amer. Heart J.* **74**: 578.
68. Kuhn, L. A. 1967. The treatment of cardiogenic shock. Part II. The use of pressor agents in the treatment of cardiogenic shock. *Amer. Heart J.* **74**: 725.
69. Soroff, H. S., H. J. Levine, B. F. Sachs, W. C. Birtwell, and R. A. Deterling, Jr. 1963. Assisted circulation. II. Effects of counterpulsation on left ventricular oxygen consumption and hemodynamics. *Circulation.* **27**: 722.
70. Lefemine, A. A., H. B. C. Low, M. L. Cohen, S. Lunzer, and D. E. Harken. 1962. Assisted circulation. III. The effect of synchronized arterial counterpulsation on myocardial oxygen consumption and coronary flow. *Amer. Heart J.* **64**: 789.
71. Leinbach, R. C., M. J. Buckley, W. G. Austen, H. E. Petschek, A. R. Kantrowitz, and C. A. Sanders. 1970. Effects of intra-aortic balloon pumping on coronary flow and metabolism in man. *Circulation.* **42** (Suppl. 3): 76. (Abstr.)