External Counterpulsation

Management of Cardiogenic Shock After Myocardial Infarction

Harry S. Soroff, MD; Charles T. Cloutier, MD;
William C. Birtwell; Linda A. Begley, RN; Joseph V. Messer, MD

• Twenty patients in cardiogenic shock following myocardial infarction were treated with external counterpulsation. Eleven patients died during or soon after treatment. One patient survived for three days and another for three weeks; both died in the hospital of complications apparently unrelated to counterpulsation. Seven patients were discharged from the hospital and remained well. The patients who responded to external counterpulsation did so within the first few hours. There seemed to be no benefit in applying counterpulsation for more than six hours. Sequential analysis of mortality statistics indicated that the 45% survival rate (which included the two short-term survivors) was a significant improvement ($P<.01$) over the usual 15% survival rate in cases of cardiogenic shock.

(*JAMA* 229:1441-1450, 1974)

EXTERNAL counterpulsation (ECP)—a method of assisting the circulation without invading the vascular system—was conceived by our group[1] and, at the same time, by Dennis et al[2] and Osborn et al.[3] We have published many reports of results in both experimental animals and normal volunteers during the last ten years.[4-18] Our studies have shown that application of a positive pressure pulse to the lower extremities during cardiac diastole can raise the diastolic pressure by 40% to 50%, while release of pressure or application of negative pressure during cardiac systole can lower the systolic pressure by about 30%. Studies in normal volunteers and in animals have indicated that ECP increases the venous return to the heart because of the unidirectional valves in the peripheral venous bed. In cardiogenic shock accompanied by myocardial ischemia, the increased coronary flow that ECP provides may improve cardiac function and thus indirectly affect the hemodynamic response to ECP.

This report describes a cooperative study—conducted over a year's time—in which 20 patients suffering from cardiogenic shock following myocardial infarction were treated with ECP.

From the departments of surgery (Drs. Soroff and Cloutier and Mr. Birtwell) and medicine (Dr. Messer), Tufts University School of Medicine, and Tufts Surgical Service (Drs. Soroff and Cloutier and Ms. Begley), and the Tufts Medical Service (Dr. Messer), Boston City Hospital, Boston. Dr. Soroff and Mr. Birtwell are now at the School of Medicine, State University of New York and Stony Brook, and the Veterans Administration Hospital, Northport, NY. Dr. Cloutier is now at the US Naval Hospital, Philadelphia. Dr. Messer is now at Rush-Presbyterian-St. Luke's Hospital, Chicago.

Reprint requests to Department of Surgery, School of Medicine, Health Sciences Center, State University of New York at Stony Brook, Stony Brook, NY 11790 (Dr. Soroff).

Methods

Selection of Patients.—Four women and 16 men, ages 47 to 78 years (an average of 63), were referred by physicians from nine different hospitals. Each patient's condition prior to ECP is summarized in Tables 1 and 2.

The diagnosis of cardiogenic shock, made initially by the referring physician, was based solely on conventional clinical criteria: recent myocardial infarction, low systolic blood pressure (80 mm Hg or less), oliguria (urine output of 30 ml/hr or less), cold and clammy skin, and mental lethargy or confusion. (Measurements of variables such as cardiac index, although very useful, were not available to us.) If, despite fluid-loading, a patient required drugs for more than four hours to maintain a systolic pressure of 80 to 100 mm Hg, the patient was considered a candidate for assisted circulation. Similarly, if diuretics increased the urine output but the arterial pressure remained low, the patient was treated with ECP. We did not exclude any patient whose physician thought that a trial of ECP was warranted and whose condition fulfilled our criteria.

Treatment Protocol.—Our ECP team was generally able to assemble at a patient's bedside with the ECP equipment in less than an hour, although in some cases we took as long as two hours. Meanwhile, the medical personnel in immediate charge of the pa-

Table 1.—Patients' Condition Prior to External Counterpulsation

Case No.*/Sex/Age, yr	Hospital†	MI‡ Yr Since Episode	MI‡ Type	ECG Diagnosis ‡	Peel Index	Arrhythmias or Heart Block §	Pacemaker	Degree of Coma, 1-4	Pulmonary Disease Clinical and X-Ray Diagnosis
Death During Assist									
4/M/57	A	...		Apical	17	PVCs	...	1	Pulmonary edema
10/F/69	B	2	IMI	AMI	28	Atrial tachycardia	Yes	4	Vascular engorgement, edema
11/M/67	C	Old	IMI	AMI	28	Ventricular tachycardia, sinus tachycardia, bradycardia, arrest, bifas block, CHB	Yes	4	Congestive heart failure, right lower lobe pneumonia
14/M/63	D	...		Anteroseptal	21	Ventricular fibrillation, arrest, ventricular premature beat	...	4	Unilateral pulmonary edema
16/F/57	C	...		Anterolateral inferior	18	Right bundle-branch block, left anterior hemiblock	...	2	Right lower lobe infiltrate, edema
20/M/47	E	...		Anteroseptal-lateral	19	Atrial and nodal tachycardia, CHB	Yes	...	Edema
Death After Temporary Hemodynamic Response									
1/M/60	C	8	AMI	IMI	27	Ventricular fibrillation, ventricular tachycardia, atrial fibrillation, bilateral bundle-branch block	...	4	Pulmonary congestion
2/M/73	A	...		IMI	22	Bradycardia, atrial fibrillation, PVC, nodal rhythm	Yes	1	Pulmonary edema
9/M/68	F	...		IMI	11	...	...	...	Lung congestion
13/F/56	C	...		Anterolateral	17	CHB	Yes	...	Pulmonary edema
17/M/59	G	6	IMI	AMI	23	PAC, PVC, sinus tachycardia, atrial tachycardia	...	2	Pulmonary edema
Short-Term Survivors									
5/M/71	F	Old	AMI	Apical	27	Sinus tachycardia	...	4	Pulmonary edema
19/M/78	C	...		Anterolateral	22	PVC, ventricular tachycardia, arrest, bifas rhythm	Yes	4	Pulmonary edema
Long-Term Survivors									
3/M/51	F		...	AMI	7	Sinus bradycardia	...	...	...
6/M/54	H		...	Anteroseptal	19	PVC, sinus tachycardia	...	1	Pulmonary edema, vascular engorgement
7/M/65	C		...	AMI	22	PVC, atrioventricular block, CHB, atrioventricular dissociation	Yes	1	Bibasilar rales
8/M/48	F		...	IMI	14	PVC with bigeminy, cardiac arrests	...	4	...
12/M/78	C		...	Anterolateral, septal	22	Nodal, PVC, ventricular tachycardia, right and left bundle-branch block	Yes	...	Rales, pulmonary congestion
15/F/60	C	10, 9, ½	AMI	Anterolateral	27	PVC, left bundle-branch block, transient bifascicular block	Yes	...	Pulmonary edema
18/M/72	I	11	MI	PMI	20	...	...	...	Bibasilar rales, chronic obstructive lung disease, pulmonary edema

*Numbered in order of admission to study.

†A indicates St. Elizabeth's; B, Newton-Wellesley; C, Boston City; D, Jordan; E, Peter Bent Brigham; F, Milford; G, Cardinal Cushing General; H, Framingham Union; I, New England Medical Center.

‡MI indicates myocardial infarction; IMI, inferior myocardial infarction; AMI, anterior myocardial infarction; PMI, posterior myocardial infarction.

§PVC indicates premature ventricular contraction; PAC, premature atrial contraction; CHB, complete heart block; bifas, bifascicular.

Table 2.—Clinical Status of Patients Before External Counterpulsation

Case No.	Infarct to Shock, hr	Hours in Shock Before External Counterpulsation	Blood Pressure, mm Hg With Pressors	Pressors		Fluid Intake, ml/duration (hr)	Urine Output†		Blood Gas Values			Central Venous Pressure, cm H_2O	Arterial Lactate, mg/100 ml‡
				Drug*	Hr		V_0	V_1	pH	Po_2, mm Hg	Pco_2, mm Hg		
Death During Assist													
4	32	13	60/40	Lev	13	1,345/8	19	4	7.37	48	24	20	32
10	108	2	70/40	Iso Met	 2	2,040/8	7	30§	7.44	63	24	28	...
11	24	9	70/58	Iso Met Lev	3.5 2.5 1.5	800/8	40	0	7.45	48	41	26	48
14	5	6	75/50	Met Lev	 4	1,000/8	0	0§	7.44	35	30	...	45
15	Admitted in shock	12	66/40	Iso Lev	10 1	2,600/8	0	7	7.42	60	28	14	90
20	24	20	54/44	Lev	20	600/8	0	60§	7.44	58	22	10§	21
Death After Temporary Response													
1	Admitted in shock	5.75	70/54	Lev	5	500/5	14	0	7.42	110	40	11	...
2	12	10	60/40	Met Iso	2 10	1,150/8	19	51	7.40	86	45	15	30
9	75	13	60/40	Met	13	200/8	12	4§	7.40	114	22	18	26
13	6	7	85/65	Lev	4	475/6	0	50§	...	...	...	28#	34
17	36	24	75/45	Met	11	870/8	2	10§	7.30	38	33	14#	...
Short-Term Survivors													
5	1	4.5	80/60	Met	2.5	2,652/8	0	40§	7.20	58	42	3	44
19	3	4	100/50	Lev	4	250/8	0	46§	7.36	57	39	20	198
Long-Term Survivors													
3	36	24	92/70	Met Lev	 23.5	1,360/10	30	10	7.38	84	38	0	13
6	7-10	14	80/60	Lev Iso	5 9	930/8	30	117§	7.41	66	35	14	12
7	108	6.5	80/50	Iso	6.5	1,520/9	10§	0	7.42	65	28	20	16
8	4	5	80/50	Met	5.5	560/7	0	40	7.50	55	30	10	19
12	24	6	90/60	Lev	6	645/5	0	50§	7.33	78	40	19	15
15	5	7	80/60	Lev	7	1,425/8	0	290§	7.42	79	47	13	49
18	8	5	80/55	Met	4	1,850/16	10	12§	7.25	91	38	12	26

*Lev indicates levarterenol bitartrate; Iso, isoproterenol hydrochloride; Met, metaraminol bitartrate.
†V_0 is urine output (ml/hr) at time of diagnosis of shock, V_1 is urine output (ml/hr) immediately preceding assist.
‡Normal value for arterial lactate is 5.75±0.81 mg/100 ml.
§Patient was given a diuretic (mannitol, furosemide, or ethacrynic acid).
¶Pulmonary artery mean pressure (mm Hg).
#Pulmonary capillary wedge pressure (mm Hg).

tient began to carry out the following procedures:

1. If necessary, a transvenous pacemaker was inserted for control of heart block. Digitalis was given if needed. Assisted ventilation through an endotracheal tube was provided if oxygenation by mask or nasal catheter proved inadequate.

2. Urine volume was measured hourly.

3. A catheter was inserted to measure central venous pressure. (In a few cases, a Swan-Ganz catheter was used to measure pulmonary artery wedge pressure.)

4. If the central venous pressure was below 10 cm H_2O, the patient was challenged with 150-ml aliquots of fluid over a one-hour period in an attempt to increase the preload of the left ventricle. For monitoring of arterial pressure, a polyethylene catheter (14 to 19 gauge) was inserted into a radial artery through an incision in the skin.

5. Arterial lactate level, pH, carbon dioxide pressure (Pco_2) and oxygen pressure (Po_2) were determined frequently. Metabolic acidosis was corrected with sodium bicarbonate.

When the ECP team arrived, the assist system was placed around the patient's lower limbs, and ECP was applied for up to two hours. Vasopressor therapy was discontinued as soon as possible—in most cases within 15 to 30 minutes. If the hemodynamic response during ECP was less than optimal, several measures could be taken. Fluids (5% glucose in water or lactated Ringer solution) were administered until the venous pressure rose to about 15 cm H_2O. Steroids (2 gm methylprednisolone sodium succinate) were given to increase the vasodilatation, and if this was ineffective, chlorpromazine (10 mg intravenously) was given. In most patients, mephentermine sulfate (500 mg/500 ml) was slowly infused during the last 15 minutes of ECP to ensure an adequate peripheral vasomotor tone following the "assist."

If a systolic blood pressure of at least 90 mm Hg could not be maintained without vasopressors, ECP

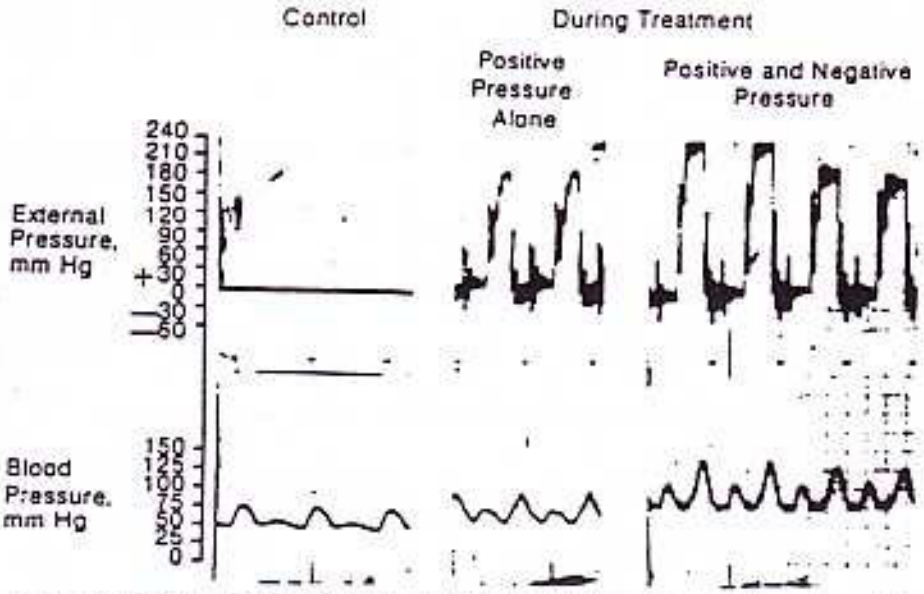

Fig 1.—Improvement in hemodynamic effects of external counterpulsation with positive-negative pressure mode as compared with positive pressure alone.

was applied for additional two-hour periods until the blood pressure was stable or the patient died.

Mode of "Assist."—The ECP equipment used in this study is a self-contained, portable console that provides for monitoring of pressure and electrocardiogram. The patient remains in bed while the actuator and pressure converter are quickly placed around the lower limbs. Nondistensible seals attached to rigid, conical leg housings with hinged covers allow application of positive pressure up to 250 mm Hg and negative pressure to −50 mm Hg over the surface of the limbs.

Initially, with a patient in shock, only the positive pressure pulse is used. The positive pressure is slowly increased during cardiac diastole until a maximum effect is observed on the diastolic pressure. This is usually achieved with the machine operating at a phasic pressure of 0 to 200 mm Hg.

Once the vascular bed has been actively dilated, and an adequate intravascular volume is ensured, the positive-negative mode of assist is begun. With the machine operating at pressures varying from −30 mm Hg during cardiac systole to +200 mm Hg during cardiac diastole, the hemodynamic response may be greatly improved, as illustrated in Fig 1. Of crucial importance, with either mode, is the synchronization of the counterpulsation pump with the action of the heart.[11]

Evaluation of Clinical Response.—*Nonsurvivors* were patients who died during ECP and those who showed some response but died soon after. In the latter category were patients whose peak systolic pressure could be maintained at 90 to 100 mm Hg without vasopressors for less than 48 hours after ECP.

Patients were considered *short-term survivors* if the blood pressure was normal without vasopressors for at least 48 hours, if tissue perfusion was adequate (as reflected in urine output and clinical appearance) for the same period of time, and if the ultimate cause of death was noncardiac in nature.

Patients were considered *long-term survivors* if they were eventually discharged from the hospital.

Sequential Analysis of Mortality Statistics.—To determine if ECP could be considered substantially better than current approaches to cardiogenic shock, we used a sequential design—a useful technique when the number of subjects is limited and studies must be done in a clinical setting where there is no practical possibility of having adequate controls or where the referring physicians consider a paired-control design unacceptable. A detailed explanation of sequential analysis is given in a classic book by Wald[11] and in other statistical texts.

Results

Of the 20 patients, 9 (45%) survived—a statistically significant ($P<.01$) improvement over the usual 10% to 20% survival rate[12] (Fig 2).

To determine whether the survivors had been at less risk than the nonsurvivors *before* ECP, we calculated each patient's Peel Index (Table 1). This index,[13] a prognostic tool for grading the severity of an infarct, takes into account a variety of factors that affect mortality—age, sex, history of heart disease, and immediate problems such as shock, congestive heart failure, electrocardiographic changes, and arrhythmias. Normally, a person with an index of 20 or more has less than a 25% chance of surviving. The average Peel Index of our survivors was 20, and the average of those who died was 21.

The average age of the survivors was 64 years; the average among those who died was 62 years.

There was little difference between survivors and nonsurvivors with respect to either the location of infarct or associated factors such as previous infarction. Four of the 11 patients who died and three of the nine survivors had had previous infarctions. Eight patients who died and five who survived were in deep coma when ECP was begun. X-ray films showed that almost all the patients had pulmonary edema, congestion, or areas of pneumonitis.

Arrhythmias and Heart Block.—Eight patients who died and eight who survived (Table 1) had various forms of arrhythmias before ECP. There were four instances of *partial* heart block in the deaths as compared with two in the survivors, and three instances of *complete* heart block in the deaths as compared with one in the survivors. Five patients who died and four who survived needed pacemakers before ECP was begun.

Onset of Shock and Timing of Treatment.—The interval from the time that the diagnosis of shock was made to the start of ECP averaged ten hours for the deaths and 8½ hours for the survivors (Table 2). All the patients were given vasopressors when

Table 3.—Patients' Clinical Condition and Requirement for Medications During External Counterpulsation

Case No.	Average Values During External Counterpulsation: Peak Systolic/ Peak Diastolic Blood Pressure, mm Hg	Urine Output, ml/hr	Central Venous Pressure, cm H_2O	Arterial Lactate, mg/ 100 ml	Blood Gas Values: pH	Po_2	Pco_2	Quality of ECP*	Mean % Increase in Diastolic Pressure†	Pressor Drugs; Steroids; Chlorpromazine‡	Serious Arrhythmias	ECP Duration, min
Death During Assist												
4	60/64	9	20	36	7.38	52	27	Fair	50		...	33
10	84/84	23	16	...	...	...	...	Fair	100	Met, Iso, Mep, Lev; Metp, 2 gm; Chl, 10 gm	Atrial tachycardia	
11	72/64	10	30	93	7.36	57	35	Poor	5	Lev, Iso; Chl, 10 gm	Complete electrical dissociation, arrest	180
14	91/99	0	...	58	7.33	80	40	Good	100	Lev; Metp, 2 gm	...	480
16	85/90	15	14	63	7.41	133	30	Good	125	Lev, Mep; Metp, 1.5 gm	...	480
20	98/99	95	325	30	7.53	40	29	Good	125	Dex, 4 ml	Ventricular tachycardia to asystole	
Death After Temporary Hemodynamic Response												
1	90/110	8	...	...	7.41	87	38	Excellent	100	Metp, 2 gm	Atrial premature beats	120
2	68/68	12	20	20	7.47	54	44	Fair	70	Iso; Metp, 1.5 gm	...	75
9	118/122	17	18	25	...	...	...	Excellent	300			75
13	97/98	80	281	37	7.27	85	41	Good	50	Metp, 1.5 gm		120
17	95/80	17	...	...	7.27	38	33	Good	77		Atrial tachycardia, atrial premature beats	120
Short-Term Survivors												
5	90/95 at end of ECP	68	3	54	7.39	50	32	Good	50	Hyd, 3 gm	...	142
19	130/155 at end of ECP	83	17	90	7.50	105	48	Excellent	300	Lev; Metp, 2 gm	...	300
Long-Term Survivors												
3	112/106	32	2	13	7.39	91	38	Good	50	...	...	111
6	112/128	76	11	12	7.43	67	34	Excellent	100	...	...	159
7	115/122	55	...	14	7.38	217	38	Excellent	140	...	...	130
8	104/107	35	15	14	7.32	85	35	Good	100	Met, Mep, Lev; Dex, 12 mg	Ventricular fibrillation, arrest	270
12	105/106	50	15	22	...	...	...	Good	76	Metp, 2.5 gm	...	204
15	92/91	35	13	...	7.39	66	36	Good	50	Lev, 10 min; Metp, 2 gm	...	205
18	122/119	11	18	24	7.47	107	24	Good	116	Met	...	120

*ECP indicates external counterpulsation; poor, little or no increase in diastolic pressure; fair, diastolic pressure equal to systolic but no significant increase in systolic pressure; good, diastolic pressure equal to systolic plus significant increase in systolic pressure; excellent, increase in systolic pressure and diastolic pressure greater than systolic pressure.

†As compared with pre-assist values.

‡Met indicates metaraminol bitartrate; Iso, isoproterenol hydrochloride; Mep, mephentermine sulfate; Metp, methylprednisolone sodium succinate; Chl, chlorpromazine; Dex, dexamethasone; Lev, levarterenol bitartrate; Hyd, hydrocortisone sodium succinate.

§Pulmonary artery mean pressure, mm Hg.

‖Pulmonary capillary wedge pressure, mm Hg.

shock was diagnosed and were on a regimen of vasopressors when ECP was begun.

Physiological Measurements.—Arterial blood pressure, taken by sphygmomanometer at the time of the diagnosis of cardiogenic shock, averaged 69/47 mm Hg in patients who died and 85/57 mm Hg in those who survived (Fig 3). The average systolic pressure of the survivors was significantly higher ($P<.001$) than that of the dying both before and during ECP. Both survivors and deaths showed similar increases in systolic pressure during the assist, but at the time ECP was begun, the patients who died were in more profound shock than the survivors. The average diastolic pressure of the survivors was also significantly higher ($P<.01$) than that of the dying both before and during ECP.

Average central venous pressure

Table 4.—Clinical Status of Patients After External Counterpulsation

Case No.	Condition After ECP*	Vasopressors Given After ECP*	Long-Term Follow-Up	Postmortem Findings
Death During Assist				
4	Could not maintain blood pressure assist; cardiac arrest during intubation	Levarterenol bitartrate	...	Occlusion of left anterior descending and circumflex coronary arteries; congestive heart failure with pulmonary congestion and edema
10	Arrest following intravenous morphine sulfate	...	...	No autopsy
11	Blood pressure not maintained when ECP discontinued	...	...	No autopsy
14	Cardiopulmonary arrest	...	...	Thrombosis of left anterior descending coronary artery; acute myocardial infarction involving anterolateral walls; atelectasis, acute pulmonary edema
16	Blood pressure not maintained without ECP	Levarterenol	...	No autopsy
20	Arrest immediately following ECP	Levarterenol Phenylephrine hydrochloride Mephentermine sulfate	...	Old and recent occlusions of right coronary artery with myocardial infarction involving all the septum and anterior third of left ventricular wall and apex; pulmonary edema
Death After Temporary Hemodynamic Response				
1	Ventricular tachycardia; cardiac arrest in 45 min	Isoproterenol hydrochloride	...	No autopsy
2†	Hemodynamically stable (with isoproterenol and glucagon) for 2 hr	Isoproterenol	...	Severe atherosclerosis of all three coronary arteries; myocardial infarction involving all the walls of the left ventricle including the interventricular septum; acute pulmonary congestion and edema
9	Stable for 2 hr, hypotension and arrest following morphine	None for 2 hr then metaraminol bitartrate	...	No autopsy
13†	Stable for 20 hr	Mephentermine for 2 hr	...	No autopsy
17†	Stable for 10 hr	...	...	Severe narrowing of all vessels with old occlusion of anterior descending arteries; old, healed posterior left ventricular infarct; recent myocardial infarction involving ⅔ of septum, anterior wall, apex and lower posterior left ventricular wall; bilateral pulmonary edema
Short-Term Survivors				
5	Blood pressure stable at 100/70 mm Hg	...	Died 3 days later of peritonitis	Peritonitis, acute pancreatitis; acute anteroseptal infarction; right and left coronaries slightly narrowed but patent
19	Stable blood pressure	...	Remained in coma and died in third week of pulmonary edema and congestion	No autopsy
Long-Term Survivors				
3	Stable		Alive 12 mo	...
6	Stable	Mephentermine	Died 8 mo later of myocardial infarction	...
7	Stable	Mephentermine	Alive 8 mo	...
8	Stable	Metaraminol bitartrate	Alive 8 mo	...
12	Stable	...	Alive 6 mo	...
15	Stable	Mephentermine	Alive 5 mo	...
18	Stable	Mephentermine	Alive 2 mo	...

*ECP indicates external counterpulsation.
†Required ECP 24 hr after first period of assist; course of second treatment described in "Results."

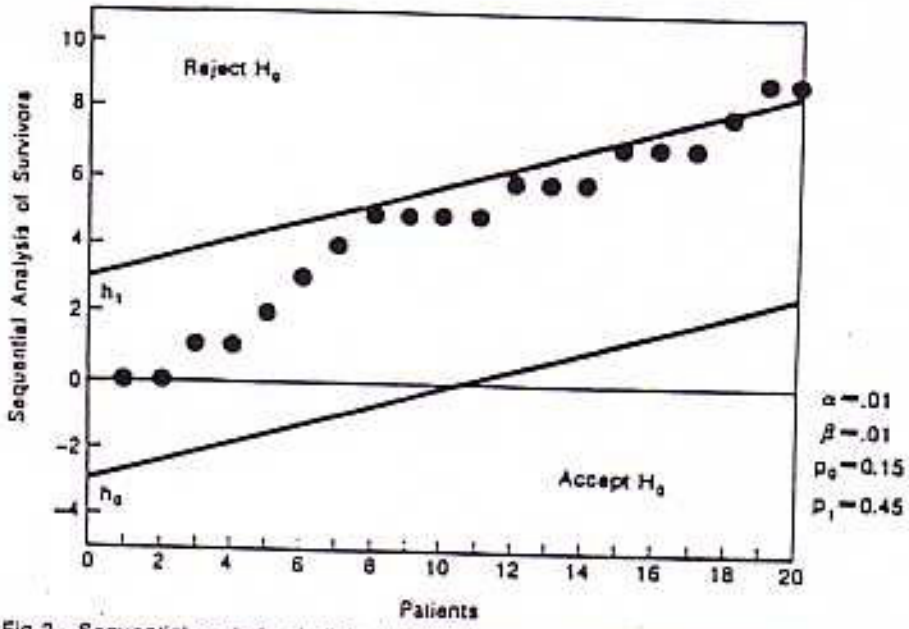

Fig 2.—Sequential analysis of clinical experience in management of patients in cardiogenic shock. P_0 is the present estimated rate of survival from cardiogenic shock; P_1 is the survival rate considered, on clinical grounds, to be worthwhile improvement over current rate; α represents probability of erroneously rejecting external counterpulsation (ECP) as a beneficial treatment; and β represents probability of erroneously accepting ECP as a beneficial treatment. Line H_0 marks points at which unfavorable hypothesis should be accepted (ie, there is no substantial improvement in survival rate when ECP is used). Line H_1 represents points at which favorable hypothesis should be accepted (ie, ECP should be considered an improvement over standard therapeutic techniques). As each consecutive patient was treated, an appropriate point was plotted on the graph, and at each point it was decided whether to continue our study.

was 19 cm H_2O in the deaths and 14 cm H_2O in the survivors. The difference was not statistically significant. As might be expected, however, the central venous pressure of the survivors fell to 11 cm H_2O during ECP, while the average in the dying was 20 cm H_2O ($P<.05$).

At the time that shock was diagnosed, the urine output (V_0 in Table 2) averaged 10 ml/hr for those who died and 16 ml/hr for the survivors. Fluid therapy was intensified at that time, and 15 of the patients who were oliguric were given diuretics. Nine responded, and by the time ECP was begun, the average urine output (V_1) was 15 ml/hr in the patients who died and 67 ml/hr in the survivors.

Biochemical Measurements.—At the time of diagnosis of shock, the average *arterial lactate concentration* of the patients who died was 32 mg/100 ml while that of the survivors was 15 mg/100 ml (Table 2). During ECP, as the clinical condition of the survivors improved, the lactate levels fell slightly, but in those who died the level rose to 38 mg/100 ml ($P<.05$).

The pH and Po_2 of the arterial blood were similar in those who died and in the survivors at the time shock was diagnosed. The average Po_2 of the survivors increased during ECP to 95 mm Hg while in those who died it remained unchanged, but the difference was not statistically significant because of a wide scatter of the data. The Pco_2, however, was significantly lower in those who died than in the survivors before ECP ($P<.05$)—perhaps reflecting a compensatory mechanism for metabolic acidosis, since the pH of the blood was similar in both groups.

Quality of Counterpulsation.—Our criteria for judging the effectiveness of ECP are given in a footnote to Table 3. In general, the hemodynamic response to counterpulsation was good even in the patients who died. The augmentation of their diastolic pressure during assist was comparable to that of the survivors (Table 3). In the deaths, the average diastolic pressure was raised only to the level of the systolic pressure (90/89 mm Hg). In the survivors, the average blood pressure was 109/114 mm Hg during ECP.

External counterpulsation was carried out for an average of 4.4 hours in the patients who died and an average of three hours in the survivors. Three patients who died (No. 14, 16, and 20) had counterpulsation repeatedly—in one case for a total of 19 hours (Table 3). Among the survivors, the longest total period of ECP was five hours.

Course of Patients After ECP.—Table 4 summarizes each patient's condition after ECP, and the available postmortem findings in the cases of those who died.

Patients 2, 13, and 17 initially responded well to ECP, and vasopressor therapy was discontinued. However, they became hypotensive several hours later, and when ECP was reapplied for one to two hours it was not effective. They all died either during or soon after the second period of ECP.

Comment

Patient Selection.—One question raised by any study such as this is whether the patients were representative of the general population of cardiogenic shock patients. A related question is whether there were any important differences between those who died and the survivors, as a result of unwitting biases in patient selection or variations in initial treatment. It happens that the two groups were of almost the same age range, their chances for survival, based on the Peel Index, were virtually identical, and the types of infarction were similar in both groups (Table 1). The sequence of entry into the study did not influence whether the patient lived or died, nor did it seem to matter which of the nine hospitals a patient was treated in. The hospitals include both university-affiliated and community-based institutions, some without house staff. Furthermore, the hospitals are widely scattered and therefore serve different types of patient populations in terms of socioeconomic strata and racial and ethnic origins.

Some might think that the demographic heterogeneity of the patients

and the variability in initial treatment cast doubt on the validity of our data, but in our opinion these are strengthening factors since they minimized the possibility of our patients, as a group, being either unusually resistant or unusually vulnerable to the sequelae of a myocardial infarction.

Diagnosis of Cardiogenic Shock.—Another question that could be raised is whether all of our patients were truly suffering from pump failure or cardiogenic shock, and whether all standard therapeutic measures had been exhausted before ECP was tried. Tables 1 and 2 show that all the patients had indeed met the usual clinical criteria of cardiogenic shock and that every effort was made to treat them by standard procedures. Future studies in a controlled environment obviously should include measurements of cardiac output and pulmonary capillary wedge pressures as criteria for application of ECP.

The diagnosis of cardiogenic shock or pump failure covers degrees of severity ranging from mild to terminal pump failure. Although the diagnosis of cardiogenic shock was made in each case according to the criteria stated earlier, it is clear from the data that in general, the patients who did not survive were in deeper shock than those who did.

Even though the Myocardial Infarction Research Units (National Institutes of Health) have established precise, quantitative criteria for diagnosing cardiogenic shock, most hospitals are not equipped to make the necessary measurements. As a rule, physicians must base their diagnoses on clinical judgment. For example, urine volume is generally considered a good indicator of renal perfusion pressure. In our patients, urine output at the time of diagnosis of shock was 30 ml/hr or less, but many of the patients responded to diuretics and fluid-loading, so that by the time ECP was begun nine of them had a urine output of over 30 ml/hr. All of them, however, were still suffering from cardiogenic shock as evidenced by low blood pressure, need for vasopressors, clammy skin, and mental confusion.

A major problem in planning the management of patients in cardiogenic shock is the difficulty of quickly

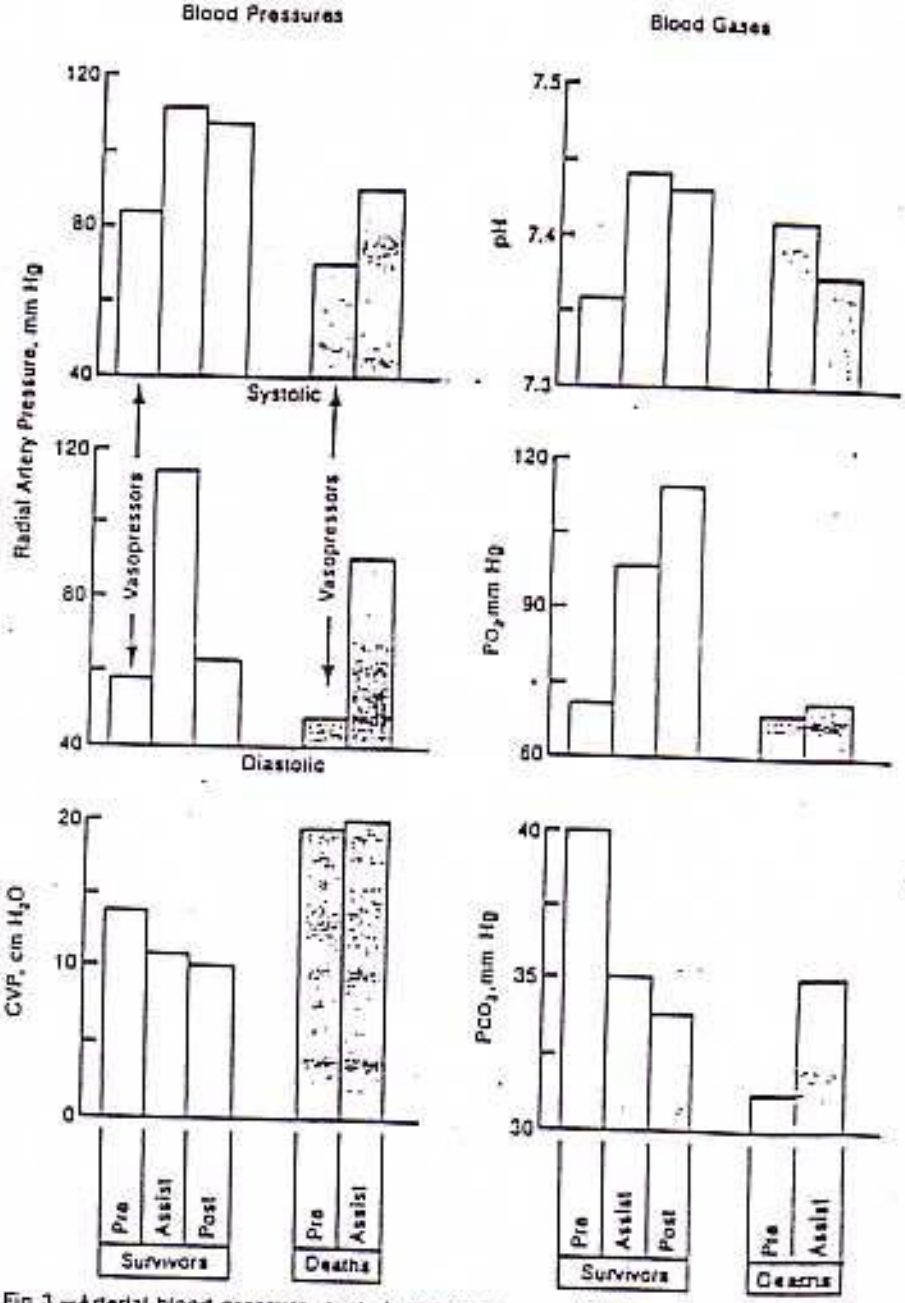

Fig 3.—Arterial blood pressure, central venous pressure (CVP), and blood gas values of 9 survivors and 11 nonsurvivors.

determining the underlying pathologic lesion. Don Michael et al,[10] in a retrospective study of 100 patients dying of cardiogenic shock secondary to myocardial infarction, identified three subgroups whose clinical courses reflected fairly distinct abnormalities. The first subgroup (57%) had diffuse cardiac ischemia with loss of function in a major portion of the myocardium. The second subgroup (15%) had a specific and limited mechanical lesion provoking shock. The third subgroup (22%) gave a history of a previous infarction, had cardiomegaly, and had a limited but critical infarction in an already grossly damaged ventricle. We think that early application of ECP might help to preserve myocardial function in the first and third groups by decreasing myocardial oxygen requirements and increasing the coronary collateral circulation. Experiments in our laboratory[1] showed that the function of an ischemic portion of the left

ventricle could be preserved and protected by early application of counterpulsation. In a control group, a 45-minute period of ischemia irreversibly damaged 85% of the ischemic tissue. When counterpulsation was applied during the ischemic period, only 23% of the tissue was irreversibly damaged, and when a 45-minute period of counterpulsation preceded the 45-minute occlusion, only 48% of the involved tissue was irreversibly damaged.

Timing of Application.—We believe, on the basis of our experimental data,[7] that the *sooner* counterpulsation is applied after the onset of a myocardial infarction the more effective it will be in protecting the viability of the myocardium. In both the survivors and the deaths in our study, the average delay, from the time that shock was diagnosed to the time that ECP was begun, was about nine hours. Ideally, ECP should be instituted within two hours.

There is also some evidence that ECP may eventually become an important tool in prevention of myocardial infarction. In one experiment,[8] we produced diffuse coronary occlusions by injection of microspheres into the coronary arteries. When ECP was applied before the injection, 15 of 30 animals (50%) survived, and when ECP was applied immediately after the injection, 12 of 25 animals (48%) survived, compared with only 11 of 41 (27%) in a control group. The difference was most noticeable and was statistically significant at higher doses of microspheres. Postmortem coronary angiograms suggested that the lower mortality in the counterpulsated groups was associated with the opening of collateral coronary channels. This concept is being extended to the study and treatment of patients with angina.[14]

Prognostic Significance of Various Measurements.—We examined the data to determine if there were any important differences between the survivors and those who died that might serve in the future selection of candidates for ECP.

At the time of the diagnosis of cardiogenic shock, the peak systolic pressure was significantly higher in the survivors than in those who died ($P<.001$), and the central venous pressure was somewhat lower. Although there was little difference in urine output at the time of diagnosis, urine output in those who died did not respond to administration of fluids or diuretics and became substantially lower at the time ECP was begun. Arterial lactate concentrations and arterial blood gases were similar in both groups at the time of diagnosis.

During ECP, the rise in both systolic and diastolic pressures was significantly greater in the survivors ($P<.001$). Central venous pressure fell in the survivors but remained high in the patients who died ($P<.05$). Arterial lactate levels rose to an even higher level in those who died, but fell in the survivors ($P<.05$).

Effectiveness of Counterpulsation.—The effectiveness of counterpulsation can be judged by the degree of diastolic augmentation that is achieved. If the diastolic pressure can be raised to the level of the systolic pressure, it indicates that the driving pressure in the coronary vascular bed is greatly improved. Experiments have shown that the coronary vascular resistance is somewhat reduced during counterpulsation[15]—an indication that dormant collateral channels may be opened during counterpulsation.

Theoretically, the advantage of the external approach to assisted circulation is that the application of a positive pressure to the lower extremities during cardiac diastole causes a decrease in the transmural pressure and creates a pressure wave that is transmitted in a retrograde fashion to the root of the aorta. The release of this pressure, or the application of negative pressure, during cardiac systole causes an increase in the transmural pressure that serves to decrease the peripheral resistance. When the external pressure is zero (ie, atmospheric pressure) during cardiac systole and 150 to 200 mm Hg during cardiac diastole, the decrease in systolic pressure is only about 5 to 10 mm Hg.[3] However, when a negative pressure of −25 to −50 mm Hg is applied during cardiac systole, the decrease in systolic pressure is about 25 to 30 mm Hg. In patients in shock, it is often difficult to document this decrease in the systolic pressure on a beat-by-beat basis because the mean systolic pressure tends to increase as the patient begins to recover. The decrease in systolic pressure has, however, been well documented in normal volunteers.[4]

There is another theoretical advantage of operating the assist device in the positive-negative mode if the patient is in profound shock. The degree to which the diastolic pressure can be augmented is limited by the volume of the arterial system of the legs. A negative pressure applied during cardiac systole tends to increase the filling of the peripheral arterial bed. With the subsequent compression of the full vascular bed during diastole, diastolic augmentation is improved.

Response of Patients to ECP.—Sequential analysis of mortality statistics indicated that the survival rate we obtained was a statistically significant improvement over the current survival rate[13] in cases of cardiogenic shock. However, the sequential analysis was not designed to quantify the effectiveness of our treatment. More carefully controlled studies are needed to further characterize the types of patients for whom ECP would be most beneficial and to determine if patients who respond to ECP might survive cardiogenic shock without the assist.

Nonetheless, from experience gained to date, it is usually possible to foresee the ultimate outcome in a patient early in the course of ECP. If a patient does not respond hemodynamically to counterpulsation despite adequate fluid-loading and the use of vasodilators, the prognosis is usually grave. The response should be noticeable within 45 minutes after the start of positive-negative pressure assist and appropriate adjunctive therapy. Patients who show a dramatic response within 45 minutes—that is, elevation of diastolic pressure above the systolic level and a gradual rise of mean and peak systolic pressures—usually survive the period of pump failure. With patients who show a good but not excellent response—elevation of diastolic pressure to the level of systolic pressure and a small rise in systolic pressure—it is difficult to assess their chances for survival until several hours have elapsed. As

can be seen from Table 3, some of the latter patients survived and some did not. In two patients (No. 16 and 20) ECP was prolonged to no avail. It appears to us, on the basis of our current data, that if a patient has not responded to external counterpulsation by six or at most eight hours, assisted circulation will not be adequate therapy. The only reasonable alternative, at that point, may be corrective coronary artery surgery—an approach that we believe should be reserved until assisted circulation has been tried. In patients who recover and are discharged from the hospital, long-term follow-up studies are needed to assess both their residual cardiac function and possible sequelae such as mitral insufficiency or ventricular aneurysm that are amenable to corrective surgery.

This investigation was supported in part by grants from the General Clinical Research Centers Program of the Division of Research Resources, National Institutes of Health (FR-54), the National Heart and Lung Institute (HE-08164-06A1, HE-08612), The John A. Hartford Foundation, Inc., Medical Innovations, Inc., and The Upjohn Company.

The following physicians participated in this study: John S. Banas, Oscar H. L. Bing, David Borkenhagen, Alfred Brilla, Robert J. Carey, Gerald L. Evans, Athanasios Fleseas, Richard Gorlin, William B. Hood, Michael Leech, Charles Lutten, James W. McDowell, Robert E. Olson, Burton Polansky, Richard M. Ragnatis, Thomas J. Ryan, Gordon A. Saunders, James J. Sidd, Samuel Stewart, and Theodore Waltuch.

Robert L. Norton, John Coleman, Frank Graham, Nubar Hagopian, and Harold S. Sauer helped design the counterpulsation equipment used in this study. Jerry L. Jones and Elaine C. Trivus aided in cardiac catheterization studies and in biochemical studies. Phyllis Childs performed biochemical determinations and helped with data analysis. Sheila O'Connell and Gail Woodhead performed special nursing functions.

This study was carried out in cooperation with Boston City Hospital, and Peter Bent Brigham Hospital, Boston; Cardinal Cushing General Hospital, Brockton, Mass; Framingham Union Hospital, Framingham, Mass; Jordan Hospital, Plymouth, Mass; Milford Hospital, Milford, Mass; New England Medical Center, Boston; Newton-Wellesley Hospital, Newton, Mass; St. Elizabeth's Hospital, Brighton, Mass; and Symmes Hospital, Arlington, Mass.

Nonproprietary Names and Trademarks of Drugs

Chlorpromazine—*Thorazine, Chlor-Pz, Cremodazine.*
Furosemide—*Lasix.*
Ethacrynic acid—*Edecrin.*

References

1. Birtwell WC, et al: Assisted circulation: V. Use of lungs as pump: Method for assisting pulmonary blood flow by varying airway pressure synchronously with EKG. *Trans Am Soc Artif Intern Organs* 9:192-201, 1963.

2. Dennis C, et al: Studies on external counterpulsation as potential measure for acute left heart failure. *Trans Am Soc Artif Intern Organs* 9:186-191, 1963.

3. Osborn JJ, Main FB, Gerbode FL: Circulatory support by leg or airway pulses in experimental mitral insufficiency. *Circulation* 28:781-782, 1963.

4. Soroff HS, et al: Synchronous external circulatory assist. *Trans Am Soc Artif Intern Organs* 10:73-78, 1964.

5. Giron F, et al: Assisted circulation by synchronous pulsation of extramural pressure. *Surgery* 60:894-901, 1966.

6. Ruiz U, et al: Assisted circulation by synchronous pulsation of extramural pressure. *J Thorac Cardiovasc Surg* 56:832-845, 1968.

7. Nishimura A, et al: Evaluation of collateral blood supply by direct measurement of the performance of ischemic myocardial muscle. *Trans Am Soc Artif Intern Organs* 16:450-454, 1970.

8. Antebi E, et al: Experimental evaluation of external circulatory assist as a treatment for coronary occlusion. *Surg Forum* 21:154-156, 1970.

9. Cloutier CT, et al: The physiologic effects of synchronous external circulatory assistance in patients in cardiogenic shock. *Surg Forum* 22:187-188, 1971.

10. Soroff HS, et al: Experimental and clinical studies in assisted circulation. *Transplantation Proc* 3:1483-1489, 1971.

11. Soroff HS, et al: Assisted circulation: II. Effects of counterpulsation on left ventricular oxygen consumption and hemodynamics. *Circulation* 27:722-731, 1963.

12. Weil A: *Sequential Analysis.* New York, Wiley Publishers, 1947.

13. Shubin H, Weil MH: Treatment of shock complicating acute myocardial infarction. *Prog Cardiovasc Dis* 10:50-64, 1967.

14. Peel AAP, et al: A coronary prognostic index for grading the severity of infarction. *Br Heart J* 24:745-760, 1962.

15. Dan Michael TA, et al: Identification of clinical subsets in cardiogenic shock. *Am J Cardiol* 29:230, 1972.

16. Banas JS, et al: Evaluation of external counterpulsation for the treatment of severe angina pectoris, abstracted. *Circulation* 46 & 46(suppl 2):74, 1972.

Albert Einstein, born in Ulm, Germany, in 1879, effected the greatest revolution in scientific theory since Copernicus. He evolved his "special" theory of relativity in 1905 while he was an examiner in the patent office at Berne, Switzerland, whereas his "general" theory, involving a new concept of gravitation, was completed about 1915. Einstein's main contributions were his theory of relativity and his work related to statistical mechanics and the quantum theory of radiation.

He was appointed a professor at the University of Zurich, Switzerland, in 1909 and at the Deutsche University in Prague in 1911. In 1913, he became a professor at the University of Berlin. Later, he emigrated to the United States, where he spent the rest of his life at the Institute for Advanced Study in Princeton, NJ. He died in 1955, and his contributions paved the way for the atomic age, and are the basis for much of the medical work done with the atom.

He has been honored philatelically by Israel, Poland, Paraguay, and the United States. Israel (Scott No. 117) honored him in 1956, shortly after his death.—M. A. Shampo and R. A. Kyle