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The clinical effects of early application of external pressure circulatory assistance (EPCA) in acute myocardial infarction were evaluated in a prospective, randomized trial involving 258 patients in 25 institutions. All patients had mild left ventricular failure and received circulatory assistance within the first 24 hours after the onset of symptoms. There were no significant differences between the treatment and control groups, consisting of 142 patients and 116 patients, respectively, with regard to age, sex, race, previous cardiac history, electrocardiographic location of myocardial infarction, Norris prognostic index, admission heart rate, blood pressure and chest roentgenogram, and time from onset of symptoms to hospital admission. There were also no differences between the treatment and control groups with regard to antiarrhythmic, positive inotropic, diuretic and vasodilator therapy. Hospital mortality was significantly decreased, compared with that of control patients, in the group receiving 4 or more hours of external pressure circulatory assistance within the first 24 hours after admission (mortality rate 6.5 percent [7 of 108] in treatment group versus 14.7 percent [17 of 116] in control group, $p < 0.05$). Circulatory assistance for 3 or more hours was also associated with a lower mortality rate in the subgroup (patients 46 or more years old) to which mortality in this study was confined (mortality rate 8.3 percent [9 of 109] in the treatment group versus 17.5 percent [17 of 97] in the control group, $p < 0.05$). For the combined group of patients with 3 or more and 4 or more hours of treatment, circulatory assistance was associated with significant lessening ($p < 0.05$ to < 0.01) of morbidity as manifested by recurrent chest pain, progression of cardiac failure, occurrence of ventricular fibrillation, change in heart size and clinical cardiac functional status at discharge. These data support further application and investigation of external pressure circulatory assistance in myocardial infarction.

As a result of advances in the management of cardiac arrhythmias in coronary care units, the major cause of mortality in patients hospitalized with acute myocardial infarction is cardiac pump dysfunction, manifested by severe left ventricular failure or cardiogenic shock.[1] This complication is directly related to loss of a critical mass of myocardium that is usually extensive, commonly involving 40 percent or more of the left ventricle.[2–4] Recent experimental and clinical studies[5,6] of myocardial infarction have demonstrated that therapeutic interventions that favorably alter the balance between myocardial oxygen supply and demand can reduce ischemic cardiac injury and limit infarct size. This approach thus has the potential of improving prognosis in acute myocardial infarction by preserving cardiac tissue and averting complications, such as pump failure, that are related to extent of myocardial damage.

Improvement in the relation between myocardial oxygen supply and demand can be achieved by increasing availability of oxygen or reducing

its requirement. Mechanical circulatory assistance elevates myocardial oxygen delivery by augmentation of arterial diastolic pressure, a major determinant of coronary blood flow, which assumes special importance in the maintenance of myocardial perfusion in the presence of obstructive narrowing of the coronary arteries.[7] Diastolic pressure augmentation can be effected by invasive techniques such as intraaortic balloon counterpulsation[8–14] or noninvasive external counterpulsation.[8,9,15,16] The latter approach has the advantages of wide applicability, ease of implementation and lack of associated trauma. Early intervention with mechanical circulatory assistance prior to the onset of severe cardiac dysfunction has been suggested[10–12] and recently applied[14] as a potential means of preserving myocardium, averting pump failure and reducing mortality in acute myocardial infarction. This report presents the results of a multicenter trial to evaluate the clinical effects of external pressure circulatory assist by a mechanical device (Cardiassist® External Counterpulsation System, Cardiassist Corporation, Hoffman Estates, Illinois) in patients with acute myocardial infarction complicated by mild left ventricular failure (Killip class II).[17]

Methods

Patients: Twenty-five cooperating institutions participated in the study, which was carried out over a 15 month period. The population evaluated consisted of 258 patients with acute myocardial infarction. The mean number of patients per institution was 9, and the range was one (two institutions) to 26 (one institution) patients per institution.

Diagnosis of myocardial infarction was by two of the three following criteria: classic history, characteristic electrocardiographic evolutionary changes and typical serum enzyme alterations. All patients fulfilled the following criteria, in addition to acute myocardial infarction, for admission to the study: mild left ventricular failure (Killip class II),[17] manifested by pulmonary rales over less than 50 percent of the lung fields; entrance into the study within 19 hours of onset of symptoms (with the goal of completion of at least 4 hours of circulatory assistance within the first 24 hours of myocardial infarction); absence of history of previously treated cardiac failure; and absence of clinical evidence of peripheral vascular disease and aortic valve insufficiency. All patients gave informed consent for entrance into the study. Allocation of patients to treatment and control groups was by random assignment as described in the Appendix.

Evaluation of left ventricular function: Left ventricular functional status on admission and during the subsequent hospital course was classified by clinical and roentgenographic criteria. Clinical classification was made according to the following criteria[17]: class I, absence of clinical complications, clear lung fields; class II, rales over less than 50 percent of the lung fields; class III, pulmonary edema with rales over 50 percent or more of the lung fields; and class IV, shock manifested by criteria for class III plus a systolic blood pressure of less than 90 mm Hg with signs of inadequate peripheral organ perfusion (diaphoresis, cyanosis, oliguria, altered mental status). Chest roentgenograms were interpreted and classified by a radiologist without knowledge of clinical classification: class I, normal lung fields; class II, redistribution of pulmonary blood flow to the upper lung fields and mild hilar congestion; class III, criteria for class II plus marked increase in prominence of pulmonary vessels of the outer lung fields; and class IV, criteria for class III plus presence of pleural effusion, and hilar congestion or cardiomegaly, or both.

Roentgenographic determination of heart size was performed on admission and on the day of, or 1 day before discharge. This evaluation[18] was based on the extent to which the transverse cardiac diameter exceeded that resulting in a cardiothoracic ratio of 0.5: normal, transverse cardiac diameter of up to 1.0 cm in excess of the latter criterion; questionable cardiac enlargement, increase in transverse cardiac diameter of more than 1.0 to 1.5 cm in excess of this criterion; definite cardiac enlargement, increase in transverse cardiac diameter of more than 1.5 cm in excess of this criterion. This analysis was included in the evaluation midway through the study and was therefore available in some patients.

External pressure circulatory assistance: Circulatory assistance was administered to the treatment group only. Each hour of treatment consisted of 50 minutes of circulatory assistance and 10 minutes of rest. There were no restrictions on any other available forms of therapy for patients in either the treatment or the control group.

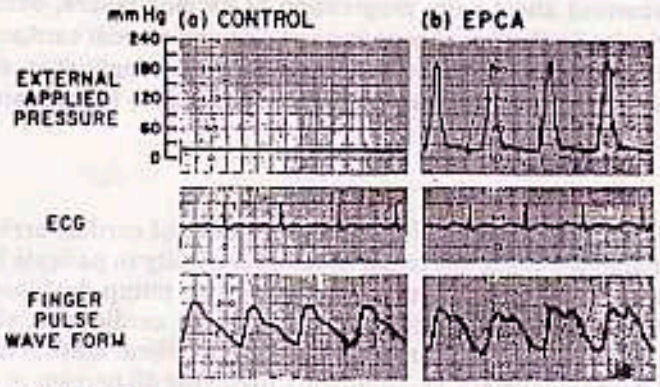

FIGURE 1. Top panel, actual external pressure applied during counterpulsation. Middle panel, electrocardiogram (ECG). Bottom panel, finger pulse waveform recorded from finger plethysmography depicting relative changes (uncalibrated). Data are recorded with patient in the external pressure circulatory assistance (EPCA) device before (a) and during (b) augmentation of diastolic pressure. The delays in transmission of central arterial pressure to the limbs and in transmission of peripheral externally applied pressure centrally account for the temporal relations between applied pressure and the finger pulse waveform. The water required to fill the leg unit accounts for the external pressure before activation of external pressure (a) and during the inactive phase of counterpulsation (b).

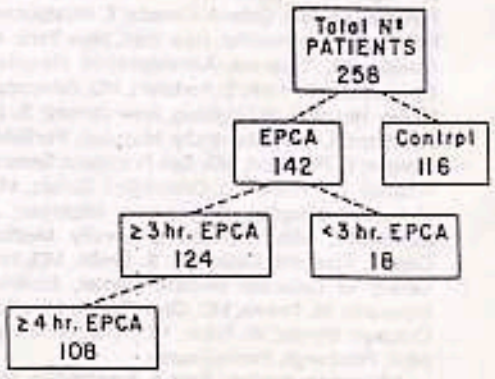

FIGURE 2. Number of patients in the control group and the groups with external pressure circulatory assistance. The number of hours indicates the total time of circulatory assistance in the first 24 hours after the onset of symptoms of myocardial infarction.

External pressure circulatory assistance was administered by a device that encloses the lower limbs from thigh to ankle in a hydraulically activated leg unit. External counterpulsation was delivered through the controlled application of positive external pressure by the leg unit. The device did not include a negative pressure phase. The timing, magnitude and duration of external pressure were each regulated to produce the desired diastolic augmentation. Diastolic augmentation was assessed by indirect recording of finger pulse waveform by a volume-sensing finger plethysmograph, with which each device is equipped (Fig. 1). Counterpulsation was effected by synchronization of mechanical activation with the electrocardiogram to produce positive pressure during diastole. The technique was applied to achieve maximal diastolic augmentation, which resulted in elevation of peak pressure during diastole to levels approximating systolic pressure (Fig. 1). External pressures ranged up to 250 mm Hg for a duration of up to 250 ms to produce satisfactory diastolic augmentation. The maximal duration of 250 ms was selected because prior experience indicated it to be the maximum necessary to produce the desired effect over a wide range of heart rates.

Evaluation of data: All data were recorded and maintained in individual patient books at each institution. A copy of the completed data record was forwarded to a central office where it was reviewed and evaluated by the project steering committee, consisting of the authors. All data were evaluated without knowledge of whether the patients were in the treatment or the control group.

Statistical analysis was performed by application of the chi square test to categorized variables and Student's two-tailed *t* test to continuous variables.

Results

Duration of treatment: Two hundred fifty-eight patients fulfilled the study criteria; 116 of the patients constituted the control group and 142 the treatment group. Of the latter patients, 108 received 4 or more hours of external pressure circulatory assistance (mean 5.0 hours, maximum 8.1 hours) completed within the first 24 hours after the onset of symptoms of myocardial infarction and 124 received the assistance for 3 or more hours (mean 4.7 hours, maximum 8.1 hours) within the first 24 hours (Fig. 2). Eighteen patients in the treatment group received less than 3 hours of treatment in the first 24 hours.

Time from onset of symptoms to completion of treatment: This interval was determined for the group receiving 4 or more hours of treatment. Completion of 4 or more hours of external pressure circulatory assistance was achieved within 12 hours of onset of symptoms in 31 patients (29 percent), within 18 hours in 45 patients (42 percent) and within 24 hours in 32 patients (29 percent). Therefore, treatment was completed within 18 hours of onset of symptoms in 71 percent of patients.

Hospital mortality: Mortality did not differ significantly ($p > 0.05$) from that of the control group for the total group of 142 patients who received external pressure circulatory assistance and for the group that received 3 or more hours of assistance in the first 24 hours (Table I). However, mortality was significantly less than that of the control group for those patients aged 46 or more years (the population in this study in which mortality occurred) who received 3 or more hours of circulatory assistance in the first 24 hours (8.3 versus 17.5 percent, $p < 0.05$) and for the entire group that received 4 or more hours of assistance in the first 24 hours (6.5 versus 14.7 percent, $p < 0.05$) (Table I). In addition, mortality from cardiac pump failure alone was significantly less than in the control patients for both the entire group that received 3 or more hours of circulatory assistance (5.7 versus 13.8 percent, $p < 0.04$) and the group that received 4 or more hours of treatment (4.6 versus 13.8 percent, $p < 0.02$) (Table II). There were no significant differences in proportion of deaths due to primary cardiac arrhythmias in the treated and control patients.

Specific subgroups of patients considered to be at increased risk were analyzed in regard to the effects of external pressure circulatory assistance on mortality. These subgroups consisted of patients with transmural myocardial infarction, anterior infarction, and a Norris index[19] greater than 6. (The Norris index is described in the Appendix.) For these analyses, the treatment

TABLE I

Mortality Rate in Control Group and Patients Treated With External Pressure Circulatory Assistance (EPCA)

	Total	Control Group	Treatment Group	p
All treated patients* vs. control group				
Patients (n)	258	116	142	
Deaths (n)	29	17	12	
Mortality rate (%)		14.7	8.4	NS
Patients with ≥3 h EPCA in first 24 h vs. control group				
Patients (n)	240	116	124	
Deaths (n)	26	17	9	
Mortality rate (%)		14.7	7.3	NS
Patients ≥ 46 yr with ≥3 h EPCA in first 24 h vs. control group				
Patients (n)	206	97	109	
Deaths (n)	26	17	9	
Mortality (%)		17.5	8.3	<0.05
Patients with ≥4 h EPCA in first 24 h vs. control group				
Patients (n)	224	116	108	
Deaths (n)	24	17	7	
Mortality (%)		14.7	6.5	<0.05

* Includes 18 patients who received less than 3 hours of external pressure circulatory assistance within the first 24 hours after onset of myocardial infarction. NS = not significant; p = probability.

TABLE II

Mortality Rate in Control and Patient Groups

Cause of Death	Control Group	Patients With ≥3 h EPCA	p	Patients With ≥4 h EPCA	p
Pump failure	13.8% (16/116)	5.7% (7/124)	<0.04*	4.6% (5/108)	<0.02*
Arrhythmia	0.9% (1/116)	1.6% (2/124)	NS*	1.9% (2/108)	NS

* Compared with control group. Abbreviations as in Table I.

TABLE III

Comparison of Clinical Data on Admission of Control Group and Patients Aged 46 or More Years Treated With 3 or More Hours of External Pressure Circulatory Assistance

Group	Age (yr)				Sex		Race		Cardiac History				ECG Location of MI		
	<50	50–59	60–69	≥70	M	F	W	NonW	AP	MI	Both	Neither	Ant	Inf	Nontrans
Control															
n	9	41	35	12	78	19	82	14	25	10	22	40	56	35	6
%	(9.3)	(42.3)	(36.1)	(12.4)	(80.4)	(19.6)	(85.4)	(14.6)	(25.8)	(10.3)	(22.7)	(41.2)	(57.7)	(36.1)	(6.2)
Treatment															
n	13	50	32	14	94	15	96	11	26	8	20	55	54	45	10
%	(11.9)	(45.9)	(29.4)	(12.8)	(86.2)	(13.8)	(89.7)	(10.3)	(23.8)	(7.3)	(18.4)	(50.5)	(49.5)	(41.3)	(9.2)
p		>0.2			>0.2		>0.3			>0.5				>0.2	

Group	HR (beats/min)				Systolic BP (mm Hg)					Radiographic Class					Norris Index[19]		
	<60	60–79	80–99	≥100	<100	100–109	110–119	120–129	≥130	I	II	III	IV	V	4–<6	6–<8	≥8
Control																	
n	7	32	33	22	6	8	14	13	56	17	67	2	3	4	26	36	31
%	(7.4)	(34.0)	(35.1)	(23.4)	(6.2)	(8.2)	(14.4)	(13.4)	(57.7)	(19.1)	(75.3)	(2.2)	(3.4)	(4.1)	(26.8)	(37.1)	(32.0)
Treatment																	
n	6	30	41	29	6	8	12	16	67	23	71	9	1	5	33	46	25
%	(5.7)	(28.3)	(38.7)	(27.4)	(5.5)	(7.3)	(11.0)	(14.7)	(61.5)	(22.1)	(68.3)	(8.6)	(1.0)	(4.6)	(30.3)	(42.2)	(22.9)
p		>0.7				>0.9					>0.1					>0.5	

Ant = anterior; AP = angina pectoris; BP = blood pressure; ECG = electrocardiographic; HR = heart rate; Inf = inferior; MI = myocardial infarction; NonW = nonwhite; Nontrans = nontransmural; p = probability; W = white.

group consisted of patients receiving 3 or more hours of circulatory assistance. Mortality in treated patients with transmural myocardial infarction was 7.1 percent (8 of 113) compared with 15.4 percent (17 of 110) in the control group ($p < 0.05$). Although mortality tended to be lower in the treatment group with anterior infarction (8.5 percent, 5 of 59) than in the control group (16.4 percent, 11 of 67), this difference was not significant ($p > 0.05$). In patients with a Norris index greater than 6, the treated group had a significantly lower mortality rate, 9.6 percent (7 of 73) versus 22.7 percent (17 of 75), ($p < 0.04$).

Clinical characteristics and time from onset of symptoms to admission (Tables III, IV and V): There were no significant differences on admission with respect to the broad set of clinical characteristics assessed between the control group and the subgroup of patients aged 46 or more years with 3 or more hours of treatment, the entire group with 3 or more hours of treatment, or the entire group with 4 or more hours of treatment. In addition, the mean time from onset of symptoms to admission to the coronary care unit was similar in the treatment and control groups: 6.9 versus 7.2 hours ($p > 0.05$).

Cardiac complications: Morbidity, as defined by several cardiac complications, was significantly less in each of the total treatment groups completing 3 or 4 or more hours of external pressure circulatory assistance, respectively, within the first 24 hours after onset of symptoms of myocardial infarction than in the control

TABLE IV

Comparison of Clinical Data on Admission of Control Group and All Patients Treated With 3 or More Hours of External Pressure Circulatory Assistance

Group	Age (yr)				Sex		Race		Cardiac History				ECG Location of MI		
	<50	50–59	60–69	≥70	M	F	W	NonW	AP	MI	Both	Neither	Ant	Inf	Nontrans
Control															
n	28	41	35	12	94	22	99	16	29	11	24	52	67	43	6
%	(24.1)	(35.3)	(30.2)	(10.3)	(81.0)	(19.0)	(86.1)	(13.9)	(25.0)	(9.5)	(20.7)	(44.8)	(57.8)	(37.1)	(5.2)
Treatment															
n	28	50	32	14	107	17	106	16	29	9	23	63	59	54	11
%	(22.6)	(40.3)	(25.8)	(11.3)	(86.3)	(13.7)	(86.9)	(13.1)	(23.4)	(7.3)	(18.5)	(50.8)	(47.6)	(43.5)	(8.9)
p		>0.3			>0.2		>0.8			>0.7				>0.2	

Group	HR (beats/min)				Systolic BP (mm Hg)					Radiographic Class				Norris Index[19]			
	<60	60–79	80–99	≥100	<100	100–109	110–119	120–129	≥130	I	II	III	IV	<4	4–<6	6–<8	≥8
Control																	
n	7	40	41	25	6	9	19	17	65	21	78	5	3	7	34	43	32
%	(5.2)	(35.4)	(36.3)	(22.1)	(5.2)	(7.8)	(16.4)	(14.7)	(56.0)	(19.6)	(72.9)	(4.7)	(2.8)	(6.0)	(29.3)	(37.1)	(27.6)
Treatment																	
n	8	36	43	34	6	10	13	16	77	28	80	10	1	8	43	47	26
%	(6.6)	(29.8)	(25.5)	(28.1)	(4.8)	(8.1)	(10.5)	(14.5)	(62.1)	(23.5)	(67.2)	(8.4)	(0.18)	(6.4)	(34.7)	(37.9)	(21.0)
p		>0.6					>0.7				>0.3					>0.5	

Abbreviations as in Table III.

TABLE V

Comparison of Clinical Data on Admission of Control Group and Patients Treated With 4 or More Hours of External Pressure Circulatory Assistance

Group	Age (yr)				Sex		Race		Cardiac History				ECG Location Of MI		
	<50	50–59	60–69	≥70	M	F	W	NonW	AP	MI	Both	Neither	Ant	Inf	Nontrans
Control															
n	28	41	35	12	94	22	99	16	29		24	52	67	43	6
%	(24.1)	(35.3)	(30.2)	(10.3)	(81.0)	(19.0)	(86.1)	(13.9)	(25.0)	(9.5)	(20.7)	(44.8)	(57.8)	(37.1)	(5.2)
Treatment															
n	22	44	31		94	14	92	14	27	7	17	57	46	50	10
%	(20.4)	(40.7)	(28.7)	(10.2)	(87.0)	(13.0)	(86.8)	(13.2)	(25.0)	(6.5)	(15.7)	(52.8)	(44.4)	(46.3)	(9.3)
p		>0.2			>0.8		>0.8				>0.5			>0.1	

Group	HR (beats/min)					Systolic BP (mm Hg)				Radiographic Class				Norris Index[18]			
	<60	60–79	80–99	≥100	<100	100–109	110–119	120–129	≥130	I	II	III	IV	<4	4–<6	6–<8	≥8
Control																	
n	7	40	41	25	6	9	19	17	65	21	78	5	3	7	34	43	32
%	(6.2)	(35.4)	(36.3)	(22.1)	(5.2)	(7.8)	(16.4)	(14.7)	(56.0)	(19.6)	(72.9)	(4.7)	(2.8)	(6.0)	(29.3)	(37.0)	(27.6)
Treatment																	
n	6	34	39	26	4	6	13	16	67	22	71	9	1	5	38	43	22
%	(5.7)	(32.4)	(37.1)	(24.8)	(3.7)	(7.4)	(12.0)	(14.8)	(62.0)	(21.4)	(68.9)	(8.7)	(1.0)	(4.6)	(35.2)	(39.8)	(20.4)
p			>0.9				>0.8				>0.4				>0.5		

Abbreviations as in Table III.

group (Table VI). Data regarding change in roentgenographically determined heart size were available for 57 percent (138 patients) of the study group because of inclusion of this factor after initiation of the study.

Other medical treatment: Analysis of pharmacologic therapy during the first 5 days of hospitalization demonstrated no significant differences ($p > 0.05$) between the groups receiving treatment (3 or more hours of treatment, age 46 or more years; total group with 3 or more hours of treatment and total group with 4 or more hours of treatment) and the control group with respect to proportion of patients receiving antiarrhythmic drugs, diuretic agents, digitalis, vasodilator drugs and propranolol and no differences with regard to analgesic or sedative therapy during the interval from 12 hours after admission through day 5. There was no relation between vasodilator therapy and the clinical outcome in either group. Data were not available for comparative analysis of therapy after day 5.

Complications of external pressure circulatory assistance: There were no complications directly attributable to this procedure. Discomfort of the lower limbs was a common complaint and some patients complained of a distressing feeling of confinement when in the device, but there was no injury or evidence of trauma from the procedure. Pulmonary embolism, which proved fatal, occurred in one patient in the treatment group, and in none of the control group.

Discussion

Validity of study: This trial of application of external pressure circulatory assistance during the first 24 hours after the onset of symptoms of myocardial infarction was associated with a reduction in hospital mortality and morbidity in certain large groups of patients with acute myocardial infarction complicated by mild cardiac failure. Several aspects of this study support a relation between this treatment and the favorable clinical outcome in the treated patients. The trial was controlled by application of randomization in the selection of the study groups. This method provides several important advantages in the design of a clinical trial and contributes considerably to the significance of the results.[20] Randomization affords an unbiased means of selecting the treatment and control groups and is the most practical approach to eliminating or reducing

TABLE VI

Morbidity in Control Group and Groups Treated With External Pressure Circulatory Assistance (EPCA)

	≥3 h EPCA		Control			≥4 h EPCA		Control		
	n	%	n	%	p	n	%	n	%	p
Recurrent chest pain (12 h to 5 days)	49/124	39.5	66/116	56.6	<0.01	44/108	40.7	66/116	56.6	<0.01
Progression of CHF (to class III or IV)	8/122	6.6	17/115	14.8	<0.04	6/106	5.7	17/115	14.8	<0.03
Ventricular fibrillation	1/115	0.9	7/99	7.1	<0.02	1/101	1.0	7/99	7.1	0.04
Change in heart size					<0.05					
Increase	3/74	4.0	6/63	9.5		2/64	3.1	6/63	9.5	
Decrease	32/74	43.2	15/63	23.8		29/64	45.3	15/63	23.8	
No change	39/74	52.7	42/63	66.7		33/64	51.6	42/63	66.7	
Discharged class I	106/120	88.3	88/115	76.5	<0.02	92/104	88.5	88/115	76.5	<0.03

CHF = cardiac heart failure; p = probability.

systematic differences in their characteristics. Further, this method is the most reliable means of limiting not only apparent bias in selection of study populations, but also those inapparent factors that could affect the outcome of an investigation of a therapeutic intervention. Adequacy of randomization of our patients was assessed by comparative statistical analysis of multiple risk factors related to prognosis in acute myocardial infarction. The results of the analyses are consistent with appropriate randomization, as reflected by comparable prevalence of these risk factors in the treatment and control groups on entry (Tables III to V).

With respect to the *unequal number of patients per institution*, we considered it mandatory to include all patients in this prospective trial in the analysis of data. Interestingly, the results of external pressure circulatory assistance were more favorable in institutions that contributed a higher number of patients than in those with fewer patients entered in the study. These differences were not significant however.

The validity of this study was supported by rigorous implementation of the protocol, randomization procedure, data acquisition and analytic methods. All patients included and excluded were reviewed and categorized at several levels of the investigation, as indicated in the Appendix, and all exclusions are accounted for. Of further importance is the representative nature of the control group in this study, in terms of hospital mortality among patients with Killip class II infarction[17], indicating that the observed differences in outcome between the treatment and control patients cannot be attributed to an atypically high mortality rate in the latter.

Role of duration of therapy in reducing mortality: The beneficial clinical effects of external pressure circulatory assistance were closely related to the duration of this therapy administered in the 24 hours after the clinical onset of acute myocardial infarction. Thus, whereas evidence of benefit in patients receiving less than 3 hours of treatment was lacking, morbidity related to infarction was reduced in the groups receiving 3 or more or 4 or more hours of treatment (Table VI). Moreover, mortality in relation to that of the control patients was reduced in only a specific subgroup of the patients treated for 3 or more hours, those aged 46 or more years, whereas it was decreased in the entire group treated for 4 or more hours (Table I). These findings demonstrate enhanced clinical benefit with greater duration of external pressure circulatory assistance, suggesting a direct relation of this therapeutic intervention to the differences in outcome in the treated and control patients. Although mortality in the treated and control patients differed significantly only in the two aforementioned groups, outcome was consistently favorable in all treated groups (Table I). Mortality related to cardiac pump failure alone was significantly less in the patients treated for 3 or more hours and those treated for 4 or more hours than in the control group (Table II). In this regard, it is reasonable that a beneficial effect on survival obtained from therapy with the potential to limit infarct size might be more directly reflected by a decrease in mortality due to pump failure than by a reduction in overall mortality.

Role of infarct size and pump failure: The most critical factor determining the clinical course of patients hospitalized with acute myocardial infarction is infarct size, because cardiac pump failure, the major cause of mortality in this setting, is the result of extensive cardiac damage.[2–4] The potential for limitation of infarct size has been demonstrated by interventions that improve the balance between myocardial oxygen supply and demand by decreasing oxygen consumption or increasing supply.[5,6] Mechanical augmentation of diastolic pressure has been utilized to achieve the latter effect.[6] In this regard, it has been suggested that mechanical circulatory assistance may have an important role in early application to control myocardial damage before hypotension and severe cardiac pump failure develop.[10–12] This concept has recently been applied with resultant evidence of limitation of myocardial injury in the subgroup of patients with anterior myocardial infarction and residual patency of the left anterior descending coronary artery.[14] External pressure circulatory assistance may provide a noninvasive means to achieve this effect.

Experimental data have demonstrated that therapy to limit ischemic myocardial injury is significantly influenced by the timing of the intervention after the onset of infarction. Thus, hyaluronidase has been associated with evidence of limitation of myocardial damage after experimental canine infarction when the agent was administered within 6 hours after coronary occlusion, whereas it had no demonstrable effect when given at 9 hours.[21] The beneficial clinical effects of external pressure counterpulsation in our patients were associated with application of treatment at a later time than that suggested as necessary by the aforementioned study. This discrepancy can be related at least in part to factors such as the inconsistency between the experimental model of myocardial infarction and the clinical entity and the multiplicity of factors that determine infarct size in man, such as the specific coronary artery involved and the site of obstruction, the presence or absence of collateral vessels and the state of myocardial oxygen demand. Nevertheless, the importance of early intervention in myocardial infarction to impede progressive ischemic damage is clear and it is noted that more than two thirds of our patients did complete treatment within 18 hours of the onset of symptoms.

Enhancement of myocardial perfusion: role of augmentation of diastolic blood pressure: Previous studies have suggested that external pressure counterpulsation may be beneficial in ischemic heart disease by improving myocardial perfusion. This improvement could involve an increase in total coronary blood flow or a favorable redistribution of myocardial blood flow. As indicated indirectly in this study and by previous direct measurements of intraarterial pressure,[15,16] external pressure counterpulsation produces considerable augmentation of diastolic blood pressure, a critical determinant of coronary blood flow, of particular importance in the presence of obstructive coronary artery

disease. Diastolic pressure augmentation possesses the major advantage of increasing arterial pressure during the period of minimal left ventricular intramural pressure, thereby producing a maximum gradient for coronary perfusion. Enhancement of myocardial perfusion by this procedure has been suggested by studies of the technique in experimental and clinical infarction demonstrating improvement in cardiac metabolism and efficiency,[22-25] a reduction in S-T segment injury pattern[26] and augmentation of regional contractile function.[27] The effect on total coronary blood flow has been inconsistent[16,21,22] although experimental studies suggest that external pressure counterpulsation may increase coronary collateral flow to ischemic myocardium.[28,29]

Complications of external pressure counterpulsation: Complications were limited to discomfort of the legs, which in a few patients may preclude this therapy. However, no local trauma or lesions were evident. One patient in the treatment group had a fatal pulmonary embolism. Although dislodging of thrombi in leg veins is a theoretic hazard with this procedure, we did not find an increased incidence of this complication with this approach.

Implications: The early results of external pressure counterpulsation in this multicenter trial of patients with acute myocardial infarction and mild (class II) cardiac failure are encouraging and support further application and evaluation of this approach in other subgroups of patients with acute myocardial infarction and other forms of ischemic heart disease. Further objective assessment of the effects of this treatment on myocardial ischemia and infarct size with current methods is also warranted.

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APPENDIX

Randomization procedure: All patients were assigned to the treatment or control groups by random allocation made at a central, independent coordinating center. To promote representative distribution of patients in the treatment and control groups at all institutions, a separate set of random tables was prepared for each institution and was utilized exclusively for its patients throughout the study. On presentation of a patient, assignment to either the control or treatment group was obtained by direct telephone call to the coordinating center, which was available on a 24-hour basis.

Exclusion of ineligible patients: The 258 patients who met the study criteria were obtained from a total group of 326 patients on whom randomization and admission to the protocol were requested. Of this initial total, 68 patients (39 of 181 [21.5 percent] from the treatment group and 29 of 145 [20.0 percent] from the control group) were ineligible on the basis of study criteria and were therefore excluded. The ineligible group included 39 patients who did not fulfill the criteria for acute myocardial infarction, 10 patients who did not fulfill criteria for clinical class II status, 13 patients who were not admitted within the prescribed time limit, 3 patients with insufficient data and 3 patients who were excluded because of a noncardiac death. Exclusion of 40 of these patients was made by the principal investigator at each institution. The remaining 28 patients were excluded by decision of the steering committee because of absence of criteria for diagnosis of myocardial infarction (10 patients), nonfulfillment of the time requirements for admission (13 patients) and noncardiac death (3 patients [2 in the treatment and 1 in the control group]). In addition to the evaluation of all patients excluded from the study by the institutional principal investigator and the steering committee, a review and confirmation of the validity of exclusion was made by a physician unassociated with the study.

Mortality in the ineligible patients: Analysis of mortality in the 68 patients ineligible for inclusion in the study revealed eight deaths in the 39 patients who had been allocated to the treatment group and three deaths in the 29 patients assigned to the control group. Four of the eight deaths in the treatment group were in patients who, although randomized to this group, did not receive external pressure circulatory assistance because of their early exclusion by the respective institutional investigators on the basis of failure to meet inclusion criteria. The specific reasons for exclusion of the nonsurvivors were: absence of myocardial infarction (treatment group, two patients), failure to fulfill clinical class II criteria (treatment group, three; control group, one); failure to meet time requirements for entry (treatment group, one; control group, one) and noncardiac death (treatment group, two; control group, one). Exclusion of five of the nonsurvivors, three from the treatment group and two from the control group, was made by the steering committee on the basis of failure to meet the time requirements for entry (treatment group, one patient; control group, one patient) and noncardiac death (treatment group, two; control group, one). The remaining six nonsurvivors were excluded by the respective institutional investigators because of absence of myocardial infarction (treatment group, two) and failure to fulfill class II criteria (treatment group, three; control group, one).

Norris index: The Norris index[19] is a prognostic index that provides a probability level for hospital mortality in patients with acute myocardial infarction on the basis of six readily measurable clinical factors on admission: (1) age, (2) electrocardiographic location of infarction, (3) systolic blood pressure, (4) heart size, (5) lung fields on roentgenography, and (6) history of myocardial ischemia. Each factor is assigned a relative weight according to the specific data, the sum of the weights equaling the index score. Mortality associated with a score of 6 to 7 is 22 percent.

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